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WORKBOOK IN

PRACTICAL NEONATOLOGY

SIXTH EDITION

RICHARD POLIN
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EDITORS:

Richard A. Polin, MD
William T. Speck Professor of Pediatrics
College of Physicians and Surgeons
Columbia University
Executive Vice-Chair Department of Pediatrics
Director, Division of Neonatology
Morgan Stanley Children's Hospital of New York—
Presbyterian
New York, New York

Mervin C. Yoder, MD
Distinguished Professor and Richard and Pauline Klingler
Professor of Pediatrics
Assistant Dean for Entrepreneurial Research
and Associate Director for Entrepreneurship
for Indiana Clinical and Translational Sciences Institute
Indiana University School of Medicine
Associate Chair for Basic Research
Attending Neonatologist
Riley Hospital for Children
Indianapolis, Indiana

ELSEVIER
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LIST OF CONTRIBUTORS

David Adamkin, MD
Professor of Pediatrics
University of Louisville
Louisville, Kentucky

Cigdem Akman, MD
Chief, Child Neurology
Director, Pediatric Epilepsy
Neurology
Columbia University Medical Center
New York, New York

Chad Andersen, MBBS
Neonatal Medicine
Women's and Children's Hospital
Adelaide, Australia

Lauren Astrug, MD
Assistant Professor of Neonatology
Department of Pediatrics
Loyola University Chicago
Chicago, Illinois

William E. Benitz, MD
Professor of Neonatology
Pediatric/Neonatal & Developmental Medicine
Stanford University
Stanford, California

Jatinder Bhatia, MD, FAAP
Professor, Department of Pediatrics
Chief, Division of Neonatology
Director, Fellowship Program, Neonatal-Perinatal Medicine
Director, Transport/ECMO/Nutrition
Vice Chair, Clinical Research
Medical College of Georgia
Augusta University
Augusta, Georgia

Shazia Bhombal, MD
Clinical Assistant Professor of Pediatrics
Division of Neonatal and Developmental Medicine
Stanford University School of Medicine
Palo Alto, California

Waldemar A. Carlo, MD
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Birmingham, Alabama

Maria Roberta Cilio, MD, PhD
Professeure Ordinaire de Neurologie Pediatrique
Université catholique de Louvain
Epileptologie pédiatrique et néonatale
Cliniques universitaires Saint-Luc
Adjunct Professor of Neurology and Pediatrics
University of California, San Francisco

Erika Claud, MD
Professor
Pediatrics and Medicine
The University of Chicago
Chicago, Illinois

Alain C. Cuna, MD
Neonatologist
Children's Mercy Kansas City
Assistant Professor of Pediatrics
University of Missouri-Kansas City
Kansas City, Missouri

Vincent Duron, MD
Assistant Professor, Surgical Director of Critical Care
Pediatric Surgery
Morgan Stanley Children's Hospital/ New York-Presbyterian
New York, New York

Lin Fangming, MD, PhD
Director of Pediatric Nephrology
Columbia University
New York, New York

Kirsten Glaser, MD
University Children's Hospital
University of Wuerzburg
Wuerzburg, Germany

Pamela Isabel Good, MD
Neonatal-Perinatal Medicine Fellow
Department of Pediatrics
Morgan Stanley Children's Hospital of New York—Presbyterian
Columbia University Medical Center
New York, New York

Cathy Hammerman, MD
Director Newborn Nurseries
Neonatology
Shaare Zedek Medical Center
Professor
Pediatrics
Hebrew University Faculty of Medicine
Jerusalem, Israel

William W. Hay, Jr., MD
Professor of Pediatrics (Neonatology)
Scientific Director, Perinatal Research Center
University of Colorado School of Medicine
Anschutz Medical Campus
Scientific Director, Perinatal Research Center
Aurora, Colorado

Kendra Hendrickson, MS, RD, CNSC, CSP
Clinical Dietitian II
Neonatal Intensive Care Unit
University of Colorado Hospital
Department of Nutrition
Aurora, Colorado

Stuart Brian Hooper, BSc(Hons), PhD
The Ritchie Centre
Hudson Institute of Medical Research
The Department of Obstetrics and Gynecology
Monash University
Melbourne, Australia

Thomas A. Hooven, MD
Assistant Professor
Pediatrics
Columbia University
New York, New York

Elie G. Abu Jawdeh, MD
Neonatal-Perinatal Medicine
Kentucky Children's Hospital
University of Kentucky College of Medicine
Lexington, Kentucky

Erik A. Jensen, MD
Department of Pediatrics
Division of Neonatology
The Children's Hospital of Philadelphia
The University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Michael Kaplan, MB, ChB
Emeritus Director
Department of Neonatology
Shaare Zedek Medical Center
Professor of Pediatrics
Faculty of Medicine
Hebrew University
Jerusalem, Israel

Martin Keszler, MD
Professor of Pediatrics
Alpert Medical School of Brown University
Associate Director of NICU
Director of Respiratory Services
Women and Infants Hospital of Rhode Island
Providence, Rhode Island

Haresh Kirpalani, MB, MSc
Professor
Neonatology, Department of Pediatrics
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
Emeritus Professor
Clinical Epidemiology
McMaster University
Hamilton, Canada

Ganga Krishnamurthy, MBBS
Assistant Professor of Pediatrics
Columbia University Medical Center
Director, Neonatal Cardiac Care
Morgan Stanley Children's Hospital of New York-Presbyterian
New York, New York

Satyan Lakshminrusimha, MBBS, MD, FAAP
Professor of Pediatrics
Chief, Division of Neonatology
Director, Center for Developmental Biology of the Lung
University at Buffalo
The Women and Children's Hospital of Buffalo
Buffalo, New York

Abbot R. Laptook, MD
Professor of Pediatrics
Alpert Medical School of Brown University
Medical Director, Neonatal Intensive Care Unit
Staff Neonatologist
Women & Infants Hospital of Rhode Island
Providence, Rhode Island

Stéphanie Levasseur, MD, FRCPC
Assistant Professor of Pediatrics
Columbia University Medical Center
Morgan Stanley Children's Hospital of New York-Presbyterian
New York, New York

Jack Lorenz, MD
Emeritus Professor of Pediatrics
Columbia University
College of Physicians & Surgeons
New York, New York

Shahab Noori, MD, MS, CBTI, RDCS
Fetal and Neonatal Institute
Division of Neonatology
Children's Hospital Los Angeles
Department of Pediatrics
Keck School of Medicine
University of Southern California
Los Angeles, California

Camilia R. Martin MD, MS
Assistant Professor of Pediatrics
Harvard Medical School
Associate Director, NICU
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Richard J. Martin, MD
Case Western Reserve University School of Medicine
Rainbow Babies& Children's Hospital
Cleveland, Ohio

Bobby Mathew, MBBS
Assistant Professor of Pediatrics
University of Buffalo
Attending Neonatologist, Associate Director
Neonatal Perinatal Medicine Fellowship Program
The Women & Children's Hospital of Buffalo
Buffalo, New York

Shahab Noori, MD
Associate Professor of Pediatrics
Keck School of Medicine of the University of Southern California, Attending Neonatologist
Children's Hospital Los Angeles and the LAC USC Medical Center
Los Angeles, California

Brenda B. Poindexter, MD, MS
Professor of Pediatrics
Section of Neonatal-Perinatal Medicine
Indiana University School of Medicine
Riley Hospital for Children at IU Health
Indianapolis, Indiana

Richard A. Polin, MD
William T. Speck Professor of Pediatrics
College of Physicians and Surgeons
Columbia University
Director, Division of Neonatology
Morgan Stanley Children's Hospital of New York—Presbyterian
New York, New York

Tara M. Randis, MD, MS
Assistant Professor
Department of Pediatrics and Microbiology
NYU School of Medicine
New York, New York

Veniamin Ratner, MD
Assistant Professor of Pediatrics
Columbia University Medical Center
Neonatologist
Morgan Stanley Children's Hospital of New York-Presbyterian
New York, New York

Kimberly J. Reidy, MD
Assistant Professor
Pediatrics/Nephrology
Children's Hospital at Montefiore/Albert Einstein College of Medicine
Bronx, New York

Ana P. Duarte Ribeiro, MD
Case Western Reserve University School of Medicine
Rainbow Babies & Children's Hospital
Cleveland, Ohio

S. David Rubenstein, MD
Professor of Pediatrics
Columbia University Medical Center
Director, Neonatal Intensive Care Unit
Morgan Stanley Children's Hospital of New York-Presbyterian
Director, Fellowship Training Program in Neonatal-Perinatal Medicine
New York Presbyterian Hospital, Columbia Campus
New York, New York

Ashley M. Reilly, PharmD
Clinical Pharmacy Specialist
Neonatal Intensive Care Unit/ Labor & Delivery
University of Colorado Hospital
Department of Pharmacy
Aurora, Colorado

Calum T. Roberts
Department of Paediatrics
Monash University
The Ritchie Centre
Hudson Institute of Medical Research
Monash Newborn
Monash Medical Centre
Melbourne, Australia

Tristan T. Sands, MD, PhD
Assistant Professor
Neurology
Columbia University Medical Center
New York, New York

Istvan Seri, MD
Fetal and Neonatal Institute
Division of Neonatology
Children's Hospital Los Angeles
Department of Pediatrics
Keck School of Medicine
University of Southern California
Los Angeles, California
First Department of Pediatrics
Faculty of Medicine
Semmelweis University
Budapest, Hungary

Michael Stark, BSc (Hons), MBChB, PhD
Associate Professor
Department of Neonatal Medicine
Women's and Children's Hospital
The Robinson Research Institute
University of Adelaide
Adelaide, Australia

Steven Stylianos, MD
Rudolph Schullinger Professor of Pediatric Surgery
Department of Surgery
Columbia University School of Physicians & Surgeons
Surgeon-in-Chief
Morgan Stanley Children's Hospital
New York, New York

Arjan B. te Pas, MD, PhD
Division of Neonatology
Department of Pediatrics
Leiden University Medical Center
Leiden, The Netherlands

Payam Vali, MD
Assistant Professor of Clinical Pediatrics
University of California Davis
Sacramento, California

Clyde J. Wright, MD
Section of Neonatology
Department of Pediatrics
University of Colorado School of Medicine and Children's Hospital Colorado
Aurora, Colorado

Tai-Wei Wu, MD
Fetal and Neonatal Institute
Division of Neonatology
Children's Hospital Los Angeles
Department of Pediatrics
Keck School of Medicine
University of Southern California
Los Angeles, California

Ariela Zenilman, MD
Columbia University Medical Center
New York, New York

PREFACE

This is the sixth edition of the *Workbook in Practical Neonatology*. There is no doubt that the practice of our discipline has changed in numerous ways since the first edition of this text was published in 1983. However, we remain passionately convinced that the study of neonatology is best conducted in a format similar to the dialogue between a learner and teacher as they "see" the patient. The dialogue is informed by the specific elements of acquired patient data that give some evidence for the status of the patient in supplement of the physical examination, and assessments for the daily plan of the patient are constructed. In each chapter, specific case studies are presented, followed by a series of questions that seek the reader to choose an intervention, and then the various approaches are discussed to bring the reader to identify the most appropriate plan of action.

As true for the first edition, this book is designed to provide an opportunity to directly solve problems as you read through the clinical scenarios. The workbook format has four objectives: to allow you to evaluate your own knowledge for each problem presented; to permit you to identify areas of knowledge in which you are deficient so that you may read up and enhance your armamentarium of knowledge; to keep you engaged and alert as you solve the problems presented and to have fun while learning.

We have recruited new authors to provide a fresh perspective on all the given areas. Each were chosen for their recognized expertise and status within the discipline, as has been the tradition since the first edition. Thus, the goal of the present edition is to provide new avenues from which to glean the available evidence, new insights into pathophysiology, and advances in treatment of critically ill neonates.

We wish to thank Angie Breckon from Elsevier for her outstanding guidance through the entire project. MCY wishes to thank his wife, Holly, children Andrew, Cait, Chris and Emily and grandchildren Isaac, Jacob, Gracie, and Charlotte for all their support. RAP wishes to thank his wife Helene, children Allison, Mitchell, Jessica and Gregory and grandchildren Lindsey, Eli, Willa, Jasper, Casey, Smith, Calla and Elliott for their love and support.

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A Physiologic Approach to Neonatal Resuscitation

Stuart B. Hooper, Arjan B. te Pas and Roberts Calum T. Roberts

INTRODUCTION

Neonatal resuscitation is commonly defined as the assistance given to infants immediately after birth as they transition to newborn life. From a physiologic perspective, this transition involves some of the most complex and profound changes that any human will likely encounter during their life. The airways that are filled with liquid during fetal life must be cleared to allow the entry of air and onset of pulmonary gas exchange, and major vascular shunts must close to separate the pulmonary and systemic circulations. It is truly an amazing feat of nature that the vast majority of infants transition through these changes with such apparent ease. As a result, it is easy to underestimate both the magnitude of the physiologic changes and the complexity and difficulty of rendering assistance to infants struggling to adapt to life after birth.

Very preterm infants commonly require assistance at birth because they are simply too immature to survive unassisted, but there is considerable debate about what assistance is required and how it should be provided. Nevertheless, a fundamental tenet of neonatal resuscitation is to recognize that at birth, newborn infants, particularly very preterm infants, are not "mini adults" but are essentially exteriorized fetuses with liquid-filled airways. As such, the type of assistance given should be tailored to suit the infant's changing physiology and its specific needs at any moment in time. For instance, what is the logic of applying ventilation strategies that facilitate pulmonary gas exchange when the gas exchange regions of the lung are liquid filled and so no pulmonary gas exchange can occur? Although this is only a transient consideration for most infants, because the airways are rapidly cleared of liquid, it is a lingering consideration in very preterm infants who have problems aerating their lungs (te Pas et al, 2008).

A key component to a successful neonatal resuscitation is understanding the physiologic changes that occur after birth and having the capacity to monitor the infant as it progresses through these changes so that the right assistance can be provided at the right time. As such, rather than utilizing an algorithm-based approach for describing currently recommended strategies for neonatal resuscitation, we will discuss the physiologic changes that occur at birth and highlight approaches that may best assist different subgroups of infants as their physiology changes. Many well-informed, recent publications have already detailed the currently recommended strategies for undertaking neonatal resuscitation from a practical perspective (Weiner et al, 2018). We intend to take a different approach and will focus on the physiology. This is because currently recommended strategies for neonatal resuscitation will likely change as our understanding of the physiology improves and better strategies for facilitating the necessary physiologic changes are identified. Indeed, much of the evidence underpinning current neonatal resuscitation guidelines is regarded as weak and/or absent (Perlman et al, 2015). The reasons for this are unclear, but it could be argued that a lack of scientific clarity regarding the physiology of transition is a major contributing factor. Nevertheless, in the following discussion, it will become evident that some of the emerging science is not consistent with current recommendations. This should not be misinterpreted as a recommendation for changing practice, but as the first important step in designing studies that will provide the required level of evidence needed to better guide practice.

ESTABLISHING PULMONARY VENTILATION

CASE 1

You are called to the delivery room to resuscitate a late preterm infant born at 34 weeks' gestation by repeat cesarean section. The 1 min Apgar score is 2. You arrive at 90 sec of life. The infant is pale with a heart rate of 30 beats/min. The infant is receiving nCPAP with 100% oxygen, but only gasping intermittently. The Sao_2 reading on the pulse oximeter is 65%. The anesthesiologist has just begun chest compressions.

Exercise 1

Question

What is the next most appropriate next step in this infant's resuscitation, and what should have been done before you arrived?

Answer

Positive pressure ventilation should have been started immediately.

From a teleologic perspective, it is logical that the physiologic changes required for survival after birth are triggered by the one event that cannot occur in utero, lung aeration. Aerating the lung and establishing pulmonary ventilation triggers the physiologic changes that underpin the transition to newborn life (Hooper et al, 2015a). However, it is far too simplistic to assume that the primary benefit of "establishing pulmonary ventilation" is reestablishing oxygen and carbon dioxide exchange lost following umbilical cord clamping. Lung aeration not only triggers the switch to pulmonary gas exchange but also triggers a very large reduction in pulmonary vascular resistance (PVR), which initiates a series of cardiovascular changes that are also essential for survival after birth (see later). Positive pressure ventilation also enhances reabsorption of lung fluid.

CASE 1 CONTINUED

With initiation of positive pressure ventilation, the heart rate increases to 120/min and the saturation increases to 85% by 7 min of life. The infant is breathing regularly at 120 breaths/min. Auscultation reveals fine rales and wet sounding rhonchi. You suspect the infant has a "wet lung syndrome."

Exercise 2

Question

When is lung liquid reabsorbed? How did the mode of delivery influence the resorption of lung liquid?

Answer

Resorption of lung liquid begins antenatally and continues during labor and delivery. However, most lung liquid is reabsorbed postnatally when spontaneous or assisted ventilations begin. Infants delivered by cesarean section do not undergo the postural changes of vaginally delivered infants; those changes help to expel liquid from the lungs.

AIRWAY LIQUID CLEARANCE BEFORE BIRTH AND DURING LABOR

Although there is some evidence to suggest that airway liquid clearance begins late in gestation before labor onset (Jain and Eaton, 2006), this is not a consistent finding, and the role of experimental artefacts is unclear with regard to the original observations (Harding and Hooper, 1996). Nevertheless, considering the capacity of the lung to clear airway liquid during labor and after birth (see later), whether small amounts of liquid are cleared before labor appear inconsequential. However, it is clear that airway liquid clearance can begin during labor and vaginal delivery (Olver et al, 2004). The release of adrenaline in response to the stress of labor activates Na^+ channels located on the luminal surface of airway epithelial cells, which promotes Na^+ reabsorption from the airways into lung tissue (Olver et al, 1986). This reverses the osmotic gradient for liquid movement across the airway epithelium, leading to liquid reabsorption, rather than secretion as occurs in utero. However, Na^+ reabsorption requires high levels of adrenaline, is relatively slow, only arises late in gestation, and so is not active in very preterm infants (Hooper et al, 2016). Similarly, as cesarean section delivery in the absence of labor avoids the stress of labor, this mechanism is unlikely to be activated in infants delivered by cesarean section without labor (Jain and Eaton, 2006).

Partial airway liquid clearance can also occur during labor as a result of induced postural changes before and during delivery of the head (te Pas et al, 2008). The fetus is forced into an exaggerated "fetal position" with the enhanced dorso–ventral flexion causing an increase in abdominal pressure and rostral displacement of the diaphragm (Harding et al, 1990). This increases intrathoracic pressures and forces liquid to leave the lungs via the trachea (Hooper and Harding, 1995; Harding and Hooper, 1996). As the fetal respiratory system is highly compliant, only small increases in intrathoracic pressure are needed for large reductions in airway liquid volumes (Hooper and Harding, 1995; Harding and Hooper, 1996). Although this mechanism is applicable to infants born vaginally, as per Na^+ reabsorption, it is not readily applicable to infants born by cesarean section, particularly in the absence of labor.

Airway Liquid Clearance After Birth

Lung aeration has significant implications for respiratory function in the newborn period, and to better understand these consequences, the process of lung aeration can be divided into a series of phases that give rise to separate challenges (Hooper et al, 2016).

1. The first phase commences at birth with liquid-filled airways, and so the primary challenge is to clear the airways of liquid, which occurs across the distal airway wall.
2. Airway liquid is cleared from the airways into the surrounding lung tissue at a much greater rate (over minutes) than it is cleared from the tissue (over hours). As such, airway liquid accumulates within lung tissue for the first few hours after birth, forming "perivascular fluid cuffs," expanding the chest wall and increasing interstitial tissue pressures, essentially making the lung edematous.
3. Airway liquid is gradually cleared from lung tissue via the circulation and lymphatics, after which lung function and mechanics stabilize.

Exercise 3

Question

What is the importance of spontaneous breathing (or positive pressure ventilation) on promoting the clearance of lung water?

Answer

To clear lung liquid from the airways and alveoli, positive pressure ventilation (either spontaneous or assisted) must begin. Ventilation moves the liquid through the airways to

the distal respiratory units, where it is absorbed into the lung interstitium and then into lymphatics.

As noted earlier, the majority of liquid remaining in the airway is cleared across the distal airway wall. For this to occur, the liquid must move distally through the airways before leaving the airways and entering the surrounding distal lung tissue (Hooper et al, 2016). This process has been observed in newborn rabbits using phase contrast x-ray imaging, showing that the air/liquid interface moves distally during each inspiration (Hooper et al, 2007; Siew et al, 2009b) (Fig. 1.1). As no further distal movement occurred between breaths, lung aeration and the creation of a functional residual capacity (FRC) occurs in a stepwise fashion, increasing with each successive inspiration (Fig. 1.1). This led to the recognition that hydrostatic pressure gradients (between airways and lung tissue) generated by inspiration are largely responsible for airway liquid clearance after birth (Hooper et al, 2007; Siew et al, 2009b). Importantly, this mechanism provides a rational explanation for why very preterm infants who have little or no capacity to reabsorb Na^+ are still able to clear their airways of liquid. As the air/liquid interface can also move proximally between breaths, causing a reduction in FRC, it is possible that liquid can reenter the airways between breaths, necessitating its reclearance with the next inspiration (Hooper et al, 2007; Siew et al, 2009b).

Exercise 4

Question

During the transition to postnatal life, what are the factors that govern whether airway liquid clearance is fast or slow?

Answer

Variables that regulate the rate of resorption of liquid include:

A. The surface area of the lung
B. Airway resistance (liquid has a higher resistance than air)
C. Resistance to moving the liquid across the walls of the distal airways
D. Tightness of the epithelial barrier

The initial resistance to air entering the lungs at birth is governed by both the resistance to moving liquid through the airways and by the resistance to moving this liquid across the distal airway wall. As water has a much higher viscosity than air, the resistance to moving air into the lungs is much greater when the airways are liquid filled compared with a few moments later when they are air filled (te Pas et al, 2009a, 2016). Consequently, airway resistance decreases markedly during the initial phase of lung aeration, as progressively more of the airways aerate and the reduction follows an exponential function that is difficult to predict (te Pas et al, 2009a, 2016).

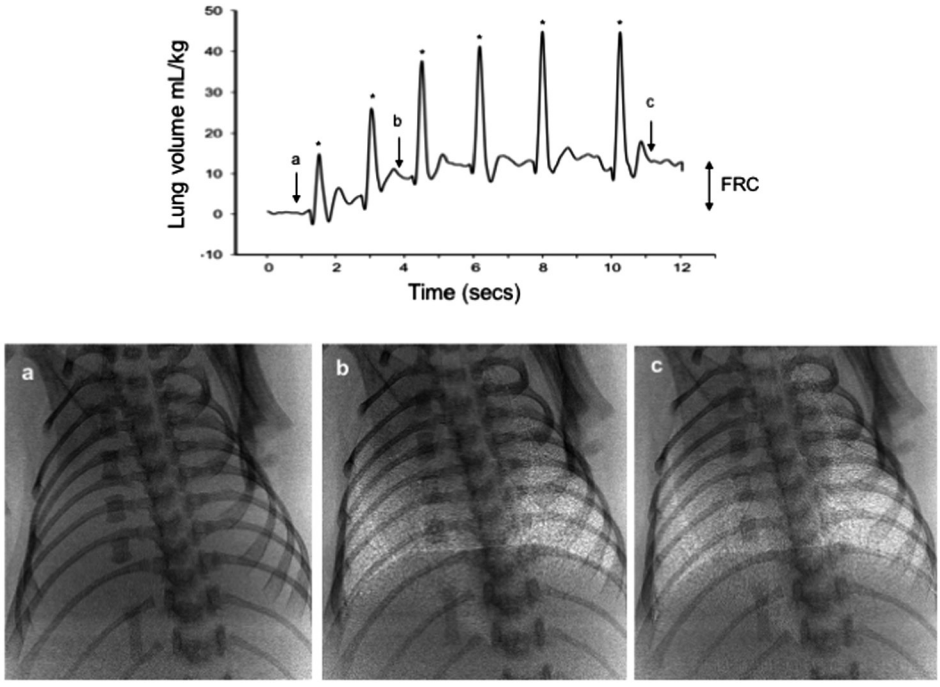

Fig. 1.1 Simultaneous plethysmograph recording and phase contrast x-ray images of a spontaneously breathing newborn rabbit during lung aeration. Upper panel: Plethysmograph recording showing 6 spontaneous breaths over a 10 sec period along with the gradual recruitment in FRC that occurs with each breath. Spontaneous breaths are the large increases in lung volume (indicated by an *) that decrease to a gradually increasing baseline (functional residual capacity: FRC). The reduction in lung volume after each breath is an artefact from the plethysmograph measurement. Bottom panel: Phase contrast x-ray images of the newborn rabbit's chest, acquired at the time points indicated on the plethysmograph recording (indicated by an arrow and the corresponding letter for each image). Little to no aeration is present in image A, whereas a significant amount of aeration is present in image C, which was acquired approximately 10 seconds later.

On the other hand, little is known about the contribution that the resistance to liquid movement across the distal airway wall makes to the overall resistance to airway liquid clearance. Based on the volume of liquid that can be cleared during one inspiration (up to 3 mL/kg), and knowing the duration of inspiration (100–200 mSec), the liquid flux across the pulmonary epithelium can be as high as 15 to 30 mL/kg/sec or 0.9 to 1.8 L/kg/min. Although transient, this is surprisingly high for liquid movement across the relatively tight pulmonary epithelium (Egan et al, 1975). A large surface area is one obvious factor that allows the lung to clear liquid at this rate, but the "tightness" of the epithelial barrier likely resists water transfer.

The immature lungs of preterm infants have airways that are smaller in diameter and have few if any alveoli. As reducing the radius of a tube increases its resistance by the 4th power and as the absence of alveoli markedly reduces the lung's surface area, the resistance to airway liquid clearance is higher in preterm infants than in term infants (te Pas et al, 2016). As a result, either the process of lung aeration will be much slower, or preterm infants will require larger inspiratory efforts or higher inflation pressures to overcome this higher resistance. This concept is at odds with current resuscitation guidelines that suggest using lower inflation pressures during the initiation of lung aeration in very preterm infants compared with term infants (Perlman et al, 2015). This recommendation is based on an extrapolation from studies in aerated lungs suggesting that higher pressures cause lung injury. However, considering it is the volume change and not the pressure per se that causes lung injury (Jobe et al, 2008) and that a liquid-filled lung is orders of magnitude less compliant than an air-filled lung (te Pas et al, 2009a), this recommendation may be flawed and requires further investigation.

Previous studies have demonstrated that the fetal pulmonary epithelium is relatively tight, which restricts the entry of even relatively small molecules into lung liquid during development (Egan et al, 1975). However, at birth these pore sizes markedly increase, which likely reduces the resistance to liquid movement across the epithelium in term newborns (Egan et al, 1975). However, it is unknown whether this occurs in preterm infants or whether it occurs to a greater degree due to the immaturity of the epithelium. Although this could reduce the resistance to liquid clearance, it may also contribute to the entry of plasma proteins into the lumen, which will interfere with surfactant function.

Exercise 5

Question

In the delivery room, how will I know when this infant's lungs are optimally aerated?

Answer

Heart rate, oxygen saturation and expired CO_2

Heart rate and peripheral oxygen saturation levels, measured using a pulse oximeter and/or ECG leads, are commonly used to assess when neonatal resuscitation has been "successful" (Dawson et al, 2010a, 2010b). The idea that an increasing heart rate is a sign of lung aeration is based on the concept that a low heart rate indicates a vagal-induced bradycardia in response to perinatal asphyxia (Dawes, 1968). As such, an increasing heart rate is assumed to reflect improved oxygenation following the onset of pulmonary gas exchange. However, it is now clear that an increase in heart rate can also occur after birth in the absence of an increase in oxygenation (Lang et al, 2015). In this instance, the increase in heart rate is secondary to an increase in PBF (in response to lung aeration), which increases venous return and left ventricular preload (Lang et al, 2015). Nevertheless, whether the increase in heart rate results from increased oxygenation or an increase in PBF, both only occur as a result of lung aeration.

An alternate indicator for lung aeration is the use of expired CO_2, which is closely related to the degree of lung aeration (Hooper et al, 2013). Indeed, it is such a sensitive indicator that it can detect breath-by-breath changes in lung aeration in parallel with the changing tidal volumes and increases much more quickly in response to lung aeration than an increase in both heart rate and oxygenation in infants (Hooper et al, 2013; Blank et al, 2014; Schmolzer et al, 2015). The close relationship between end-tidal expired CO_2 levels and tidal volumes is because CO_2 exchange is surface-area limited during lung aeration. As CO_2 has a high solubility, its diffusion across the pulmonary epithelium is very efficient and is not normally surface-area limited. As such, end-tidal CO_2 levels are commonly used to estimate pulmonary arterial blood Pco_2 levels and can be used to calculate cardiac output (Trillo et al, 1994). However, when the lung is not fully aerated, the surface area available for gas exchange at end inspiration is dependent on the size of the tidal volume (Hooper et al, 2013). When tidal volumes are larger, the surface area for gas exchange increases, which increases the efficiency of CO_2 exchange.

Although CO_2 monitoring in the delivery room is currently not routine, in combination with tidal-volume monitoring, it provides a reliable method for assessing the effectiveness of pulmonary ventilation immediately after birth. Indeed, considering that the dead space of the lower airways is 2 to 3mL/kg and that the pharynx is expandable (Crawshaw et al, 2017), it is possible to achieve significant tidal volumes (3–4 mL/kg) without gas entering the gas exchange regions of the lung. As such, the baby would appear to be ventilated, but oxygenation levels and heart rate would likely remain low. However, the absence of any expired CO_2 would indicate that the gas exchange regions are not being ventilated. Some of the new respiratory function monitors include the ability to measure expired CO_2 levels, although increasing dead-space volume is an issue, and are most effectively used in combination with tidal-volume monitoring. Alternatively, a colorimetric CO_2 indicator, which changes color in response to expired CO_2, can be used to indicate when gas exchange has commenced (Blank et al, 2014).

Exercise 6

Question

During resuscitation, what alternate resuscitation strategies might be used to improve uniform lung aeration and better ventilation in this infant?

Answer

Increase in positive end expiratory pressure (PEEP) or sustained lung inflation

Recognition that airway liquid clearance after birth results from the generation of hydrostatic pressure gradients (between airways and lung tissue) has provided opportunities for developing strategies that facilitate this process in very preterm infants. Indeed, in a simplistic sense, all that is required is to apply a gas pressure to the airways to overcome the high resistance of moving liquid through the airways and across the distal airway wall. This rationale is consistent with the current recommendations for using either intermittent positive pressure ventilation (iPPV) or continuous positive airway pressure (CPAP) in combination with the infant's spontaneous breathing to assist preterm infants initiating pulmonary gas exchange after birth (Perlman et al, 2015; Weiner et al, 2018).

However, the big question is how much pressure should be applied? Indeed, if the applied pressure is too low, it will be insufficient to overcome the resistance required to move the liquid distally through the airways. If it is too high, then there is a risk of causing overinflation and lung injury in lung regions that have already aerated (Jobe et al, 2008). To add to the complexity, as the airway resistance dramatically decreases (by ~100 fold) with airway liquid clearance, the pressures required to move the liquid at any given flow rate will also greatly reduce (te Pas et al, 2016). Considering the huge variability expected between individual infants at birth, particularly with the amount of liquid present in the airways and the level of inspiratory effort each will apply, stipulating a single set inflation pressure or CPAP level to assist preterm infants to aerate their lungs at birth ignores this complexity. Clearly the pressure required will be different in different infants and will change as the lung aerates. Although we now have a grasp of the complexities involved in facilitating lung aeration in very preterm infants, the challenge is to apply this knowledge in a useful and practical manner (Jobe, 2011).

During lung aeration, ideally the respiratory support applied should change in accordance with the change in resistance caused by airway liquid clearance. High airway pressures could be applied initially when the resistance is high, which decrease as the airway resistance decreases to avoid overinflation and lung injury. However, to decrease the applied pressure in synchrony with the decreasing resistance requires complex feedback information regarding the changing airway resistance. Although modern ventilators can measure airway resistance on a breath-by-breath basis, they are rarely used in the delivery room even if the infant is intubated. Instead, low-technology devices such as resuscitation bags or t-piece devices are more commonly used, mostly in combination with noninvasive ventilation (Schmolzer et al, 2010; Schilleman et al, 2013). These provide little or no opportunity to measure airway resistance and provide little information on how to modify the required ventilation parameters as lung mechanics change unless it is combined with a respiratory function monitor. It seems counterintuitive that sophisticated ventilators and monitoring equipment are commonly used in the NICU once the lung has aerated and respiratory mechanics have stabilized, but they are not routinely used in the delivery room when respiratory mechanics are rapidly changing and respiratory function is very difficult to manage in a safe and effective way.

SUSTAINED INFLATION DURING RESUSCITATION

The movement of air into the lung at birth is primarily determined by airway resistance and the applied pressure gradient, as defined by $F = \Delta P/R$; where F is flow, ΔP is the pressure gradient and R is airway resistance, which includes the resistance to moving liquid across the distal airway wall. As flow equals volume (V) divided by time (T), the factors determining the movement of air (inflation volume) into the lung can be defined as $V = (\Delta P \times T)/R$. As such, the main controllable factors determining inflation volume are the applied pressure gradient (ΔP) and time (T) over which the pressure is applied (inflation time). Although increasing the inflation pressure can overcome the high initial resistance, as the resistance decreases with lung aeration, there is a high risk of overinflating and injuring the lung if the pressure is not simultaneously reduced. Alternatively, increasing the inflation time using a slower, sustained inflation (SI) allows lower inflation pressures to be used. Although the initial flow of gas into the lung is slow, it rapidly increases as more of the airways aerate and the resistance decreases (te Pas et al, 2016). Theoretically, this approach has multiple advantages, as during a sustained inflation the lung's end inflation volume is self-limiting and determined by the inflation pressure, which can be much lower than the pressure required to initially aerate the lung with a shorter inspiratory time.

As different lung regions aerate at different rates, a SI allows more lung regions to aerate during a single inflation (te Pas et al, 2009b, 2009a). This has important implications for lung injury, because during the subsequent inflation, air will rapidly flow into and expand aerated lung regions first due to the much lower airway resistance. Therefore if the inflation time is short (as occurs with iPPV), the entire tidal volume will only enter aerated regions, potentially causing overexpansion and injury in those regions with little further lung aeration (Siew et al, 2009a, 2011). Furthermore, as gas exchange only occurs when the distal gas exchange regions aerate, there is no reason to terminate the inflation to allow exhalation when these regions are liquid filled. These explanations underpin the rationale for providing a SI for the first inflation after birth, but the benefits described in animal studies have not been replicated in humans (van Vonderen et al, 2014a; Lista et al, 2015). Although the reasons are

unclear, in animal studies the SI was applied with an endotracheal tube, whereas in all human studies, the SI was applied noninvasively, usually with a face mask (including the SAIL trial). This is a major point of difference (see later), and studies that are restricted to comparing a SI with conventional ventilation in intubated infants may possibly reveal results that are as clear cut as the animal studies.

Exercise 7

Question

What are the adverse effects of higher levels of PEEP or sustained inflation during resuscitation?

Answer

High levels of PEEP or a prolonged sustained inflation can decrease venous return and reduce cardiac output.

Recent studies have suggested that a stepwise PEEP recruitment maneuver (up to 20 cmH_2O) that extends over 2 to 3 minutes can achieve better postmaneuver lung mechanics than an SI (McCall et al, 2016). This suggestion is consistent with the concept that lung aeration is a function of applying an elevated pressure over an extended period, and the results show significant improvements in lung mechanics (Tingay et al, 2016, 2017). However, applying this maneuver ignores the cardiovascular consequences of applying high elevated airway pressures that increase intrathoracic pressures for an extended period. Simple physics dictates that as soon as intrathoracic pressures exceeds central venous pressure, then all venous return to the heart will cease and, as such, cardiac output must decrease (see later). Furthermore, in the aerated lung, high PEEP levels reduce PBF, and this effect on PBF is not completely reversed following the reduction in PEEP (Polglase et al, 2005). Although this adverse effect of increased intrathoracic pressure on PBF is applicable to both a sustained inflation and PEEP recruitment maneuver, a sustained inflation does not influence the time related increase in PBF, perhaps because sustained inflation is only 10 to 30 seconds long (Sobotka et al, 2011). However, the PEEP recruitment maneuver can take 2 to 3 minutes (Tingay et al, 2016, 2017), and it is unclear how it influences the increase in PBF at birth. There is also a need to be cautious of any rebound in cardiac output, as per a Valsalva maneuver that may occur post maneuver.

Whether a sustained inflation or a PEEP recruitment strategy is the most effective approach for aerating the lung remains unclear, and more studies are required. In particular, there is much debate about what is the most appropriate starting pressure and duration of the sustained inflation. However, evidence from animal studies indicate that these are not the correct starting points (McCall et al, 2016), particularly as a "one-size-fits-all" approach is unlikely to be successful in different infants (te Pas et al, 2009a, 2016). Targeting a set inflation volume instead of a fixed inflation time and using a ramped pressure increase, which is then held constant once gas starts to move into the lungs, may be more appropriate (Polglase et al, 2014; McCall et al, 2016; te Pas et al, 2016). Measurement of CO_2 levels in the expired air can then indicate whether a second inflation is needed. This approach is easy to implement in animals, but its application in humans will depend on the use of sophisticated approaches to monitor newborns immediately after birth (McCall et al, 2016).

CASE 1 CONTINUED

At 60 min of life the infant's respiratory rate is 120/min. There is intermittent grunting. The inspiratory oxygen concentration is 100% to achieve a saturation of 90%.

Exercise 8

Question

Why is this infant tachypneic?

Answer

The increased water in the interstitium of the lung has reduced the infant's lung compliance and reduced its inspiratory reserve volume by expanding the chest wall and flattening the diaphragm.

At birth, the liquid residing in the airways following the first breath is rapidly cleared into lung tissue, forming perivascular fluid cuffs (Bland et al, 1980). As liquid clearance from the tissue takes hours, the volume of liquid residing in the airways at birth must be accommodated within the lung's interstitial tissue during this time (Bland et al, 1980; Miserocchi et al, 1994). This has consequences for respiratory function in the newborn period (Berger et al, 1996), including an increase in interstitial tissue pressure (Miserocchi et al, 1994). This in turn increases the potential for liquid to reenter the airways during expiration and expansion of the chest wall (Hooper et al, 2007; McGillick et al, 2017). Indeed, although the liquid has cleared from the airways, it remains within the thorax, forcing the chest wall to expand to accommodate both the liquid and the air that creates the newly formed FRC (Hooper et al, 2007; McGillick et al, 2017).

Exercise 9

Question

Assuming this infant's lung water is increased, how can respiratory function be improved?

Answer

Increasing the positive end expiratory pressure

It is both fortuitous and necessary that the newborn's chest wall is very compliant so that it can easily expand without further increasing interstitial tissue pressures and opposing FRC formation. This explains the importance of applying an end expiratory pressure on the airways during the immediate newborn period (Siew et al, 2009a). The positive airway pressure not only prevents the lung from collapsing but also opposes the elevated interstitial pressure and prevents liquid reentering the airways during expiration (Siew et al, 2009a). Phase contrast x-ray imaging in ventilated very preterm rabbits (Figs. 1.2 and 1.3) has clearly demonstrated that a FRC will not develop, largely due to liquid

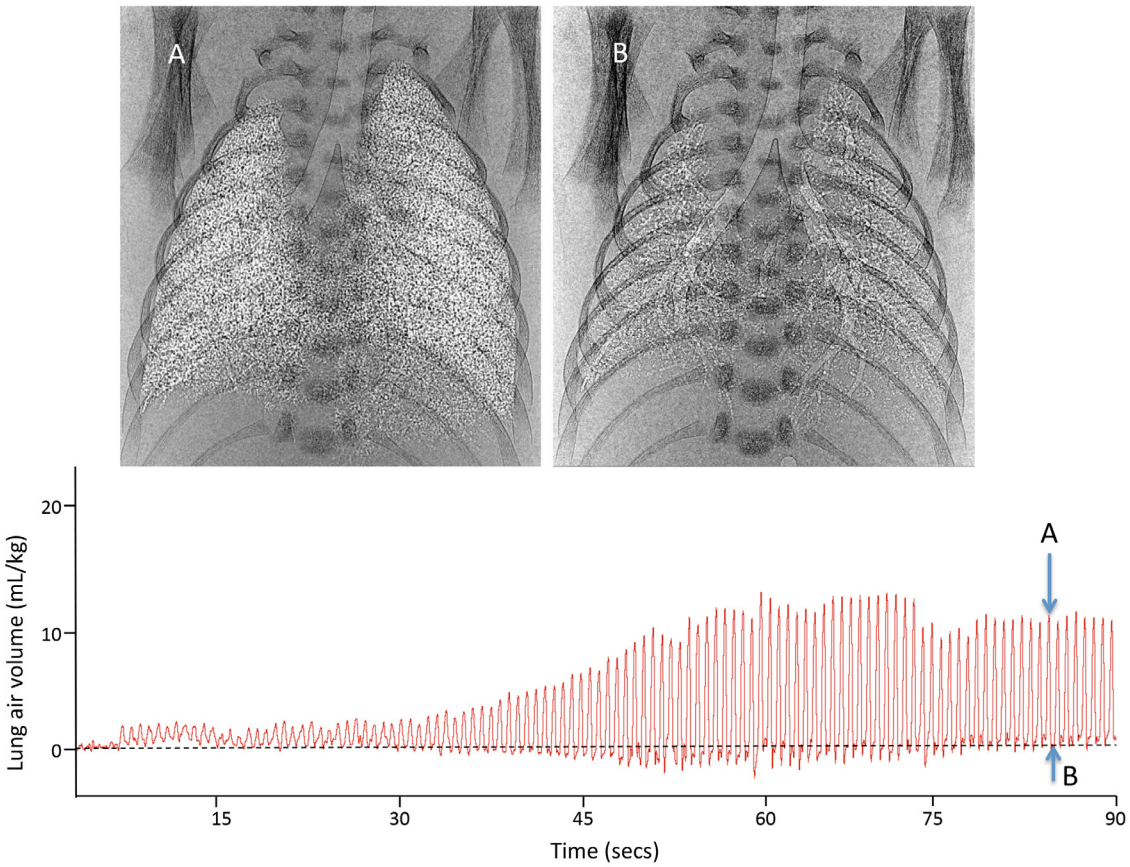

Fig. 1.2 Phase contrast x-ray images and a plethysmograph recording of a preterm newborn rabbit immediately after birth ventilated from birth in the absence of a positive end expiratory pressure (PEEP). In the absence of PEEP, preterm rabbits failed to develop a functional residual capacity (FRC) resulting in liquid reentry or airway collapse at end expiration. Phase contrast x-ray images (**A** and **B**) were recorded at each time point on the plethysmograph trace. Image A was acquired at end inspiration, whereas image B was acquired at FRC.

reentry into the airways, in the absence of an end expiratory pressure (Siew et al, 2009a).

Exercise 10

Question

Does this infant have transient tachypnea of the newborn? (TTN)

Answer

The infant's clinical signs are consistent with TTN.

As the volume of airway liquid differs greatly between individuals at birth (Harding and Hooper, 1996), the volume of liquid entering lung tissue will also vary, causing large variations in lung tissue and chest wall mechanics. For instance, accommodating larger liquid volumes in lung tissue increases chest wall expansion (including flattening of the diaphragm), reduces FRC, increases lung tissue stiffness (McGillick et al, 2017) and likely further increases pulmonary interstitial tissue pressures and pressure within the fluid cuffs surrounding pulmonary blood vessels (Bland et al, 1980; Miserocchi et al, 1994). These consequences may explain the pathology associated with transient tachypnea of the newborn (TTN). Indeed, the tachypnea maybe caused by expansion of the chest wall and flattening of the diaphragm, which reduces the infant's inspiratory reserve volume. This limits the infant's capacity to increase tidal volume, making an increase in respiratory rate the primary option for increasing minute ventilation and CO_2 clearance. Because of the increased respiratory rate, many of these infants develop a respiratory alkalosis. Furthermore, the associated reduction in FRC commonly induces expiratory braking and grunting, which is another characteristic of infants with TTN.

Exercise 11

Question

How long will the tachypnea persist?

Answer

The tachypnea can resolve in a day or two or last as long as 5 to 7 days as liquid is reabsorbed.

Although TTN is usually transient and self-resolving, some infants exhibit continuing respiratory morbidity for up

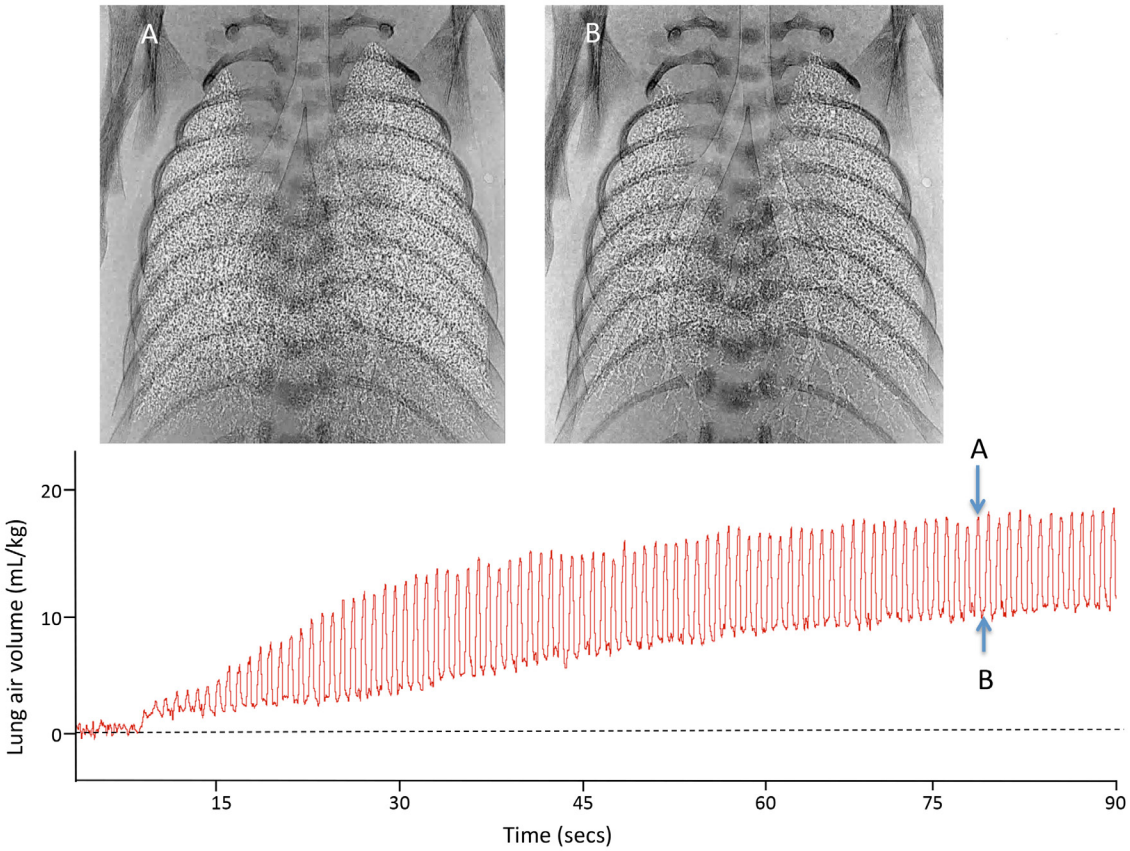

Fig. 1.3 Phase contrast x-ray images and a plethysmograph recording of a preterm newborn rabbit immediately after birth ventilated from birth with a positive end expiratory pressure (PEEP) of 5 cmH_2O. With this level of PEEP, preterm rabbits gradually develop a significant functional residual capacity (FRC) with most distal airways (not all, see basal lung regions) remaining aerated at FRC. Phase contrast x-ray images (**A** and **B**) were recorded at each time point on the plethysmograph trace. Image A was acquired at end inspiration, whereas image B was acquired at FRC.

to 72 hours, and some develop persistent pulmonary hypertension (Jain and Dudell, 2006; Ramachandrappa and Jain, 2008). Thus the morbidity associated with TTN may not be unidimensional, as the consequences of too much liquid in lung tissue should resolve as the liquid is cleared. It is possible that some infants experience continuing morbidity due to lung injury associated with bidirectional liquid movement across the epithelium. In newborn rabbits, liquid can reenter the airways at FRC due to the elevated pressures in lung tissue, which is then recleared during the subsequent inspiration/inflation (Hooper et al, 2007; Siew et al, 2009b).

Liquid entry rates into lung tissue during inspiration are very high, and although liquid movement back into the airways is considerably lower, 1 to 2 mL/kg can reenter the airways over a 1 to 2 sec expiratory time in newborn rabbits (Hooper et al, 2007; Siew et al, 2009b). As the liquid is recleared during the next inspiration, bidirectional liquid movement across the pulmonary epithelium is likely a normal feature of lung aeration (Hooper et al, 2007; Siew et al, 2009b). However, unlike the kidney, which has a fenestrated epithelium, the pulmonary epithelium is not designed for sustained high liquid flux rates. It is possible that if lung tissue liquid volumes are elevated, the propensity for airway liquid reentry increases, leading to increased bidirectional liquid movement across the airway wall, resulting in lung injury. Thus although the respiratory morbidity associated with TTN may initially be caused by too much liquid within lung tissue, lung injury may be responsible for the continuing morbidity in some TTN infants. Nevertheless, this explanation provides an understanding for why CPAP, which opposes airway liquid reentry, can be used to treat TTN.

CASE 1 CONTINUED

The infant continues to receive nCPAP with 100% oxygen. Because of intermittent episodes of bradycardia and hypoxemia, he required positive pressure ventilation using nasal prongs (nIPPV). However, the Sao_2 only rises to 90%. You consider intubating this infant but worry about injuring the lung with positive pressure ventilation.

Exercise 12

Question

Why was the noninvasive positive pressure ventilation (nIPPV) ineffective?

Answer

Noninvasive positive pressure ventilation is often ineffective because the vocal cords adduct during apnea and prevent the positive pressure from being transmitted to the lower airway. In addition, the dead-space volume of the nasopharynx may be considerable and mean that higher pressures and tidal volumes are needed when using noninvasive ventilation.

Until recently, intubation and mechanical ventilation were the most common form of respiratory support for very preterm infants. However, as it is invasive and associated with a higher risk of lung injury, noninvasive respiratory support has become the preferred method of respiratory support (Finer et al, 2010). But this change has occurred without understanding how noninvasive respiratory support interacts with the infant's physiology at birth. In particular, the physiologic significance of an endotracheal tube, which bypasses the infant's upper airway, has been largely overlooked. As a result, it is widely assumed that iPPV is equally effective when applied noninvasively as when applied via an endotracheal tube, which ignores the role of the larynx in regulating gas flow into and out of the lung.

When applied via an endotracheal tube, iPPV bypasses the larynx and has direct access to the sublaryngeal airways, unless they are blocked with mucous or foreign matter (e.g., meconium). However, when applied noninvasively (usually via a mask), airflow must pass through the upper airways and larynx before entering the trachea and lower airways. As the larynx can seal the airways even against very high pressures (>100 mm Hg), a patent airway is heavily dependent on whether the larynx is open during noninvasive ventilation.

In adults, the larynx is mostly open except during swallowing, some postural movements, and abdominal evacuation, etc. However, regulation of the larynx in the fetus and newborn is very different from in the adult (Harding et al, 1986; Praud et al, 1992). Before birth, airway liquid is secreted across the pulmonary epithelium, and while it flows out of the lungs via the trachea, the fetal larynx acts to restrict the rate of efflux to maintain the lungs in a hyperexpanded state (FRC of 35–40 mL/kg vs. 20–25 mL/kg after birth) (Hooper and Harding, 1995; Harding and Hooper, 1996). This is because lung expansion provides the primary stimulus for lung growth (Hooper and Harding, 1995; Harding and Hooper, 1996). During apnea, the larynx adducts to restrict liquid loss from the airways, causing it to accumulate within the airways and expand the lung. During fetal breathing movements (FBM), the larynx opens and liquid leaves the lungs at an increased rate, despite contractions of the diaphragm (Hooper and Harding, 1995; Harding and Hooper, 1996). Thus the larynx plays an important role in maintaining fetal lung expansion by adducting during apnea and preventing airway liquid loss. As this fetal pattern of laryngeal activity persists into newborn life (Crawshaw et al, 2017) it has major implications for the effective application of noninvasive ventilation in the newborn. It also reinforces the concept that infants, particularly very preterm infants, are not "mini adults" but are essentially exteriorized fetuses at birth and, therefore, automatically extrapolating treatment strategies from adult medicine may not be helpful.

In the context of neonatal resuscitation, the consequence of having a fetal pattern of laryngeal activity in the newborn is that apneic infants will mostly have a closed larynx. This has recently been demonstrated using phase contrast x-ray imaging (Crawshaw et al, 2017), whereby the patency of the larynx was found to depending on whether the newborn was apneic (closed larynx) or in a stable breathing pattern (open larynx). As a closed larynx prevents iPPV from ventilating the lung, no matter how much pressure is applied (Crawshaw et al, 2017), iPPV will be ineffective in apneic infants until they become so hypoxic and bradycardic that the larynx relaxes. Laryngeal closure is most likely seen as "airway obstructions" and explains why noninvasive ventilation in the delivery room has a high failure rate, requiring intubation (Schmolzer et al, 2010; Schilleman et al, 2013). However, if the newborn is breathing, the larynx will open, allowing iPPV to assist spontaneous breaths to aerate the lung (Crawshaw et al, 2017). Thus in contrast to ventilation via an endotracheal tube, the success of noninvasive ventilation is dependent on the presence of spontaneous breathing, when the larynx must open.

During noninvasive ventilation, particularly with a face mask, the dead-space volume may be significantly larger than in intubated infants. This is because of the contribution of the nasopharynx to the overall dead-space volume, which increases in relative size as the infant gets smaller (Nieves et al, 2018). As such, a 2 kg infant is estimated to have a nasopharynx dead-space volume of 2 mL/kg (Nieves et al, 2018) and in addition, the pharynx has been shown to expand further in response to an inflation pressure during iPPV (Crawshaw et al, 2017). This raises a number of questions about targeting the same tidal volumes during iPPV in intubated and mask-ventilated infants. Indeed, this is consistent with the finding that tidal volumes were significantly reduced following intubation, despite receiving the same inflation pressure, in infants previously receiving iPPV via a facemask (van Vonderen et al, 2014b).

Exercise 13

Question

If an infant is apneic at birth, should noninvasive ventilation be tried in the delivery room?

Answer

Noninvasive ventilation (NiPPV) might be acceptable once the apnea has resolved. Although NiPPV might not ventilate the infant more effectively (because of vocal cord adduction), it can provide a higher mean airway pressure.

From a physiologic perspective, an infant who is apneic at birth, particularly if it has good tone, will most likely have an adducted larynx (see earlier) that prevents noninvasively applied iPPV from ventilating the lung (Crawshaw et al, 2017). Although this scientific knowledge has come from animal studies, physiologic recordings from preterm infants during sustained inflation studies indicate that this also

occurs in humans (van Vonderen et al, 2014a; Lista et al, 2015). If the infant doesn't commence breathing, it will progressively become more hypoxic and will eventually lose tone and become bradycardic. Although all of these facts have been well documented scientifically, it is unclear at what point reflexes, such as those controlling laryngeal adduction, are lost as the asphyxia worsens. Nevertheless, it appears that at some point the larynx relaxes, despite the infant being apneic, which allows positive pressure ventilation to be delivered noninvasively (Schmolzer et al, 2010; Schilleman et al, 2013). Although noninvasive iPPV may eventually be successful, clearly the respiratory support is not optimal if the infant first becomes hypoxic and bradycardic before ventilation is successful. This raises the question as to whether current recommendations incorrectly assume that, when using noninvasive respiratory support, iPPV is a reliable "backup" for apneic infants. Instead, as closure of the larynx may render iPPV ineffective, perhaps the focus should shift toward stimulating breathing and avoiding known causes of apnea, such as hypoxia.

Exercise 14

Question

In an apneic infant, what other strategies might be helpful in the delivery room?

Answer

Physical stimulation and caffeine

As the larynx is mostly open during breathing in newborns, except when making expiratory braking maneuvers (e.g., grunting) (Crawshaw et al, 2017), it seems logical that stimulating breathing should be the primary focus of noninvasive respiratory support in the delivery room. This can be achieved by applying physical stimulation and avoiding hypoxia (as it inhibits breathing) and by giving respiratory stimulants such as caffeine (Dekker et al, 2017a, 2018). Recent studies have attempted to assess how—and how much—physical stimulation should be applied in the delivery room (Dekker et al, 2017b; Gaertner et al, 2018). In one study, standardizing and increasing the application of a physical stimulus was found to increase oxygenation in preterm infants, despite the use of a significantly lower Fio_2 and an unexpected increase in physical stimulation within the control group (Dekker et al, 2018). This was thought to result from an increase in minute ventilation (tidal-volume × respiration rate), which wasn't quite significant. Similarly, it has been shown that the administration of caffeine into the umbilical vein (using a butterfly needle) within the first few minutes after delivery can significantly increase breathing efforts in preterm infants (Dekker et al, 2017a). Thus rather than waiting for the infant to reach the NICU, it is both feasible and potentially beneficial to administer caffeine as soon as possible after birth.

Exercise 15

Question

How should the inspiratory oxygen concentration be regulated when noninvasive ventilation is used?

Answer

ILCOR recommends starting resuscitation with 21% to 30% oxygen in preterm infants. Theoretically, higher inspiratory oxygen concentrations used immediately after birth may stimulate respirations, but oxygen requirements decrease exponentially thereafter. Therefore, if an increased concentration of oxygen is used, it should be rapidly weaned. Infants who remain bradycardic despite use of 30% oxygen should receive 100% oxygen and positive pressure ventilation until the bradycardia is resolved.

The role of oxygen in stimulating/sustaining spontaneous breathing efforts in preterm infants at birth has been overshadowed by the debate on starting Fio_2 levels and the risk of hyperoxia-induced organ injury. This risk has been very well documented and prompted a change in the 2010 international guidelines, recommending that respiratory support for preterm infants should change from starting in high Fio_2 levels to low levels (30%) or air (Perlman et al, 2010). However, this change also coincided with a switch in the preferred respiratory support for preterm infants, which switched from invasive to noninvasive ventilation (Morley and Davis, 2008; Morley et al., 2008) without recognizing that a change to lower initial Fio_2 levels may affect spontaneous breathing. Presumably this was not considered to be important because it was assumed that iPPV is equally effective when applied noninvasively as it is when applied via an endotracheal tube.

A retrospective study in preterm infants has shown that increasing Fio_2 levels can significantly increase respiratory efforts; however, oxygen requirements usually decrease exponentially thereafter (van Vonderen et al, 2013). It was surmised that the initial high Fio_2 was required to provide a large air/blood Po_2 gradient to increase oxygenation and stimulate breathing when the surface area for gas exchange was initially low. However, the resulting increase in respiratory effort increased lung aeration and exponentially increased the capacity for gas exchange due to an exponential increase in surface area (van Vonderen et al, 2013). Thus although high Fio_2 levels may be required initially to stimulate and/or support breathing at birth, the requirement likely decreases exponentially as the lung aerates. Nevertheless, in view of the requirement for oxygen to stimulate and support breathing at birth in infants receiving noninvasive respiratory support, the debate over starting Fio_2 levels seems to be esoteric and not particularly useful. Clearly, this will depend on the infant's oxygenation level at delivery, the level of respiratory effort, the level of stimulation (either physical or chemical) and the degree of lung aeration at any one moment in time during a process that changes exponentially. This is an extraordinarily complex question and it is highly unlikely to have one correct answer, as the need will vary considerably between infants. This brings into question the rationale of current trials trying to find a starting Fio_2 that can be applied to all infants. Instead, the complexity emphasizes the need to be able to rapidly titrate Fio_2 as required (to avoid both hypoxia and hyperoxia) and to measure the infant's oxygenation to guide titration, with the understanding

that the capacity for oxygen exchange can increase exponentially as the lung aerates (van Vonderen et al, 2013).

FACILITATING THE CARDIOVASCULAR TRANSITION AT BIRTH

Exercise 16

Question

How does lung aeration affect the cardiovascular transition at birth?

Answer

Lung aeration initiates the cardiovascular transition at birth by increasing pulmonary blood flow (PBF) and increasing venous return to the left ventricle.

As indicated earlier, aerating the lung at birth is not just about transferring the site of respiratory gas exchange to the lung. Lung aeration also plays a vital role in initiating the cardiovascular transition at birth by stimulating a large decrease in PVR (Hooper et al, 2015c). This is responsible for increasing PBF (10–30 fold) and allowing the pulmonary circulation to accept 100% of right ventricular output while also allowing pulmonary arterial pressures to substantially decrease (Hooper et al, 2015c). The increase in PBF is not just important for enhancing pulmonary gas exchange but is also vital for taking over the role of providing preload for the left ventricle and thereby sustaining cardiac output (Fig. 1.4). The decrease in PVR along with the increase in afterload caused by removal of the placental circulation may also contribute to closure of the ductus arteriosus (DA) and separation of the two circulations (Hooper et al, 2015c).

Exercise 17

Question

Why is the increase in PBF so important after birth?

Answer

The increase in PBF allows the lungs to serve as the organ of gas exchange and helps to maintain cardiac output by

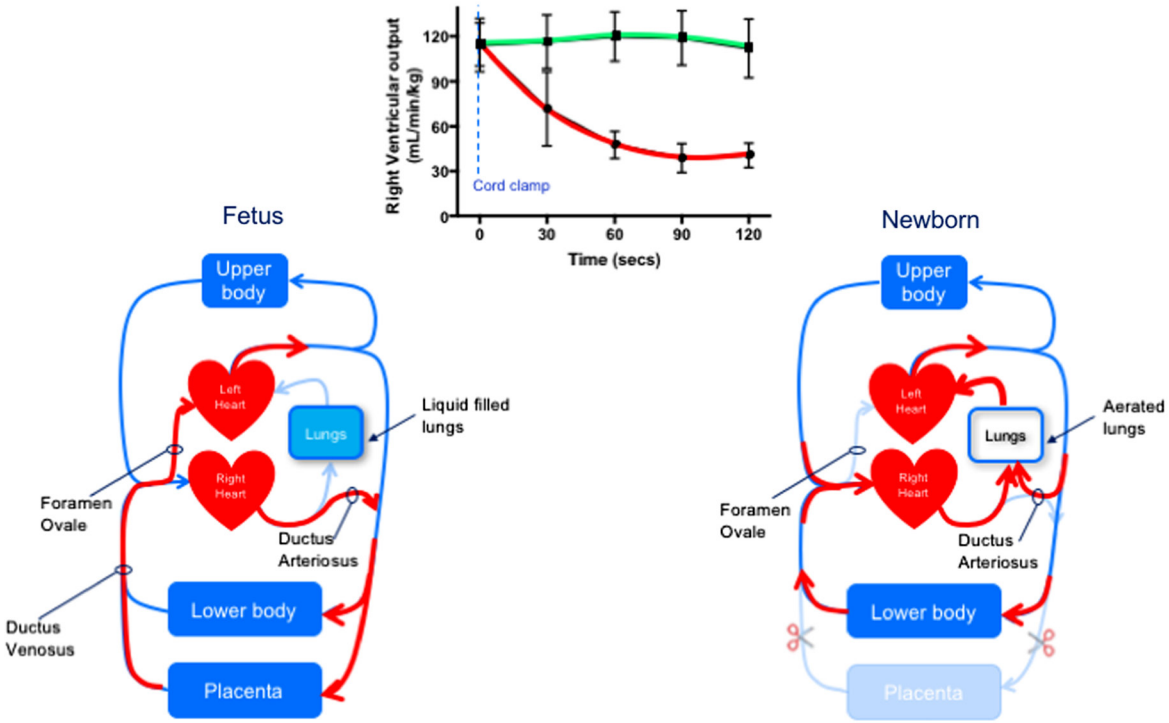

Fig. 1.4 Diagrammatic representation of the fetal and newborn circulation, also showing the changes in right ventricular output if the cord is clamped before *(red)* or after *(green)* ventilation onset. In the fetus, pulmonary vascular resistance (PVR) is high, and so the majority of right ventricular output flows through the ductus arteriosus (DA) with only a small amount flowing through the lungs. As a result, pulmonary blood flow (PBF) is low, and so much of the preload supplying the left ventricle is derived from the placenta, with umbilical venous return flowing via the ductus venosus and foramen ovale to directly enter the left side of the heart. After birth, when the umbilical cord is clamped, the supply of umbilical venous return to the left ventricle is lost, and so cardiac output decreases until the lungs aerate and PBF increases to restore preload for the left ventricle. However, if the lungs aerate and PBF increases before the umbilical cord is clamped, the supply of preload for the left ventricle can immediately switch from umbilical to pulmonary venous return following cord clamping. The reduction in PVR following lung aeration causes blood to flow from the systemic into the pulmonary circulation (left to right) through the DA, which greatly contributes to the increase in PBF. (Right ventricular output values are replotted data from Bhatt et al, 2013.)

taking over the role of providing venous return to the left ventricle.

Fetal Circulation: the Starting Point

To understand the extent of the cardiovascular changes at birth, it is important to first understand the starting point for the transition, which is the structure and function of the fetal circulation (Fig. 1.4). Before birth, the lungs are not involved in gas exchange, and the main role of PBF is to provide oxygen and nutrients for developing lung tissue. In contrast, after birth, PBF is vital for the efficient exchange of respiratory gases and supplies 100% of venous return to the left ventricle. In the fetus, instead of flowing through the lungs, much (up to 90%) of right ventricular output passes through the DA and directly enters the descending aorta (Fig. 1.4). Although it is often perceived that PVR in the fetus is fixed at a high level, this is not correct (Polglase et al, 2004). During development, PVR gradually decreases as the pulmonary vascular network grows and develops (Rudolph, 1979). This leads to a large increase in the cross-sectional area of the pulmonary vascular bed, particularly with the formation and growth of small vessels and alveolar capillaries. As such, the capacity of premature infants to dilate their pulmonary vascular bed and reduce PVR must be limited, because the vascular bed has yet to develop a large cross-sectional area. In the fetus, PBF can also vary markedly depending on fetal activity (Polglase et al, 2004). It can increase during periods of FBM, increasing 8- to 10-fold during periods of accentuated FBMs (Polglase et al, 2004). This is likely due to the reduction in thoracic pressure and an expansion-induced increase in alveolar capillary caliber (as occurs in adults), because the increase in PBF is closely associated with each individual breath (Polglase et al, 2004).

As PBF is low during fetal life, pulmonary venous return is unable to provide the left ventricle with sufficient venous return (preload) to sustain its output (Rudolph, 1979). Instead, the left ventricle obtains the majority of its preload from umbilical venous return, which flows via the ductus venosus (DV) and foramen ovale (Rudolph, 1979) (Fig. 1.4). As a result, the left ventricle receives oxygenated blood directly from the placenta (site of gas exchange), which accounts for the higher oxygenation levels in preductal arteries (arteries that branch off the aorta upstream of the DA/aorta junction) (Rudolph, 1979); this is analogous to the adult, as the left ventricle also receives the oxygenated blood, but in this case from the lungs.

Exercise 18

Question

What is the relationship between PBF and flow through the ductus arteriosus in fetal life?

Answer

Blood flow through the ductus arteriosus at birth can be right to left, bidirectional, or left to right depending on how quickly PVR diminishes. Ultimately most preterm infants exhibit left-to-right blood flow through the ductus arteriosus before it closes.

The relationship between PBF and flow through the DA is highly dynamic and simply determined by the pressure gradient between the pulmonary and systemic circulations (Hooper, 1998). In turn, these are controlled by downstream resistances in the two circulations. When PVR is high, the majority of right ventricular output flows across the DA into the systemic circulation, whereas PBF in the left and right pulmonary arteries is bidirectional (Figs. 1.4 and 1.5). During systole, PBF is forward (antegrade) in direction, entering the lungs, but during most of diastole, blood flows retrogradely, away from the lungs, leaving the pulmonary circulation and entering the systemic circulation through the DA (Crossley et al, 2009) (indicated by negative PBF in Fig. 1.5). Thus blood flows through the DA continuously, from the pulmonary and into the systemic circulation (right-to-left), throughout the cardiac cycle (Fig. 1.5); in contrast, flow in the main pulmonary trunk (upstream of the DA and left and right pulmonary arteries) is reduced to zero during diastole (Rudolph, 1979).

During FBM, PVR decreases and mean PBF increases, which is almost entirely due to a reduction in retrograde flow when diastole coincides with the reduction in intrathoracic pressure during each breath (Polglase et al, 2004). As a result, right-to-left shunting through the DA decreases and the contribution of right ventricular output to flow in the systemic circulation is reduced. This competitive relationship between flow in the pulmonary and systemic circulations persists after birth (see later), for as long as the DA remains open (Bhatt et al, 2013; Blank et al, 2017).

Transitioning the Circulation From a Fetal Into a Newborn Circulatory Pattern

At birth, lung aeration stimulates a 10- to 30-fold increase in PBF, and although the precise mechanisms are still unclear, numerous factors are involved that act in combination or in a hierarchical manner (Hooper et al, 2015c). As in adults, oxygen is a potent stimulus for pulmonary vasodilation in the fetus, which is thought to be mediated by NO release. Other factors include the release of vasodilators and an increase in lung recoil caused by the formation of surface tension (Gao and Raj, 2010). More recently, x-ray imaging has been used to examine the spatial relationship between ventilation and perfusion within the lung during lung aeration (Lang et al, 2014). Partial lung aeration caused a global increase in PBF (Fig. 1.6), increasing similarly in both aerated and unaerated lung regions, irrespective of whether the ventilation gas was air, 100% O_2, or 100% N_2 (Lang et al, 2015). Clearly, an increase in oxygenation is not responsible, although ventilation with 100% O_2 enhanced the PBF increase in aerated lung regions (Lang et al, 2015). Subsequent studies revealed that vagal denervation could block the global response to lung aeration, suggesting that a neural reflex was involved that may be triggered by J-receptors activated by the movement of liquid into lung interstitial tissue during lung aeration (Lang et al, 2017).

Irrespective of the mechanism, these studies demonstrate the potential for a ventilation–perfusion mismatch in the

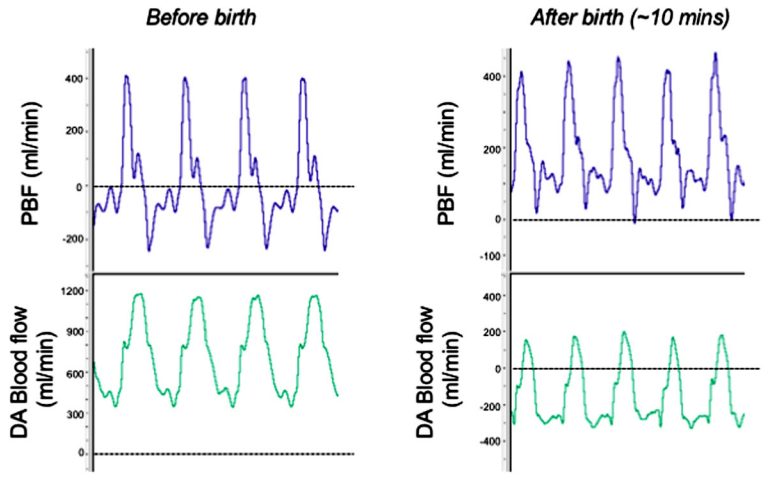

Fig. 1.5 Blood flow waveforms in the left pulmonary artery and in the ductus arteriosus (DA) before and immediately after birth. Before birth, pulmonary blood flow (PBF) flows toward the lungs (positive flow) only briefly during systole and then during late systole and throughout most of diastole, PBF is mostly retrograde (negative value), flowing away from the lungs and passing through the DA. This retrograde PBF accounts for the high levels of diastolic flow in the DA during fetal life. After birth, the decrease in pulmonary vascular resistance facilitates antegrade flow in the pulmonary arteries throughout the cardiac cycle, with relatively high flows occurring even during diastole. These diastolic flows are due to the left-to-right shunting (indicated by negative flows) through the DA, contributing to flow during this time. Although net blood flow across the DA is predominantly left to right, the flow waveform demonstrates distinct bidirectional characteristics due to the changing pressure gradient across the DA associated with the cardiac cycle.

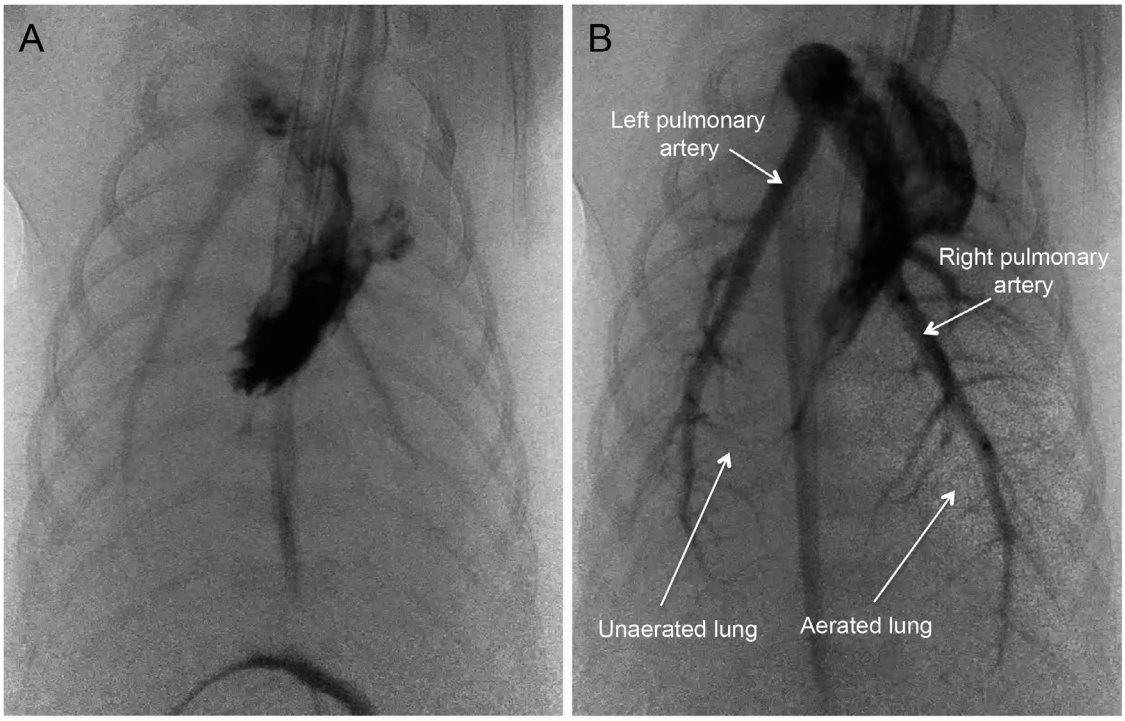

Fig. 1.6 Simultaneous phase contrast and angiographic x-ray images of a near term rabbit kitten before lung aeration (**A**) and following partial aeration of the right lung (**B**). Before lung aeration, blood flow in the left and right pulmonary arteries is low. In B, aerated lung regions can be seen as "speckle" in the image and are due to x-ray refraction at the air/water interface. Although only part of the right lung is aerated, blood flow is increased in both the left and right pulmonary arteries. Aerated and unaerated lung regions are indicated by arrows

lung at birth and raises the question as to whether this mismatch is problematic or advantageous. Indeed, it is possible this spatial "disconnect" (Fig. 1.6) may be advantageous, as the decrease in PVR and increase in PBF is more vital for the infant's survival than complete lung aeration. This is because the increase in PBF is vital for maintaining left ventricular preload and cardiac output after birth (Bhatt et al, 2013), whereas only partial lung aeration is needed to achieve sufficient gas exchange for survival.

Both right and left ventricles contribute to the increase in PBF (Fig. 1.4) after lung aeration (Crossley et al, 2009) because the decrease in PVR allows the lung to accept 100% of right ventricular output and at the same time causes pulmonary arterial pressures to decrease. This reverses the pressure gradient between the pulmonary and systemic circulations, causing blood flow through the DA to reverse (compared with the fetal state), mostly flowing left to right (Figs. 1.4 and 1.5) (Crossley et al, 2009). As such, PBF into the lung occurs continuously throughout the cardiac cycle, with left-to-right DA flow maintaining elevated PBF during diastole (Figs. 1.4 and 1.5) and contributing up to 50% of total PBF (Crossley et al, 2009). This redirection of blood flow, originating from both left and right ventricles through the lungs, "steals" blood flow from the lower body and placenta (Blank et al, 2017), if the cord is still intact (see later) (Fig. 1.4). During this time, while most of the DA blood flow is left to right, instantaneous flow is bidirectional; right to left initially during systole and then left to right during late systole and throughout diastole (Fig. 1.5). This is thought to be because the pressure wave emanating from the right ventricle reaches the pulmonary artery/DA junction before the pressure wave coming from the left ventricle reaches the DA/aorta junction (Hooper et al, 2015c). As a result, flow is initially right to left and then rapidly changes to left to right as the pressure gradients change. It is currently unclear whether the resulting turbulence contributes to DA closure.

Exercise 19

Question

What are the physiologic advantages of delayed cord clamping?

Answer

Infants who are delivered after delayed cord clamping exhibit greater hemodynamic stability and have greater blood volumes and decreased need for RBC transfusion. In preterm infants, there are lower incidences of intraventricular hemorrhage and necrotizing enterocolitis.

Delayed Umbilical Cord Clamping (DCC) and Placental Transfusion

Delayed umbilical cord clamping (DCC) after birth is not a new concept, as it dates back to Aristotle and has been revisited by many commentators over the centuries, including Erasmus Darwin (Charles Darwin's grandfather) in 1801 (Darwin, 1801). However, immediate cord clamping became standard practice following implementation of the active (vs. expectant) management of the third stage of labor, which is aimed at reducing the risk of postpartum hemorrhage (PPH) (Begley et al, 2011). The three components of this approach were early administration of a potent uterotonic (e.g. oxytocin), immediate cord clamping, and gentle traction on the cord to reduce the length of third stage.

Although this active management strategy significantly reduces the risk of PPH, it also significantly reduces birth weights because of a lower blood volume (Begley et al, 2011). This indicates that although it has very clear benefits for the mother, it may have adverse implications for the infant that were not broadly considered upon implementation. As oxytocin administration at the end of third stage of labor is equally as effective at reducing the risk of PPH (Soltani et al, 2010), the need for immediate cord clamping to reduce the risk of PPH has become obsolete. This raises the question about the need for immediate versus delayed cord clamping, as the timing within third stage does not have an impact on the mother's risk of PPH.

For many years the debate around the timing of cord clamping has focused on the concept of "placental transfusion," whereby DCC advocates claim that after birth a volume of blood moves from the placenta into the infant, giving the infant a "blood transfusion" (McDonald et al, 2013); this explains the higher birth weights in infants delivered with "expectant" versus "active" management of third stage of labor (Begley et al, 2011). The concept of placental transfusion is largely based on studies that used radiolabelled (^{125}I) albumin to measure blood volumes in infants who received cord clamping at different times after birth (Yao et al, 1969). Numerous studies have reported increased birth weight changes, hematocrits, hemoglobin levels, and iron stores and reduced need for transfusions in infants receiving delayed cord clamping (McDonald et al, 2013).

Exercise 20

Question

What is physiologic based cord clamping (PBCC)?

Answer

With physiologic based cord clamping or baby-directed umbilical cord clamping, the timing of cord clamping is based on the infant's physiology rather than on a set period after birth. It supports preload (and cardiac output) at a time when umbilical venous return is ending. Clinically it means delaying clamping of the umbilical cord until lung aeration has been established.

The Physiology of Umbilical Cord Clamping at Birth

As highlighted earlier, cord clamping at birth removes umbilical venous return as a source of preload for the left ventricle, making it dependent on PBF and any residual flow through the foramen ovale for preload (Hooper et al, 2015c) (Fig. 1.4). In addition, arterial pressure (afterload) is greatly increased by cord clamping due to the loss of the low-resistance placental circulation (Bhatt et al, 2013), which

during fetal life receives a large proportion (30%–50% depending on GA) of cardiac output (Rudolph, 1985). As a result, the combined loss of preload and the increase in afterload cause a large reduction in cardiac output, which remains reduced until the lungs aerate, PBF increases and the supply of preload is restored (Bhatt et al, 2013) (Fig. 1.4). On the other hand, if the lung aerates and PBF increases before the umbilical cord is clamped, then the elevated PBF can immediately take over the role of providing preload for the left ventricle when umbilical venous return is lost (Bhatt et al, 2013) (Fig. 1.4). As a result, cardiac output is sustained throughout the transition. This has been termed physiologic based cord clamping (PBCC) (Kluckow and Hooper, 2015) or baby-directed umbilical cord clamping (Blank et al, 2018), whereby the timing of cord clamping is based on the infant's physiology rather than on a set period after birth. In addition, if PVR is reduced before the umbilical cord is clamped, the increase in arterial pressure (afterload) caused by cord clamping is reduced because the pulmonary circulation is able to serve as an alternate low resistance pathway for blood to flow (Bhatt et al, 2013). In view of these findings, many now believe that ideally the timing of umbilical cord clamping should be delayed until after the lungs have aerated and PBF has increased (Knol et al, 2018). Two recent feasibility studies have provided the first evidence indicating the potential benefits of resuscitating infants on the cord (Blank et al, 2018; Brouwer et al, 2018).

Physiologic Based Umbilical Cord Clamping

Whatever the explanation for "placental transfusion," it is unfortunate that this concept has been the only focus of debate over DCC. Indeed, such a unidimensional focus ignores the known benefits of DCC that have a logical scientific explanation (e.g., maintenance of cardiac output during transition), leading to (1) a series of poorly designed clinical studies, (2) an unproductive circular debate between the risk of hypovolemia/anemia and hyperbilirubinemia (Weeks and Bewley, 2018) and (3) the belief that time is the major benefactor of delayed cord clamping, irrespective of the infant's physiologic state and whether it needs resuscitation. It also limits thinking on the way in which this very simple procedure, which has no cost, can be most effectively applied and in which infants it will have most benefit. For instance, a Tanzanian study has shown that for every 10 sec delay (up to 2 min) between breathing onset and umbilical cord clamping, there is a 20% reduction in mortality and/or admission into intensive care (Ersdal et al, 2014).

Recognition that immediate cord clamping may have an adverse impact on cardiovascular function in the immediate newborn period first arose with the formation of the Dawson nomograms (Dawson et al, 2010a, 2010b). The aim of developing these nomograms was to describe the normal heart rate and oxygenation ranges for healthy term (and preterm) newborn infants to provide target ranges immediately after birth for infants requiring resuscitation. They showed that 50% of normal healthy term infants had a heart rate under 100 bpm at 1 min after birth (Dawson et al, 2010b). This was surprising, as the infants were thought to be well oxygenated and healthy, and so a chemoreceptor mediated vagal bradycardia was considered unlikely. Instead, it was suggested that a reduction in venous return was responsible (Dawson et al, 2010b), which prompted the study demonstrating that cord clamping before ventilation onset causes a marked reduction in cardiac output (Bhatt et al, 2013). More recently, two studies have examined the feasibility of resuscitating infants while still "on the cord," and both have found a much higher heart rate than would be expected from the Dawson nomograms (Blank et al, 2018; Brouwer et al, 2018). This suggests that (1) immediate cord clamping has a much wider adverse impact (lower than desired heart rate and cardiac output) than expected and (2) new nomograms will be required for infants receiving physiologic based cord clamping.

Although current guidelines recommend that DCC should be applied to healthy term infants not requiring resuscitation (Perlman et al, 2015), these infants are likely to benefit least. Based on the available scientific evidence, infants who are likely to receive the greatest benefit of PBCC are those who have the longest delay between delivery and the onset of pulmonary ventilation (Hooper et al, 2015b). As the increase in PBF will also be delayed and/or reduced in magnitude, the switch from umbilical to pulmonary venous return for providing left ventricular preload will also be reduced or delayed. These include very preterm infants and infants with lung hypoplasia who have difficulty in aerating their lungs and have a poorly developed pulmonary vascular bed at birth. Other infants likely to benefit include apneic infants with poor tone at birth as a result of intrauterine hypoxia (see later).

Currently there is still no robust scientific explanation for the net movement of blood from the placenta into the infant during DCC after birth. Nevertheless, it is important to understand the mechanisms involved, because if the causes are unknown, it is difficult to identify the factors that impede or prevent it. Suggested mechanisms include uterine contractions, gravity, an increase in pulmonary blood volume with the increase in PBF, and a decrease in intrathoracic pressure caused by inspiration, but none of these explanations have been substantiated scientifically (Hooper and Kluckow, 2018).

The absence of an explanation for placental transfusion is not proof that it does not occur, but it may be that our understanding of the underlying circumstances is inaccurate. Indeed, the debate concerning placental transfusion has entirely focused on blood volume accumulation within the newborn after birth without any thought as to what happens to fetal blood volume before birth, during labor. This is a major oversight, as the common assumption is that fetal blood volume remains constant before birth and then suddenly increases after birth due to placental transfusion. Alternatively, it is possible that the fetus loses blood volume into the placenta during labor, perhaps due to increased dorso–ventral flexion imposed by uterine contractions (Harding et al, 1990). As such, an apparent "placental transfusion" after birth may result from restoration of this blood

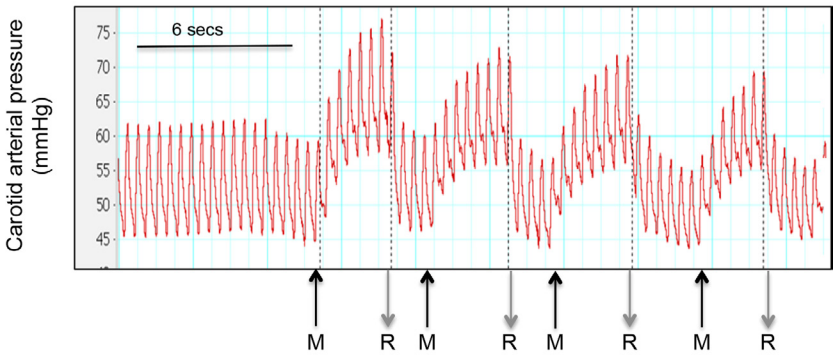

Fig. 1.7 Changes in carotid arterial pressure in response to four consecutive umbilical cord "milkings." Each cord milk is indicated "M," whereas the cord release that occurred at the end of each milk is indicated by "R." Note the large increases in arterial pressure that occurred with each milk.

volume back into the infant as the two circulations come back into balance. This would explain why placental transfusion is less evident following cesarean section deliveries and provides a much more compelling argument for DCC. That is, rather than the infant acquiring blood volume and red blood cells that it never had during fetal life, which increases the risk of hyperbilirubinemia, maybe it is simply reclaiming the blood volume and red blood cells it temporarily lost during delivery.

Exercise 21

Question

Does umbilical cord milking (UCM) provide the same benefits as DCC?

Answer

Depending on the circumstances, umbilical cord milking and delayed cord clamping can both transfer a volume of blood to the newborn infant. The potential for transfer is more rapid with UCM, but it also causes large changes in arterial pressure and flow that are potentially injurious. This may explain the increased likelihood of intraventricular hemorrhage in infants under 28 weeks' gestation. As studies now show that resuscitation can occur while infants are still attached to the cord, it is debatable whether the urgent need for resuscitation is a compelling argument for replacing DCC with UCM.

UCM involves squeezing the cord between thumb and finger and then sliding them along the cord, forcing blood to move from the cord into the infant. Depending on the protocol, this can be done before or after cord clamping and either once or multiple times. UCM has been proposed as an alternative to DCC, providing the infant with a blood transfusion in a shorter period (Katheria et al, 2018). This is thought to be desirable, allowing the infant to gain a blood transfusion while still allowing rapid transfer to a resuscitation table if the infant requires some form of intervention (Katheria et al, 2014, 2017). Although clinical evidence suggests that UCM provides benefits over immediate cord clamping, a recent scientific study has raised several concerns (Blank et al, 2017). When the cord remains unclamped and is milked several times, whether a net volume of blood is transferred into the newborn depends on the milking protocol (Blank et al, 2017). As milking the cord necessarily causes cord occlusion, each milk of the cord produces arterial pressure and cerebral blood flow changes that are identical to immediate cord clamping (Fig. 1.7), effectively replicating the adverse effects multiple times (Blank et al, 2017). Other concerns that are yet to be answered relate to forcing blood under pressure into the low-pressure venous circulation and the release of cellular debris and cytokines into the newborn circulation if milking occurs more than once.

The underlying assumption of UCM is that the primary benefit of DCC is placental transfusion (Katheria et al, 2017), which is clearly wrong. Like immediate cord clamping, if the milking occurs before the lungs have aerated, venous return and cardiac output must be reduced as the volume entering the newborn with each milk is only a small fraction of umbilical venous flow. The argument for UCM versus DCC centers around time and the need to initiate resuscitation as soon as possible (Katheria et al, 2017). However, the perception that UCM is a time-condensed equivalent of DCC reduces the focus on the more important issue of developing perinatal (as opposed to neonatal) resuscitation teams that can overcome the logistics of resuscitating infants on the cord, which is likely to be the most efficacious approach.

EXERCISE 22

Question

How does DCC influence the infant's body temperature during resuscitation with an intact cord?

Answer

Although still anecdotal, scientific studies suggest that the requirement for external heat input to maintain newborn body temperature with the cord intact is less than that required following cord clamping.

The management of body temperature in newborn infants in the delivery room is important, particularly in preterm infants. Depending on whether the infant is full term or preterm, this is usually achieved by drying the infant, replacing wet towels with dry ones, use of a radiant heat warmer, and placing a hat on the infant's head to reduce heat loss (Weiner et al, 2018). In addition, preterm infants are commonly placed within a plastic wrap to further reduce heat loss and maintain body temperature. Although it is unclear whether body temperature is more or less of a problem during DCC, logistically, it is likely that all of the procedures that have been adopted can also be applied in infants during delayed cord clamping. Indeed, "resuscitation tables" that have or are being developed for this purpose include heated mats and/or an overhead radiant warmer to maintain the infant's temperature (Brouwer et al, 2018). Similarly, studies not employing the use of a table are simply resuscitating the infant on a heat pad on the mother's legs (Blank et al, 2018).

However, it is possible that the infant's body temperature control will be more stable and less prone to rapid reductions if it is resuscitated with an intact cord, because the placenta is still within the mother and should heat the infant's blood as it perfuses the placenta. Although still anecdotal, scientific studies suggest that the requirement for external heat input to maintain newborn body temperature with the cord intact is less than that required following cord clamping. On the other hand, considering the contribution of warmed placental blood to maintaining the infant's body temperature, applying the same heat loss/heat input procedures as are applied in infants with a cord that has been ligated may increase the risk of hyperthermia in infants resuscitated with an intact cord (i.e., with delayed cord clamping).

MANAGING THE ASPHYXIATED INFANT

From a medicolegal perspective, "birth asphyxia" usually refers to the severest form of asphyxia, but the physiologic reality is that perinatal asphyxia is a continuum, ranging from the prolonged and very severe to transient and milder forms. Irrespective of the severity, the initial physiologic response to perinatal asphyxia is identical and well described (Dawes, 1968). Initially, it involves a chemoreceptor mediated, vagal-induced, bradycardia, apnea, a mild hypertension, and an inhibition of body movements, along with a marked redistribution of cardiac output to increase blood flow and maintain oxygen supply to the heart and brain (Reuss and Rudolph, 1980). As the asphyxia is prolonged, the response diverges depending on the severity of the reduction in oxygenation. With less severe reductions, the increase in blood flow to the heart and brain maintains oxygen delivery to these vital organs to sustain their function, with the increase in blood flow being very closely matched with the decrease in blood oxygen content (organ O_2 delivery = blood O_2 content × organ blood flow) (Reuss and Rudolph, 1980). This adaptive response is so effective that the fetus can survive for days, weeks, and even months, with the later resulting in the "brain sparing" associated asymmetric fetal growth restriction. In addition, an inhibition of fetal breathing and body movements contribute to the maintenance of oxygen delivery to the heart and brain through a reduction in total body oxygen consumption (Rurak and Gruber, 1983).

CASE 2

A term infant is born to a woman with an acute placental abruption via a spontaneous vaginal delivery. Following delivery, the obstetrician palpates the umbilical cord and detects a heart rate of 20 beats/min.

Exercise 23

Question

What are the physiologic advantages of resuscitating an infant with severe asphyxia with an intact cord?

Answer

When cord clamping occurs immediately after birth in an asphyxiated infant, it reduces cardiac output (as the low resistance placental circuit is removed) and interferes with the neonate's ability to adapt to asphyxia and protect the brain and myocardium. However, ventilating the lungs of a depressed infant before the cord is clamped is technically complex, requires special equipment, and is still unproven.

In most developed countries with good obstetric management, the most common form of perinatal asphyxia is the less severe, mildly asphyxiated infant who is apneic and bradycardic, with little or no tone at birth and low initial Apgar scores. These infants are unable to initiate breathing at birth (due to a hypoxic inhibition of breathing), and current guidelines recommend immediate umbilical cord clamping and transfer to a stable platform for resuscitation (Perlman et al, 2015). However, it is questionable (and controversial) as to whether this is the correct approach. As indicated earlier, the physiologic response to protect the brain from hypoxia is to increase cerebral blood flow through a redistribution of cardiac output (Reuss and Rudolph, 1980). In the absence of an increase in PBF, cord clamping reduces cardiac output (Bhatt et al, 2013), which undermines the newborn infant's capacity to adapt to the asphyxia and maintain oxygen delivery to the heart and brain, increasing the risk of hypoxic/ischemic brain injury. In essence, it deprives the infant from using the primary defense mechanism that it has against hypoxia, which is a redistribution of cardiac output.

On the other hand, ventilating the lungs before the cord is clamped is complex but has theoretical advantages. It avoids the delay in resuscitation onset caused by the time required for cord clamping and transferring the infant to a resuscitation table and avoids the loss in cardiac output caused by cord clamping before PBF has increased. It also allows for a recovery in the infant's oxygenation with a relatively stable cardiac output that is physiologically determined rather than being artificially limited by cord clamping.

The latter may be important during the recovery phase, limiting the rebound hypertension and cerebral hyperperfusion that classically follows an asphyxiating event (see later). Whatever the benefit, all the physiologic evidence to date indicates that the neonatologist's mantra "ventilation is the key to neonatal resuscitation" is highly accurate, and the most recent evidence suggests that it should also take precedence over separating the infant from its mother by clamping the cord.

If the asphyxia is severe, the increase in blood flow to the heart and brain is insufficient to sustain oxygen delivery to these organs, which results in a gradual reduction in myocardial contractility and cardiac output that in turn causes a reduction in blood pressure (Klingenberg et al, 2012). Eventually, blood pressure falls to a point where blood flow ceases, although electrical activity in the heart can continue for some time (Sobotka et al, 2015). Scientifically, it is unclear precisely at which point ventilation of the lung by itself is insufficient to restore cardiac function, resulting in the need for chest compressions and adrenaline. In newborn lambs, aerating and ventilating the lungs before mean arterial pressures fall below ~20 mm Hg can rapidly restore cardiac function (Klingenberg et al, 2012; Polglase et al, 2017), but when blood pressures decrease below 20 mm Hg, adrenaline, chest compressions, and ventilation are all required to restore cardiac function (Sobotka et al, 2015). As cardiac output is already low, clamping the umbilical cord has little impact on cardiac output, which raises the question of whether resuscitation with an intact cord has any benefits. Indeed, it could be argued that having a low-resistance placental circulation still in circuit may impede the return of spontaneous circulation during chest compressions by limiting the increase in diastolic pressure. However, recent scientific studies suggest that resuscitating with an intact cord has no impact on the return of spontaneous circulation and has the additional benefit of limiting the rebound hypertension and cerebral hyperperfusion that follows a successful resuscitation (Polglase et al, 2017). This is because the low resistance placental circulation acts as a pressure-release valve that limits the increase in pressure. This is potentially very important because the rebound postasphyxial overshoot in blood pressure exposes the maximally vasodilated cerebral circulation to high pressures, causing cerebral microvascular hemorrhage (Polglase et al, 2017).

However, there is an important scientific caveat to the prospect of resuscitating severely asphyxiated infants while the cord is intact. That is knowing when it is safe to clamp. This is because the rebound hypertension results from a major increase in sympathetic drive to the cardiovascular system, among other systems, which forms the basis of the fight or flight response. This response has a finite duration (up to 10 minutes) and the optimal benefit is achieved if cord clamping occurs after the rebound phase is complete. However, if the cord is clamped at the peak of the response, the potential to cause harm is increased rather than reduced (Polglase et al, 2017). This is because clamping the cord suddenly increases systemic vascular resistance in the middle of a hypertensive episode, thereby increasing the pressure and further protracting the hypertensive state (Polglase et al, 2017). Under this scenario, it may be prudent to delay clamping the cord until after the increased sympathetic response has abated, which maybe indicated by a reduction in heart rate. This caveat underpins the importance of fully understanding the science.

SUMMARY

At birth the infant rapidly undergoes major and very complex changes to its respiratory and cardiovascular systems, making the ideal approach for providing assistance equally as complex. This raises several questions, such as why is the level of sophistication applied to assisting infants in the delivery room markedly less than the level of sophistication commonly applied in the NICU? Although "logistical issues" is the most common response, as our understanding of the physiology improves, this response is being overwhelmed by the realization of the complexity involved and the potential for the resuscitation to cause harm, particularly in preterm infants. Perhaps we should change both our terminology and our thinking on neonatal resuscitation and move toward developing all-inclusive perinatal resuscitation teams that focus on assisting infants as they progress from a fetus to newborn rather than having to resuscitate them after they have become a neonate. Similarly, it is highly unlikely that a standardized resuscitation approach will be suitable for all infants. Infants are delivered in a variety of different states and at any one moment in time, the infant's physiology will be progressing (or not) along the complex continuum between the fetal and newborn states. As such they will likely require different types and levels of assistance and we need to establish better methods of assessing and assisting infants as they pass though these different stages. For instance, initially assistance should focus on airway liquid clearance, because gas exchange cannot commence until the gas exchange regions aerate, and aeration is also required to stimulate PBF and maintain cardiac output. However, strategies should be rapidly adaptable to suit the large changes in lung mechanics as the medium filling the airways changes from liquid to air. Furthermore, immediately following lung aeration, it is important to be cognizant of the consequences of liquid accumulating in lung tissue, particularly in how this affects lung mechanics and increases the risk of airway liquid reentry.

Although the shift to noninvasive respiratory support reduces the risk of lung injury, it does not equate with ventilation administered via an endotracheal tube. In particular, the efficiency of noninvasive respiratory support is largely dependent on the presence of spontaneous breathing. This is required to ensure that the larynx is open and that if iPPV is necessary, the airway is not obstructed, allowing gas to enter the lower airways. As such, factors that stimulate breathing

(oxygen and caffeine) should be considered and factors that inhibit breathing (hypoxia) should be avoided. Furthermore, as the nasopharynx regions adds a significant dead-space volume and is expandable, it is likely that tidal volumes required to adequately ventilate the gas exchange regions during noninvasive ventilation will be larger than in an intubated infant.

For decades it has been taught that the key to neonatal resuscitation is ventilation of the lung. Clearly, this has been a vital message, and even after 50 or more years, this message remains as the central most important component of neonatal resuscitation strategies. Nevertheless, maybe the message should be slightly modified to "aeration and ventilation of the lung" to also reflect the important role of lung aeration in stimulating the increase in PBF and maintaining cardiac output during transition. This sends a subtle message that neonatal resuscitation is not just about establishing pulmonary gas exchange, as it also triggers the cardiovascular changes at birth. Indeed, as indicated earlier, perhaps this message should be reinvigorated, suggesting that aeration and ventilation of the lung should take precedence even over clamping of the umbilical cord and separating the infant from its mother.

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Abstract: The physiologic changes required for an infant to transition from fetal to newborn life largely involve the respiratory and cardiovascular systems and are extensive and very complex. The airways must be cleared of liquid so that the lungs can take over the role of gas exchange, and vascular shunts must close to separate the pulmonary and systemic circulations, allowing both circulations to function at very different pressures. As these physiologic changes are triggered by lung aeration, airway liquid clearance is not only important for establishing pulmonary gas exchange but is also vital for triggering the circulatory changes at birth. This is achieved by stimulating a large increase in pulmonary blood flow, which facilitates pulmonary gas exchange and takes over the role of supplying preload for the left ventricle lost following umbilical cord clamping. As infants are born under different conditions and at different stages along the continuum between a fetus and newborn, a singular approach to neonatal resuscitation is unlikely to be applicable to all infants. Instead, the approach should be adapted to suit the rapidly changing needs of the infant as it transitions to newborn life. However, this requires a good understanding of the physiology involved and the ability to monitor and assess the infant's changing physiology so that the right assistance can be applied at the right time. Nevertheless, "establishing pulmonary ventilation" remains the key objective of neonatal resuscitation and will also likely take precedence over clamping the umbilical cord.

Key words: Birth, respiratory function, airway liquid clearance, preterm birth, transient tachypnea of the newborn

2

Perinatal Hypoxia-Ischemia

Abbot R. Laptook

Perinatal asphyxia is a challenging condition because it represents a modifiable etiology for neonatal encephalopathy with the use of hypothermia. This contrasts with other etiologies of neonatal encephalopathy that are not amenable to treatment, such as cerebral malformations, strokes, congenital acquired infections, teratogenic exposures, and cerebral hemorrhages. To be effective, hypothermia needs to be initiated early in life, typically within 6 hours following birth based on results from multiple clinical trials (Azzopardi et al, 2009; Gluckman et al, 2005; Jacobs et al, 2011; Shankaran et al, 2005; Simbruner et al, 2010). The implication for clinicians is that they need to be well versed with perinatal asphyxia and understand facets of presentation, stabilization, diagnosis, medical management, and hypothermia treatment. The cases presented in this chapter were chosen to address some of these issues. It is important to recognize that for many management issues, data is available to guide what not to do and not necessarily justify the optimal strategy.

Perinatal asphyxia is a complex entity because it is difficult to readily translate the physiologic concept of asphyxia into an easy clinical definition. Asphyxia represents an impairment of gas exchange and is characterized by hypoxia and hypercapnia. Central to the pathogenesis of asphyxia-induced brain injury is ischemia, reductions in cerebral blood flow. Hence the use of the term perinatal hypoxia–ischemia as an alternative to asphyxia. Impaired gas exchange will result in ischemia depending on the duration and extent of hypoxia and/or hypercapnia. The clinical manifestation of brain involvement secondary to asphyxia is encephalopathy with or without seizures. Correlations between physiologic derangements (hypoxia, hypercapnia, and ischemia) and the presence and severity of encephalopathy are most readily recognized at the extremes of aberrant gas exchange. The concordance between more moderate abnormal gas exchange and encephalopathy is not as clear and reflects limited tools to assess fetal condition (fetal heart rate tracing, sonography, Doppler ultrasound, scalp pH, umbilical cord blood gases) and measure cerebral blood flow in utero and/or following birth. In view of the importance of hypoxia and ischemia in the pathogenesis of tissue injury, the term hypoxic–ischemic encephalopathy (HIE) is often used interchangeably with perinatal asphyxia.

STABILIZATION FOLLOWING POSSIBLE PERINATAL ASPHYXIA

CASE 1

Case Summary: A female was born at $37^{4}/_{7}$ weeks to a 39-year-old gravida 6, now para 3 mother and had a birth weight of 3720 g. The mother presented to the hospital with decreased fetal movement, and fetal heart rate monitoring revealed a nonreassuring heart rate tracing (category III, minimal variability and presence of decelerations). Prenatal laboratory assessments were unremarkable except for colonization with group B *Streptococcus* (GBS). The mother was not in labor, membranes were intact, and the presentation was vertex. An emergent cesarean section was performed, and rupture of membranes revealed meconium-stained fluid. The infant was nonvigorous, underwent drying and warming, but remained limp and cyanotic and without respiratory effort. Resuscitative measures included positive pressure ventilation, 100% oxygen for poor color and low oxygen saturation (SpO_2), which always remained 40% to 45% with 100% oxygen. The infant remained hypotonic; had Apgar scores of 1, 4, 5, and 6 at 1, 5, 10, and 15 minutes respectively; and was transferred to the NICU at 22 minutes after birth. The umbilical vein and artery pH and blood gases, respectively, were pH 7.06 and 6.89, Po_2 under 20 mm Hg and under 20 mm Hg, Pco_2 68.2 mm Hg and 110.0 mm Hg, and a base excess −11.9 and −14.3 mmol/L. Admission vital signs included a heart rate of 152 bpm, respiratory rate of 40 breaths/minute, blood pressure of 51/24, mean of 33 mm Hg, and an axilla temperature of 37.0°C. On examination, the infant had minimal spontaneous movement; breathing was synchronous with ventilator breaths, slightly weak pulses, and a prolonged capillary refill time and a harsh murmur along the left sternal border. The admission blood glucose concentration was 151 mg/dL and hematocrit was 47%.

Exercise 1

Questions

1. The initial arterial blood gas in the NICU at 90 minutes was a pH 7.07, Pco_2 65 mm Hg, Po_2 23 mm Hg and a base

excess −11.7 mmol/L. What should be the target range of Pco_2 for an infant with the above history?
A. 20 to 30 mm Hg
B. 31 to 40 mm Hg
C. 41 to 50 mm Hg
D. Over 50 mm Hg

2. Which oxygen saturation range would be most appropriate for stabilizing and caring for the infant?
A. 85% to 89%
B. 96% to 100%
C. 80% to 84%
D. 92% to 98%

3. What core body temperature should be used to care for this infant upon NICU admission and initial stabilization?
A. 36°C
B. 37°C
C. 33.5°C
D. 36.5° to 37.5°C

4. What range of blood glucose concentrations would be acceptable and optimal for this infant during stabilization after admission to the NICU?
A. >150 mg/dL
B. 50 to 80 mg/dL
C. 30 to 45 mg/dL
D. 100 to 150 mg/dL

5. Due to the clinical assessment of hypoperfusion and low blood pressure on admission, volume expansion was ordered. A peripheral intravenous line was started. Which fluid would be most appropriate in this setting?
A. Packed red blood cells, type O negative, unmatched, emergency release
B. 10% dextrose
C. Normal saline
D. Albumin 5%

6. Following volume expansion, clinical perfusion and blood pressure improved. An initial chest x-ray revealed a right-sided pneumothorax resulting in a shift of the mediastinum. Clinical assessment of chest wall movement appeared adequate using pressure support ventilation with a peak inspiratory pressure of 30 cm mm Hg and a PEEP of 8 cm mm Hg. A follow-up arterial blood gas at 150 minutes indicated a pH of 7.39, Pco_2 of 35.2 mm Hg, Po_2 of 30 mm Hg, and base deficit of −4.4 mmol/L; however, the SpO_2 values remained fixed at 50%. Pre- and postductal SpO_2 values did not differ. Based on the cord blood gas values, the infant qualified for a neurologic assessment for the use of hypothermia. In what order should the following be done?
A. Adjust the ventilator settings as needed, and perform a needle aspiration of the pneumothorax. If there is no improvement in SpO_2 value, obtain an echocardiogram and follow by a neurologic assessment.
B. Initiate hypothermia therapy first and then deal with pulmonary and possibly cardiac involvement.
C. Perform a neurologic examination before analgesic medications, give analgesia, and place a chest tube in the right pleural space. Obtain an echocardiogram to exclude congenital heart disease and then consider initiating hypothermia therapy.
D. Obtain an echocardiogram, give analgesia, and evacuate the right pneumothorax. Evaluate for hypothermia therapy.

7. Should this infant be provided seizure medication prophylaxis, and if yes, with what medication?
A. Yes, phenobarbital
B. No
C. Yes, levetiracetam
D. Yes, lorazepam

Answers

1. The correct answer is C. Arterial carbon dioxide tension ($Paco_2$) is extremely important in the stabilization of an infant after impaired gas exchange before birth. The cerebral vasculature is very sensitive to changes in $Paco_2$: Increases in $Paco_2$ result in cerebral vasodilatation and an increase in cerebral blood flow (CBF) provided that perfusion pressure is not impaired. Conversely, reductions in $Paco_2$ reduce CBF (Rosenberg et al, 1982). The risk of an infant having hypo- or hypercapnia after asphyxia is high given impairments of respiratory drive, concomitant respiratory morbidities (e.g., meconium aspiration) and compensation for associated metabolic acidemia. The latter variables can impede the clinician's ability to regulate the $Paco_2$ in a desired range. Data from the Neonatal Research Network Induced Hypothermia trial examined the association between hypocapnia in the first 12 hours after birth and 18 to 22 month outcome among neonates with moderate or severe HIE (Pappas et al, 2011). The results indicate that both the minimum $Paco_2$ and a calculated cumulative exposure of time with a $Paco_2$ under 35 mm Hg are associated with death or disability at 18 to 22 months. The results are depicted graphically in Fig. 2.1. A similar analysis from the CoolCap trial confirmed the association between hypocapnia and an unfavorable outcome. Answers A and B are therefore not correct, and there may be unintended consequences of $Paco_2$ above 50 mm Hg on the cerebral vasculature after hypoxia–ischemia.
2. The correct answer is D. The relationship between arterial oxygen tension and saturation (SpO_2) and outcome after asphyxia is less clear compared with the effects of hypocapnia. A goal SpO_2 needs to reflect the balance of avoiding excessively low SpO_2 and potentially restricting tissue oxygen delivery with avoiding excessively high SpO_2 and exacerbating oxidative injury (Thornton et al, 2017). Answers A through C do not reflect this balance. One retrospective cohort study analyzed data from the prehypothermia era and demonstrated that severe hyperoxemia (PaO_2 >200 mm Hg) significantly increased the odds of death, cerebral palsy, or neurosensory deficits at 2 years of age (Klinger et al, 2005).
3. The correct answer is D. A core temperature of 36.5° to 37.5°C is recommended by the *Textbook of Neonatal*

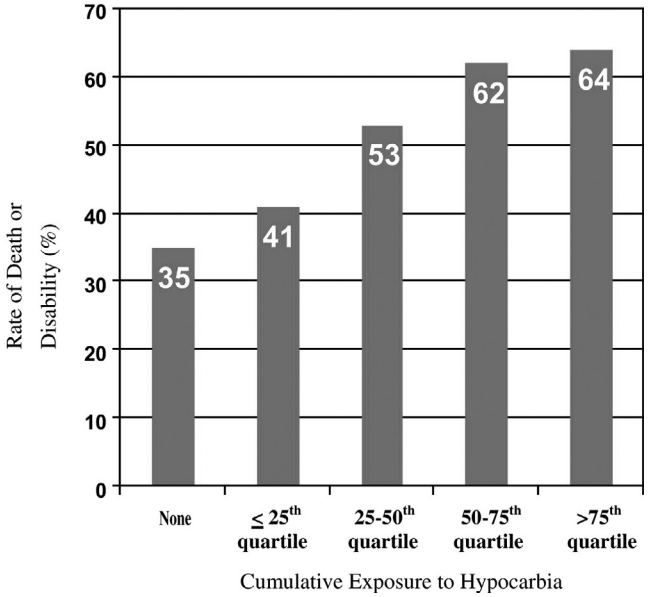


Fig. 2.1 There is an increasing rate of death or disability with greater cumulative hypocarbia. Cumulative exposure to hypocarbia was calculated from the difference between 35 mm Hg and the sampled P_{CO_2} multiplied by the duration of time spent below 35 mm Hg. (From Pappas A, Shankaran S, Laptook AR, et al: Hypocarbia and adverse outcome in neonatal hypoxic-ischemic encephalopathy, *J Pediatr* 158:752–8 e1, 2011.)

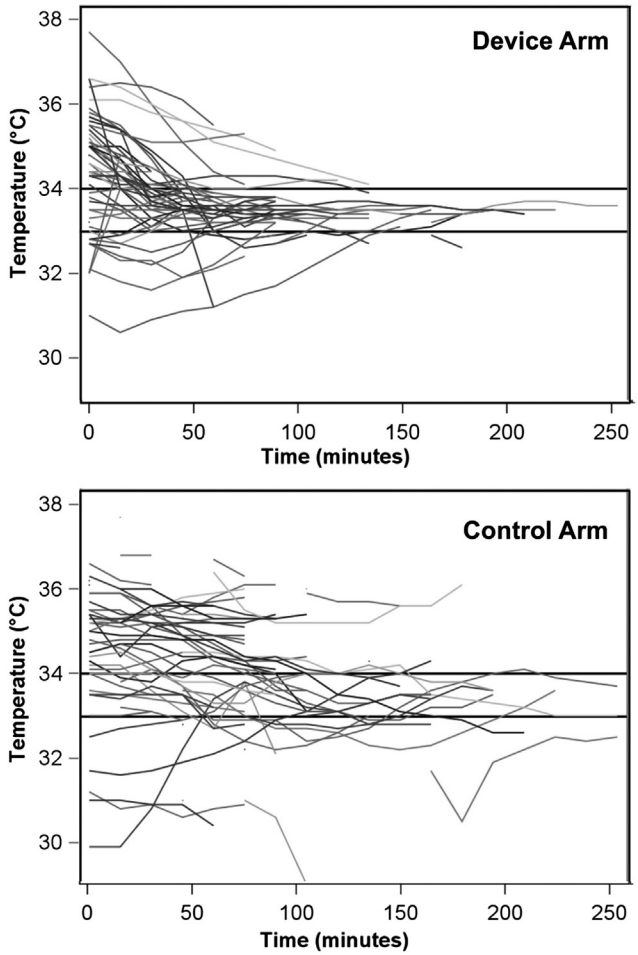


Fig. 2.2 The profile of core temperatures among infants undergoing initiation of hypothermia therapy on transport for infants actively cooled with a device (top panel) and those undergoing passive cooling (control, bottom panel). The target temperature range was 33 to 34°C (horizontal lines) and each patient is represented by a separate line from the initiation of the transport (time 0) to arrival at the center providing hypothermia. (From Akula VP, Joe P, Thusu K, et al: A randomized clinical trial of therapeutic hypothermia mode during transport for neonatal encephalopathy, *J Pediatr* 166:856–61 e1–2, 2015.)

Resuscitation (American Academy of Pediatrics and American Heart Association, 2016). Similar to any other sick newborn in the delivery area and on admission to the NICU, the goal should always be to stabilize vital functions before specific therapies are considered. There are anecdotal reports of turning off warmers in the delivery room of late-preterm and term newborns undergoing resuscitation to allow passive cooling in anticipation of initiating therapeutic hypothermia. However, resuscitation is only one piece of evidence in the decision to use hypothermia therapy. As indicated in Fig. 2.2, passive cooling is an ineffective means to cool and can lead to excessively low temperatures, which are potentially hazardous (Akula et al, 2015).

4. The correct answer is B. Perinatal asphyxia may be associated with hypo- or hyperglycemia. Whether the blood glucose concentration contributes to asphyxial brain injury is difficult to discern from clinical data and reflects the limitations of retrospective cohort analyses. However, in animal work, hypoglycemia affects short-term markers of brain dysfunction (e.g., ATP concentration, see Fig. 2.3) (Laptook et al, 1992) more than hyperglycemia in the setting of brain ischemia. Consistent with laboratory observations, an analysis of the CoolCap trial suggested that the rate of death or disability at 18 months is lowest among infants with normoglycemia, intermediate in hyperglycemia, and highest in hypoglycemic infants (Basu et al, 2016).
5. The correct answer is C. In the absence of blood loss, there is no indication to provide packed cells or whole blood for volume expansion given the time needed to obtain blood even if not cross-matched. Volume expansion typically narrows to a choice between normal saline and 5% albumin. A recent review suggests that there is little data to support the use of 5% albumin over normal saline (Shalish et al, 2017). With severe impairment of gas exchange, as evidenced by an arterial cord pH 6.89, there is likely to be a capillary leak. Both normal saline and 5% albumin will leak into the interstitial space, but use of albumin may exacerbate the leak because albumin in the interstitial space may pull water with it. The use of packed red blood cells minimizes leaks into the interstitium relative to normal saline or 5% albumin but is not recommend due to time and absence of cross-matching. Given the potential for myocardial dysfunction following asphyxia, volume expansion should be used judiciously.
6. The correct answer is C. The infant is approaching 3 hours after birth and a decision about hypothermia therapy is

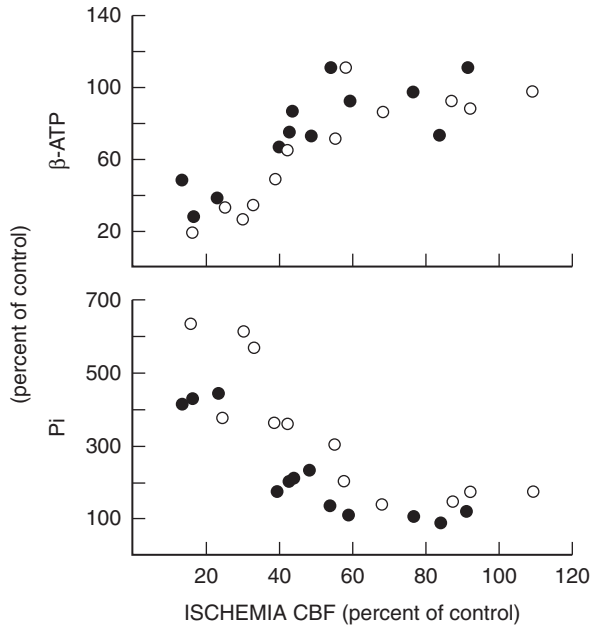


Fig. 2.3 Newborn piglets underwent brain ischemia (x axis, ischemia CBF expressed as a percent of control blood flow) and the effects on cerebral concentrations of β-ATP (top panel) and Pi (inorganic phosphorus, bottom panel) are plotted for hyperglycemic and hypoglycemic conditions (solid and open symbols, respectively). Animals that were hypoglycemic did not maintain ATP concentrations as well as animals with high blood glucose concentrations. Pi, a breakdown product of ATP, showed an inverse relationship to ATP. (From Laptook AR, Corbett RJ, Arencibia-Mireles O, et al: Glucose-associated alterations in ischemic brain metabolism of neonatal piglets, *Stroke* 23:1504–11, 1992.)

needed. However, SpO_2 values have been fixed at 50%, and evacuation of the pneumothorax should take priority to potentially relieve hypoxemia. An important issue is the use of analgesia, which can markedly change neurologic findings of level of consciousness, tone, spontaneous activity, etc. Although a case may be made for needle aspiration to avoid use of analgesia in treating the air leak, a pneumothorax may readily recur when on positive pressure ventilation, especially if the mean airway pressure is high. An echocardiogram before initiating hypothermia therapy is ideal because hypothermia was studied in infants without major congenital anomalies. In this case the neurologic examination indicated a moderate encephalopathy, fentanyl was given, a right chest tube was placed, an echocardiogram indicated suprasystemic pulmonary artery hypertension, and hypothermia therapy was subsequently initiated.

7. The correct answer is B. There is limited data to support anticonvulsant medication for seizure prophylaxis. Much of the interest stems from a small randomized trial (n = 40) to determine whether 40 mg/kg of phenobarbital given to infants following perinatal asphyxia reduces the incidence of neonatal seizures and improves outcome (Hall et al, 1998). There was a trend toward a reduction in seizures (27%, p =.11) and a significant improvement in outcome at 3 years (p =.003) was noted, but the sample size was small and more than 20% of enrolled infants did not complete the protocol or undergo follow-up. There is no consensus that anticonvulsant prophylaxis is beneficial. However, surveillance for seizures is an integral part of care after perinatal asphyxia because the presence of clinical (Glass et al, 2009) and electrographic seizures (Azzopardi et al, 2009) has been associated with worse outcome.

DIAGNOSIS—A CONTRAST OF 2 CASES

CASE 2

Case Summary A: A male infant was born at $36^{0}/_{7}$ weeks to a 43-year-old, gravida 2 now para 1 mother with a birth weight of 2610 g. The pregnancy was uncomplicated and the mother presented to the hospital with 1 hour of severe abdominal pain and decreased fetal movement. Assessment revealed fetal bradycardia and an emergent cesarean section was performed. The mother was not in labor and membranes were intact. At birth the infant was nonvigorous and without spontaneous movements, respiratory effort, grimace or tone. The heart rate was initially 60 bpm but was undetectable at 1 minute after birth. Resuscitation included positive pressure ventilation, intubation, chest compressions, and epinephrine via the endotracheal tube and then via an umbilical venous catheter. Apgar scores were 0, 0, 3, and 4 at 1, 5, 10, and 15 minutes, respectively. The umbilical venous pH and blood gases were pH 6.91, Pco_2 72 mm Hg, Po_2 28 mm Hg, base excess −19.5 mmol/L and the corresponding values for the umbilical artery were pH 6.75, Pco_2 96.4 mm Hg, Po_2 under 20 mm Hg, and base excess under −20 mmol/L. A placental abruption was found at delivery. Neurologic examination at 2.5 hours of age using the NICHD-modified Sarnat scoring indicated a moderate encephalopathy, and hypothermia therapy was initiated shortly thereafter.

Case Summary B: A female infant was born at $40^{3}/_{7}$ weeks to a 37-year-old, gravida 2 now para 1 mother with a birth weight of 3440 g. The mother presented to the hospital in labor after an unremarkable pregnancy. The pregnancy was considered low risk and care was provided in an alternative birthing suite for mothers who desire a normal physiologic birth within a tertiary care facility. Labor progressed to a vaginal delivery after meconium-stained amniotic fluid was noted. The infant was unexpectedly depressed at birth and pediatrics was not in attendance. After initial warming, drying, and stimulation, the obstetric staff started positive pressure ventilation. The pediatric team arrived at 2 minutes after birth and was told that the amniotic fluid was meconium stained, but the intermittent fetal heart monitoring was reassuring. The baby had poor tone, color, and respiratory effort and was intubated for meconium, but none was present and the endotracheal tube was removed. Reintubation was performed for poor respiratory effort and use of 60% Fio_2. The heart rate was always greater than 100 bpm. The Apgar scores were 2, 4, 4, 6, and 7 at 1, 5, 10, 15, and 20 minutes after birth. An umbilical venous gas was pH 7.20, Pco_2 41.2 mm Hg, Po_2 < 20 mm Hg, and base

excess −11.7 mmol/L. An umbilical arterial sample could not be obtained.

On admission to the NICU, the infant had poor perfusion and was given 10 cc/kg of normal saline after establishing vascular access, but the mean blood pressures were always over 40 mm Hg. Blood glucose concentration was unremarkable, and an arterial blood gas at less than 60 minutes had a pH 7.29, Pco_2 19.2 mm Hg, Po_2 72.8 mm Hg, and base excess −14.6 mmol/L. The hematocrit was 51%, the white blood count was 31.5 × 10^3/mcl, and the platelet count was 367 × 10^3/mcl. A neurologic examination at 2.0 hours of age using the NIHCD-modified Sarnat scoring indicated a moderate encephalopathy, and was notable for eyes open but without responsiveness, excessive movements that could not be reduced with consoling and/or holding, repetitive sucking movements that were continuous for more than 1 hour, and intermittent tonic posturing more prominent in the upper extremities. Hypothermia therapy was initiated shortly thereafter.

Exercise 2

Questions

1. Which are clinical criteria to indicate the need for a neurologic examination for the evaluation to use hypothermia?
   A. Use of positive pressure ventilation for 5 minutes at birth irrespective of fetal acid–base state
   B. Any base deficit >7 mmol/L at <60 minutes of age
   C. An Apgar score of <7 at 5 minutes
   D. Any pH <7.0 or base deficit >16 mmol/L at <60 minutes of age
2. What stage of encephalopathy do the following findings of Case B represent (eyes open but without responsiveness, excessive movements that could not be reduced with consoling and/or holding)?
   A. Moderate encephalopathy
   B. Mild encephalopathy
   C. Severe encephalopathy
   D. None
3. In multiple trials of hypothermia, an amplitude-integrated EEG (aEEG) was used as a third tier of inclusion criteria if clinical/biochemical criteria were met and a neurologic examination indicated moderate or severe encephalopathy. Which of the following aEEG recordings would merit the initiation of hypothermia therapy (Fig. 2.4)?
   A. C, D, and E
   B. A, B, and C
   C. D and E
   D. B and C
4. Is the use of hypothermia appropriate for the cases summarized above?
   A. Case A only
   B. Case B only
   C. Neither case
   D. Both cases
5. Which of the following etiologies should be considered or evaluated to support an association between an intrapartum event and development of encephalopathy:
   A. Brain structure (malformation, stroke, hemorrhage)
   B. Infection (sepsis, meningitis, pneumonia, herpes simplex virus)
   C. Maternal medications/anesthesia
   D. Electrolyte and/or mineral in balance
   E. Inborn errors of metabolism
   F. All of the above

Answers

1. The correct answer is D. All clinical trials of hypothermia for perinatal asphyxia used a tiered approach to determine eligibility (Table 2.1). Listed in the table are the clinical and/or physiologic criteria used as the initial steps to determine whether an infant merits a neurologic evaluation. Clinical and/or biochemical measures are the first tier, and the purpose is to identify infants with a high likelihood of an impairment of gas exchange proximate to delivery. The cutoff values of answer D are those from the NICHD-induced hypothermia trial (Shankaran et al, 2005); other trials used similar or slightly different cut points. In the absence of a blood gas or more modest acidemia, additional criteria are needed (e.g., a perinatal event, persistently low Apgar scores out to 10 minutes, or need for ventilation over the first 10 minutes). Neurologic examinations and potentially an aEEG are then used to determine the presence of moderate or severe encephalopathy, that is, the impact of a peripartum event. As recently demonstrated, universal cord blood gas screening combined with a threshold pH 7.10 or under to trigger neurologic examinations can increase the number of infants identified with moderate or severe encephalopathy at the expense of screening more infants (Vesoulis et al, 2018). Determination of the need for hypothermia therapy should occur as soon as feasible and before 6 hours of age.
2. The correct answer is B. Table 2.2 lists the neurologic signs of the modified Sarnat assessment used to categorize the stage of encephalopathy. Mild encephalopathy is classically characterized by a hyper-alert state, which can also feature irritability, normal muscle tone, overactive stretch reflexes, potentially increased tone with stimulation and irritability, weak suck, low threshold to elicit a brisk Moro reflex, mydriasis, and tachycardia (Sarnat and Sarnat, 1976). An important feature of the neurologic examination following asphyxia is that an infant may display a mix of findings that span normal, mild, moderate, and severe encephalopathy (Natarajan et al, 2018). Specific neurologic findings are combined per the clinical trial or guidelines followed to determine a level of encephalopathy.
3. The answer is A. Recording C, D, and E represent a continuous extremely low voltage pattern, a burst suppression pattern, and a flat tracing, mainly isoelectric, respectively. When such recordings occurred in the first 6 hours following perinatal asphyxia, they were associated with poor neurodevelopmental outcomes (Hellstrom-Westas et al, 1995).

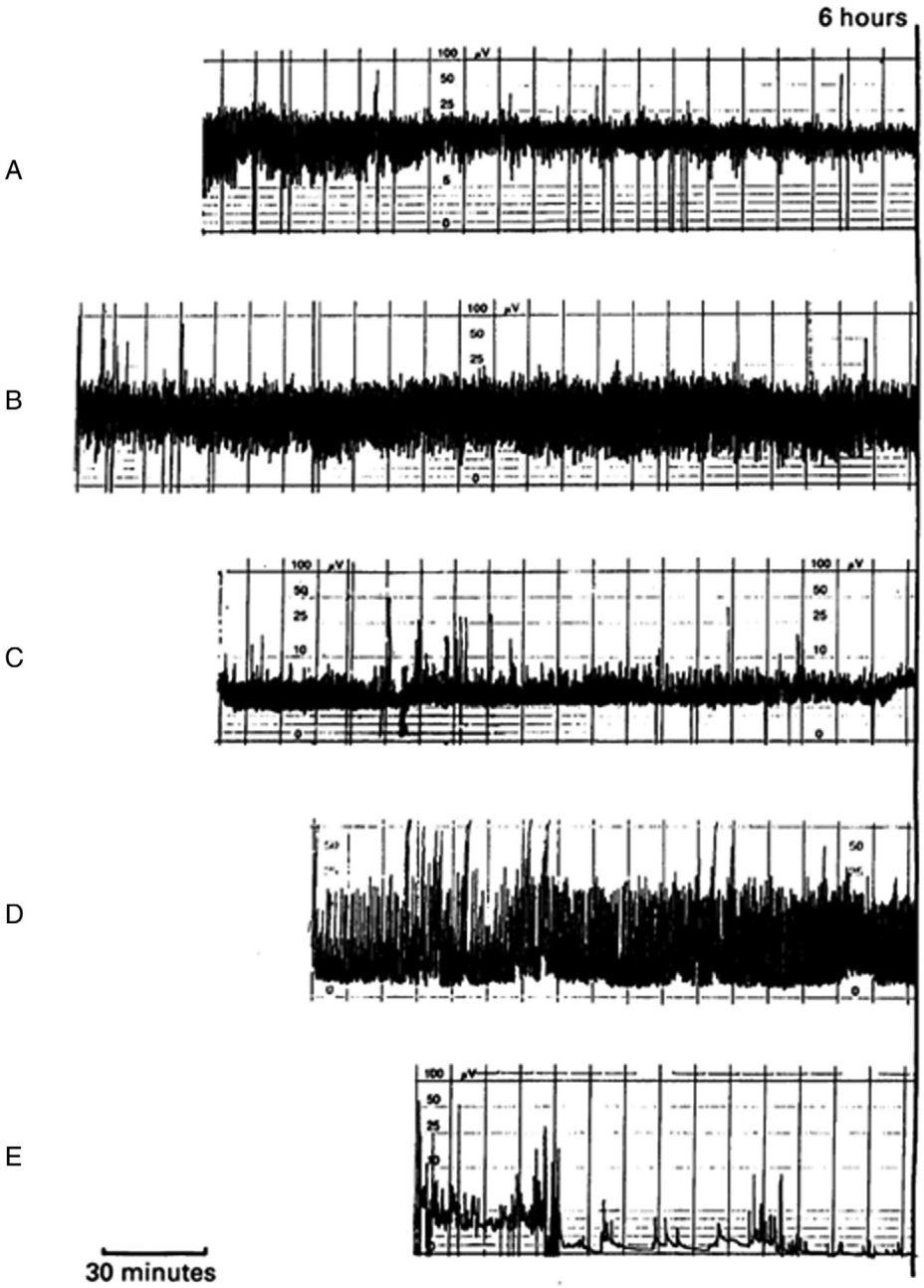


Fig. 2.4 AEEGs were recorded within 6 hours of birth among 47 term infants following perinatal asphyxia. The aEEG represents a semilog plot of the raw EEG channel, which has been amplified, band pass filtered, compressed, and smoothed. EEG postacquisition processing creates a band of EEG activity that can be identified by voltage criteria (upper and lower margins) and other pattern characteristics. The patterns displayed are A) continuous normal voltage, B) continuous normal voltage in an infant who had received phenobarbital, C) continuous extremely low voltage pattern, D) burst suppression pattern, and E) flat, mainly isoelectric. (From Hellstrom-Westas L, Rosen I, Svenningsen NW: Predictive value of early continuous amplitude integrated EEG recordings on outcome after severe birth asphyxia in full term infants, *Arch Dis Child Fetal Neonatal Ed* 72:F34–8, 1995.)

Slightly different criteria were used for the CoolCap (Gluckman et al, 2005) and the TOBY (Azzopardi et al, 2009) trials; infants were eligible if the aEEG was moderately abnormal (upper margin voltage >10 μV and lower margin <5 μV), severely abnormal (upper margin <10 μV), or demonstrated electrographic seizures.

4. The correct answer is D. Case A is straightforward; there is a sentinel event in an uncomplicated pregnancy followed by fetal acidemia, need for resuscitation, and encephalopathy. The likelihood is very high at less than 6 hours that there has been perinatal asphyxia, which is acute, and hypothermia therapy is appropriate. A search

TABLE 2.1 Clinical and/or Physiologic Criteria as a First Step to Evaluate the Neurologic Examination

Author	Gestational Age (wks)	Criteria
Gluckman[a] (Gluckman et al, *Lancet* 2005;365:663–670)	≥36	Acidemia (pH <7.0 or BD >16 mmol/L) at <60 min OR At 10 min, either Apgar ≤5 or continued resuscitation
Shankaran (Shankaran, *NEJM* 2005;353:1574–1584)	≥36	Acidemia (pH <7.0 or BD >16 mmol/L) at <60 min OR Acidemia (pH 7.01–7.15 or BD 10–15.9 mmol/L) + acute perinatal event + Apgar ≤5 or ventilation for first 10 min
Simbruner[a] (Simbruner, *Pediatrics* 2010;126:e771–778)	≥36	≥1 of the following criteria: Apgar <5 at 10 min, need for continued resuscitation at 10 min, pH <7.0, or BD >16 mmol/L at <60 min
Jacobs[a] (Jacobs, *Arch Pediatr Adol Med,* 2011;165: 692–700)	≥35	Two of the following criteria: Apgar ≤5 at 10 min, continued ventilation at 10 min, pH <7.0, or BD >12 mmol/L at <60 min

[a]Infants meeting the clinical and or physiologic criteria then underwent neurophysiological assessment with either an amplitude integrated EEG or a standard EEG to further qualify for a neurologic examination.

TABLE 2.2 Neurologic Signs of the Modified Sarnat Classification of Encephalopathy

	STAGE OF ENCEPHALOPATHY		
Category	**Mild**	**Moderate**	**Severe**
Level of consciousness	Hyperalert, irritable, high pitched cry	Lethargic	Supor/coma
Spontaneous activity	Normal or decreased	Decreased	No activity
Posture	Mild flexion of distal joints	Distal flexion, complete extension	Decerebrate
Tone	Normal or slightly increased	Hypotonia or hypertonia (focal or generalized)	Flaccid or rigid
Primitive Reflexes			
Suck	Weak	Weak or a bite	Absent
Moro	Low threshold to illicit	Incomplete	Absent
Autonomic Function			
Pupils	Mydriasis	Constricted	Dilated, deviated, nonreactive
Heart rate	Tachycardia	Bradycardia	Variable heart rate
Respirations	Hyperventilation	Periodic breathing	On ventilator with or without spontaneous breaths

for other organ systems dysfunction and exclusion of other etiologies is appropriate, along with gathering more data to characterize the integrity of the brain (serial neurologic examinations, EEG, magnetic resonance imaging [MRI]). Case B is more challenging because a sentinel event or any fetal concern was not noted. This case illustrates the importance of blood gases from the umbilical cord and/or the infant at less than 60 minutes for an objective measure of impaired gas exchange. Within the first 6 hours, the clinical team had evidence of impaired gas exchange in utero, need for resuscitation at birth, and moderate encephalopathy without an obvious etiology for the infant's condition. It is appropriate to initiate hypothermia because it is an efficacious and well-tolerated therapy. However, given the limited data, it is critical to gather additional information in support of a hypoxic–ischemic encephalopathy (other organ systems dysfunction, exclusion of other diagnoses, and characterizing the brain integrity). A postdelivery huddle with obstetric colleagues indicated that there was greater uncertainty about fetal well-being, emphasizing the importance of postevent review with our obstetric colleagues.

5. The correct answer is F. The reasons listed in the answer to question 4 apply to this question.

SUPPORTIVE MANAGEMENT FOLLOWING PERINATAL ASPHYXIA

CASE 3

Case Summary: A female, birth weight of 2420 g, was born at $34^{1}/_{7}$ weeks to a 19-year-old primiparous mother in a hospital with a level II NICU. The mother, who had been hospitalized for prolonged and premature rupture of membranes (PPROM), had received betamethasone. Additionally, she was colonized with group B *Streptococcus* and received 7 days of antibiotics before birth. Labor was induced secondary to the PPROM. The second stage of labor was prolonged and a vaginal delivery followed; a tight nuchal cord was present that needed to be cut at delivery. At birth the infant was nonvigorous, positive pressure ventilation was used for 3 minutes, and the infant was transitioned to CPAP and triaged to the level II NICU. Apgar scores were 2, 4, and 8 at 1, 5, and 10 minutes respectively and the umbilical venous and arterial blood gas was a pH 7.33 and 7.15, P_{CO_2} 42 mm Hg and 77 mm Hg, and a base excess −3.7 and –3.6 mmol/L, respectively.

Initial stabilization included use of a high-flow canula with 50% inspired oxygen, which was weaned over the first 16 hours. The infant had poor perfusion, low blood pressure (31/12 mm Hg), blood glucose concentration of 72 mg/dL, and a blood gas at 90 minutes indicated a pH 7.15, P_{CO_2} 39 mm Hg, P_{O_2} 136 mm Hg, and a base excess −14.5 mmol/L. An umbilical venous catheter was placed, 10 mL/kg normal saline was given, and perfusion and blood pressure improved. The admission physical examination was notable for molding of the head, parietal bruising, and cephalohematoma. The tone and activity were initially decreased, but the infant was easily aroused and had intact primitive reflexes. The infant was started on antibiotics. The white count was unremarkable, the hematocrit was 38.7%, and the platelet count was 232 $\times 10^3$/mcL. The mother and baby were 0 positive and DAT negative.

Exercise 3

Questions

1. In a newborn at risk for a prior interval of hypoxia–ischemia, what parameters if any should be monitored for organ system dysfunction?
   A. Central nervous system
   B. None—in this case there was no objective evidence of impaired gas exchange as indicated by the cord blood gases
   C. Central nervous system, hematologic, renal, hepatic, pulmonary, metabolic, and cardiac dysfunction
   D. Central nervous system and cardiopulmonary dysfunction
2. Which imaging/physiologic testing should be considered for additional information to supplement serial neurologic examinations of infants following perinatal asphyxia?
   A. Electroencephalogram
   B. Computerized axial tomography (CAT)
   C. Magnetic resonance imaging
   D. A, B, and C
   E. A and C
3. What is the most common hematological abnormality on a complete blood count following perinatal asphyxia?
   A. Anemia
   B. Leukopenia
   C. Thrombocytopenia
   D. Increased nucleated red blood cells
4. How much "maintenance" crystalloid fluid should be administered to this infant/day?
   A. 50 cc/kg/day
   B. 150 cc/kg/day
   C. 60–80 cc/kg/day
   D. 80–100 cc/kg/day

Hospital course at the level II NICU: At 16 hours, more bruising and swelling of the scalp were noted. The neurologic assessment was notable for irritability and abnormal movements thought to be neuro-irritability and/or encephalopathy. A repeat hematocrit was 27.9%, and the platelet count fell to 155 $\times 10^3$/mcL. A computed tomography (CT) scan was obtained that indicated a large scalp hematoma with soft tissue swelling of the overlying scalp and a possible small supratentorial left-sided subdural hematoma. Gray–white matter differentiation was not well defined. Packed red cells were transfused and phenobarbital 20 mg/kg was given for irritability. At 24 hours, the infant had abnormal movements and staring suspicious for seizures, and the infant was transported to a level III/IV regional NICU.

5. Did this infant experience perinatal asphyxia?
   A. No, based on the absence of metabolic acidosis on the umbilical cord gases
   B. Yes, based on the presence of a metabolic acidosis at 90 minutes of age
   C. There is not enough information to draw this conclusion at this point in time

Hospital course at the level III/IV NICU: The admission physical examination at 30 hours of age was notable for stable vital signs, prominent bruising, and bogginess to the head with pitting edema of the scalp crossing suture lines, mild retractions in 30% F_{IO_2} on a high flow nasal cannula, soft abdomen, and no hepatosplenomegaly. The infant was irritable with handling, displayed hypertonic extremities and decreased central tone, staring episodes with intermittent nystagmus, and bicycling movements of the lower extremities, which were suppressible. The urine output was noted to be less than 1 mL/kg/hr, and blood work indicated a Na 134 mmol/L, K 6.0 mmol/L, total CO_2 10 mmol/L, BUN 23 mg/dL, creatinine 1.7 mg/dL, Ca 7.1 mg/dL, P 10.2 mg/dL, glucose 84 mg/dL, AST 508 IU, ALT 136 IU, albumin 3.0 g/L, lactic acid 9.7 mmol/L, hematocrit 32%, and platelets 69 $\times$ 10^3/mcL. A peripheral blood smear was unremarkable. Over the next 24 hours, the infant remained oliguric, the Na dropped to 124 mmol/L, K was unchanged, the BUN and creatinine rose to 41 mg/dL and 2.7 mg/dL, and a metabolic acidosis became more prominent (capillary blood gas, pH 7.16, P_{CO_2} 23.4 mm Hg, base excess −18.6 mmol/L). Fluid administration was reduced to 40 mL/kg/d, platelets

were transfused, an abdominal sonogram was unremarkable, and an EEG indicated an abnormal background without evidence of seizures. An echocardiogram indicated severe biventricular systolic dysfunction, an ejection fraction of 25% to 30%, right ventricular pressure at systemic level, and severe tricuspid regurgitation and mild mitral regurgitation.

6. What is the most likely etiology for the hyponatremia?
   A. Excessive free water administration with a secondary dilutional hyponatremia
   B. Syndrome of inappropriate antidiuretic hormone release
   C. Acute tubular necrosis of the kidney
   D. Congenital adrenal hyperplasia
   E. Renal sodium loss due to reduced proximal tubular sodium reabsorption associated with prematurity
7. What is the most likely reason for this infant's anemia and thrombocytopenia?
   A. Disseminated intravascular coagulopathy
   B. Hemolytic anemia
   C. Subgaleal bleed
   D. Retroperitoneal hematoma
8. What is the most likely etiology for this infant's metabolic acidosis after transfer to the level III NICU?
   A. Renal parenchymal injury
   B. Myocardial involvement secondary to hypoxia–ischemia
   C. Inborn error of metabolism
   D. Renal tubular acidosis due to bicarbonate wasting associated with prematurity
9. What neuroprotective therapy, if any, could be provided to this infant upon admission to the level III/IV NICU?
   A. Hypothermia
   B. Erythropoietin
   C. Xenon
   D. Stem cells
   E. Allopurinol
   F. None of the above

Answers

1. The correct answer is C. When there is clinical suspicion for a hypoxic–ischemic event, surveillance for multiple organ system dysfunction is appropriate because cardiac output is redistributed to preserve blood flow to "critical" organs (brain, heart, adrenal gland, and placenta for the fetus) and shunted away from less critical organs (kidney, gastrointestinal tract, liver, muscle, skin) (Cohn et al, 1974) (Fig. 2.5). Depending on the organ system, monitoring for dysfunction can be done expectantly (e.g., clinical course for pulmonary status) or with specific testing (e.g., creatinine, urine volume, platelet count). The umbilical cord blood gases did not indicate a metabolic acidosis and at first glance may suggest the absence of impaired gas exchange. However, there was a tight nuchal cord, which may act to "clamp" the umbilical cord, and blood gases at delivery may not reflect the fetal condition. The blood gas at 90 minutes (base excess −14.5 mmol/L) and the initial poor perfusion and hypotension support impaired gas exchange. The change in base excess is often termed a "tissue washout" of lactate following hypoxia–ischemia.
2. The answer is E. EEG is a very sensitive but nonspecific tool that provides information regarding the impact of an event/disease process on the brain. EEG can supplement clinical examinations by providing information about the extent of electrical activity (amplitude, continuity, frequency) symmetry of activity, maturation, and paroxysmal patterns (Fig. 2.6). Brain MRI is the best imaging mode to assess the presence, distribution, and extent of

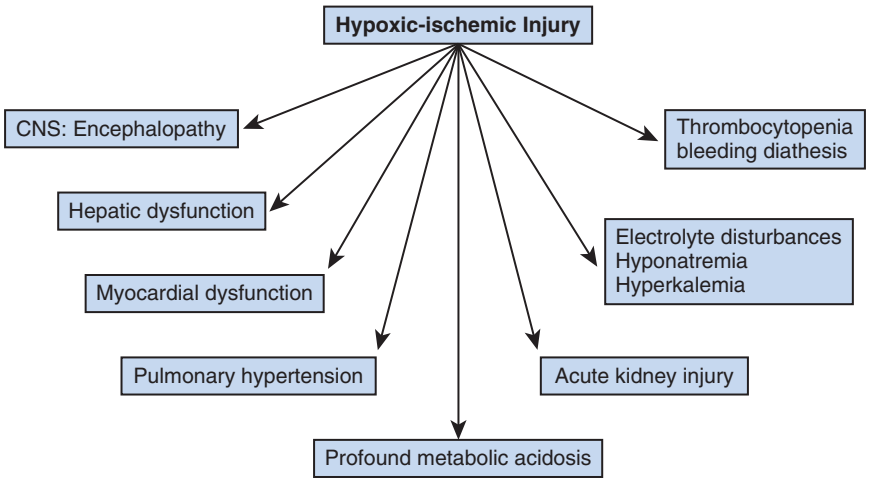
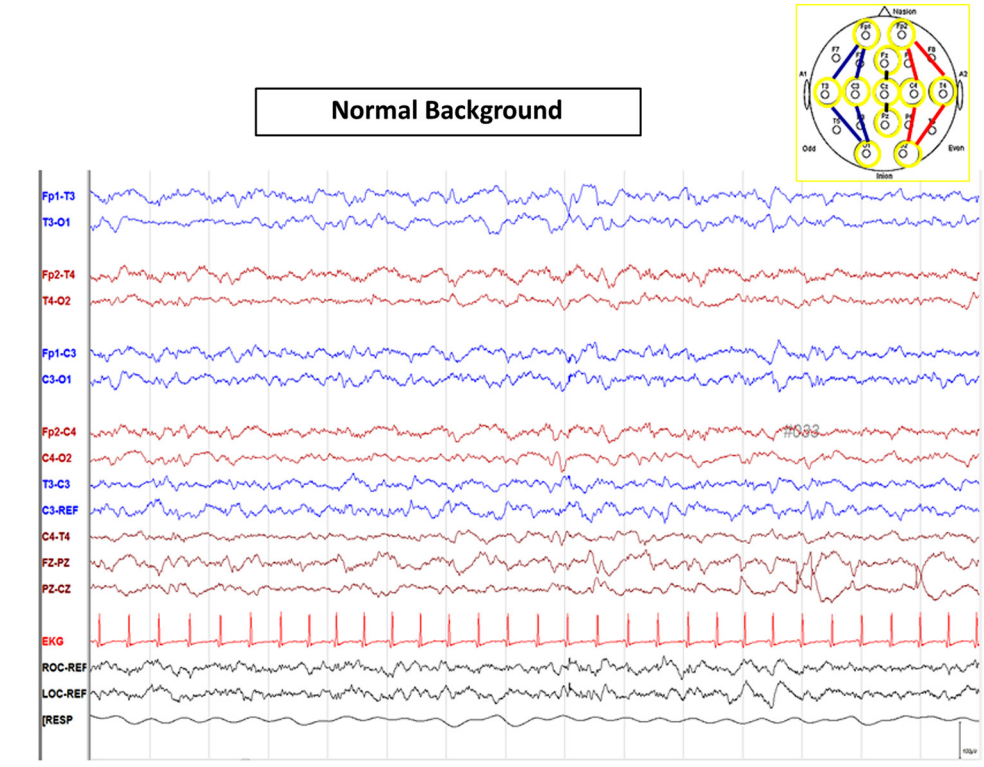
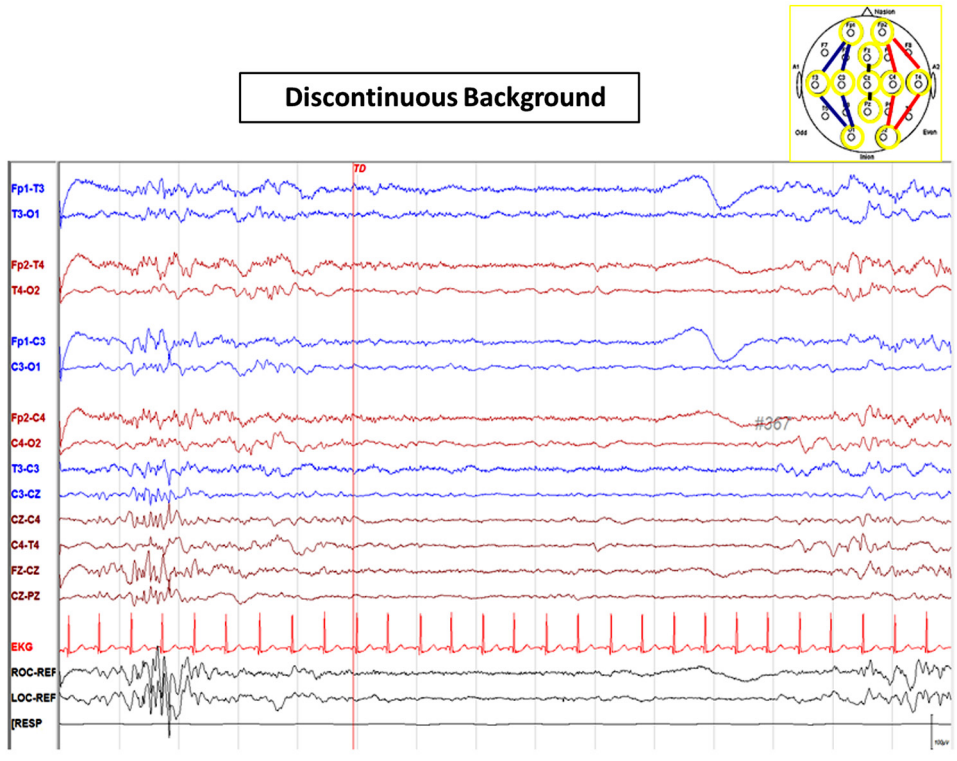


Fig. 2.5 Perinatal asphyxia results in an impairment of gas exchange, which if prolonged or of a severe extent can result in clinically important hypoxia–ischemia with injury of any organ system in the body. There is typically hemodynamic compensation in response to hypoxia–ischemia characterized by a redistribution of cardiac output away from less vital organs (kidney, gastrointestinal tract, muscle, etc.) to preserve blood flow to more vital organs (brain, heart, adrenal gland, placenta). The success of compensatory mechanisms will depend on many variables, such as fetal growth parameters, coexistent inflammatory conditions, and preconditioning events.



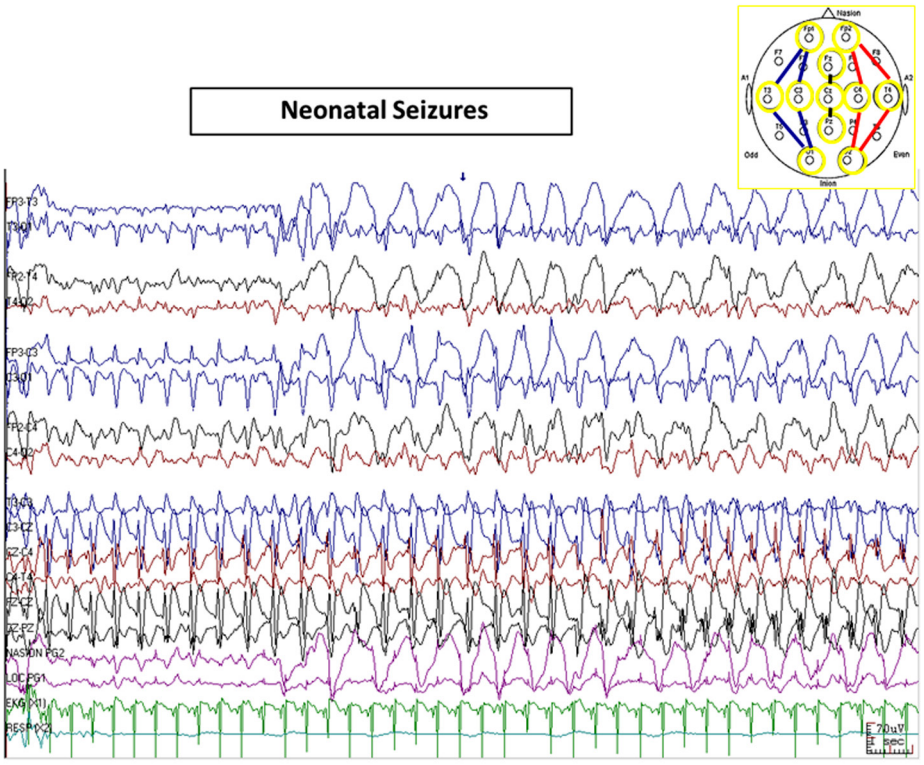
A



B

Fig. 2.6 EEG is an inexpensive, noninvasive bedside tool for infants at risk of encephalopathy. Abnormalities on newborn neurologic examination may be subtle, and an EEG can help assess presence of encephalopathy by the background activity (panels A and B) but does not provide the etiology of encephalopathy. EEG is the gold standard for the diagnosis of seizures (panel C). Clinical suspicion of seizures is often in disagreement with EEG evidence and the presence or absence of seizures changes the prognosis of encephalopathy.

Continued



C

Fig. 2.6,cont'd

injury. Timing of brain MRI will influence which sequences are most helpful. In general, diffusion-weighted imaging provides more information related to hypoxia–ischemia in the first 3 to 5 days following an event, whereas conventional T1 and T2 imaging provide better information after 7 days from an event (American College of Obstetricians and Gynecologists and American Academy of Pediatrics, 2014). However, knowledge of when a hypoxic–ischemic event occurred is often uncertain in the absence of a sentinel event.

3. The correct answer is C. Randomized trials indicate that thrombocytopenia is more common among infants receiving hypothermia compared with usual thermal care practices (Jacobs et al, 2013). Reductions in circulating total WBC and leukocytes among cooled infants compared with control infants have been reported, but the sample size of this report was limited to 65 neonates (Jenkins et al, 2013).
4. The correct answer is A. Hemodynamic instability at birth may require volume expansion to insure an adequate intravascular volume after hypoxia–ischemia. Once the infants hemodynamics are stable, crystalloid fluid administration should be limited due to potential renal dysfunction, which is common after hypoxia–ischemia with or without hypothermia. Keeping fluids restricted is prudent until there is more information regarding renal function and or Syndrome of inappropriate anti-diuretic hormone secretion (SIADH).
5. The correct answer is C. One of the challenges in diagnosing perinatal asphyxia is that a single diagnostic test is not available. As reviewed in the ACOG/AAP publication *Neonatal Encephalopathy and Neurologic Outcome* (American College of Obstetricians and Gynecologists and American Academy of Pediatrics, 2014), a series of data points are needed to establish a higher likelihood of perinatal asphyxia. This is less of an issue when there is a clear sentinel event (e.g., uncomplicated pregnancy and labor, sudden abdominal pain, complete placental abruption, emergent delivery, infant resuscitation, fetal acidemia and encephalopathy). In this case perinatal asphyxia is in the differential, but an intracranial hemorrhage or other lesion associated with a fall in hematocrit needs to be considered. The description of this infant is one in which the neurologic findings progressed over the first 24 hours after birth.
6. The correct answer is C. Acute tubular necrosis is supported by the rising creatinine concentration. SIADH can occur following asphyxia but is difficult to invoke in the presence of a rising creatinine. Serum and urine osmolality is helpful to confirm the absence of SIADH. Often overlooked is the utility of a urine analysis.
7. The correct answer is C. A subgaleal bleed is not specific to a hypoxic–ischemic event, but the examination and imaging are consistent with this diagnosis. Infants can lose a large portion of their blood volume into the subgaleal space and can consume clotting factors that can further

exacerbate bleeding. Serial head circumference measurements should be followed closely. Bleeding due to Disseminated intravascular coagulopathy (DIC) is a consideration, but the peripheral smear does not favor this diagnosis. Small subdural hematomas are common after vaginal delivery.

8. The correct answer is B. All of the choices could result in a metabolic acidosis, but in the setting of CNS dysfunction pointing to hypoxia–ischemia, myocardial dysfunction needs to be considered first. Inborn errors of metabolism are an important consideration (e.g., mitochondrial disorders) but are obviously rare.
9. The correct answer is F. The infant was admitted to the level III NICU at 30 hours of age beyond the typical 6-hour window when hypothermia is started and beyond the 6- to 24-hour window when late hypothermia has been studied with some efficacy (Laptook et al, 2017). Other promising neuroprotective therapies include erythropoietin, melatonin, inhaled xenon, stem cells, and cannabinoids (Martinello et al, 2017). Data to justify their use are not available, and randomized trials are starting for some of these therapies.

HYPOTHERMIA THERAPY

CASE 4

Case Summary: A male, birth weight of 3910 g, was born at $40^{3}/_{7}$ weeks to a 27-year-old, gravida 4 now para 2 mother at a level III/IV NICU. Data were based on a 9-week ultrasound and the mother was induced due to the gestational age. The fetus had a low fetal heart rate (105–110 bpm) during labor, but moderate variability and spontaneous accelerations were reassuring. As labor progressed, late decelerations were noted and a decision was made to expedite delivery with the use of vacuum. A tight nuchal cord was noted at delivery. At birth the infant had absent respiratory effort, no tone or movement or grimace. Resuscitation included positive pressure ventilation for 4 minutes, followed by intubation with an increase in heart rate above 100 bpm and an increase in Spo_2, but color and perfusion remained poor. Apgar scores were 0, 3, 4, and 4 at 1, 5, 10, and 15 minutes after birth, and the infant was transported to the NICU. The umbilical cord venous blood gas was pH 7.21, Pco_2 50.0 mm Hg, Po_2 50.9 mm Hg, and base excess −8.1 mmol/L. The umbilical arterial blood gas was pH 6.82, Pco_2 110.0 mm Hg, Po_2 32.3 mm Hg, and base excess −17.7 mmol/L.

On NICU admission the infant was poorly perfused, hypotensive with mean blood pressures of 20 mm Hg, and breathing with ventilator support. The initial blood glucose concentration was 12 mg/dL, and stabilization included establishing vascular access and bolus of glucose (200 mg/kg) and normal saline (20 cc/kg). On the initial blood count, the hematocrit was 31%, white blood count was 9.3×10^3/mcL (unremarkable differential), and platelets were 171×10^3/mcL. There were 12% nucleated red cells and a reticulocyte count of 4.1%. A blood culture was sent, and antibiotic therapy was started. The first blood gas at 60 minutes had a pH 6.88, Pco_2 28.8 mm Hg, Po_2 78.1 mm Hg, and base excess −20 mmol/L. A transfusion of packed red blood cells was given after additional normal saline was administered. A Kleihauer Betke stain on maternal blood was negative for fetal red cells. A neurologic examination at 90 minutes of age using the NIHCD-modified Sarnat scoring indicated a severe encephalopathy and hypothermia therapy was initiated at 2 hours of age.

Exercise 4

Questions

1. What is the appropriate core temperature target when using whole-body hypothermia therapy for an infant with perinatal asphyxia?
   A. 33.0°C
   B. 34.5°C
   C. 32.0°C
   D. 33.5°C
2. What is the appropriate duration of reduced core temperature during hypothermia therapy?
   A. 60 hours
   B. 120 hours
   C. 96 hours
   D. 72 hours
3. What is an appropriate rate of rewarming following hypothermia therapy?
   A. Over 2 hours
   B. 0.5°C/hour
   C. Over 24 hours
   D. Over 48 hours
4. What is the most common complication/laboratory abnormality attributable to hypothermia therapy?
   A. Renal failure
   B. Persistent pulmonary hypertension
   C. Hepatic dysfunction
   D. Shivering
   E. Thrombocytopenia

Answers

1. The correct answer is D. The depth of temperature reduction used in the first series of hypothermia trials was remarkably similar and was extrapolated from preclinical investigation and pilot studies in newborn infants. Clinical trials cooled to 33.5°C for whole-body cooling and 34.5°C for head cooling (Azzopardi et al, 2009; Gluckman et al, 2005; Jacobs, 2011; Shankaran et al, 2005; Simbruner et al, 2010). Trials of hypothermia in newborns indicated that cooling reduced death or disability at 18 to 24 months, but more than 40% of the hypothermia group had an outcome of death or disability. Whether cooling to a lower temperature could improve outcome further was unknown. The NICHD Neonatal Research Network subsequently conducted a randomized trial to compare cooling to 33.5°C with 32.0°C as part of a factorial design (Shankaran et al, 2014, 2017). The results indicated that outcomes were not improved if cooled to 32.0°C compared with 33.5°C. These results are consistent with

TABLE 2.3 Outcome of Infants With HIE at 18 to 22 Months After Different Cooling Regimens

Outcome	72 hrs at 33.5°C N = 92	72 hrs at 32.0°C N = 84	120 hrs at 33.5°C N = 93	120 hrs at 32.0°C N = 78
Death or disability %	29.3	34.5	34.4	28.2
Death %	9	18	19	19
Disability %	23	20	19	11

The outcome (death or disability) at 18 to 22 months of infants 36 weeks' and later gestation with moderate or severe encephalopathy HIE) following perinatal asphyxia randomized to different cooling regimens of temperature depth and duration. Disability was typically severe and included any of the following: Bayley III cognitive score under 70, gross motor function classification system score of 3 to 5, or neural sensory deficits (hearing, vision).

parallel studies performed in neonatal rat pups (Wood et al, 2016).

2. The correct answer is D. In the initial hypothermia trials, the duration of cooling was uniformly 72 hours based on preclinical investigation in fetal sheep. For the same reason that deeper cooling was studied, longer cooling was investigated as part of a factorial design, randomized trial performed by the Neonatal Research Network. The results indicated that outcomes were not improved if cooled for 120 hours compared with 72 hours (Table 2.3). These results are consistent with parallel studies performed in fetal sheep (Davidson et al, 2015).
3. The correct answer is B. There is scant data in newborns to guide how to rewarm infants rapidly. The rate of 0.5°C/hr represents the rate used by most clinical trials. Rapid rewarming (over 1–2 hours) may alter cardiopulmonary hemodynamics in addition to cerebral function, but objective data to support these concerns are not available.
4. The correct answer is E. Among 11 randomized controlled trials involving more than 1500 term and late-preterm infants with moderate or severe encephalopathy from perinatal asphyxia, therapeutic hypothermia reduced the composite outcome of death or major neurodevelopmental disability at 18 months (typical risk ratio of 0.75) (95% confidence interval of 0.68–0.83) (Jacobs et al, 2013). Hypothermia, as used in clinical trials, is well tolerated but thrombocytopenia was more frequent among cooled infants, along with sinus bradycardia. Thrombocytopenia can usually be managed with replacement transfusions. Some degree of renal injury and acute tubular necrosis is common after perinatal asphyxia, but it is not increased in frequency with hypothermia therapy.

Hospital course: In spite of aggressive fluid administration with blood products, crystalloid infusions and bicarbonate therapy, the negative base excess never corrected. Dopamine and dobutamine were started for pressor support, and the blood pressure increased. An echocardiogram indicated a structurally normal heart, without pulmonary artery hypertension, and suggestion of being underfilled. The infant remained oliguric and became edematous. Over the first 36 hours, platelet counts fell to 68 $\times$ 10^3/mcL and frank bleeding occurred from a replogle tube, endotracheal tube, umbilicus, and peripheral intravenous sites, which did not respond to blood product replacement therapy. A Polymerase chain reaction (PCR) for herpes was sent, and acyclovir therapy was started. A cranial ultrasound indicated a structurally normal brain without evidence of bleeding. Intensive care was subsequently redirected after consultation with the family. The placental examination was notable for delayed villous maturation, scattered chorionic villi with stromal karyorrhexis, and widely scattered avascular villi, consistent with fetal vascular malperfusion.

Questions

5. The clinical team is concerned for the potential of an intracranial hemorrhage. What is the most appropriate mode of imaging for this infant?
   A. Bedside cranial sonography
   B. Magnetic resonance imaging
   C. Computerized axial tomography
   D. Skull films
6. Intermittent lip smacking and sucking activity are noted without a change in vital signs. What is the appropriate next step?
   A. Start the baby on an antiepileptic drug and progressively increase the dose until symptoms abate.
   B. Image the brain.
   C. Start sedative-hypnotic medications.
   D. Observe further and if the activity continues start an anticonvulsant drug and obtain an EEG and/or an aEEG.
7. What complication merits consideration for stopping hypothermia therapy?
   A. Thrombocytopenia
   B. Persistent pulmonary artery hypertension
   C. Renal failure
   D. Disseminate intravascular coagulation with clinical bleeding and a new onset large intracranial hemorrhage
   E. Continued seizures (either clinically or electrographically) in spite of multiple antiepileptic drugs

Answers

5. The correct answer is A, bedside cranial sonography. In general, MRI is the imaging mode of choice to determine the extent and distribution of injury. Although MRIs can be acquired while on hypothermia therapy (Boudes et al, 2015), infants who are critically ill with ongoing hypothermia are difficult to transport to an MRI scanner even if the NICU has a magnet in the unit. Furthermore, image acquisition typically takes up to 30 minutes for an MRI. In contrast, sonography can be done at the bedside to avoid moving a critically ill infant. Although sonography visualizes the central portion of the brain better than the

periphery, large clinically important lesions should be evident.

6. The answer is D. A wait and see approach is appropriate when there is uncertainty regarding abnormal movements and there is no evidence that the activity is acutely compromising cardiopulmonary function. Because perinatal asphyxia is the most common cause of neonatal seizures (Glass et al, 2016), initiation of antiepileptic treatment is appropriate if signs persist and other abnormalities have been excluded given that immediate EEG monitoring may be not be readily available. Whether seizures are observed or not, EEG or aEEG monitoring should be part of the care of an infant being treated with hypothermia, especially because some seizures are subclinical. Despite the use of hypothermia, seizure rates are similar to those reported in the pretherapeutic hypothermia era. Emerging data suggest that the seizure profile has been altered by hypothermia (lower overall seizure burden, shorter duration of seizures). EEG monitoring is especially pertinent for infants undergoing cooling, who may be sedated. An aEEG is useful, but shorter-duration seizures are more likely to be missed (Boylan et al, 2015). Many of these concerns have provided the rationale for development of NeuroNICUs with a broader focus on newborns at risk for brain injury (Van Meurs et al, 2018).
7. The correct answer is D. Therapeutic hypothermia is the only neuroprotective therapy that has been demonstrated to reduce an important outcome, death, or disability at 18 to 22 months in rigorous randomized trials. When contemplating stopping an effective therapy, there should be consideration that the reason to stop carries a high risk of death or disability and that it cannot be managed with aggressive supportive care as would be the case for the other choices.

CASE 5

CONTROVERSIES IN HYPOTHERMIA THERAPY

Case Summary: This is a 2630 g female born at $37^{1}/_{7}$ weeks to a 31-year-old gravida 2, now para 2 mother. The pregnancy was uncomplicated until the day before delivery when the mother presented with symptoms of pregnancy-induced hypertension. Antepartum laboratory assessment was unremarkable except for GBS colonization. Induction of labor was initiated due to hypertension, and delivery was affected by an emergent cesarean section due to a nonreassuring fetal heart rate. Membranes were ruptured at delivery and the infant was nonvigorous, without spontaneous respiratory effort or movement and no audible heart rate. Resuscitation included drying, suctioning, and stimulation; positive pressure ventilation by a Neopuff; and intubation. Apgar scores were 0, 5, 5, and 6 at 1, 5, 10, and 15 minutes, and the infant was transported to the NICU. The umbilical artery blood gas was pH 6.75, Pco_2 above 110 mm Hg, Po_2 under 20 mm Hg, and base excess less than −20 mmol/L.

On NICU admission the vital signs were stable (heart rate 146 bpm, respiratory rate 60 bpm, blood pressure 61/32 mm Hg) except for an axilla temperature of 35.6°C. Clinical perfusion was adequate, but the infant was given 10 cc/kg of normal saline in response to the cord blood gas. The blood glucose concentration and complete blood count were unremarkable. After stabilization, a neurologic examination was performed at 2 hours after birth using the NICHD modified Sarnat staging (Shankaran et al, 2005). The examination indicated normal findings except for an incomplete Moro reflex and use of mechanical ventilation (infant was spontaneously breathing).

Exercise 5

Questions

1. Should hypothermia treatment be initiated at less than 6 hours of age?
   A. Yes, because the cord blood gas and neurologic abnormalities have been associated with brain injury on MRI.
   B. Yes, because fetal acidemia of this extent invariably is associated with brain injury.
   C. No, because this there is no data from clinical trials to support that hypothermia benefits in such a baby.
   D. Yes, because there is a high likelihood that the neurologic condition will progress and the infant will demonstrate moderate or severe encephalopathy beyond 6 hours.
2. If the infant is cooled, what should the duration of hypothermia be?
   A. 72 hours
   B. 24 hours
   C. 12 hours
   D. 48 hours
3. Are there any diagnostic tests that can help guide the duration of cooling if the latter is undertaken?
   A. Diffusion weighted imaging
   B. Proton and phosphorus magnetic resonance spectroscopy
   C. Near infrared spectroscopy
   D. Brain specific proteins measured in the plasma (S100b, ubiquitin carboxy-terminal hydrolase-L1, interleukin 1, 6, TNFα)
   E. Neurologic examination
   F. EEG
   G. None of the above

Answers

1. The correct answer is C. Clinical practice is changing, and many centers choose to provide hypothermia to infants without moderate or severe encephalopathy (Oliveira et al, 2018), but it is without evidence from a clinical trial. The use of hypothermia for mild encephalopathy (encephalopathy that does not meet moderate or severe extent) reflects reports of MRI-associated injury among infants with mild encephalopathy (with or without cooling) (Walsh et al, 2017), the potential for infants to progress in the extent of encephalopathy after 6 hours, and the view that hypothermia is a well-tolerated therapy where benefit

outweighs potential harm. Knowledge gaps in this area include lack of a consensus definition of mild encephalopathy, absence of early childhood neurodevelopmental outcome, and potential deleterious effects of a therapy that may not be needed (mother–infant bonding, breastfeeding, sleep patterns, etc.). A prospective observational cohort of infants with mild encephalopathy indicates that MRI abnormalities occur but at a lower frequency than reported in retrospective studies (Prempunpong et al, 2018). A small cohort with follow-up supports worse developmental outcome at near school age among infants with mild encephalopathy (Murray et al, 2016). It is unknown whether hypothermia therapy can modify school-age outcomes.

2. The correct answer is A. The only evidence-based data regarding duration of cooling come from a randomized clinical trial that supports 72 hours compared with 120 hours of cooling (Shankaran et al, 2017). If cooling is undertaken, there is minimal data regarding treatment for less than 72 hours. Preclinical data support more benefit from 72 hours compared with 48 hours of hypothermia (Davidson et al, 2018). In a small cohort of infants with mild encephalopathy, brain injury was observed after early discontinuation of hypothermia (Lally et al, 2018).
3. The correct answer is G. A high priority for perinatal research is the identification of biomarkers, which can be used in real time to guide therapy (e.g., addition of adjuvant therapies). Although many of the listed answers can help with prognosis, none of them have been used to potentially modify treatment regimens.

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Abstract: Perinatal asphyxia is a challenging condition because it represents a modifiable etiology for neonatal encephalopathy with the use of hypothermia. This contrasts with other etiologies of neonatal encephalopathy, which are not amenable to treatment such as cerebral malformations, strokes, congenital acquired infections, teratogenic exposures, and cerebral hemorrhages. To be effective, hypothermia needs to be initiated early in life, typically within 6 hours following birth based on results from multiple clinical trials. The implication for clinicians is that they need to be well versed with perinatal asphyxia and understand facets of presentation, stabilization, diagnosis, medical management, and hypothermia treatment. The cases presented in this chapter were chosen to address some of these issues. It is important to recognize that for many management issues, data is available to guide what not to do and not necessarily justify the optimal strategy.

Keywords: perinatal asphyxia, hypothermia therapy, neonatal encephalopathy, hypoxic–ischemia, neuroprotective

3

Fluid and Electrolyte Management in the Newborn Intensive Care Unit

Pamela Good, John M. Lorenz, and Richard A. Polin

Fluid and electrolyte management is an important and challenging part of the initial care of any very premature or critically ill newborn. The transition from fetal to neonatal life is associated with major changes in fluid and electrolyte homeostasis and total body balance. Before birth, the fetus has a constant and ready supply of water and electrolytes; homeostasis is largely a function of maternal and placental mechanisms. After birth, newborns must rapidly assume responsibility for their own fluid and electrolyte homeostasis in an environment in which water and electrolyte availability and losses are much more variable and less subject to feedback control than in utero. Moreover, significant contraction of the extracellular fluid (ECF) space occurs with the transition from fetal to neonatal life. In very premature newborns, this transition is also associated with a change in internal potassium (K) balance: K shifts from the intracellular fluid (ICF) space to the ECF space. The goal of fluid and electrolyte therapy in the immediate postnatal period is not to maintain fluid and electrolyte balance but to allow the appropriate changes in balance to occur without detrimental perturbations in fluid and electrolyte status.

FETAL FLUID BALANCE

The fetus receives all of its 1995 water for growth transplacentally. Placental water balance is regulated by aquaporins, which are found throughout the female genital tract. Net water fluxes are relatively small (Faichney et al, 2004), but larger volumes of water are exchanged between the fetus, amniotic fluid, and maternal circulation (Fig. 3.1).

Early in gestation, the fetus is about 95% water, with the vast majority in the extracellular fluid space. As gestation progresses, the percentage of total body water decreases because of the accumulation of body solids (protein, fat, and minerals) (Fig. 3.2). As a proportion of body weight, the extracellular fluid space decreases and intracellular water increases because fetal growth later in gestation occurs by cell enlargement rather than by cell division. The average term fetus contains 3000 mL of water, of which 1000 mL is intracellular and 350 mL is intravascular. Urine output is brisk during fetal life and may reach 1000 mL/day at term gestation.

In fetuses with abnormal growth, there are perturbations in body composition. For example, large for gestational age (LGA) infants have higher total body fat and mineral content but less lean body mass (Hammami et al, 2001). In growth-restricted infants, total body water is increased (compared with appropriately grown infants). That reflects decreased protein and mineral accumulation in the growth-restricted population (Hohenauer and Oh, 1969). Furthermore, adipose tissue is markedly reduced at term gestation.

BODY WATER AND SODIUM BALANCE IN THE NEONATE

A weight loss of about 5% to 12% is almost invariable during the first week of life in preterm infants (Bauer and Versmold, 1989; Lorenz et al, 1982; Shaffer et al, 1987). Although inadequate caloric intake may contribute to this weight loss, multiple studies have found that it results in large part from contraction of the ECF space after birth (Bauer and Versmold, 1989; Bauer et al, 1991; Hartnoll et al, 2000; Heimler et al, 1993; Shaffer et al, 1986; Shaffer and Meade, 1989) (Fig. 3.3). The following data suggest that contraction of the ECF space is physiologic:

- It occurs in spite of large variation in water and sodium (Na) intake (Lorenz et al, 1982; Shaffer and Meade, 1989).
- It occurs even if caloric/protein intake mitigates postnatal weight loss (Heimler et al, 1993).
- When postnatal weight loss is regained, ECW volume per kg body weight remains stable at the new lower level (Singhi et al, 1995).
- Attenuation of this decrease may be associated with increased morbidity (Bell and Acarregui, 2008; Costarino et al, 1992; Hartnoll et al, 2000).

DIURESIS AND NATRIURESIS

Negative total body water (TBW) and total body sodium (TBNa) balances are associated with contraction of ECF space. In most infants, the excretion of water and Na that occurs as a result of contraction of the ECF space in the first few days of life is not gradual. In fact, a characteristic pattern of fluid and electrolyte adaptation, which is largely independent

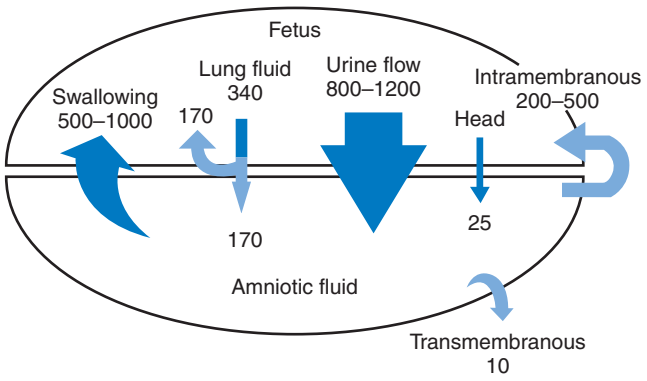

Fig. 3.1 Water flux between the fetus and amniotic fluid during late gestation, shown in mL per day. (From Gilbert WM, Brace RA: Amniotic fluid volume and normal flows to and from the amniotic cavity. *Semin Perinatol* 17:150–157, 1993.)

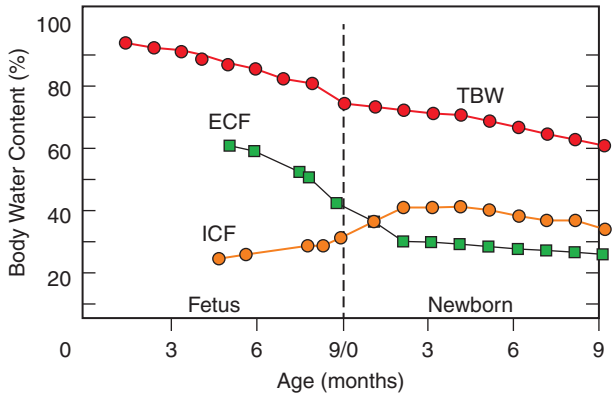

Fig. 3.2 Changes in body water compartments through advancing gestational age and postnatally. (Reproduced with permission from Friis, HB: Body water compartments in children: changes during growth and related changes in body composition, *Pediatrics* 28: 169–181, 1961 by the AAP.)

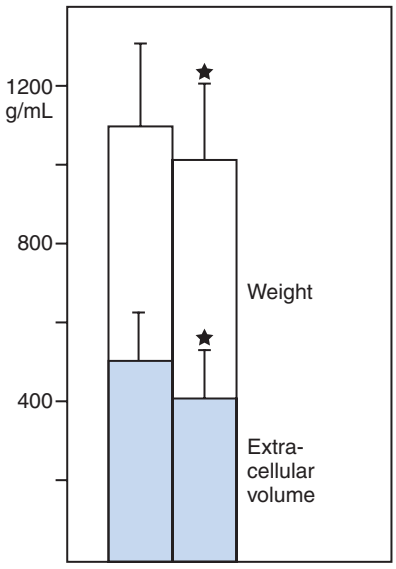

Fig. 3.3 Postnatal changes in body weight, extracellular fluid volume, and sodium balance in very premature infants. (From Bauer K, Versmold H: Postnatal weight loss in preterm neonates less than 1,500 grams is due to isotonic dehydration of the extracellular volume, *Acta Paediatr Scand Suppl* 360:37–42, 1989.)

of fluid and electrolyte intake, is observed in the first week of life in the majority of very low birth weight (VLBW) newborns (Bidiwala et al, 1988; Costarino et al, 1985; Lorenz et al, 1982; Lorenz et al, 1995). Usually three phases can be distinguished. Table 3.1 summarizes the changes in fluid and electrolyte balance, ECF volume, and renal function associated with each phase. Tables 3.2, 3.3, and 3.4 summarize recommended water, Na, and K intakes during the first month of life.

During the first 12 to 48 hours of life, the urine flow rate is low (0.5–3 mL/kg/hour), regardless of intake. Therefore during this prediuretic phase, excretion of Na and K is also quite low; insensible water loss (IWL) is the major route of water loss. At the same time, the low glomerular filtration rate (GFR) in the immediate perinatal period limits the infant's ability to excrete water and electrolyte loads.

As the diuretic/natriuretic phase begins, an abrupt increase in urinary water and Na occurs independent of water and Na intake and heralds contraction of the ECF space. Early in the diuretic/natriuretic phase, serum Na concentration ($[Na^+]$) often rises because water balance is more negative than sodium balance. The majority of body weight loss occurs during this phase. A fall in serum K concentration ($[K^+]$) can be anticipated as increased delivery of water and Na to the distal nephron stimulates K secretion and kaliuresis. As the ECF space stabilizes at an appropriate volume, urinary water and electrolyte excretion decrease and begin to vary appropriately with intake.

This negative TBW and TBNa balance and reduction of ECF volume during the postnatal diuresis/natriuresis in the immediate newborn period may represent excretion of fetal pulmonary fluid, which is absorbed from the alveolar space and interstitium of the lung before delivery and in the immediate postnatal period.

POTASSIUM

The serum $[K^+]$ rises in the first 24 to 72 hours after birth in very premature infants, even in the absence of exogenous K intake or renal failure (Lorenz et al, 1997; Sato et al, 1995). This increase results from the shift of K from the ICF space to the ECF space; urine outputs are usually normal in affected infants (i.e., nonoliguric hyperkalemia). The magnitude of this shift correlates roughly with the degree of prematurity. Clinically significant hyperkalemia rarely occurs after 30 to 32 weeks of gestation (Sato et al, 1995). In contrast, nonoliguric hyperkalemia used to be fairly common in infants weighing less than 1000 grams at birth or born before 28 weeks' gestation (Fukada et al, 1989; Gruskay et al, 1988; Lorenz et al, 1997; Shaffer et al, 1992; Stefano and Norman, 1993). However, the use of antenatal steroids and enhanced postnatal nutrition have decreased the risk of nonoliguric hyperkalemia (Omar et al, 2000) in extremely low birth weight (ELBW) infants.

GLUCOSE

With the clamping of the umbilical cord at birth, the supply of glucose and other nutrients from the mother ceases and

TABLE 3.1 Postnatal Renal, Fluid, and Electrolyte Adaptation in Very Premature Newborns

Phase	Prediuretic	Diuretic/Natriuretic	Homeostatic
Age	~ Birth–2 days	~ 1–5 days	After ~ 2–5 days
Urine output	Low	Abrupt ↑↑	↓ then α intake
Sodium excretion	Minimal	Abrupt ↑↑	↓ then α intake
Potassium excretion	Minimal	Abrupt ↑↑	↓ then α intake
Water balance	< intake − IWL	Markedly negative	~ α sodium balance
Sodium balance	~ negative	Markedly negative	Stable, then positive with growth
Potassium balance	~ negative	Markedly negative	Stable, then positive with growth
ECF volume (mL)	Stable or ~ ↓	Abrupt ↓↓	1. α sodium balance 2. ↑ with growth
Creatinine clearance	Low	Abrupt ↑↑	± ↓ then gradual ↑ with maturation

ECF, Extracellular fluid; *IWL*, insensible water loss.

TABLE 3.2 Guidelines for Initiating and Adjusting Fluid and Electrolyte Therapy in Appropriate for Gestational Age Infants Nursed Naked in an Incubator With 50% Ambient Humidity and Ambient Air Temperature in the Neutral Thermal Range

Transition Phase (First 3–5 days of life)

Weight Grams	Weight loss % of bw	Water mL/kg/day	Na mEq/kg/day	Cl mEq/kg/day	K mEq/kg/day
<1000	10%	90–140	0–1	0–1	0
1001–1500	8%–10%	80–120	0–1	0–1	0–1
1501–2000	6%–8%	70–100	0–1	0–1	0–1
>2000	6%–8%	60–80	0–1	0–1	0–1

BW, birth weight.

TABLE 3.3 Guidelines for Initiating and Adjusting Fluid and Electrolyte Therapy in Appropriate for Gestational Age Infants Nursed Naked in an Incubator With 50% Ambient Humidity and Ambient Air Temperature in the Neutral Thermal Range

Stabilization Phase (5–14 days of life)

Weight Grams	Weight loss % of bw	Water mL/kg/day	Na mEq/kg/day	Cl mEq/kg/day	K mEq/kg/day
<1000	0%	80–120	2–3	2–3	1–2
1001–1500	0%	80–120	2–3	2–3	1–2
1501–2000	0%	80–120	2–3	2–3	1–2
>2000	0%	80–120	2–3	2–3	1–2

BW, birth weight.

TABLE 3.4 Guidelines for Initiating and Adjusting Fluid and Electrolyte Therapy in Appropriate for Gestational Age Infants Nursed Naked in an Incubator With 50% Ambient Humidity and Ambient Air Temperature in the Neutral Thermal Range

Growth Phase (>14 days of life)

Weight Grams	Weight Gain g/kg/day	Feedings mL/kg/day	Na mEq/kg/day	Cl mEq/kg/day	K mEq/kg/day
<1000	15–20	150–200	3–5	3–5	2–3
1001–1500	15–20	150–200	3–5	3–5	2–3

neonatal glucose production begins. As a result, serum glucose concentration ([GLU]) falls sharply over the first 45 to 90 minutes of life (Heck and Erenberg, 1987; Metzger et al, 2010; Srinivasan et al, 1984). In response to this fall in serum glucose concentration, there are abrupt increases in the levels of epinephrine, norepinephrine, and glucagon with a concomitant fall in insulin. Although the effect of these counterregulatory hormones on glucose metabolism is not as robust as in the adult, these responses mobilize glucose from glycogen stores and promote gluconeogenesis. Glucose utilization averages 4 to 8 mg/kg/minute in term and preterm newborns (Bier et al, 1977; Sunehag et al, 1993). Endogenous glucose production may be inadequate to maintain a normal serum [GLU] in infants with prematurity, perinatal stress, or intrauterine growth restriction. In this case exogenous administration of glucose at a rate that matches the rate of glucose utilization is necessary to conserve glycogen stores and prevent hypoglycemia (Tryala et al, 1994).

Premature infants are also at increased risk for hyperglycemia with exogenous glucose infusions because of a decreased hepatic responsiveness to insulin and a greater metabolic clearance rate for insulin (Farrag et al, 1997).

CASE 1: HYPONATREMIA

Ms. G is admitted at 25 weeks' gestation with advanced cervical dilation. She is given two doses of betamethasone and monitored on the antepartum unit. At 26 weeks' gestation she goes into labor and delivers a 750 gram male infant. He is placed on a radiant warmer, covered with a thin plastic wrap, intubated, and transferred to an isolette with 85% relative humidity. The infant has umbilical venous and arterial catheters placed and receives dextrose containing IV fluids at a rate of 120 mL/kg/day. Serum electrolytes show [Na+] 137 mEq/L at 8 hours of life, 133 mEq/L at 16 hours of life, and 131 mEq/L at 24 hours of life. The following morning the infant has made 0.9 mL/kg/hour of urine and at that time, the infant weighs 755 grams.

Exercise 1

Questions

1. Why has this infant developed hyponatremia?
2. What corrective measures should be taken?
3. How much sodium should be administered in the first few days of life?

Answers

1. Serum sodium concentrations are dependent on total body water and total body sodium content. Before the very low birth weight (VLBW) infant begins to diurese (the prediuretic phase), sodium losses are low because the urinary output is diminished (see later) and urine sodium concentrations are low. The range of urine Na losses is 1 to 3 mmol/kg/day (Bidiwala et al, 1988). As a result, the serum sodium concentration is primarily affected by changes in total body water. During the prediuretic phase (first 24–36 hours of life) urine production and urine flow rates are diminished with a range of 0.5–3 mL/kg/hour (Lorenz, 1995). Stool water losses are also low, and insensible water losses account for the majority of water loss. When initiating IV fluids, the clinician must estimate insensible water losses and adjust water administration based on each patient's individual needs. This infant has relatively low urine output with falling serum sodium and a mild increase in body weight (~1%). Most infants will lose weight by day 2 of life, but in this case the infant has gained weight. This infant's water intake has exceeded water losses and he has developed hyponatremia. In addition, with any increase in intravascular volume, sodium excretion will increase secondary to the release of atrial natriuretic peptide.
2. The infant's water intake should be decreased to account for less insensible water losses than anticipated. In this case a 20 mL/kg/day decrease in total fluids would be appropriate.
3. No sodium should be administered, because the newborn infant needs to contract the extracellular fluid space (containing excess sodium) to undergo the physiologic transition to postnatal life.

CASE 1 CONTINUED

The rate of fluid administration is decreased from 120 mL/kg/day to 100 mL/kg/day. The following day the infant's urine flow rate increased to 3.5 mL/kg/hour; the infant now weighs 720 grams. The serum [Na^+] is 138 mEq/L. After discussing the physiologic contraction of the extracellular fluid space in VLBW infants on morning rounds, the pediatric resident asks if there are risks associated with providing excess fluid and interfering with that process. Several randomized controlled trials have examined the risks associated with liberal versus restricted fluid administration in preterm infants early in life. A metaanalysis of these studies showed a significant increase in the incidence of necrotizing enterocolitis and patent ductus arteriosus in infants who received higher IV fluid rates that resulted in little to no weight loss. The groups who received lower fluid intake had greater weight loss without a significant increase in dehydration (Bell and Acarregui, 2014).

CASE 2: HYPERNATREMIA

Ms. Y is seen for a routine visit at her obstetrician at 28 weeks' gestation and is found to have hypertension and preeclampsia. She is admitted to the antepartum unit and receives two doses of betamethasone. She develops severe preeclampsia and delivers a female infant weighing 900 grams at $28^{6}/_{7}$ weeks' gestation. The infant is resuscitated on a radiant warmer under a thin plastic wrap, then placed in an isolette with 80% relative humidity. She is supported with continuous positive airway pressure (CPAP) and has umbilical venous and arterial catheters placed. On the first day of life 10% dextrose and water is administered at a rate of 100 mL/kg/day. The following day the rate of fluid administration is left unchanged at 100 mL/kg/day because the urine output is low and the serum [Na^+] is 132 mEq/L; the infant's weight is unchanged. On day 2 of life, the infant's urine output increases to 5.5 mL/kg/hour and the serum [Na^+] is 147 mEq/L. At this time the infant weighs 820 grams.

Exercise 2

Questions

1. Why has this infant developed hypernatremia?
2. What changes do you anticipate in the infant's fluid and electrolyte status and the infant's weight over the next days? Over the next weeks?
3. What changes should be made in fluid therapy?

Answers

1. This infant has begun to diurese, resulting in increased water and sodium losses. The majority of VLBW infants begin this process between 24 to 48 hours of life. In the early diuretic phase, urinary water losses generally exceed urinary sodium losses, which results in a rise in serum sodium levels. As the diuretic phase continues, there is a significant rise in the glomerular filtration rate and increase in fractional excretion of sodium. The increased fractional excretion of sodium ultimately reduces the serum sodium concentration. Therefore, early in the diuretic phase, free water losses exceed sodium losses and serum [Na] rise (Bidiwala et al, 1988). The infant described in this case has experienced a rapid rise in urine output and an increase in serum sodium levels. She has also lost ~9% of her birth weight in 1 day. Taken together, this is suggestive of early diuresis with free water losses in excess of sodium losses.
2. The diuretic phase has variable duration in VLBW infants, beginning anywhere between 24 to 48 hours of life and lasting through 72 to 96 hours of life (Bidiwala et al, 1988). Over the next few days one might expect the water balance to continue to be negative, but later in the diuretic phase urinary sodium losses will result in a net negative sodium balance (Bidiwala et al, 1988; Lorenz, 1996). After the diuretic phase, infants transition to a homeostatic phase where sodium and water balance are more dependent on sodium and water intake.
3. Serum sodium concentrations should be closely monitored during the diuretic phase. In most instances, after initially rising, serum [Na] will fall because of a marked increase in the fractional excretion of sodium in the diuretic phase. It is usually not necessary to increase the rate of fluid administration unless the serum sodium concentration exceeds 150 mEq/L. The infant's weight, urine output, and serum electrolytes should be monitored closely as fluids will need to be titrated throughout the diuretic phase and likely decreased when the infant enters the homeostatic phase. Sodium intake should be limited until serum [Na] is stable or falling in the diuretic phase.

CASE 3: HYPERKALEMIA

Ms. Z is admitted at 23 weeks' gestation in preterm labor. She progresses rapidly and delivers a 23-week gestation male infant before receiving antenatal corticosteroids. The 500-gram infant is resuscitated on a radiant warmer under a thin plastic wrap, intubated, and then placed in an isolette with 80% relative humidity. Umbilical venous and arterial catheters are placed, and dextrose-containing intravenous fluids are initiated at 140 mL/kg/day. The infant is warm and well perfused and has a mean arterial blood pressure of 25 mm Hg. The urine output over the first 12 hours of life is 1.8 cc/kg/hour. At 8 hours of life the $[K^+]$ rises to 6.9 mmol/L and at 24 hours of life it is 7.8 mmol/L.

Exercise 3

Questions

1. Why is the serum potassium rising?
2. What are this infant's risk factors for nonoliguric hyperkalemia?
3. What is the best treatment for this infant's hyperkalemia?

Answers

1. During the first 1 to 3 days of life, the serum potassium concentration rises in all infants under 1500 grams as potassium shifts from the intracellular space to the extracellular space. In extremely low birth weight infants, the rise in serum potassium values can be excessive. In infants with nonoliguric hyperkalemia, it is associated with a decrease in the activity of erythrocyte Na/K/ATPase and a lower glomerular filtration rate (Stefano et al, 1993; Gruskay et al, 1988). This physiologic abnormality is labeled nonoliguric hyperkalemia, because the serum [K] rises but urine output remains normal.
2. This infant's extreme prematurity and lack of prenatal corticosteroids are major risk factors for nonoliguric hyperkalemia. The amount of potassium that shifts from the intracellular to the extracellular space is inversely proportional to the gestational age of the infant. Studies performed before the routine use of prenatal corticosteroids suggested that 30% to 50% of infants weighing less than 1000 grams or born before 28 weeks' gestational age experience nonoliguric hyperkalemia (Omar et al, 2000).
3. Treatment of hyperkalemia is essential, because hyperkalemia with cardiac arrhythmia can be fatal. One goal of therapy is to shift potassium into the intracellular space with insulin and glucose and/or albuterol. Treatment to facilitate potassium excretion with ion resins (Kayexalate) has also been used, but it is much less effective and has significant risks (see later). Therapy can also be aimed at mitigating the arrhythmogenic effects of hyperkalemia using intravenous calcium. There have been very few randomized controlled trials assessing treatment strategies for nonoliguric hyperkalemia. There is evidence for the use of insulin and glucose preferentially over the use of rectal cation resin (Kayexalate) in decreasing the duration of hyperkalemia (Malone, 1991; Yassen et al, 2008). Moreover, hypernatremia (Filippi et al, 2004), intraventricular hemorrhage, necrotizing enterocolitis (Rugulotto et al, 2007), and bowel impaction with perforation (Bennett et al, 1996) have also been reported with the use of cation exchange resins. Therefore the use of cation exchange resins is no longer recommended for treatment of hyperkalemia. The addition of albuterol inhalation decreases serum potassium more rapidly than

glucose and insulin treatment alone (Singh et al, 2002). Both treatments appear to be safe and without significant side effects, but the number of patients studied in these trials is small (Vegmal and Ohlsson, 2012). A reasonable approach would be to start with inhaled albuterol while initiating insulin and glucose infusions. Serum dextrose concentrations must be monitored closely while titrating the rate of insulin infusion.

CASE 4: INSENSIBLE WATER LOSS

Ms. Z is admitted at 25 weeks' gestation with preterm premature rupture of membranes. She receives two doses of betamethasone and delivers a 25 weeks' gestation female infant by a spontaneous vaginal delivery. The infant emerges limp, apneic, and cyanotic and is resuscitated on a radiant warmer using chest compressions and intubation. An umbilical venous line is placed, and the infant is placed in an isolette with 40% relative humidity. Mechanical ventilation is continued with heated, humidified air. Intravenous fluids containing 10% dextrose and water are begun at a rate of 120 mL/kg/day. The infant's birth weight is 650 grams. Urine output over the first 24 hours of life is 0.5 cc/kg/hour; 10 hours later, the infant weighs 615 g. The serum sodium concentration rises from 136 mEq/L to 146 mEq/L 24 at hours of life.

Exercise 4

Questions

1. Why is this infant's serum sodium concentration rising?
2. What are this infant's risk factors for relatively high insensible water losses?
3. Calculate the sensible and insensible water losses for this child.
4. What are some strategies available to decrease insensible water losses?

Answers

1. This infant is still in the prediuretic phase. Therefore increased excretion of free water in the diuretic phase is not a logical explanation for the rise in serum sodium. The serum sodium concentration is rising because of high insensible water losses.
2. There are many variables that affect insensible water loss, including gestational age of the infant, postnatal age, relative humidity of the isolette, humidity of inhaled gas, and the ambient temperature of the environment. Insensible water loss in the form of transepidermal water loss is higher in infants born at earlier gestation, and is highest in the early postnatal period, on day of life 1 to 2 (Table 3.5). This infant is 25 weeks' gestation on day of life 1, putting it at high risk of increased transepidermal water losses (Agren et al, 1998). She had a prolonged resuscitation in an open top isolette and then was placed in an isolette with 40% relative humidity, increasing the risk of high transepidermal water losses due to a low ambient humidity. This should be taken into consideration when initiating intravenous fluids.

TABLE 3.5 Transepidermal Water Loss as a Function of Gestational and Postnatal Age

Gestational Age (Weeks)	Birth Weight (Kg)	Insensible Water Loss[a] by Postnatal Age <1, 3, 7, 14, 21, 28
25–27	0.860	128, 71 , 43, 32, 28, 24
28–30	1.340	42, 32, 24, 18, 15, 15
31–36	2.110	12, 12, 12, 9, 8, 7
37–41	3.600	7, 6, 6, 6, 6, 7

[a]cc/kg/24 hrs.: Measurements made at 50 % relative humidity
From Lorenz JM: Maintenance fluid requirements. In Polin RA, Spitzer A, editors: *Fetal and neonatal secrets,* 2nd ed, Philadelphia, 2007, Hanley & Belfus, pp 154–190. From data from Hammarlund K, Sedin G, Strömberg B: Transepidermal water loss in newborn infants VIII. Relation to gestational age and postnatal age in appropriate and small for gestational age infants, *Acta Paediatr Scand* 72:721–728, 1983.

3. Water is lost through sensible water loss (in the form or urine and stool) and insensible loss (in the form of evaporative water loss from the skin and lungs). Stool water loss is minimal when infants are receiving nothing by mouth, and very low birth weight infants cannot sweat. Therefore sensible water loss can be approximated based on urinary output. This infant's urine output is 0.5 mL/kg/hour; therefore sensible water loss is 8 mL. If one knows the total fluid intake, urine output, and change in weight of an infant in a given interval, one can estimate insensible water loss using the following equation:
   Insensible water loss = intake − output − change in weight.
   In this case the infant received 120 mL/kg/day intake and made 8 mL of urine over 24 hours. The infant's weight changed by 35 g. Insensible water loss = 77 mL/kg/day.
4. Several steps can be taken to minimize insensible water losses. Minimizing transepidermal water loss will have a large impact on insensible water loss. High ambient humidity results in a lower transepidermal water vapor pressure gradient decreasing evaporative water loss. Resuscitating infants under a thin plastic wrap increases the ambient humidity surrounding the infant. Caring for infants in high ambient humidity after resuscitation is also essential. Isolette humidity can be set as high as 90%, which reduces transepidermal water loss to 10% of that of transepidermal water loss in isolettes with 50% relative humidity (Agren et al, 1998; Hammarlund et al, 1983). Relative humidity within the isolette should be gradually decreased in the first week of life to allow the skin to mature. Antenatal steroids have been shown to decrease insensible water losses. Inhaling humidified gas will also decrease insensible water loss through the respiratory tract because respiratory water losses account for about 25% of insensible water losses.

CASE 5: ASSESSMENT OF RENAL FUNCTION

A 1000 gram, growth-restricted, female infant is born following a 32 weeks' gestation via a spontaneous vaginal delivery.

The mother received two doses of betamethasone and tocolysis with indomethacin so that antenatal steroids could be administered. The delivery was complicated by maternal fever and chorioamnionitis. The infant is now 1 day old and being managed with CPAP in a humidified isolette. Total parenteral nutrition containing 2.5 grams/kg of amino acids is administered at 120 mL/kg/day, and trophic enteral feeds are initiated. She is receiving ampicillin and gentamicin out of a concern for early onset sepsis. On the day of birth, the infant's serum creatinine was 1 mg/dL. At 24 hours of age, the serum chemistry panel shows [Na^+] of 139 mEq/L, [K^+] of 4.4 mEq/L, BUN of 22, and creatinine of 1.1 mg/dL. The infant is making 1 mL/kg/hour of urine.

Exercise 5

Questions

1. Does this infant have impaired kidney function?
2. What are the risk factors for neonatal kidney injury?
3. What would you expect to happen to the serum creatinine over the next few days? Weeks?
4. What other markers are available to assess kidney function and kidney injury?

Answers

1. In children and adults, kidney function is assessed by measuring serum creatinine. Impaired kidney function has traditionally been defined as elevated serum creatinine and nitrogenous waste (blood urea nitrogen). However, interpreting serum creatinine levels is particularly challenging in the newborn. In the immediate period after birth, serum creatinine reflects maternal creatinine (Lao et al, 1989). Additionally, filtered creatinine can be reabsorbed in the proximal tubules. In ELBW infants, therefore, serum creatinine levels will increase postnatally, leading to an underestimation of renal function (Guignard and Drukker, 1999). Once maternal creatinine has been cleared, creatinine in the newborn is determined by his or her muscle because it is a degradation product of muscle creatine and phosphocreatine. Muscle mass varies by gender, gestational age, and size of the infant. In the days following birth, term infants have a rapid rise in the glomerular filtration rate, creatinine clearance increases, and serum creatinine values fall. In preterm infants, glomerular filtration increases at a slower rate because preterm infants have reduced numbers of functioning glomeruli and, therefore, fewer filtering units (Cain et al, 2010). In the smallest premature babies, serum creatinine concentrations rise in the first days after birth and then fall over several weeks until reaching equilibrium (Fig. 3.4). The degree of initial rise in creatinine and the time it takes to reach equilibrium are dependent on gestational age, with the most preterm infants having more significant increases in serum creatinine and longer times to reach equilibrium (Bateman et al, 2015). In this case the baby had a slight increase in serum creatinine over the first day of life. This is likely normal, but this value needs to be followed over days to weeks to ensure an appropriate decrease in serum creatinine.
2. Nephrotoxic medication exposure is a known risk factor for kidney injury. In this case the fetus was exposed to indomethacin and the newborn infant was exposed to gentamicin, both of which are nephrotoxic. Preterm birth and low birth weight are also risk factors for kidney injury, likely due to decreased nephron endowment associated both with prematurity and intrauterine growth restriction (Selewski et al, 2015).
3. The clinician would expect this infant's serum creatinine to fall over the next few days, reaching equilibrium by 5 to 6 weeks after birth (Bateman et al, 2015).
4. There are several promising biomarkers of kidney function and injury that may be useful in the neonatal population. Serum cystatin C is a low molecular weight protein that is filtered by glomeruli and metabolized by renal tubules. It is produced by all nucleated cells and therefore is not dependent on muscle mass. Urinary cystatin C is elevated in preterm infants with acute kidney injury, and levels increase up to 24 hours before changes in creatinine, making it a promising biomarker for kidney injury in preterm babies (Hanna et al, 2016). Studies using a combination of serum cystatin C and creatinine have shown its utility in more precisely assessing renal function in late preterm babies born between 31 and 37 weeks' gestation (Abitbol et al, 2014). Urine neutrophil gelatinase-associated lipocalin (NGAL) is a biomarker of tubuloepithelial injury and has been studied in infants with congenital heart disease undergoing cardiac repair as an early marker of kidney injury. Urinary NGAL can be detected in preterm infants, and it is elevated in preterm infants with acute kidney injury (Hanna et al, 2016). But it also correlates with the infant's inflammatory status, making it difficult to interpret as a sole marker of kidney injury (Suchojad et al, 2015).

CASE 6: BPD, DIURETICS, AND ELECTROLYTE DISTURBANCES

A former 25 week infant is now 37 weeks corrected gestational age. He was intubated immediately after birth and remains on intermittent positive pressure ventilation with a peak inspiratory pressure of 30 mm Hg, a PEEP of 5 mm Hg, a ventilator rate of 25 breaths per minute, and an oxygen requirement of 25%. He has been on diuretic therapy with enteral furosemide for the last 3 weeks. Electrolytes are obtained and his [Na^+] is 130 mEq/L, [K^+] is 3.2 mEq/L, and serum chloride is 88 mEq/L.

Exercise 6

Questions

1. What is the etiology of these electrolyte abnormalities?
2. What electrolyte abnormalities can be seen with chronic furosemide use?
3. What therapy is indicated?
4. What are the risks associated with furosemide use in this patient population?

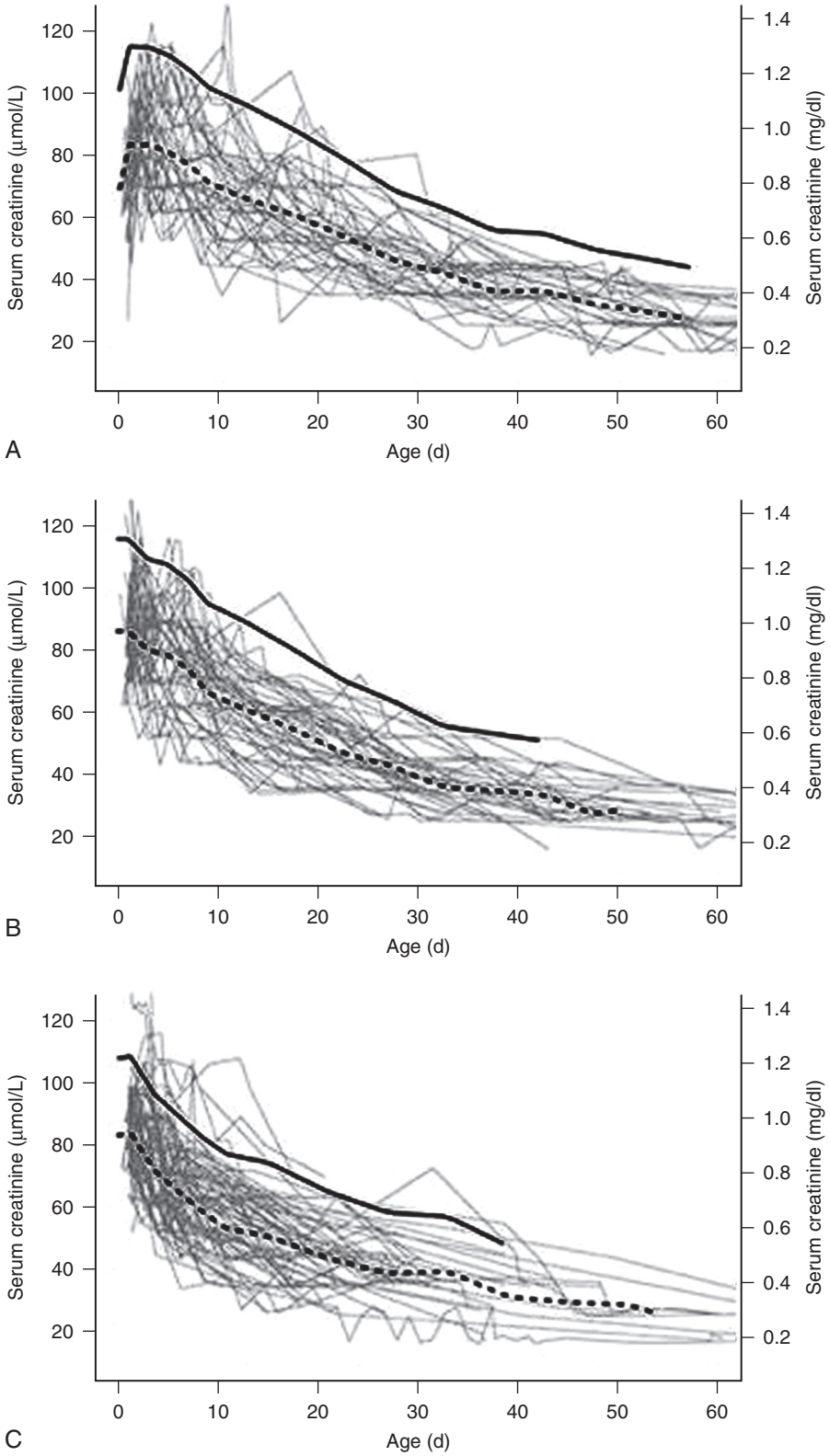

Fig. 3.4 Change in plasma [Creat] in preterm infants without risk factors for acute renal failure over the first 10 days of life as a function of gestational age. (From Bateman DA, Thomas W, Parravicini E, et al: Serum creatinine concentration in very-low-birth-weight infants from birth to 34–36 wk postmenstrual age, *Pediatric Research* 77:696–702, 2015.)

Answers

1. Most of these electrolyte disturbances are due to furosemide. Furosemide is a potent diuretic that acts to inhibit the sodium potassium 2 chloride (NaK2Cl) cotransporter in the thick ascending loop of Henle. Chronic use of loop diuretics such as furosemide can cause significant electrolyte disturbances such as those seen in this case. Because 25% of sodium is reabsorbed in the thick ascending loop of Henle by the NaK2Cl transporter and the capacity of the distal nephron to reabsorb sodium is relatively limited, patients on loop diuretics can have substantial urinary sodium losses with resultant hyponatremia. Chloride reabsorption is also inhibited by furosemide, and potassium secretion is stimulated by increased water and sodium delivery in the distal nephron with resultant hypochloremia and hypokalemia. Increased delivery of sodium and chloride to distal parts of the nephron results in increased tubular secretion of hydrogen causing metabolic alkalosis, which can worsen the metabolic alkalosis resulting from hypochloremia and hyperkalemia. Under normal circumstances the lumen of the loop of Henle is positively charged and this creates an electrical gradient for the reabsorption of calcium and magnesium. This gradient is reduced with inhibition of the NaK2Cl transporter; therefore, there is decreased calcium and magnesium reabsorption, causing hypocalcemia and hypomagnesemia (Ramanathan, 2008).
2. Increased urinary losses of sodium, potassium, and chloride led to hyponatremia, hypokalemia, and hypochloremia in this patient. KCl supplementation should be initiated. Particular attention must be paid to potassium, as it is primarily located intracellularly. Therefore, serum potassium levels are late indicators of total body potassium stores. Primary treatment of the metabolic alkalosis is rarely indicated, because metabolic alkalosis will resolve as hypochloremia and hypokalemia are corrected. Reduction of free water intake or reduction of the furosemide dosing frequency is necessary depending on whether total body sodium is appropriate. However, assessing the appropriateness of total body sodium content is very difficult, requiring a trial and error approach. If hyponatremia is severe, supplementation with sodium may be indicated until serum sodium returns to a safer level.
3. As mentioned earlier, furosemide results in increased urinary calcium losses, which in some cases can cause nephrocalcinosis (Gimpel et al, 2010). Furosemide is also a risk factor for sensorineural hearing loss in premature babies, particularly when used in conjunction with aminoglycosides (Borradori et al, 1997).
   - Fluid and electrolyte disturbance are commonly noted in preterm infants.
   - An understanding of the physiology underlying perinatal fluid homeostasis will help to ameliorate marked changes in body composition.

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Abstract: Fluid and electrolyte management is a challenging and essential part of the care of premature or critically ill newborns. Inappropriate fluid and electrolyte administration can increase neonatal morbidities. An improved understanding of perinatal renal physiology allows for better clinical care. The following principles of fluid and electrolyte management are key. All preterm infants are born with an expanded extracellular fluid space that contracts as infants diurese postnatally. No sodium or potassium should be provided in the first days of life in preterm infants with respiratory distress syndrome. Insensible water losses are greatly increased in preterm infants and are inversely correlated with gestation age. Serum electrolytes must be monitored closely as preterm infants undergo the physiologic transition to postnatal life.

Keywords: Fluids, Electrolytes, Kidneys, Diuresis, Natriuresis, Insensible losses

4

Glucose Metabolism

David H. Adamkin

INTRODUCTION

Cornblath and Reisner established nearly 60 years ago that neonatal hypoglycemia was a significant cause of neonatal morbidity and mortality, yet the definition and management of neonatal hypoglycemia have remained unclear. The management of low blood glucose levels is one of the most frequently encountered issues in the newborn nursery. The blood levels of glucose upon which we base our decision making remain a matter of expert opinion rather than being evidence based. The truth is the data needed to establish blood glucose levels that should be treated in the newborn have not been definitive enough to gain consensus.

In fact, the lack of consensus has led to further confusion for the clinician, as two pediatric organizations, the Committee of the Fetus and Newborn of the American Academy of Pediatrics (COFN AAP) and the Pediatric Endocrine Society (PES) have provided expert opinion on the management of neonatal hypoglycemia that suggested different ranges of actionable blood glucose levels (Figs. 4.1, 4.2).

We will examine the controversies and discuss screening and management of neonatal hypoglycemia. An understanding of transitional neonatal hypoglycemia and postnatal glucose homeostasis is essential to develop strategies to keep infants out of the NICU because of hypoglycemia while still preventing neurologic sequelae.

CASE 1

A 34-year-old primigravida after an uncomplicated pregnancy is admitted in labor at 36 weeks' gestation. The perinatal screening tests are negative, including a negative screen for group B *Streptococcus* (GBS) at 35 weeks' gestation. Membranes rupture occurred 2 hours before vaginal delivery. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. The male infant weighs 2700 grams. The mother has planned to exclusively breastfeed the baby, and she begins in the delivery room with what is described as a "sluggish" first feed. Shortly thereafter, mother and baby are transferred to a postpartum room.

Before the baby being breastfed at 4 hours of age, the nurse on a routine assessment thinks the baby has slight tremors and she performs a point-of-care (POC) glucose level and it is 36 mg/dL. Apparently, the infant looks well enough to breastfeed because the nurse advises the mother to feed again. The nurse also suggests that after this breastfeeding the mother should supplement the infant with 1 oz of a term infant formula. She tells the mother that she will check the glucose again 1 hour after the formula feed to make sure the baby is no longer hypoglycemic. The mother is very disappointed that she will have to abandon her plan to exclusively breastfeed and wonders if it is absolutely necessary to give the formula. The follow-up POC glucose level is 52 mg/dL 1 hour after the formula feeding supplement, and the nurse's note does not document any further tremors.

The nurse calls you at home and discusses the findings and tells you that the mother is disappointed about having to give formula supplement to her baby. You have your smartphone with you and you pull up the Glucose APP, "Sugar Wheel" (Fig. 4.1) based on the algorithm from the Clinical Report—Postnatal Glucose Homeostasis in Late-Preterm and Term Infants published in *Pediatrics* in March 2011 from the American Academy of Pediatrics (AAP) Committee on Fetus and Newborn (COFN) (Fig. 4.2).

Exercise 1

Questions

1. Should this late preterm infant have been screened sooner than age 4 hours?
2. Is this infant symptomatic, and does the infant's glucose level (<40 mg/dL) require an immediate intervention?
3. Should a plasma glucose concentration have been sent to the laboratory at the same time as the POC glucose in this baby?
4. Should the infant simply have been left to continue breastfeeding, and are there other options?
5. Do infants who are exclusively breastfed have lower plasma glucose concentrations than those fed infant formulas?

Answers

1. Yes, this baby met high-risk criteria for neonatal hypoglycemia and should have been screened sooner because the baby was late preterm.
2. Yes, the tremors could be symptoms of hypoglycemia. Because symptoms of neonatal hypoglycemia are nonspecific, they often occur in newborns who are

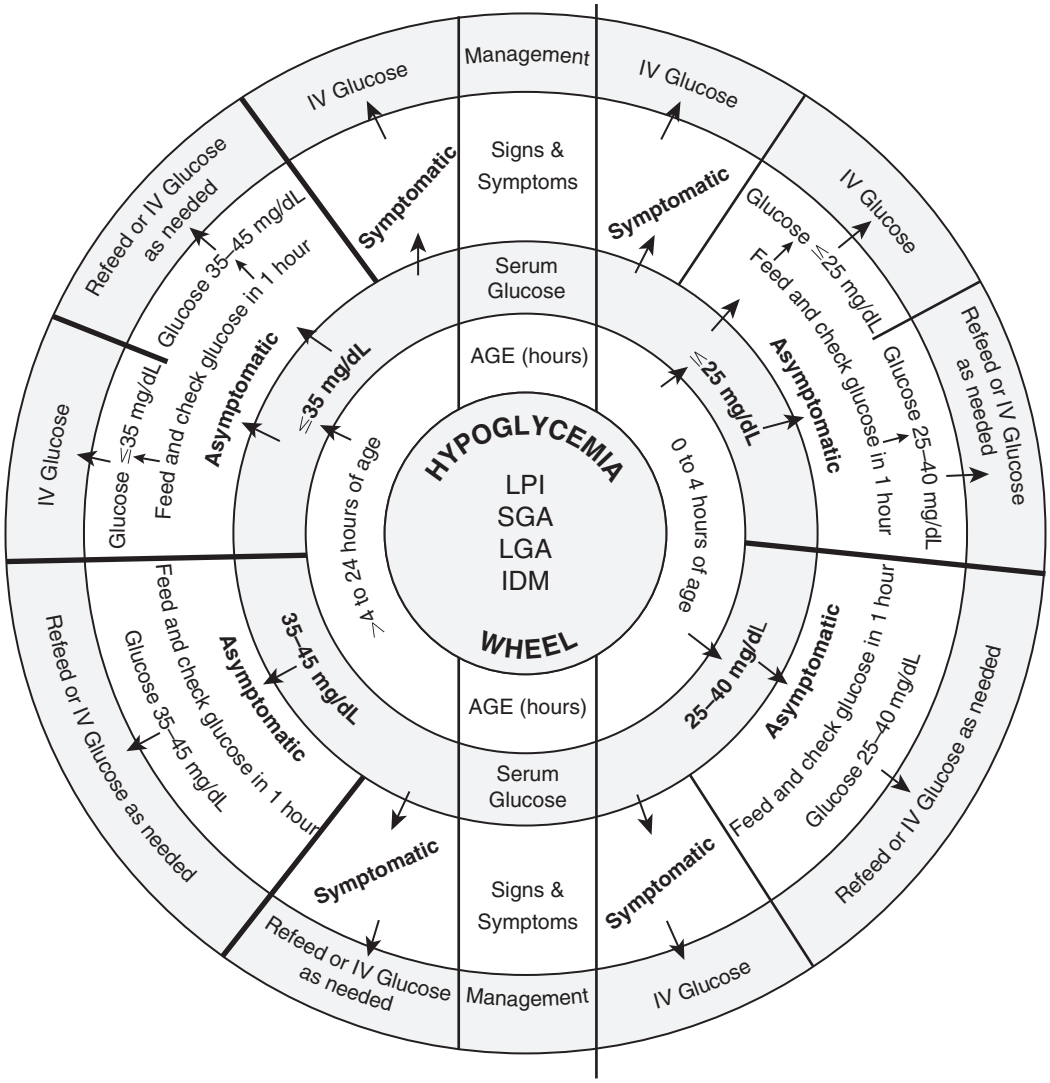

Fig. 4.1 Sugar Wheel nomogram for postanatal glucose homeostasis.

normoglycemic and have other problems. Jitteriness is just as likely among normoglycemic infants and those with a variety of other conditions. In addition, equally low blood glucose values are found in infants with no clinical signs ("asymptomatic hypoglycemia"). Therefore the presence or absence of symptoms cannot necessarily be used to discriminate between normal and abnormal blood glucose levels.

3. If symptoms are suspected and POC level is under 40 mg/dL, an immediate plasma glucose should be sent to the laboratory.
4. Yes, it is possible to have just continued the breastfeeding, because the symptoms were very mild and were actually associated with acceptable glucose levels. Other strategies might have included use of dextrose gel or donor human milk.
5. Breastfed infants may have lower plasma glucose levels than formula-fed infants.

After birth, the normal newborn infant's plasma glucose concentration falls below levels that were prevalent in fetal life. This is part of the normal transition to an extrauterine existence, and through a series of triggers, the infant activates endocrine and metabolic events associated with successful adaptation. When this adaptation fails, perhaps secondary to immaturity or illness, there is a limitation of substrate supply, which may disturb cerebral function and potentially result in neurologic sequelae. A low plasma glucose may be indicative of this process but is not per se diagnostic. What is meant by "low"? How low is "too low"? At what glucose level does hypoglycemia lead to irreversible changes in brain structure or function?

CASE 2

A term, appropriate for gestational age (AGA) male was born by elective cesarean section after an uneventful pregnancy to

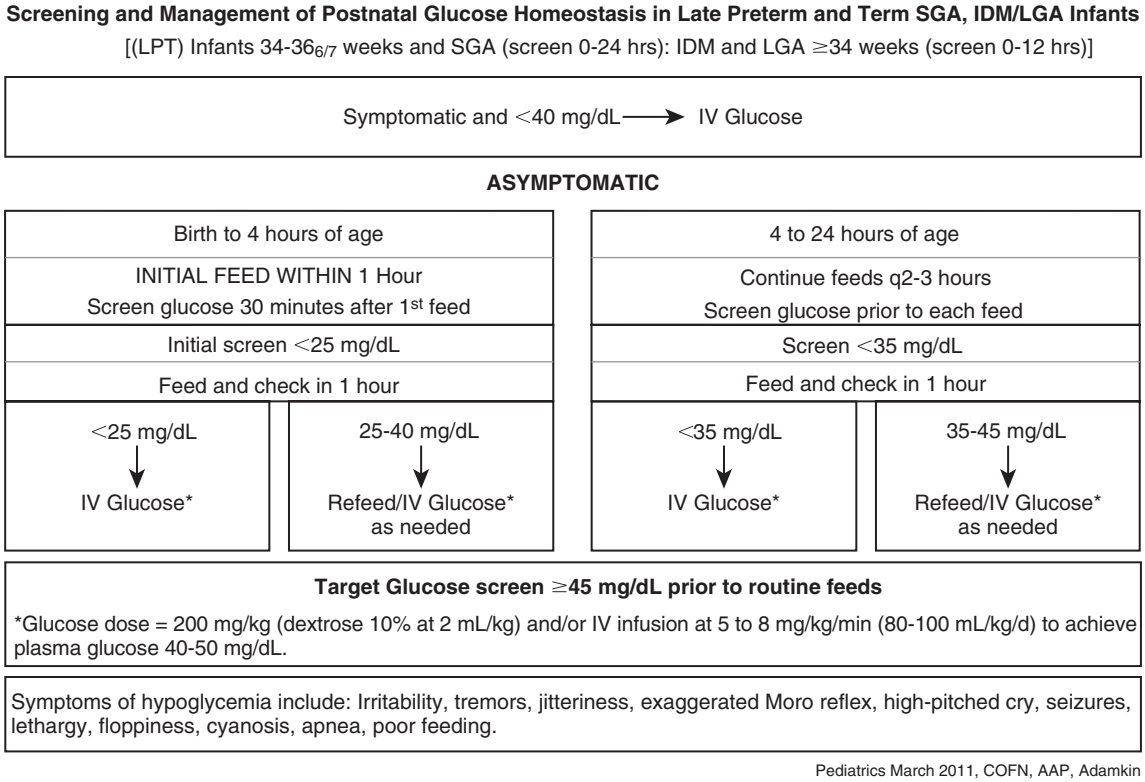

Fig. 4.2 Screening and management of postnatal glucose homeostasis from the AAP Committee on Fetus and Newborn. (From Adamkin DH: Postnatal glucose homeostasis in late-preterm and term infants, *Pediatrics* 127[2]: 576, 2011).

a 30-year-old gravida 3 para 2 woman. Prenatal screening studies were normal, and Apgar scores were 6, 7, and 8 at 1, 5, and 10 minutes respectively. The baby seemed to have "wet lungs" in the delivery room and briefly received blow-by oxygen. By 3 minutes of age, oxygen saturations values were normal, and the respiratory distress resolved. On admission to the well-baby nursery at 30 minutes of age, this well-appearing infant had a POC glucose done apparently because of the cyanosis in the delivery room, and it was 27 mg/dL. A plasma glucose was then sent off ,and it was 29 mg/dL. The infant was fed formula at 1.5 hours of age, and the repeat POC at 2 hours of age was 39 mg/dL.

Exercise 2

Questions

1. Was this baby's initial POC screen necessary?
2. When should screening for hypoglycemia take place, and was this infant's screen obtained at the physiologic nadir for plasma glucose values?

Answers

1. The initial screen was not necessary, as this baby was asymptomatic and had not yet been fed.
2. In high-risk populations, screening for hypoglycemia should take place after the first feed. Yes, this sample taken within the first hour of life would represent the physiologic nadir for plasma glucose values.

POSTNATAL GLUCOSE HOMEOSTASIS AND TRANSITIONAL NEONATAL HYPOGLYCEMIA

Maintenance of glucose homeostasis via initiation of glucose production is one of the critical transitional physiologic events that must take place as the fetus adapts to extrauterine life. It is not uncommon for the transition to be difficult and result in an alteration in glucose homeostasis and an infant with a low plasma glucose level.

The fetus depends on maternal supply and the placental transfer of glucose, amino acids, free fatty acids, ketones, and glycerol for its energy supply. The normal lower limit of fetal glucose concentration is approximately 54 mg/dL (3 mmol/L) over most of gestation. Fetal glucose production does not take place under normal conditions.

The ratio of insulin to glucagon in the fetal circulation plays a critical role in regulating the balance between glucose consumption versus energy stored. The high fetal ratio results in activation of glycogen synthesis and suppression of glycogenolysis through the regulation of hepatic enzymes used for these pathways (Fig. 4.3). Therefore in the fetus glycogen synthesis is enhanced and glycogenolysis is minimized. There is a rapid increase in hepatic glycogen during the last 30% of

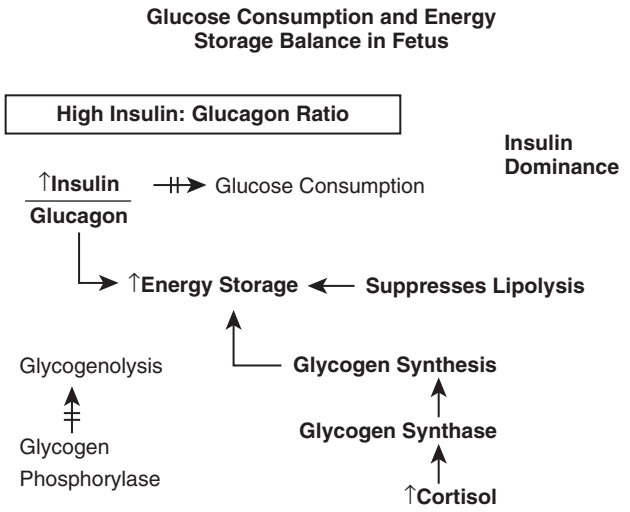

Fig. 4.3 Fetal maintenance of anabolic state promoting energy storage.

fetal life. This marked increase is associated with an increase in both circulating insulin and cortisol. The high insulin/glucagon ratio also suppresses lipolysis, which allows for energy to be stored as subcutaneous fat. This subcutaneous and hepatic reservoir establishes a ready substrate supply for the fetus to transition metabolically and establish postnatal glucose homeostasis (Fig. 4.3).

The dependence of the fetus on maternal glucose necessitates significant changes in regulation of glucose metabolism at birth following the abrupt cessation of umbilical glucose delivery. A number of physiologic changes allow the newborn to maintain glucose homeostasis (Fig. 4.4). Catecholamine concentrations increase immediately after delivery, and this stimulates glucagon secretion. Therefore the insulin/glucagon ratio falls postnatally. This ratio is important because it drives events both in utero and during the postnatal adaptation to a decreasing glucose supply.

When glycogen synthase is inactivated and glycogen phosphorylase is activated following birth, this leads to stimulation of glycogenolysis and inhibition of glycogen synthesis, which is the exact opposite of the in utero fetal milieu. The release of glucose from glycogen provides a rapidly available source of glucose for the neonate the first few hours after delivery. The estimates are that for the term infant the hepatic glycogen supplies enough glucose for the first 10 hours. It is very important that other mechanisms eventually come into play to maintain glucose homeostasis (Fig. 4.4).

The next important pathway for postnatal glucose homeostasis is gluconeogenesis. The high insulin/glucagon ratio after delivery induces enzymes required for gluconeogenesis. Free fatty acids are released secondary to surging catecholamines, which also increase glycerol and amino acid levels. By 4 to 6 hours of life, the term infant is capable of significant gluconeogenesis.

Until an exogenous supply of glucose is provided, either enterally or intravenously, hepatic glucose production is the most significant source of glucose to meet the needs of the infant. To maintain normal levels of hepatic glucose production, the infant must have the following:

- Adequate stores of glycogen and gluconeogenic precursors (fatty acids, glycerol, amino acids, and lactate)
- Concentrations of hepatic enzymes necessary for glycogenesis and gluconeogenesis
- Normally functioning endocrine system (counterregulatory hormones, human growth hormone [HGH], and cortisol)

If any of these systems are not in place, then there is a disruption of glucose homeostasis, which increases the chances for neonatal hypoglycemia.

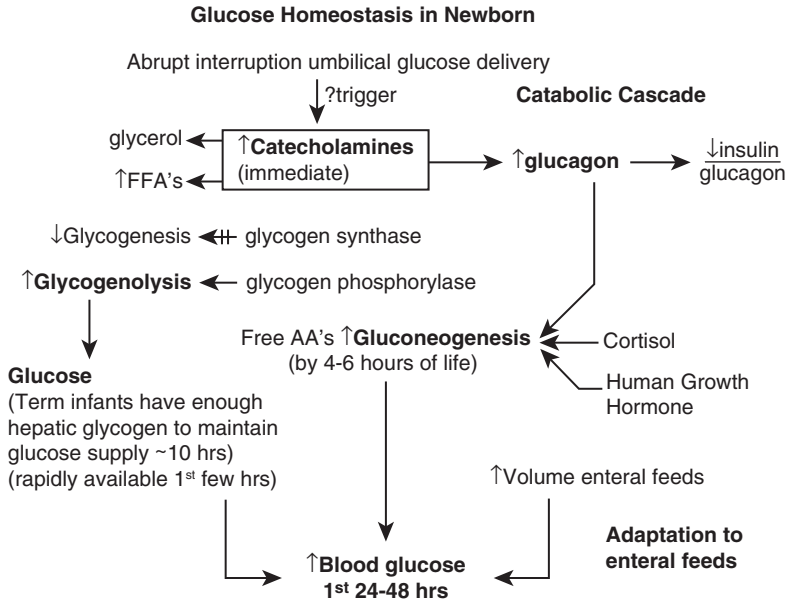

Fig. 4.4 Adaptations around delivery and over the first 24 hours of life to establish postnatal glucose homeostasis.

It has long been thought that preterm infants during the first 3 days of life had lower glucose values than term infants and they tolerated these lower levels better. This misconception came from the observation of lower plasma glucose levels in preterm infants who were commonly starved the first few days of life. These low values are no longer observed in preterm infants because of early intravenous nutrition and/or enteral feedings. However, within the first few hours after birth, the preterm infant has a significantly greater fall in glucose levels than in term infants, suggesting that they are less able to adapt to the cessation of intrauterine nutrition. Gluconeogenic ability is limited in preterm infants, possibly because of immaturity of the enzymatic pathways.

AAP RECOMMENDATIONS FOR SCREENING AND MANAGEMENT

The physiologic responses described earlier were used by the AAP to determine the ranges for action and considered the rising levels for the asymptomatic infant from birth to 4 hours of age (transition), and then 4 to 24 hours of age (Fig. 4.2). The AAP chose to name the figure Screening and Management of Postnatal Glucose Homeostasis rather than using the word hypoglycemia in the title. It seemed more logical to address the adaptation rather than to recommend absolute glucose levels needing treatment.

The AAP view of postnatal glucose homeostasis is that the infant's blood glucose concentration is about 70% of the maternal level at birth and falls rapidly to a nadir by 1 hour of age as low at 20 to 25 mg/dL (Fig. 4.5, 4.6). This nadir is prevalent in healthy neonates and seen in all mammalian newborns. These levels are transient and begin to rise over the first hours and days of life. This observation is considered part of the normal adaptation for postnatal life that helps establish postnatal glucose homeostasis. Are there advantages to having a lower blood glucose concentration compared with adults the first 48 hours? A decrease in glucose concentration soon after birth might stimulate physiologic processes that are required for survival, including promoting glucose production through gluconeogenesis and glycogenolysis. Furthermore, the decrease in glucose concentration enhances oxidative fat metabolism, stimulates appetite, and may help adapt to fast-feed cycles.

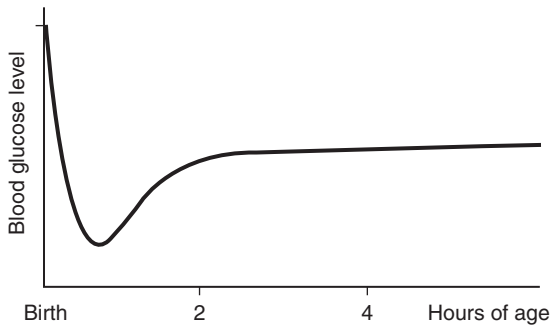

Fig. 4.5 Blood glucose concentration transition from fetus to neonate over the first hours of life. (From Srinivasan G, Pildes RS, Cattaman G: Plasma glucose values in normal neonates: a new look, *J Pediatr* 109[1]:114–117, 1986.)

The AAP guideline during the first hours of transition uses the lower ranges of glucose values, not the mean values from fetal and neonatal data (Fig. 4.6). It also emphasizes the clinical examination and condition of the infant. The AAP also investigated whether there was any reliable level of neuroglycopenia (the critical threshold of plasma glucose where brain injury occurs). No absolute level has been identified.

PEDIATRIC ENDOCRINE SOCIETY RECOMMENDATIONS FOR SCREENING AND MANAGEMENT

Following publication of the AAP recommendations, the PES provided a detailed description of this transitional neonatal hypoglycemia by examining metabolic and hormonal responses at various levels of plasma glucose (Table 4.1). The strategy is routinely used in pediatric endocrinology for evaluation of hypoglycemia in older infants and children. This helps explain differences between the two organizations in their recommendations. The PES focuses on the concentration of glucose at which metabolic counterregulation occurs and that is used to define a "safe" lower limit for blood glucose concentration.

This unique period occurs during the first 48 hours in all mammals, not just human babies. It is characterized by a relative hyperinsulinism (transitional hyperinsulinism), low levels of ketones, inappropriate preservation of glycogen, and mean blood glucose levels at the nadir of 55 to 65 mg/dL. This resembles a known form of congenital hyperinsulinism in which the plasma glucose threshold for suppression of insulin secretion is lowered. This 55 to 65 mg/dL range, which is the mean range at the nadir, turns out to be the same level below which adults and older children demonstrate neurogenic symptoms. Therefore this observation along with the rest of the metabolic profile led the PES to suggest this was the critical range of glucose to maintain in newborn infants the first 48 hours.

The PES further argued that this range is where adults and older children activate neuroendocrine and metabolic mechanisms profiles for brain protection. The endocrine society also recognized that by 72 hours or so of life, glucose levels in the newborn rise to levels similar in older children and adults. Therefore the PES concluded that hyperinsulinemia accompanied by suppressed levels of ketones and inappropriately large glycemic responses to glucagon and epinephrine were consistent with a hypoketotic hyperinsulinemia.

When this transient form of hyperinsulinism ends and the glucose stimulus for insulin secretion matures, plasma glucose levels rise to over 70 mg/dL. Distinguishing transient neonatal hypoglycemia from a suspected persistent hypoglycemic disorder during an infant's first 48 hours is very difficult. The PES thus recommends delaying any diagnostic evaluation until after 2 to 3 days of life to diagnose a *persistent hypoglycemic disorder.*

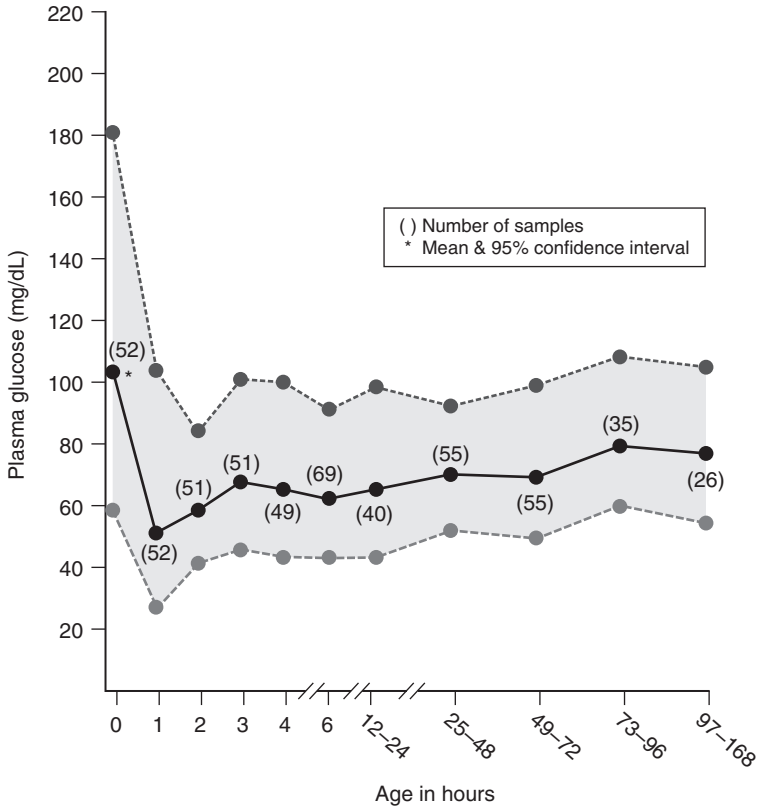

Fig. 4.6 Plasma glucose concentrations in full-term, appropriately grown newborns without any prenatal or neonatal complications. (Adapted from Srinivasan G, Pildes RS, Cattaman G: Plasma glucose values in normal neonates: a new look, *J Pediatr* 109[1]: 115, 1986; and Marconi AM, Bozetti P, Ferraro MM, et al: Relationship of maternal fetal glucose concentrations in the human from midgestation until term, *Metabolism* 37[4]: 358–363, 1988.)

TABLE 4.1 Postnatal Glucose Treatment Targets: PES

High-risk newborns without a suspected congenital hypoglycemia disorder	0–48 h	>50 mg/dL
	>48 h	>60 mg/dL
Neonates with suspected congenital hypoglycemia disorder and those requiring IV glucose to treat hypoglycemia	Any time	>70 mg/dL
The PES Set the above Thresholds Based on the Following Observations about the Impact of Specific Glucose Concentrations in Adults:		
55–65 mg/dL	Brain glucose utilization becomes limited	
50–55 mg/dL	Neurogenic symptoms (palpitations, tremor, anxiety, sweat, hunger, paresthesia) perceived	
<50 mg/dL	Cognitive function impaired (neuroglycopenia, characterized by confusion, seizures, coma)	

IV, Intravenous; *PES,* Pediatric Endocrine Society
Adapted from Stanley C, Rozance P, Thornton MB, et al: Reevaluating transitional neonatal hypoglycemia: mechanism and implications for management, *J Ped* 166:1–6, 2015.

The PES document also noted that the plasma glucose concentrations of normal newborns studied from the 1950s and 1960s (when babies were fasted between 8 and 27 hours) were remarkably stable (mean value was 57 mg/dL) and unaffected by the timing of initial feeding or the interval between feeds. However, this fails to recognize that feedings do affect infants whose glucose concentrations are low, and although this appears to be a regulated process, it is not for those at greatest risk from hypoglycemia.

The fundamental question of how best to manage asymptomatic newborns with low glucose concentrations remains unanswered. Balancing risks of overtreating newborns with

low glucose concentrations who are undergoing normal transition following birth against the risks of undertreating those in whom low glucose concentrations are pathologic, dangerous, and/or a harbinger of serious metabolic disease remains a challenge.

CASE 3

You are called to an emergency delivery for a 21-year-old primigravida woman at term gestation with no prenatal care and evidence of fetal distress. Rupture of membranes occurred 10 hours before delivery and Apgar scores were 6 and 7 at 1 and 5 minutes of life respectively. The male infant is vigorous in the delivery room with scant meconium staining, but the infant is macrosomic. The mother did not know if she had any abnormalities with glucose levels before or during the pregnancy. The baby weighs 4240 grams, and the length and head circumference (HC) are at the 50th percentile on the postnatal growth curves. The infant feeds sluggishly at 1 hour of age. At 6 hours of age, before the next feeding, he appears lethargic and jittery. He is offered a term formula but feeds poorly; the POC glucose level is 10 mg/dL.

Exercise 3

Questions

1. What risk factors does this baby have for postnatal hypoglycemia?
2. When should this baby have been fed?
3. When should first screen for hypoglycemia have been performed?
4. Why is this symptomatic?
5. How should this infant be managed at 6 hours of life?
6. If treated and corrected by hour 48 of life, will the glucose level at 6 hours of life cause brain injury?

Answers

1. This infant is macrosomic with a disproportionately smaller HC and length, so you are concerned about gestational diabetes. Maternal diabetes is a risk factor for both the AAP COFN and PES.
2. This infant was described as vigorous in the delivery room and therefore despite being macrosomic was able to feed within the first hour of life. There was no reason to immediately screen for a low glucose value, because the baby was asymptomatic.
3. The infant should have been screened 30 min after the first feeding, which was described as sluggish.
4. It is very likely this infant is hyperinsulinemic. Moreover, he has only received one small feeding before becoming symptomatic at 6 hours of age when the next feeding was offered.
5. This symptomatic hypoglycemic infant needs immediate attention with intravenous glucose.
6. No, we don't know the likelihood of brain injury except that prolonged and symptomatic hypoglycemia with seizures increases the risk of neurologic impairment (Box 4.1).

BOX 4.1 Conditions That Should Be Present Before Considering That Long-Term Neurologic Impairment Might Be Related to Neonatal Hypoglycemia

1. Blood or plasma glucose concentrations below 1 mmol/L (18 mg/dL). Such values definitely are abnormal, although if transient there is no study in the literature confirming that they lead to permanent neurologic injury.
2. Persistence of such severely low glucose concentrations for prolonged periods (hours, >2–3 hours, rather than minutes, although there is no study in human neonates that defines this period)
3. Early mild-to-moderate clinical signs (primarily those of increased adrenalin [epinephrine] activity), such as alternating central nervous system (CNS) signs of jitteriness/tremulousness versus stupor/lethargy or even brief convulsion, that diminish or disappear with effective treatment that promptly restores the glucose concentration to the statistically normal range (>45 mg/dL)
4. More serious clinical signs that are prolonged (many hours or longer), including coma, seizures, respiratory depression and/or apnea with cyanosis, hypotonia or limpness, high-pitched cry, hypothermia, and poor feeding after initially feeding well; these are more refractory to short-term treatment
5. Concurrence of associated conditions, particularly persistent excessive insulin secretion and hyperinsulinemia with repeated episodes of acute, severe hypoglycemia with seizures and/or coma (although subclinical, often severe, hypoglycemic episodes occur in these conditions and might be just as injurious)

From Rozance P, Hay W: Hypoglycemia in newborn infants: features associated with adverse outcomes, *Biol Neonate* 90:84, 2006.

DEFINITION OF HYPOGLYCEMIA

A consistent definition of hypoglycemia does not exist in the literature or in clinical practice. When the first neonates were recognized as having significant hypoglycemia in the mid-1950s, the infants had striking clinical manifestations, often seizures, and their blood sugar values were consistently below 20 to 25 mg/dL (1.1–1.4 mmol/L). The abnormal signs cleared quickly after increasing the blood glucose concentration to above 40 mg/dL (2.2 mmol/L). Now 60 years later, after 40 mg/dL became the "critical" level for hypoglycemia, our understanding of the metabolic disturbances and genetic defects underlying aberrations in postnatal glucose homeostasis has increased dramatically. However, this increase in knowledge, if anything, has led us further from what we need to know about blood glucose concentrations in the newborn infant. How low is too low?

In a review of current textbooks, there is no consensus definition for hypoglycemia; recommended values range from 18 mg/dL (1 mmol/L) to 70 to 100 mg/dL (3.8–5.5 mmol/L). It is interesting to note that the definition of neonatal hypoglycemia has gone up decade by decade over the last 40 years (Fig. 4.7). The easiest diagnosis of hypoglycemia may be the situation in which the symptoms associated with a low blood

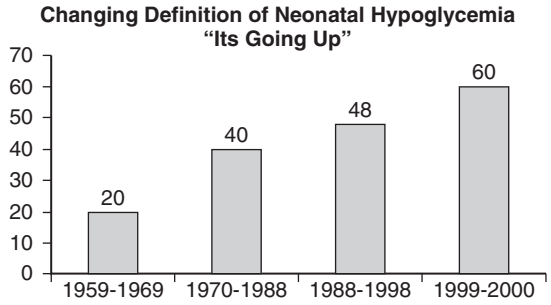

Fig. 4.7 Plasma glucose concentrations considered representing hypoglycemia over the last 40 years.

sugar resolve when the blood sugar concentration is increased. Apart from this clinical situation, the diagnosis of hypoglycemia is much more complex.

OPERATIONAL THRESHOLDS

Hypoglycemia represents an imbalance between glucose supply and utilization and may result from many different regulatory mechanisms (Box 4.2). In 2000 Cornblath proposed an operational definition for neonatal hypoglycemia. An operational threshold is an indication for action but is not diagnostic of a disease. One uses available clinical and experimental data to define the lower level of normoglycemia. The belief is that the neonate can safely tolerate these levels at specific ages and under established conditions.

Cornblath first suggested an operational level for plasma glucose of 30 to 36 mg/dL during the first 24 hours of life for healthy full-term or late preterm (34–37 weeks' gestation) formula-fed infants. If the glucose concentration fell below that operational level after a feeding or recurred, he suggested increasing the plasma glucose levels above 45 mg/dL. This absolutely does not imply that the lower plasma glucose concentrations alone produce mental or developmental abnormalities. He also suggested that the operational threshold might be increased to 45 to 50 mg/dL (2.5–2.8 mmol/L) or higher in a sick, low birth weight, or premature infants suspected of having increased glucose requirements as a result of sepsis, hypoxia, or other major systemic illness.

Finally, he recommended that beyond 24 hours of age, this operational threshold may be increased to 40 to 50 mg/dL. Values below the operational threshold level are an indication to raise the plasma glucose levels and do not imply neuroglycopenia or that neurologic injury is likely. Infants at all ages and gestations with repetitive, reliable plasma glucose values less than 20 to 25 mg/dL should be given parenteral glucose and monitored at regular intervals to ensure that these low values do not persist or recur.

When the low plasma glucose levels are prolonged or recurrent, they may result in acute systemic effects and neurologic sequelae. Cornblath stresses that it is not possible to define a plasma glucose level that requires intervention in every newborn infant because there is uncertainty over the level and duration of hypoglycemia that causes damage, and little is known of the vulnerability of the brain at various gestational ages. He emphasized that significant hypoglycemia is not and can never be defined by a single number that can be applied universally to every individual patient. Rather, it is characterized by a value(s) that is unique to each individual and varies with both their state of physiologic maturity and the influence of pathology. It can be defined as

BOX 4.2 Pathogenesis of Hypoglycemia in Neonates

Excess Utilization	Inadequate Production or Substrate Delivery
Hyperinsulinism: IDM, erythroblastosis, LGA, SGA, or islet cell or other endocrine pathology	Inadequate or delayed feedings or parenteral delivery of calories
Increased calorie expenditure for thermoregulation in LBW and SGA infant	Aberrant hormonal regulation of glucose or lipid metabolism: hypothalamic, pituitary, and peripheral endocrine disorders
Increased calorie expenditure because of excess muscle activity: increased work of breathing in respiratory distress, drug withdrawal, CNS irritability	Transient developmental immaturity of critical metabolic pathways reducing endogenous production of glucose and/or other substrates
Circulatory or respiratory diseases that shift energy metabolism from aerobic to anaerobic pathways: hypoxemia, hypotension, hypoventilation, septic shock	Deficient metabolic reserves of precursors or glucose-sparing substrates
Relative excess of glucose-dependent tissues: high brain:liver ratio in SGA infants	Deficient brain glucose transporters: posthypoxia-ischemia, inherited glucose transporter defects
Inborn errors of metabolism resulting in inadequate glucose-sparing substrates: free fatty acids, ketones, glycerol, amino acids, lactate	Suppression of gluconeogenesis, glycogenolysis, and hepatic glucose release by inappropriately high circulating insulin levels in conditions associated with hyperinsulinism
Acute brain injury causing increased brain glucose utilization: seizures, intoxication, meningitis, encephalitis, or hypermetabolism following acute brain injury (hypoxia-ischemia, trauma, hemorrhage)	

CNS, Central nervous system; *IDM,* infant of diabetic mother; *LBW,* low birth weight; *LGA,* large for gestational age; *SGA,* small for gestational age

From Cornblath M, Ichord R. Hypoglycemia in the neonate, *Semin Perinatol* 24(2):138, 2000.

the concentration of glucose in the blood or plasma at which the individual demonstrates a unique response to the abnormal milieu caused by the inadequate delivery of glucose to a target organ (for example, the brain).

Treatment should be guided by clinical assessment and not by glucose concentration alone. The infant displaying neurologic signs requires more urgent elevation of plasma glucose concentration than the asymptomatic one, regardless of the individual plasma glucose concentration.

The National Institutes of Health conference on Knowledge Gaps and Research Needs for Neonatal Hypoglycemia concluded the following concerning operational thresholds: "The so-called operational thresholds are useful guidelines to take appropriate actions. However, the recommendations are not based on evidence of significant morbidity if no actions are taken. Similarly, there is no evidence that outcomes improve if actions are taken at the operational threshold value. All published definitions providing singular values or ranges have been arbitrary and developed for analytical and grouping purposes."

RESOLVING DIFFERENCES IN THE AAP AND PES RECOMMENDATIONS FOR CRITICAL GLUCOSE THRESHOLDS

Recently the AAP COFN ratified for another 5 years their statement on postnatal glucose homeostasis (Fig. 4.2). Around the same time, a reevaluation of transitional hypoglycemia was published by the PES (Table 4.1). A recent editorial called "Imperfect Advice" contrasts the two organizations' approaches.

The AAP clinical report is not inclusive of all preterm infants, but it focused on late preterm as well as small for gestational age (SGA) and large for gestational age (LGA) term infants and infants of diabetic mothers (IDM) at-risk patients. Of course, symptomatic infants are all screened. Preterm infants under 34 weeks' gestation were not included in the algorithm, based on the assumption that the vast majority of more immature infants would be cared for in the NICU, where routine screening is in place. The PES expanded the list for screening to not only include symptomatic infants and the same risk groups as the AAP document but suggested screening those infants experiencing perinatal stress (birth asphyxia, cesarean section for fetal distress), maternal preeclampsia, meconium aspiration syndrome, prematurity or postmaturity, family history of genetic hypoglycemia, congenital syndromes, or abnormal physical features (Box 4.3). The PES does not offer screening times. Its targets for therapy include under 50 mg/dL the first 48 hours, and when intravenous fluids are required a value of over 60 mg/dL should be achieved. It emphasizes the need for careful attention so that cases of persistent hypoglycemia after 48 to 72 hours are not missed (Box 4.4 and 4.5). A major focus of the PES report was to prioritize strategies to diagnose persistent hypoglycemic syndromes before discharge in at-risk infants.

BOX 4.3 Neonates Who Are at Increased Risk of Hypoglycemia (PES)

1. Neonates with symptomatic hypoglycemia
2. Neonates who had perinatal stress
   - Birth asphyxia/ischemia; cesarean section for fetal distress
   - Maternal preeclampsia/eclampsia or hypertension
   - Intrauterine growth restriction (small for gestational age birth weight)
   - Meconium aspiration syndrome, erythroblastosis fetalis, polycythemia, hypothermia
3. Congenital syndromes (such as Beckwith-Wiedemann), abnormal physical features (such as midline facial malformation, microphallus)
4. Family history of a genetic form of hypoglycemia
5. Large for gestational age birth weight
6. Premature or postmature delivery
7. Infant of diabetic mother

From Thornton PS, Stanley CA, De Leon DD, et al: Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children. *JPeds* 167:(6):238–245,2015.

The AAP guidance only applies to the first 24 hours of life. Actionable ranges of 25 to 40 mg/dL for the first 4 hours of life and then 35 to 45 mg/dL from 4 hours to 24 hours of age are the operational thresholds for the AAP. Glucose levels rise after the first 48 hours of life and should be similar to those of older children by 72 to 96 hours of age.

The AAP recommendation for treatment below the actionable range after feeding is based on individual risk assessment and examination of the infant. Target glucose concentrations when intravenous fluids are required should exceed 45 mg/dL.

What is clear with all recommendations is that the greater the glucose threshold that is set for screening and the more often these tests are done, the more often asymptomatic patients with low glucose levels will be identified. That has the potential to result in a neonatal intensive care admission and separation from mother for an asymptomatic infant and to be a hindrance to successful breast feeding.

PHYSIOLOGIC RESPONSES TO HYPOGLYCEMIA AND BRAIN INJURY

There is no easy way to study glucose insufficiency in human infants as a cause of acute neuronal injury. The glucose concentration is only an indicator of glucose insufficiency; the other factors to consider when determining glucose insufficiency include cerebral blood flow, cerebral glucose utilization rate, and cerebral uptake and metabolism of alternative fuels (see later), as well as the duration of the hypoglycemia and the presence of associated clinical complications. Plasma or blood glucose concentration, however, may be the only practical laboratory measure available to assess glucose insufficiency and response to treatment. A thorough physical examination assessing for signs and symptoms (Box 4.6) of

BOX 4.4 Classification of Persistent Neonatal Hypoglycemia

Hyperinsulinemia
Persistent hyperinsulinemic hypoglycemia of infancy
- Sporadic
- Familial
- Focal beta-cell adenoma
- Hyperammonemic hyperinsulinism

Beckwith-Wiedemann syndrome

Endocrine Disorders
Panhypopituitarism
Growth hormone deficiency
Adrenocorticotropic hormone deficiency
Adrenal insufficiency
Glucagon deficiency
Epinephrine deficiency

Glycogen Storage Disease (GSD)
Glucose-6-phosphatse deficiency (GSD type 1)
Debrancher deficiency (GSD type III)

Disorders of Gluconeogenesis
Fructose 1,6-diphosphatase deficiency
Pyruvate-carboxylase deficiency
Phosphoenol pyruvate-carboxykinase deficiency

Disorders of Fatty Acid Oxidation
Carnitine-acylcarnitine translocase deficiency
Very long-chain acyl-CoA dehydrogenase deficiency
Long-chain acyl-CoA dehydrogenase deficiency
Medium-chain acyl-CoA dehydrogenase deficiency
Multiple acyl-CoA dehydrogenase deficiency

Disorders of Amino Acid and Organic Acid *Metabolism*
Maple syrup urine disease
Propionic academia
Methylmalonicacidemia
Isovalericacidemia
Multiple carboxylase deficiency
3-Hydroxy-3-methylglutaryl CoA lyase deficiency

Mitochondrial Disorders
3-Methylglutaconicaciduria

Glycosylation Disorders
Systemic Disorders
Hepatic failure
Congestive heart failure

CoA, Coenzyme A.
Uhing MR and Kleigman: Glucose, calcium, and magnesium. In Fanaroff AA and Fanaroff JM: *Klaus & Fanaroff's care of the high-risk neonate,* ed 6, 2012, Elsevier, p 295.

BOX 4.5 Neonates in Whom to Exclude Persistent Hypoglycemia Before Discharge

- Neonates with severe hypoglycemia (e.g., an episode of symptomatic hypoglycemia or requiring IV dextrose to treat hypoglycemia
- Neonates unable to consistently maintain preprandial plasma glucose concentrations >50 mg/dL by day 3
- Family history of a genetic form of hypoglycemia
- Congenital syndromes (e.g., midline facial malformations, microphallus)

BOX 4.6 Signs and Symptoms of Hypoglycemia in Newborn Infants

General Findings
Abnormal cry
Poor feeding
Hypothermia
Diaphoresis

Neurologic Signs
Tremors and jitteriness
Hypotonia
Irritability
Lethargy
Seizures

Cardiorespiratory Disturbances
Cyanosis
Pallor
Tachypnea
Apnea
Cardiac arrest

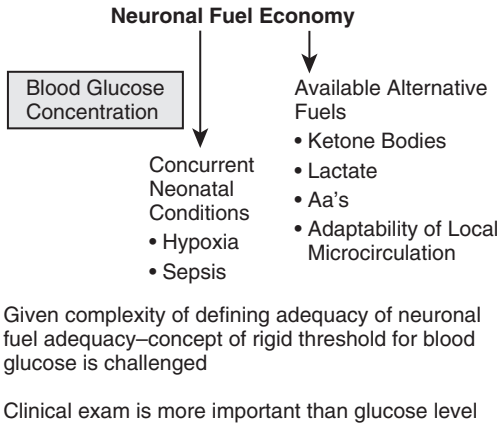

Fig. 4.8 Factors that play a role in energy available for the central nervous system including blood glucose concentrations.

hypoglycemia and particularly neurologic abnormalities may help distinguish those infants with low blood glucose concentrations who are adequately compensating. Fig. 4.8 shows the many factors (neuronal fuel economy) that must be considered in evaluating the infant with a low blood glucose concentration. The clinical examination of the infants is an important part of the approach advocated by the AAP.

Another important neuroprotective response to hypoglycemia is the capacity to accommodate changes in the rate of cerebral glucose metabolism by substituting alternate energy

substrates. The best characterized alternative fuel for the brain during hypoglycemia is lactate. Observations from animal data indicate that lactate entry into the tricarboxylic acid cycle may help compensate for decreased glucose metabolism. Lactate is the product of an astrocyte-neuronal lactate shuttle, which can supply the neurons with lactate for energy during periods of glucose deprivation. Brain glycogen is stored in the astrocyte, which makes this shuttle another important source of neuroprotection.

It appears that the human brain has the capacity to metabolize ketone bodies. Therefore the ability of the neonatal brain to utilize ketone bodies is almost certainly another form of neuroprotection during hypoglycemia. In healthy, term infants, plasma ketone bodies increase to a maximum concentration on days 2 and 3. Additionally, the ketone bodies increase further when the glucose concentration in the blood is low. However, preterm infants do not show similar patterns of ketone response and appear to have a lower capacity to mobilize ketones as an alternative fuel. It is also clear that formula feeding as a clinical intervention for hypoglycemia has a suppressive effect on early ketogenesis.

There are considerable differences in regional susceptibility in the brain to hypoglycemia that contribute to the pattern and distribution of injury, but the reported changes have not been consistent. Some animal and human neonatal imaging studies have indicated vulnerability to hypoglycemia in the occipital region, striatum, cingulate cortex, and hippocampus. However, recent clinical and imaging studies have indicated more diverse cerebral injury in infants with significant clinical symptoms of hypoglycemia. A study including 35 term infants with symptomatic hypoglycemia (86% of infants with a blood glucose <35 mg/dL and seizures) extended the spectrum of magnetic resonance imaging (MRI) abnormalities to the white matter, deep nuclear gray matter, and cortical infarction. Therefore an MRI should be a routine investigation for the newborn infant with symptomatic hypoglycemia to define the nature of any cerebral injury.

It must be emphasized, however, that studies like these relate to infants who sustained severe and prolonged hypoglycemia with encephalopathy. There is currently no imaging evidence that mild hypoglycemia of any duration causes brain injury or that asymptomatic hypoglycemia of any duration causes brain injury.

Identifying Risk Factors for Neonatal Hypoglycemia

The AAP COFN report on the management of hypoglycemia included late preterm (34–36$^{6}/_{7}$ weeks' gestation), infants of diabetic mothers (IDM), and small or large for gestational age term infants (SGA and LGA). It did not recommend against screening other at-risk groups but instead focused on the most likely newborns with asymptomatic hypoglycemia. A paper was published not long after the AAP guideline that prospectively looked at the incidence of hypoglycemia by their definition (plasma glucose concentrations less than 47 mg/dL). About 75% of the patients had measurement through 48 hours of life. Fifty-one percent of the patients had a glucose under 47 mg/dL, and 19% had a glucose level under 36 mg/dL, confirming the decision of the AAP to focus on these patients. This incidence of hypoglycemia was higher than other studies because of the higher numerical level defining hypoglycemia. Thirty seven percent of patients with hypoglycemia in this study had their first episode after three normal screens, and 6% had their first episode after 24 hours. This indicates that hypoglycemia may be a concern for longer periods than older studies suggest and that three normal screens may not be adequate. This study also found that there was no difference in the timing, severity, or incidence of low glucose among the four groups. The problem is the study was not designed to provide evidence that any numerical cutoff for hypoglycemia is more valid than another.

CASE 4

A 37-year-old gravida 4 para 4 woman delivers a 3400 g male infant with Apgar scores of 9 and 9 at 1 and 5 minutes, respectively, after an uncomplicated pregnancy and labor. The mother has breastfed all of her other children successfully and breastfeeds this infant at 45 minutes of age in the delivery room. A bedside glucose is obtained right after the feeding and it is 27 mg/dL.

Exercise 4

Questions

1. Should this infant have been screened for hypoglycemia?
2. Should the screen occur immediately following the feeding?
3. How does glucose homeostasis differ in breastfed and formula-fed infants?
4. If you use the PES recommended levels will it change the actionable levels to treat low glucose levels, and does it address feedings?

Answers

1. This infant does not meet any of the risk categories for screening and management of postnatal glucose homeostasis and, importantly, is not symptomatic.
2. Glucose screens during the first 4 hours of life are taken 30 minutes after feedings. Thereafter, screens precede feedings for optimal management.
3. Breastfed infants are believed to have higher ketone levels than formula-fed infants, the principal alternate metabolic fuel for the brain, thus sparing the need for glucose. The AAP recommends breast milk within the first hour of life and a feeding interval between 2 and 3 hours to promote breastfeeding and maintain glucose levels. The PES noted that the breastfed infant consumes very few calories from colostrum during the first days after birth. However, despite being "relatively fasted, mean glucose values are remarkably stable." Therefore the PES concluded that glucose values are unaffected by feeding.
4. Using mean (PES) glucose values versus lower range (AAP) glucose values guarantees there will be significant differences in interpretation for actionable levels for

asymptomatic infants. Feeding is more important for patients in the lower ranges of plasma glucose and is affected by timing of initial feed and intervals of feeding.

NEURODEVELOPMENTAL OUTCOMES IN INFANTS WITH HYPOGLYCEMIA

As noted earlier, the AAP guideline during the first hours of transition uses the lower ranges of glucose values, not the mean from fetal and neonatal data. It also emphasizes the clinical examination and condition of the infant. The AAP also looked at neurodevelopmental data to determine whether there was any validated level of neuroglycopenia (the critical threshold of plasma glucose where brain injury occurs).

The fundamental question of how best to manage asymptomatic newborns with low glucose concentrations remains unanswered. Balancing risks of overtreating newborns with low glucose concentrations during the normal transition versus the risks of undertreating those in whom low glucose concentrations are pathologic and/or a harbinger of serious metabolic disease remains a challenge.

The neurodevelopmental outcome approach is to find the critical threshold of plasma glucose associated with brain injury or where neuroglycopenia occurs in the newborn. In the adult, this is 50 mg/dL. Neuroglycopenia is the level at which there is an inadequate supply of glucose for the brain. This level is not known for the newborn. The neurodevelopmental approach was profoundly influenced by a multicenter nutrition study from the UK published in 1988. The study evaluated blood glucose levels drawn daily initially then weekly until discharge on 661 infants under 1850 g at birth who were enrolled in a nutrition study looking at early diets and cognitive outcomes. They found that a critical glucose level under 47 mg/dL would reliably predict adverse outcomes. The number of days below this value was strongly related to reduced scores for mental and motor development at 18 months corrected age. Similar but less dramatic differences were found when the children were seen again as part of a larger study when the children were 7 to 8 years old. These findings have profoundly influenced neonatal care across the developed world ever since. This value of 47 mg/dL became a worldwide standard and was applied to term healthy (AGA) neonates as the gold standard critical threshold, even though this study had no term infants in it. The authors themselves suggested in a letter written later that there is "difficulty providing causation when an observational approach is used and that when such observations generate hypotheses or legitimate clinical concerns, this should stimulate future studies and randomized controlled trials."

Almost 25 years later from the UK came a prospective trial including infants under 32 weeks' gestation who had blood glucose levels measured daily for the first 10 days of life. Forty-seven had a blood glucose level under 47 mg/dL on at least 3 days of the first 10 days of life. All were matched for appropriate variables with those who never had a value under 47 mg/dL. No differences were found in developmental progress or physical disability at 2 years of age. Eighty-one percent of the cohort were matched again at 15 years of age, and they were almost identical for full-scale IQ. The inclusion of children who had a level under 47 mg/dL for more than 4 days and another group under 36 mg/dL on three occasions did not alter these results. They "found no evidence that recurrent low blood glucose levels, (<47 mg/dL) in the first 10 days of life pose a hazard to preterm infants." This study does not imply that low blood glucose levels cannot be damaging in preterm infants.

Studies from the Children with Hypoglycemia and Their Later Development (CHYLD) research group included serial follow-up and subcutaneous continuous monitoring with glucose sensors. These studies included a large prospective cohort of term and late preterm neonates at risk for hypoglycemia, the same groups identified by the AAP. They defined hypoglycemia as under 47 mg/dL plasma glucose concentration. Fifty-three percent of 404 at-risk infants (late preterm SGA and LGA infants and IDM) became hypoglycemic. They found no increase in risk for neurosensory impairment at 2 years of age with hypoglycemia. They also performed blinded interstitial continuous glucose monitoring and noted that intermittent blood sampling missed 25% of episodes of blood glucose levels under 47 mg/dL. Even with aggressive treatment, including dextrose gel, nearly 25% of infants experienced 5 hours of glucose concentration under 47 mg/dL. Risks of impairment were not increased even in those infants with hypoglycemia that was unrecognized (interstitial monitoring) and therefore not treated. It is noteworthy that higher glucose levels after treatment for hypoglycemia were associated with neurodevelopmental impairment. Those infants who spent a larger proportion outside the central range of 54 to 72 mg/dL in the first 48 hours of life had worse outcomes.

In a subsequent study, McKinlay et al evaluated 614 term and late preterm at risk for hypoglycemia using intermittent sampling and interstitial monitoring. The study included patients without hypoglycemia and both treated and untreated infants with hypoglycemia. Hypoglycemia was defined as plasma glucose under 47 mg/dL. Infants were screened and treated with the aim of keeping plasma glucose concentrations over 47 mg/dL. Surprisingly, there were long and undetected periods of hypoglycemia detected only on interstitial monitoring. Almost one out of four had hypoglycemic episodes not detected on intermittent sampling. Twenty-five percent of those undetected episodes lasted over 5 hours during the first week of life.

Neurosensory impairment or processing difficulty at age 2 was reported among four subgroups, including a reference group who never had hypoglycemia, any episode of hypoglycemia, over 3 days of hypoglycemia, or severe hypoglycemia (<36 mg/dL). There was no association between hypoglycemia and neurodevelopmental outcome at age 2 years. However, data on the 4.5 year follow-up demonstrated executive function difficulties in those infants suffering more than one episode of hypoglycemia. This was found only with continuous glucose monitoring, not with intermittent sampling.

A unique perinatal cohort reported from Arkansas included 1400 infants tested at 10 years of age who had a

single glucose level in the first hours of life. The single low transitional glucose level was correlated with fourth grade examinations in literacy and mathematics from across the state. A second glucose value was obtained to document glucose values, but there were no further determinations. Glucose levels of interest ranged between below 30 mg/dL and 45 mg/dL. Transient hypoglycemia occurred in 6.4%, 10.3%, and 19.3% of newborn infants with cutoff values of 35, 40, or 45 mg/dL. They found that a single episode of hypoglycemia, defined as under 40 mg/dL that resolved by 3 hours of age, was associated with a 50% reduction in the odds of achieving proficiency in literacy and numeracy at age 10. This group of patients represented all the births during a calendar year, so they were mostly made up of late preterm and term infants. There was little information about the management strategies for hypoglycemia and no reported rates for breastfeeding. It is also possible that the exposure group might have had further exposure to hypoglycemia because only the first two blood glucose levels were measured, and recurrent low glucose levels are common in at-risk infants throughout the first week.

As yet, there is no reason to assume the link between transitional neonatal hypoglycemia and subsequent poor academic performance is causal. It is possible that a brief period of hypoglycemia is a marker for other perinatal issues, perhaps including adverse events during abnormal intrauterine development.

Should we now consider universal screening of all newborns because the Arkansas study suggests transient hypoglycemia may be associated with poorer academic achievement at 10 years? Screening is only justified when you can affect outcome with a screening test. The brief period of hypoglycemia in the Arkansas study was diagnosed at 90 minutes of age, but the actual result wasn't available until 30 minutes after that. The second measurement showing resolution came 70 minutes after the first screen or at 3 hours of age. It is unlikely that any intervention could shorten the exposure to the brief period of hypoglycemia.

Several studies have evaluated whether exogenous glucose or earlier feedings will prevent low glucose concentrations. The studies by Coors et al and Hegarty et al used prophylactic dextrose gel administered to newborn infants at risk for hypoglycemia to increase the initial blood glucose concentrations. In the study by Coors et al, prophylactic dextrose gel did not reduce transient neonatal hypoglycemia or NICU admissions for hypoglycemia. In contrast, the study by Hegarty et al demonstrated that dextrose gel reduced the incidence of hypoglycemia and NICU admissions. A letter to the editor concluded that "providing exogenous glucose to all newborns would apply to the vast majority of term and even many later preterm infants who appropriately do not receive exogenous glucose and normally suckle ad lib. Normal physiologic processes, common throughout the animal kingdom, particularly in mammals, respond to the fall in glucose concentrations that starts almost immediately after birth and produces a robust increase in glycogen breakdown, followed by gluconeogenesis, release of endogenous glucose from the liver, and breakdown of fat to provide alternative fuels to glucose. Providing exogenous glucose would very likely interfere with this normal physiologic response to declining glucose concentrations."

The clinical report from the Committee on the Fetus and Newborn provides a practical guide for the screening and subsequent management of neonatal hypoglycemia in at-risk late preterm (34–$36^{6}/_{7}$ weeks' gestational age) and term infants. The report does not identify any specific value or range of plasma glucose concentrations that potentially could result in brain injury. Instead, it is a pragmatic approach to a controversial issue for which evidence is lacking but guidance is needed. It is clear from the neurologic data that much is yet to be learned and the recommendations are expert opinion based. Providing guidance without all the evidence is implicitly understood with the AAP document.

WHICH INFANTS TO SCREEN

Healthy full-term infants born after an entirely normal pregnancy and delivery and who have no clinical signs do not require screening. Routine measurement of blood glucose concentrations should only be undertaken in infants who have clinical manifestations or who are known to be at risk of a compromised metabolic adaptation. The AAP clinical report was not inclusive of all premature infants and focused only on the late preterm infant. This recommendation assumed that the vast majority of more premature infants would be cared for in intermediate care or in the neonatal intensive care unit, where routine screening is already in place.

Because plasma glucose homeostasis requires gluconeogenesis and ketogenesis to maintain normal rates of fuel use, neonatal hypoglycemia most commonly occurs in infants with impaired gluconeogenesis and/or ketogenesis, which may occur with excessive insulin production, altered counter regulatory hormone production, an inadequate substrate supply, or a disorder of fatty acid oxidation. Neonatal hypoglycemia commonly occurs in infants who are small for gestational age, infants born to mothers who have diabetes, and late preterm infants. Also included are LGA infants because it is difficult to exclude maternal diabetes or maternal hyperglycemia (prediabetes) with standard glucose tolerance tests.

A large number of other maternal and fetal conditions may also place infants at risk of neonatal hypoglycemia (Box 4.2). For the AAP clinical report, it was assumed that clinical signs would be common with these conditions, and it is likely that patients with such conditions would be monitored and that plasma glucose analyses were being performed (Box 4.6).

WHEN TO SCREEN

Plasma glucose should be measured as soon as possible (minutes, not hours) in any infant who manifests clinical signs (Box 4.6) compatible with low blood glucose concentration (i.e., the symptomatic infant). Neonatal glucose

concentrations decrease after birth to as low as 30 mg/dL or less during the first 1 to 2 hours after birth and then increase to higher, more stable concentrations, generally above 45 mg/dL by 12 hours after birth. Values under 40 to 45 mg/dL occur in as many as 5% to 15% of normal newborn infants. Data on the optimal timing and intervals for glucose screening are limited. It seems inappropriate to make early blood glucose measurements on any baby during this immediate fall after delivery, because the normal physiologic decrease cannot be distinguished from the abnormal. Fortunately, even in the absence of any enteral nutrition intake, the blood glucose rises by 3 hours of age. Even in the infant at risk for hypoglycemia, a blood glucose measurement is best avoided during the first 2 hours after birth in the asymptomatic infant. There is the real danger that measurements made at this time are self-fulfilling prophecies. No studies have demonstrated harm from a few hours of asymptomatic low glucose levels during this postnatal period establishing physiologic homeostasis.

Blood glucose concentrations show a cyclic response to an enteral feed, reaching a peak by about an hour after the feed and the nadir just before the next feed is due. Because the purpose of blood glucose monitoring is to identify the lowest blood glucose level, it makes most sense to measure a value immediately before the next feeding.

The AAP guideline recommends the frequency and duration of screening for at-risk groups based on risk factors specific to the individual infant. After 24 hours, repeated screening before feeds should be continued if plasma glucose concentrations remain lower than 45 mg/dL.

LABORATORY MEASUREMENTS OF GLUCOSE

Accurate and rapid measurement of blood glucose concentration is the cornerstone of the management of glycemic status in the neonate. Ideally, it would be rapid, accurate, inexpensive, and require a small volume of blood. Unfortunately, none of the available devices or methods has met all the required attributes for detection of low blood glucose in the neonatal population. When neonatal hypoglycemia is suspected, the plasma or blood glucose must be determined immediately by using one of the laboratory enzymatic methods (glucose oxidase, hexokinase, or dehydrogenase method). Plasma glucose tends to be 10% to 18% higher than whole-blood values because of the higher water content of plasma.

Although a laboratory determination is the most accurate method of measuring the glucose concentration, the results are not available quickly enough for rapid diagnosis of a low blood glucose level, which thereby delays potential interventions and treatments. Bedside reagent test-strip glucose analyzers can be used if the test is performed carefully and the clinician is aware of the limited accuracy of these devices. This bedside or point-of-care (POC) testing is done to obtain an estimate of the glucose concentration quickly and conveniently. Although the results of these tests are used for clinical decisions, there are several pitfalls. At present, there is no POC that is sufficiently reliable and accurate in the low range of blood glucose to allow it to be used as the sole method to screen for hypoglycemia. Test-strip results may vary as much as 10 to 20 mg/dL versus the actual plasma glucose concentration. Unfortunately, this variation is greatest at low blood glucose concentrations.

Because of limitations with rapid bedside methods, the blood or plasma glucose concentration must be confirmed by laboratory testing ordered stat. A long delay in processing the specimen can result in a falsely low concentration because erythrocytes in the sample metabolize the glucose in the plasma. This problem can be avoided by transporting the blood in tubes that contain a glycolytic inhibitor such as fluoride. Treatment of the suspected neonatal hypoglycemia should not be postponed while waiting for laboratory confirmation. However, there is no evidence that such treatment will mitigate neurologic sequelae.

CLINICAL SIGNS OF HYPOGLYCEMIA

The clinical signs of neonatal hypoglycemia are not specific and include a wide range of local or generalized manifestations that are common in sick neonates (Box 4.6). The signs and symptoms of isolated hypoglycemia can be viewed as systemic manifestations of glucopenia (e.g., episodes of cyanosis, apnea, irritability, poor sucking or feeding,) and/or manifestations of central nervous system glucose deficiency (neuroglycopenia; e.g., changes in level of consciousness, tremors, irritability, lethargy, seizures, exaggerated Moro reflex, coma). The manifestations of neuroglycopenia include the full spectrum of acute encephalopathy. Coma and seizures may occur with prolonged neonatal hypoglycemia (plasma or blood glucose concentrations lower than 10 mg/dL range) and repetitive hypoglycemia.

Because avoidance and treatment of cerebral energy deficiency is the principal concern, greatest attention should be paid to neurologic signs. The clinical manifestations should subside within minutes to hours in response to adequate treatment with intravenous glucose if hypoglycemia alone is responsible. Cornblath and colleagues have suggested that the Whipple triad be fulfilled: (1) a low blood glucose concentration, (2) signs consistent with neonatal hypoglycemia, and (3) resolution of signs and symptoms after restoring blood glucose concentrations to normal values.

PERSISTENT HYPOGLYCEMIC DISORDERS

Some neonates can be identified by various clinical features as being high risk for severe hypoglycemia during the first 48 hours of life. Other infants are at risk for persistent hypoglycemia beyond 48 hours of life (Box 4.4). These include not only the rare infants with genetic hypoglycemic disorders, such as congenital hyperinsulinism or hypopituitarism, but also those with relatively more common prolonged neonatal hyperinsulinism (also referred to as perinatal stress hyperinsulinism) associated with birth asphyxia, intrauterine

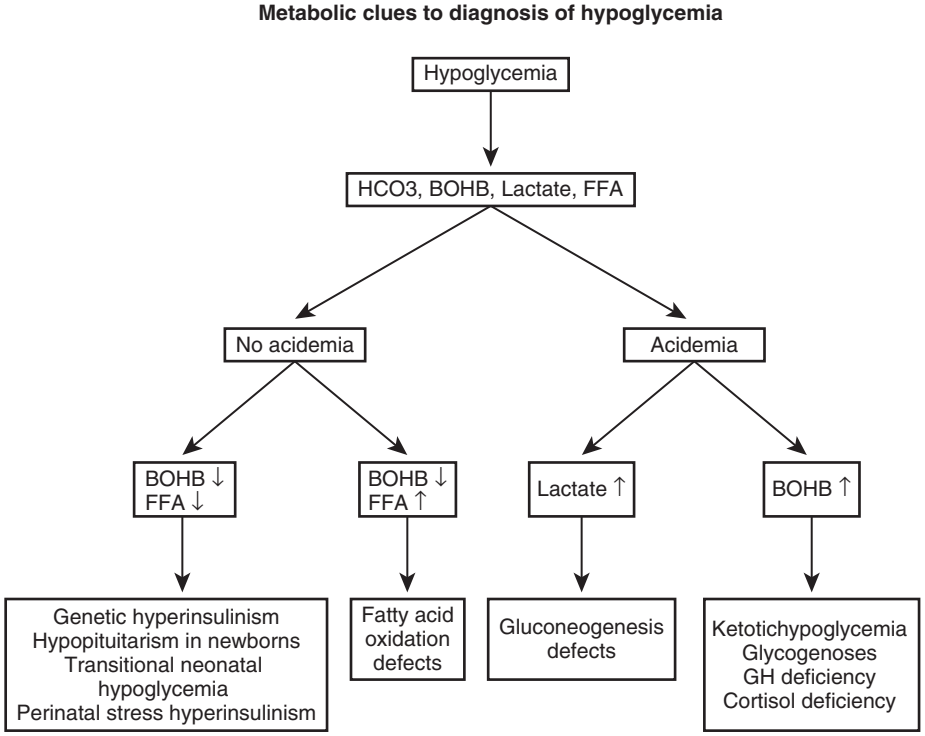

Fig. 4.9 Algorithm showing how the major categories of hypoglycemia may be determined with information from the critical sample. *BOHB,* Beta-hydroxybutyrate; *FFA,* free fatty acids; *GH,* growth hormone. (From Thornton PS, Stanley CA, DeLeon DD, et al: Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in neonates, infants, and children, *J Pediatr* 167:238–245, 2015.)

growth restriction, or born to women with toxemia of pregnancy. Fig. 4.9 provides an algorithm showing how the major categories of persistent hypoglycemic disorders may be determined from the critical sample of beta-hydroxybutyrate, free fatty acids, and growth hormone.

To increase the detection of these persistent hypoglycemic syndromes, it is prudent to use both the AAP and PES recommendations. It makes sense to use the AAP algorithm for the first 24 hours and then use over 45 mg/dL as an operational threshold for 24 to 48 hours. Discharge should be delayed for infants who required intravenous fluids for symptomatic or asymptomatic low glucose levels or those with borderline low glucose levels after 72 hours using the PES recommendations for over 65 to 70 mg/dL through several normal feed–fast cycles. More data on the frequency and success of diagnosing persistent hypoglycemia will be necessary to support this strategy.

DEXTROSE GEL FOR TREATMENT OF HYPOGLYCEMIA

In a secondary analysis of the Sugar Babies Study, infants were randomized to 40% dextrose gel or placebo for a low blood glucose value. After subjects received the gel, feeding was attempted either by direct breastfeeding, expressed breast milk, formula, or a combination of these based on maternal preference. The response to treatment with buccal gel (dextrose or placebo) and feeding was assessed by measuring the glucose concentration 30 minutes after the gel was administered.

The mean increase in glucose concentration for all hypoglycemic episodes was 11.7 mg/dL. Infants who received dextrose gel had a 3.0 mg/dL larger increase in glucose concentration than those who received placebo gel. Formula feeding, whether combined with direct breastfeeding or expressed breast milk or not, was associated with a larger increase in glucose concentration (3.8 mg/dL) compared with infants who did not receive formula. Furthermore, the response to dextrose gel was independent of the formula response, suggesting an "additive" rather than "synergistic" effect of formula feeding versus dextrose gel.

A Cochrane review, including two trials with 312 infants, concluded that treatment with 40% dextrose gel reduces the incidence of mother–infant separation for treatment of hypoglycemia and increases the likelihood of full breastfeeding after discharge compared with the placebo gel. No evidence suggests occurrence of adverse effects during neonatal period or at 2 years of age. Oral dextrose gel should be considered first line treatment of infants with neonatal hypoglycemia.

CONCLUSION

There is need for rigorous long-term studies comparing thresholds of treatment to determine whether outcomes can be affected by early and aggressive treatment of transitional associated hypoglycemia. In addition, the levels that are treated after 4 hours in asymptomatic infants need similar study. Until these studies are available, expert opinion is relied on to interpret evidence, which is lacking.

Current evidence does not appear to support a specific concentration of glucose in the neonate that identifies neuroglycopenia. We are unable to predict the acute or chronic irreversible neurologic damage will result if this critical level is reached. Dextrose gel may help keep mothers and infants together, breastfeeding, and out of the NICU.

As history has shown, every time there are more answers in neonatal hypoglycemia they seem to raise more questions when it comes to the management of neonatal hypoglycemia.

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Abstract: Low blood glucose levels are one of the most frequently encountered issues in the newborn nursery. The blood levels upon which we base our decision making are more a matter of expert opinion than being based on solid evidence. The data needed to establish consensus on low blood glucose levels do not exist yet. The American Academy of Pediatrics Committee on Fetus and Newborn and the Pediatric Endocrine Society (PES) have offered advice on management and also for the PES an appeal for trying to diagnose persistent hypoglycemic syndromes before discharge. Postnatal glucose homeostasis and transitional neonatal hyperinsulinemia has advanced our understanding of metabolic and hormonal responses to various levels of plasma glucose. This unique first 48 hours occurs in all mammals not just humans and controversy exists about whether it is physiologic and affords benefits to the newborn. However, hypoglycemia represents an imbalance between glucose supply and utilization and may result from different regulatory mechanisms. It is certain that persistent low glucose levels that lead to neurologic symptoms are morbid and must be prevented and/or treated emergently. A new therapy using dextrose gel to treat low blood glucose level appears promising and the use of continuous glucose monitoring may offer more insight into the undiagnosed episodes of hypoglycemia that intermittent blood sampling misses.

Keywords: Hypoglycemia, Transitional Neonatal Hyperinsulinemia, Operational Thresholds, Persistent Hypoglycemia, Dextrose Gel, Continuos glucose monitoring

5

Neonatal Hyperbilirubinemia

Michael Kaplan, Cathy Hammerman

INTRODUCTION

Neonatal jaundice is the most common physiologic variant encountered in the newborn. More than 60% of healthy term neonates, and even a greater percentage of breastfed infants, display some degree of visible jaundice during the first week of life. Usually the body's regulatory mechanisms succeed in keeping the serum total bilirubin (STB) level within physiologic levels, and therefore at a concentration that is nontoxic. Indeed, STB concentrations within this range may even have beneficial antioxidant properties.

On occasion, STB levels may increase and significant hyperbilirubinemia may develop. Not all degrees of hyperbilirubinemia are necessarily dangerous, but because of the potential for the STB to continue to rise, phototherapy may be indicated. By facilitating bilirubin elimination, further rise of STB may be limited, thereby preventing the potential for bilirubin neurotoxicity. Rarely, the STB may increase to extreme levels at which bilirubin neurotoxicity may occur. In these cases, bilirubin—especially the unbound fraction—may enter vulnerable brain cells, especially the basal ganglia and auditory nerve tissue, causing acute bilirubin encephalopathy with the potential for progressing to the chronic form of bilirubin neurotoxicity, choreoathetoid cerebral palsy (kernicterus).

It is not our intention in this chapter to provide yet another all-inclusive treatise on neonatal hyperbilirubinemia. Rather, following some background information regarding neonatal hyperbilirubinemia, the reader will be presented with some actual clinical cases drawn from the authors' experience. The reader is encouraged to put himself or herself in the "driver's seat" and actually manage the patients, making clinical decisions from the options provided. The cases will provide the opportunity for in-depth discussions of the issues at hand and focus on practical issues that the practitioner may encounter on a daily basis.

THE SERUM TOTAL BILIRUBIN: WHAT DOES IT REPRESENT?

CASE 1

A 36 weeks' gestation, otherwise healthy infant aged 24 hours was being discussed on rounds in the regular newborn nursery. The STB was 15.0 mg/dL. The professor asked the residents what this value actually meant. The following possibilities were suggested.

Exercise 1

Question

Which answer do you think is correct?

A. One resident plotted the result on the hour-specific bilirubin nomogram. Because the value was greater than the 95th percentile, this resident concluded that increased hemolysis was present.
B. The second resident related to the late prematurity of this infant. The bilirubin conjugating system is immature, he claimed, resulting in the increased STB.
C. The third resident claimed that the pathogenesis of the high STB value was multifactorial and that both increased bilirubin production and hemolysis contributed to its development.

Answer

The third resident (C) supplied the correct answer. He correctly argued that several physiologic or pathophysiologic processes contributed to the STB. He claimed that no single process is responsible for an STB value at any point in time but that the STB value represents a combination of processes acting in tandem. The first resident's answer (A) was incorrect because although increased hemolysis may have been present, he did not take bilirubin elimination into account. Similarly, the second resident (B) correctly identified late prematurity with diminished conjugation ability of the infant as a risk factor but neglected to take the potential for increased hemolysis into account.

The STB: a Delicate Balance of Forces

Equilibrium Between Bilirubin Production and Elimination

The STB at any point in time, in any newborn, represents a combination of forces both affecting heme catabolism with subsequent bilirubin production, on the one hand, and bilirubin elimination—regulated by the processes of bilirubin conjugation and excretion—on the other. In the newborn, reabsorption of bilirubin from the bowel, as part of the enterohepatic circulation, adds to the bilirubin pool to be subsequently eliminated. As long as these processes remain in

equilibrium, the STB may rise to physiologic levels but should not pose a threat to an otherwise healthy term newborn without hemolysis.

Lack of Aforesaid Equilibrium

Should this delicate balance become compromised and bilirubin production exceed bilirubin elimination, the equilibrium will fail and hyperbilirubinemia may result. Severe hemolysis per se or immature bilirubin conjugation in and of itself may not necessarily result in hyperbilirubinemia. For example, an infant with blood type A, born to a woman with blood type O who has a positive direct antiglobulin test (DAT, also known as the Coombs test), can be expected to be a strong bilirubin producer but may not necessarily develop hyperbilirubinemia, should the bilirubin conjugation and elimination processes be well functioning. On the other hand, moderate hemolysis coupled with immaturity of UDP-glucuronosyltransferase 1A1 (UGT1A1, the bilirubin conjugating enzyme) as might occur in a late preterm infant, may result in lack of equilibrium between the aforementioned processes with resultant hyperbilirubinemia. A third cause of lack of equilibrium may result from nonfunction of the conjugation system in the absence of any hemolysis, as in Crigler-Najjar syndrome.

This concept has been likened to the filling of a kitchen sink with water. Provided the drainage is functional, an influx of water may not result in the water level increasing. Partial blockage of the drain may lead to a high water level even with a partly opened tap. Kaplan et al demonstrated this concept mathematically by using a production–conjugation index, which illustrates the contribution of the combined forces of bilirubin production and conjugation to the STB at any point in time. The blood carboxyhemoglobin concentration (corrected for inspired CO), an index of heme catabolism, and the serum total conjugated bilirubin (a reflection of intrahepatocytic conjugated bilirubin) have been used as components of this index. A rising index suggests an increasing lack of equilibrium between production and excretion.

It should be obvious that when evaluating a hyperbilirubinemic infant, both etiologic factors contributing to increased bilirubin production and diminished bilirubin conjugation should be taken into consideration. Given the unreliability of hematological indices to reflect hemolysis in the newborn, it may be difficult to distinguish disorders associated with increased production or increased excretion. These processes may include exaggerated heme catabolism (hemolysis), immaturity of UGT1A1, and reabsorption of bilirubin from the bowel to reenter the bloodstream. Immaturity in the enzyme UGT1A1 may be compounded by presence of the $(TA)_n$ polymorphism in the promoter of the *UGT1A1* gene (*UGT1A1*28*), resulting in diminished gene expression with decreased enzyme activity (Gilbert syndrome). Poor feeding may result in sluggish peristalsis and bowel stasis with increased reabsorption of bilirubin via the enterohepatic circulation. Factors affecting lack of equilibrium between the processes contributing to the serum total bilirubin are summarized in Table 5.1.

TABLE 5.1 Factors Affecting Lack of Equilibrium Between the Processes Contributing to the Serum Total Bilirubin at any Specific Point in Time

Increased hemolysis
Immaturity of the bilirubin conjugating enzyme, UDP-glucuronosyltransferase 1A1 (UGT1A1)
(TA)n promoter polymorphism of the encoding gene *UGT1A1* with resultant diminished gene expression and enzyme activity (associated with Gilbert syndrome in adults)
Enterohepatic circulation

Is the STB Predictive of Bilirubin Neurotoxicity?

Although, for practical purposes, the STB is used as the tool for the management of neonatal hyperbilirubinemia, including the indications for phototherapy and exchange transfusion, this test is actually not a good predictor of bilirubin-related neurologic outcome. Although it is unlikely that an otherwise healthy term infant with no obvious hemolytic condition will develop bilirubin neurotoxicity at STB levels under 25 mg/dL, there is actually no specific cutoff point at which an STB level will or will not be predictive of neurotoxicity. Certainly not all newborns with extreme hyperbilirubinemia go on to develop choreoathetoid cerebral palsy. For example, in one study of 140 newborns with STB values above 25 mg/dL who were treated with phototherapy or exchange transfusion, overall, 5-year outcomes were not significantly different from those of randomly selected controls. In a reanalysis of data from the Collaborative Perinatal Project, there was no relationship, overall, between maximum STB levels and subsequent IQ scores. However, in both these studies, the presence of a positive DAT resulted in a poorer prognosis. (See section on hemolysis.) Similarly, of 249 newborns admitted to a children's hospital in Cairo, Egypt, all of whom had STB values 25 mg/dL and above, there was little correlation between admission STB and acute bilirubin encephalopathy. However, in babies with hemolytic risk factors including Rh incompatibility, ABO incompatibility, and sepsis, the threshold STB for identifying babies with bilirubin encephalopathy was lower relative to those without these factors.

If the STB Is Not a Good Predictor of Bilirubin Neurotoxicity, Then What Is?

Predictive Value of Serum Unbound Bilirubin

Several studies have suggested that the unbound bilirubin fraction may be a more accurate predictor of bilirubin toxicity—including choreoathetoid cerebral palsy and sensorineural hearing loss—than STB, both in term and preterm infants. Use of the unbound fraction as an indication for

institution of phototherapy or for performing exchange transfusion would take much of the guesswork out of the decision-making process and permit better identification of the infant at risk for brain damage. Currently, however, unbound bilirubin determinations are in the main unavailable for routine clinical use, and STB remains the cardinal laboratory indication used for clinical decision making in hyperbilirubinemic newborns.

DEFINITIONS

Jaundice and Hyperbilirubinemia

The terms jaundice and hyperbilirubinemia are sometimes, incorrectly, used interchangeably.

Jaundice refers to a yellow coloring of the sclera, skin, and mucous membranes caused by infiltration from the serum of the yellow pigment bilirubin. *Hyperbilirubinemia*, on the other hand, relates to a measurement of serum or transcutaneous bilirubin, the result of which is greater than an accepted norm.

The Hour-Specific Bilirubin Nomogram

In infants 35 weeks' gestation or greater, a useful definition of hyperbilirubinemia is a STB value greater than the 95th percentile for age in hours on the Bhutani et al hour-specific bilirubin nomogram (Fig. 5.1). Use of the nomogram adjusts for the dynamic changes in STB during the first postnatal week and obviates the concept whereby a single STB value is regarded as representative of hyperbilirubinemia. Thus an infant with an STB value of 10.0 mg/dL at 12 hours will be regarded as hyperbilirubinemic, whereas the same concentration 48 hours later will have little significance.

Variations on This Definition

In newborns with lower gestational ages or with risk factors for hyperbilirubinemia, according to the 2004 AAP guidelines, phototherapy may be indicated at levels of STB below the 95th percentile. Thus many newborns receiving treatment may not actually meet these criteria for hyperbilirubinemia. Variations on this definition, to accommodate intervention with phototherapy, include use of an STB value within 1 mg/dL of the indications for phototherapy or an STB value exceeding the 75th percentile on the bilirubin nomogram.

Bilirubin Encephalopathy and Kernicterus

The terms acute bilirubin encephalopathy and kernicterus are often used interchangeably, although the AAP recommends differentiating these two conditions (AAP, 2004). *Acute bilirubin encephalopathy* relates to the acute manifestations of bilirubin neurotoxicity seen during or immediately following an episode of extreme hyperbilirubinemia. Permanent features of choreoathetoid cerebral palsy may ensue, but reversal, when appropriately treated, has been reported.

Kernicterus, on the other hand, refers to chronic and permanent sequelae attributable to bilirubin neurotoxicity, the result of bilirubin deposition in the target nuclei of the brain.

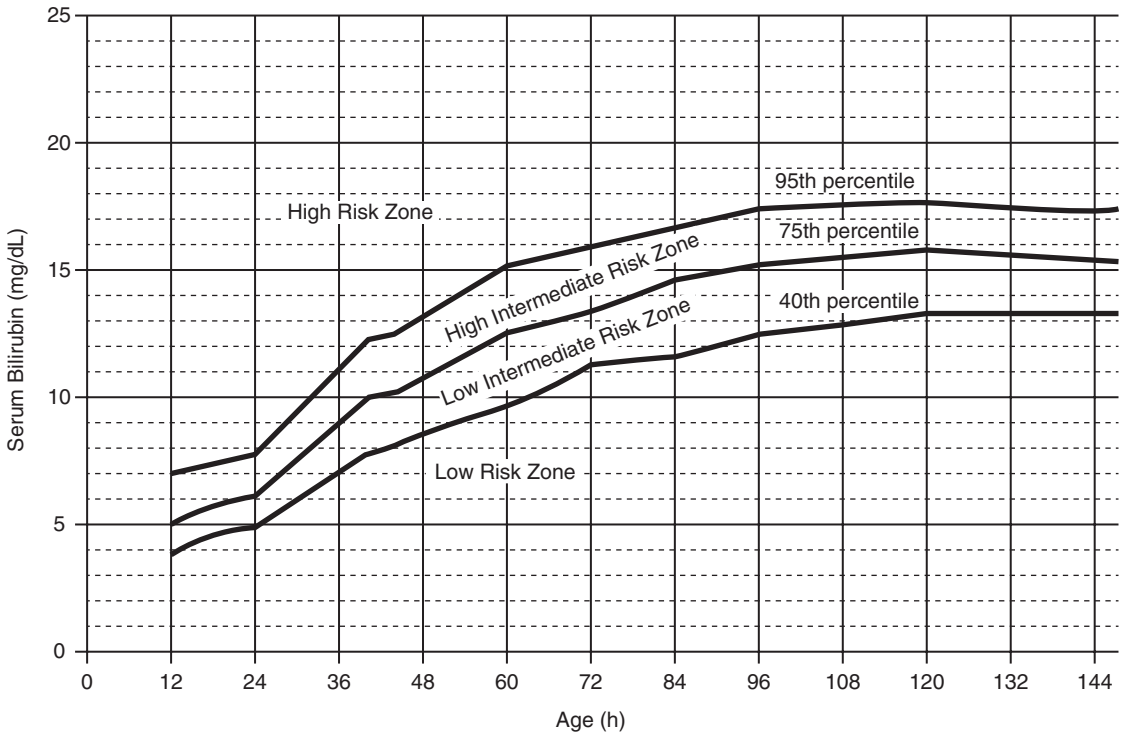


Fig. 5.1 Nomogram for designation of risk in 2840 well newborns at ≥36 weeks' gestational age with birth weight of ≥2000 g or ≥35 weeks' gestational age and birth weight of ≥2500 g based on the hour-specific serum bilirubin values. (Reproduced with permission from Bhutani VK, Johnson L, Sivieri EM, Predictive ability of a predischarge hour specific bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. *Pediatrics*;103:6–14, 1999.)

PHYSIOLOGY OF BILIRUBIN PRODUCTION AND METABOLISM

An understanding of the basic concepts of bilirubin physiology is necessary for perceptive management of the hyperbilirubinemic newborn. As detailed reviews of this subject are available in standard texts, only an outline will be provided here as a basis for comprehension of the subsequent portions of the chapter. Variations in bilirubin physiology peculiar to the newborn, contributing to the development of hyperbilirubinemia, are interspersed among the descriptions of basic bilirubin physiology.

A. Bilirubin Formation

Most heme is produced by the destruction of red blood cells (RBC) in the reticuloendothelial system, although some is produced from turnover of hemoproteins such as myoglobin. Heme itself is catabolized to biliverdin by the enzyme heme oxygenase 1 and thence to bilirubin. This bilirubin component is termed unconjugated or indirect bilirubin. In newborn infants, the RBC mass is larger, the turnover of the RBC is more rapid, and the cell lifespan is shorter than in adults. There is thus a relatively large heme load that contributes to the bilirubin pool.

B. Bilirubin Binding to Serum Albumin; Unbound Bilirubin

To facilitate transportation to the liver, indirect bilirubin is bound to serum albumin. This step is very important in our current understanding of the pathophysiology of bilirubin neurotoxicity. As long as the bilirubin molecule is bound to albumin, it is not expected to cross the blood–brain barrier and to cause bilirubin neurotoxicity. Should the albumin-binding sites be saturated and the bilirubin unable to bind, unbound, or free, bilirubin will result. The unbound bilirubin fraction is thought to be that capable of entering bilirubin-sensitive brain cells and causing neurotoxic damage. Potential causes of unbound bilirubin formation, raising the risk for neurotoxicity, should always be kept in mind when evaluating an infant for hyperbilirubinemia. Some causes potentiating unbound bilirubin formation are listed in Table 5.2.

TABLE 5.2 Some Causes of Unbound Bilirubin Formation

Hypoalbuminemia
Excessive hemolysis even in the presence of normal serum albumin concentrations
Metabolic acidosis
Hypothermia
Sepsis
Drugs such as sulfa-containing antimicrobials
Prematurity (possible)

C. Bilirubin Uptake

Uptake Genes

Uptake of bilirubin into the liver is controlled by the solute carrier organic anion transporter protein 1B1, *SLCO1B1,* also known as *OATP2.* Varying expression of this sinusoidal transporter gene, the result of polymorphisms, may affect bilirubin kinetics and metabolism. For example, the *SLCO1B1*1b* variant is associated with neonatal hyperbilirubinemia in Taiwanese newborns, especially when coupled with *UGT1A1* variants. Similarly, coexpression of *SLCO1B1*1b* with G6PD A− was associated with hyperbilirubinemia in a study from the United States.

D. Bilirubin Conjugation and Elimination

The Importance of UDP-Glucuronosyltransferase 1A1 (UGT1A1)

Following uptake into the hepatocyte, indirect bilirubin is conjugated with glucuronic acid to form water soluble mono- and diglucuronides. These complexes are known as conjugated or direct bilirubin. The enzyme controlling the conjugation process is UGT1A1. Immaturity of UGT is an important contributor to hyperbilirubinemia in both term and preterm infants. In term infants, activity of UGT is only about 1% that of adults, and it is even less in preterm infants. Developmental immaturity with slowing of the conjugation process is actually the bottleneck of the neonatal bilirubin elimination process and the reason that the majority of newborns exhibit some degree of visible jaundice during the postnatal period.

Genetic Control of Bilirubin Conjugation

There is increasing appreciation that the modulation of serum bilirubin levels and the development of hyperbilirubinemia may be under genetic control. A detailed account of all the genes contributing to bilirubin metabolism is beyond the scope of this text. Because of the practical nature of the enzyme UGT1A1, its genetic control is discussed in some detail.

The enzyme UGT1A1 is encoded by the gene *UGT1A1,* mapped to chromosome 2q37. This gene contains both a noncoding promoter region and a coding region. Polymorphisms of the promoter region, such as the $(TA)_n$ polymorphism, result in diminished expression of a normally formed enzyme and are associated with Gilbert syndrome. On the other hand, coding area mutations as seen in Crigler-Najjar syndrome result in an abnormally structured enzyme that has no or little conjugating ability. Coexpression of genes, presence of several mutations or polymorphisms, and interactions with environmental factors may potentiate the genetic contribution to the pathophysiology of neonatal hyperbilirubinemia. A paradigm of this concept may be found in the pathophysiology of neonatal hyperbilirubinemia in glucose-6-phosphate dehydrogenase (G6PD) deficient neonates, in which interaction between environmental factors (triggering hemolysis), the G6PD deficiency in and of itself, and $(TA)_n$ promoter polymorphisms of *UGT1A1 (UGT1A1*28)* may potentiate severe hyperbilirubinemia.

E. Excretion of Bilirubin Into the Bowel and the Enterohepatic Circulation

Direct bilirubin is secreted into the bile and then to the bowel from which it is excreted in the stool. The presence of the enzyme beta-glucuronidase in the colon deconjugates bilirubin-glucuronides and allows the reabsorption of bilirubin into the bloodstream, thereby adding to the bilirubin pool. A delay in enteral feeding or poor intake may diminish intestinal motility. The resultant increased bowel stasis with decreased elimination will allow for even greater reabsorption of bilirubin.

INCREASED HEMOLYSIS: A RISK FACTOR FOR HYPERBILIRUBINEMIA AND BILIRUBIN NEUROTOXICITY

Given the universal immaturity of the enzyme UGT1A1, it is fair to suggest that almost all newborns have suboptimal bilirubin conjugation. Taking the bilirubin production–conjugation equilibrium into account, it stands to reason that hemolysis must therefore be a cardinal factor in the pathogenesis of hyperbilirubinemia in many newborns.

ABO ISOIMMUNIZATION

CASE 2

Baby AB was born at term gestation to a blood group O, Rh-negative mother. On admission to the nursery, the nurses thought that the baby's skin had a yellow tinge. The physician believed this was only very mild jaundice and chose to ignore it. An astute nurse, however, took an STB at age 12 hours, the result of which was 9.2 mg/dL. "Not very high," responded the physician. By the next day (28 hours) the STB value was 15 mg/dL.

Exercise 2

Question

What would you do?

A. Observe the baby and repeat the STB in another 24 hours
B. Place the infant under intense phototherapy and repeat the STB in 4 to 6 hours
C. Begin phototherapy and proceed to exchange transfusion

Answer

The correct answer is B, but this baby had not been correctly managed from the outset. A baby born to a blood group O mother may be at risk for neonatal hyperbilirubinemia if the infant's blood type is A or B. The second risk factor for severe hyperbilirubinemia was the presence of jaundice shortly after birth, with an STB concentration significantly above the 95th percentile. Answers A and C are incorrect. There is no need at this point to proceed to exchange transfusion, as the rise in STB in many cases of ABO isoimmunization may be modulated by intense phototherapy and IVIG administration.

One hour after phototherapy began, these laboratory results were reported: Infant's blood group B, Rh positive, DAT strongly positive, Hb 12.0 g/dL, Hct 36%, reticulocyte count 6%. The anemia in association with an elevated reticulocyte count in a newborn with jaundice and hyperbilirubinemia noted before 24 postnatal hours suggests that hemolysis is occurring.

After 6 hours of intensive phototherapy, a repeat STB value is 18.3 mg/dL.

Question

What should be done now?

A. Continue phototherapy and repeat the STB in 12 hours
B. Exchange transfusion
C. Administer intravenous immune globulin (IVIG), 1 g/kg.

IVIG in Immune Hemolytic Anemia

Answer

In the authors' practice, we would choose option C. Answer A is incorrect because waiting 12 hours in the presence of hemolysis might allow the bilirubin to rise to a dangerous level. Answer B might be considered a valid option. However, in the authors' experience, administration of IVIG has dramatically reduced the need for exchange transfusion in infants with ABO incompatibility. In an infant with ABO incompatibility, administration of IVIG is very effective in preventing a further increase in STB and decreasing the need for exchange transfusion. In other isoimmunizations such as Rh, anti-c, or anti-E, IVIG therapy may be less effective but may be instrumental in slowing the rise in STB before blood products for exchange transfusion become available. In studies using measurement of carboxyhemoglobin (COHb), a sensitive index of heme catabolism, in responders to IVIG, the rate of hemolysis is diminished. IVIG therapy is recommended in the therapeutic armamentarium of the AAP guideline (2004) for the management of immune-mediated hemolysis.

In fact, this baby did respond to an infusion of IVIG. The rise in STB was curtailed and exchange transfusion avoided. In the authors' experience, an aggressive approach to ABO incompatible infants including (1) a high rate of awareness of babies born to blood group O mothers, (2) identification of early jaundice, (3) intense phototherapy according to AAP recommendations, and (4) IVIG administration should the STB continue to rise despite phototherapy has diminished the need for exchange transfusion in ABO incompatible newborns.

Increased Risk for Bilirubin Neurotoxicity Associated With Hemolysis

It is generally believed that neonates with hemolytic disease are at a higher risk for bilirubin-induced neurotoxicity than those whose hyperbilirubinemia is not due to a hemolytic process. Whereas an STB concentration of 20 to 24 mg/dL may be associated with bilirubin encephalopathy and kernicterus in a neonate with Rh isoimmunization, in the absence of a hemolytic condition, a healthy term infant will rarely be endangered by STB concentrations in that range. The mechanism by which hemolysis increases the risk of bilirubin neurotoxicity has not been elucidated. Because the unbound

bilirubin fraction is thought to be that which crosses the blood–brain barrier, it seems logical that babies with hemolytic conditions should have higher unbound bilirubin fractions than their nonhemolyzing counterparts. However, this has not been demonstrated to date. A high rate of bilirubin production over a short period, typical of increased hemolysis, may offset the effect of bilirubin distribution into the tissues, a process that may be effective in moderating the rise in STB.

Several studies support the concept of increased severity of bilirubin neurotoxicity in the face of hemolysis. In a study performed in Turkey, a positive DAT, used as a presumed marker of hemolysis in infants with Rh isoimmunization or ABO incompatibility, was associated with lower IQ scores and a higher incidence of neurologic abnormalities than in controls who were not DAT positive. A similar observation was made in Norway in the 1960s; DAT-positive males who had STB levels above 15 mg/dL for longer than 5 days had IQ scores lower than those observed in the general population. In the Jaundice and Infant Feeding Study, IQ values in the subgroup of DAT-positive infants with TSB above 25 mg/dL were significantly lower than hyperbilirubinemic infants who were DAT negative. Finally, in a reanalysis of the data from the Collaborative Perinatal Project, the presence of a positive DAT in infants with a TSB of 25 mg/dL and above was associated with decreased IQ scores.

Recent case series of infants with kernicterus from the United States, Canada, the United Kingdom and Ireland, and Denmark indicate that hemolysis (with or without isoimmunization) plays a major role in the etiology of hyperbilirubinemia. Hemolytic conditions including ABO incompatibility with or without a positive DAT and G6PD deficiency topped the list of conditions in which a specific etiology for the hyperbilirubinemia was determined. Although Rh isoimmunization is now rarely encountered in Western countries, the condition is still rampant in developing countries. On the other hand, immigration patterns, ease of travel, and the recent influx of Middle Eastern refugees to the West have made G6PD deficiency a condition no longer limited to the countries to which it was indigenous but potentially encounterable in virtually any country in the globe.

AAP Recommendations Regarding Babies With Hemolysis

In its 2004 guidelines, the AAP placed special emphasis on identifying neonates with hemolytic conditions. Infants with early jaundice (<24 hours postdelivery) or those who have rapidly increasing bilirubin values (that jump percentiles on the hour-specific bilirubin nomogram) should be suspected of having ongoing hemolysis. Similarly, blood group incompatibility with a positive DAT and other known hemolytic disease including G6PD deficiency are regarded as major risk factors for the development of severe hyperbilirubinemia. Although the complete blood count (CBC) may be helpful in detecting severe hemolysis in cases of isoimmunization, there may be overlap in values between babies with and without hemolysis, and the CBC may not be sufficiently sensitive to detect many cases of hemolysis in the early neonatal period.

TABLE 5.3 Some Important or Commonly Occurring Causes of Increased Hemolysis

A. Immune conditions
ABO immunization
Rh (D) isoimmunization (in the main eliminated in Westernized countries, still common in developing countries)
Some rarer immune conditions anti-c, anti-C anti-e, anti-E anti-Kell anti-Duffy anti-Kidd
B. Nonimmune conditions
Red cell enzyme deficiencies G6PD deficiency Pyruvate kinase deficiency Other rare RBC enzyme deficiencies
Red cell membrane defects Hereditary spherocytosis Elliptocytosis Ovalocytosis Stomatocytosis Pyknocytosis
Hemoglobinopathies Unstable hemoglobinopathies
General conditions Sepsis Extravasated blood (cephalhematoma, ecchymosis, adrenal hemorrhage, subdural hemorrhage)

G6PD deficiency is especially notorious in demonstrating normal hemoglobin and hematocrit values in the presence of extremely high STB values, most likely attributable to hemolysis.

In cases of overt hemolysis including isoimmune hemolytic disease and G6PD deficiency, the Subcommittee on Hyperbilirubinemia of the AAP recommends a more aggressive approach to management of hyperbilirubinemia, including initiation of phototherapy or performing of exchange transfusions at lower levels of STB than in neonates without obvious hemolytic etiologies. A list of some commonly occurring etiologies of hemolysis can be seen in Table 5.3. For a comprehensive listing, the reader is referred to standard textbooks.

G6PD DEFICIENCY: AN IMPORTANT CAUSE OF KERNICTERUS

CASE 3

Baby GP, a male infant, was born at term gestation in the United States to parents who were immigrants from Greece. The parents reported that a previous child in their family, also born in the United States, had been treated with phototherapy. At the time of discharge of the current baby at

48 hours, the STB was 11.0 mg/dL (the 75th percentile on the bilirubin nomogram). The infant was breastfeeding, apparently successfully.

Exercise 3

Question

What would you advise the parents?

A. See a pediatrician within 2 to 3 days in accordance with AAP guidelines (2004).
B. Assess the baby as being relatively risk free for hyperbilirubinemia. See a pediatrician by age 2 weeks.
C. This infant is at high risk for significant neonatal hyperbilirubinemia. He should be seen by a pediatrician or medical professional within 48 hours (or sooner should the infant become yellow).

Answer

None of these answers is correct. This infant was at high risk for severe hyperbilirubinemia based on the history of a sibling requiring phototherapy and the family's Mediterranean Basin origin. The discharging pediatrician did not recognize these risk factors. Furthermore, the STB was already in the intermediate high-risk zone. Based on these risk factors in a male, breastfeeding baby (additional risk factors), this infant should have had a repeat STB within 24 hours. The parents should have been instructed how to recognize jaundice and what to do should their infant become jaundiced.

At age 5 days, the baby became lethargic and refused to nurse. The parents called the pediatrician's office but were told that the first available appointment was at 2:00 p.m. the next day. Following onset of seizures, the parents took the baby to the emergency room. The triage nurse exclaimed: "This baby looks like a pumpkin!" While waiting to be seen by a doctor, the baby became apneic and required intubation and ventilation. Phenobarbital was administered, and 1.5 hours later the STB was reported as 35 mg/dL. The baby was admitted to the pediatric ward, an IV placed, antibiotics administered, and phototherapy commenced. Blood was ordered for an exchange but because of a technical problem, delivery of the blood was delayed for 3 hours.

Acute Bilirubin Encephalopathy: to Exchange or Not to Exchange?

Question

While waiting for the blood for the exchange transfusion, there was a discussion between the doctors attending to this case regarding the efficacy of performing an exchange transfusion in a baby who already had signs of bilirubin encephalopathy (apathy, poor feeding, seizures, apnea).

A. One physician argued that bilirubin encephalopathy is associated with irreversible neurologic injury (kernicterus). Therefore why perform a potentially dangerous procedure in a baby who is already damaged?
B. Another physician stated that the early signs of bilirubin encephalopathy can be reversed when the STB is promptly lowered by exchange transfusion and intense phototherapy. Some of these infants develop normally.

Answer

The second physician is correct. There have been reports of reversal of the bilirubin neurotoxicity process with prompt lowering of the STB by exchange transfusion, even in cases already manifesting signs of bilirubin encephalopathy. The AAP guideline (2004) recommends immediate performance of exchange transfusion should an infant manifest signs of acute bilirubin encephalopathy. (See later discussion.) The initiation of intensive phototherapy while waiting for the blood for the exchange transfusion is the correct response.

In the current case, exchange transfusion via the umbilical vein was commenced 7 hours after arrival at the emergency room. A G6PD assay on blood that had been sampled before the exchange transfusion was very low, indicative of G6PD deficiency. On questioning, it became apparent that a neighbor had prepared a traditional Mediterranean meal for the parents that included fava beans. The infant was probably exposed to the bean metabolites via breast milk. The child is currently 7 years old and has choreoathetotic cerebral palsy.

Severe Hyperbilirubinemia Associated With G6PD Deficiency: Unpredictable and Unpreventable

The AAP regards kernicterus as a condition that should generally be preventable. G6PD deficiency, however, may be one important reason that this goal may be unreachable. G6PD deficient newborns sometimes have acute episodes of severe jaundice in which STB rises in an exponential fashion. These episodes are by and large unpreventable and unpredictable and occur even when all preventive measures are undertaken and exposure to known triggers of hemolysis avoided. However, had the diagnosis been made and the parents appropriately educated, much could have been done to facilitate treatment in the early stages of the hyperbilirubinemia, before the onset of signs of bilirubin encephalopathy, or at a point when bilirubin encephalopathy may still have been reversible with appropriate treatment.

What went wrong? This baby was inadequately managed and evaluated by the pediatricians both in the hospital and in the community setting. Some pediatricians in North America regard G6PD deficiency as a condition prevalent in the Middle East or Mediterranean Basin, with little relevance to their own practices. Although the indigenous distribution of G6PD deficiency characteristically includes Central and West Africa, Mediterranean countries, the Middle East, and parts of Asia, G6PD-deficient individuals are found throughout the world. About 12% of African American males are G6PD deficient. G6PD deficiency comprised more than 20% of the 125 cases reported in the US-based Kernicterus Registry, confirming its overrepresentation in its contribution to bilirubin neurotoxicity. Similar contributions of G6PD deficiency to extreme hyperbilirubinemia and kernicterus have been reported from Canada and the United Kingdom and Ireland. A list of population subgroups in the United States at risk for G6PD deficiency appears in Table 5.4.

TABLE 5.4 Population Subgroups at Risk for G6PD Deficiency in the United States

African American
Italian
Greek
Immigrants from the Middle East, India, South-East Asia and China
Sephardic Jews especially of Middle Eastern origin
Central and Western Africa descent
Brazil

Will G6PD Screening Help?

The parents of this baby should have been warned of the high-risk nature of their ethnic background with regard to the potential for G6PD deficiency. Had the baby been born in Greece, G6PD deficiency would have been screened for as part of a national screening program and the parents given preventive instructions even before the screening results becoming available. Several countries with a high incidence of G6PD deficiency have reported screening programs—in combination with parental education—with observational evidence of a decreased number of cases of kernicterus. With the exception of Washington, DC, and Pennsylvania in the United States, there is no obligation to screen otherwise healthy babies for this condition. Discussions have, however, commenced regarding the feasibility and whether it is economically worthwhile to establish such a program in the United States. Screening will not prevent the acute hemolytic attacks, but knowledge that their infant is G6PD deficient, in combination with parental education, should heighten parental and medical caretaker awareness, facilitate earlier referral to medical centers, and result in earlier institution of effective therapy. Many infants with bilirubin encephalopathy were readmitted at or around 5 days of age and had been discharged from birth hospitals as "healthy." It will therefore be important to perform screening for G6PD deficiency, obtain the results, and instruct the parents before discharge from the birth hospital. Recent studies in Cleveland, Ohio, have shown that this goal is feasible in the United States. In the authors' institution, targeted screening aimed at ethnic groups known to be at high risk for G6PD deficiency has been ongoing for decades.

Although the trigger of hemolysis in G6PD-deficient babies frequently cannot be identified, the parents of this baby should have been warned of the dangers of eating fava beans, using clothes that had been stored in naphthalene containing mothballs, or of using drugs or medications without consulting a doctor beforehand. The office pediatrician should have given instructions to his staff that an infant whose parents complain of jaundice should be seen immediately and not be given an appointment for the following day. Similarly, the emergency room triage nurse who recognized the extreme jaundice in this baby should have recognized the emergent nature of the situation and called a physician immediately. An STB should have been taken stat and intensive phototherapy started even before the results becoming available. Attention to these details may have prevented permanent bilirubin neurotoxicity.

Moderate G6PD Deficiency Associated Hyperbilirubinemia: a Potentially High-Risk Condition

Some G6PD-deficient infants develop a more moderate form of hyperbilirubinemia. We do not know the natural history of this form, as most infants are treated with phototherapy with good response, although a few do require exchange transfusion. The pathophysiology of the jaundice is attributed to a moderate degree of increased heme catabolism, as demonstrated by studies of endogenous carbon monoxide production, in combination with diminished bilirubin conjugation, the result of presence of a promoter polymorphism of *UGT1A1,* associated with Gilbert syndrome (*UGT1A1*28*). These infants are at risk for severe hyperbilirubinemia as the imbalance between bilirubin production and conjugation may be exacerbated should the infant come in contact with a hemolytic trigger or if prematurity further diminishes the bilirubin conjugation ability.

Falsely Normal G6PD Testing

If taken during an acute hemolytic episode, a G6PD test may be reported as falsely normal even in a severely G6PD deficient individual. The reason for this apparent discrepancy is that during hemolysis, older RBCs that have lower levels of G6PD activity are destroyed, leaving younger RBCs with higher G6PD activity intact. Such newborns should be regarded as G6PD deficient for the purpose of management. An accurate G6PD result can be expected several months later when RBCs have regenerated. Genetic analysis is another option but may not always be feasible.

Female heterozygosity may also lead to equivocal results on quantitative G6PD testing. Because of nonrandom X chromosome inactivation, the phenotype will usually give intermediate results but may range from low (deficient) to normal. It may be prudent to regard females from high-risk ethnic groups with intermediate or even normal G6PD enzyme values as G6PD deficient for the purpose of evaluation and treatment of hyperbilirubinemia.

CLINICAL EFFECTS OF SEVERE NEONATAL HYPERBILIRUBINEMIA

Kernicterus: a Never Event?

Kernicterus has been regarded as a preventable condition, but despite formulation of comprehensive guidelines in the United States, Canada, and other countries (including the United Kingdom, South Africa, Israel, Netherlands, and Norway), kernicterus continues to occur in Westernized countries with well-organized healthcare systems. Kernicterus is not surprising in low- and middle-income countries with poorly functioning health systems. Although the incidence of kernicterus relative to the number of deliveries in any developed country is low, the results of bilirubin neurotoxicity are permanent and long lasting, with major

implications for the affected infants, their families, and society. The incidence of extreme hyperbilirubinemia and kernicterus in industrialized countries varies. Kernicterus is estimated to occur in Denmark at the rate of 1 in 64,000 (1994–1998) or 1 in 79,000 (1994–2003), the United Kingdome and Ireland 1 in 150,000, Canada 1 in 43,000, and California 0.44 in 100,000. The incidence of severe neonatal hyperbilirubinemia in Canada decreased from 1 in 2480 in 2002 to 2004 to 1 in 8352 in 2011 to 2013, a factor of 3.5 (95% confidence interval 2.72–4.47). This decrease was attributable to introduction of Canadian hyperbilirubinemia guidelines in 2007 combined with increased physician awareness of severe hyperbilirubinemia.

Bilirubin toxicity—manifest as acute bilirubin encephalopathy with the potential for kernicterus or the less devastating bilirubin auditory neuropathy and bilirubin-induced neurologic dysfunction (BIND)—most likely will not have been encountered by the majority of readers. On the other hand, pediatricians and neonatologists spend much of the time devoted to newborns in predicting, monitoring, and treating hyperbilirubinemia to prevent the STB from reaching a neurotoxic level. Although a comprehensive account of bilirubin neurologic disease is beyond the scope of this chapter, we will in the ensuing paragraphs briefly describe the clinical picture of newborns who have been exposed to and affected by high levels of STB.

Acute Bilirubin Encephalopathy

The early clinical features giving rise to the suspicion of acute bilirubin encephalopathy include severe lethargy and poor feeding in a very icteric baby who has previously been feeding well. Granted, these signs are nonspecific, but in the presence of severe jaundice, encephalopathy should be suspected and therapy instituted without delay. Spasm of the extensor muscles results in opisthotonus and back arching. Muscle tone may fluctuate between hypo- and hypertonia, and a high-pitched cry frequently develops. Impairment of upward gaze results in the setting-sun sign, and fever, seizures, apnea, and death may follow.

Associated with acute bilirubin encephalopathy may be a kernicteric facies (Fig. 5.2). These facial features include a combination of features: (1) the setting-sun sign (paresis of upward gaze), (2) eyelid retraction, and (3) facial dystonia. In combination, these signs make the infant seem stunned, scared, or anxious. A fourth sign, dysconjugate or wandering eyes, may also occur. Recognition of this peculiar facial pattern should help identify a baby who is developing bilirubin encephalopathy.

Chronic Athetoid Cerebral Palsy: Kernicterus

The clinical picture of acute and chronic bilirubin neurotoxicity is due to deposition of bilirubin in the basal ganglia neural tissue. Kernicterus comprises a tetrad including:

- Abnormal muscle control, movements and muscle tone typical of choreoathetoid cerebral palsy
- Auditory processing disturbance, with or without hearing loss

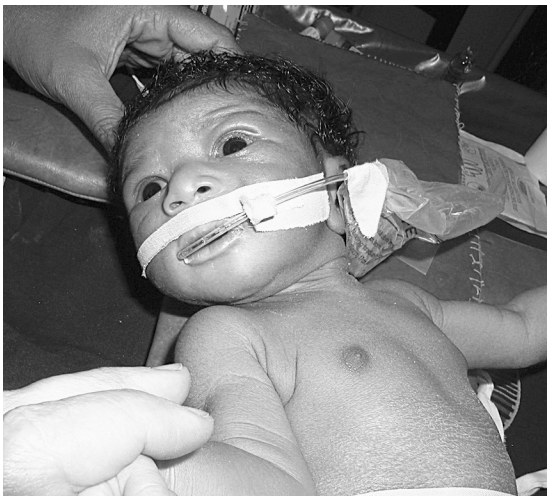


Fig. 5.2 Kernicteric facies in a baby with acute bilirubin encephalopathy. Note the setting-sun sign (paresis of upward gaze), eyelid retraction, and facial dystonia, making the infant seem stunned, scared, or anxious. (Photograph courtesy Tina Slusher, MD, from that physician's personal collection, taken in Nigeria with mother's permission.)

- Oculomotor impairments resulting in paralysis of upward gaze
- Enamel dysplasia of the teeth

The following description of 25 cases of kernicterus in California portrays the dismal picture of these chronically affected children. Seventy-two percent were male. At a mean (SD) age of 7.8 (3.9) years, 60% did not walk at all, and only 16% were able to walk independently. Only 52% could self-feed, and a feeding tube was in place in 12%. Severe or profound mental retardation or severe disablement was found in 36%. There was no evidence of mental retardation in 32%. Epilepsy was found in 20%. Severe, profound, or untestable visual or hearing impairment was documented in 25% and 56% of cases, respectively, and only 36% had normal hearing. Motor spasticity was seen in 32%, ataxia and dyskinesis in 12% each, and hypotonia in 8%.

SUBTLE BILIRUBIN ENCEPHALOPATHY AND AUDITORY NEUROPATHY

Bilirubin-Induced Neurologic Dysfunction (BIND)

Bilirubin encephalopathy may not always manifest as the classic, chronic picture of kernicterus. In some, BIND may result in subtle bilirubin encephalopathy. These children have less severe injury than those with classic kernicterus but nevertheless show signs attributable to bilirubin neurotoxicity. The spectrum of neurologic manifestations in BIND includes subtle disturbances of hearing, disorders of auditory processing known as auditory neuropathy/dyssynchrony, visual motor paralysis, and disorders of speech, language, and cognition. Hearing loss or auditory neuropathy may be isolated or in combination with additional manifestations of kernicterus. Cognitive disturbances may also be evident.

Auditory Neuropathy/Dyssynchrony

Auditory neuropathy associated with hyperbilirubinemia is not simply a sensorineural hearing loss but is the result of dysfunction at the level of the auditory brainstem or nerve. Thus the cochlear hair cells remain intact, but the central auditory nerve tissue or auditory brain center are affected. Functionally, auditory neuropathy or dyssynchrony is characterized by absent or abnormal brainstem auditory evoked potentials but with normal inner ear function. In these cases, hearing screening using automated auditory brainstem responses (testing neural tissue) will identify the condition. However, evoked otoacoustic emission studies, reflecting cochlear hair cell inner ear function, may be normal. If the latter technology is used exclusively, the auditory neuropathy may remain undiagnosed. Affected patients may be able to hear, as documented on audiogram, and to respond to sounds appropriately, but their ability to decode speech and language and interpret the sounds they are hearing may be hindered. Awareness of bilirubin auditory neuropathy is of practical importance, as cochlear implantation has been used successfully in children with this condition.

LATE PREMATURITY

CASE 4

A 36-week gestation, male breastfed infant was to be discharged at 48 hours. The predischarge STB was 11.0 mg/dL. Both mother's and infant's blood groups were O, Rh positive. The parents are Caucasian.

Exercise 4

Question

Which of the following physicians is correct in their assessment?

A. The first pediatrician was not concerned, as the STB was not very high, in his evaluation. He claimed that this was a case of nonhemolytic jaundice.
B. His partner, in contrast, insisted that this baby has risk factors for neonatal hyperbilirubinemia and requires very close observation.

Every STB Value Should Be Plotted on the Bilirubin Nomogram

Answer

The pediatrician did not plot the STB value on the nomogram. Had he done so, he would have seen that the value was on the 75th percentile (the beginning of the intermediate high-risk range). Because of bilirubin dynamics during the first week of life, it is essential to plot every STB value on the nomogram. A value of 11.0 mg/dL at 24 hours will be above 95th percentile, in the high-risk zone; at 48 hours, it will fall on the 75th percentile, at the beginning of the intermediate high-risk zone; and at 72 hours on the 40th percentile, bordering on the low-risk zone. Each percentile has different risk values for the potential to develop severe hyperbilirubinemia. Regardless of the actual STB value, the higher the hour-specific percentile value, the greater the risk for subsequent hyperbilirubinemia. Furthermore, should more than one STB determination be available, the STB trajectory can be evaluated. A trajectory running parallel to the graph may be cautiously reassuring, whereas a trajectory that is jumping percentiles may be indicative of hemolysis and predictive of subsequent hyperbilirubinemia. Although the low-risk zones on the nomogram (<75th percentile) have traditionally been regarded as minimal or moderate risk for subsequent hyperbilirubinemia, this may not be entirely true. Recent studies of newborns readmitted for hyperbilirubinemia determined a false negative predischarge bilirubin screen in many instances. For example, in a study from Israel, Bromiker et al reported that of 143 infants readmitted for hyperbilirubinemia, 4.2% had predischarge STB values in the 40th percentile or below range (low-risk zone), and 28% were in the intermediate low-risk zone (41st–75th percentile) predischarge. These and other results support the AAP recommendation that every newborn should be seen by a health authority within a few days of discharge to detect those developing jaundice, or with preexisting jaundice that is increasing, that is not recognized by the parents.

In this case, the pediatrician did not take some risk factors into consideration. As discussed earlier, the conjugating ability of newborns 37 weeks' and earlier gestation is low. Even early term newborns (37–38 weeks' gestation) exhibit a decreased ability to conjugate bilirubin and therefore are at higher risk for hyperbilirubinemia than those born after 38 weeks' gestation. Studies have demonstrated that a combination of predischarge STB in conjunction with gestational age has an excellent predictive accuracy for subsequent hyperbilirubinemia (see discussion later). Breastfeeding and male sex further add to the complexities of this case and compound the risk for hyperbilirubinemia.

Physician B was correct. Although it is not mandatory to observe this infant in hospital, he should have been seen by a healthcare professional within 1 or 2 days of discharge. Whether the jaundice in this infant was nonhemolytic or not will be discussed later.

Jaundice Associated With Prematurity

Jaundice in premature infants is more common and severe than in full-term neonates. STB concentrations peak around the fifth day of life. The major reason for the frequency of jaundice in premature infants is developmental immaturity of the UGT1A1 bilirubin-conjugating enzyme. In premature infants, bilirubin toxicity may occur at lower concentrations of bilirubin than in term infants, and any visible jaundice in a preterm infant should be closely monitored.

Jaundice Associated With Late Preterm Infants

Late preterm gestation (newborns born between $34^{0}/_{7}$ and $36^{6}/_{7}$ completed weeks) is another important risk factor for the development of severe neonatal hyperbilirubinemia. An immature bilirubin conjugative capacity is implied in the potential severity of jaundice in these infants. Coexpression of late prematurity with additional icterogenic factors such as

G6PD deficiency may enhance the jaundice. Management of late preterm infants as if they were term infants, with early discharge and lack of appropriate follow up, may be a major contributor to the bilirubin-related morbidity in these cases.

"Nonhemolytic Jaundice": Is There Such an Entity?

In the absence of known or obvious etiologies for neonatal hyperbilirubinemia, some pediatricians have used the term "nonhemolytic jaundice." Although there may be some cases of true nonhemolytic jaundice, such as breastfeeding jaundice or Crigler-Najjar syndrome, categorization of hyperbilirubinemic newborns as nonhemolytic may lessen the degree of concern regarding the potential for bilirubin neurotoxicity. The presence of a hemolytic condition does not categorically imply that the jaundice or hyperbilirubinemia is necessarily due to this condition. Conversely, absence of an identifiable etiology does not necessarily imply that increased hemolysis is not part of the pathophysiology of the jaundice. Studies using the endogenous production of CO have demonstrated that many jaundiced babies do, in fact, have a hemolytic component to their jaundice, even in the absence of a defined hemolytic condition. In a multicenter, multinational study using end-tidal CO concentration corrected for ambient CO (ETCOc), Stevenson et al reported the mean ETCOc value for 1370 infants who completed the study was 1.48 ± 0.49 ppm. The 120 newborns who developed any TSB concentration above 95th percentile on the hour-specific nomogram had significantly higher ETCOc values than those who did not (1.81 ± 0.59 ppm vs. 1.45 ± 0.47 ppm, $p < 0.0001$).

However, high bilirubin production was not a prerequisite for the development of hyperbilirubinemia. Some babies with low bilirubin production nevertheless did develop hyperbilirubinemia, whereas others with high production rates did not. These findings confirm that both bilirubin production and its elimination contribute to the STB at any point in time. Additional studies using both ETCOc and blood carboxyhemoglobin (COHbc) levels have demonstrated greater endogenous production of CO, reflective of increased heme catabolism in many newborns, even in the absence of a specific diagnosis associated with increased hemolysis. It appears, therefore, that many hyperbilirubinemic babies do have some degree of increased heme catabolism with the potential of bilirubin neurotoxicity. Using new generation sequencing, Christensen et al provided a diagnosis for hemolysis in cases that previously would have been regarded as idiopathic. Absence of an obvious etiology associated with increased hemolysis for hyperbilirubinemia should not result in us labeling newborns as nonhemolytic. This practice may result in a sense of complacency and lack of recognition of babies with increased potential for bilirubin neurotoxicity.

Recent re-availability of a device for noninvasive bedside testing for ETCOc should contribute to the detection of hemolysis and identify neonates at higher risk for extreme hyperbilirubinemia and bilirubin neurotoxicity. Study of ETCOc in combination with STB or transcutaneous bilirubin (TcB) should help determine whether the pathophysiology of hyperbilirubinemia in a specific newborn is primarily hemolytic or due to elimination disorders. A recent study by Bhutani et al concluded that high ETCOc implies increased hemolysis, whereas high STB in the face of a normal ETCOc implies a predominantly conjugative deficiency.

TABLE 5.5 Some Important Causes of Hyperbilirubinemia Due to Diminished Bilirubin Conjugation

Prematurity
Late prematurity
Hypothyroidism
Pyloric Stenosis
Gilbert syndrome
Crigler-Najjar syndromes types 1 and 2

DIMINISHED BILIRUBIN CONJUGATION AND NEONATAL HYPERBILIRUBINEMIA

Diminished bilirubin conjugation may result in hyperbilirubinemia independently or in conjunction with increased bilirubin production. Some important causes of hyperbilirubinemia due to diminished conjugation are found in Table 5.5.

Gilbert Syndrome

Gilbert syndrome is a benign disorder that produces mild unconjugated bilirubinemia in about 6% of adults. Both defective hepatic uptake of bilirubin and decreased hepatic UGT activity have been demonstrated. In individuals with Gilbert syndrome, the UGT1A1 conjugating enzyme is normally structured but not fully functional because of diminished gene expression. This is because the noncoding, rather than coding, area of the gene is affected. In Caucasian populations, the genetic basis of the reduced gene expression lies in the presence of additional TA repeats ($[TA]_7$ or occasionally $[TA]_8$ instead of the wild type $[TA]_6$] in the TATAA box in the promoter region of the *UGT1A1* gene (*UGT1A1*28*). In and of itself, the $(TA)_7$ promoter polymorphism has not been associated with severe hyperbilirubinemia, but it may in combination with additional factors. Kaplan et al demonstrated that a dose-dependent genetic interaction between G6PD deficiency and $(TA)_7$ promoter polymorphism increased the incidence of a TSB above 15 mg/dL dramatically when these two factors occurred together. In Asian populations, interaction between G6PD deficiency and coding area *UGT1A1* mutations *(UGT1A1*6)* exacerbate hyperbilirubinemia. An interaction between $(TA)_7$ promoter polymorphism and hereditary spherocytosis increasing hyperbilirubinemia has been documented.

BREASTFEEDING AND BREAST MILK JAUNDICE

CASE 5

A male term infant was born to parents who were second cousins. The infant was breastfed. The STB was 20.0 mg/dL

on day 3 of life. Phototherapy was instrumental in decreasing the STB value, and the baby was discharged only to be readmitted 3 days later with an STB value of 23.0 mg/dL.

Exercise 5

Question

What is the most likely diagnosis?

Answer

At this point, the leading diagnosis is *breastfeeding jaundice.* Breastfeeding jaundice occurs in the first postnatal days. Lack of proper technique, engorgement, cracked nipples, small amounts of milk, and fatigue may impair effective breastfeeding on the part of the mother. Neonatal factors such as an ineffective suck may be common in late-preterm infants. The result may be ineffective breastfeeding, underhydration, delayed meconium passage, and intestinal stasis leading to an increased enterohepatic circulation and increased bilirubin load.

Breast milk jaundice, on the other hand, occurs after the first 3 to 5 days of life. Mutations of the *UGT1A1* gene, including a $(TA)_7$ promoter polymorphism *(UGT1A1*28)*, or the G71R mutation *(UGT1A1*6)* can contribute to the development of hyperbilirubinemia in breastfed infants. More severely affected neonates may achieve peak levels as high as 20 to 30 mg/dL with no obvious evidence of hemolysis or illness. Interruption of nursing and substitution with formula feeding for 1 to 3 days usually causes a prompt decline of the STB concentration, especially when STB concentrations reach levels that might be of danger to the infant. On resumption of nursing, the STB does not usually increase. Most infants with breast milk jaundice can be observed without other interventions. However, if prolonged, one must determine that other pathology is not existent, and fractionation of bilirubin, thyroid testing, and urine cultures should be considered.

In the baby presented here, the sequence of readmission and phototherapy repeated itself several more times. Laboratory investigations revealed a normal CBC, a direct bilirubin value 0.3 mg/dL, normal thyroid function tests, and no evidence of infection. Both maternal and newborn blood groups were A Rh positive and the DAT was negative.

Question

What if anything, should be done next?

A. This is clearly a nonhemolytic situation and no further testing or interventions are necessary.
B. Indirect hyperbilirubinemia in a breastfed infant indicates breastfeeding jaundice. Breastfeeding should be discontinued.
C. Pay attention to the family history: The parents are second cousins. Consider evaluation for Crigler-Najjar syndrome. Treat the baby with phototherapy to prevent the STB concentrations from rising to potentially neurotoxic levels.

Crigler-Najjar Syndrome

Answer

C is the correct answer. Although breastfeeding jaundice definitely should be taken into consideration, it does not usually result in in a sequence of readmissions for hyperbilirubinemia. Response B would have been the correct response early on in this baby's management, but the repeated readmissions should have made the breastfeeding jaundice an unlikely possibility. The UGT1A1 gene was sequenced in the baby and both parents. A coding area mutation associated with Crigler-Najjar syndrome was found, homozygous in the baby and heterozygous in both parents.

Crigler-Najjar syndrome type I is a rare autosomal recessive disease characterized by an almost complete absence of hepatic UGT activity. In this situation, the coding area of the UGT gene is mutated, resulting in a structurally abnormal enzyme with no or little bilirubin-conjugating ability. Severe unconjugated hyperbilirubinemia may develop and kernicterus may occur should the STB not be vigorously controlled with phototherapy. The diagnosis can now be obtained by sequencing the UGT1A1 gene. Liver transplant offers definitive treatment for the disease, but in a multicenter report, 7 of 21 (33%) transplanted children had already developed some form of brain damage by the time of their transplantation.

Crigler-Najjar syndrome type II is more common than type I disease and is typically benign. The occurrence of kernicterus is rare. Unconjugated hyperbilirubinemia occurs in the first days of life and may be exacerbated by fasting, illness, and anesthesia. Phenobarbital may be used as a simple clinical tool to differentiate between type II and type I diseases. Jaundiced neonates with type II disease respond to oral administration of phenobarbital with a sharp decline in STB, whereas individuals with type I disease do not respond in this way. Beyond the neonatal period, there should be no long-term risk of kernicterus.

Hypothyroidism

About 10% of congenitally hypothyroid neonates may develop prolonged jaundice due to diminished UGT activity, and testing for thyroid function should be performed in these cases. This form of jaundice is encountered less frequently than in the past, because with modern methods of routine metabolic screening the diagnosis of hypothyroidism and institution of therapy should be available in the first postnatal days. The mechanism of this association may be impairment of hepatic uptake and reduced hepatic ligandin (carrier protein) concentrations. Absence of thyroid hormone may delay hepatic bilirubin enzyme and transport development.

EFFECT OF RACE AND ETHNIC BACKGROUND ON NEONATAL HYPERBILIRUBINEMIA

CASE 6

A male term infant was born to African American parents. There was no blood group incompatibility. The infant was breastfed and apparently healthy. At 50 hours of life, a predischarge STB result was 10.0 mg/dL. When plotted on the hour-specific nomogram, it fell between the 40th and 75th percentiles.

Exercise 6

Question

Which of the following statements is correct?

A. This is a term infant with an STB value in the intermediate low-risk range. He can be safely sent home; there are no special concerns.
B. This infant is of African American heritage and at very low risk for neonatal hyperbilirubinemia.
C. This infant is potentially at high risk and should be followed according to AAP guidelines with the same vigilance as a Caucasian infant.

Answer

C is the correct answer. Within the African American population, there is a subset at risk for extreme hyperbilirubinemia and kernicterus. Additional risk factors in this case include male sex and breastfeeding. Until recently, black heritage has been regarded as protective against hyperbilirubinemia. Indeed, the AAP (2004) statement on hyperbilirubinemia lists black ethnicity among conditions *decreasing* the risk of hyperbilirubinemia. However, black race does seem to contribute to the development of kernicterus. Black ethnicity comprises 25% of the US-based Kernicterus Registry and was overrepresented in the UK and Ireland survey. Some of these cases may be due to concurrent G6PD deficiency and others due to disadvantaged social status. Kernicterus is rampant in West and Central Africa. In a recent study from California, Wickremasinghi et al confirmed a lower incidence of moderate hyperbilirubinemia (STB ≥20 mg/dL) in black infants, an equal incidence of STB 25 mg/dL or above in black and Caucasian infants, and an increased incidence of hazardous hyperbilirubinemia (STB ≥30 mg/dL) in black neonates compared with white infants. Low-risk categorization of black newborns may therefore no longer be appropriate, and answers A and B are incorrect

Additional Racial Aspects of Hyperbilirubinemia

Asians are another population group at risk for neonatal hyperbilirubinemia. Some of the increased risk may be due to a high incidence of the G71R mutation of UGT1A1, *(UGT1A1*6)* associated with Gilbert syndrome, in Asian populations. Native Americans are also at high risk for neonatal hyperbilirubinemia.

PREDISCHARGE EVALUATION FOR PREDICTION OF HYPERBILIRUBINEMIA

In normal, healthy term babies, there is a natural progression of STB levels during the first days of life to a peak between the third and fifth postnatal day. Current practice in many countries is to discharge babies around 48 hours (or earlier). This means that the peak STB will be reached when the infant is already at home, thereby placing much of the onus for recognition of hyperbilirubinemia on the parents and community services. It is therefore essential to assess every infant for the risk of developing subsequent hyperbilirubinemia and to ensure adequate follow-up to detect developing hyperbilirubinemia.

Universal Predischarge Screening

In their clarification to the 2004 AAP guideline, Maisels et al recommend universal predischarge bilirubin screening using either STB or TcB readings to assess the risk of subsequent severe hyperbilirubinemia. These authors suggest a structured approach incorporating not only the bilirubin reading reflected as a percentile value but also gestational age and the presence or absence of risk factors. The underlying basis for this approach is that the higher the predischarge bilirubin percentile, the lower the gestational age, and the higher the number of risk factors, the greater will be the chance of developing subsequent hyperbilirubinemia. These recommendations are not evidence based but representative of expert opinion. The risk factors that are most predictive of significant hyperbilirubinemia include:

- Lower gestational age
- Exclusive breastfeeding, the latter especially if the nursing is not going well and there is excessive weight loss
- Jaundice appearing in the first 24 hours
- Bilirubin trajectory crossing percentiles on the nomogram
- Hemolytic conditions
  - Isoimmune hemolytic disease of the newborn
  - G6PD deficiency
- Older sibling who had jaundice
- Cephalohematoma or ecchymosis
- East Asian race

A Practical Approach to Follow up for Hyperbilirubinemia

To ease the screening process and facilitate formulation of a follow up plan, Maisels et al provide an algorithm for the predischarge screen. Those neonates who do not meet the AAP criteria for phototherapy are followed up according to a suggested protocol based on predischarge STB or TcB risk zone, gestational age 35 to 37 weeks or 38 weeks and above, and the presence of risk factors.

False Negative Predischarge Bilirubin Screening

As already pointed out, recent studies have shown that some infants readmitted for significant hyperbilirubinemia had a predischarge bilirubin screen in the low-risk zones on the nomogram, indicating a false negative screen. A predischarge screen in the low-risk zones should not, therefore, result in complacency, and the results of these studies confirm the AAP (2004) recommendations that every newborn should be evaluated for developing jaundice within 2 to 3 days of discharge.

TRANSCUTANEOUS BILIRUBINOMETRY

Transcutaneous bilirubinometry (TcB) is a technology for the noninvasive, instantaneous point-of-care estimation of the STB. To date, this technique has been used primarily in the hospital setting but has been successful in the outpatient setting as well. Visual inspection, which was for decades the mainstay for deciding which infant needs a bilirubin test performed, is notoriously inaccurate. TcB takes the guesswork out of bilirubinometry. TcB should be regarded as a screening tool and not as a substitute for actual STB measurement. The

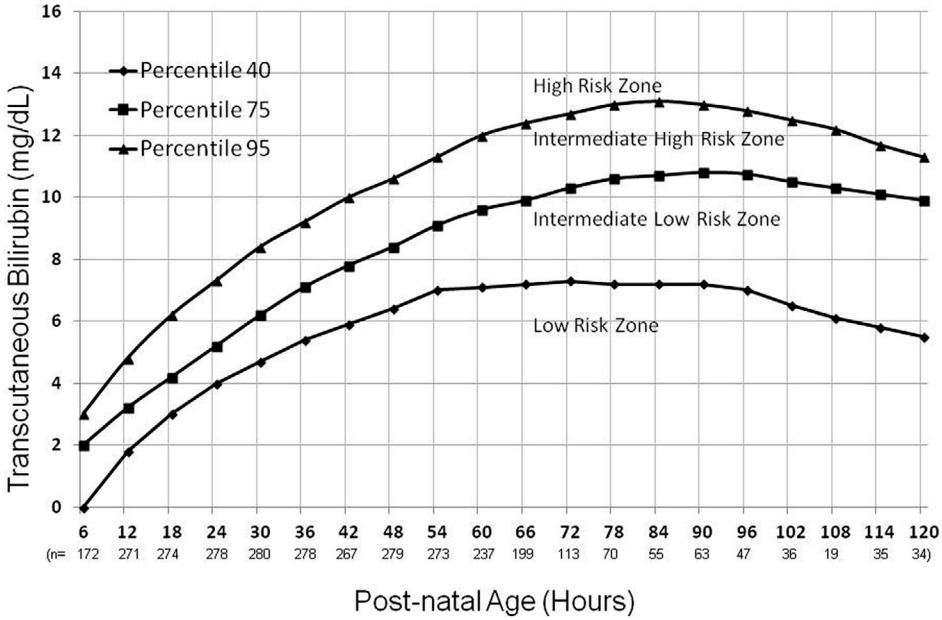


Fig. 5.3 An example of a transcutaneous bilirubin nomogram (constructed in Israel). (Reproduced with permission from Bromiker et al: Israel transcutaneous bilirubin nomogram predicts significant hyperbilirubinemia. *J Perinatol* 37[12]:1315–1318, 2017.)

technique involves a flash of light entering the skin and subcutaneous tissues and measurement of the degree of yellowness. After correcting for skin color and hemoglobin, an estimated STB level is reported.

In general, TcB tends to underestimate the actual STB, although in a Nigerian study it was shown to overestimate the STB reading in black African neonates. In their clarification to the 2004 AAP guidelines, Maisels et al suggest measuring STB if (1) the TcB is 70% of the STB value recommended for phototherapy, (2) the TcB is above the 75th percentile on the bilirubin nomogram or above the 95th percentile on a TcB nomogram, and (3) a postdischarge TcB value is above 13 mg/dL.

TcB nomograms have been constructed from several population groups, an example of which can be seen in Fig. 5.3.

TREATMENT OF NEONATAL HYPERBILIRUBINEMIA

Newborns 35 Weeks' Gestation and Above

The mainstays of treatment for neonatal hyperbilirubinemia include phototherapy and exchange transfusion, AAP-generated graphs for which can be seen in Fig. 5.4. The indications, technologies, and equipment required have been comprehensively described in the 2004 AAP hyperbilirubinemia guidelines with clarifications in the 2009 statement of Maisels et al, and a 2011 technical report on phototherapy by Bhutani et al from the Committee on the Fetus and Newborn. These statements relate to infants of 35 weeks' gestational age and above and are still applicable. The indications take into account not only the actual STB value but also the time and percentile of this value, gestational age, and the presence of risk factors. The higher the STB percentile, the lower the gestational age, and the greater the number of risk factors, the sooner treatment should be initiated. The 2004 AAP guidelines emphasize that in considering the indications for phototherapy and exchange transfusion, the direct-reacting (or conjugated) bilirubin level should **not** be subtracted from the total. However, the statement continues, in unusual circumstances in which the direct bilirubin is above 50% of the total bilirubin, consultation with an expert in the field is recommended as there are no data to provide guidance for therapy.

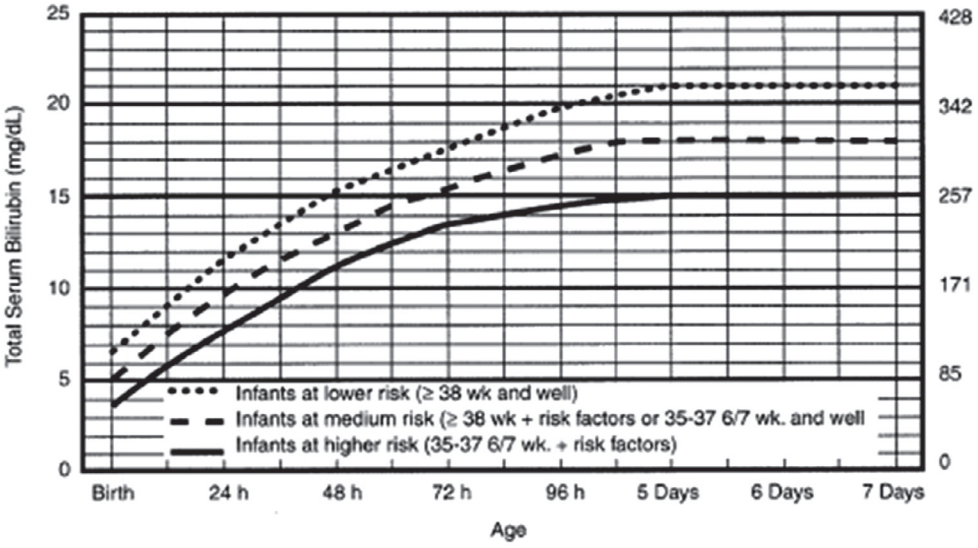
With regard to phototherapy, the 2009 clarification emphasizes the need to take risk factors for bilirubin neurotoxicity into account when making the decision to initiate phototherapy or perform an exchange transfusion. Neurotoxicity risk factors may increase the risk of neurologic damage in infants with severe hyperbilirubinemia. Neurotoxicity risk factors listed in the statement include

- Isoimmune hemolytic disease
- G6PD deficiency
- Asphyxia
- Sepsis
- Acidosis
- Albumin ≤3.0 mg/dL

The statement also provides algorithms that give recommendations for management, phototherapy, and follow-up taking into account not only bilirubin measurements but also gestation and risk factors for subsequent hyperbilirubinemia (Fig. 5.5).

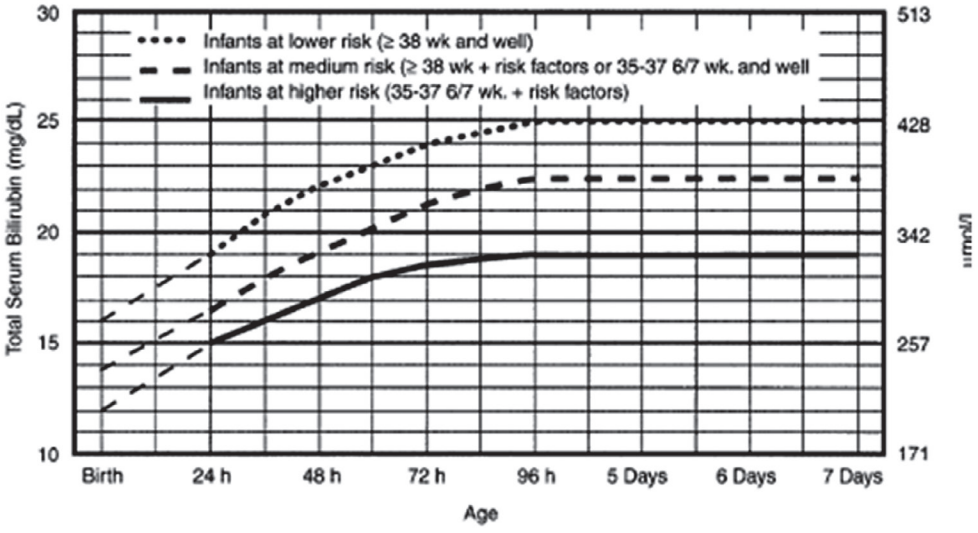
Cardinal points of the 2011 Committee on Fetus and Newborn technical report include that the effectiveness of phototherapy light is enhanced by:

- Emission of light in the blue–green range that overlaps the in vivo plasma bilirubin absorption spectrum (460–490 nm)



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0g/dL (if measured)
- For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.

A



- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high pitched cry) or if TSB is ≥5 mg/dL (85 μmol/L) above these lines.
- Risk factors - isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate B/A ratio (See legend)
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin
- If infant is well and 35-37 6/7 wk (median risk) can individualize TSB levels for exchange based on actual gestational age.

B

Fig. 5.4 (A) AAP-generated graph of indications for phototherapy for neonates ≥35 weeks' gestation. The graph includes three sets of indications based on gestational age and the presence or absence of risk factors. (Redrawn with permission from American Academy of Pediatrics Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation, *Pediatrics* 114:297–316, 2004.) (B) AAP-generated graph of indications for exchange transfusion for neonates ≥35 weeks' gestation. The graph includes three sets of indications based on gestational age and the presence or absence of risk factors. (Redrawn with permission from American Academy of Pediatrics Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation, *Pediatrics* 114:297–316, 2004.)

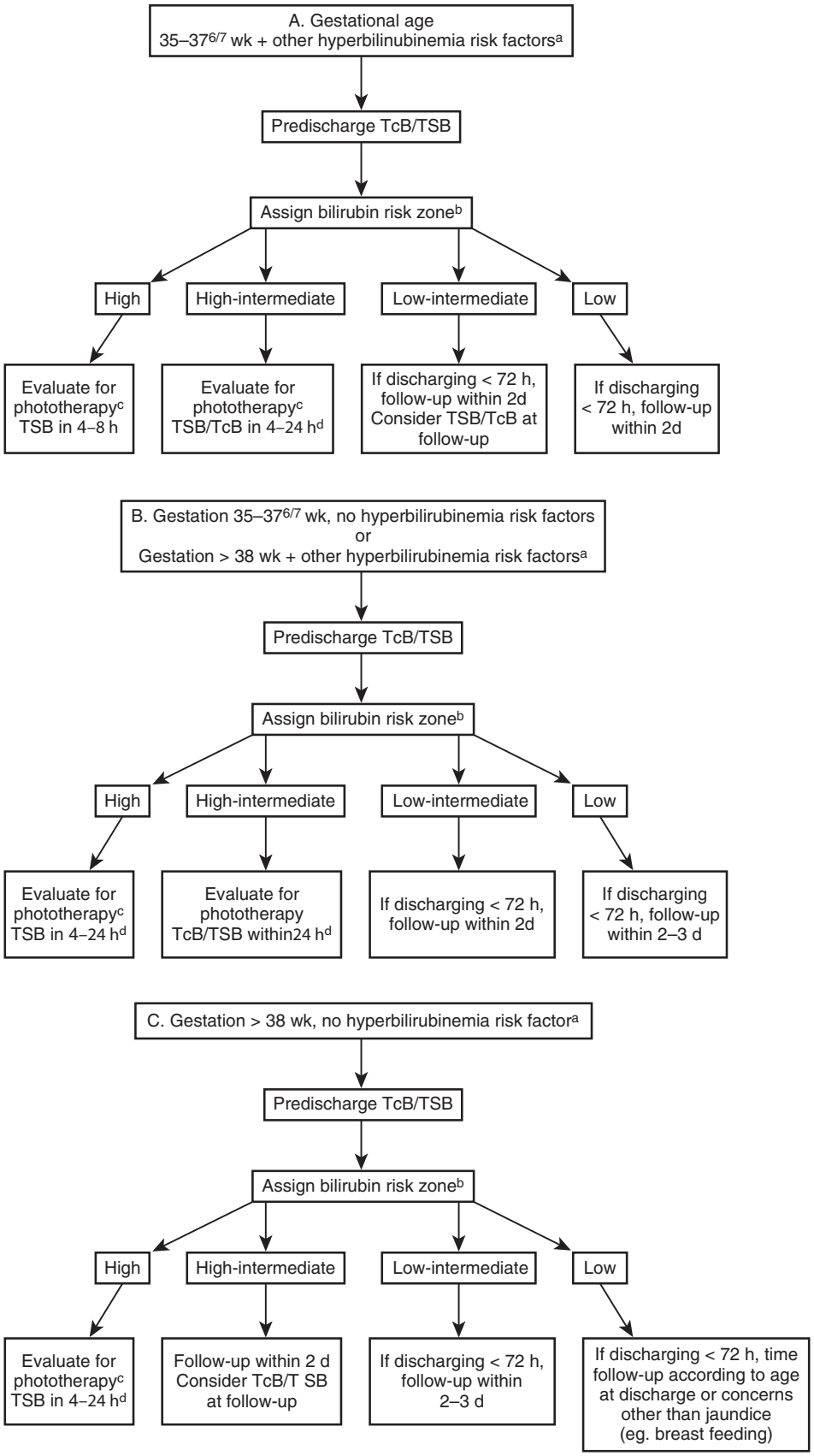


Fig. 5.5 Algorithms providing recommendations for management and follow-up according to predischarge bilirubin measurements, gestation, and risk factors for subsequent hyperbilirubinemia. (Reproduced with permission from Maisels et al, Hyperbilirubinemia in the newborn infant > or =35 weeks gestation: an update with clarifications. *Pediatrics* 124:1193–1198, 2009.)

- Irradiance of at least 30 $\mu W/cm^{-2}/nm^{-1}$ (confirmed with an appropriate irradiance meter calibrated over the appropriate wavelength range). The report adds that much higher irradiance (>65 $\mu W/cm^{-2}/nm^{-1}$) might have (as yet unidentified) adverse effects. Therefore the irradiance should be limited to that controlling any further increase in the STB and facilitating its decrease.
- Illumination of maximal body surface
- Demonstration of a decrease in total bilirubin concentrations during the first 4 to 6 hours of exposure

Additional points in the technical report include measurements of serial bilirubin measurements based on the rate of decrease. Phototherapy should be introduced urgently in cases of excessive hyperbilirubinemia, and procedures should be conducted while the infant receives phototherapy. Phototherapy may be interrupted briefly for feeding, parental bonding, or nursing care once a decrease in serum bilirubin has been detected. Possible rebound should be taken into consideration following discontinuation of phototherapy. Factors increasing the risk of clinically significant rebound include DAT positivity, gestational age under 37 weeks, and commencement of phototherapy at 72 postnatal hours or earlier.

Premature Infants <35 Weeks' Gestation

Management of hyperbilirubinemia in the premature infant under 35 weeks has been unclear, with a wide range of STB values suggested for various gestational ages and birth weights. Recently a suggested protocol—albeit nonevidence based—has been proposed that will hopefully standardize the treatment delivered to these infants (Table 5.6) (Maisels et al, 2012). Other protocols including guidelines for premature infants include the UK-based NICE guidelines and Norwegian, Dutch, and South African guidelines.

TABLE 5.6 Guidelines for Phototherapy and Exchange Transfusion in Premature Infants[a]

	Phototherapy	Exchange Transfusion
Gestational age (wk)	***Initiate phototherapy total bilirubin (mg/dL)***	***Total serum bilirubin (mg/dL)***
<27⁰⁄₇	5–6	11–14
28⁰⁄₇ – 29⁶⁄₇	6–8	12–14
30⁰⁄₇ – 31⁶⁄₇	8–10	13–16
32⁰⁄₇ – 33⁶⁄₇	10–12	15–18
34⁰⁄₇ – 34⁶⁄₇	12–14	17–19

In a footnote to their table, the authors of these guidelines make clarifications, some of which are summarized below:

1. The levels of STB at which phototherapy or exchange transfusion is recommended are not based on good evidence.
2. The wide ranges and overlapping of values between gestational age groups reflect a degree of uncertainty in the formulation of these guidelines.
3. Use the lower values in any given range for babies at high risk for bilirubin neurotoxicity, including lower gestational age, sepsis, clinical instability, serum albumin level <2.5 g/dL, or rapidly rising STB levels suggestive of hemolysis.
4. Indications for exchange transfusion apply to infants in whom STB levels continue to rise to exchange transfusion levels despite intense phototherapy.
5. Exchange transfusion is indicated in a baby who shows signs of acute bilirubin encephalopathy.
6. Use the total bilirubin value for decision making. Do not subtract the direct or conjugated bilirubin value from the total value.
7. Use the postmenstrual (adjusted) age for phototherapy indications.
8. Prophylactic phototherapy is an option in premature infants ≤26 weeks' gestation.
9. In infants <1000 g birth weight, because of possible increased mortality associated with phototherapy in this group, start with lower levels of irradiance and increase this should the STB levels continue to rise.

[a]Suggested by four US-based neonatologists who were involved in the preparations of the 2004 AAP guidelines, the 2009 clarification, or both.

From Maisels MJ, Watchko JF, Bhutani VK, et al: An approach to the management of hyperbilirubinemia in the preterm infant less than 35 weeks of gestation, *J Perinatol* 32:660–664, 2012.

Low Bilirubin Kernicterus

Low bilirubin kernicterus occurs in premature infants at levels of bilirubin lower than one would expect to be associated with neurotoxicity and at levels lower than those indicating phototherapy or exchange transfusion. Therefore this condition may be unpreventable even if current phototherapy and exchange transfusion guidelines are strictly abided by.

Low bilirubin kernicterus is a condition that was encountered in the past in autopsy examinations of premature infants in whom the serum bilirubin did not reach levels that were thought to be neurotoxic. It is still encountered today in premature infant survivors who did not have very high serum bilirubin levels but who do have clinical and magnetic resonance imaging (MRI) evidence of kernicterus. Low bilirubin kernicterus has been defined as the occurrence of kernicterus at serum bilirubin levels below commonly recommended exchange transfusion thresholds. Because of the low nature of the serum bilirubin in this situation, in the range not necessarily obligating phototherapy, the condition is unpredictable and the consequences refractory. It is not known what factors potentiate bilirubin neurotoxicity at low levels of serum bilirubin. Some factors that have been implicated include low serum albumin (almost ubiquitous in sick, unstable premature infants) and comorbid central nervous system injury, including intraventricular hemorrhage, periventricular leukomalacia, and infection. Given the occurrence of the condition at low levels of serum bilirubin, it is unlikely that the condition will be eliminated, barring a significant lowering of exchange transfusion thresholds, with the potential of bringing in its wake a plethora of complications (infections, hemorrhage, blood pressure instability, and necrotizing enterocolitis) associated with this procedure, especially in unstable preterm infants.

SPECIAL INVESTIGATIONS IN KERNICTERUS

MRI Findings in Kernicterus

The MRI pattern seen in infants affected with kernicterus is typified by the appearance of hyperintensity of the globus pallidus, subthalamic nucleus, and other brainstem nuclei and is frequently bilateral. It is not known, however, whether these MRI changes are apparent in all cases of kernicterus and what their relationship is to long-term prognosis. For example, in a recent Canadian study, MRI findings consistent with kernicterus were initially present in three infants who were subsequently clinically and developmentally normal. On the other hand, the same authors report two infants with a normal MRI early on who subsequently had abnormal developmental outcomes on follow-up.

Brainstem Auditory Evoked Response (BAER)

Because auditory neural tissue is sensitive to the effects of bilirubin toxicity, the brainstem auditory evoked response (BAER) offers an early and sensitive measure of bilirubin-induced CNS dysfunction. Early signs include increased latency and decreased amplitude of waves III and V, progressing to absence of these waveforms, and finally to complete absence of all activity. Automated ABR can be used at the bedside as a rapid test of auditory function in a neonate with severe hyperbilirubinemia. Absence of automated ABR, or a change from "pass" before the hyperbilirubinemia, may be indicative of bilirubin neurotoxicity.

Cochlear Implants

Development of the cochlear implant technique may offer a ray of light to those affected by auditory bilirubin neurotoxicity. Although the cochlear itself is unaffected by bilirubin neurotoxicity, cochlear implantation has been successful in restoring hearing to sufferers of bilirubin auditory nerve toxicity. The mechanism of its function in bilirubin auditory neuropathy is not clear, but it is thought that direct stimulation of the auditory nerve improves nerve function in a way that regular cochlear stimulation cannot. Shapiro and Popelka noted that premature infants with bilirubin auditory neuropathy have responded well to cochlear implantation, adding hope to the improvement of auditory function in this group of children.

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Abstract: Neonatal jaundice is a commonly occurring condition. Usually the serum total bilirubin remains within physiologic levels but may increase to potentially dangerous concentrations and on occasion to extreme levels with the danger of bilirubin neurotoxicity. Neonatal hyperbilirubinemia is the most common cause for readmission in the neonatal period. Imbalance between the bilirubin production and elimination processes—the results of increased hemolysis relative to bilirubin excretion—upsets the equilibrium and results in hyperbilirubinemia. Phototherapy is the mainstay of therapy, with exchange transfusion held in reserve for those not responding to that treatment.

Keywords: Bilirubin, bilirubin encephalopathy, hemolysis, kernicterus, bilirubin conjugation, phototherapy, exchange transfusion

6

Practical Parenteral Nutrition

Kendra Hendrickson, Ashley Reilly, Jatinder Bhatia, William W. Hay, Jr.

INDICATIONS

Parenteral nutrition (PN) is used to provide nutrients to newborn infants who cannot tolerate full enteral nutrition or who have contraindications to enteral nutrition (Table 6.1).

Intravenous feeding is essential, but it should not be a sole substitute for enteral nutrition unless the infant has absolutely no capacity for enteral feedings. Such conditions are rare and usually short term, such as intestinal obstructions (atresias or totally obstructing bands), malformations (gastroschisis, severe omphalocele), or early gut infarctions and perforations. Many infants may be able to feed enterally in very small amounts, especially if an ostomy is placed distal to the obstruction.

One of the most common indications for PN is preterm birth. The majority of somatic growth and nitrogen and mineral accretion takes place during the third trimester. The ideal postnatal nutrition for preterm infants is one that results in postnatal growth (rate and body composition) similar to that of the normal, healthy, growing fetus in utero at the same gestational age as the newly born preterm infant. Achieving this rate of growth after preterm birth is difficult and challenging. Most of the "growth restriction" that develops in preterm infants after birth is the result of undernutrition, particularly from delayed enteral feeding. Other reasons include diseases that may preclude enteral nutrition, delay in starting appropriate PN, intolerance to enteral feeds, and inappropriate feedings or feeding strategies.

The more preterm and smaller an infant is born, the more urgent immediate and adequate parenteral nutrition becomes. To ensure continued nutrition that is close to the amount the fetus was receiving for normal metabolism and growth, most neonatal intensive care units (NICU) keep stock PN solutions in the pharmacy that are available for immediate use 24 hours a day before customized PN solutions can be ordered. These generally provide sufficient dextrose to maintain normal plasma glucose concentrations and sufficient amino acids to prevent protein breakdown and establish early positive protein balance.

Growth during this period of parenteral nutrition is likely to be suboptimal for two reasons. First, current stock PN solutions were not designed for optimal amino acid and mineral metabolism right after birth. Second, there are many physiologic and metabolic instabilities in the first few days after birth that produce stress hormones that interfere with positive protein balance and growth. Stock PN solutions also do not contain lipid and usually are not administered with IV lipid emulsions. Therefore they are calorically insufficient for promoting protein synthesis and net protein accretion (net protein balance).

Exercise 1

Questions

1. In which of the following cases should PN be initiated?
   A. Term infant with gastroschisis
   B. 1-month-old former 26-week preterm infant with abdominal distension and portal venous air on abdominal x-ray
   C. 3-month-old former 26-week preterm infant with a chylothorax
   D. 35-weeks' gestational age (GA) preterm infant in septic shock secondary to group B *Streptococcus* (GBS) sepsis
   E. Newborn preterm infant on a planned feeding advance of GI priming and <30 mL/kg/day increase due to intermittent feeding intolerance
   F. All of the above
2. Which intervention would be the LEAST likely next access attempt for a newborn infant who lost their peripheral line while receiving stock PN and trophic feeds?
   A. Insert a new peripheral intravenous line (PIV)
   B. Place a umbilical venous catheter (UVC)
   C. Surgically place a catheter (Broviac or Hickman)
   D. Place a percutaneous inserted central catheter (PICC)

Answers

1. **F is correct.** See Table 6.1. PN is indicated when full enteral nutrition cannot be achieved and may be particularly useful in catabolic conditions.
2. **C is correct.** A new PIV should be attempted, especially because it is usually easy to insert a new PIV. However, it is only appropriate for short-term access. A UVC, the least painful and invasive central access, could be attempted in a newborn infant if the umbilical vein is patent. UVCs have increased infection risk after 1 to 2 weeks. If a UVC placement is unsuccessful and longer term access is sought,

TABLE 6.1 Indications for Parenteral Nutrition

Prematurity <32 weeks and <1800 g, and some infants <35 weeks and <2200 g with delayed initiation or advancement of enteral feeds

Impaired Bowel Integrity
Necrotizing enterocolitis (NEC)
Bowel perforation
Congenital GI anomalies
Diaphragmatic hernia

Impaired Perfusion
Hypotension/hemodynamic instability
Hypoxic–ischemic encephalopathy/cooling
Congenital heart disease

Impaired Motility
Ileus (meconium, surgical, septic)
Hirschsprung's disease
Intestinal atresia

Impaired Absorption
Chylothorax

TABLE 6.2 Routes of Parenteral Nutrition Administration

	Peripheral	Central
Advantages	Economical, easy access, useful for short duration, lowest risk for catheter-related infections	Higher osmolarity allows for concentrated nutrition, long-term access
Disadvantages	Dislodgement, infiltration, osmolarity <1000 mOsm/L, calcium content low or omitted, provides limited nutrition (limited dextrose concentration of 12.5% or less)	Infection, vascular embolization, spasm of the vessel, perforation, cardiac tamponade, ischemia, hemorrhage, sepsis

a PICC line would be the next option and is appropriate for longer term access. The last, and most invasive option, would be a surgically centrally placed (Broviac or Hickman) catheter. Although infection risk is low, it is highly invasive with placement and removal requiring a surgeon. Therefore it would only be considered once all other options are exhausted or it is known that an infant will require very long-term access. See Table 6.2 for additional differences in peripheral and central access.

CASE 1

A 750 g AGA preterm infant is born following a 26-week gestation by C-section due to preterm, premature rupture of membranes and incompetent cervix. The resuscitation is unremarkable and the infant is placed on CPAP 6 cm H_2O at 35% Fio_2 following surfactant administration in the delivery room. At 1 hr of age, the infant's plasma glucose concentration is 36 mg/dL. A stock PN of 10% dextrose and 3% amino acids is being infused through the UVC. Antibiotics were ordered after blood cultures were obtained.

Exercise 2

Questions

1. Which of the following statements regarding PN and enteral neonatal nutrition is FALSE?
   A. Normal fetal metabolic and growth rates and nutritional requirements stop with birth, precluding routine use of IV nutrition.
   B. The smaller and more preterm and less developed the infant, the less body stores (protein, fat, and glycogen) are available to provide nutrients for metabolic needs.
   C. The metabolic—and thus the nutrient—requirements of the newborn are equal to or greater than those of the fetus of the same gestational age.
   D. First-week protein and energy intakes are associated with improved 18-month developmental outcomes in preterm infants.
2. Which of the following statements regarding Stock PN and protein and glucose supply is TRUE?
   A. Stock PN solutions containing 10% dextrose and 3% amino acids can be stored in the neonatal pharmacy indefinitely.
   B. At an infusion rate of 80 mL/kg/day, commonly formulated stock PN solutions provide adequate short-term dextrose and amino acid supplies.
   C. There is no need to continue to measure the plasma glucose concentration as the infant is receiving IV dextrose.
   D. There is no need to check electrolytes or calcium and phosphorous concentrations until the second or third day of life when enteral feeding is started.

Answers

1. **A is false and the correct answer.** PN is important right after birth because normal fetal metabolic and growth rates and nutritional requirements do not stop with birth. Furthermore, the smaller and more preterm, the less body stores (protein, fat, and glycogen) are available to provide nutrients for metabolic needs. Intravenous feeding is always indicated when normal metabolic needs are not met by enteral feeding. Additionally, the metabolic and nutrient requirements of the newborn are equal to or greater than those of the fetus of the same gestational age. Thus the newborn infant should receive the same nutrition as the fetus of the same gestational age to maintain normal metabolism and growth. PN is particularly important to ensure full protein and energy supplies to maintain neuronal development. First week protein and energy intakes are associated with improved 18-month developmental outcomes in preterm infants, as well as greater adult lean body mass and higher resting energy expenditure.

TABLE 6.3 Parenteral Nutrition Calories and Calculations

	Calories per Gram	Calorie Distribution	Normal Laboratory Values	Concentrations and Calculations
Amino Acids	4 kcal/g	8%–10%		NOTE: Ordered as % (g/dL) or as g/kg/day (Volume infused ÷ Volume ordered) × grams/kg = g/kg of protein delivered g/kg of protein delivered × 4 kcal/g = kcal/kg from protein
Lipid Emulsion	10 kcal/g	30%–50%	TG <250 mg/dL	20% emulsion = 20 g fat/dL (0.2 g/mL) 10 kcal/g × 0.2 g/mL = 2 kcal/mL mL/day × 2 kcal/mL ÷ kg = kcal/kg from lipid mL/day ÷ 5 ÷ wt (kg) = g lipid/kg NOTE: Often infused separately from the other TPN components
Dextrose	3.4 kcal/g	50%–60%	Glucose 54–106 mg/dL	Ordered as % Dextrose (g/dL) **GIR calculations** (mL/hr × g/dL × 1000 mg/g) ÷ (kg × 60 min/hr × 100 mL/dL) = mg/kg/min mL/kg/d × g/dL × 0.007 = mg/kg/min mg/kg/min × kg ÷ 0.167 ÷ mL/hr = % dextrose (g/dL) **Dextrose Calorie Calculations** mL/hr × hr infused × g/dL ÷ 100 × 3.4 kcal/g ÷ kg = kcal/kg from dextrose

2. **B is correct.** Stock PN solutions can be stored in the pharmacy for immediate use, but like all pharmaceuticals, they cannot be stored indefinitely. A common stock PN mixture is 10% dextrose and 3% amino acids. At 80 mL/kg/day, this solution would provide 5.5 mg/kg/min of glucose (see Table 6.3 for calculations), which is appropriate for most preterm neonates. Because individual infants vary in response to dextrose infusions, one should always monitor the infant's glucose concentration frequently to ensure that normal values are maintained. This standard stock PN mixture will provide 2.4 g/kg/day of amino acids, still less than the 3.5-4 g/kg/day of amino acids that are needed in very preterm infants to restore *in utero* protein accretion and body growth (see Table 6.4). Stock PN solutions often are not supplemented with calcium and phosphorous salts, but both should be added to a customized PN within the 1st 24 to 48 hours. Plasma calcium and phosphorous as well as routine electrolytes should be measured within the 1st 24 hours as electrolyte disturbances are commonly observed after very preterm birth.

CASE 2

A 28-week gestation infant is born weighing 1.1 kg. Stock PN with 10% dextrose and 3% amino acids is started upon delivery at 80 mL/kg/day.

Exercise 3

Questions

1. How many nonprotein calories and how much protein are provided by this stock PN and will this be enough energy and protein to prevent protein breakdown in this infant?
   A. 27 kcal/kg/day and 2.4 g/kg/day
   B. 40 kcal/kg/day and 3 g/kg/day
   C. 22 kcal/kg/day and 4 g/kg/day
   D. 160 kcal/kg/day and 2 g/kg/day
2. Which of the following statements about IV dextrose infusion is FALSE?
   A. IV dextrose infusion should provide 30% to 50% of total caloric intake if no enteral feeding is provided.
   B. Excess IV dextrose infusion intake increases the incidence and severity of hyperglycemia.
   C. Glucose intolerance and hyperglycemia does not occur at glucose infusion rates <10 mg/kg/min.
   D. The glucose utilization rate is 2 to 4 mg/kg/min in term infants and 4 to 6 mg/kg/min in very preterm infants.

Answers

1. **A is correct.** 10% dextrose has a dextrose concentration of 10 g/100 mL. At an infusion rate of 80 mL/kg/day, it provides 27 kcal/kg/day (80 ml/kg/day × 10 g/dL ÷ 100 × 3.4 kcal/g of glucose = 27 kcal/kg/day). 3% amino acids has an amino acid concentration of 3 g/100 mL. At an infusion rate

TABLE 6.4 Basic Advance of Macronutrients

	Initial	Advancement		Goal
Oil Source(S)		**Less than 1250 g**	**Greater than 1250 g**	
Amino Acids, g/kg/day	2.5-3.5	0.5-1	---	3.5-4
Dextrose, mg/kg/min	4.5-5.5	0.5-1	1.5-2	7-9
Fat Emulsion, g/kg/day	1-2	0.5-1	1.5-2	3-3.5

of 80 mL/kg/day it provides 2.4 g/kg/day of amino acids. At least 1.5 g/kg/day of parenteral amino acids is necessary to prevent significant protein breakdown (catabolism). Thus while the energy from just the dextrose infusion may be insufficient to promote full utilization of the 2.4 g/kg/day of amino acids for net protein balance, it is sufficient, along with the amino acid infusion, to prevent protein breakdown.

2. **C is false and the correct answer.** The normal glucose utilization rate is 2 to 4 mg/kg/min in term infants and 4 to 6 mg/kg/min in very preterm infants. These rates provide 30% to 50% of total caloric intake if no enteral feeding is provided. IV dextrose above these rates is the principal cause of neonatal hyperglycemia, but other conditions contribute to this problem, making it common. Many of these infants also have stress-induced catecholamine, cortisol, and glucagon surges that suppress insulin secretion and promote glycogen breakdown and gluconeogenesis and reduce peripheral insulin and glucose sensitivity. Excessive dosing of IV lipids also aggravates hyperglycemia by providing competitive lipid carbon for oxidation and by producing cofactors in the liver from beta-oxidation of fatty acids that promote the regulatory enzymes in the gluconeogenic pathway. Most preterm infants and term infants continue to produce glucose from their liver at about 2 to 3 mg/kg/min. Furthermore, hepatic glucose production, even in preterm infants, is not easily suppressed by high glucose or insulin concentrations. If the parenteral dextrose infusion rate is >5 to 7 mg/kg/min, then total glucose utilization capacity will be exceeded, resulting in progressively increasing glucose concentrations. Increasing glucose infusion rate (GIR) above 8 to 10 mg/kg/min almost always contributes to hyperglycemia, which has many adverse consequences, including increased CO_2 production, lipogenesis, and development of a fatty liver with inflammation and steatosis.

   Glucose intolerance can occur in preterm infants even at a GIR of 6 mg/kg/min or lower, especially when glucose is infused without amino acids. Coinfusion of amino acids can reduce glucose concentrations and the incidence of hyperglycemia, as amino acids increase insulin secretion and promote anabolism (protein synthesis and protein balance) that requires energy production from glucose oxidation. Absence of enteral nutrition also contributes to the pathogenesis of hyperglycemia by limiting production of gut incretins, which stimulate insulin secretion. Infants of extremely low birth weight (ELBW) are very susceptible to hyperglycemia, further aggravating the overall nutritional status of these fragile infants. Reducing the GIR by coinfusing a lower dextrose fluid, reducing total fluids overall, or advancing feeds are effective ways to normalize glucose levels.

CASE 2 (continued)

On day 2, customized PN is ordered; 10% dextrose is continued, but amino acids are increased to 4 g/kg/day and intravenous lipids are started at 2 g/kg/day.

Exercise 4

Questions

1. How many calories are needed to achieve a growth rate of 15 to 20 g/kg/day in this infant on PN?
   A. 90 to 100 kcal/kg/day
   B. 60 to 80 kcal/kg/day
   C. 110 to 130 kcal/kg/day
   D. 140 to 160 kcal/kg/day
2. Which of the following statements about protein requirements in this newborn infant is CORRECT?
   A. Preterm infants should receive 2 to 2.5 g/kg/day of protein when receiving PN.
   B. Protein intakes of 4 to 4.5 g/kg/day are recommended for preterm infants with slow weight gain.
   C. The protein requirements of preterm infants are greater than those of term infants.
   D. Protein intakes >3.5 g/kg/day may result in high uric acid and creatinine levels.
3. Which of the following statements about PN amino acid practice is TRUE?
   A. Starting with higher amino acid intakes of 3 g/kg/day administered in the first few days of life is safe and decreases the incidence of extrauterine growth restriction.
   B. Current PN amino acid mixtures provide optimal amino acid supplies and plasma concentrations of all essential and nonessential amino acids for very preterm infants.
   C. Providing more amino acids, even above requirements, will improve growth and neurodevelopmental outcomes.

D. Only 3% amino acid solutions should be used to prevent osmotic injury to blood vessels and red blood cells.

4. Which of the following statements about IV lipid emulsions is FALSE?
   A. IV lipid emulsions must be started at 0.5 g/kg/day.
   B. Excess IV lipids often produce hypertriglyceridemia, a sign of reduced plasma lipid clearance.
   C. IV lipids produce carbon competition with glucose for oxidation, contributing to hyperglycemia.
   D. Advancing IV lipids to 3 to 3.5 g/kg/day is important for providing nonprotein calories for achieving positive energy balance and supporting protein synthesis and net protein balance.
   E. IV lipid emulsions do not contain sufficient amounts of docosahexaenoic acid (DHA) to meet normal fetal accretion of this essential polyunsaturated fatty acid (LCPUFA).

Answers

1. **A is correct.** The energy provided should meet the basal metabolic rate plus the energy cost of growth and losses (gastrointestinal, urinary, skin, others). To achieve a growth rate of 15 to 20 g/kg/day, the preterm infant requires 110 to 130 kcal/kg/day enterally. When all nutrition is PN, 90 to 100 kcal/kg/day should meet the growth needs, because there is no energy spent for digestion and absorption, and fecal losses are minimal. Energy losses are minimized by the use of a controlled thermoneutral environment and fluid losses are ameliorated by the use of humidification (which are further reduced by humidification of inhaled air/oxygen gases with assisted ventilation). See Table 6.3 to calculate the caloric content of PN solutions.
2. **C is correct.** Current pediatric amino acid solutions were initially formulated to meet the requirements of infants and children and provide a plasma amino acid profile similar to that of term 30-day-old breastfed infants. As such, they contain insufficient amounts of many amino acids, particularly essential and conditionally essential amino acids. It is fundamental that during fetal life, fractional growth rate and fractional protein synthetic rates, which determine amino acid requirements, decline with gestation. Fetal animal studies and the factorial method for assessing fetal protein requirements in human infants at 24 to 30 weeks' gestation show that 3.6 to 4.8 g/kg/day of amino acids support the more rapid growth at these early gestational ages. The average value of 4 g/kg/day is recommended as the guideline for infants after birth but of the same gestational age as the rapidly growing normal human fetus. At later gestational ages, less protein (amino acids) is needed; for example, 2.5 to 3.5 g/kg/day between 30 to 36 weeks and 1.5 to 2 g/kg/day at term (which is the amount provided by full breast feeding of mature mother's milk). These manufactured solutions contain essential amino acids and conditionally essential amino acids such as tyrosine and taurine. The delivery of gestational age–appropriate amounts of amino acids along with adequate energy results in positive nitrogen balance and a decrease in loss of body weight, thereby reducing time to regain birth weight. It is estimated that, in the absence of exogenous intake, endogenous protein losses are 0.5 to 1 g/kg/day for infants receiving only dextrose in the infusion. Protein should provide 8% to 10% of total calories; providing more than 10% of the gestational age–appropriate amount of protein is unnecessary and does not increase net protein accretion or body growth rate.
3. **A is correct**. Early introduction of amino acids in PN is safe, results in a positive nitrogen balance, and improves glucose tolerance, most likely by increasing insulin and IGF-1 secretion and enhancing protein synthesis that requires glucose for energy. More recent studies reveal that starting with higher amino acid intakes of 3 g/kg/day administered in the first few days of life is safe and decreases the incidence of extra uterine growth restriction. Answer B is incorrect, because current IV amino acid solutions were not developed to provide optimal individual amino acid delivery for newborn infants, including very preterm infants, infants with intrauterine growth restriction (IUGR), and especially infants with early postnatal physiologic and biochemical instability. Answer C is incorrect because the imbalance in plasma essential, conditionally essential, and nonessential amino acids provided in current neonatal IV amino acid solutions is not improved by simply increasing the IV amino acid intake (infusion) rate. Perhaps as a result of these limitations, there is only limited evidence that increased IV amino acid supply during the first days after birth improves growth or neurodevelopmental outcomes. Instead, neurodevelopment is improved when greater amounts of amino acids (and total protein when milk feedings are added) are given *with higher amounts of energy,* both carbohydrate and lipid. Maintaining the gestational age–appropriate protein intake supports brain growth as measured by head circumference and subsequent magnetic resonance imaging of the brain, even into adolescence. Commonly accepted recommendations for preterm infants are shown in Table 6.4, although there is considerable variability among NICUs in this practice. Intakes of amino acids higher than 4 g/kg/day right after birth have not been shown to further enhance protein balance, even in extremely preterm infants born between 23 and 28 weeks' gestation who require the higher amino acid and protein intakes for optimal growth. Answer D is incorrect because up to 5% amino acid solutions can be infused slowly through central venous catheters when concentrating PN to avoid over hydration and hyperglycemia.
4. **A is false and the correct answer** (see Table 6.4). IV lipid emulsions can be started at higher rates, up to 2.5 to 3.5 g/kg/day, but the most common practice is to start at about 1 to 2 g/kg/day and advance by 0.5 to 2 g/kg/day (slower rates for smaller, more preterm infants, faster rates for larger, less preterm infants) each

day up to 3 to 3.5 g/kg/day. Answer B is true, as many preterm infants—especially those born extremely preterm and of extremely low birth weight—have limited lipoprotein lipase activity (and other lipases), limiting their capacity for plasma lipid clearance. Although many use an upper limit of 200 to 250 mg/dL for serum triglyceride concentrations, there is no specific pathology associated with high levels of triglycerides, and they only indirectly indicate that oxidative metabolism of fatty acids released by lipases from triglycerides might be limited. Answer C is true because IV lipids can release sufficient amounts of fatty acids that produce carbon competition with glucose for mitochondrial oxidation, contributing to hyperglycemia. Similarly, hyperglycemia from excess IV dextrose infusion rates and other processes limit fatty acid carbon oxidation and their beneficial effect on energy balance. IV lipid emulsions do not, however, contain carnitine palmitoyltransferase (CPT), the enzyme necessary for transporting long chain fatty acids into mitochondria for oxidation. Milk and preterm formulas do contain reasonable amounts of CPT, indicating that IV nutrition with lipids requires some enteral feeding to allow sufficient fatty acid oxidation for achieving positive energy balance. Answer D is true because advancing IV lipids to 3 to 3.5 g/kg/day is important for providing nonprotein calories, for achieving positive energy balance, and supporting protein synthesis and net protein balance. Answer E is true. IV lipid emulsions do not contain sufficient amounts of docosahexaenoic acid (DHA) to meet normal fetal accretion of this essential polyunsaturated fatty acid (LCPUFA). Even fish oil–based IV lipid emulsions, which do contain some DHA, do not contain enough DHA to produce normal fetal DHA deposition rates. Fetal white adipose tissue accumulation during last trimester of n-3 fatty acid is about 45 to 65 mg/day (mostly as 22:6n-3, or DHA). A 1 kg preterm infant fed human milk containing 3.7 g fat/dL with 0.2% to 0.4% fatty acids as 22:6n-3 (DHA) at an enteral feeding volume of 180 mL/kg/day would receive only 13 to 25 mg 22:6n-3 DHA/day, clearly below normal in utero accretion rates. Preterm infants fed increased 22:6n-3 DHA may have higher visual acuity, particularly at 2 and 4 months, and improved Bayley mental development and MacArthur Communicative inventories at 12 months, but longer term studies have not shown a clear benefit to any aspect of neurodevelopment of supplemental DHA. Thus the current diet for preterm infants is deficient in this essential fatty acid, but the long-term significance of this deficiency is not known, nor is how these infants would develop if fed to sufficiency.

CASE 3

A 29-week gestation infant is on 6 cm H_2O CPAP with 30% Fio_2 and is breathing 50 to 60 breaths per minute without signs of respiratory distress. The infant is on stock PN, with a new custom PN providing 4 g/kg/day of amino acids, 10% dextrose, and lipids at 2 g/kg/day ordered for this evening. Enteral feedings are started with unsupplemented donor milk at 20 mL/kg/day with a plan to advance by 30 mL/kg/day after 3 days of trophic feeds.

Exercise 5

Questions

1. Which of the following is correct?
   A. The amino acid/dextrose/lipid infusion amounts should be decreased in amounts equivalent to the advanced enteral feeding nutrient amounts.
   B. PN infusion rates plus enteral feeding volumes should be adjusted to maintain 4 g/kg/day protein intake, plasma glucose concentrations between 54 and 106 mg/dL (3–6 mmol/L), and plasma triglyceride concentrations <250 mg/dL.
   C. The amino acid infusion rate should be decreased to 2 g/kg/day to avoid uremia (elevated blood urea nitrogen [BUN]), hyperammonemia, toxic amino acid concentrations, and adverse neurodevelopmental outcomes.
   D. Total energy intake should be increased to 120 or more kcal/kg/day to meet the protein intake of 4 g/kg/day, using the ratio of 30 kcal per g protein for all protein intake rates.
2. Which of the following is TRUE?
   A. Amino acid concentrations in standard IV amino acid solutions are balanced toward nonessential amino acids.
   B. IV glutamine is required to promote protein balance and reduce infections.
   C. Cysteine may be added to daily PN mixtures because it is a conditionally essential amino acid in extremely preterm infants that may be important during rapid growth periods.
   D. Carnitine should be added to all PN solutions starting on day 1 and continued as long as the infant is receiving PN regardless of enteral feeding advancements of milk or formula.
3. Which of the following statements about lipid emulsions is TRUE?
   A. Exclusive soybean oil IV lipid emulsions contain all of the required fatty acids, antiinflammatory products, and lack inflammatory substances such as phytosterols.
   B. Phytosterols are important for lipid solubility and thus should be added to all IV lipid emulsions.
   C. Fish oil (exclusive or partial) IV lipid emulsions have a higher n-3/n-6 ratio, which may have antiinflammatory properties that reduce parenteral nutrition–associated cholestatic liver disease (PNALD) and contribute to improved developmental outcomes.
   D. Use of IV lipid emulsions with mixtures of oils has been proven to improve outcomes.

Answers

1. **B is correct.** It is important to maintain the necessary protein and energy intakes required for growth as PN is reduced and enteral feedings are advanced. Maintaining sufficient protein and energy intake and meeting the needs for metabolism and growth are essential, but individual nutrients should be adjusted to ensure normal plasma nutrient and metabolic product concentrations. Answer A is incorrect, because this will lead to under nutrition as donor milk does not have sufficient protein to maintain normal protein balance and promote growth if IV amino acid infusion rates are decreased too quickly. Not uncommonly, PN is often reduced abruptly to allow for removal of central lines or because of poor peripheral IV access. However, this can produce a period of several days when there is inadequate protein and energy intake. Answer C is incorrect. Some clinicians have raised concerns about the adverse effects of higher early amino acid infusion rates on neurodevelopment because of the possibility of causing hyperaminoacidemia, metabolic acidosis, uremia, and hyperammonemia, but most studies have not shown such adverse outcomes. In fact, BUN concentrations and ammonia concentrations should both increase slightly with increased amino acid infusion rates if the amino acids are appropriately oxidized and producing ammonia and the liver is functioning well to remove ammonia through the urea cycle. There is little correlation between plasma BUN and ammonia concentrations and amino acid infusion rates in the acceptable range. Abnormally high amino acid concentrations generally are the result of excessive and unnecessary infusion rates (>4 g/kg/day) and limited urinary urea excretion. Caution should be used in giving high amino acid infusion rates to infants with impaired liver or renal function from hypoxic-ischemic injury that prevents ammonia detoxification by the damaged liver and urea and ammonia excretion by the damaged kidney. In contrast, the most common metabolic complication of IV amino acid solutions is lower than needed plasma concentrations of essential and some conditionally essential amino acids, as well as unbalanced amino acid concentrations, which together will limit anabolism and net protein balance. Furthermore, there are many examples of improved morbidities with optimal amino acid infusion rates. For example, a lower incidence of chronic lung disease has been reported in infants receiving higher intakes (4 g/kg/day) than in those receiving 3 g/kg/day, but whether this is due to improved lung growth directly from the amino acids or from amino acid production of IGF-1 is uncertain. Answer D is incorrect, because the protein-to-energy ratio is curvilinear; that is, there is not a fixed protein-to-energy ratio across the range of metabolizable, nonprotein energy intakes. It should be underscored that nitrogen retention increases with increasing energy intake up to about 80 to 90 kcal/kg/day, but at higher energy (caloric) intakes, there is no increased gain in net protein balance. The latter is achieved only with greater protein intakes. At low energy intakes, more energy improves protein balance, but greater amounts of energy, from both carbohydrate and lipid, above the amount needed for protein balance only contribute to greater fat accretion (see Table 6.3).
2. **C is correct.** Cysteine may be considered an essential amino acid in preterm infants, especially in infants less than 33 to 34 weeks' gestation, particularly during rapid growth. Cysteine is important for protein accretion and is added as cysteine hydrochloride 40 mg/g amino acid (not to exceed 100 mg/kg/day). Because the cysteine is added as a hydrochloride acid, it will lower the pH of the infusate and increase solubility of calcium and phosphorous. Cysteine is added at the time of compounding due to stability issues. Answer A is incorrect because the ideal PN solution for preterm infants is unknown. Currently, three formulations are available in the United States, and data to date do not allow firm conclusions of superiority of one over the other. Pediatric formulations used for preterm and term neonates contain higher concentrations of branched-chain amino acids (leucine, isoleucine, valine) and decreased amounts of methionine and phenylalanine due to their potential toxicity at very high concentrations (not seen with current solutions infused at customary rates). Neonates have additional amino acids that are considered conditionally essential (tyrosine, glutamine, arginine, cysteine, glycine, proline, and perhaps citrulline), but many of these are not provided in sufficient amounts to maintain overall normal metabolic, protein balance, and growth rates. Tyrosine is not present in these solutions but may be added as N-acetyl tyrosine, although there is no proven advantage to growth or metabolic conditions with this form of tyrosine. Answer B is incorrect. Glutamine, the most abundant amino acid in plasma and human milk, is not included in PN solutions because of decreased solubility. However, supplementation of glutamine in preterm infants has not been shown to improve mortality, rates of sepsis, or length of NICU stay. Therefore IV glutamine supplementation is not currently recommended; rather, it is provided with enteral feeding of milk or formula. Answer D is incorrect. Carnitine is another essential amino acid not included in available neonatal IV amino acid solutions. It is provided in human milk and has been added to preterm formulas. It is important for transport of long chain fatty acids across the inner mitochondrial membrane in all cells, making fatty acids available for energy production. Plasma levels decline without dietary supplementation. It is an accepted additive for long term PN (>2 weeks) when it does appear to increase hepatic cytosolic beta oxidation of long

TABLE 6.5 Lipid Emulsions

	Intralipid®	Omegaven®	Smoflipid®
	100% Soybean	Fish 100%	Soy 30% Olive 25% MCT 30% Fish 15%
Linoleic, g/L	88–124	1–7	28–50
Linolenic, g/L	8–22	<2	3–7
Palmitic, %	7–14	0.25–1	7–12
Oleic, %	19–30	0.6–1.3	29
DHA, mg/L	0	14.4–30.1	2.3
Alpha-Tocopherol, mg/dL	3.8	15–29.6	16.3–22.5
Phytosterols, mg/L	343	0	48

Intralipid®, Omegaven®, Smoflipid® manufactured by Fresenius Kabi

chain fatty acids. However, there is no evidence that even with this cytosolic oxidation there is improved energy balance or protein accretion.

3. **C is correct**. Exclusive fish oil–based lipid emulsions provide DHA, relatively large amounts of alpha-tocopherol, and no phytosterols (Table 6.5). An exclusive fish oil product (Omegaven®) is available in the United States under compassionate-use and research protocols only. It usually is given in combination with other lipid emulsions to provide a more balanced mix of fatty acids. n-3 fatty acids or very long chain polyunsaturated fatty acids (VLCPUFA) such as DHA have beneficial effects on the developing brain and retina and may be considered conditionally essential in preterm infants. Studies have demonstrated that the use of the fish oil emulsion can reverse or at least ameliorate hepatic dysfunction in infants and children with PNALD, but the quantity of fish oil emulsion required has not been determined, and variation in response among large numbers of subjects remains untested. Answer A is incorrect. Lipid emulsions, derived mainly from soybean and safflower oil, contain neutral triglycerides, glycerol, and phospholipids for emulsification. The most commonly used emulsion in the United States is soybean oil derived. It has no DHA and little α-tocopherol (vitamin E, as an antiinflammatory substance), and it contains medium chain fatty acids and large amounts of phytosterols. Answer B is incorrect. Phytosterols have been associated with Kupffer cell activation and inflammation, leading to hepatic injury and cirrhosis. Their elimination from nonsoybean oil IV lipid emulsions may be as or more important in preventing or ameliorating PNALD than the benefits assumed for fish oil and other short (oleic) and long chain polyunsaturated essential fatty acids (specifically, DHA) or antiinflammatory substances such as alpha-tocopherol. Answer D is incorrect. It is weighted to linoleic n-6 long chain fatty acids, producing a higher n-6/n-3 fatty acid ratio. Mixed soybean, olive, and fish oil–based emulsions containing medium chain fatty acids, alpha-tocopherol, significant amounts of DHA, and decreased amounts of n-6 PUFAs are available in Europe, and one has recently been introduced in the United States (Smoflipid®). It does contain phytosterols but in amounts much lower than the exclusive soybean oil product. To date there is no consistent evidence that the mixed-oil emulsions improve specific outcomes, particularly as the amount and duration of IV lipid emulsion use is diminishing with earlier and faster advancement of enteral feeding of milk.

CASE 3 (continued)

The first set of laboratory values are obtained at 24 hours of life: Na 138 mEq/L, K 4.2 mEq/L, Cl 108 mEq/L, HCO_3 19 mEq/L, glucose 109 mg/dL. The infant's urine output has been 2.2 mL/kg/hour. The infant is receiving 100 mL/kg/day of 4 g/kg/day of amino acids, a 10% dextrose solution, and 2 g/kg/day of lipids.

Exercise 6

Question

1. What electrolytes need to be added?
   A. 3 mEq/kg sodium acetate, 2 mEq/kg potassium acetate
   B. 2 mEq/kg sodium acetate, 1 mEq/kg potassium acetate
   C. No sodium and 2 mEq/kg potassium acetate
   D. No sodium or potassium

Answer

1. **D is correct.** Guidelines for mineral intakes are summarized in Table 6.6. Sodium is not needed during the first few days of life. All infants are born with an expanded extracellular fluid space and increased total body sodium content. The postnatal diuresis is responsible for removing fluid and ridding the body of excess sodium. A delayed diuresis or provision of maintenance sodium in the first few days of life has been associated with an increased risk of bronchopulmonary dysplasia. Furthermore, most ill or physiologically unstable preterm infants receive significant amounts of sodium in arterial line solutions and drugs such as ampicillin and heparin. Potassium should

TABLE 6.6 Electrolytes and Minerals

		TYPICAL REQUIREMENTS	
mEq/kg/day	Initial	Less than 1000 g	Greater than 1000 g
Sodium	0–1	4–8	3–4
Potassium	0–1	3–4	2–3
Calcium	0–2	3.5	3.5
Phosphorus	0–1	2–3	2–3
Chloride	0	2–7	2–7
Acetate	0–1	As needed	As needed

be added to the PN after the diuresis has been established. Many NICUs add calcium to the first PN solutions, although there is limited rational evidence for this practice other than perhaps to preserve myocardial contractility. The risk of adding calcium without phosphorus is significant, however, as calcium supplement alone increases the risk of hypophosphatemia.

CASE 4

A 25-week gestation infant is receiving low volume GI priming feeds and PN. The electrolyte concentrations on DOL 5 are reported as: Na 136 mEq/L, K 4.4 mEq/L, Cl 96 mEq/L, HCO_3 22 mEq/dL, phosphorus 5 mg/dL, glucose 95 mg/dL. The infant's urine output is 2.8 mL/kg/hour. The weight decreased 40 g. The infant is receiving 127 mL/kg/day of a 10% dextrose solution, 4 g/kg/day of amino acids, 2.5 g/kg/day of lipids. Current electrolyte and mineral content is sodium phosphate 3 mEq/kg, potassium acetate 3 mEq/kg, and calcium gluconate 3.5 mEq/kg. Arterial line fluids provide 2 mEq/kg of additional sodium acetate.

Exercise 7

Questions

1. What adjustments should be made to the electrolytes?
   A. Increase sodium acetate by 2 mEq/kg and decrease potassium acetate by 1 mEq/kg
   B. Replace all acetate with chloride
   C. Provide more chloride while maintaining sodium and potassium intake
   D. No changes
2. The current calcium to phosphorus provision is:
   A. Not optimal; the infant is hyperphosphatemic. Reduce the intake of phosphorous immediately.
   B. Suboptimal for day of life 5
   C. An inappropriate ratio, adjust to keep 1:1
   D. Appropriate in both amount and ratio
3. Which of the following are standardly included during the first weeks of PN therapy?
   A. Multivitamin and trace elements
   B. Iron
   C. Ranitidine
   D. Heparin
   E. All of the above
   F. A and D
4. If a Multitrace package is used, which trace elements do not align with current recommended requirements?
   A. Selenium
   B. Manganese
   C. Zinc
   D. Both A and C
   E. All of the above
5. PN now contains 4 g/kg/day amino acids, 12.5% dextrose, 3 g/kg/day lipid, 3 mEq/kg sodium acetate, 1 mEq/kg potassium chloride, 2 mEq/kg potassium phosphate, 2.6 mEq/kg calcium gluconate, pediatric MVI 1.5 mL/kg, 0.2 mL/kg Multitrace neonatal, and selenium 1.5 mcg/kg. What adjustments are needed to decrease risk of hepatotoxicity?
   A. Move all phosphorus to sodium phosphorus and reduce the intake of manganese
   B. Remove calcium gluconate
   C. Remove copper
   D. All of the above

Answers

1. **C is correct.** Sodium and potassium are within normal limits and infant is meeting required amounts (see Table 6.6). The diuretic phase should be completed and the infant should no longer be wasting bicarbonate in the urine. Therefore the focus needs to be changed to administering more chloride in the PN and IV fluids. Acetate and chloride intakes are generally considered in terms of ratios/percentages. For this infant, you may consider changing the arterial line fluids to 0.45% Sodium Chloride, which would result in a ratio of 60% acetate/40% chloride.
2. **D is correct**. The reported phosphorus level is normal for a newborn infant; laboratories frequently report adult ranges for phosphorus levels and may incorrectly categorize a level such as this as high. Intravenous calcium and phosphorus supplementation should be started in high-risk infants soon after birth with an optimal Ca/P ratio of 1:1 on a molar basis, 1.3 to 1.7:1 on a mg/mg basis, and 1 to 1.3:1 on a mEq/mEq basis to maximize accretion of both minerals. Given that this order is using mEq, the ratio is appropriate. The solubility of calcium and phosphorus in PN solutions depends on temperature (better at higher temperatures), amino acid concentrations (better with higher concentration), glucose concentration, pH, sequence of addition of calcium and phosphorus to the solution, the calcium and phosphorus ratio, and the presence of lipid. Adding cysteine to enhance protein balance lowers the pH and improves calcium and phosphorus solubility. Ionized calcium should be measured in such situations, particularly with hypoxic or ischemic conditions. Caution should be taken if calcium is infused into a peripheral IV catheter, as severe tissue necrosis and sloughing can occur with extravasations and even minor leaks. Some intensive care units avoid peripheral calcium administration entirely except in emergencies, such as hypocalcemic seizures or shock.

   Supplementation of calcium and phosphorous in PN provides 60% to 70% of the intrauterine mineral requirements; higher amounts are limited by their solubility in solution. See Table 6.6 for calcium and phosphorus advancement goals. Preterm infants are relatively osteopenic at birth because calcium is transferred mainly during the third trimester. Small for gestational age (SGA) infants with IUGR may have received even less calcium and phosphorus in utero and can develop a refeeding condition in which phosphorous concentrations can fall quite low. Therefore in such infants, phosphorus levels should be checked frequently until stable while receiving adequate nutrition. Hypophosphatemia in a refeeding syndrome

typically becomes apparent around 3 days following refeeding and may occur in the presence of IUGR. Respiratory and neuromuscular failure may result from the hypophosphatemia secondary to the refeeding syndrome. A decrease in effective diaphragmatic contractility secondary to inadequate adenosine triphosphate (ATP) may be the primary mechanism for the observed respiratory failure. Phosphorus levels are not included on standard electrolyte and basic metabolic panels, so they must be ordered separately.

3. **F is correct.** Vitamins for PN are provided as MVI Pediatric for the duration of PN therapy (Table 6.7) and trace elements such as zinc, copper, manganese, chromium, and selenium can be added (Table 6.8). Heparin 0.5 to 1 unit/mL should be added to PN solutions administered through a central catheter to maintain the patency of the catheter. Peripheral IVs may last longer with heparin in their infusate. Preterm infants have low iron stores, but they are at increased risk of developing iron deficiency anemia in early infancy. Because of concerns regarding iron overload, production of reactive oxygen species, and altered immune function, the timing of iron supplementation remains controversial. Ranitidine is no longer recommended as an additive. Recent studies demonstrated that by reducing normal gastric acidity, ranitidine reduces growth of microbes that are important for gut development and function and thus may increase the risk of necrotizing enterocolitis (NEC), pneumonia, and death in preterm infants.
4. **E is correct**. Recommendations have changed for zinc and manganese (see Table 6.8); therefore individual supplementation instead of a Multitrace package may be necessary. Selenium is not included in the Multitrace package and must always be added separately.
5. **A is correct.** There is significant aluminum contamination in albumin, blood products, certain medications, and PN components. Preterm infants are at high risk of aluminum accumulation and toxicity as they often require PN for many days and have immature kidneys incapable of excreting aluminum efficiently. Calcium gluconate and phosphate salts are high in aluminum content but are required by premature infants in substantial amounts to promote bone mineralization. The FDA has set limits for aluminum content of PN components but manufacturers are often unable to meet these restrictions. Healthcare providers should make a concerted effort to use the least contaminated products such as using sodium phosphate in preference to potassium phosphate, but there is no available alternative to calcium gluconate for PN compounding at this time.

   Manganese (Mn) is potentially neurotoxic and hepatotoxic. As Mn is a ubiquitous contaminant in PN solutions, more recent guidelines have lowered the acceptable amount, which is below that provided in the standard Multitrace product (Table 6.8). Mn supplementation should be omitted with any signs of hepatic dysfunction or cholestasis.

   In the past it was recommended to remove copper (Cu) in the presence of PN-associated liver disease. Because there have been reports of copper deficiency in such situations, however, some recommendations have changed to maintaining or reducing PN Cu while monitoring serum Cu on a biweekly or monthly basis in patients receiving long-term PN.

TABLE 6.7 Vitamin Components of TPN

Vitamins and Minerals	Vitamin Package 1.5–2 mL/kg/day	Recommended Intake
Vitamin A, IU/kg	690–920	700–1500
Vitamin D, IU/kg	96–160	40–160
Vitamin E, IU/kg	2.1–2.8	2.8–3.5
Vitamin K, mcg/kg	60–80	10–100
Thiamin, mcg/kg	360–480	200–350
Riboflavin, mcg/kg	336–560	150–200
Niacin, mg/kg	5.1–6.8	4–6.8
Vitamin B_6, mcg/kg	300–400	150–200
Folate, mcg/kg	42–56	56
Vitamin B_{12}, mcg/kg	0.3–0.4	0.3
Pantothenic Acid, mg/kg	1.5–2	1–2
Biotin, mcg/kg	6–8	5–8
Vitamin C, mg/kg	24–32	15–25

TABLE 6.8 Trace Elements for Parenteral Nutrition

mcg/kg/day	Multitrace-4 Neonatal Dose: 0.2 mL/kg/day	Recommended Intake
Chromium	0.17	0.05–0.2
Copper	20	20
Manganese	5	1
Selenium	0	1.5–4.5
Zinc	300	400

CASE 5

A 24-week gestation infant weighs 650 g and is receiving PN at 3 mL/hr containing 10.5% dextrose solution, 4 g/kg/day of amino acids and lipid infusing at 0.45 mL/hr via a peripheral venous central catheter (PICC). 1 mL/hr of 0.45% sodium acetate is running through an aterial line. Feeds of breast milk, 2 mL every 6 hours, were started yesterday. Total fluids are 148 mL/kg/day, not including lipids or trophic feeds. A recent glucose level was 135 mg/dL.

Exercise 8

Questions

1. In the middle of the night the infant's PAL must be pulled. Given the situation, what is the best course of action?
   A. Order D5W to run at 1 mL/hr along with the PICC
   B. Increase feeds to 8 mL every 6 hours
   C. Increase PN to 4 mL/hr
   D. Order a new bag of 0.45% sodium acetate to run through the PICC with the PN fluid

2. Later, the infant weighs 750 g and is receiving 144 mL/kg/day. Enteral feedings are increased to 3 mL every 2 hours. What should the PN rate be to maximize nutrition?
   A. 4.5 mL/hr
   B. 4 mL/hr
   C. 3 mL/hr
   D. 2 mL/hr

Answers

1. **D is correct.** Ordering a new bag of 0.45% sodium acetate to infuse through the PICC will maintain the total fluids goal and current GIR and avoid an unplanned reduction of sodium intake by 2.8 mEq/kg/day. A is incorrect. Adding D5W to coinfuse with the PN will increase the GIR by 1.4 mg/kg/min and possibly result in hyperglycemia. B is incorrect. A change in the rate of feedings would be appropriate only if it followed the patient's feeding advancement plan, but that is not likely given how recently enteral feedings were started. C is incorrect. Increasing the PN rate to 4 mL/hr would increase the GIR by 2.7 mg/kg/min and the AA delivery to 5.3 g/kg/day.
2. **C is correct.**

   Total fluids: 144 mL/kg/day × 0.75 kg ÷ 24 hr = 4.5 mL/hr

   Feeds: 3 mL × 12 feeds/day ÷ 24 hr = 1.5 mL/hr

   Therefore the PN rate will be: 4.5 − 1.5 = 3 mL/hr

   If the PN was ordered at the total fluid rate, as is still a common practice, the infant would have received 67% of the desired nutrient delivery. In this scenario, the PN would have delivered 2.7 g/kg/d of AA compared with 4 g/kg/day when concentrated.

   Nutrition delivery can be greatly improved by concentrating PN. However, care must be taken to avoid providing excessive nutrients when combined with advancing enteral nutrition. There also are limitations to what can be compounded into small volumes of PN. Additionally, a plan must be in place for unexpected cessation of feeds so that concentrated PN rate is not inappropriately increased above the ordered rate. Working with a pharmacist and dietitian is recommended.

CASE 6

A female neonate was born via cesarean section at 28 weeks' gestation to a 25-year-old primigravida woman. Apgar scores were 5 and 7 at 1 and 5 minutes of life. She required positive pressure ventilation, intubation, and surfactant administration in the delivery room. Her birth weight was 820 g. She was admitted to the NICU, placed on mechanical ventilation, and a UVC was inserted.

Exercise 9

Questions

1. On admission, what is the most appropriate IV solution for this newborn?
   A. 10% dextrose at 80 mL/kg/day
   B. 5% dextrose and 4% amino acid solution at 100 mL/kg/day
   C. 10% dextrose and 3% amino acid solution at 80 mL/kg/day
   D. 10% dextrose and 1% amino acid solution at 100 mL/kg/day
2. What are the advantages of using a central line for parenteral nutrition administration?
   A. Central lines have a lower rate of infectious complications than PIVs.
   B. Central lines can deliver dextrose concentrations >12.5%, but PIVs cannot.
   C. Lipid emulsions can only be administered through a central catheter.
   D. Central lines require lower doses of heparin than PIVs.
   E. Central lines may be left in place until discharge from the hospital and used as needed.

Answers

1. **C is correct**. The order provides an adequate amount of protein (2.4 g/kg/day) and GIR (5.6 mg/kg/min) for the first day of life, but these rates will be insufficient for total PN (TPN) and will at a minimum require frequent measurements of plasma glucose to ensure the dextrose infusion rate is sufficient to prevent hypoglycemia. Answer A is incorrect because no protein is given. Answer B is incorrect, because it provides a GIR of 3.5 mg/kg/min, which is low and likely contribute to hypoglycemia. However, it may be reasonable for a starting rate as long as plasma glucose concentrations are measured and adjusted to keep plasma glucose concentration within the normal range (54−106 mg/dL [3−6 mmol/L]). Furthermore, the amount of amino acids (4 g/kg/day) provided with choice B is excessive for day 1. Answer D is incorrect because it provides an insufficient amount of protein (1 g/kg/day). (See Table 6.4).
2. **B is correct.** See Table 6.2.

CASE 6 (continued)

At 27 hours of life, total fluids are increased to 100 mL/kg/day and a new PN is ordered with 10% dextrose, amino acids of 3 g/kg/day, and lipids at 1 g/kg/day. Six hours after new fluid is started, the serum glucose concentration is 250 mg/dL.

Exercise 10

Question

1. Which of the following strategies may be immediately helpful in reestablishing euglycemia?
   A. Decrease the dextrose concentration from 10% to 3%.
   B. Increase the dose of amino acids to 4 g/kg/day.
   C. Increase the dose of intravenous lipid.
   D. Administer insulin and check serum glucose in 30 minutes.
   E. Decrease GIR by lowering PN rate and coinfusing a solution with a lower dextrose concentration.

Answer

1. **E is correct**. Decreasing the GIR incrementally usually works over several hours and prevents potentially adverse osmotic shifts of water into cells. This can be achieved by manipulating rates and/or dextrose concentrations to lower the GIR by 1 to 2 mg/kg/min. Advancing enteral feedings will promote production of incretins from the gut which increase insulin production. Answer A is incorrect; using a dextrose concentration of 3% decreases the GIR to less than 4 mg/kg/min and may cause hemolysis because the solution is hypotonic. Answer B is incorrect; increasing the amount of amino acids infused might decrease the serum glucose concentration by increasing endogenous insulin secretion, but this does not lower the glucose concentration quickly. Answer C is incorrect; excess IV lipid promotes hepatic glucose production and competes with glucose carbon for oxidation and therefore may promote hyperglycemia. Answer D is incorrect; insulin can be used, but is difficult to titrate and increases the risk of hypoglycemia.

CASE 6 (continued)

The following laboratory values are obtained on day 2: Na 145 mEq/L, K 4.8 mEq/L, Cl 118 mEq/L, HCO_3 18 mEq/L, BUN 40 mg/dL, creatinine 0.81 mg/dL, glucose 127 mg/dL, Ca 8.1 mg/dL, magnesium 1.8 mg/dL, phosphorous 4.1 mg/dL, triglycerides (TG) 130 mg/dL, total bilirubin 7 mg/dL with a direct bilirubin 0.5 mg/dL. The infant's urine output is 0.8 mL/kg/hr. She is receiving 100 mL/kg/day of a 10% dextrose solution, 3 g/kg/day of amino acids, and 1 g/kg/day of lipids. Her weight has not changed significantly since birth.

Exercise 11

Questions

1. What changes should be made in her PN?
   A. Increase total fluid to 125 mL/kg/day, increase dextrose to 12.5%, decrease amino acids to 2 g/kg/day, and increase lipids to 2 g/kg/day. Add potassium phosphate.
   B. Leave the PN solution unchanged.
   C. Increase total fluid to 125 mL/kg/day, leave the dextrose unchanged, increase amino acids to 3.5 g/kg/day, and leave lipids unchanged. Add potassium phosphate.
   D. Decrease total fluid to 80 mL/kg/day, increase amino acids to 3.5 g/kg/day, leave the dextrose unchanged, and increase lipids to 2 g/kg/day. Add potassium phosphate.
   E. Continue total fluids at 100 mL/kg/day, decrease dextrose to 7.5%, increase amino acids to 4 g/kg/day, and increase lipids to 2 g/kg/day.
2. What laboratory tests should be ordered for the next day?
   A. Serum chemistries (Na, K, Cl, CO_2, glucose, Ca, P) and triglyceride levels
   B. Serum chemistries (Na, K, Cl, CO_2, BUN, glucose, Mg, Ca, P) and liver function studies (transaminases and alkaline phosphatase)
   C. Serum ammonia and lipid profile
3. Which of the following is the most correct statement regarding electrolyte and mineral requirements in PN for this infant?
   A. Sodium, iron, and calcium should be added as soon as PN is initiated.
   B. Sodium should be routinely added if the serum Na is <130 mEq/L. Potassium should be added when renal function is adequate.
   C. Maintenance sodium should be added once the diuresis is well established. Potassium should be withheld until renal function is deemed adequate.

Answers

1. **E is correct.** The infant's rising serum sodium concentration reflects either increased insensible water losses or increased excretion of "free water" relative to sodium excretion. Therefore interventions to decrease insensible water losses should be instituted, but total fluids should not be increased. Amino acids should be increased to 4 g/kg/day to meet protein requirements for a preterm infant with that degree of immaturity. An increase in BUN to 40 mg/dL may be a sign of reduced urine output (or increased protein utilization and oxidation), but it is a normal value and the protein intake should be advanced (not decreased). Increasing the amount of amino acids will permit the addition of more calcium and phosphorus in the parenteral solution because the pH will be lowered and the solubility of calcium increased. The infant is mildly hyperglycemic. Total GIR, therefore, should be decreased by decreasing the dextrose concentration while the fluid infusion rate is maintained. Plasma glucose concentrations should be checked again. The dose of intravenous lipids should be increased by 0.5 to 1 g/kg/day, to increase the caloric intake; it is unlikely that this will make the mild hyperglycemia worse, but this should be considered a possibility.
2. **A is correct.** This infant needs monitoring of routine serum chemistries as fluid balance and renal function are established, particularly if there is concern for renal dysfunction. Glucose levels should be checked to monitor the mild hyperglycemia. Triglyceride levels can be determined while advancing the dose of intravenous lipid. Liver function tests should only be checked if the direct bilirubin is elevated. In infants needing PN for more than 2 weeks, liver function tests should be monitored. (See Table 6.9).
3. **C is correct.** There is a physiologic contraction of the extracellular fluid space that occurs secondary to a postnatal diuresis in every newborn infant, although this usually is delayed by 2 to 3 days in preterm infants with respiratory distress syndrome. Sodium should be restricted to 0 to 1 mEq/kg/day in the intravenous solution until the diuresis is well established. Postdiuresis, when urine output begins to slow, repletion of sodium can start. Extremely premature infants have decreased renal tubular reabsorption and may require additional sodium to maintain normal levels. (See Table 6.6). Given the low urine output, potassium should be withheld until renal function is established and nonoliguric hyperkalemia is unlikely. Calcium and phosphorus should be started on day 1 to 2 of life.

TABLE 6.9 Laboratory Monitoring While on PN

	Initial	Once Stable
Glucose	every 4–6 hours	1–2 times daily
Electrolytes	Daily for 1–4 times	Extend out to twice weekly, then weekly for long-term PN
Phosphorus	Twice weekly	Weekly
Calcium	Twice weekly	Weekly/bimonthly
Triglycerides	Twice weekly	Weekly/biweekly
Alkaline Phosphatase	—	After 2 weeks, monthly
Fatty Acid Levels	—	Consider in infants on <1 g/kg lipids who are demonstrating poor growth
Direct Bilirubin	—	After 2 weeks

CASE 7

On day of life 4 an infant receives a PN at 120 mL/kg/day containing 12.5% dextrose, 3.5 g/kg/day amino acid, and 20% lipids (0.5 mL/hr) continuously over 24 hours. The infant's weight is 0.72 kg.

Exercise 12

Questions

1. What amount of energy does he receive from the nonprotein calories in PN?
   A. 78 kcal/kg/day
   B. 80 kcal/kg/day
   C. 84 kcal/kg/day
   D. 93 kcal/kg/day
   E. 125 kcal/kg/day
2. Assuming that at 2 weeks of life this infant is still receiving PN and enteral feedings and he now weighs 0.8 kg, what is his targeted whole body weight growth rate?
   A. 10 to 15 g/day
   B. 15 to 20 g/day
   C. 30 to 35 g/day
   D. An infant on PN is unlikely to gain weight

Answers

1. **C is correct.** See Table 6.3 for calculations.
   - Lipid emulsion: (0.5 mL/hr × 24 hours × 2 kcal/mL) ÷ 0.72 kg = 33 kcal/kg/day
   - Dextrose solution: 120 mL/kg/day × 12.5 g/dL × 0.034 kcal/g = 51 kcal/kg/day
   - Total Energy: 33 + 51 = 84 kcal/kg/day
2. **B is correct.** Ideally, postnatal growth of preterm infants should mimic *in utero* fetal growth at the same gestational age. The average fractional growth rate of the normal human fetus from midgestation to the late preterm period (up to about 36 weeks) is 17 g/kg/day. The average fractional growth rate of 17 g/kg/day can be achieved by a protein intake of 3.5 to 4 g/kg/day at 27 weeks that produces a net protein balance of 2 g/kg/day (300 mg/kg/day of nitrogen retention). Thus at 27 weeks and at a body weight of approximately 0.8 kg, the expected weight gain is 18 to 25 g/kg/d, which is 15-20 grams per day.

CASE 8

An AGA infant who was born at 24 weeks' gestation develops severe NEC at day of life 19 and requires an exploratory laparotomy, resection of 2 cm of necrotic intestine, and an ostomy.

Exercise 13

Before surgery, recorded weight is 770 g. The plasma glucose concentration was 151 mg/dL; no other laboratory results are available. Current fluids are D10W with 3 mEq/dL NaCl and 2 mEq/dL K acetate at 4.3 mL/hr.

Question

1. Which of the following would be the most appropriate PN order for this infant?
   A. 5% dextrose with 2 g/kg/day amino acids, no Smoflipid®
   B. 10% dextrose at a rate of 5.1 mL/hr
   C. 6% dextrose with 4 g/kg/day amino acids, 1 g/kg/day Smoflipid®
   D. 8.5% dextrose with 4 g/kg/day amino acids, 2 g/kg/day Smoflipid®

Answer

1. **D is correct**. The current GIR is 9.4 mg/kg/min; the infant is hyperglycemic and under stress. Therefore reducing the GIR by 1 to 2 mg/kg/day is warranted. This infant is at significant risk for malnutrition and requires calories (appropriate GIR and Smoflipid® to reduce risk of PNALD) and protein (4 g/kg/day amino acids) for healing.

CASE 8 (continued)

Trophic feeds are resumed 8 days later. After 1 day of feeds, the infant decompensates; there is concern for infection and the infant is placed on an oscillator and kept NPO for 4 days. Feedings are resumed a second time for 6 days before the infant is made NPO for a PDA ligation. Ostomy output is minimal during this time.

Exercise 14

Questions

1. What complications related to provision of nutrition would you be concerned for in this case?
   A. Parenteral nutrition associated cholestasis and hepatocellular injury
   B. Metabolic bone disease and anemia
   C. Central line–associated bloodstream infections
   D. Short bowel syndrome and "dumping"
   E. All of the above
2. A direct bilirubin was checked and found to be 3 mg/dL. What actions should be taken?
   A. Restart enteral feeds and continue Smoflipid®.
   B. Request a surgery consultation for bowel reanastomosis and closure of the ostomy.

TABLE 6.10 Complications of PN

Metabolic	Short-term	Hyperglycemia Electrolyte imbalance Hyperlipidemia
	Long-term	Metabolic bone disease PN-associated liver disease Growth failure Aluminum toxicity
Related to Administration	Infectious	Sepsis Liver abscess
	Mechanical	Infiltration Extravasation Thrombosis Pericardial effusion Pleural effusion Arrhythmias

C. Start ursodiol and sodium chloride supplements via gavage to decrease cholestasis and replenish sodium.
D. Start phototherapy to decrease bilirubin.
E. Remove copper and manganese from PN.

Answers

1. **E is correct**. Complications associated with PN use can be classified as metabolic (generally short-term complications), hepatotoxic (long-term complication), mechanical, or infectious (short- and long-term). (See Table 6.10.) Most of the metabolic complications can be prevented using a stepwise advancement in the constituents and careful monitoring. Infectious complications can be prevented by aseptic line insertion and careful maintenance, including sterile change of infusion solutions, minimizing access to the line for administering other medications or blood products, and removing the catheters when enteral feeds are progressing well and have reached 120 mL/kg/day.

   Hepatic dysfunction, including PN-associated liver disease, is of multifactorial etiology and can manifest after only 2 weeks of initiation of PN. The risk factors are the duration of PN, the delay in initiation of enteral feeding, and the degree of prematurity. It is most common in extremely preterm, ELBW infants who have a prolonged period of feeding intolerance, infants with gastroschisis or omphaloceles, and in infants with short gut syndromes following surgical resection usually for severe NEC. The earliest biochemical derangement is an increase in serum bile acids. This is followed by a rise in direct bilirubin, alkaline phosphatase, and gamma-glutamyl transferase; transaminases increase last. At the cellular level, it manifests as cholestasis that can advance to portal fibrosis and cirrhosis. Multiple strategies have been proposed for prevention and treatment of PNALD, including limiting the amount of lipid infused, "cycling" of PN (not generally recommended in preterm infants), administering ursodiol to treat cholestasis, and, most importantly, the early introduction and continuation of enteral feeds.

2. **A is correct**. The most helpful action in preventing the progression of disease would be to restart enteral feeds, preferably with mother's own milk or, second best, donor milk, advancing slowly as tolerated. Bowel reanastomosis could potentially resolve the dumping and allow him to tolerate enteral feedings. Intravenous lipids should be decreased if using an exclusive soybean oil mixture, as there is a strong association with soy lipid emulsions and hepatocellular injury. Alternatively, Smoflipid® (see Table 6.5) could be used, which has less soybean oil (30%), increased antiinflammatory DHA from 15% fish oil, other important fatty acids from olive oil (25%) and medium chain triglycerides (30%) which are more efficiently metabolized. Ursodiol is given enterally so it cannot be currently used in this infant. Direct hyperbilirubinemia is generally considered a contraindication for phototherapy. It is no longer recommended to remove copper without defined deficiency, but manganese might be removed from the PN.

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Abstract: Parenteral nutrition (PN) is used to provide nutrients to newborn infants who cannot tolerate full enteral nutrition or have contraindications to enteral nutrition. Intravenous feeding is essential, but it should not be a sole substitute for enteral nutrition unless the infant has absolutely no capacity for enteral feedings. Such conditions are rare and usually short term, such as intestinal obstructions (atresias or totally obstructing bands), malformations (gastroschisis, severe omphalocele), or early gut infarctions and perforations. Such infants may be able to be fed enterally in very small amounts, especially if an ostomy is placed distal to the obstruction. One of the most common indications for PN is preterm birth. The more preterm and smaller an infant is born, the more urgent immediate and adequate parenteral nutrition becomes. The majority of somatic growth and nitrogen and mineral accretion takes place during the third trimester. The ideal postnatal nutrition for preterm infants is one that results in postnatal growth (rate and body composition) similar to that of the normal, healthy, growing fetus in utero at the same gestational age as the newly born preterm infant. Achieving this rate of growth after preterm birth is difficult and challenging. Most of the "growth restriction" that develops in preterm infants after birth is the result of under nutrition, particularly from delayed enteral feeding. Other reasons include diseases that may preclude enteral nutrition, delay in starting appropriate PN, intolerance to enteral feeds, and inappropriate feedings or feeding strategies.

Keywords: Parenteral nutrition, Preterm infant, Neonate, Protein, Carbohydrates, Glucose, Lipids

7

Enteral Nutrition

Brenda B. Poindexter, Camilia R. Martin, MD, MS

Evidence is increasingly accumulating that nutritional inadequacies in the early neonatal period have both short- and long-term consequences. Nonetheless, provision of adequate nutritional support to the high-risk premature infant remains a significant clinical challenge. Among extremely premature infants, duplicating rates of in utero growth remains an elusive goal and postnatal growth failure remains a common complication of neonatal intensive care. This chapter contains exercises designed to help those who care for premature infants to review enteral nutrient requirements, identify strategies to optimize provision of nutrition, and describe the importance of adequate postnatal growth. In addition, areas where further research is needed to determine optimal nutritional support to improve outcomes in this population are emphasized.

NUTRIENT REQUIREMENTS

The current recommendations for enteral nutrient intake for very low birth weight (VLBW; less than 1500 g) premature infants are presented in Table 7.1. These recommendations are based on current evidence and consensus of an expert panel. It is important to recognize that a combination of both parenteral and enteral nutrition is needed during the early phase of nutritional support of premature infants to avoid nutrient deficits that contribute to postnatal growth failure. Fortification of human milk (both maternal and donor) is also necessary to meet these nutrient requirements to support optimal growth and outcomes. Although meeting these recommendations can be particularly challenging in extremely low birth weight (ELBW) infants, standardized feeding protocols have been shown to be associated with improved outcomes in this population, including the number of days to reach full enteral feedings and the number of days of total parenteral nutrition.

These recommendations for nutrient intake are for most stable, growing VLBW infants. An individualized approach to account for nutrient deficits, disease factors such as bronchopulmonary dysplasia or necrotizing enterocolitis (NEC), rate and proportion of both weight gain and linear growth, and the predominant source of enteral feeding may necessitate adjustment to meet the needs of some infants. It is important to point out that energy requirements are lower (85–95 kcal per kg/day) if the infant is receiving parenteral nutrition. Although most clinicians focus on daily enteral intake in terms of volume (mL per kg/d) or calories (kcal per kg/d), protein intake should be carefully considered, as inadequate protein intake is associated with poor growth and adverse neurodevelopmental outcomes in ELBW infants. A comparison of estimated protein intake is shown in Table 7.2. As will be discussed later in this chapter, erroneous assumptions made about the nutrient content of human milk before the addition of fortifier or after handling and storage may inadvertently result in suboptimal nutrient intake (especially energy and protein).

INITIATION AND ADVANCEMENT OF ENTERAL NUTRITION

CASE 1

A 27-week gestation female is delivered by cesarean section because of worsening maternal preeclampsia. Her birth weight is 635 g. She was placed on bubble continuous positive airway pressure (CPAP) in the delivery room and has been stable overnight on less than 30% supplemental oxygen. Upon her admission to the NICU, starter parenteral nutrition (PN) with 10% dextrose and 3 g/kg/day of intravenous amino acids was initiated through an umbilical venous line. On rounds, her bedside nurse inquires as to when the baby will start to receive enteral feedings.

Exercise 1

Question

1. Which of these statements reflects an evidence-based decision related to the initiation of enteral feedings in this infant?
   A. PN is supplying the infant with all necessary nutrients; enteral feeding should be delayed until the infant is no longer at risk of developing NEC.
   B. Feedings should not be initiated until the umbilical line is removed.
   C. Feedings can be initiated using half-strength premature formula.
   D. Enteral feedings (10–20 mL/kg/day) with human milk should be initiated today.

TABLE 7.1 Recommended Enteral Intakes for Premature VLBW Infants

Nutrient	per kg/day	per 100 kcal
Fluids, mL	135–200	-
Energy, kcal	110–130	-
Protein, g	3.5–4.5	3.2–4.1
Lipid, g	4.6–6.6	4.4–6
Carbohydrate, g	11.6–13.2	10.5–12
Calcium, mg	120–200	109–182
Phosphate, mg	60–140	55–127
Iron, mg	2–3	1.8–2.7
Vitamin D, IU	400–1000	-

Adapted from Koletzko B, Poindexter B, Uauy R, editors: *Nutritional Care of Preterm Infants Scientific Basis and Practical Guidelines,* Vol. 110, 2014, World Review of Nutrition and Dietetics Karger.

TABLE 7.2 Protein Intake With Enteral Feedings at 150 mL/kg/d

	Protein (g/kg/d)
Donor human milk (assume 0.7–1 g/dL)	1.05–1.5
Preterm human milk (assume 1.4–1.6 g/dL)	2.1–2.4
Preterm human milk + human milk fortifier (24 kcal/oz)	3.5–4.5
Preterm formula (24 kcal/oz)	3.6–4.3
Transitional/postdischarge formula (22 kcal/oz)	3.1
Term formula	2.1

Answer

1. **D.** Although the infant is receiving a reasonable intake from PN, it is important that consideration is given to beginning enteral feedings as early as possible. There are known benefits of early enteral feedings in premature neonates, and conversely, potential detriment to postnatal intestinal adaptation with a prolonged absence of any enteral feedings. If maternal milk is not available, donor human milk can be used so that the initiation of enteral feedings is not delayed. The presence of an umbilical line does not preclude the initiation of low-volume enteral feedings. Furthermore, there is no evidence to support the use of diluted or half-strength formula as an effective strategy to decrease the risk of NEC.

Initiation of Enteral Nutrition

Decisions related to introduction and advancement of enteral feedings present several dilemmas for clinicians and have the potential to have an impact on important morbidities such as NEC and late-onset sepsis. Although the fear of NEC has historically driven a delayed approach to enteral feeding, there are a number of reasons to recommend early initiation of enteral nutrition in premature infants. In a piglet model of neonatal nutrition, a delay in enteral feedings resulted in a decrease in cell proliferation in the small intestines, a decrease in superior mesenteric artery blood flow, and an increase in apoptosis.

Minimal enteral feedings, also known as trophic feedings, are typically defined as low-volume (less than 24 mL/kg/day initiated within 96 hours of birth and continued for 1 week) feedings that do not provide sufficient calories to support somatic growth but help to promote maturation of the structure and function of the premature intestinal tract (also known as "gut priming"). Few studies have specifically evaluated the effect of early trophic feeding versus a similar duration of enteral fasting in ELBW or VLBW infants. The most recent Cochrane review included nine trials with a total of 754 VLBW infants (and very few ELBW infants included); this metaanalysis found no evidence of benefit or harm of early trophic enteral feeding, including no difference in the incidence of NEC.

Having a standardized feeding protocol for VLBW that includes initiation of enteral nutrition within 6 to 48 hours of birth has been associated with improved outcomes, including a reduction in the number of days of parenteral nutrition, a reduced risk of NEC, and reduced rates of late-onset sepsis. Indeed, a risk factor for progression from medical to surgical NEC is having never received any enteral feeding.

The presence of umbilical lines, including an umbilical arterial catheter, is not a reason to withhold enteral nutrition. Current evidence has not supported the theoretical concern of the umbilical catheter reducing intestinal blood flow or increasing medical complications during trophic feedings. In addition, the common practice of withholding enteral feedings during treatment for a patent ductus arteriosus has recently been called into question. A randomized clinical trial demonstrated that continuation of trophic feedings at 15 mL/kg/d during treatment with indomethacin versus no enteral feedings resulted in fewer days to achieve full enteral feedings (defined as 120 mL/kg/d) with no increase in complications including NEC or spontaneous intestinal perforation.

If available, expressed maternal milk should be provided as the initial feeding. The initiation of early enteral nutrition should not be delayed until maternal milk is available; donor human milk can be used as a bridge until maternal milk supply is established. Several clinical studies have demonstrated reductions in the number of days to achieve full enteral feeding, total number of days that enteral feeds are withheld, and days of hospital stay. Oral colostrum care is not a substitute for minimal enteral nutrition.

Advancement of Enteral Nutrition

There is no universal consensus on the optimal rate of advancement of enteral feedings in ELBW and VLBW infants. The rate of advancement is one potentially modifiable risk factor—with too rapid of feedings being associated with NEC and sustained level of trophic feedings or too slow of advancement resulting in longer time to full enteral feedings and prolonged use of central venous lines and parenteral nutrition. Neither early versus late initiation of enteral feedings nor slow versus fast enteral advancement were shown to

reduce NEC as summarized in recent systemic reviews. Several studies have shown a decrease in the incidence of NEC with the implementation of standardized feeding protocols.

Investigators in the United Kingdom have recently completed the speed of increasing milk feeds trial (SIFT; NCT01727609). Approximately 2800 VLBW infants were enrolled in this multicenter trial, and infants were randomized to slower or faster (18 versus 30 mL/kg/day) advancement of feedings until they reached full milk feedings (defined as 150 mL/kg/d). The primary outcome is survival without moderate or severe neurodevelopmental disability at 24 months corrected age. A published report of these data is pending but will be critical in confirming in VLBW infants the short-term benefits previously reported of a faster feeding advancement and adding to the literature that practice is without potential harm.

A recent randomized clinical trial evaluated early progressive feeding (without a period of trophic feeding) and delayed progressive feeding after a 4-day course of trophic feeding in 60 ELBW infants. The primary outcome was the number of full enteral feeding days in the first month after birth; infants randomized to early progression of feeding were found to have a 2-day advantage in the number of full enteral feeding days and a reduction in the number of days of parenteral nutrition. Of note, these investigators found no difference in the composite outcome of NEC or death between groups, although the study was not adequately powered to detect a difference in NEC.

Intrauterine Growth Restriction (IUGR)

According to the 2013 Fenton Growth Curve, the birth weight of the infant in this case is at the 9th percentile and is thus considered growth restricted. IUGR infants have an increased risk of NEC. As a result, it is common practice to delay initiation of enteral nutrition to theoretically reduce the compromise to an already perceived compromised gut. However, this strategy is not evidence-based and has been challenged in several studies. A delay in the initiation of enteral feedings (>48 hrs) in growth-restricted infants with abnormal umbilical artery Doppler waveforms did not lead to a lower risk of NEC; in contrast, feedings initiated within 48 hours reduced the time to full enteral feedings (with a concomitant reduction in the days requiring parenteral nutrition) and reduced the risk of cholestasis. This has been recently confirmed in a cohort of 62 growth-restricted babies in which early versus late enteral feeding had earlier discontinuation of PN and time to regain birth weight without an increase in NEC incidence.

HUMAN MILK

CASE 2

The attending obstetrician requests an antenatal consult for a 26-year-old primigravida who has presented at 24 weeks estimated gestational age with premature labor with rupture of membranes and imminent delivery.

Exercise 2

Question

Which of the following statements regarding provision of human milk to premature infants should be included in the consult?

1. Mother's own milk supports the preterm infant's developing immune system.
2. Premature infants who receive their mother's own milk have a lower incidence of sepsis and NEC.
3. Premature infants who receive mother's own milk demonstrate improved developmental outcomes compared with formula-fed premature infants.

Answer

All of the above statements are true.

Given these and other important benefits, the use of mother's own milk should be encouraged for all premature infants. The use of mother's own milk as the primary diet for preterm infants was affirmed in policy statements from the American Academy of Pediatrics and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN).

Several studies have demonstrated the immunologic benefits of human milk for premature infants, including higher concentrations of secretory IgA, lysozyme, lactoferrin, and interferon in preterm human milk. Provision of mother's own milk may also enhance colonization of the infant's intestinal tract with beneficial commensal organisms. The incidence of infection, bronchopulmonary dysplasia, and NEC are decreased in preterm infants who receive mother's own milk. In addition, observational studies in ELBW infants have shown an association between exposure to mother's own milk and improved neurodevelopmental outcomes at 18 to 22 months' corrected age and at preschool age (30 months). The number of days in the first postnatal month that an infant received >50% breast milk was positively correlated with deep nuclear gray matter volume at term equivalent and cognitive and motor outcomes at 7 years of age. In another study, maternal milk was also found to decrease the need for rehospitalization between NICU discharge and 30 months' corrected age.

It is important to recognize that many mothers who deliver prematurely will choose to express milk for their infant once they are properly informed of the numerous benefits. All caregivers providing care to ELBW and VLBW infants should be knowledgeable with respect to the many benefits of mother's own milk and must be committed to ensuring that all mothers in their care are equipped to express their breast milk. Many units have successfully implemented quality improvement initiatives to increase human milk usage in preterm infants.

CASE 3: BANKED DONOR HUMAN MILK

After observing your conversation with the mother, the neonatal nurse practitioner in the NICU asks your opinion

regarding the use of banked donor human milk if the mother is unable to provide enough milk for her infant.

Exercise 3

Question

Which of the following statements are true based on currently available evidence?

1. Donor milk is pasteurized to minimize risk of infection.
2. Pasteurization preserves all immunologic benefits of human milk.
3. The nutrient composition of banked donor milk is comparable to preterm human milk.
4. Premature infants who receive donor milk demonstrate similar rates of weight gain as those who are fed premature formula.

Answer

Only the first statement is true.

Pasteurized donor human milk is recommended for premature infants if mother's own milk is not available. Donors are screened for infectious risk and the milk is heat pasteurized to avoid bacterial and viral contamination.

The use of donor human milk in neonatal intensive care units continues to increase, as has the number of milk banks in the Human Milk Banking Association of North America (HMBANA). These milk banks usually obtain milk from donors who delivered term infants, resulting in a lower protein content than preterm maternal milk. Most HMBANA banks will randomly pool batches of milk from three to five donors to decrease variability, and some will strategically combine milk to target specific caloric and/or protein density. Macronutrient content of pooled donor milk has been evaluated, with some investigators reporting an average protein content less than 1 g/dL and energy content less than 15 kcal/oz in samples analyzed. Although pasteurization does not alter fatty acid levels in donor milk, the content of docosahexaenoic acid (DHA) and arachidonic acid (ARA) were lower than what has been previously reported in human milk. The lactational stage of the milk accounts for much of the variation reported in protein, amino acid, and fatty acid content seen in donor milk. The pasteurization process for donor milk reduces bioactive components such as macrophages, neutrophils, secretory IgA, lactoferrin, and lysozyme. Although pasteurization does not appear to affect levels of human milk oligosaccharides, the significance of differences in these compounds between donor and maternal milk remains unclear. Future research should be directed at optimizing pasteurization to preserve the beneficial properties of human milk and pooling of donors to achieve optimal levels of nutrients such as protein and other nonnutritive components of human milk.

A number of studies have evaluated growth of premature infants receiving donor human milk. Most observational studies have found lower rates of weight gain and linear growth in infants receiving predominantly donor milk, although other more recent studies have found adequate growth when donor milk is appropriately fortified. A recent multicenter randomized trial was conducted at four centers in Canada to evaluate neurodevelopment at 18 months in VLBW infants randomized to receive preterm formula versus fortified donor human milk as a supplement to maternal breast milk. Although there was not a significant difference in the composite cognitive score on the Bayley Scales of Infant Development III between the two diets, a higher proportion of infants in the donor milk group were found to have a cognitive score less than 85 (consistent with moderate impairment). A high proportion of infants in both groups received maternal milk in this study, potentially contributing to confounding of the results. Another large randomized trial is underway to evaluate the impact of donor human milk on neurodevelopmental outcomes in ELBW infants receiving minimal maternal milk (NCT01534481).

CASE 4: COMPOSITION OF PREMATURE HUMAN MILK

Shortly after completion of the antenatal consult, a 710 g female is delivered at 24 weeks estimated gestational age. Her mother is instructed in the use of a hospital-grade electric breast pump and is expressing milk every 3 hours. Five days after delivery, the mother is pumping approximately 9 oz of milk each day.

Exercise 4

Question

Which of the following statements regarding the composition of this mother's milk in the first week after delivery are true?

1. The protein content is lower now than it will be after 4 weeks of lactation.
2. Milk expressed at 2 weeks is sufficient to meet all nutrient requirements of this infant.
3. Expressed milk has higher content of calcium and phosphorus than preterm formula.

Answer

None of the above statements are true.

A thorough understanding the nutrient content of human milk is needed to make informed decisions about provision of optimal nutritional support to premature infants. The composition of milk expressed by women who deliver prematurely is different from that of women who deliver at term. In the first 2 weeks of lactation, the protein content of preterm human milk is typically 1.4 to 1.6 g/dL. Over time, the protein content steadily declines to that of term milk (average 1.0 g/dL). Despite the higher content of protein and some minerals, preterm human milk alone does not meet all nutrient requirements of extremely premature infants and requires fortification. During the transition to full-volume enteral feedings, supplemental parenteral nutrition is needed to meet the recommended intake of nutrients.

CASE 5: FORTIFICATION OF HUMAN MILK

The former 24 week extremely premature infant is now 5 days of age and weighs 700 g (10 g below her birth weight).

She is receiving approximately 60 mL/kg/d of her mother's own milk and supplemental parenteral nutrition.

Exercise 5

Question

Which of the following alterations should be made to her feeding regimen?

1. Change to premature formula to achieve better weight gain
2. Add human milk fortifier (HMF)
3. No changes are required; weight gain is adequate for a premature infant

Answer

The correct response is 2.

Preterm human milk provides insufficient quantities of protein, energy, sodium, phosphate, and calcium to meet the estimated needs of the preterm infant. To meet needs for growth and to avoid osteopenia, a number of multicomponent human milk fortifiers are available. Current options for multicomponent fortification of human milk include bovine human milk fortifier (HMF) and human milk–based fortifier (HMBF). A human milk–derived cream supplement and a liquid protein supplement are also available if additional energy or protein are needed beyond the standard HMF. Depending on the volume of maternal milk available, high-caloric preterm formula can also be used. Given the potential risk of infectious complications, the use of powdered products should be avoided. Input from a neonatal dietitian is invaluable when individualizing decisions related to fortification.

To minimize nutrient deficits and optimize postnatal growth, early fortification of human milk is recommended (before an enteral volume of 100 mL/kg/d is reached). Some experts suggest that fortification of human milk can be introduced at much lower volumes (40–60 mL/kg/d). A prospective observational study reported improved weight gain and linear growth in a cohort of premature infants (birth weight ≤1250 g) with HMBF started at 60 mL/kg/d. As a strategy for fortification of human milk is prescribed, it is important to take into consideration the alterations in protein content that take place as lactation progresses to ensure that requirements are met. The use of multicomponent bovine HMF is associated with short-term improvements in weight gain, linear growth, and head circumference growth. The data are insufficient to evaluate the effect of fortifiers on long-term growth outcomes and neurodevelopment.

Randomized trials comparing bovine HMF to HMBF have been confounded with the use of bovine preterm formula. Although infants randomized to a sole diet of donor human milk fortified with HMBF were found to have a lower incidence of NEC than those randomized to bovine HMF, infants in the bovine HMF group also received a base diet of preterm formula. Adequately powered trials comparing bovine HMF to HMBF with a base diet of maternal and/or donor human milk are needed to assess the impact on important outcomes such as NEC.

A recent study compared HMBF to bovine HMF in a blinded randomized clinical trial in premature infants weighing less than 1250 g and found that the use of HMBF did not improve feeding tolerance compared with fortification with bovine HMF.

CASE 6: PRETERM FORMULA

A former 29-week gestation female (birth weight 1250 g) is now 3 weeks of age, and the mother's milk supply is not adequate despite excellent support from a lactation counselor. The mother has not consented for use of donor human milk. The medical student asks what types of formulas are available for premature infants.

Exercise 6

Question

Which of the following statements regarding premature infant formulas are true?

1. Like human milk, lactose is the exclusive source of carbohydrate in premature formulas.
2. In contrast to formulas designed for term infants, premature formulas supply 40% to 50% of the total lipid content as medium chain triglycerides.
3. The protein composition of premature formulas is predominantly casein based.
4. The protein content of premature formula is similar to fortified human milk.
5. The calcium and phosphorus content of premature formulas is lower than that of term formula.

Answer

Statements 2 and 4 are true; the remaining statements are all false.

Lactose is the only source of carbohydrate in both term and preterm human milk. The carbohydrate content of premature formulas, on the other hand, is a blend of 40% to 50% lactose and 50% to 60% glucose polymers (such as corn syrup solids). Premature infants have low levels of intestinal lactase activity; consequently, the reduced lactose content of premature formulas theoretically enhances digestion. Glucose polymers are easily digested by alpha-glucosidase enzymes (sucrase, isomaltase, maltase, glucoamylase). These enzymes, in contrast to lactase, are abundant in the small intestine of premature infants and approximate adult levels much sooner.

Human milk supplies approximately 50% of total calories from fat. Preterm formulas contain medium chain triglycerides (MCT) to compensate for low levels of intestinal lipase and bile salts in premature infants. In addition, most formulas are now supplemented with DHA and ARA, long chain polyunsaturated fatty acids found in human milk and thought to be important for brain and retinal development.

The protein content of premature formulas is higher than term formulas. Standard preterm formulas supply 3.3 to 3.6 g/100 kcal. Patterned after human milk, premature formulas

are whey predominant. Soy-based formulas are not routinely recommended for the premature infant, as they contain significantly less phosphorus and may result in metabolic bone disease. In addition, the phytates in soy formulas can interfere with iron absorption.

MONITORING GROWTH AND OUTCOMES

The two most common growth curves to track growth by gestational and postmenstrual age are the Olsen Growth Chart and the Fenton Growth Chart, revised. The Olsen Growth Chart is based on a large US population and tracks growth from 23 to 41 weeks gestational age, using a separate chart for male and females. The Fenton Growth Chart monitors growth from 22 weeks gestational age to 10 weeks postterm and is modeled to match the postnatal data to the WHO growth standards. Once a preterm infant surpasses the Olsen or Fenton Growth Charts, growth can be monitored using the WHO Growth Chart (birth to 24 months) or the CDC Growth Charts. The corrected age up to 2 years should be used when plotting the growth of former preterm infants on the CDC or WHO Growth Charts.

Debate continues regarding how to optimally monitor growth in preterm infants. No growth chart captures the varying postnatal growth patterns in critically ill preterm infants and whether these varying growth patterns accurately predict health and long-term outcomes.

Exercise 7

Question

Which of the following answers best represents the percentage of VLBW infants who are identified as being small for gestational age at birth?

1. 90%
2. 74%
3. 22%
4. 10%

Answer

The correct answer is 3.

Small for gestational age (SGA) is a term used to describe an infant whose weight is less than the 10th percentile for a given gestational age. It is important to recognize that not all premature infants are small for gestational age at birth. Large multicenter studies have reported that approximately 22% of VLBW and 17% of ELBW infants are small for gestational age at the time of birth.

A cohort study of infants born at less than 27 weeks' gestation found that SGA infants had higher mortality and were more likely to have postnatal growth failure, prolonged mechanical ventilation, and postnatal steroid use compared with non-SGA infants. An increased risk of death or neurodevelopmental impairment was also observed in SGA infants. At 24 months corrected age, significantly more children born SGA than appropriate for gestational age (AGA) will be below the 10th percentile for weight, length, and head circumference.

Postnatal Growth Failure – Incidence and Etiology

Postnatal growth failure is a common complication of extreme prematurity. Although only 17% of ELBW infants are SGA at the time of birth, by 36 weeks postmenstrual age, the majority of these infants will have experienced suboptimal growth. The NICHD Neonatal Research Network reported that 79% of VLBW infants born between 2003 and 2007 had a weight less than the 10th percentile at 36 weeks postmenstrual age. The Vermont Oxford Network reported a decline in postnatal growth failure from 64.5% in 2000 to 50.3% in 2013. Although improved, a substantial proportion of VLBW infants experience postnatal growth failure. Observational studies have shown that differences in nutritional practices, particularly differences in protein intake, account for the largest difference in growth among premature infants.

Question

Which of the following neonatal factors are associated with postnatal growth failure in extremely low birth weight infants?

1. Male gender
2. Need for respiratory support at 28 days
3. Necrotizing enterocolitis
4. All of the above

Answer

The correct response is all of the above.

Although the risk of postnatal growth failure is inversely related to birth weight and gestational age, there are also many neonatal factors associated with poor in-hospital growth of premature infants, including duration of mechanical ventilation, use of postnatal steroids, severe intracranial hemorrhage/periventricular leukomalacia, and NEC. Many of the morbidities that are associated with slow growth velocity, such as NEC, also affect the provision of nutritional support and the utilization of nutrients supplied.

CASE 7: CONSEQUENCES OF POSTNATAL GROWTH FAILURE

A former 25-week gestation female is now 11 weeks of age. At the time of birth, her weight, length, and head circumference were all at the 50th percentile for gestational age. She regained her birth weight at 10 days of age and achieved full enteral feeds at 14 days of age. At 36 weeks postmenstrual age (PMA), both her weight and weight–length ratio are less than the 10th percentile.

Question

Which of the following statements regarding her growth are true?

1. Although the infant has experienced growth faltering and is SGA at 36 weeks CA, she will more than likely experience catch-up growth and be AGA when she is 18 months CA.

2. The infant's growth has been suboptimal, but this will not affect her neurodevelopmental outcome.

Answer

Neither statement is true.

Although rates of postnatal growth failure among premature infants are improving, it is still a significant problem, particularly given that in-hospital growth failure is occurring at a critical time in development. The relationship between poor in-hospital weight gain and head circumference growth and adverse neurodevelopmental outcomes such as low Bayley cognitive scores, moderate–severe cerebral palsy, and severe neurodevelopmental impairment is well established. In addition, the relationship between linear growth and neurodevelopment is increasingly recognized. Indeed, improved linear growth is associated with significant increases in language, cognitive, and motor scores at 2 years of age. Consequently, it is important to monitor not only weight but also length (with length board) and head circumference on a weekly basis to identify and intervene for growth faltering in the neonatal intensive care unit.

SPECIAL CONSIDERATIONS

CASE 8: BRONCHOPULMONARY DYSPLASIA

A 580 g, 24 weeks of gestation male was delivered by precipitous vaginal birth to a mother with suspected chorioamnionitis. The infant was intubated and received three doses of surfactant. On day 2, due to increasing respiratory support and Paco2 retention, the infant's ventilator strategy was changed from conventional mechanical ventilation to high frequency oscillatory ventilation. By 2 days of age, he was receiving parenteral nutrition infusing at 160 mL/kg/d that provided 3.5 g/kg/d amino acids, 4 g/kg/d lipid, and 12.8 g/kg/d carbohydrate (total of 94 kcal/kg/d). On day 4, a patent ductus arteriosus (PDA) was suspected, and the infant was fluid restricted to 130 mL/kg/d and given a course of indomethacin. The following day an echocardiogram (ECHO) revealed a closed PDA, but there was no improvement in his respiratory status. As a result, the infant was started on a trial of furosemide. Enteral nutrition was begun on day 5 and over the next few weeks his enteral feedings were slowly advanced to achieve full enteral nutrition at a restricted volume of 130 mL/kg/day of mother's milk and human milk fortifier (final caloric concentration 24 kcal/oz) providing a total of 104 kcal/kg/d. At 28 weeks of gestation, his weight is 760 g, which according to the 2013 Fenton Growth Curve is at the 9th percentile for his postmenstrual age.

An appropriate next step in managing nutrition for this infant may include:

1. Continue current management. Energy needs are being met, and growth failure is inevitable in this critically ill neonate. The infant just needs time for the nutritional supports to begin to demonstrate good growth.
2. Increase total daily kilocalories by introducing high calorie preterm formula for two to three feedings per day.
3. Check and correct any electrolyte abnormalities.
4. Increase fortification of mother's milk to provide a greater amount of total daily kilocalories.

Options 3 and 4 should be conducted next to optimize nutrition and growth.

The approach to an infant with evolving bronchopulmonary dysplasia (BPD) or established BPD is not unlike the approach or recommendations for the critically ill neonate. However, the clinician must be cognizant of the nutritional ramifications of bedside medical practices and nutritional strategies that are prescribed to infants with evolving severe lung disease. Such practices, including fluid restriction, diuretic delivery, and provision of postnatal steroids, will affect overall nutritional delivery and resultant growth.

During the early postnatal period, macronutrient recommendations previously discussed for all preterm infants should be achieved, with parenteral nutrition begun as soon as possible after birth. Although this was initially accomplished in this case, after reducing the total volume of PN with fluid restriction, the total kcals/kg/day delivered decreased from 94 to 85 and total daily carbohydrate intake fell from 12.8 g/kg to 10.4 g/kg. He is already receiving the maximum recommended daily protein and lipid amounts; thus, to provide more calories adjusting the total dextrose may be helpful if euglycemia can be maintained. Simply returning the total carbohydrate delivery to 13 g/kg/day, similar to the amount the infant was receiving before fluid restriction, would return total energy to 94 kcal/kg/d. In this scenario, the glucose infusion rate (GIR) before fluid restriction was 8.3 mg/kg/minute. After fluid restriction with the compensatory increase in dextrose delivery, the GIR was 9.0 mg/kg/minute; thus it is anticipated that the infant will tolerate these adjustments.

The approach to initiation and advancement of enteral feedings for an infant with persistent or evolving lung disease should not be different from other premature infants; although it is possible that critically ill infants may demonstrate a greater degree of enteral feeding intolerance and take longer to achieve full enteral feedings. More important, however, is the knowledge that there are no established or proven contraindications to enteral feedings in the critically ill premature infant with lung disease.

Infants with severe lung disease require more energy to sustain growth compared with infants without BPD and may require up to 120 to 150+ kcal/kg/day in the chronic, convalescent phase. If the infant is fluid restricted and/or receiving diuretics or steroids, careful attention must be given to closely following electrolytes and growth. Electrolyte derangements should be corrected and protein and total energy needs must be met, especially during fluid restriction and diuretic therapy. At full enteral feedings using breast milk fortified to 24 calories per ounce, the infant is only receiving 104 kcal/kg/d, thus providing additional calories to meet his total energy needs is warranted.

Vitamin D and iron delivery should also parallel the recommendations for other preterm infants. Vitamin A delivery for infants under 1000 g at 5000 IU IM three times per week for 4 weeks has been shown to reduce the incidence of BPD.

Implementation of this practice has been variable across centers due to availability and cost issues.

POSTDISCHARGE NUTRITION

CASE 9: POSTDISCHARGE NUTRITION IN THE BREAST-FED INFANT

The benefits of a mother's own milk are well established. The use of human milk in the NICU and the need for fortification to meet the specific needs of the preterm infant during NICU hospitalization has been discussed in a previous case.

In preparation for discharge from the NICU to home, continued fortification of breast milk still may be necessary. The decision to fortify breast milk after discharge is based on the growth patterns observed while in the NICU and whether the discharge weight is within acceptable range for the infant's PMA. It is recommended that intrauterine growth restricted infants and those who developed extrauterine growth restriction (EUGR) while in the hospital (with a subnormal weight for PMA) be discharged with additional calories to optimize their growth potential. The number of additional calories to add should be individualized based on the infant's growth patterns. Evidence for using a postdischarge formula versus a standard term formula is inconsistent, although it may be most helpful in the IUGR/EUGR infant.

There is insufficient data regarding whether calorie supplementation is best offered mixed in with expressed breast milk or provided as separate formula feedings. Ideally, strategies that minimize disruption of breast milk feedings should be implemented.

Changing the in-hospital diet to the discharge diet is recommended a few days before discharge to assess the possibility of feeding tolerance, evaluate growth on the discharge diet, provide discharge teaching to the family, and to allow time to change the diet if the nutritional goals are not being met.

Studies are limited on the optimal duration of breast milk specifically for the former preterm infant. Currently for term infants the AAP recommends exclusive breastfeeding for a minimum of 6 months. This may be a challenge for preterm infants, as the duration of exclusive breastfeeding is less for preterm infants compared with term infants. Undoubtedly this is due to the difficulties in providing maternal breast milk to a hospitalized preterm infant for a prolonged period. Lactation support during NICU hospitalization and extended into the postdischarge period may improve these rates.

CASE 10: POSTDISCHARGE NUTRITION IN THE FORMULA-FED INFANT

GS was a former 29-week premature male infant whose clinical course was complicated by mild respiratory distress syndrome (RDS). He weaned from NC oxygen to room air at 32 weeks corrected gestational age. He has had no episodes of apnea or bradycardia for 3 to 4 weeks. He is now 37 weeks corrected gestational age and is taking all feeds orally with 24 kcal/oz premature formula and has been demonstrating excellent weight gain. The mother is no longer expressing human milk and will qualify for assistance from WIC.

Exercise 8

Question

Which formula would be most appropriate at discharge for this infant?

1. Standard term formula (20 kcal/oz)
2. Standard premature formula (24 kcal/oz)
3. Elemental formula
4. Transitional/postdischarge premature formula (22 kcal/oz)

Answer

Either 1 or 4 may be acceptable depending on the infant's growth patterns and current weight for postmenstrual age.

The evidence is mixed regarding routinely using a standard formula or an enriched transitional formula (also referred to as a postdischarge formula) for all preterm infants after discharge. A recent Cochrane Systemic Review found no consistent evidence to recommend postdischarge formula. In fact, the continued use of preterm formulas may achieve better growth outcomes. Theoretically, there may be some benefit in using enriched, transitional care formulas in the most vulnerable group of infants who were born growth restricted or were less than the 10th percentile for postmenstrual age in one or more anthropometric measures at discharge (extrauterine growth restriction), as these may be indicators of acquired and ongoing nutritional deficits. Preterm infants who are not less than the 10th percentile for PMA but who require additional calories to maintain an appropriate growth velocity are likely able to meet their nutrient goals with a concentrated standard formula.

Iron and Vitamin Supplementation

Preterm infants should be supplemented with 400 IU of vitamin D for the first year of life. For the formula-fed infant, supplementation should be continued until the daily intake of formula exceeds 1000 mL per day. Once this volume is exceeded, the daily requirement for vitamin D can be achieved with formula alone. Supplementation for the breastfed infant should continue throughout the first year of life.

Without iron supplementation, the preterm infant is at risk for iron deficiency and its associated complications. Specific recommendations for iron deficiency vary among pediatric organizations. Although all agree that supplementation should continue throughout the first year of life, the specific dose recommended during this time frame differs, with the minimum being 2 mg/kg/day. This amount may be achieved with formula if the infant is predominantly formula fed; otherwise the infant should receive iron supplementation either as stand-alone iron drops or as part of a multivitamin preparation.

Although concerns have been raised regarding the increased risk in premature infants of adult-onset hypertension and metabolic syndrome, this remains controversial, and the risk is likely not uniform for all preterm infants (i.e. AGA

versus SGA/IUGR). In contrast, there is sufficient evidence to demonstrate an increased risk of poor long-term neurodevelopment outcomes secondary to poor growth in the hospital and postdischarge through the first 18 months of life. However, there is little impact of attained growth on the risk of adult-onset diseases during this same period. Thus unless new evidence suggests the contrary, growth during infancy should be closely monitored and supported to achieve growth patterns that are within appropriate ranges for the infant's postmenstrual age using standard growth curves.

Future studies are needed to more clearly define the nutrient requirements of preterm infants both during their initial hospitalization and postdischarge thereafter to minimize complications and optimize growth and neurodevelopment. The optimal rate of catch-up growth for this high-risk population has yet to be defined.

CASE 11: POSTDISCHARGE NUTRITION IN THE LATE-PRETERM INFANT

A 2550 g, $35^{2}/_{7}$ weeks' gestation female infant is born by vaginal delivery to a 32-year-old primiparous mother. At 48 hours of age, the infant is being assessed for discharge to home. She is now 2346 g, down 8% of birth weight. The infant has two to three wet diapers per 24 hours and she breastfeeds every 2 hours, but her mother is unsure whether she is producing milk. The infant is neurologically appropriate during the discharge physical examination, and her care providers have no concerns.

Nutritional management and discharge planning should include:

1. An outpatient visit within 48 hours after discharge by pediatrician
2. Access to a lactation consultant
3. Close monitoring of growth every 2 to 4 weeks
4. Iron supplementation
5. Vitamin D supplementation

All of the above should be arranged to optimize nutritional delivery and minimize the readmission risk in this late-preterm infant.

Much of our attention in nutrition and growth in the preterm infant has been focused on the lower gestational age infants (<34 weeks of gestation). However, increasing attention is being placed on evaluating the medical needs and outcomes of the late-preterm infant ($34^{0}/_{7}$–$36^{6}/_{7}$ weeks of gestation), a gestational age category representing more than 70% of all preterm infants. The data demonstrate that these infants—compared with term infants—are at increased risk for transitional medical issues such as hypothermia, hypoglycemia, hyperbilirubinemia, respiratory distress, and poor feeding. Some of these issues may not be evident until after discharge, accounting for a high incidence of readmissions in this gestational age group. As a result, late-preterm infants warrant specific medical monitoring and nutritional practices that optimize their growth and outcomes.

Compared with term infants, late-preterm infants are at increased risk for altered brain development, particularly reduced gray matter volume. This may account for the increased risk of impaired long-term neurodevelopmental outcomes in this population compared with healthy, term infants. Although the link between poor postnatal growth and neurodevelopmental status has not been made in the late-preterm infant, it is a plausible hypothesis given the strength of this association in more immature infants.

Appropriate establishment of enteral feedings in the late-preterm infant should be monitored closely during the early postnatal period. This can be done in the newborn nursery, but some hospitals have established guidelines to perform such monitoring in the special care nursery or NICU, especially for infants less than 36 weeks of gestation. An advantage in monitoring in the NICU includes greater likelihood for mothers to initiate and sustain breastfeeding.

As with all newborns, breast milk is the preferred diet. It is critical to have appropriate lactation support for the mother due to an increase risk of transitional difficulties in establishing breastfeeding in this population both in the hospital and after discharge. Difficulties in feeding may not be evident until after discharge from the hospital and thus can possibly be missed unless there is regular contact with a health professional. Additionally, late-preterm infants are at risk for poor growth compared with term infants. If growth is not being adequately maintained as expected for age, additional calorie supplementation should be considered.

If the family chooses formula as the primary diet, a standard term formula can be used. However, if growth is inadequate, an enriched, transitional care formula providing 22 kcal/oz can be used as a nutritional strategy to optimize growth. Recommendations for iron and vitamin D for the late-preterm infant are the same as previously described above.

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8

Anemia

Michael J. Stark, Haresh M. Kirpalani and Chad C. Andersen

INTRODUCTION

Anemia is a term typically used to describe either a low hemoglobin (Hb) or hematocrit (Hct). Although the word *anemia* is loosely used in clinical medicine, the exact meaning is difficult to define as it is not binary. Instead, the meaning of an individual Hb or Hct value is relative, requiring interpretation in contemporaneous clinical context.

Although oxygen dissolves in the fluid-based plasma compartment of blood, the amount dissolved is inadequate at standard pressure and temperature to satisfy the needs of aerobic metabolism. Hemoglobin, an iron-containing tetrameric protein located in the red cell, overcomes this problem and is used for transport of molecular oxygen from the lung to the cell.

Commencing late in gestation and continuing throughout the first postnatal months of life, the molecular form of hemoglobin changes from a fetal to an adult configuration. This changes the protein globin structure, altering its affinity for oxygen. Physiologically, the unique characteristic of fetal hemoglobin is that it has a high affinity for oxygen. This allows the fetus, who is in a hypoxemic in utero environment, to draw oxygen away from maternal, adult Hb at the maternal–fetal interface in the placenta. Following birth, in a relatively normoxic milieu, the newborn red cell lineage is programmed to change to producing lower affinity adult Hb. A developmental abnormality of globin chain synthesis (such as thalassemia) can be unmasked during this transition if the infant is genetically at risk.

All newborns, regardless of gestation, develop a physiologic transitional anemia. This reflects an initial failure of the bone marrow to respond to signaling from renal-derived erythropoietin. For the preterm—as opposed to the full-term—newborn this anemia typically commences earlier and is both deeper and longer in duration. Termed *anemia of prematurity,* this process is almost universal in the premature newborn, frequently prompting a red cell transfusion. Characteristically, this transfusion is triggered by commonly accepted clinical signs. Though it would be preferable to use indications tested by large randomized trials, these are, unfortunately, not yet available. This pattern of anemia in the preterm newborn should be differentiated from "pathologic anemia," the result of either abnormalities of production or consumption (including bleeding and hemolysis).

Anemia is usually well tolerated in the newborn, particularly if it is a gradual process, until a critical level or threshold is reached. By contrast, a more rapid, acute fall in Hb concentration with hypovolemia (anemic shock) is much less well tolerated and typically requires an emergent response.

The chapter begins with the physiology of oxygen handling, including developmental transition from an intra to extrauterine environment and changes to Hb–oxygen affinity before setting out an etiologic basis of anemia. Lastly, the chapter will separate hypovolemic anemia (a reduction in the total circulating blood and plasma volume) from euvolemic anemia (a constant or normal circulating blood volume but with a low red cell volume and often an increased plasma volume). We then provide an outline of available therapeutic options, including both exogenous erythropoietin and allogeneic adult red cell transfusion.

Clinical questions and case reports are added to frame important principles in the approach to anemia in the newborn.

HOW TO APPROACH ANEMIA IN NEWBORN

Beginning in clinical context lets us frame a common clinical situation. What if the junior resident informs you that baby Michael has an Hb of 8.5 g/dL? How can this clinical concern be approached systematically?

Although the Hb value is important, it is only relevant in a clinical context. Thus further information is required before the implications of this single Hb value can be understood and addressed by the treating team.

Both gestation and chronologic age are important, as are the clinical signs of anemic hypovolemia, such as relative tachycardia, low BP, and elevated lactate. In addition, the timing of presentation often provides clues as to the likely diagnosis. Early anemia, at the time of birth, is typically the result of hemorrhage or hemolysis (typically isoimmunization). A blood film will usually differentiate these conditions, and a reticulocyte or nuclear red cell count will separate subacute/chronic from acute hemorrhage. Presentation in the first week is typically related to ex utero hemolysis (though both

in utero and ex utero hemolysis may coexist) and/or hemorrhage. In the preterm baby, the hemorrhage may be clinically apparent (pulmonary) or not (brain, liver capsular, etc.). Later anemia, after the second week, is usually the result of upstream conditions (as mentioned earlier) though in the preterm may be anemia of prematurity, whereas in the term newborn it is more typical of physiologic anemia. Persistent anemia after this time is usually either nutritional or genetic (Fig. 8.1).

Understanding the physiology of oxygen handling is particularly important, as Hb is a single constituent part of a complex physiologic process. For this reason, we have begun the chapter with a short section on physiology to provide a foundation that will be helpful throughout the chapter.

PHYSIOLOGY OF OXYGEN DELIVERY

The movement of oxygen from the atmosphere to the cell flows down a well-maintained concentration gradient from the alveolus to the mitochondrion. This carefully choreographed process has many checks and balances but relies on the following physiologic processes: alveolar ventilation, hemoglobin binding to oxygen, blood flow, and passive diffusion.

The pathway ensures oxygen delivery from the lung to the tissues. Oxygen is essential for aerobic metabolism and energy production. Although glucose can be metabolized without oxygen, it is far less efficient. For example, a molecule of glucose generates 1270 kJ in aerobic conditions versus 67 kJ in anaerobic conditions (Nunn, 1987). The cascade in partial pressure of oxygen concentration from a high level in the atmosphere/lung to a much lower (yet adequate) level at the tissue is summarized schematically by Nunn (Fig. 8.2).

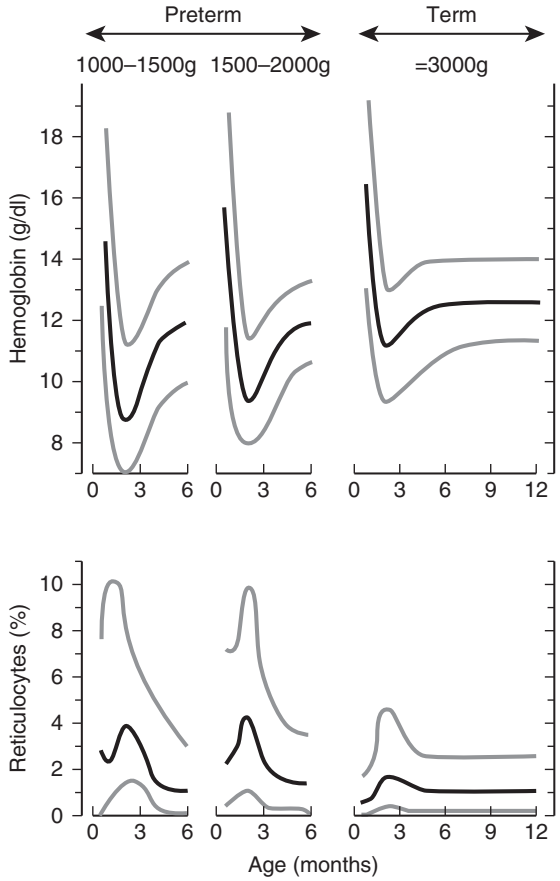

Fig. 8.1 Mean hemoglobin and reticulocyte values in term and preterm infants (Grey = upper range, black = lower range of normal). Infants born preterm become anemic earlier in the postnatal period with hemoglobin concentrations returning to normal later. (From Dallman PR: Anemia or prematurity, *Annu Rev Med* 32:143, 1981.)

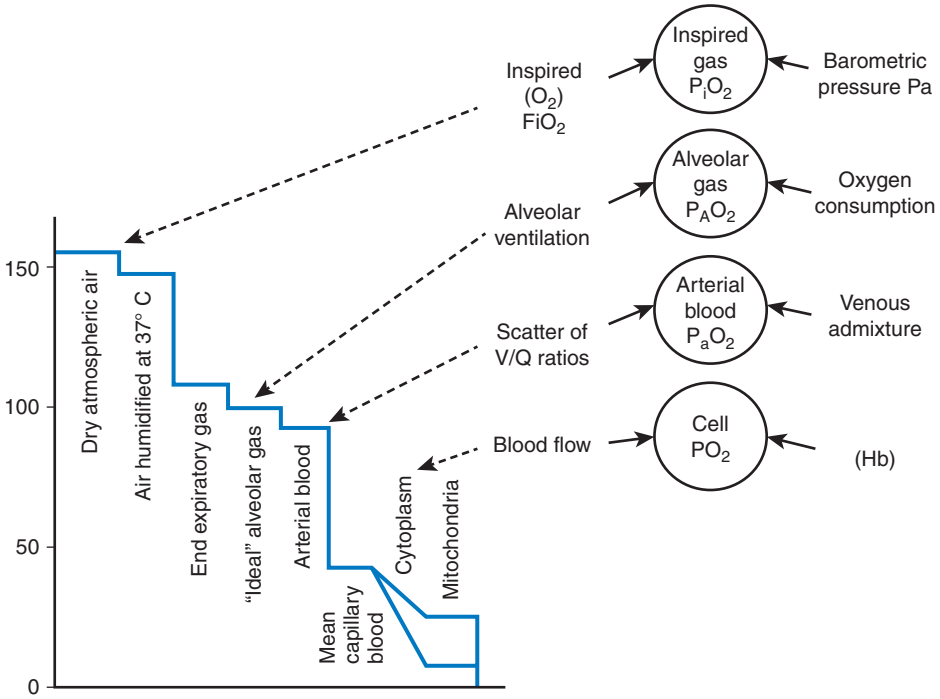

Fig. 8.2 Schematic of the path down a concentration gradient of oxygen from the alveolus (PaO_2) to the mitochondria (P_{O_2}). (Adapted from Nunn JF: *Applied respiratory physiology,* ed 3, London, 1987, Butterworths).

Step One: The Alveolar–Endothelial Interface

According to Fick's law of diffusion, the rate of transfer of a gas across a permeable membrane is directly proportional to the tissue area and the pressure gradient and inversely related to the tissue thickness (West, 2015). This important relationship highlights potential pathology. A likely impairment to diffusion from a widened pulmonary interstitium may occur with alveolar exudate in the setting of primary surfactant deficiency in a preterm newborn.

Step Two: From the Alveolus to the Bloodstream

Once in the fluid plasma compartment, oxygen diffuses rapidly across the red blood cell (RBC) membrane and is taken up by Hb located within the cytoplasm of the red cell. Normal hemoglobin is a tetramer consisting of four protein subunits (globin), each with a heme moiety comprising an iron atom within a porphyrin ring. This complex structure is of itself important for red cell shape, which undergoes conformational changes in response to oxygen binding. In total, each gram of Hb molecule can bind 4 moles or 16 grams of oxygen, which is the equivalent of approximately 1.39 $ml.g^{-1}$. The affinity of hemoglobin for oxygen varies as a result of developmental changes to several important variables. These include the structure of Hb, the influence of organic phosphate (2,3 diphosphoglyceric acid DPG), and other exogenous factors, such as temperature, pH, and carbon dioxide (Bohr effect). The key to these complex interactions is the effect of each factor on the sigmoid (nonlinear) shape of the relationship between oxygen and Hb. The Hb–oxygen dissociation curve is particularly relevant in normoxic conditions ensuring uptake of oxygen in an oxygen-abundant environment and subsequent release of oxygen in an oxygen poor setting (Fig. 8.3). The long, flat upper section enables high oxygen saturation over a wide range of alveolar partial pressures. In contrast, the steep middle section at lower partial pressures is more likely encountered in the smaller capillaries where oxygen is unloaded and the Bohr effect (rightward shift in dissociation curve) becomes important.

2,3 DPG is an organic phosphate that binds to the globin chain thereby altering Hb–oxygen affinity. The intraerythrocyte concentration of 2,3 DPG is in flux, dependent on pH.

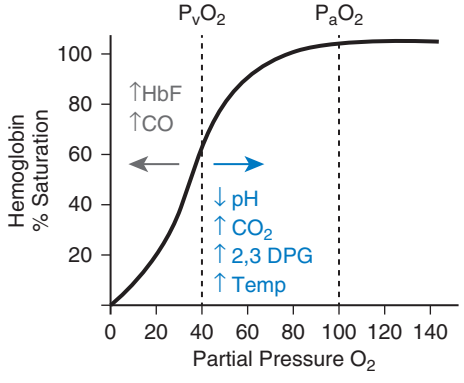

Fig. 8.3 The effect of temperature, 2,3 DPG and carbon dioxide on the Hb-oxygen dissociation curve. (From *West's respiratory physiology, the essentials,* ed 10, Philadelphia, 2016, Wolters Kluwer)

Step 3: Oxygen Transport to the Tissue

Blood flow, hemoglobin concentration, and hemoglobin oxygen saturation are the principal determinants of systemic oxygen delivery. Tissue oxygen delivery also depends on the oxygen gradient and distance between the capillary and the cell. However, in the microvasculature, where distance is reduced and the pressure gradient is the highest (Simmonds et al, 2014), the latter two factors do not greatly alter the system and are of minor importance. A value known as the critical mixed venous oxygen threshold—defined as the value before the onset of anaerobic respiration—is conceptually important, though particularly difficult to measure, especially in newborns (Andersen et al, 2017).

The combination of Hb concentration with oxygen saturation is termed the oxygen content (CaO_2 (arterial) and CvO_2 (venous)). See equation:

$$CaO_2 = \{1.39 \bullet [tHb - \{metHb + HbCO\}] \bullet Hbsat/100) + (0.003 \bullet PaO_2)\}$$

where 1.39 is the amount of oxygen bound to Hb; tHb is the total Hb.

The oxygen content value represents the body's oxygen store located in both venous and arterial compartments. The oxygen balance within each newborn is in a constant flux, as oxygen consumption is balanced by delivery and extraction. This dynamic relationship is often represented theoretically by a simple figure (Fig. 8.4).

At rest, almost all humans operate with an *excess* of delivery over consumption, resulting in **aerobic** conditions. As delivery falls (e.g., in hypoxic conditions), consumption increases (e.g., in disease states including fever), or both occur in combination, oxygen extraction increases (Schulze et al, 1995).

$$\text{Oxygen extraction (OE)} = \frac{\text{Oxygen consumption}}{\text{Oxygen delivery}}$$

However, the increase in oxygen extraction is limited both by the maintenance of a minimum concentration gradient (as shown in Fig. 8.5) and by the amount of oxygen stored on Hb. Eventually, if tissue demand exceeds this threshold of compensation with consumption being restricted or limited by delivery (so-called dependence on oxygen supply), this heralds the onset of **anaerobic** metabolism and subsequent lactic acidosis.

The complexity and dynamic balance between oxygen delivery and consumption make it evident that there can be no single Hb threshold that consistently results in anemic hypoxia. Moreover, this value need not be stable within an infant over time. In fact, oxygen delivery and consumption will vary within and between newborns. For this reason, the Hb or Hct thresholds used in most clinical trials are based on population-derived best guesses rather than individual physiology. Ideally an individualized approach would be more scientific, though this is currently not feasible in practice (Andersen, 2015).

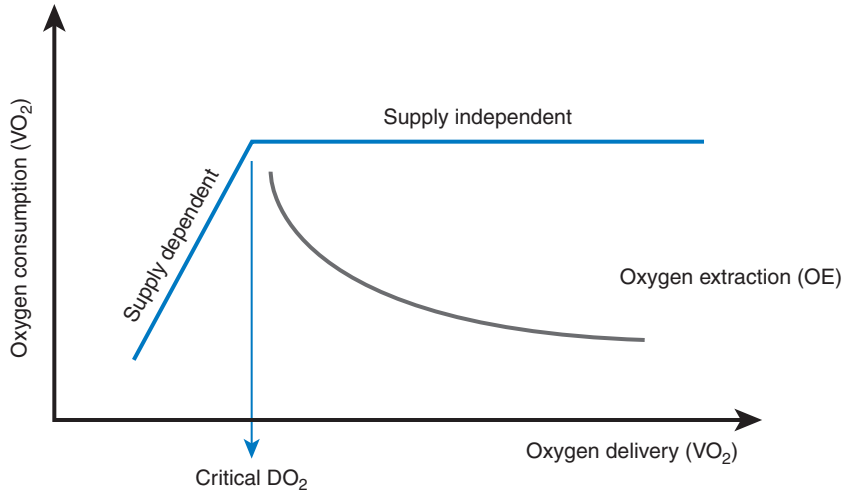

Fig. 8.4 Schematic representation of the relationship between systemic oxygen consumption (VO_2), delivery (DO_2), and extraction (OE). The critical or anaerobic threshold can be identified from a change in the gradient of the curve or as a result of accumulation of lactate. (From Andersen CC et al: A theoretical and practical approach to defining "adequate oxygenation" in the preterm newborn, *Pediatr* 139[4]:2, 2017).

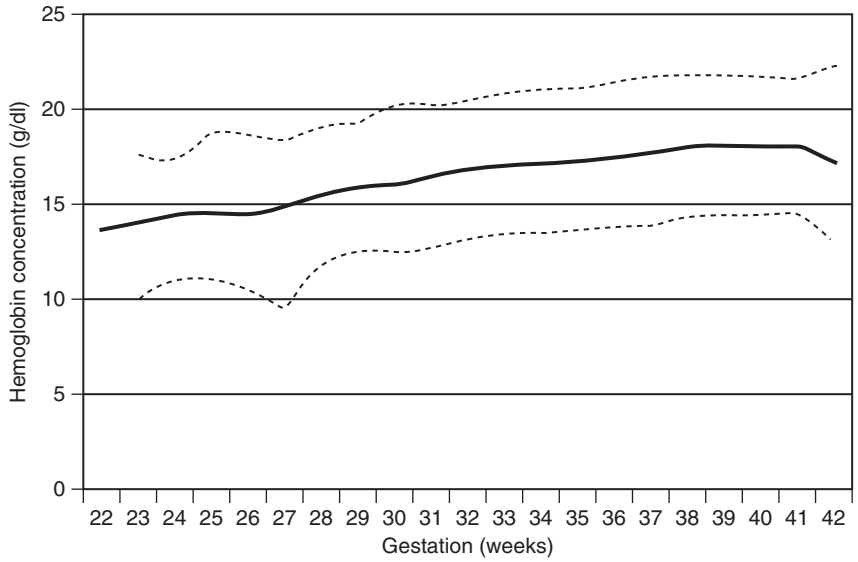

Fig. 8.5 Changes in hemoglobin concentration from 22 to 42 weeks' gestation (lines represent the 5th, mean, and 95th percentile). (Adapted from Jopling J, et al: Reference ranges for hematocrit and blood hemoglobin concentration during the neonatal period: data from a multihospital healthcare system, *Pediatr* 123:e333–337, 2009).

Flow of RBC in the Circulation

Nitric oxide is one of the key determinants of vascular tone in the microcirculation balancing local vasodilation with vasoconstriction. The red cell uses nitric oxide (NO) signaling in a paracrine method to alter the local dynamics of the microcirculation. Whereas free Hb scavenges NO avidly, Hb located within the red cell acts much more slowly. This has important clinical consequences in conditions of intravascular hemolysis, such as might occur in sickle cell disease. In such conditions, free Hb "mops" up NO, reducing vasodilation, and therefore becomes an additional disadvantage to oxygen delivery. In contrast, deoxyHb reduces nitrite to NO, thereby promoting hypoxic dilatation (Owusu et al, 2012).

NORMAL HEMATOLOGICAL VALUES

Hemoglobin

Hemoglobin is a complex structure located in the red cell. The hemoglobin tetramer consists of four globin chains, each surrounding a heme moiety. The heme moiety is the active site of oxygen binding and comprises an iron atom within a porphyrin ring. There are six known globin chain variants. Fetal Hb, designated HbF, comprises two alpha and two gamma chains. It is alkali resistant and has a high affinity for oxygen. Fetal Hb makes up between 50% to 85% of hemoglobin in the newborn but in healthy individuals will disappear by 3 to 4 years of age.

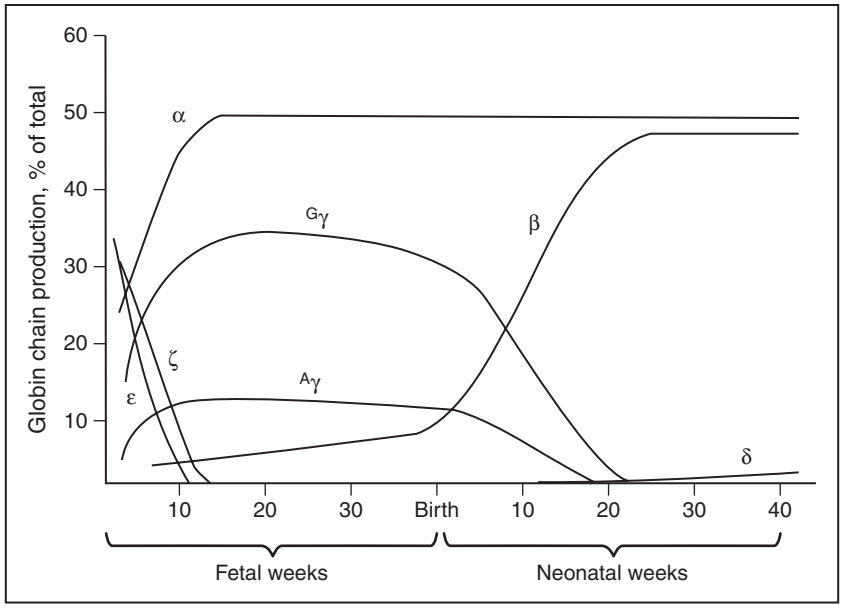

Fig. 8.6 Developmental changes to hemoglobin chain production during antenatal and the immediate postnatal period. (Adapted from Rimion DL, editor: *Emery & Rimion's principles and practice of medical genetics*, San Diego, 2013, Academic Press, pp 1–44.)

Ontogeny of Hemoglobin and Globin Chains

Hb concentrations gradually increase with advancing gestation (see Fig. 8.5). Epsilon (or embryonic) globin is the first globin chain produced. This is quickly followed by α- and γ-globin. Fetal hemoglobin (HbF [$\alpha_2\ \gamma_2$]) is produced from 4 to 5 weeks gestation and depending on gestational age accounts for up to 70% to 90% of the total erythrocyte hemoglobin (Fig. 8.6). Adult hemoglobin (Hb A [$\alpha_2\ \beta_2$] and Hb A_2 [$\alpha_2\ \delta_2$]), is produced from 6 to 8 weeks but remains in low concentrations until the third trimester. In the postnatal period, the relative concentrations of HbF and HbA change with HbF concentrations falling to approximately 2% by 1 year of age. By 10 weeks' gestation, hemoglobin concentration is approximately 9 g/dL, increasing throughout gestation until reaching a plateau over the last 6 to 8 weeks of pregnancy. As a result, Hb concentrations at term are typically between 16 to 17 g/dL. In addition, it should be noted that Hb may rise by 1 to 2 g/dL from the effect of placental transfusion and as a result of relative dehydration in the early neonatal interval.

Hemoglobin vs. Hematocrit

Hemoglobin is typically expressed as a concentration per unit volume, that is, the amount in grams per liter or deciliter of whole blood. Hematocrit is the volume of red blood cells as a proportion of total blood volume. Both are used interchangeably in definitions of anemia and in trials of transfusion thresholds. A mathematical conversion is set out here.

$$\text{Hemoglobin (Hb)} = \text{hemoatocrit (Hct)}/3$$

Erythrocyte maturation is regulated by growth factors produced by the fetus. Erythropoietin (Epo), a 30 to 39 kDa glycoprotein that binds to specific cell surface receptors on erythroid precursors, is the primary regulator of fetal erythropoiesis (Vora and Gruslin, 1998). Epo does not cross the placenta and is produced by the fetus in the liver (Dame et al, 1998). During the first and second trimester, cells of monocyte/macrophage origin produce Epo with manufacture regulated by an oxygen-sensing mechanism involving hypoxia inducible factor (HIF-1). As such, the primary stimulus for Epo production is hypoxia with or without anemia. Fetal Epo increases until birth with serum concentrations normally ranging between 5 and 100 mU/mL compared with 0 to 25 mU/mL observed in healthy adults. However, in comparison to mature newborns, preterms have a poorer bone marrow response, which is one of the important factors resulting in *anemia of prematurity* (Brown et al, 1984). Nonetheless, Epo therapy may still have a therapeutic role. (See later discussion.)

Physiology of Red Cell Production

Several factors are involved, of which the principal components are erythropoietin and iron balance.

Erythropoietin (Epo)

Although the function of erythropoietin has been well described, the mechanism translating changes in tissue oxygen to red cell production has only been defined recently. This is understood to be mediated by a family of transcription factors called hypoxia inducible factors (HIFs), with HIF-A being the most important. In tissue hypoxia, HIF-A rises and in turn stimulates Epo. Knock-in experiments confirm a potential role of HIF-A and its mediators in pathology of polycythemia. Moreover, HIF-A also induces the expression of vascular endothelial growth factor (VEGF), important for angiogenesis and lung alveolarization.

The rapid release of RBCs in response to hypoxia may result in still immature RBCs (nucleated) being circulated. This has been proposed as a biomarker of extent and timing of fetal hypoxia (Buonocore et al, 1999). The time response is over 24 hours duration, making this a potential "timer" of the degree of relatively chronic fetal hypoxia (Christensen et al, 2014). There have been many attempts made to use the physiology of hypoxia as a guide to transfusion. Direct measures of Epo (Meyer et al, 1992) and VEGF (Tschirch et al, 2009) have been tried. More complex methods of measuring either available oxygen in vitro, *p*50 (Wardle et al, 1998), or oxygen tissue saturation in the brain (Andersen, 2015) have also been tested. As of yet, none have been found robust, diagnostically useful, and practical viable.

Iron Balance

Iron is a key component of the molecule of hemoglobin and thus is the pivot around which the molecule can bind oxygen. For this reason, the body's iron balance is important for modifying the circulating RBC mass. Because free iron reacts quickly with oxygen (the Fenton reaction) to produce reactive oxygen species (ROS), it is bound to the protein transferrin in the blood, whereas in the cell it is bound to ferritin. The liver senses the amount of iron-transferrin product and will secrete the hormone hepcidin in response, which will in turn raise the protein ferroportin. This regulates small bowel and spleen release of iron into the bloodstream. If iron deficient, the liver releases erythroferrone, which blocks hepcidin and stimulates release of iron from the duodenum and spleen and liver. This is summarized in Fig. 8.7.

Other Controllers of Erythroblastosis

Although a detailed review of these is outside the scope of this chapter, the reader should be aware that a host of other transcription factors apart from HIFs are likely to be named as important in the near future. Of these, the forkhead box 03 protein (FOX03) is likely the most important. This is known to regulate the final stages of erythroid maturation in the bone marrow.

Range of Normal Red Blood Cell Indices in the Fetus and Neonate

The effect of gestational age on hematocrit, hemoglobin, mean corpuscular volume, and reticulocytosis in shown in Table 8.1 (Christensen, 2000). Erythrocyte indices vary across gestation and continue to change through the first year of life. Hematocrit (Hct) increases from 30% to 40% during the second trimester before reaching 50% to 63% at term. As the practice of deferred umbilical cord clamping has become routine, much higher hematocrit levels are frequently observed (Jopling et al, 2009). Lastly, Hct and Hb vary according to the sampling site with higher levels from capillary samples.

With advancing gestation, erythrocyte size and volume decrease. This continues in the postnatal period with values reaching those commonly seen in adults by 1 year of age. Mean corpuscular volume (MCV) decreases from over 180 fL in the embryo, to 130 to 140 fL by midgestation, and, finally, 115 fL by the end of pregnancy. A low MCV (values below the fifth percentile) at birth is most commonly seen in α-thalassemia trait or hereditary spherocytosis but may also be caused by fetal iron deficiency as a result of chronic feto-maternal hemorrhage (FMH) or twin-to-twin transfusion syndrome. In the postpartum period, MCV continues to fall, more quickly in preterm infants, such that by 1 year of age mean MCV is typically 82 fL.

There is also marked variability in erythrocyte shape and deformability. Neonatal erythrocytes have higher mean corpuscular hemoglobin concentrations (MCHC) remaining constant at 33 to 34 g/dL from approximately 32 weeks' gestation through to adulthood. Several conditions affect RBC volume because of compression of hemoglobin, such as in hereditary spherocytosis, ABO incompatibility, or microangiopathic hemolytic anemia. These are all associated with elevated MCHC as the surface area of the RBC decreases while the hemoglobin concentration remains stable (thus being relatively more concentrated).

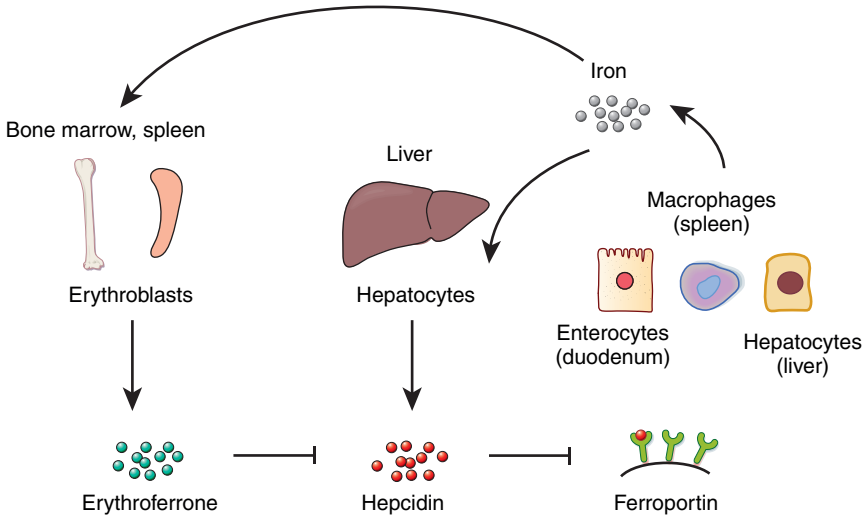

Fig. 8.7 Schematic diagram of the interaction between iron metabolism and erythropoiesis. (From Liang R and Ghaffari S: Advances in understanding the mechanisms or erythropoiesis in homeostasis and disease, *British Journal of Haemoatology* 174:661, 2016.)

TABLE 8.1 Changes in Hematocrit, Hemoglobin, Mean Corpuscular Volume, and Reticulocyte Count With Advancing Gestational Age

Gestational Age (wk)	Hematocrit (%)[a]	Hemoglobin (g/dL)	MCV (fl)	Reticulocytes (%)
18–20[b]	36 ± 3	11.5 ± 0.8	134 ± 9	NR
21–22[b]	38 ± 3	12.3 ± 0.9	130 ± 6	NR
22–23[b]	38 ± 3	12.4 ± 0.9	125 ± 1	NR
24–25	63 ± 3	19.4 ± 1.5	135 ± 0	6.0 ± 0.5
26–27	62 ± 3	19.0 ± 2.5	132 ± 14	9.6 ± 3.2
28–29	60 ± 3	19.3 ± 1.8	131 ± 14	7.5 ± 2.5
30–31	60 ± 3	19.1 ± 2.2	127 ± 13	5.8 ± 2.0
32–33	60 ± 3	18.5 ± 2.0	123 ± 10	5.0 ± 1.9
34–35	61 ± 3	19.6 ± 2.1	122 ± 10	3.9 ± 1.6
36–37	64 ± 3	19.2 ± 1.7	121 ± 12	4.2 ± 1.8
Term	61 ± 3	19.3 ± 2.2	119 ± 9	3.2 ± 1.4

MCV, Mean corpuscular volume; *NR,* not reported.
[a]Values reported as the mean ± standard deviation.
[b]Fetuses in utero.
From Christensen RD: Expected hematologic values for term and preterm neonates. In Christensen RD, editor: *Hematologic problems of the neonate,* Philadelphia, 2000, Saunders, p 120.

In the preterm newborn, erythrocyte life span is typically 35 to 50 days compared with 60 to 90 days in the term newborn and 120 days in adults (Pearson, 1967). Red cell deformability is a particularly important determinant of red cell life span in vivo. This is principally governed by three factors: the surface-area/volume relationship, the viscosity of the cytoplasm of the cell, and intrinsic differences in the fetal and neonatal erythrocyte membrane. Fetal and neonatal erythrocytes are also at increased susceptibility to oxidative injury from differences in glycolytic and pentose phosphate pathways (Bracci et al, 1988). Oxidative injury will result in increased glutathione instability, Heinz body formation, methemoglobinemia (MetHb), and ultimately hemolysis in situations of severe hypoxia and/or acidosis (Perrone, 2012).

Rates of hemoglobin synthesis and erythrocyte production are low in the immediate postnatal period due to the dramatic increase in tissue oxygenation. This is further compounded by a shortened red cell life span and plasma dilution with an increase in blood volume related to growth. Whereas the reticulocyte count is elevated at birth, the postnatal period is typically characterized by a significant fall in erythropoiesis. This results in an Hb nadir between 9 and 11.2 g/dL in full-term infants at approximately 4 to 8 weeks of age (Saarinen and Siimes, 1978). Reticulocyte counts subsequently increase in response to the Hb nadir as a result of erythropoiesis. For the preterm or very low birth weight newborn, this postnatal fall is exaggerated. This occurs for a variety of reasons, including significant phlebotomy losses in addition to the down regulation of endogenous erythropoiesis from the effect of "top up" transfusions (Brown et al, 1984). These factors together lead to a significantly greater fall in hemoglobin concentration in the first few weeks of life in the preterm compared with term newborn. [Dallman, 1981]). Conversely, newborns exposed to *in utero* hypoxemia, such as those born small for gestational age or those born at higher altitudes, tend to have a higher high red cell mass, or polycythemia.

DISORDERS OF ANEMIA

Let us return to the original clinical story. What if the junior resident informs you that baby Michael has a Hb of 8.5 g/dL? The cause of anemia can be sort by sequential reasoning. An example follows.

If Michael is a newly born baby and

1. the cord SBR is elevated, the blood film shows fragmentation, and the DCT is positive, then baby Michael likely has blood group incompatibility.
2. the cord SBR is not elevated, the blood film shows reticulocytosis, and the DCT is negative, then baby Michael likely has had a subacute hemorrhage, probably feto–maternal.

This simple approach will allow the reader to develop a list of likely causes that will require confirmation with further investigation. In addition to a method to sort diagnosis, a further approach to therapy is dependent on the clinical circumstance.

For example if baby Michael has:

1. hypovolemic anemia with commensurate hemodynamic instability (or shock) and raised HR, low BP, and clinically poor circulation with elevated lactate, then he requires prompt RBC transfusion.
2. normovolemic anemia with a normal HR and BP for gestational age and clinically sound circulation with normal lactate concentration, then transfusion can be deferred.

Definition of Anemia

There are a number of approaches to the definition of anemia in the newborn. Statistically, anemia can be defined as the red cell number, Hct or Hb less than 2 SD below the mean value.

TABLE 8.2 Normal Hematologic Values in Healthy Term Infants[a] During the First Year of Life

	AGE(mo)[b]						
	0.5 (n = 232)	**1 (n = 240)**	**2 (n = 241)**	**4 (n = 52)**	**6 (n = 52)**	**9 (n = 56)**	**12 (n = 56)**
Hemoglobin (mean ± SE)	16.6 ± 0.11	13.9 ± 0.1	11.2 ± 0.06	12.2 ± 0.14	12.6 ± 0.1	12.7 ± 0.09	12.7 ± 0.09
−2 SD	13.4	10.7	9.4	10.3	11.1	11.4	11.3
Hematocrit (mean ± SE)	53 ± 0.4	44 ± 0.3	35 ± 0.2	38 ± 0.4	36 ± 0.3	36 ± 0.3	37 ± 0.3
−2 SD	41	33	28	32	31	32	33
RBC count (mean ± SE)	4.9 ± 0.03	4.3 ± 0.03	3.7 ± 0.02	4.3 ± 0.06	4.7 ± 0.05	4.7 ± 0.04	4.7 ± 0.04
−2 SD + 2 SD	3.9 − 5.9	3.3 − 5.3	3.1 − 4.3	3.5 − 5.1	3.9 − 5.5	4.0 − 5.3	4.1 − 5.3
MCH (mean ± SE)	33.6 ± 0.1	32.5 ± 0.1	30.4 ± 0.1	28.6 ± 0.2	26.8 ± 0.2	27.3 ± 0.2	26.8 ± 0.2
−2 SD	30	29	27	24	24	25	24
MCV (mean ± SE)	105.3 ± 0.6	101.3 ± 0.3	94.8 ± 0.3	86.7 ± 0.8	76.3 ± 0.6	77.7 ± 0.5	77.7 ± 0.5
−2 SD	88	91	84	76	68	70	71
MCHC (mean ± SE)	314 ± 1.1	318 ± 01.2	318 ± 1.1	327 ± 2.7	350 ± 1.7	349 ± 1.6	343 ± 1.5
−2 SD	281	281	283	288	327	324	321

MCH, Mean corpuscular hemoglobin; *MCHC,* mean corpuscular hemoglobin concentration; *MCV,* mean corpuscular volume; *RBC,* red blood cell; *SD,* standard deviation; *SE,* standard error of the mean.

[a]These values were obtained from a selected group of 26 healthy term infants followed up at the Helsinki University Central Hospital who were receiving continuous iron supplementation and who had normal values for transferrin saturation and serum ferritin.

[b]Values at the ages of 0.5, 1, and 2 months were obtained from the entire group, and those at the later ages were obtained from the iron-supplemented infant group after exclusion of iron deficiency.

From Saarinen UM, Slimes MA; Developmental changes in red blood cell counts, and indices of infants after exclusion of iron deficiency by laboratory criteria and continuous iron supplementation, *J Pediatr* 92;414, 1978.

This approach, however, is likely to include a small percentage of values in normal, normoxic, stable newborns. An example of this approach is shown in Table 8.2. Alternatively, anemia can be defined by a physiology-based approach. An example would be to define the Hb value adjacent to the onset of anaerobic respiration. This can be identified from either a change in the slope (steeper) of the oxygen delivery–consumption curve or accumulation of lactate (Andersen and Stark, 2012). Although this *physiologic* approach to the definition of anemia may be the ideal, it is too impractical for general application.

Usually, anemia is defined more loosely, using a mix of clinical criteria and expert opinion (NBA, 2016). In preterm newborns, the Hb or Hct values so compiled form the basis of comparison in randomized trials (Bell et al, 2005; Kirpalani et al, 2006) (a high or a low transfusion threshold). Regardless of definition, the etiology of anemia can be considered under the broad headings of reduced production, hypovolemia, or bleeding.

Reduced Production

Neonatal anemia in term newborns secondary to decreased erythrocyte production is quite rare. Of known causes, congenital infections with a marrow suppression of erythrocyte production are most common. Other causes include genetically determined abnormalities, bone marrow replacement syndromes, and maternal nutritional deficiencies.

Congenital infection may lead to bone marrow failure and hemolysis. There are a number of bacterial and viral infections that result in hemolysis and subsequent anemia. Parvovirus B_{19}, however, selectively infects erythroid precursors and inhibits both growth and maturation. Infection in children and adults is benign, often characterized by fever, vomiting, diarrhea, and a maculopapular exanthem of the face (slapped-cheek syndrome). However, infection in pregnant women may result in profound fetal anemia and nonimmune hydrops. Although the fetal anemia and hydrops may resolve, the fetus is at significant risk of demise. In utero transfusions are not infrequently used to successfully treat this reversible condition in affected fetuses. Other infections associated with neonatal anemia include congenital malaria and human immunodeficiency virus (HIV), either the result of primary infection or secondary to maternal antiviral therapy.

Nutritional Anemia

In developed countries, nutritional anemia is infrequent in the newborn, and yet it is the most common cause of anemia after the first 3 to 6 months and in the first year of life. Iron deficiency, characterized by hypochromic, microcytic red cells with a low hematocrit, is rare at birth. If present, it is commonly the result of either acute prenatal or significant chronic blood loss, for instance in the context of chronic feto–maternal hemorrhage or twin-to-twin transfusion syndrome. More commonly however, it develops over the first

weeks and months of life with preterm neonates at particular risk from with inadequate nutritional (iron) supplementation. The use of Epo to prevent and treat anemia in preterm infants can also result in iron deficiency when iron supplementation is inadequate. There is an interaction between total iron stores and the weaning from milk with possible inadequate iron supplementation. This is further influenced by the movement toward deferred cord clamping and the likelihood of adverse intellectual development (Chaparro et al, 2006). Worldwide, avoiding iron deficiency in infancy is the most important reason to employ deferred cord clamping.

Red cell folate concentrations represent total body folate stores. Folate deficiency can result in a megaloblastic anemia, with the MCV generally greater than 110 fL. Folate deficiency can result from a folate-poor diet (as is the case with weaned infants fed goat's milk) or from congenital folate malabsorption, defective cellular folate uptake, and inborn errors of folate metabolism. Supplementation is particularly important in situations of increased erythropoiesis.

Vitamin B12 deficiency anemia is also rare in the newborn. It can occur in breastfed infants of deficient mothers. B_{12} deficiency may also be the result of malabsorption in newborns with short-gut syndrome and with inborn errors of metabolism, including deficiency of haptocorrin and transcobalamin (Watkins and Rosenblatt, 2011). Other less frequent deficiencies in the newborn include vitamin E deficiency, which results in a hemolytic anemia. This hemolysis is related to the vitamin's actions as an antioxidant, inhibiting peroxidation of polyunsaturated fatty acids (PUFAs).

Finally, copper deficiency, characterized by sideroblastic, hypochromic anemia, may occur in low birth weight premature infants when enteral or parenteral nutrition is poor in quality or in conditions associated with chronic diarrhea with severe malnutrition.

Genetic Syndromes

Congenital syndromes may primarily diminish or inhibit red cell production or secondarily alter the red cell mass through hemolysis. Syndromes associated with anemia in the neonatal period and infancy is outlined in Table 8.3.

Fetal and Neonatal Hemorrhage

Hemorrhage occurring before birth or during delivery is usually a transplacental process from abnormalities of placentation, such as twin-to-twin transfusion or feto–maternal hemorrhage (FMH), or as a result of antepartum hemorrhage and vasa previa.

TABLE 8.3 Congenital Syndromes Associated with Anemia

Syndrome	Genetic Characteristics	Hematologic Phenotype
Diamond Blackfan anemia	Autosomal recessive (AR); sporadic mutations and autosomal dominant (AD) inheritance have been described	Steroid responsive hypoplastic anemia, macrocytic after 5 months of age
Shwachman Diamond syndrome	AR – mutations in Shwachman Bodian Diamond syndrome (SBDS) gene, chromosome 17q11	Neutropenia most common, anemia and thrombocytopenia can occur
Fanconi pancytopenia	AR – multiple gene abnormalities (at least 5 genetic subtypes)	Steroid responsive hypoplastic anemia, reticulocytopenia, some macrocytic RBCs, shortened RBC life span
Aase syndrome	AR, possible AD	Steroid responsive hypoplastic anemia that improves with age
Pearson's syndrome	Mitochondrial DNA abnormalities, X-linked or AR	Hypoplastic sideroblastic anemia unresponsive to pyridoxine
Osteopetrosis	AR – defective resorption of immature bone	Hypoplastic anemia caused by marrow suppression
Congenital dyserythropoietic anemias (CDA)	AR	Type I: megaloblastic erythroid hyperplasia and nuclear chromatin bridges between cells Type II: erythroblastic multinuclearity and positive acidified serum test result
Peutz Jeghers syndrome	AD	Iron deficiency anemia from chronic blood loss
Dyskeratosis congenita	X-linked recessive, locus Xq28, some cases AD	Hypoplastic anemia usually presenting between 5–15 years of age
X-linked α-thalassemia/ mental retardation (ATR-X and ATR-16) syndromes	ATR-X: X-linked recessive, mapped to Xq13.3 ATR-16: mapped to 16p13.3, deletions of α-globin locus	ATR-X: hypochromic, microcytic anemia; mild form of hemoglobin H disease ATR-16: more significant hemoglobin H disease
Thrombocytopenia-absent radius syndrome (TAR)	AR	Hemorrhagic anemia, possibly hypoplastic anemia as well
Osler hemorrhagic telangiectasia syndrome	AD, mapped to 9q33–34	Hemorrhagic anemia

Feto–Maternal Hemorrhage

FMH is almost universal in pregnancy but of little consequence if small in volume (Sebring and Polesky, 1990). However, in a very small number, FMH can have a significant clinical impact, including hydrops fetalis and even in utero death. Typically, the hemorrhage is slow and subacute, although occasionally newborns may present with anemia from combined subacute or chronic blood loss in addition to an acute process. This may result in biventricular heart failure with persistent pulmonary hypertension, hypovolemic shock, and subsequent neurologic injury. Lastly, FMH (from an Rh-positive newborn) may sensitize an antigen-negative mother, resulting in isoimmunization in future pregnancies.

The Kleihauer-Betke laboratory test is frequently used to detect fetal red blood cells in the maternal circulation. Quantitative estimation of the volume of the FMH is possible using the formula: 2400 × the ratio of fetal to maternal cells = 1 mL of fetal blood. Caution is required in conditions that elevate maternal HbF production.

CASE 1

Baby Ezekiel is born at term by emergency cesarean section after a history, from his mother, of reduced fetal movements in the previous 24 hours. The cardiotocograph (CTG) showed a sinusoidal trace. He is in fair condition at birth, breathing spontaneously, although he is noted to be slightly grunting and pale by clinical attendants. He is assigned Apgar scores of 5 and 8 before being taken to the neonatal nursery.

On arrival he has a HR 140, systolic BP 40 mm Hg, and an Sao_2 88% in 21% inspired oxygen but 98% with 30% inspired oxygen. On further examination the liver and spleen are slightly enlarged.

Exercise 1

Questions

1. What investigations would you perform?

An assessment of the infant's acid–base status and degree of anemia is urgently needed. In this case, the cord arterial blood gas shows a pH 7.20, a lactate concentration of 16 mmol/L, and Hb concentration of 4.9 g/dL. A completed blood picture shows a similar Hb with high nucleated red blood cell count (NRBC) and marked polychromasia on the blood film. His CaO_2 is 6.6 mL/dL.

2. Which of the following laboratory tests would be diagnostic in this instance?
   A. Kleihauer test on the mother's blood
   B. Both maternal and infant blood groups
3. What immediate intervention is needed?
4. What is the importance of the CaO_2 and how might it affect the infant's management?

Discussion

Baby Ezekiel is blood group O positive, direct Coombs test negative. He has undergone a fetomaternal hemorrhage, likely acute on chronic as indicated by signs of hypovolemic shock in the context of an elevated NRBC. The diagnosis is confirmed with the positive Kleihauer test ("ghost" fetal cells in maternal circulation) in his mother. He requires an urgent blood transfusion, as the anemia is partly hypovolemic. This is indicated by the HR, BP, and lactate suggesting that the tissue perfusion is bordering on anaerobic. The absence of either a tachycardia or overt hypotension indicates that there has been enough time for the circulating blood volume to be restored.

Arterial oxygen content (CaO_s) is a mathematical summary of the blood oxygen carrying capacity. It is a calculated value that includes Hb concentration, Hb oxygen saturation, and oxygen dissolved in the plasma phase. The value is typically included on the printed blood gas result. This calculated value includes two of the three key components of oxygen delivery, thus it may be a theoretically important measure of overall oxygen status in the newborn. We have set out the meaning, importance, and utility of this value previously (Andersen, 2015).

Placental Abruption, Placenta Previa, and Vasa Previa

Obstetric complications can be a significant source of fetal blood loss. Although placental abruption is more common in pregnancies complicated by chronic or pregnancy induced hypertension, the risk is also increased in the setting of fetal growth restriction, prolonged rupture of membranes, chorioamnionitis, maternal cigarette smoking, and advanced maternal age. Although the typical presentation includes vaginal bleeding, a tender uterus, and uterine irritability with contractions, a retro-placental bleeding may delay recognition. If accompanied by fetal hemorrhage, there may be rapid development of fetal anemia, hypovolemia, and fetal demise. In clinical situations where blood loss is more subacute, there may be fetal hypoxia with presentation in the neonatal period characterized by compensatory increases in reticulocytes and normoblasts in response to chronic anemia.

Placenta previa is the result of placental implantation in a low-lying position covering some or all of the cervical os. By contrast, fetal vessels not embedded in the placental body but traversing the placental end of the umbilical cord and the fetal surface of the placenta characterize vasa previa. Laceration of these vessels may occur on membrane rupture or with cervical dilatation if they are situated close to the cervical os. These newborns typically present with acute fetal tachycardia and anemic shock following the onset of vaginal bleeding in labor.

CASE 2

Belle is carrying monochorionic diamniotic twins in her third pregnancy. She has had little antenatal care and presents at 25 weeks' gestation with threatened preterm labor (from polyhydramnios). After immediate stabilization with tocolysis, Belle has an ultrasound, which shows that the twins have twin-twin transfusion syndrome (TTTS). One twin has polyhydramnios, whereas the other has oligohydramnios with abnormal (elevated) placental resistance and head sparing on middle cerebral artery Doppler. After antenatal steroids, the twins are delivered because of concern about immediate in utero safety.

Exercise 2

Questions

1. What other antenatal therapies are possible in the context of TTTS?

Discussion

In this case scenario, the donor twin has normovolemic anemia, whereas the recipient twin more likely has hypervolemic polycythemia with concurrent pulmonary hypertension. Amnioreduction or fetoscopic laser photocoagulation is typically used in pregnancies complicated by TTTS. Fetoscopic laser photocoagulation interrupts the placental anastomoses that give rise to TTTS. Selective coagulation of arteriovenous, arterioarterial, and venovenous anastomoses is preferred to functionally separating the placenta into two regions, each supplying one of the twins (Simpson, 2013).

CASE 2 CONTINUED

Twin A is 850 g, has an opening Hb of 5.0 g/dL, an arterial lactate of 12 mmol/L, and is clinically hydropic. Following early administration of surfactant, she is ventilated using conventional ventilation with mean airway pressure (MAP) 10 cmH_2O, Fio_2 25%, CO_2 45 mm Hg, and Sao_2 of 96%. Her HR is 160, mean BP is 28 mm Hg, and her circulation is hyperdynamic. Her CaO_2 is 6.6 mL/dL. An echocardiogram soon after admission to the nursery shows a structurally normal heart with fractional shortening of 30% and an open ductus arteriosus with shunt left to right throughout the cardiac cycle. In contrast, twin B weighs 900 g and is a ruddy purple color. She has an opening Hb 25.0 g/dL and arterial lactate 5 mmol/L. She is also ventilated using a high frequency ventilator with MAP 13 cmH_2O and an Fio_2 85%. An arterial blood gas demonstrates a CO_2 45 mm Hg and a Sao_2 90%. Her HR is 145, the systolic BP is 30 mm Hg. There is a pre (right hand)/post (left hand or either foot) ductal difference in Sao_2 of approximately 8%. Her CaO_2 is 31 mL/dL. An echocardiogram soon after arrival shows a structurally normal heart with D-shaped flattening of interventricular septum, fractional shortening 28%, and an open ductus arteriosus with shunt that is all right to left.

Exercise 3

Questions

1. What is the significance of the cardiac ultrasound findings in each twin?

Discussion

The donor twin, Twin A, is more likely to develop heart failure with a heart that tends to be large and hyperdynamic. In contrast, the recipient twin, Twin B, typically has biventricular hypertrophy and dilatation, and in advanced cases, contractile impairment with signs of massive tricuspid regurgitation (to indicate a relevant degree of right ventricular insufficiency as a sign of a prehydropic state) (Fesslova et al, 1998). Case control studies have reported the incidence of severe PPHN in TTTS to be in the order of 26 to 30 in 1000 TTTS newborns, most of whom were recipients. This is thought to be a result of both increased pulmonary vascular resistance from vasoactive substances and volume overload (Gijtenbeek et al, 2017).

The donor twin requires transfusion, preferably with fresh packed RBC (<7 days of age), although evidence for this is weak. Otherwise the clinician should consider euvolemic exchange with high Hct donor cell. In contrast, the recipient twin requires reverse partial exchange to reduce polycythemia and possible hyperviscosity.

Intrapartum Hemorrhage

Hemorrhage and anemia may also occur as a direct result of trauma to the newborn during delivery. Presentation may be variable, ranging from hypovolemic shock evident soon after delivery to progressive pallor, tachycardia, and hypotension during the first 24 hours of life with later hyperbilirubinemia. Alternatively, other organ-specific bleeding may occur. Normal vaginal and instrumental deliveries may also give rise to subgaleal hemorrhage and cephalohematomas, subdural, subarachnoid, intraventricular, and/or epidural hemorrhage, each of which may lead to anemia. The incidence of intracerebral and extraaxial hemorrhage is also increased in newborns with coexistent coagulation abnormalities such as hemophilia or platelet alloimmunization (NAIT).

Intraabdominal hemorrhage may be seen after difficult deliveries with prolonged traction or abdominal compression. This is particularly true for vaginal breech delivery in preterm infants. Presentation may be at any time from soon after birth to several days following delivery and may involve abdominal distension with discoloration or progressive shock secondary to hypovolemia. Hepatic hemorrhage is associated with compression and rotation of the abdomen during extraction (French and Waldstein, 1982). Whereas presentation may be delayed as a result of tamponade from the liver capsule, liver rupture results in hemoperitoneum and hypovolemic shock. Similarly, but even less common, splenic hemorrhage may be the result of birth trauma or of organomegaly secondary to extramedullary hematopoiesis. Adrenal hemorrhage is sometimes seen as an incidental finding in abdominal ultrasounds but rarely can be large enough to result in anemia or corticosteroid deficiency.

CASE 3

Isaac is delivered at term by elective cesarean section. He requires forceps lift out, although he is in very good condition. He is assigned Apgar scores 8 and 9. He is transferred to the maternity ward with his mother shortly after delivery. At 4 hours of age, Isaac is found by the postnatal midwife to be pale and off color. His head circumference is 2 cm larger than at birth. The attendant medical officer diagnoses a large subgaleal hematoma with a midline parieto–occipital fluctuant, "boggy" mass.

He is taken immediately to the nursery. On arrival he was pale, has a HR 140, a systolic BP of 35 mm Hg, and is normothermic. An intravenous line is sited, a blood culture taken,

and antibiotics prescribed. A venous blood gas shows an Hb 8.0 g/dL. A coagulation profile is also sent. His platelet count is 120,000.

Exercise 4

Questions

1. What is the difference between a cephalohematoma and subgaleal hemorrhage?
2. Why measure clotting factors in the context of a subgaleal hemorrhage?

Discussion

Subgaleal hemorrhage is potentially life threatening, thus requiring early recognition, close monitoring, and targeted therapy. Bleeding into the subgaleal space occurs as a result of tearing of the bridging emissary veins connecting the scalp veins to the dural sinuses. Blood accumulates between the galea aponeurotica (the epicranial aponeurosis) and the periosteum of the skull, a large potential space that can accommodate the entire circulating blood volume. Typically, subgaleal hemorrhage presents with the finding of ballotable fluid in the dependent regions of the head and can rapidly progress to hypovolemia and anemic shock. As a result, treatment is focused on restoration of blood volume and correction of any coagulopathy.

A cephalohematoma is typically smaller and confined by the periosteum to a single bone of the skull, whereas a subgaleal hematoma accumulates as a boggy mass between the galea aponeurotica (the epicranial aponeurosis) and the periosteum of the skull. Although giant cephalohematoma may result in anemia, this is quite unusual. The most common consequence is unconjugated hyperbilirubinemia in the immediate newborn period.

It is important to obtain coagulation status for two reasons. First, babies with subgaleal hemorrhage will often have disseminated intravascular coagulopathy (DIC) from consumption of platelets and coagulation factors. Second, an underlying coagulation disorder may be present but difficult to differentiate in the acute situation with secondary loss of factors. The immediate treatment is identical and involves restoration of circulatory blood volume.

CASE 3 CONTINUED

Isaac is resuscitated with fresh O negative blood because of concern about hypovolemic anemic shock. His coagulation profile is deranged as a result of extensive bleeding. Thus he also receives platelets and plasma-derived clotting factors.

Hemolysis

Hemolysis is a common cause of anemia in the newborn. It is characterized by reduced red blood cell life span, hemoglobinuria, unconjugated hyperbilirubinemia, and hepatosplenomegaly, if long standing. Common causes of hemolysis in the newborn period are listed in Table 8.4.

TABLE 8.4 Common Causes of Hemolysis in the Neonatal Period

Hemolysis in the Neonate
Intrinsic Hemolysis
Enzymopathies
Hexose monophosphate shunt abnormality, such as G^PD, Embden-Meyerhof defect (glycolysis), such as pyruvate kinase
Other
Hemoglobinopathies
α-thalassemia
β-globin cluster deletions
Unstable hemoglobins
Red blood cell membrane defects
Hereditary spherocytosis
Hereditary elliptocytosis and related disorders
Hereditary stomatocytosis
Extrinsic Hemolysis
Isoimmunization
Rh sensitization
ABO
Others (Duffy, Kell, Lewis)
Maternal autoimmune disorders
Maternal medication use
Microangiopathic anemias
DIC
Sepsis
Congenital infection (TORCH, malaria)
Vascular-related causes
Kasabach–Merritt syndrome
Large vessel thrombosis
Severe aortic coarctation
Arteriovenous malformation
Oxidant exposure
Other
Galactosemia
Prolonged or recurrent acidosis

Sepsis and Disseminated Intravascular Coagulopathy (DIC)

Hemolysis with DIC is most commonly seen in overwhelming sepsis, with both gram-positive and gram-negative organisms. Hemolytic anemia may also be a complication of viral sepsis, including cytomegalovirus, enterovirus, and herpes simplex virus infection.

CASE 4

Matthew is delivered at term gestation through particulate meconium-stained liquor. His mother Veronica had a long labor with fever and fetal tachycardia. He is warm and tachycardic at birth. He has respiratory distress with an increasing oxygen requirement and is taken promptly to the nursery. On arrival, Matthew has a temperature of 38°C, HR 185, systolic BP 35 mm Hg, and RR 70 with Sao_2 of 90% in 70% oxygen. His initial arterial blood gas has a pH 7.05, CO_2 75 mm Hg, paO_2 65 mm Hg, and lactate of 10 mmol/L.

Matthew deteriorates following arrival and is intubated by the senior clinician with a 3.5 endotracheal tube. He has bloody meconium filling the endotracheal tube and a "white out" on subsequent chest radiograph. He commences high-frequency oscillatory ventilation with MAP of 24 cmH_2O, Hz 10, amplitude 32, and Fio_2 of 90%. An inotrope and vasoconstrictor are commenced to support his BP.

His laboratory investigations show a coagulopathy with INR 2.5, fibrinogen 5.4 mg/dL, aPTT 85 seconds, and elevated D-dimers. A complete blood picture shows a Hb of 10 g/dL with elevated WBC and platelet count of 85,000. He is commenced on broad spectrum antibiotics.

When Matthew is 12 hours of age, the laboratory rings to say that the blood culture is positive for gram-negative organism. At 18 hours he has a large pulmonary hemorrhage resulting in tachycardia, hypotension with lactic acidosis, and a fall in Hb to 8.0g/dL.

Exercise 5

Questions

1. Why is this infant anemic?
2. Does this baby require a transfusion?

Discussion

Matthew likely has congenital pneumonia with septic shock. This is an uncommon but rapidly evolving clinical scenario caused by either gram-positive or gram-negative organisms.

We have included this difficult clinical scenario for further discussion, as there is little literature to guide transfusion therapy in this instance. Matthew likely has a number of concurrent problems including a consumptive coagulopathy (DIC) with possible hemolysis (toxin derived) and blood loss. This process will take time to settle even with appropriate antibiotic therapy. Furthermore, a newly born baby is unable to compensate for rapid blood loss with resulting hypovolemic anemia. It could be argued that emergency transfusion is most needed, though the clinician will also want to monitor thrombocytopenia and treat the coagulopathy. Thus it is likely that the attendant clinician will be in close communication with the local blood bank to plan blood product support in this unusual, but often life-threatening, scenario.

Isoimmunization

Red cell antigens in the ABO, MN, Rh, Kell, Duffy, and Vel systems are present from the fifth to seventh week of gestation, but antibody production occurs much later. By 30 to 34 weeks' gestation, about 50% of infants will have some measurable anti-A or anti-B antibodies. Isoimmunization from ABO incompatibility is the most common cause of hemolytic disease in the newborn period and can occur during a first pregnancy. Presentation is variable and may range from little or no evidence of hemolysis to severe hemolytic disease with marked erythrocyte destruction.

With the development of blood group screening and prevention of Rhesus sensitization with use of RhoGAM (RhD immunoglobulin), the incidence of isoimmunization has decreased dramatically. Severely affected fetuses are at significant risk of hydrops and fetal demise from anemia. Following delivery, anemia in the early neonatal period is due to ongoing hemolysis, whereas subsequent late anemia (1–3 months of age) is usually the result of reduced erythrocyte production.

Isoimmunization secondary to anti-Kell antibodies typically causes milder hyperbilirubinemia. However, anti-Kell sensitization appears to blunt erythropoiesis, resulting in a decreased reticulocyte response.

CASE 5

Rachael presents in her second pregnancy with rising titers of RhD. Her baby, Jessica, is born at 36 weeks' gestation by vaginal delivery following induction of labor for abnormal MCA Doppler. Baby Jessica is crying at birth and requires no resuscitation apart from tactile stimulation. She is assigned Apgar scores of 9 at both 1 and 5 minutes. Her birth weight is 2.62 kg. An arterial cord bilirubin is 154 μmol/l (9 mg/dL) and Hb 107 g/L. The completed blood picture shows polychromasia with marked red cell fragmentation.

Exercise 6

Questions

1. What is the significance of the abnormal MCA Doppler?
2. Which of the following laboratory tests would help to establish a diagnosis? (a) Blood group and Direct Coombs test, (b) indirect Coombs test, (c) red cell smear for morphology?

Answers

The abnormal MCA Doppler is an indication of the severity of the anemia. Baby Jessica is blood group A RhD positive and the direct Coombs positive. Anti-D antibody is detected on elution studies. This is diagnostic of Rh isoimmunization or hemolytic disease of the newborn.

1. What is a direct Coombs test?
2. What are elution studies and why are they used?
3. How should the infant be managed?

Discussion

Infant Jessica has classical Rh isoimmunization following likely sensitization in Rachael's previous pregnancy. The direct Coombs test is a test of maternal antibody coating the fetal–newborn red blood cells. Elution studies are used to define the likely antibody mediating hemolysis. The process of elution is aimed at removal of antibody bound to the surface of the RBC with subsequent identification following separation of fluid from cellular compartments.

Baby Jessica will require intensive phototherapy in addition to consideration of intravenous immunoglobulin and exchange transfusion. If this were Rachael's first pregnancy to term and you encountered this problem, you should ensure you have inquired about prior pregnancies, including termination. In the era of anti-RhD prophylaxis, the incidence of classic RhD disease has greatly declined. If Rachael has received prophylaxis and a similar picture arises, attention should be given to the minor Rhesus and other potential antigens (Bollason et al, 2017). Isoimmunization with

rapidly rising unconjugated bilirubin requires prompt admission to the nursery for intensive phototherapy (Management of hyperbilirubinemia in the newborn infant, 2004). Hemoglobinuria, a sign of intravascular hemolysis, may also be present. The transfusion laboratory should be notified that an exchange transfusion might be required in the next few hours. Consideration should be given to using pooled intravenous immunoglobulin (IVIG), which may modify the disease (Zwiers et al, 2018). Although the metaanalysis of IVIG use in isoimmunization reports a reduction in the need for exchange transfusion, applicability is limited because of low to very low quality of the available evidence (Zwiers et al, 2018). There remains a need for further studies of the use of IVIG for the treatment of alloimmune hemolytic disease of the newborn with blinding of the intervention and sufficient sample size to assess the potential for serious adverse effects.

Exercise 7

Questions

1. What is the purpose of exchange transfusion?
2. What are the risks of exchange transfusion?
3. Why is the blood irradiated?

Discussion

The purpose of exchange transfusion is to reduce unbound bilirubin and circulating maternal antibody and increase Hb. More than one exchange transfusion may be required. Exchange transfusion needs to be carefully planned and administered, as it is not without risk and complication (Chitty et al, 2013). Catheter insertion is not, of itself, benign. The most common risk is either over- or underexpansion of the circulating volume by simple error of calculation of return volumes. If blood volumes are exchanged rapidly, this may increase the risk of intestinal perforation as a result of hypoxic ischemia and microthrombi. In addition, both apnea and bradycardia may occur during an exchange transfusion. Biochemical disturbances including hyperkalemia or hypocalcemia may be observed. Both thrombocytopenia and coagulation disorders are possible, although thrombocytopenia is the most likely abnormality. Practice is variable, but in many countries, blood used for exchange transfusion is irradiated to kill donor white blood cells, thereby reducing the risk of graft versus host disease (GVHD) in the host.

Congenital Red Blood Cell Defects

Defects of hemoglobin synthesis, grouped under the umbrella term thalassemia, show significant clinical variation due to developmental differences in globin chain synthesis. As the primary hemoglobin in fetal life in HbF ($\alpha_2\gamma_2$) includes the alpha moiety, disorders of α-globin may have significant fetal manifestations unlike disorders of β-globin, which present later and tend to be less severe as a result of ongoing compensatory production of HbF. Disease severity is typically associated with the number of absent α-globin genes. Single α-globin gene deletion is characterized by an asymptomatic carrier state and affects 28% of African Americans. α-Thalassemia trait is the result of 2 α-globin gene deletions and has an incidence of 3% in African Americans. This condition is characterized by microcytosis, hypochromia, and mild anemia. Hemoglobin electrophoresis in the α-thalassemia trait is normal, although some studies have reported minor increases in Bart's hemoglobin (2%–8%) that is transiently present in neonates and detectable in many newborn screening laboratories. Microcytosis in the newborn period is characteristically caused by alpha thalassemia, whereas iron deficiency is the most likely cause in childhood. Hemoglobin H disease results from 3 α-globin gene deletions and presents with similar appearances on blood film to α-Thalassemia trait. Finally, homozygous α-Thalassemia is the result of deletion of all four α-globin genes and usually leads to progressive severe hemolytic anemia in utero with biventricular failure, hydrops, and fetal demise.

Unlike α-globin disorders, conditions related to structural variation in β-globins, such as β-thalassemia trait and sickle cell disease, do not produce abnormalities in red cell indices at birth. This is because β-globin chain production is not sufficiently developed in contrast to γ-globin chain production. β-thalassemia trait is usually found in the older infant or child from an elevation of hemoglobin A_2 and/or hemoglobin F on electrophoresis assays.

Hemolysis may also result from enzymatic disorders that affect erythrocyte metabolism. Glucose-6-phosphate dehydrogenase (G6PD) deficiency leaves erythrocytes vulnerable to oxidative stress from inadequate levels of reduced glutathione. G6PD deficiency may present with neonatal jaundice, congenital nonspherocytic hemolytic anemia, and acute hemolysis after exposure to oxidative stress. Pyruvate kinase deficiency is the most common abnormality of the Embden–Meyerhof pathway and can present in the newborn and early childhood interval with jaundice and anemia.

CASE 6

Baby boy Jeremiah is delivered at 28 completed weeks following spontaneous preterm labor. He is in good condition, despite little antenatal preparation, and is assigned Apgar scores of 6 and 9. He receives mask continuous airway pressure (CPAP) in the delivery room to facilitate cardiopulmonary transition and is taken to the nursery and placed in a closed incubator with ambient humidity. He is started on bubble CPAP of 6 cmH2O in room air. He has an HR of 150, mean BP of 30 mm Hg, and Sao_2 of 95%.

An intravenous catheter is placed in his left hand and a venous complete blood picture, blood culture, and blood gas specimen are sent to the laboratory. He is given broad-spectrum antibiotics intravenously.

The laboratory staff calls to inform you that baby Jeremiah has a red cell shape abnormality with both red cell fragmentation and polychromasia on the film.

Exercise 8

Questions

1. What are the most common abnormalities of red blood cell shape in newborns?
2. What other laboratory tests are important?
3. What is the implication of polychromasia?

Discussion

Membrane defects reduce deformability and lead to hemolysis in the fetus and newborn. Hereditary spherocytosis (HS) is the most common of the membrane disorders resulting in an abnormally shaped erythrocyte. It is inherited as an autosomal dominant condition but can also be the result of a new mutation. It is due to defects in erythrocyte membrane proteins such as spectrin, ankyrin, band 3, and protein 4.2. Anemia and jaundice present in more than 50% of individuals in the neonatal period. Although increased osmotic fragility is diagnostic, this can also be seen with erythrocytes in other hemolytic states such as ABO incompatibility with further testing required to distinguish these two disorders. Diagnosis of these conditions is much easier now with direct gene testing. Typically, red cell shape abnormalities result in nonhemolytic unconjugated hyperbilirubinemia with attendant risks of bilirubin encephalopathy, particularly as Jeremiah is preterm. Intensive phototherapy initially should be used, though exchange transfusion should be considered in this scenario, as the clinician will have difficulty with both unconjugated bilirubinemia and evolving anemia.

The laboratory scientist often describes polychromasia, meaning *of many colors,* when both mature and immature (nucleated red blood cells) erythrocytes are found in the circulation. This implies that the process is at least subacute in duration.

Anemia of Prematurity (AOP)

This nonspecific term is typically used to describe the pattern of anemia in preterm newborns. This pattern will likely be altered by the practice of deferred cord clamping, which results in higher initial Hb concentrations in preterm infants.

Anemia of prematurity is characteristically normocytic and normochromic with reticulocytopenia and is most commonly seen in preterm newborns beyond 4 weeks of postnatal age. This is an exaggerated state, analogous to the "physiologic" anemia seen in term newborns at 8 to 12 weeks postnatal age. It varies in severity with the degree of prematurity, severity of underlying illness, and the nutritional status of the infant. AOP is multifactorial, but central to this condition is a blunted response to Epo that, in the preterm newborn, has a shorter half-life and is metabolized faster. This is compounded by shorter erythrocyte life span, hemodilution secondary to rapid growth, and frequent need for blood tests to guide the provision of clinical care.

A wide range of symptoms has been attributed to AOP. These include apnea and bradycardia, lethargy, poor feeding, increasing oxygen requirement, and poor weight gain (Whyte and Kirpalani, 2011). However, there is little evidence that transfusion, in response to these symptoms of AOP, results in symptom resolution. Nonetheless, rising oxygen or ventilator requirements generally prompt transfusion. Although reductions in phlebotomy-associated blood losses, provision of adequate supplemental iron, and deferred cord clamping have reduced transfusion exposure for the very preterm newborn, optimal transfusion thresholds in this population are still unclear.

The uncertainties of transfusion include the possible associations between transfusion in the very preterm neonate and subsequent morbidity and mortality, including necrotizing enterocolitis, bronchopulmonary dysplasia, and intraventricular hemorrhage (Keir et al, 2016). Although erythropoiesis-stimulating agents such as Epo may reduce transfusion and donor exposure in very preterm newborns, more rigorous and standardized transfusion criteria or guidelines—coupled with reducing the volume of blood lost through phlebotomy—may have the greatest impact in decreasing transfusion requirements in both term and preterm infants.

One other consideration regarding transfusion in the newborn is the need to minimize donor exposure. This was alluded to earlier in the section on Epo. There is an ongoing risk from transfusion-related infection. Although there have been enormous advances in prevention, these have often come after iatrogenic harm. For example, prevention of HIV took several years before adequate screening in the Western world was in place. Screening for HIV and hepatitis B is now such that risk is very low (Fig. 8.8). However, "exotic" new infections are still being seen, especially in the era of international travel (e.g., Chagas disease, malaria, Nile Valley virus). Hence with the blood bank, multipacks should be prepared from single donor blood as much as possible. Practice varies by site in policies for parent donor. If these are implemented, care should be taken to perform adequate safety screening in that situation, just as for any blood donations.

CASE 7

Nathaniel is delivered normally following rapid spontaneous labor at 24 weeks' gestation. His mother, Michelle, is given antenatal steroids only 6 hours before delivery. He is in good condition and assigned Apgar scores 6 and 8. The placenta is delivered immediately after. Unfortunately, there is no time for deferred cord clamping.

Scenario A

Nathaniel is given a single dose of surfactant and ventilated for RDS. He requires a MAP 12 cmH_2O, Fio_2 of 40%, and has a preductal Sao_2 of 92%. His arterial is systolic BP is 25 mm Hg while receiving 5 mcg/kg/min of dobutamine. He has a structurally normal heart with good systolic function on ECHO. In addition, he has a ductus of 1.8 mm size with a left-to-right shunt throughout the cardiac cycle. An Hb obtained from the arterial line is 10.5 g/dL. He has a falling but still elevated lactate 5.5. His CaO_2 is 13.4 mL/dL.

Exercise 9

Questions

1. What criteria are used to determine packed red cell transfusion in a preterm newborn?
2. What is a storage lesion?

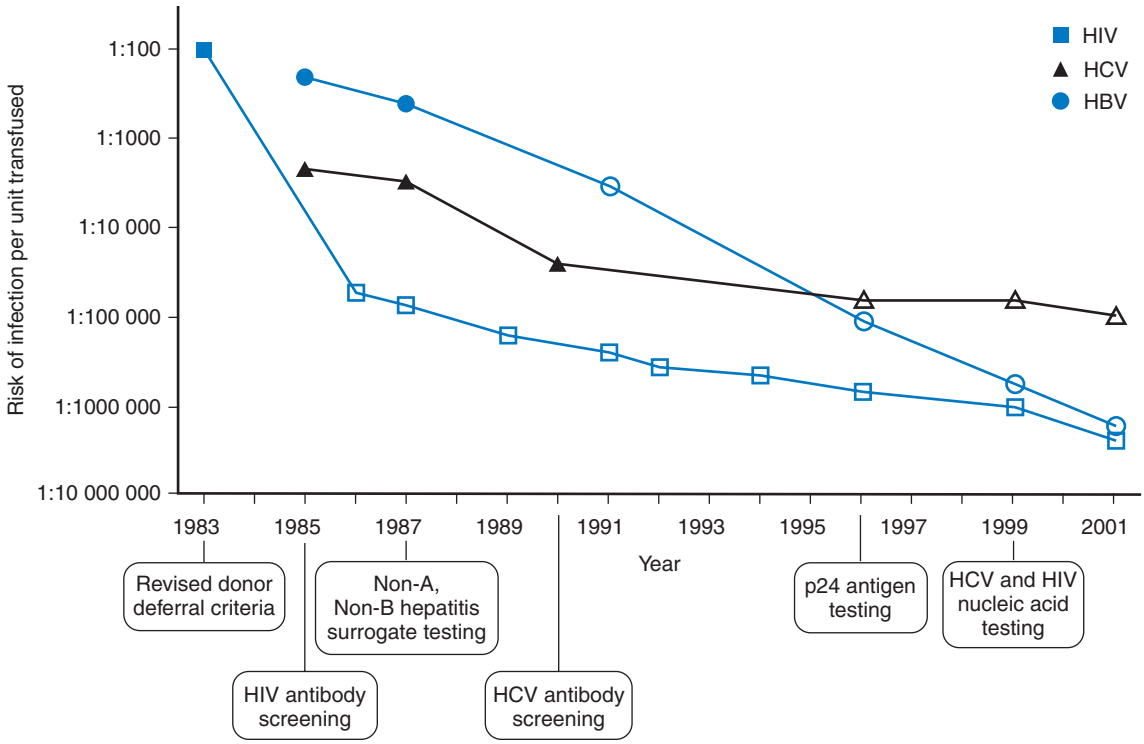

Fig. 8.8 Risk of transfusion-related infection. (From Lubin NL: Transfusion safety: where are we today? *Ann N Y Acad Sci* 1054:325–41, 2005.)

Discussion

Nathaniel is anemic (median Hb at birth is 16.5 g/dL) with mild hypotension. The timing and volume of transfusion in the first days of life in a very preterm newborn remain unclear despite a number of randomized trials. Nonetheless, many clinicians will use the PINT/IOWA trials (Kirpalani et al, 2006; Bell et al, 2005) or Cochrane summary (Whyte and Kiriplani, 2011) to address transfusion thresholds. These trials consider Hb or Hct thresholds that vary according to illness acuity and chronologic age. In addition, most clinicians use a volume of 10 to 15 mL/kg, but there is little guidance for this practice. Before deciding volume of transfusion, one should first consider the likely volume status of the circulation—namely, is it hypovolemic, normovolemic or hypervolemic? In addition, is there cardiopulmonary stability?

Stored blood deteriorates over time, resulting in hemolysis, liberation of intracellular potassium, reduced deformability, increased fragility, and a fall in 2,3 DPG. Together this combination is described as a "storage lesion" affecting oxygen uptake and release.

Scenario B

At 5 weeks of age, Nathaniel is on CPAP 7 cmH_2O in 35% Fio_2 and has a capillary Hb of 7.8 g/dL.

Exercise 10

Question

1. What are the common reasons that the hemoglobin concentration falls for very premature newborns in the NICU?
2. What are reasonable transfusion thresholds in preterm infants?

Discussion

Nathaniel has typical normovolemic anemia of prematurity. This anemia characteristically occurs as a result of phlebotomy losses and a recalcitrant bone marrow, as described earlier. As postnatal age increases, most clinicians tend to be more tolerant of lower hemoglobin or hematocrit values, unless there is an acute change in oxygen needs or if the infant requires surgery. Red transfusion should be directed by evidence from aforementioned randomized trials.

There remains a wide variation in clinical practice with respect to transfusion thresholds in preterm infants with anemia of prematurity (Guillen et al, 2012). For infants less than 28 weeks' gestation or of extremely low birth weight and not receiving respiratory support, an Hb threshold for transfusion of 9.5 to 12.0 g/dL is reasonable. With advancing postnatal age, threshold values for transfusion decrease. Infants receiving respiratory support (supplemental oxygen, high-flow nasal cannula, CPAP, or positive pressure ventilation) had higher thresholds. It is important to acknowledge that the threshold for transfusion may also be influenced by other factors, including anticipated blood loss, quality of nutrition, severity of illness, and the site of sampling. Table 8.5 outlines the proposed consensus guidelines for transfusion thresholds for preterm infants recently published by the National Blood Authority (NBA, 2016).

TABLE 8.5 Hemoglobin Transfusion Thresholds for Preterm Infants

	Hg (g/dL)	
Postnatal Week	No Respiratory Support	Respiratory Support (e.g., Supplemental Oxygen, High-Flow Nasal Cannula, CPAP, Positive-Pressure Ventilation
1	10–12	11–13
2	8.5–1.1	10–12.5
>3	7.0–10	8.5–11

From National Blood Authority (NBA): *Patient blood management guidelines: module 6- neonatal and paediatrics,* Canberra, Australia, 2016, NBA.

PART E AVOIDANCE AND MANAGEMENT OF ANEMIA

Deferred Cord Clamping

Deferred cord clamping in term and preterm infants not requiring resuscitation is currently recommended by the International Liaison Committee on Resuscitation (Perlman et al, 2015). Metaanalysis of the available randomized trials in preterm infants shows a reduction in hospital mortality in preterm infants who have deferred compared with immediate cord clamping (Fogarty et al, 2018). However, there appears to be no benefit in either major morbidity or neurodevelopmental outcome. This appears to be the case particularly in extremely preterm infants and in those who required active resuscitation. In term infants, deferred cord clamping for at least 1 minute is likely to reduce the risk of iron deficiency at 3 to 6 months (McDonald et al, 2013). This is an important finding for the newborn delivered in resource-poor countries.

Erythropoietin and Anemia of Prematurity

The weight of evidence is slowly beginning, at the time of this writing, to swing toward the use of early Epo or other erythrocyte stimulating agents (ESAs). The clearest answer to whether it is of benefit lies in the pooled analysis of all known trials in the Cochrane Collaboration (Ohlsson and Aher, 2017). This latest version pools data from randomized controlled trials, comparing placebo against early administration of either erythropoietin (low ≤500 IU/kg/week) and high (>500 IU/kg/week) or analogs such as darbepoetin (included as erythrocyte stimulating agents). In total, there are now 34 studies enrolling 3643 infants. The pooled results show that ESAs do reduce the risk of one or more RBC transfusions' risk ratio (RR) 0.79, 95% confidence interval (CI) 0.74 to 0.85; typical risk difference (RD) −0.14, 95% CI −0.18 to −0.10; I^2 − 69% for RR, and 62% for RD (moderate heterogeneity). It should be noted that these data were of low quality with much data unblinded. Furthermore, the actual volume by which transfusion was reduced was only 7 mL/kg, which may not be clinically meaningful in a very preterm newborn. More importantly, there is no statistically significant reduction in the number of donor exposures.

Interestingly, apart from the outcome of transfusion, there was also an effect on two other complications of extreme prematurity. Necrotizing enterocolitis was significantly reduced in the ESA group compared with the placebo (typical RR 0.69, 95% CI 0.52–0.91; typical RD −0.03, 95% CI −0.05 to −0.01; I^2 = 0% for RR, and 22% for RD (low heterogeneity)). Even more tantalizingly, there was an effect on Bayley-II Mental Development Index (MDI) at 18 to 24 months in the ESA group (weighted mean difference [WMD] 8.22, 95% CI 6.52–9.92; I^2 = 97% [high heterogeneity]; three studies, 981 children). However, the pooled data do not include the firmly negative results of the largest trial that specifically examined this important outcome (Natalucci et al, 2016). New trials are in progress to examine this crucial question.

Risks of Epo in Treating Anemia of Prematurity

The principal risk that has offset the small benefit in averting transfusions in very preterm newborns has been possible exacerbation of retinopathy of prematurity (ROP). The etiology of ROP has been traced to a developmental surge in VEGF, another hypoxic responsive hormone, at around 32 to 34 weeks corrected age. Because Epo is similar to VEGF in its functions, especially on the eye (Heidary et al, 2009), it was only natural that would be a focus on ROP in trials of Epo. Early pooled data suggested a rise in the rate of ROP greater than stage 3. However, the most recent Cochrane metaanalysis markedly downgrades that apparent risk to be no longer statistically significant (RR 1.24 [0.81, 1.90]). This finding is corroborated by an additional independent metaanalysis (Rimion, 2013).

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Abstract: Anemia is a term used to describe deficiency of hemoglobin or low hematocrit. Although the word *anemia* is loosely used in clinical medicine, an exact definition is difficult to quantify. All newborns, regardless of gestation, develop a physiologic transitional anemia. This reflects an initial failure of the bone marrow to respond to signaling from renal-derived erythropoietin. For the preterm—as opposed to the full-term—newborn, this anemia typically commences earlier and is both deeper and longer in duration. This pattern of anemia in the preterm newborn should be differentiated from "pathologic anemia," the result of either abnormalities of production or consumption (including bleeding and hemolysis). This chapter will describe the physiology of oxygen handling, including developmental transition from an intra- to extrauterine environment and changes to Hb–oxygen affinity before setting out an etiologic basis of anemia. The causes of hypovolemic (a reduction in the total circulating blood and plasma volume) versus euvolemic (a constant or normal circulating blood volume but with a low red cell volume and often an increased plasma volume) anemia will be described and currently available therapeutic options discussed, including the roles of both exogenous erythropoietin and allogeneic adult red cell transfusion.

Keywords: neonate, preterm, anemia, hemolysis, anemia of prematurity

9

Respiratory Distress Syndrome

Alain C. Cuna and Waldemar A. Carlo

INTRODUCTION

Respiratory distress syndrome (RDS) is a developmental lung disease of preterm infants primarily caused by inadequate production of surfactant. Infants with RDS have difficulty maintaining adequate functional residual capacity (FRC), leading to alveolar atelectasis, hypoventilation, and ventilation-perfusion mismatch. Affected infants present shortly after birth with worsening tachypnea, nasal flaring, grunting, retractions, hypercapnia, and hypoxemia. Extensive research in the management of RDS has led to major improvements in the care of preterm infants and increased survival. In this chapter, we summarize the most current evidence-based management of RDS.

CASE 1

A 31-year old gravida 2 para 1 mother presents to the local community hospital at 32 weeks' gestation due to leaking vaginal fluid since earlier that day and increasing regular, painful uterine contractions. She has a history of previous preterm delivery at 28 weeks' gestation. She is concerned about the risk of RDS in this infant, as she remembers her previous preterm daughter was ventilated for several days after she was born.

Exercise 1

Questions

1. Which of the following prenatal interventions will have the MOST beneficial effect in reducing the severity of RDS in this case?
   A. Delivery is advised as the infant is moderately preterm and risk of RDS is negligible.
   B. Antenatal steroids should be administered to accelerate fetal lung maturity and improve infant outcomes.
   C. Tocolysis to delay preterm delivery would not be effective and thus should not be offered given her previous history of preterm delivery.
2. Which of the following statements is TRUE regarding tocolysis to delay preterm delivery?
   A. Short-term tocolysis is beneficial to allow for administration of antenatal steroids and transfer to tertiary facility.
   B. Maintenance therapy with tocolytics is effective for preventing preterm birth and improving neonatal outcomes.
   C. The tocolytic agent of choice to delay preterm delivery is a calcium channel blocker.

Answers

1. **B.** Antenatal steroids should be administered to accelerate fetal lung maturity and improve infant outcomes.
2. **A.** Short-term tocolysis is beneficial to allow for administration of antenatal steroids and transfer to tertiary facility.

EFFECTIVE PRENATAL CARE FOR DECREASING RDS

Prevention of Preterm Delivery

The most effective way of decreasing the risk and severity of RDS is to prevent preterm delivery. Unfortunately, effective interventions for preventing preterm birth remain limited. Factors that increase risk for preterm delivery include previous history of preterm labor, multiple gestation, and short cervix. Mothers identified as high risk for preterm labor should be closely monitored during pregnancy, and interventions to prevent preterm delivery (such as progesterone administration or cerclage placement) should be considered when appropriate. Elective cesarean delivery without labor for late preterm infants (34-36 weeks' gestation) should also be avoided, as the risk for RDS remains increased in this population compared with term infants.

Antenatal Steroids for Pharmacologic Acceleration of Fetal Lung Maturity

For mothers who go into preterm labor or are at imminent risk for preterm delivery, antenatal corticosteroids should be given immediately. Antenatal corticosteroids promote accelerated maturity of the fetal lung and remain one of the most important interventions to decrease RDS and improve outcomes. The most recent Cochrane metaanalysis of antenatal steroids for fetal acceleration of lung maturity showed that antenatal steroids significantly reduce the incidence of RDS (RR 0.66, 95% CI 0.56-0.77) and overall neonatal mortality

in preterm infants (RR 0.69, 95% CI 0.59-0.81). Long-standing recommendations from the American College of Obstetricians and Gynecologists call for routine administration of antenatal steroids to women between 24 to 34 weeks of gestation who are at risk of preterm delivery. Antenatal corticosteroids should also be considered for pregnant women as early as 23 weeks of gestation and to those between 34 and 36 weeks' gestation in light of recent evidence showing benefits to steroid-exposed infants born within this gestational age range.

Transfer to Tertiary Facility

Not all delivery centers have adequate equipment and skilled personnel to take care of preterm infants. Mothers at risk for imminent preterm delivery should thus be transferred to tertiary care facilities whenever possible. Transfer of a pregnant mother is preferable to neonatal transport, as studies have consistently shown better survival and long-term outcomes for infants born in referral centers.

Tocolytic Therapy

Tocolytic therapy to delay preterm delivery has not been shown to improve neonatal outcomes. Nevertheless, short-term use is recommended to allow completion of antenatal corticosteroids and transfer of the mother to a tertiary facility. Common tocolytic agents include calcium channel blockers, nonsteroidal antiinflammatory drugs, beta-adrenergic receptor agonists, and magnesium sulfate. Although efficacy is generally similar, potential side effects on mother and infant can differ widely. Tocolytic therapy should thus be individualized based on each patient's unique circumstances.

CASE 2

A 22-year-old pregnant woman was rushed to the emergency room due to rupture of membranes and onset of labor at 26 weeks' gestation. She received a dose of betamethasone, started on magnesium sulfate for tocolysis, and transferred to the regional perinatal center for further management. Upon admission to labor and delivery, her cervix was noted to be 3 cm dilated. Magnesium sulfate was continued, and she was able to receive a second dose of betamethasone. However, she continued to have uterine contractions with progressive cervical dilation. The NICU team was called, and preparations were made for imminent vaginal delivery.

Exercise 2

Questions

1. Immediately following delivery, the infant was noted to have weak cry and spontaneous movement. Based on the 2015 American Heart Association guidelines on neonatal resuscitation, which of the following umbilical cord management should be performed?
   A. Delayed cord clamping
   B. Cord milking or stripping
   C. Immediate cord clamping
2. The infant was brought to the radiant warmer, where a quick assessment revealed the infant is not breathing and has a heart rate of 80 beats per minute. Which of the following interventions is most appropriate?
   A. Bag-mask ventilation with initial Fio_2 of 30%
   B. Bag-mask ventilation with initial Fio_2 of 60%
   C. Continuous positive airway pressure (CPAP) with initial Fio_2 of 30%
   D. CPAP with initial Fio_2 of 60%

Answer

1. **A.** Delayed cord clamping
2. **A.** Bag-mask ventilation with initial Fio_2 of 30%

DELIVERY ROOM STABILIZATION

Optimal delivery room resuscitation is important in decreasing neonatal morbidity, including RDS. The most recent guidelines on Neonatal Resuscitation 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care.

Delayed Cord Clamping

Delayed clamping of the umbilical cord for 30 to 60 seconds following delivery allows for blood flow from the placenta to the infant to continue, resulting in an increase in blood volume and blood pressure. A metaanalysis of randomized controlled trials (18 studies, 2834 infants) of early versus delayed cord clamping in preterm infants showed that delayed cord clamping decreased hospital mortality (RR 0.70, 95% CI 0.51-0.95) and reduced the need for blood transfusions by 10%. Current guidelines regard delayed cord clamping as reasonable for preterm infants who are breathing or crying immediately after birth. Cord milking or stripping of the unclamped umbilical cord several times to push blood toward the infant has been suggested as an alternative to delayed cord clamping, especially in cases when the preterm infant is clearly depressed and immediate resuscitation is desired. However, routine cord milking is currently not recommended, as further studies are needed to establish its effectiveness and safety—particularly in the resuscitation of depressed preterm infants.

Thermoregulation

Thermoregulation in the delivery room is important, as both hypothermia and hyperthermia are associated with increased neonatal morbidity and mortality. Preterm infants are especially vulnerable and require advanced preparation. Before a delivery, the room temperature is ideally set at 26° to 28° C (79°–82° F) and the radiant warmer turned on to maximum power. Warm blankets and a hat should also be available. For preterm infants less than 32 weeks' gestation, additional strategies are recommended to prevent hypothermia. Placing the preterm infant immediately in a plastic bag without drying decreases evaporative heat loss while still allowing in heat from the radiant warmer. Warm humidified resuscitation gas and additional exothermic mattress may also be used.

The overall goal is to maintain body temperature between 36.5° C and 37.5° C.

Ventilation

The most important step in stabilization at birth is establishment of effective ventilation. Preterm infants are especially at risk and frequently need support to establish adequate ventilation because of their immature airways and surfactant deficiency. A quick assessment of the infant's need for respiratory support includes evaluation of the heart rate and respiratory effort. If the heart rate is less than 100 beats per minute or if the infant is apneic or gasping, positive pressure ventilation via bag-mask or T-piece is needed. Placement of electrocardiographic leads may be considered for more rapid and accurate measurement of heart rate, as clinical assessment by auscultation or palpation can be challenging especially in preterm infants. Care should be exercised with the inflation pressures because excessive tidal volume is associated with lung injury. Inadequate pressure can lead to ineffective ventilation and is also harmful. Sustained lung inflation—a technique whereby relatively high peak inspiratory pressure is administered for more than 5 seconds—has been evaluated as an alternative to intermittent positive pressure breaths for establishment of adequate FRC, but there remains insufficient evidence for its effectiveness and safety.

Oxygenation

Optimal management of oxygenation is also important, as both inadequate and excessive oxygenation are potentially harmful to newborn infants. Resuscitation with 100% oxygen may increase mortality compared with room air resuscitation in term and late preterm babies. Though few studies have been performed in preterm infants, there is some evidence to suggest that low oxygen strategy for resuscitation of preterm infants may be more beneficial compared with resuscitation with 100% oxygen. Current guidelines recommend starting resuscitation of preterm infants $<$ 35 weeks of gestation with low oxygen (21%–30%) and titrating supplemental oxygen using a blender to target the normal gradual increase in oxygen saturations following birth (80%–85% at 5 minutes, 85%–95% at 10 minutes).

CASE 3

A preterm male infant at 25 weeks' gestation was delivered vaginally and was noted to be crying and breathing immediately after birth. After 30 seconds of delayed cord clamping, he was received by the resuscitation team in a warm blanket and immediately placed under a radiant warmer and inside a plastic bag without drying. A quick assessment revealed poor respiratory effort and HR less than 100 despite gentle stimulation. Positive pressure ventilation was initiated via bag-mask device with appropriate pressures and 30% oxygen, and a pulse oximeter was placed on his right hand to allow targeted administration of oxygen. At 3 minutes, he had spontaneous breathing with a HR greater than 100 beats per minute.

Exercise 3

Question

Which of the following is the most appropriate next step in the management of this infant?

A. Continue positive pressure ventilation via bag-mask device
B. Intubate and administer surfactant
C. Provide continuous positive airway pressure (CPAP)

Answer

C. Provide continuous positive airway pressure (CPAP)

PROPHYLACTIC INTUBATION WITH SURFACTANT ADMINISTRATION VERSUS PROPHYLACTIC CPAP INITIATED AT DELIVERY

On the basis of trials showing benefits of early surfactant administration over later treatment, the practice of routinely intubating preterm infants in the delivery room to administer surfactant became widespread. This practice, however, exposes preterm infants who may not have needed mechanical ventilation to unnecessary ventilator-associated lung injury. Recent trials have evaluated an alternative strategy of prophylactic CPAP initiated at delivery, with later intubation and surfactant administration reserved for infants who failed CPAP. This less invasive strategy, evaluated in three large randomized controlled trials (RCTs) including 2364 preterm infants born at less than 30 weeks' gestation, was shown to decrease rate of intubation in the delivery room and decrease overall duration of mechanical ventilation. A metaanalysis of these trials demonstrated a small but significant treatment effect of decreasing death or bronchopulmonary dysplasia (BPD) at 36 weeks (RR 0.89, 95% CI 0.81–0.97) with prophylactic CPAP. Based on this evidence, prophylactic CPAP started at delivery for spontaneously breathing extremely preterm infants with RDS is recommended as an alternative and potentially better practice than prophylactic intubation.

CASE 4

A preterm infant born at 27 weeks' gestation with birth weight of 900 g is admitted to the NICU on nasal CPAP. Over the past hour, his work of breathing has increased significantly. His oxygen requirement to maintain oxygen saturations at goal range increased from 25% to 55%, and his most recent arterial blood gas shows pH of 7.32, P_{CO_2} of 52 mm Hg, P_{O_2} of 50 mm Hg, and HCO_3 of 22 mEq/L. He had two brief, self-resolving apneic spells in the past hour.

Exercise 4

Questions

1. For which of the following indications would you consider intubating this infant and administering surfactant?
   A. Increasing work of breathing
   B. Oxygen need of 55%
   C. P_{CO_2} of 52 mm Hg

D. Brief, self-resolving apneic spells
E. None of the above

2. Which of the following statement is true regarding surfactant at this time?
   A. Synthetic surfactant is superior to natural surfactant
   B. A single dose of surfactant is as effective as multiple doses of surfactant
   C. Earlier surfactant therapy is superior to late surfactant therapy

Answers

1. **B.** Oxygen need of 55%
2. **C.** Earlier surfactant therapy is superior to late surfactant therapy

INDICATIONS FOR INTUBATION AND SURFACTANT ADMINISTRATION

Although early CPAP at birth is a safe and effective form of respiratory support for preterm infants with RDS, CPAP does not completely eliminate the need for intubation, surfactant administration, or mechanical ventilation. Data from RCTs that assessed early CPAP versus routine intubation at birth demonstrated that 45% to 51% of infants randomized to early CPAP eventually needed to be intubated and given surfactant. Criteria used to determine CPAP failure differed slightly among the different RCTs and included (1) Fio_2 greater than 40% to 60% to meet target oxygen saturations, (2) Paco2 greater than 60 mm Hg to 65 mm Hg, (3) apnea requiring intervention, and (4) hemodynamic instability. Interestingly, increased work of breathing based on subjective assessment was not a criterion for CPAP failure in any of the studies.

SURFACTANT THERAPY

Surfactant therapy is one of the most important advances in neonatal care that has significantly reduced mortality of preterm infants with RDS. Numerous clinical trials have shown that surfactant therapy decreases mortality, air leak syndromes, and the combined outcome of BPD or death. Many RCTs have been completed that delineate optimal surfactant treatment strategies including the type of surfactant, dose of surfactant, route of administration, and timing of therapy. More recent studies are focusing on alternative approaches to surfactant administration that avoid intubation.

Type of Surfactant: Animal-Derived Versus Synthetic

The two main types of surfactant are animal derived (contains surfactant proteins) and synthetic (protein free). A Cochrane review comparing animal-derived and synthetic surfactant shows that treatment with animal-derived surfactants results in fewer deaths (RR 0.89; 95% CI 0.79–0.99) and fewer pneumothoraces (RR 0.65; 95% CI 0.55–0.77). A newer type of synthetic surfactant (called lucinactant) that contains surfactant protein analogs is approved for the prevention and treatment of RDS. Metaanalysis of two studies comparing a protein containing synthetic surfactant with animal-derived surfactants did not show significant differences in clinical outcomes.

Dosing of Surfactant: Single Versus Multiple

A single dose versus multiple doses of surfactant has been studied in randomized clinical trials, and a Cochrane metaanalysis showed that treatment with multiple doses of surfactant reduced pneumothoraces, with a trend to reduce deaths. Studies of higher versus lower dose of surfactant also showed that a dose of 200 mg/kg versus 100 mg/kg resulted in better oxygenation, less need for repeat doses, and fewer deaths.

Prophylactic Versus Selective Surfactant

Prophylactic surfactant is a strategy wherein surfactant is administered within 30 minutes of birth (typically while still in the delivery room) to infants at high risk of RDS, with the goal of decreasing the severity of RDS before the disease has set in. In contrast, selective surfactant involves treatment when RDS is already established (typically within the first 12 hours of life) when a specified criterion of RDS severity is met. A Cochrane metaanalysis of studies comparing these two strategies demonstrated that surfactant administered prophylactically results in decreased neonatal mortality (RR 0.61; 95% CI 0.48–0.77) and decreased pneumothorax (RR 0.62; 95% CI 0.42–0.89) compared with selective surfactant.37 However, most of the studies included in the metaanalysis were conducted before routine application of CPAP in the delivery room was widely practiced. When restricted to studies that routinely practiced early CPAP at birth, a metaanalysis revealed that infants receiving prophylactic surfactant actually had higher rates of BPD or death (RR 1.12; 95% CI 1.02–1.24).

Early Selective Versus Delayed Selective Surfactant

Selective or rescue surfactant therapy for established RDS can further be classified as early (within 2 hours after birth) and delayed. In a Cochrane metaanalysis of trials comparing early versus delayed selective surfactant therapy, earlier surfactant treatment for RDS decreased death, air leak, and BPD. Studies included in this review were also conducted before routine CPAP at birth was widely practiced. Whether the benefits of early selective surfactant remain for infants stabilized with prophylactic CPAP at birth is unclear.

Alternative Methods of Surfactant Administration

Surfactant is traditionally administered directly into the trachea via an endotracheal tube, which, although effective, exposes infants to potential harm from intubation and mechanical ventilation. Some studies have thus evaluated alternative methods of surfactant administration that minimize or avoid the need for intubation and mechanical ventilation. One strategy, called INSURE (INtubate – SURfactant – Extubate to CPAP), involves intubation, early surfactant

administration, and brief ventilation (for less than 1 hour) followed promptly by extubation to nasal CPAP. A meta-analysis of six randomized trials comparing INSURE to selective surfactant and continued mechanical ventilation demonstrated that INSURE is beneficial in decreasing need for mechanical ventilation (RR 0.67, 95% CI 0.57–0.79), air leak syndromes (RR 0.52, 95% CI 0.28–0.96), and BPD (RR 0.51, 95% CI 0.26–0.99). Compared with the strategy of early CPAP at delivery as discussed earlier, a metaanalysis of nine trials (1551 infants) demonstrated no differences in outcomes between prophylactic INSURE or early CPAP.

Another strategy that avoids intubation and mechanical ventilation altogether is surfactant administration via thin intratracheal catheter placed under direct visualization with laryngoscopy in spontaneously breathing infants. A metaanalysis of six RCTs that enrolled a total of 895 infants demonstrated reduction in mechanical ventilation (RR 0.66, 95% CI 0.47–0.93) and the composite outcome of BPD or death (RR 0.75, 95% CI 0.59–0.94) using this method of less invasive surfactant administration (LISA) via thin catheter compared with traditional administration with endotracheal tube.

CASE 5

A preterm infant born at 27 weeks and weighing 1000 g was admitted to the NICU. She was supported with early CPAP at birth but eventually needed intubation due to increasing Fio_2 requirement of more than 50%. Following successful intubation and surfactant administration, the respiratory therapist asks for ventilator settings to put the patient on.

Exercise 5

Questions

1. Which of the following ventilator settings would you start with?
   A. Rate of 30 breaths per minute (bpm), inspiratory time of 0.8 seconds, peak inspiratory pressure (PIP) of 20 cm H_2O for tidal volume of 8 mL per breath, PEEP of 8 cm H_2O
   B. Rate of 60 bpm, inspiratory time of 0.3 seconds, PIP of 15 cm H_2O for tidal volume of 4 mL per breath, PEEP of 4 cm H_2O
2. At 5 days of life, she has gradually weaned on the ventilator with current settings as follows: rate of 15 bpm, PIP of 12 cm H_2O, PEEP of 4 cm H_2O, and Fio_2 of 30%. Her blood gas shows pH of 7.32, Pco_2 of 48 mm Hg, Po_2 of 60 mm Hg, and HCO_3 of 21 mEq/L. The team has decided for a trial of extubation. Which of the following interventions would increase her chances of successful extubation?
   A. Extubation to CPAP
   B. Prophylactic caffeine
   C. Extubation following a 24-hour trial of endotracheal tube CPAP
   D. All of the above
   E. A and B only

Answers

1. **B.** Rate of 60 bpm, inspiratory time of 0.3 seconds, PIP of 15 cm H_2O for tidal volume of 4 mL per breath, PEEP of 4 cm H_2O
2. **E.** A and B only

MECHANICAL VENTILATION STRATEGIES IN RDS

Although mechanical ventilation is necessary and life saving in many preterm infants with RDS, it is known to cause lung injury and may lead to complications including air leak syndromes and BPD. Knowledge of proper management of preterm infants on mechanical ventilation is thus important, with the goal of promoting adequate gas exchange while preventing or minimizing lung injury.

Low Tidal Volume, Low Peak Inspiratory Pressure

Inspiratory pressures used in pressure-limited ventilation should be the lowest possible to maintain adequate gas exchange but minimize volutrauma. Adequacy of peak inspiratory pressure (PIP) can be determined initially by assessing chest rise, which should be gentle and not excessive. Exhaled tidal volume as measured by the ventilator may also be used, with a goal tidal volume of 4 to 6 mL/kg body weight. Subsequent changes in PIP can then be based on blood gases. In volume-targeted ventilation, a physiologic tidal volume of 4 to 6 mL/kg can be set with the ventilator automatically adjusting inflation pressures to achieve the targeted tidal volume. The most recent Cochrane review comparing volume-targeted versus pressure-limited ventilation found that volume-targeted ventilation resulted in decreased death or BPD at 36 weeks' gestation (RR 0.73, 95% CI 0.59–0.89) and decreased rates of pneumothorax (RR 0.52, 95% CI 0.31–0.87).

Moderate Positive End Expiratory Pressure

Adequate positive end expiratory pressure (PEEP) is needed to prevent alveolar collapse, improve FRC, and improve ventilation-perfusion matching. A PEEP of 4 to 5 cm H_2O is usually adequate to achieve this goal in infants with RDS. Low PEEP can cause alveolar collapse at the end of expiration and increase lung injury from atelectrauma (repeated collapse and reexpansion of alveoli). High PEEP can lead to overdistention of alveoli, which may decrease venous return and preload, thus decreasing cardiac output. High PEEP can also decrease lung compliance.

Fast Ventilator Rate and Short Inspiratory Time

The use of fast ventilator rates ($\geq$60 breaths per minute) and short inspiratory times results in fewer air leak syndromes and a trend for lower mortality compared with slow rates and long inspiratory times. Preterm infants with RDS can tolerate fast rates because their respiratory system has low compliance and low resistance and thus a short time constant.

Permissive Hypercapnia

Permissive hypercapnia is a ventilatory strategy aimed at reducing ventilator-associated lung injury by allowing mild hypercapnia instead of targeting normocapnia. This practice is widely used in neonatology based on evidence from small trials as well as data from the SUPPORT trial, which combined early CPAP with permissive hypercapnia strategy (Pco_2 ≤65 mm Hg with pH ≥7.20) practiced from birth until extubation.

Another trial—the Permissive Hypercapnia in Extremely Low Birthweight Infants (PHELBI) trial—compared two permissive hypercapnia target Pco_2 ranges (40–60 mm Hg versus 55–75 mm Hg). This trial, which did not use a pH limit compared with all other trials of permissive hypercapnia, was stopped before the targeted enrollment was achieved because interim analysis showed no benefit (no difference in BPD or death) and potential harm (higher incidence of necrotizing enterocolitis [NEC]) in the higher permissive hypercapnia group. Long-term follow-up of PHELBI study was reassuring in that neurodevelopmental outcomes did not differ between the two groups. Thus, based on best available evidence, mild to moderate levels of hypercapnia that targets 50 to 65 mm Hg appear safe and effective, but severe permissive hypercapnia that targets 55 to 75 mm Hg soon after birth without a pH limit as tested in the PHELBI trial should be avoided.

EXTUBATION

Prompt weaning and subsequent extubation are essential to minimize lung injury in preterm infants with RDS. Extubation may be considered in preterm infants with good respiratory drive who are able to maintain an acceptable Pco_2 (<65 mm Hg with a pH >7.20) while receiving minimal ventilator support (rate of ≤20 bpm, low PIP/tidal volume, and Fio_2 ≤50%). Several strategies have been evaluated in Cochrane reviews to increase chances of successful extubation. Extubation from low ventilator rates improves chances of successful extubation compared with extubation from endotracheal tube CPAP. Extubation to nasal CPAP with or without augmented intermittent positive pressure ventilation is also effective in preventing postextubation failure. Extubation to high PEEP (7–9 cm H_2O) compared with low PEEP (4–6 cm H_2O) decreased the risk of extubation failure in a small randomized trial. Methylxanthines, such as caffeine, increase the respiratory drive and also reduce risk of extubation failure.

CASE 6

A 27-week female infant was delivered vaginally due to preterm labor. At birth, she had spontaneous breathing with a HR above 100. She was supported by early CPAP, and oxygen was titrated to target oxygen saturations. By 10 minutes, she was on 40% oxygen to reach oxygen saturations above 85%. Upon admission to the NICU, her oxygen saturations are now 99% on CPAP at 40% oxygen.

Exercise 6

Question

1. What oxygen saturations would you target on this infant?
   A. 85% to 95%
   B. 85% to 89%
   C. 91% to 95%
   D. 96% to 99%

Answer

C. 91% to 95%

OXYGENATION TARGETS

Supplemental oxygen plays a vital role in the treatment of RDS, but extremes in oxygen may also be detrimental. A Cochrane metaanalysis of restricted versus liberal oxygen exposure concluded that there was insufficient evidence to determine the optimal target range for maintaining blood oxygen levels in preterm infants. To address this clinical dilemma, five large multicenter randomized trials assessed the effect of targeting lower oxygen saturations (85%–89%) versus higher oxygen saturations (91%–95%) in extremely preterm infants. These RCTs were designed to have similar methods and outcome measures to allow for a prospective individual patient metaanalysis. The primary outcome of this collaboration, called the Neonatal Oxygen Prospective Meta-analysis (NeOProM), is the composite outcome of death or major disability at 18 to 24 months of age.

The SUPPORT trial (n = 1316) conducted in the United States was the first RCT completed. In this study, the primary outcome of severe retinopathy of prematurity (ROP) or death did not differ between the two different oxygen saturation groups. However, death before discharge was unexpectedly higher in the lower saturation group (RR 1.27, 95% CI 1.01–1.60, number needed to harm = 27), whereas severe ROP was lower in the lower saturation group (RR 0.52, 95% CI 0.37–0.73, number needed to benefit = 11). The Benefits of Oxygen Saturation Targeting (BOOST) II trials (United Kingdom, Australia, and New Zealand) also assessed the effects of lower versus higher target oxygen saturations. The UK and Australian trials were stopped before enrollment was completed because the interim analysis showed that, similar to SUPPORT, targeting lower oxygen saturations led to a significant increased risk of death. The Canadian Oxygen Trial (COT) showed a trend for increased death in infants in the lower oxygen saturation target group. A Cochrane meta-analysis of these trials demonstrated increased incidence of death (RR 1.16, 95% CI 1.03–1.31) and NEC (RR 1.24, 95% CI 1.05–1.47) among infants in the lower target range compared with the higher target range. No significant differences in neurodevelopment or blindness were noted between the two treatment groups on follow-up. Based on this evidence, it is now recommended to target oxygen saturations of 91% to 95% for extremely preterm infants receiving supplemental oxygen therapy.

CASE 7

A male infant was delivered at 35 weeks by vaginal delivery to a 30-year-old mother due to preterm labor. At delivery, he had poor respiratory effort that improved with bag-mask ventilation and CPAP. He quickly transitioned to room air and was transferred to the well-baby nursery. At 2 hours of life, he started having increased work of breathing. On physical examination, he was tachypneic, grunting, with nasal flaring and moderate subcostal retractions. Pulse oximetry showed oxygen saturations at 84%.

Exercise 7

Questions

1. Which of the following are possible causes of this infant's respiratory distress?
   A. Respiratory distress syndrome
   B. Pneumothorax
   C. Infection
   D. Persistent pulmonary hypertension of the newborn
   E. All of the above
2. Which of the following would you include in the initial evaluation of this infant?
   A. Arterial blood gas
   B. Chest x-ray
   C. Complete blood count
   D. Blood culture
   E. All of the above

Answers

1. **E.** All of the above
2. **E.** All of the above

DIFFERENTIAL DIAGNOSIS OF RDS

Although RDS is the most common cause of respiratory distress in preterm infants during the immediate newborn period, vigilance for other causes of respiratory distress remains important. Among the more important differential diagnoses to consider are infection, transient tachypnea of the newborn, pneumothorax, persistent pulmonary hypertension of the newborn, congenital lung malformations, and critical congenital heart disease.

Infection

It is difficult to distinguish RDS from early onset sepsis in the immediate newborn period, as both can present similarly with signs of respiratory distress. Thus it is prudent to do a screening workup for sepsis and consider empirical antibiotics especially if factors that increase the risk for infection (such as maternal fever, prolonged rupture of membranes, maternal chorioamnionitis, or group B streptococcus colonization) are present. In contrast, preterm delivery due to maternal indications such as preeclampsia or placental abruption are associated with a decreased infection risk.

Transient Tachypnea of the Newborn

Distinguishing transient tachypnea of the newborn (TTN) from RDS can be challenging. TTN, which is thought to arise from delay in reabsorption of fetal lung fluid, is more often seen following delivery by cesarean section without labor. Symptoms include tachypnea, grunting, retractions, and cyanosis requiring minimal to no oxygen supplementation. The chest x-ray can be helpful and typically reveals hazy lungs with fluid in the intralobar fissures. Infants with TTN rarely need ventilator support and recover over 1 to 4 days, usually with just supportive treatment.

Pneumothorax

Pneumothorax often occurs in infants with underlying lung disease (such as RDS, meconium aspiration, pulmonary hypoplasia, congenital lobar emphysema) that requires high inflation pressures delivered via bag-mask, T-piece, or mechanical ventilator. Signs include respiratory distress, asymmetric chest wall movement, and decreased breath sounds on the affected side. Positive bedside transillumination can suggest the presence of a pneumothorax, but a chest x-ray is helpful for definitive diagnosis. Treatment may require evacuation of air by needle thoracentesis and/or chest tube insertion, but spontaneous resolution can happen even in ventilated neonates.

Persistent Pulmonary Hypertension of the Newborn

A rapid decline of pulmonary vascular resistance is expected postnatally as the fluid-filled lungs expand with air. In persistent pulmonary hypertension of the newborn (PPHN), pulmonary vascular resistance remains elevated, hampering blood flow to the lungs and resulting in right to left shunt at the foramen ovale or ductus arteriosus leading to profound hypoxemia. Any disease process that interferes with the normal postnatal transition can cause infants to develop PPHN, including perinatal asphyxia, early onset sepsis, severe RDS, and meconium aspiration. Signs may include differential oxygenation of preductal and postductal blood, severe cyanosis, tachypnea, grunting, flaring, retractions, and shock. The chest x-ray typically shows minimal lung disease with decreased pulmonary vascular markings. Diagnosis is made clinically and by echocardiography.

Congenital Lung Malformations

Congenital lung malformations may also present with respiratory distress in the newborn period. Examples include diaphragmatic hernia, congenital pulmonary airway malformation, bronchopulmonary sequestration, tracheoesophageal fistula, bronchogenic cyst, and lobar emphysema. Although some of these malformations are now detected prenatally with ultrasound, a chest x-ray is still needed postnatally to evaluate for these conditions.

Critical Congenital Heart Disease

Critical congenital heart diseases typically present with cyanosis with minimal to no signs of increased work of breathing.

The majority of infants with critical congenital heart diseases are now detected by prenatal ultrasound. Of note, total anomalous pulmonary venous return with obstructed pulmonary veins is particularly difficult to detect on prenatal ultrasound and can closely mimic RDS postnatally. An echocardiogram is indicated whenever critical congenital heart disease is suspected.

INITIAL DIAGNOSTIC EVALUATION IN RDS

Chest X-Ray

Infants with different types of lung disease can present with very similar signs of respiratory distress. Following a thorough history and physical examination, the chest x-ray is probably the single most helpful diagnostic test for newborns with respiratory distress and should always be part of their initial evaluation. In RDS, the three characteristic radiographic features are low lung volumes, diffuse fine granular lung pattern, and air bronchograms.

Arterial Blood Gas

An arterial blood gas, which includes the pH and the partial pressures of arterial carbon dioxide ($Paco_2$) and oxygen (PaO_2), provide information critical to assess gas exchange. In infants with RDS, the blood gases typically show low Pao_2, high $Paco_2$, and mixed respiratory and metabolic acidosis. The blood gas results help determine how the infant's lungs are functioning and the level of respiratory support needed.

Sepsis Workup

Because infection and RDS present similarly in the newborn period, a sepsis workup should be included in the evaluation of most infants with persistent respiratory distress. Initial tests include a complete blood count (CBC) and a blood culture. Findings in the CBC with a low to moderate predictive value for sepsis include a low white blood cell count (less than 5000), low absolute neutrophil count (less than 1500), and high immature to total neutrophil count (greater than 0.2). The blood culture is the gold standard for sepsis, and results should be followed until no growth of organisms occurs in the culture bottles for at least 48 hours. A urine culture is not indicated, as urinary tract infections are uncommon at birth. The incidence of meningitis in healthy-appearing infants or infants with RDS is also low, and a lumbar puncture may not be necessary, except when the blood culture is positive or if the clinical picture strongly suggests bacterial sepsis.

Echocardiography

Echocardiography is needed whenever congenital heart disease is suspected, such as in infants with persistent hypoxemia despite intubation and surfactant therapy. Echocardiography can also be helpful in diagnosing persistent pulmonary hypertension of the newborn, although results must be correlated clinically, as elevated right-sided heart pressures are an expected normal finding in the immediate postnatal period.

CASE STUDY 8

A preterm male infant was born at 25 weeks' gestation. He benefited from antenatal steroids for acceleration of lung maturity and early CPAP at birth, but eventually required intubation with surfactant administration. He is now 4 days old and remains on mechanical ventilation using lung protective strategies. During rounds, the parents ask what other interventions can be done to help their son.

Exercise 8

Question

1. Which of the following pharmacologic adjunct(s), started within the first week of life, could be beneficial in this preterm infant who remains on mechanical ventilation for RDS?
   A. Caffeine citrate to decrease apnea of prematurity
   B. Vitamin A supplementation to promote lung development
   C. Postnatal steroids to improve lung function and facilitate extubation
   D. All of the above
   E. A and B only

Answer

E. A and B only

PHARMACOLOGIC ADJUNCTS

Caffeine

Caffeine is a potent respiratory stimulant that enhances sensitivity to carbon dioxide through its inhibitory effect on adenosine receptors in the brain. In a large multicenter randomized trial, preterm infants treated with caffeine had shorter duration of CPAP and mechanical ventilation and were less likely to develop BPD compared with preterm infants treated with placebo. Long-term follow-up of infants also showed better survival without increased neurodevelopmental disability among infants treated with caffeine. Routine administration of caffeine before extubation or shortly after is recommended and is typically started several days after birth and discontinued at around 34 to 36 weeks' postmenstrual age. Some observational studies suggest that early initiation (within the first 1–2 days after birth) of caffeine decreases BPD compared with later treatment. However, evidence from small randomized trials indicate no benefit and even potential harm with early caffeine therapy.

Vitamin A

Vitamin A is a fat-soluble micronutrient important for the differentiation, orderly growth, and maintenance of the respiratory epithelium. Preterm infants with lower levels of

vitamin A are more likely to develop BPD, and clinical trials have demonstrated that vitamin A supplementation results in a modest but significant decrease in risk of BPD. A Cochrane metaanalysis demonstrated a decrease in risk for BPD with vitamin A supplementation compared with placebo (RR 0.87, 95% CI 0.77–0.99, NNTB = 11). The standard regimen of vitamin A supplementation (5000 international units intramuscularly given three times a week for 4 weeks) is typically started within the first 4 days after birth.

Postnatal Steroids

Postnatal steroids are potent antiinflammatory agents that have been shown in randomized trials to improve lung function and facilitate weaning from the ventilator. Its routine use, however, is not recommended because of adverse effects on the developing brain. A Cochrane review of 29 trials (n = 3750) concluded that although early systemic steroids (≤7 days) reduce BPD (RR 0.79, 95% CI 0.71–0.88), it increases the risk for cerebral palsy (RR 1.45, 95% CI 1.06–1.98). Similar concerns were found with late systemic steroids (>7 days), which decreased BPD (RR 0.82, 95% CI 0.70–0.96), but were associated with an increased risk of neurologic abnormalities on follow-up (RR 1.81, 95% CI 1.05–3.11). Rather than routine use of postnatal steroids, an individualized approach that targets the highest-risk infants may be considered. Based on evidence from a metaregression analysis, systemic steroids can be beneficial in decreasing death or cerebral palsy when administered to infants with high risk for BPD (e.g., ventilated at 14 days of age) whereas treatment can be harmful when risk for BPD is low.

Other approaches that aim to minimize harm of postnatal steroids while remaining effective at decreasing BPD continue to be explored. Early low-dose hydrocortisone, which may have less detrimental effects on the developing brain, has been shown in one large multicenter trial to increase survival without BPD (OR 1.48, 95% CI 1.02–2.16). Early budesonide therapy, administered intratracheally together with surfactant during the first days after birth, also showed benefit of decreasing death or BPD (RR 0.58, 95% CI 0.44–0.77). On the other hand, early and prolonged inhaled steroids, although beneficial in decreasing BPD, resulted in an increase in mortality (RR 1.37, CI 1.01–1.88). Additional research is needed to determine safety and effectiveness of these newer approaches to postnatal steroids.

CASE 9

A preterm infant was born at 27 weeks' gestation with a birth weight of 950 g. He is now 7 days old and remains intubated on mechanical ventilation. His echocardiogram reveals a moderate PDA with left-to-right shunting. His blood pressure and urine output remain within normal limits for gestational age, and his Fio_2 requirement remains stable at 30%. A question was raised during rounds whether he would benefit from treatment for PDA closure.

Exercise 9

Question

1. Which of the following outcomes will result from a treatment course with ibuprofen for PDA closure?
   A. Closure of PDA
   B. Decrease in BPD
   C. Decrease in NEC
   D. All of the above

Answer

A. Closure of PDA

PATENT DUCTUS ARTERIOSUS AND RDS

Numerous studies have associated PDA with poor neonatal outcomes including worsening RDS, BPD, and NEC. The pathophysiologic effects of PDA are attributed to excessive left-to-right shunting resulting in increased pulmonary blood flow and decreased systemic blood flow. The increase in pulmonary blood flow can lead to pulmonary edema, poor lung compliance, and impaired gas exchange, whereas decreased systemic blood flow (i.e., "ductal stealing") can cause decreased perfusion to the kidneys and gastrointestinal tract. These effects, together with the association of PDA with several morbidities, prompted several investigators to test the hypothesis that closure of PDA would improve outcomes. Evidence from randomized controlled trials and metaanalysis, however, concluded that apart from closing the ductus, interventions to close the PDA provided no benefit in neonatal outcomes compared with placebo.

The lack of long-term benefit, the potential harm associated with interventions used for PDA closure, and the high rate of spontaneous closure are beginning to influence clinicians to take a more conservative, individualized approach to PDA closure. Infants with birth weight over 1000 g have a high rate of spontaneous closure and rarely require treatment. For infants with birth weight under 1000 g, rate of spontaneous closure is smaller, and selective treatment may be considered for those with signs of pulmonary and hemodynamic compromise, including persistent or increased ventilator support, hypotension, heart failure, or renal impairment.

CASE 10

A 1-day-old infant born at 26 weeks' gestation was initially managed with early CPAP in the delivery room but subsequently needed intubation for increasing oxygen requirement (>50%). She received surfactant and was placed on conventional ventilator with settings that provided 6 mL/kg of tidal volume with each mechanical breath. Two hours after surfactant therapy, her oxygen was gradually weaned to 30% but her ventilator settings remained the same, with exhaled tidal volumes now reading 8 mL/kg. Four hours after surfactant therapy, the nurse calls that she is now needing 80% Fio_2 to maintain her target oxygen saturations. On examination,

she is tachypneic, with severe subcostal retractions, and has diminished air entry to the left lung.

Exercise 10

Question

1. Which of the following is most likely to be causing this infant's sudden respiratory decompensation?
   A. Pneumothorax
   B. Endotracheal tube obstruction
   C. Pulmonary hemorrhage
   D. A and B
   E. A, B, and C

Answer

A. Pneumothorax

COMPLICATIONS OF RDS

With major advances in neonatal care, most infants with RDS survive. Nevertheless, some infants develop serious complications either related to RDS itself or as adverse effects from the life-saving treatments they receive. Complications from RDS and its treatment can be classified as either acute or chronic. Acute complications include pneumothorax and pulmonary hemorrhage, and chronic complications include BPD and ROP.

Pneumothorax

Pneumothorax is caused by rupture of overdistended alveoli with the escaped air collecting in the pleural space. It is often seen in infants with severe RDS treated with mechanical ventilation or CPAP, although spontaneous cases can also occur. Major risk factors include use of high PIP, high tidal volume, high PEEP, prolonged inspiratory times, inadequate expiratory time, high flow rates, and patient–ventilator asynchrony. Careful attention should be given to delivered tidal volumes, especially following surfactant therapy when lung compliance improves significantly. Management strategies that decrease the risk of pneumothorax include avoidance of high PIP and PEEP, use of faster rates ($\geq$60 bpm) with shorter inspiratory times ($<$0.5 seconds), prompt administration of surfactant following intubation, and rapid weaning from the ventilator.

Pulmonary Hemorrhage

Pulmonary hemorrhage is bleeding from within the lungs associated with abrupt respiratory decompensation. The usual clinical picture is a ventilated preterm infant with RDS who received surfactant therapy and suddenly presents with frank blood or blood-tinged secretions from the trachea associated with worsening clinical picture (hypoxia, hypercapnia, hypotension, and bradycardia). It most often occurs during the first few days after birth when pulmonary vascular resistance drops and pulmonary blood flow through PDA acutely increases, leading to an exaggerated hemorrhagic pulmonary edema. Risk factors include prematurity, mechanical ventilation, surfactant therapy, PDA, sepsis, and coagulopathy. Treatment is mainly supportive and includes increased ventilator support, blood transfusion, inotropes, correction of coagulopathy if present, and antibiotics for possible sepsis.

Bronchopulmonary Dysplasia

Mechanical ventilation and oxygen therapy are life-saving cornerstones of treatment for RDS. These interventions, however, are also injurious to the immature lungs and contribute to an arrest in lung development that leads to BPD. Thus judicious management of preterm infant with RDS is important to prevent or alleviate BPD. Strategies that minimize mechanical ventilation, such as routine CPAP with selective surfactant therapy and less invasive approaches to give surfactant without intubation, provide a modest but significant benefit of decreasing risk of BPD.

Retinopathy of Prematurity

ROP is a potentially blinding disease that can arise as a complication of oxygen therapy for RDS. Oxygen should be carefully titrated with guidance from pulse oximetry but even with the best titration, ROP can develop. The ideal target range at which to keep oxygen saturations remains unclear. Results from five large multicenter trials indicate that targeting lower oxygen saturations (85%–89%) decreases risk for ROP but also increases the risk for death and NEC. An individual patient metaanalysis (NeOProM) of these studies is underway and may help provide additional insights into subgroups of patients who are most likely to benefit from a lower saturation range.

CONCLUSION

Management of RDS begins with good prenatal care, especially administration of antenatal steroids for mothers at risk for preterm birth. Proper stabilization at birth is also important, with emphasis on prophylactic CPAP for infants who breathe spontaneously following resuscitation. Postnatal respiratory management includes close monitoring to evaluate need for intubation and surfactant therapy and meticulous mechanical ventilation management of those intubated. Pharmacologic adjuncts shown to be beneficial include caffeine therapy started several days after birth and selective postnatal steroids for high-risk infants who remain mechanically ventilated at around 2 weeks of life. Other promising interventions include less invasive means of administering surfactant to avoid or lessen lung injury from mechanical ventilation. Trials that evaluated different oxygen and carbon dioxide ranges have also provided useful knowledge, although optimal targets for each remain to be determined. This chapter reviews the most current evidence-based management of preterm infants with RDS and classifies the treatments as interventions that reduce negative outcomes (Table 9.1), interventions that may be promising but require further evaluation (Table 9.2), and interventions that may be harmful (Table 9.3).

TABLE 9.1 Interventions That Reduce Negative Outcomes in Preterm Infants With RDS

Intervention	Effects	RR	95% CI	Reference
Antenatal steroids for accelerating fetal lung maturity	Reduced:			Roberts et al, 2017
	• Death	0.69	0.59–0.81	
	• RDS	0.66	0.56–0.77	
	• IVH	0.55	0.40–0.76	
	• Early onset sepsis	0.60	0.41–0.88	
	• NEC	0.50	0.32–0.78	
Delayed vs immediate cord clamping	Reduced:			Fogarty et al., 2018
	• Death	0.70	0.51–0.95	
	• transfusion for anemia	0.91	0.85–0.97	
Prophylactic CPAP vs prophylactic intubation	Reduced:			Subramaniam et al, 2016
	• BPD	0.89	0.79–0.99	
	• BPD or death	0.89	0.81–0.97	
	• need for mechanical ventilation	0.50	0.42–0.59	
Surfactant (animal derived) for treatment of RDS	Reduced:			Seger & Soll, 2009
	• Death	0.68	0.57–0.82	
	• Pneumothorax	0.42	0.34–0.52	
	• BPD or death	0.83	0.77–0.90	
Animal-derived vs protein-free synthetic surfactant	Reduced:			Ardell et al, 2015
	• Death	0.89	0.79–0.99	
	• Pneumothorax	0.65	0.55–0.77	
Multiple vs single doses of surfactant	Reduced:			Soll & Ozek, 2009
	• Pneumothorax	0.51	0.30–0.88	
	• Trend toward reduced death	0.63	0.39–1.02	
Prophylactic vs selective surfactant	Reduced:			Soll & Morley, 2001
	• Death	0.61	0.48–0.77	
	• Pneumothorax	0.62	0.42–0.89	
Early vs delayed selective surfactant	Reduced:			Bahadue & Soll, 2012
	• Death	0.84	0.74–0.95	
	• BPD	0.69	0.55–0.86	
	• BPD or death	0.83	0.75–0.91	
	• Pneumothorax	0.69	0.59–0.82	
Early surfactant with brief ventilation vs selective surfactant with continued mechanical ventilation	Reduced:			Stevens et al, 2007
	• Mechanical ventilation	0.67	0.57–0.79	
	• Air leak	0.52	0.28–0.96	
	• BPD	0.51	0.26–0.99	
Faster ventilator rate (≥60 bpm) vs slower ventilator rate (<60 bpm)	Reduced pneumothorax	0.69	0.51–0.93	Greenough et al, 2008
Volume-targeted vs pressure-limited ventilation	Reduced:			Kligenberg et al, 2017
	• BPD or death	0.73	0.59–0.89	
	• Pneumothorax	0.52	0.31–0.87	
Vitamin A	Reduced:			Darlow et al, 2016
	• BPD	0.87	0.77–0.99	
	• BPD or death	0.92	0.84–1.01	
Caffeine	Reduced BPD	0.63	0.52–0.76	Schmidt et al, 2006

BPD, Bronchopulmonary dysplasia; *CPAP,* continuous positive airway pressure; *IVH,* intraventricular hemorrhage; *NEC,* necrotizing enterocolitis; *RDS,* respiratory distress syndrome.

TABLE 9.2 Interventions That May Be Promising but Require Further Evaluation

Intervention	Effects	RR	95% CI	Reference
Less invasive surfactant administration vs intubation for surfactant delivery	Reduced:			Aldana-Aguirre et al, 2017
	• Mechanical ventilation	0.66	0.47–0.96	
	• BPD or death	0.75	0.59–0.94	
Late postnatal steroids	Reduced BPD or death	0.76	0.68–0.85	Doyle et al, 2014
	No increase in cerebral palsy	1.12	0.79–1.60	
Early low-dose hydrocortisone	Increased survival without BPD	1.48	1.02–2.16	Baud et al, 2016
Early budesonide with surfactant	Reduced BPD or death	0.58	0.44–0.77	Yeh et al, 2016

BPD, Bronchopulmonary dysplasia.

TABLE 9.3 Interventions That May Be Harmful in Preterm Infants With RDS

Intervention	Effects	RR	95% CI	Reference
Prophylactic surfactant vs CPAP at birth and selective surfactant	Increased BPD or death	1.12	1.02–1.24	Rojas-Reyes et al, 2012
Lower (85%–89%) versus higher (91%–95)% oxygen saturations	Increased:			Askie et al, 2017
	• Death	1.16	1.03–1.31	
	• NEC	1.24	1.05–1.47	
Early postnatal steroids	Reduced BPD or death	0.89	0.84–0.95	Doyle et al, 2014
	Increased cerebral palsy	1.45	1.06–1.98	
Early and prolonged inhaled steroids	Reduced BPD or death	0.71	0.53–0.97	Bassler et al, 2018
	Increased death	1.37	1.01–1.86	

BPD, Bronchopulmonary dysplasia; *CPAP,* continuous positive airway pressure.

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Abstract: Respiratory distress syndrome (RDS) is a developmental lung disease of preterm infants primarily caused by inadequate production of surfactant. Infants with RDS have difficulty maintaining adequate functional residual capacity (FRC), leading to alveolar atelectasis, hypoventilation, and ventilation-perfusion mismatch. Affected infants present shortly after birth with worsening tachypnea, nasal flaring, grunting, retractions, hypercapnia, and hypoxemia. Extensive research in the management of RDS has led to major improvements in the care of preterm infants and increased survival. In this chapter, we summarize the most current evidence-based management of RDS.

Keywords: respiratory distress syndrome; prematurity; management; evidence-based practices; lung

10

Principles of Mechanical Ventilation

Martin Keszler MD

Safe and effective respiratory support of newborn infants requires a good understanding of pulmonary physiology, familiarity with the available evidence regarding management of respiratory failure and knowledge of the capabilities of the ventilators at one's disposal. The clinician must also recognize that individualized patient care is the best approach, and that requires frequent assessment of the patient's response to treatment and regular assessment of all available information, including physical examination, assessment of patient–ventilator interaction and observation of the ventilator waveforms. Blood gas analysis and chest radiographs complete the picture but are not sufficient by themselves to provide full assessment of the adequacy of respiratory support.

Neonatal respiratory support has improved substantially over the past few decades and with the increased use of antenatal steroids and less invasive surfactant administration, many very premature babies can be successfully treated with noninvasive respiratory support. However, although mechanical ventilation has greatly reduced mortality from pulmonary causes, serious morbidity, including bronchopulmonary dysplasia (BPD) remains high. With increased use of antenatal steroids and improved delivery room stabilization, most moderately preterm and many very preterm infants can be supported noninvasively, thus avoiding ventilator-associated lung injury (VALI). Invasive ventilation is largely reserved for the relatively small number of the most immature or very sick term infants, resulting in less experience for trainees and practitioners. These more immature patients may be uniquely susceptible to lung injury because of the very early stages of lung development at which they are born, making it that much more critical to employ ventilation strategies that minimize VALI. However, some degree of lung injury is probably inevitable in mechanically ventilated extremely preterm infants even with optimal respiratory support.

UNIQUE CHALLENGES IN MECHANICAL VENTILATION OF NEWBORN INFANTS

Sophisticated microprocessor-based ventilators with advanced features enabling effective synchronized ventilation are now widely available. However, better technology can only improve outcomes if used with care and with optimal ventilation strategies that are appropriate for the specific condition being treated. A good understanding of the many unique aspects of a newborn infant's respiratory physiology will help the clinician use the sophisticated tools at his/her disposal to best advantage.

Lung Mechanics

Small infants with poorly compliant (stiff) lungs have very short time constants (a measure of how rapidly gas moves in and out of the lungs) and thus rapid respiratory rates with very short inspiratory times. Their limited muscle strength and a ribcage that lacks sufficient rigidity make it difficult to maintain adequate end-expiratory lung volume and tidal volume. Use of adequate end-expiratory pressure and ventilator design that allow the baby to trigger ventilator inflation with minimal inspiratory effort and minimal trigger delay are essential.

Uncuffed Endotracheal Tubes

Neonates are generally ventilated using uncuffed endotracheal tubes (ETT) because of a concern about injury to the tracheal mucosa; therefore, some degree of gas leak around the ETT is present in most infants. The small size of the tubes also makes inflatable cuffs difficult to incorporate without compromising lumen size. However, large ETT leak makes tidal volume estimation increasingly inaccurate, making volume targeted ventilation more challenging. The ETT leak increases with time if prolonged ventilation is required, because the larynx and trachea are progressively dilated by the cyclic stretch of many thousands of positive pressure inflations per day. The leak varies from moment to moment because the ETT is inserted only a short distance beyond the larynx; thus the leak will change with any change in the infant's head position and movement of the ETT up and down in the trachea.

Measurement of Tidal Volume

The importance of accurate tidal volume (V_T) measurement in extremely small infants is obvious, considering that these infants are ventilated with a tidal volume in the range of 2 to 5 mL. Some ventilators not specifically designed for newborn

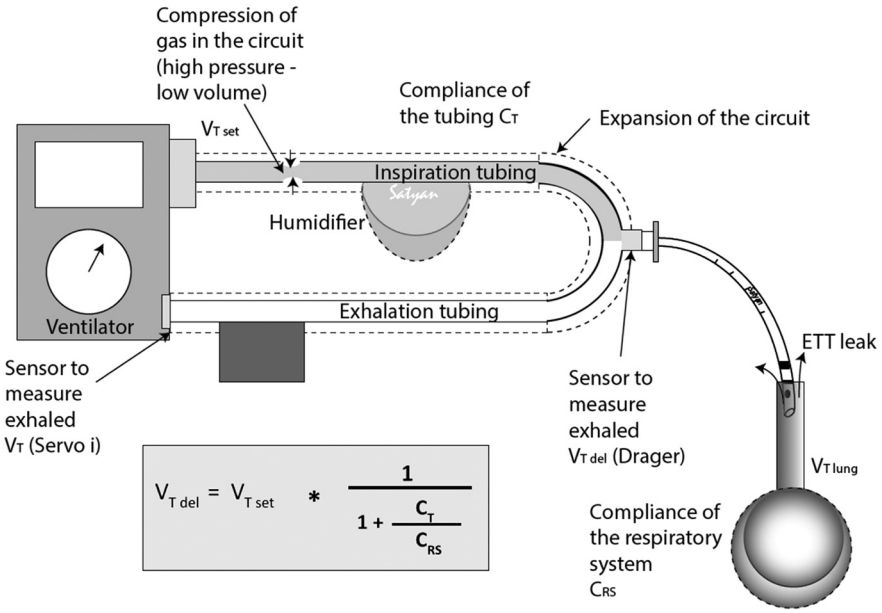

Fig. 10.1 Volume-controlled ventilation controls the tidal volume delivered into the proximal end of the patient circuit. Compression of gas within the circuit and expansion of the circuit tubing and endotracheal tube (ETT) leak leads to variable loss of tidal volume. The volume delivered into the lungs (V_T del) of a very small preterm infant is only a fraction of the set tidal volume ($V_{T\ set}$), because the proportion of $V_{T\ set}$ that reaches the lungs is determined by the relative compliance of the patient's lungs (largely a function of patient size) and the ventilator circuit.

infants measure flow and calculate V_T at the ventilator end of the patient circuit rather than at the airway opening. This remote placement avoids extra wires and the added instrumental dead space of a flow sensor at the airway opening but results in large overestimation of the true V_T, because of compression of gas in the circuit, distention of the circuit, and leak around the ETT. The loss of tidal volume in the circuit is proportional to the compliance of the ventilator circuit and humidifier (and the compressibility of the volume of gas they contain), relative to the compliance of the patient's lungs (Fig. 10.1). In large patients with a cuffed ETT, the volume measured at the ventilator correlates reasonably well (using appropriate corrections) with the actual V_T entering the lungs. In tiny infants whose lungs are very small and thus relatively noncompliant, the loss of volume to the circuit is proportionally much larger and not easily corrected, especially in the presence of significant ETT leak.

INDICATIONS FOR MECHANICAL VENTILATION

The purpose of mechanical ventilation is to maintain acceptable gas exchange with a minimum of adverse effects. These include lung injury, air-leak syndrome, hemodynamic impairment, nosocomial infection, and brain injury. Secondary objectives are achieving adequate lung aeration, reducing exposure to high oxygen concentrations, and reducing the work of breathing. Indications for mechanical ventilation include absent or inadequate respiratory effort and signs of impending respiratory failure, such as frequent apnea, high and rising P_{CO_2} level, persistent high oxygen requirement (F_{IO_2} >0.40–0.50), and excessive work of breathing despite optimized noninvasive support. Because there is a clear association between the length of ventilator support and development of chronic lung disease, ventilator support should be weaned as rapidly as possible, and the infant should be extubated to some form of noninvasive support at the earliest opportunity.

CHOOSING THE VENTILATOR MODE AND INITIAL SETTINGS

The choice of ventilator modes may be limited by the equipment available in the neonatal intensive care unit (NICU). Most modern ventilators are capable of providing the basic modes of synchronized ventilation, which include synchronized intermittent mandatory ventilation (SIMV), assist-control ventilation (AC), and pressure support ventilation (PSV) but may also include hybrid or dual-control modes. Not all widely used devices and modes are optimal for small preterm infants. Ventilators that are designed primarily for adult/pediatric patients but are capable of also supporting neonates (so-called universal ventilators) have a variety of modes, some of which have never been evaluated in newborn infants and thus should be avoided.

As described earlier, the volume-controlled ventilation mode that is available on these devices controls the volume delivered into the proximal (ventilator) end of the circuit (known as V_{set}), not the tidal volume entering the patient's lungs (V_{deliv}) and thus overestimates the true tidal volume,

especially when a large leak around the ETT is present. For these reasons, pressure-controlled ventilation (commonly referred to as time-cycled, pressure-limited ventilation in the neonatal literature) became the standard ventilation mode in the NICU. More recently, modifications of pressure-controlled ventilation that provide volume targeting have become available. These modalities, collectively known as volume-targeted ventilation, make it possible to combine the advantages of pressure-controlled ventilation and relatively stable delivered tidal volume (Keszler, 2013).

CASE 1: EXTREMELY LOW BIRTH WEIGHT INFANT WITH RDS

You are attending the delivery of a 700 g, female infant born at 25 weeks' gestation after rapid preterm labor with no time for antenatal steroids. The infant has a good heart rate but minimal respiratory effort, and despite stimulation and application of CPAP with a few positive pressure inflations via the T-piece resuscitator (using a peak inflation pressure [PIP] of 25 cm H_2O to achieve minimal chest rise), her color remains poor and her spontaneous respiratory effort is inadequate. You decide to intubate and initiate mechanical ventilation. You remember that your transport ventilator is only capable of basic pressure-controlled ventilation without patient triggering, known as intermittent mandatory ventilation (IMV).

Exercise 1

Question

What would be your initial ventilator settings?

A. PIP 25 cmH_2O, positive end-expiratory pressure (PEEP) 6 cmH_2O, rate 50/minute, inflation time (Ti) 0.3 seconds, fraction of inspired oxygen concentration (Fio_2) adjusted to maintain a saturation of 90% to 95%
B. PIP 15 cmH_2O, PEEP 6 cmH_2O, rate 25/minute, Ti 0.3 s, Fio_2 (to maintain a saturation of 90%–95%)
C. PIP 25 cmH_2O, PEEP 3 cmH_2O rate 50, Ti 0.3 s, Fio_2 (to maintain a saturation of 90%–95%)
D. PIP 25 cmH_2O, PEEP 6 cmH_2O, rate 50/minute, Ti 0.5 s, Fio_2 (to maintain a saturation of 90%–95%)

Answer

Choice A. Here, as always, you need to consider the disease process, the size of the infant, and the infant's general condition. Because there is little respiratory effort, you must provide essentially all of the baby's respiratory support. Therefore you should choose a respiratory rate that is appropriate for the tiny infant in front of you, namely 50 to 60 breaths/minute. Because you just used the T-piece resuscitator, select a PIP that is adequate to get a minimal chest rise. The basic functionality of a conventional mechanical ventilator is much like that of the T-piece resuscitator (Fig. 10.2).

Although your PIP was 25 cmH_2O using the T-piece resuscitator, it is a relatively high pressure, which indicates the infant has not yet achieved adequate lung aeration nor cleared lung fluid from her lungs. You now need to select an inspiratory time (Ti) and positive end-expiratory pressure (PEEP). Appropriate inspiratory time depends on the time constants of the respiratory system of your patient. Time constant is a measure of how rapidly gas moves in and out of the baby's lungs and reflects lung mechanics, as well as patient size. In simple terms, tiny babies with low lung compliance and normal airway resistance (i.e., your patient) have very short time constants, so you would choose a Ti of about 0.3 s. Large infants with high airway resistance would need a longer Ti. Adequacy of inspiratory and expiratory time is best verified by examining the flow waveform on the ventilator display, as discussed later in this chapter. PEEP is critical in achieving and maintaining adequate lung inflation. Achieving an "open lung"—that is a lung that is optimally inflated with good ventilation–perfusion matching and even distribution of tidal volume—is a key element in lung-protective ventilation strategies and should be guided by the infant's

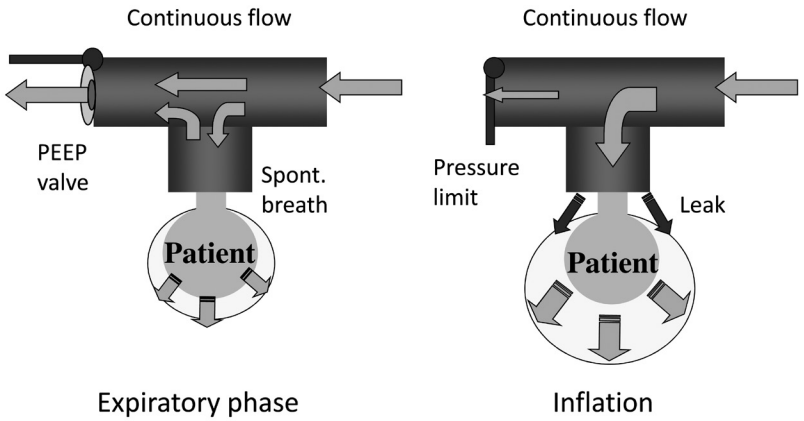

Fig. 10.2 Basic function of pressure-controlled ventilation is similar to a T-piece resuscitator. During the expiratory phase, the expiratory valve is open and there is continuous flow in the circuit. A PEEP valve maintains a distending pressure and the patient can breathe spontaneously from the circuit. When the expiratory valve closes, the circuit is pressurized and gas enters the lungs in proportion to the pressure in the circuit and the compliance of the lungs. Gas leakage around the uncuffed endotracheal tube is not a problem, as plenty of fresh gas is available to maintain inflation pressure.

oxygen requirement. A high Fio_2 usually indicates inadequate lung volume recruitment that results in ventilation–perfusion mismatch. Your goal is to get the Fio_2 below 0.30, so you should select a PEEP of 6 cmH_2O and increase in increments of 1 cmH_2O to a maximum of 8 cmH_2O if high oxygen requirement persists.

ASSESSMENT OF VENTILATOR SUPPORT AND SUBSEQUENT ADJUSTMENTS

CASE 1, CONTINUED

You and your patient arrive safely in the NICU. The mode of ventilation is changed to SIMV using the prior settings but a lower rate, because the infant is now starting to breathe. Settings are: PIP of 25 cmH_2O, PEEP of 7 cmH_2O, rate 45/min, Ti 0.3 s, and Fio_2 of 0.32. Your respiratory therapist administers surfactant via endotracheal tube while you are preparing to place umbilical arterial and venous catheters. When you finally get appropriate line placement an hour later and obtain a blood gas, you are pleased to see that the PaO_2 is 655 mm Hg but dismayed that the Pco_2 is 28 mm Hg with a pH of 7.47. You recall that hypocapnia and alkalosis increase the risk of periventricular leukomalacia and severe intraventricular hemorrhage in very in preterm infants.

Exercise 2

Question 1

Why did the hypocapnia develop?

Answer

Remember that with pressure-controlled ventilation, the amount of gas that enters the lungs (V_T) is determined by the inflation pressure (PIP−PEEP) and the compliance of the respiratory system. Compliance is a measure of how much volume (in mL) enters the lungs for any given change in airway pressure (Compliance = $\Delta V/\Delta P$). For example, if a pressure of 15/5 (PIP/PEEP, cmH_2O) produces a tidal volume of 5 mL, the compliance is $5/(15-5) = 0.5$ mL/cmH_2O. At least three factors combined to improve lung compliance, which in turn increased the tidal volume with a fixed inflation pressure of 25 cmH_2O. First, PEEP was appropriately increased to optimize lung inflation. Lung compliance improves when lung volume is optimized, so it was predictable that V_T would improve and thus Pco_2 would drop. Second, currently available surfactants rapidly improve lung aeration and lung compliance (increasing the tidal volume). Finally, with adequate respiratory support and passage of time, residual lung fluid should have cleared, also improving compliance and gas exchange.

Question 2

What could you have done differently to avoid the hypercapnia?

Answer

There are two things that would have prevented this problem. When using pressure-controlled ventilation, the measured tidal volume needs to be monitored closely—this is more accurate than relying on visual assessment of chest rise or auscultating breath sounds—and adjustments to inflation pressures need to be made as often as necessary to avoid inadvertent overventilation when changes in lung compliance are occurring. The period soon after initiation of mechanical ventilation is a time of rapid change, and the clinical team may be distracted by procedures, admission documentation, etc., making close clinical observation challenging. A better alternative is to use a volume-targeted mode of ventilation that responds automatically and in real time to changes in lung compliance and patient respiratory effort and thus maintains relatively stable tidal volume.

CASE 1, CONTINUED

You do not feel sufficiently comfortable with volume-targeted ventilation, so you chose to manually adjust PIP. Over the next few hours you lower the PIP to 18 cmH_2O with a gradual rise of the Pco_2 to 38 mm Hg. It is important to avoid rapid changes in minute ventilation and Pco_2, because such changes increase the risk of intracranial hemorrhage in extremely preterm infants with a vulnerable cerebral circulation. (Ambalavanan, Carlo et al. 2015)

Following surfactant administration, the Fio_2 decreases to 0.24, and the infant appears comfortable on the current ventilator settings. The infant is making adequate spontaneous respiratory effort, so you continue to lower the ventilator rate progressively to 18/min over the next 2 days. Although the Pco_2 remains adequate in the mid to high 40s, the nurse complains that the baby has become more tachypneic, and the oxygen requirement is creeping back up to 0.35.

Exercise 3

Question

What is the cause of the tachypnea and rising oxygen requirement?

Answer

More than one explanation is possible in this scenario, but tachypnea in a mechanically ventilated infant suggests that the ventilator support is inadequate. Careful observation of the infant and the ventilator display will reveal important clues as to the cause. Blood gas measurement and chest radiograph may be helpful but will not provide the whole story. In this case, the most likely explanation is the limited muscle strength of the extremely premature infant, coupled with the high airway resistance of the small endotracheal tube. Remember that SIMV provides positive pressure inflations in synchrony with the patient's effort only at the rate that you set. Spontaneous breaths in excess of that rate are not supported. Your suspicion is confirmed by noting that the infant's respiratory rate is 70 to 90 breaths/minute with mild to moderate retractions and periodic pauses. You also notice that the tidal volume display is fluctuating between 3 and 6mL/kg with spontaneous breaths and mechanical inflations, respectively. The 3 mL tidal volume the infant is able to generate on her own barely

clears the dead space of the upper airway, endotracheal tube, and flow sensor. Thus it contributes little to alveolar minute ventilation, the portion of the total ventilation that actually reaches the alveoli and participates in gas exchange (Fig. 10.3). To maintain adequate ventilation, relatively large mechanical inflations of around 6 mL/kg are needed. As ventilator rate is decreased, the infant must increasingly rely on her spontaneous effort, but she can only muster this inefficient rapid, shallow breathing (Fig. 10.4). Her high work of breathing increases oxygen consumption and may lead to fatigue, thus impairing extubation efforts. For these reasons, SIMV is not an optimal mode of ventilation for these tiny infants.

Exercise 4

Question

What would you do to overcome this problem?

Answer

Leaving high-frequency ventilation aside for the moment, you have the option of staying with SIMV and adding pressure

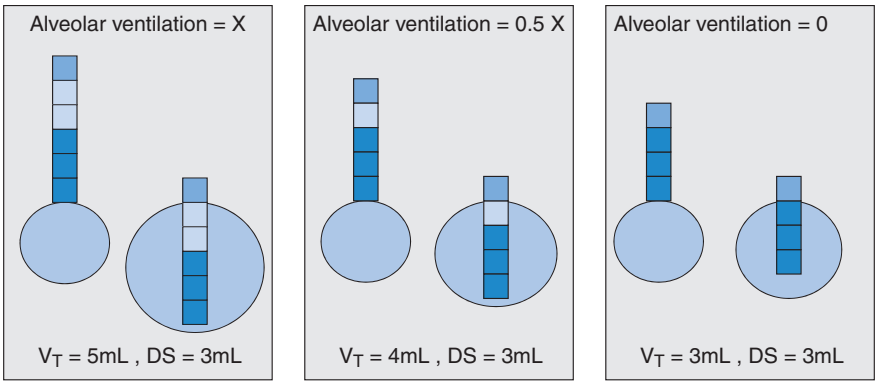

Fig. 10.3 Classical respiratory physiology teaches us that at the end of exhalation, there is exhaled gas (dark boxes) in the large airways that will enter the lungs before any fresh gas (light boxes) can reach the lungs. Therefore alveolar tidal volume = tidal volume − dead space volume. Anatomic dead space is 2mL/kg. In this illustration, the anatomic dead space plus instrumental dead space = 3 mL, typical for a 1 kg infant. In the left panel, we have a tidal volume (V_T) of 5 mL and a dead space volume of 3 mL; thus 2 mL of fresh gas enters the alveoli. Reducing V_T from 5 to 4 mL is a 20% reduction in total V_T but a 50% reduction in alveolar V_T. Further reduction of V_T to 3 mL would theoretically result in no alveolar ventilation. Although there is probably some admixture beteween fresh gas and dead space gas, rapid shallow breathing is very inefficient.

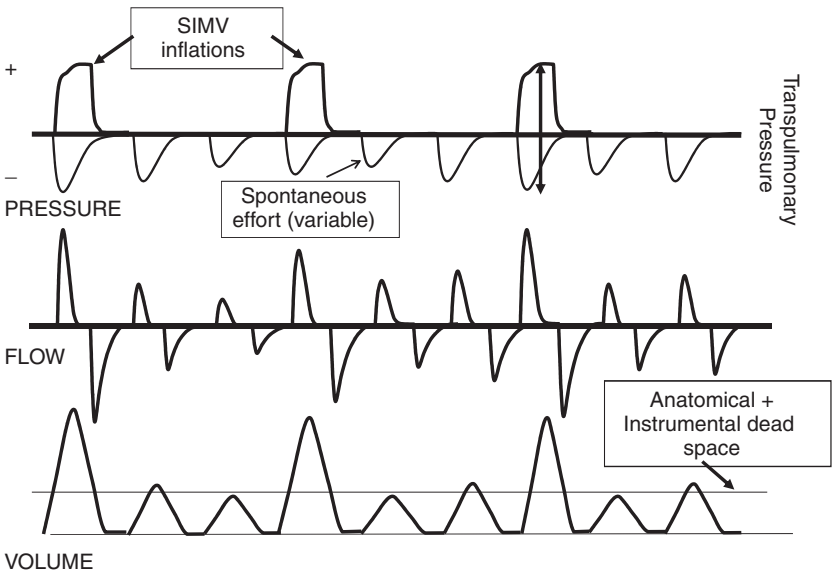

Fig. 10.4 Breathing pattern of a small infant on synchronized intermittent mandatory ventilation (SIMV). Standard airway pressure, flow, and volume curves are shown in the upper, middle, and lower panels, respectively. Spontaenous respiratory effort of the infant, which is not seen on the ventilator display, is added to the pressure waveform as a negative pressure deflection. Because of high resistance of small endotracheal tubes and weak respiratory effort of extremely preterm infants, the tidal volume of unsupported spontaneous breaths often fails to clear anatomic and instrumental dead space.

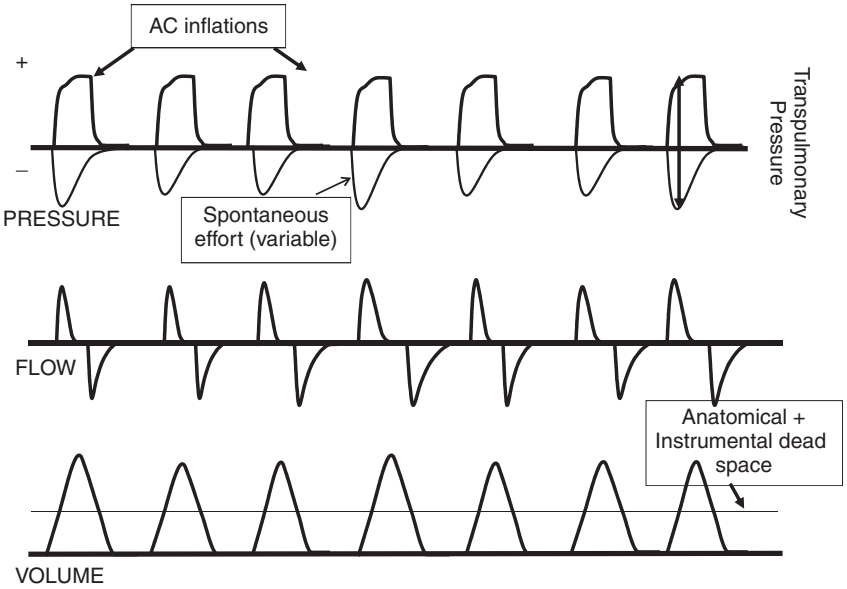

Fig. 10.5 Improved breathing pattern with assist control ventilation. Every breath is supported, thus easily clearing dead space volume. The tidal volume is more consistent and lower than with SIMV.

support (PS) to her spontaneous breaths or to change to a synchronized mode that supports every spontaneous breath, such as assist control (AC) or pressure support ventilation (PSV). Adding PS to boost the infant's spontaneous effort to achieve an adequate tidal volume will help the situation, but you now have to decide how much pressure boost to provide and subsequently you will need to figure out which of the two different ventilation patterns to adjust.

The first question is relatively easy to answer. You would typically start with a low value of, say 6 cmH_2O above PEEP, and see what V_T you now achieve with the supported spontaneous breaths and how comfortable (or not) the infant is. You should target a physiologic V_T of about 4 mL/kg; the infant should be breathing comfortably with a rate of less than 65/min. There are no established rules for how to gradually withdraw ventilator support in an infant receiving SIMV + PS, but one reasonable way is to continue to wean the SIMV rate and maintain PS at a pressure sufficient to maintain an adequate V_T with spontaneous breaths. Once the SIMV rate is down to 10 to 15/minute, and PSV pressure is not more than 6 cmH_2O with an Fio_2 less than or equal to 0.30, extubation to noninvasive ventilation is usually possible.

Assist control supports every spontaneous breath of the infant, thus achieving adequate and more consistent V_T (Fig. 10.5). The ventilator rate is driven by the infant's respiratory effort and therefore the ventilator will cycle at the infant's breathing rate—this is the "assist" part. If the infant fails to breathe, the ventilator will take over immediately at the set backup rate, typically 40 per minute (the "control" part). The backup rate should be just below the infant's spontaneous breathing rate; think of it as a safety net. In a small infant who is triggering the ventilator at a rate of 60/min when breathing actively, a backup rate of 25 or 30/minute would be too low and result in a large drop in minute ventilation and rise in $Paco_2$, which is potentially dangerous. The tidal volume needed with AC is substantially lower than with SIMV, usually around 4 to 5 mL/kg, because every breath is supported and easily clears dead space. It is important to understand that the tidal volume entering the lungs results from the combined inspiratory effort of the infant (when present) and the positive inflation pressure delivered by the ventilator (Fig. 10.6). Inspiratory time, PIP, and PEEP are set in a similar fashion to SIMV. Weaning is accomplished by

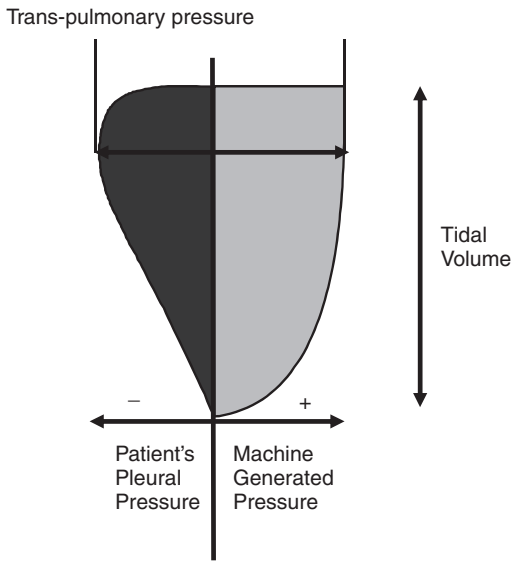

Fig. 10.6 With synchronized ventilation, the infant's spontaneous inspiratory effort (dark shaded area) is additive to the positive pressure generated by the ventilator (light area). Together, this transpulmonary pressure results in the tidal volume that enters the patient's lungs. The ventilator only measures and displays the machine-generated positive pressure. When ventilator inflation pressure is reduced, the infant gradually assumes a grater proportion of the transpulmonary pressure and therefore achieves respiratory muscle training during the weaning process.

lowering PIP, leaving the rate unchanged, because it is only a safety backup. This way, the work of breathing is gradually transferred from the ventilator to the infant.

Pressure support ventilation (PSV), when used as a stand-alone mode on specialty neonatal ventilators, is identical to AC, except that the ventilator inflation is flow cycled rather than time cycled. This means that, rather than having a fixed inspiratory time, the ventilator cycles off when inspiratory flow declines to a set percentage of peak flow, typically about 15% (Fig. 10.7). This method eliminates the inspiratory hold and makes for more complete synchrony. The infant now has control over both onset and termination of ventilator inflation and the inspiratory time is automatically adjusted in response to changing lung mechanics. Ventilator settings and weaning are similar to AC. Because the Ti is usually shorter than with AC, PSV typically results in a lower mean airway pressure, which could lead to atelectasis if PEEP is not adjusted to maintain the same mean airway pressure. Table 10.1 summarizes key features of the basic modes of synchronized mechanical ventilation.

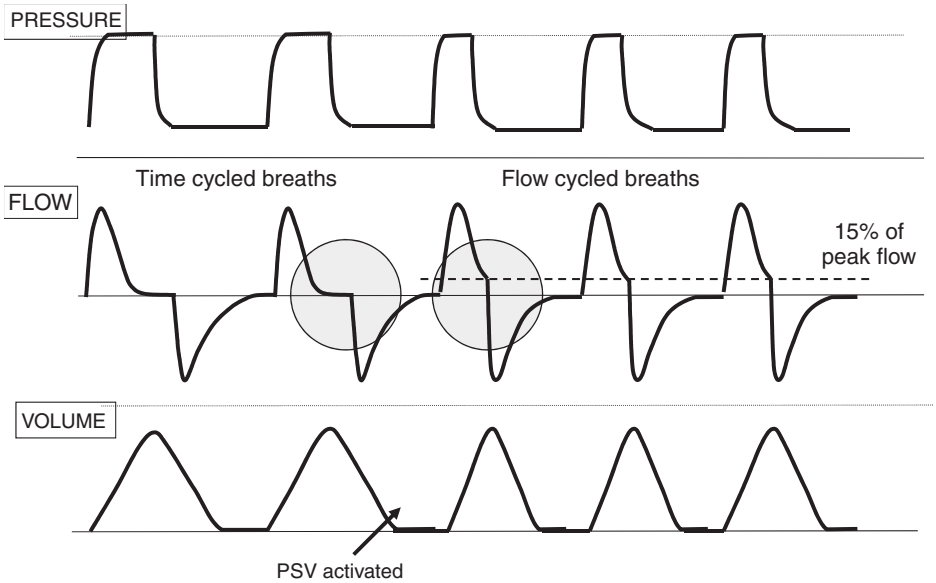

Fig. 10.7 The left side of the tracing shows time-cycled ventilation with a fixed inspiratory time, which typically results in an inspiratory hold—a period of time with no further gas flow but continued delivery of peak inflation pressure. The left side shows flow cycling, which means the ventilator cycles into exhalation once inspiratory flow drops to a set proportion of peak flow, thus eliminating inspiratory hold. In this way, the inspiratory time is automatically adjusted in response to patient inspiratory effort and changing lung mechanics. This more natural breathing pattern results in more complete synchrony.

TABLE 10.1 Basic Modes of Mechanical Ventilation

	Patient Triggering	Advantages	Drawbacks
IMV	None		Asynchrony
SIMV	Set rate is patient triggered and time cycled, additional breaths are not supported. Clinician controls ventilator rate.	Simplicity, less affected by auto-triggering	High work of breathing, uneven V_T, rapid shallow breathing
SIMV + PS	Set rate is patient triggered and time cycled. Additional breaths are patient triggered, supported with a pressure above PEEP, and time cycled.	Reduces work of breathing, provides more adequate support, faster weaning than SIMV	Complicated, results in two different types of ventilator inflations More complicated weaning
AC	Every spontaneous breath is supported and time cycled. Patient controls ventilator rate.	More adequate support, smaller V_T, faster weaning than SIMV	Potentially affected by auto-triggering with some ventilators
PSV	Every spontaneous breath is supported and flow cycled. Patient controls ventilator rate.	As AC, plus more complete synchrony	Ti may be too short when time constants are very short. Shorter Ti leads to lower mean airway pressure and thus needs increased PEEP.

AC, Assist-control; *IMV,* intermittent mandatory ventilation; *PEEP,* positive end-expiratory pressure; *PS,* pressure support; *PSV,* pressure support ventilation; *SIMV,* synchronized intermittent mandatory ventilation; *Ti,* inspiratory time; V_T, tidal volume.

TAILORING VENTILATOR SETTINGS AND STRATEGY TO UNDERLYING PATHOPHYSIOLOGY

CASE 2: TERM INFANT WITH MECONIUM ASPIRATION SYNDROME (MAS)

You admit a 1-hour-old, 4200 g infant who was born through thick meconium by emergency cesarean delivery. The infant required intubation in the delivery room because of poor respiratory effort and inadequate response to positive-pressure ventilation by mask. Thick meconium was noted in the trachea upon intubation. You initiate ventilation with SIMV, PIP of 24 cmH_2O, Ti of 0.5 s, and PEEP of 6 cmH_2O. Because the infant has no spontaneous respiratory effort, you set the ventilator rate at 50/min and titrate the Fio_2 to maintain adequate oxygen saturation. The chest radiograph shows typical appearance of MAS with patchy infiltrates and mild degree of air trapping. An arterial blood gas (ABgG) reveals a pH of 7.24, Pco_2 of 52 mm Hg, Po_2 of 67 mm Hg, and BE −8. You check the ventilator display (kudos for doing that) and notice that the tidal volume (V_T) is 4.5 mL/kg, which seems reasonable to you. You also realize that to generate a larger V_T, you would need to raise the PIP. You are reluctant to go higher than the current value, so you choose instead to increase the ventilator rate to 60/min, hoping to bring down the Pco_2. You are dismayed to see that the repeat ABG shows the Pco_2 has risen to 61 mm Hg with a pH of 7.19. A repeat chest radiograph shows even more prominent air trapping. You therefore decide that the problem must be excessive PEEP and accordingly lower the PEEP to 4 cmH_2O. Disappointingly, neither the chest x-ray nor the blood gas improves.

Exercise 5

Question

Why is the Pco_2 continuing to rise?

Answer

This infant's condition (MAS) is well known to result in increased alveolar dead space due to air trapping and heterogeneous lung inflation. Published evidence indicates a need for a tidal volume of about 6 mL/kg to achieve adequate alveolar minute ventilation (Sharma et al, 2015). Therefore the initial respiratory acidosis was predictable.

The problem with increasing the rate, rather than PIP (to increase V_T) is twofold. First, when the V_T is mostly ventilating dead space, increasing the rate has relatively little impact on alveolar minute ventilation. Second, this is a large baby with high airway resistance, which leads to longer time constants. Time constants are a measure of how rapidly gas gets in and out of the lungs. Larger lungs require more time to fill and empty; high airway resistance and better compliance also increase time constants, which mathematically are the product of airway resistance and absolute lung compliance. Thus the higher rate resulted in insufficient expiratory time and worsening air trapping, leading to further CO_2 retention (Fig. 10.8, left panel). Lowering the set PEEP does not have much impact, because the problem is dynamic PEEP caused by incomplete exhalation.

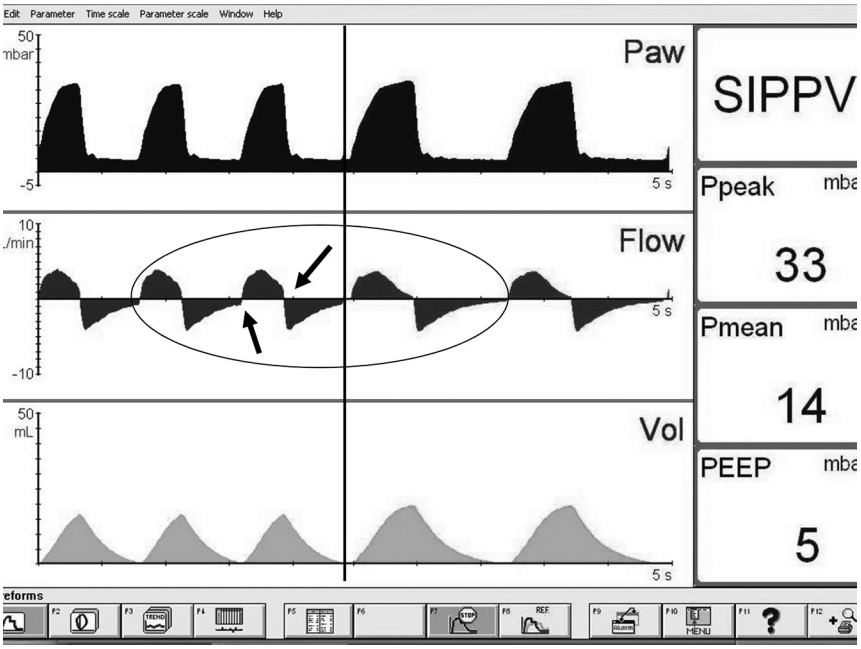

Fig. 10.8 Adequacy of inspiratory and expiratory time settings is best evaluated by examining the flow waveform. The left side of the panel shows that the set expiratory time is insufficient to allow complete exhalation because there is still active flow out of the lungs when the next inflation is triggered (arrow). Similarly, inspiratory flow has not returned to baseline when the ventilator cycles on (second arrow). The right side of the panel shows that with a slower ventilator rate (i.e., longer expiratory time) the expiratory flow has returned to zero before the next inflation and the inspiratory flow has also dropped to baseline before exhalation.

CASE 2 (CONTINUED)

Unfortunately, you have not yet figured this out. The bedside nurse points out that the baby has become quite active and is now "fighting the ventilator." You decide that this is probably the reason for the poor gas exchange and order a dose of fentanyl to stop the baby from interfering with your ventilator support. Alas, though the baby is now quiet and the nurse is happy, the blood gas has deteriorated even more.

Exercise 6

Question

Why did sedation fail to work?

Answer

Inadequate respiratory support, especially when it results in substantial degree of acidosis, leads to air hunger and agitation. The baby "fighting the ventilator" is a manifestation of this air hunger and should prompt a reassessment of the ventilation strategy, which includes physical assessment, examination of the ventilator graphics and perhaps a chest radiograph. Suppressing the baby's activity with a sedative or narcotic masks the infant's distress, which is an important clinical sign of adequacy (or inadequacy) of respiratory support. Taking away the baby's spontaneous respiratory effort that was contributing to—rather than interfering with—ventilation caused the P_{CO_2} to rise further.

CASE 2 (CONTINUED)

Having consulted with your in-house ventilation "guru," you correct your error by lowering the rate to 45/minute (ventilator graphics confirm that expiratory time is now adequate – Fig. 10.8, right panel) and increasing the PIP to 28 cmH_2O. The PEEP is increased back to 6 cmH_2O. You are relieved to see the P_{CO_2} come down to 46 mm Hg and the pH rise to 7.32. You allow the fentanyl to wear off and are pleased to see that the infant now looks comfortable. All is well overnight with improving the P_{CO_2} and pH. The chest radiograph has improved with resolution of air trapping and only mild diffuse haziness. The F_{IO_2} has weaned to 0.25. Another day passes and you begin to wonder why no further progress is evident. The baby remains quiet and seems to be only infrequently breathing above the ventilator backup rate now at 40/min. With little respiratory effort from the infant, you are reluctant to lower the ventilator rate further.

Exercise 7

Question

Why is your patient not breathing, and why has ventilator weaning stalled?

Answer

Evolving sepsis or a neurologic problem should be considered in the differential diagnosis, but most likely, the problem here is that you have taken away the baby's respiratory drive. A blood gas showing a neutral or alkalotic pH would confirm your suspicion. With adequate circulatory status and renal function, the metabolic acidosis is likely to have resolved by now unmasking a relative respiratory alkalosis. Secondly, the disease process of MAS evolves over time. As particulate meconium is cleared from the airways, air trapping gives way to more homogeneous picture of surfactant inactivation and inflammation. More homogeneous lung aeration has brought about a reduction in alveolar dead space, so that a greater proportion of each tidal volume participates in gas exchange, rather than being wasted as dead space ventilation. Resolution of lung disease also leads to better lung compliance, all of which has caused relative overventilation. The ventilator is providing all the necessary minute ventilation and thus the infant's own respiratory drive has been suppressed. To facilitate weaning, ventilator settings need to be low enough to ensure adequate respiratory drive (i.e., pH $<$7.35).

COMPLICATIONS OF MECHANICAL VENTILATION

CASE 3: PRETERM INFANT WITH RDS

You are taking over the care of a 29-week, 1100 g white male born via precipitous vaginal delivery to a mother with type 1 diabetes mellitus. There was no time for antenatal steroids. The infant was vigorous at birth but tachypneic with moderate retractions and a high F_{IO_2} requirement; therefore he was placed on CPAP of 5 cmH_2O. Over the next few hours, his F_{IO_2} rose to 0.50 with increasing tachypnea. The ABG shows pH 7.29, P_{aCO_2} 49, P_{aO_2} 61, HCO_3 21, and BE −3. Your colleague increased CPAP to 6 cmH_2O with little clinical improvement, but the blood gas values remain acceptable.

Exercise 8

Question

What would be the appropriate next step?

Answer

Although the gas exchange is adequate, you should be concerned about the high oxygen requirement, which suggests a ventilation–perfusion mismatch due to diffuse microatelectasis.

You have three reasonable options:

1. Continue noninvasive support but increase CPAP progressively to a maximum of 8 cmH_2O or until F_{IO_2} drops below 0.35. (This option would be preferable, as it is best to optimize existing intervention before implementing more invasive steps.);
2. Intubate and give surfactant via endotracheal tube and then continue mechanical ventilation; or
3. Intubate, give surfactant via endotracheal tube and then extubate quickly back to noninvasive support (this is known as the INSURE—**IN**tubate, give **SUR**factant and **E**xtubate—technique).

Several less invasive surfactant administration approaches that avoid endotracheal intubation are being evaluated, but these have not yet become widely routine.

CASE 3 (CONTINUED)

Unfortunately, you were busy for several hours with an unexpected delivery of 27-week triplets, so you were unable to implement any of the three options above. Now that the rest of the NICU is under control, you are able to turn your attention back to this infant, who now requires an Fio_2 of 0.72. There is persistent tachypnea and worsening episodes of apnea. You see no alternative but to intubate the infant and administer surfactant. You start the infant on SIMV with rate of 30, PIP 22, Ti 0.35, PEEP 5, and $Fio_2 = 0.55$. The ABG shows: pH 7.21, $Paco_2$ 57 mm Hg, PaO_2 53 mm Hg, HCO_3 22 meq/L, and BE −3. You are not happy with the marginal pH and PaO_2 with a measured tidal volume of only 3.5ml/kg, so you increase the SIMV rate to 40 and PIP to 26. Initially oxygen saturation (SPO_2) improves and Fio_2 comes down to 0.45 with a better V_T and good chest wall movement, but 30 minutes later the oxygen saturation measured using a pulse oximeter (SpO_2) falls into the 70s with signs of poor perfusion. The ventilator is alarming "low minute ventilation," and the first thing you notice when you rush to the bedside is that the abdomen is quite distended.

Exercise 9

Question

What's happened, and what should you do about it?

Answer

More than one explanation is possible for this acute event. The first thing you must rule out is the possibility that the endotracheal tube became dislodged and is now in the esophagus. A quick glance at the flow waveform on the ventilator should help: If there is gas flow going in during inflation but none or very little coming out during expiratory phase, esophageal intubation should be suspected. Auscultation over the stomach and both lungs should confirm or rule out this complication. The other likely cause is a tension pneumothorax, an emergent complication that requires prompt recognition and treatment. Your examination reveals diminished breath sounds on the right with displacement of the heart sounds into the left chest. Transillumination confirms the diagnosis, and while a STAT chest radiograph is being taken, you prepare to decompress the tension with needle aspiration, followed by closed thoracostomy tube placement.

Question

Why did this baby develop a pneumothorax? Was there something you could have done to prevent it?

Answer

This scenario maximized the likelihood of pneumothorax. This infant has severe RDS because of prematurity, maternal diabetes, absence of antenatal steroids, and male gender, all of which are known risk factors for severe disease. He received insufficient distending airway pressure, as evidenced by a high and increasing oxygen requirement, which indicates extensive microatelectasis. Lung injury resulting from mechanical ventilation in the face of extensive atelectasis is termed *atelectrauma* (Keszler and Sant'Anna 2015). Because of gravity, the atelectasis is not evenly distributed but is concentrated in the dependent regions of the lungs, with most of the tidal volume entering the aerated, nondependent portion of the lungs. This maldistribution of tidal volume results in overstretching of this portion of the lung (volutrauma) and eventually alveolar rupture (Fig. 10.9).

The additional delay in intubation allowed more atelectasis to develop and made it more difficult to reverse, because atelectasis causes surfactant inactivation. Exogenous surfactant will preferentially distribute to the open portion of the lungs, making the inhomogeneity more pronounced. This is the reason that the Fio_2 only came down modestly after surfactant administration. Finally, the response to the poor gas exchange was not optimal. The higher rate and PIP increased the tidal volume and minute ventilation but did not address the atelectasis. This resulted in a large tidal volume entering only a portion of the lungs, predictably leading to lung injury and acute air leak.

The appropriate course of action would have included more aggressive use of distending pressure (PEEP) earlier on; 5 to 6 cmH_2O is insufficient to achieve lung volume recruitment in severe RDS, but your colleague apparently suffers from the common affliction I refer to as PEEP-o-Phobia, the fear of using adequate distending airway pressure. So, option 3 would have been appropriate, but much earlier than when you took over the case. Diffuse atelectasis is easier to prevent than to reverse. A brief trial of higher CPAP level was still a good option at that time, but if it did not bring the Fio_2 down to less than 0.40 fairly quickly, intubation and surfactant administration were indicated.

Surfactant is known to reduce the risk of air leak, thus it should not be withheld if the infant has a substantial oxygen requirement. Given that initially the infant was vigorous and relatively large, rapid extubation after surfactant administration (INSURE) would likely have been successful earlier, but not when intubation was finally performed in this infant. The response to suboptimal gas exchange after intubation should have focused on reopening the atelectatic portion of the lung to achieve more even distribution of the tidal volume. This is accomplished by the use of sufficiently high PEEP when using conventional ventilation, or alternately may be an indication for the use of high-frequency ventilation (see later in this chapter).

CASE 3, CONTINUED

A chest tube is successfully placed, and the PEEP is increased to 7 cm H_2O. The chest radiograph shows resolution of the pneumothorax and improved lung aeration. You are pleased to be able to wean Fio_2 in response to improving Spo_2. One hour later, the ABG shows pH 7.52, $Paco_2$ 26 mm Hg, Pao_2 89 mm Hg, and BE of −3.

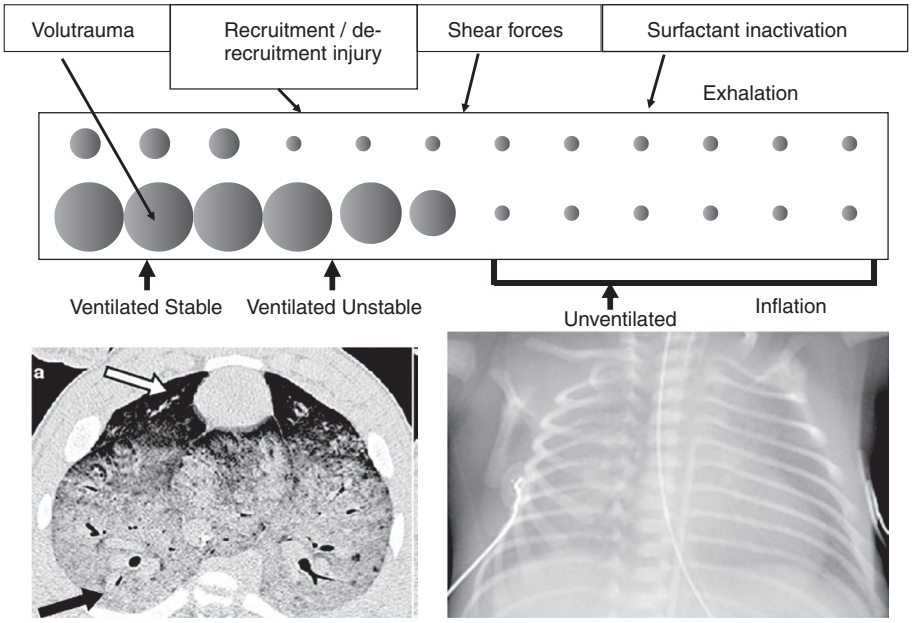

Fig. 10.9 The complex process known as atelectrauma results from ventilating lungs with extensive atelectasis. Although chest radiographs lead us to think that atelectasis affects the lungs diffusely (right lower panel), a CT scan shows that atelectasis is concentrated in the dependent portion of the lungs and that the nondependent regions contain the aerated lung (left lower panel). The different populations of terminal lung units are illustrated in the cartoon in the upper panel. LaPlace's law (P = 2*surface tension/radius) teaches us that the aerated alveoli need less pressure to expand further than those that are collapsed and thus have a very small radius. As a result, gas will enter the already aerated portion of the lung preferentially, causing overexpansion with each respiratory cycle, resulting in volutrauma even with a normal tidal volume. The atelectatic portion of the lungs is also being affected adversely by outpouring of protein-rich edema fluid that inactivates surfactant. The ventilated but unstable alveoli undergo repeated alveolar collapse and expansion and shear forces at the boundary between aerated and unaerated lung incur further damage. Adequate lung volume recruitment and keeping the lung open throughout the respiratory cycle achieves even distribution of tidal volume and mitigates all the factors involved in ventilator-associated lung injury.

Exercise 10

Question

Why is this infant hypocapnic?

Answer

Once more, the limitations of pressure-controlled ventilation are revealed. Resolution of the pneumothorax, administration of surfactant, and your ventilator adjustment achieved the goal of improving lung aeration and thus resulted in better lung compliance. The result was predictable and could potentially have been prevented by vigilant observation of chest rise and measured tidal volume, but in practice, we seldom respond rapidly enough with manual adjustments to avoid this complication.

VOLUME-TARGETED VENTILATION

CASE 3, CONTINUED

You are now convinced that volume-targeted ventilation (VTV) is a good idea and therefore you decide to change the infant to assist control with volume guarantee (AC + VG), one of the common modalities of VTV.

Exercise 11

Question

How does VG work and what settings do I chose?

Answer

Volume guarantee is a modality of pressure-controlled ventilation with volume targeting. The user selects a target V_T based on the infant's specific diagnosis, size, and postnatal age and a pressure limit up to which the ventilator may adjust the inflation pressure (PIP limit). The device then compares the exhaled V_T of the previous inflation to the target V_T and adjusts the working PIP up or down up to the PIP limit to maintain V_T near the target value (Fig. 10.10). In essence, it does automatically and in real time what a bedside caregiver would do under ideal circumstances if there were no other patients to look after and no need to eat or sleep. The ventilator continuously monitors delivered V_T and makes adjustments to inflation pressure in order to avoid over- or underventilation (Fig. 10.11). If the V_T target cannot be reached with the working PIP at the PIP limit, an alarm will sound alerting the user of the low V_T situation. This serves as an early warning that there has been a change in the infant's respiratory status and should prompt an evaluation of the infant's condition.

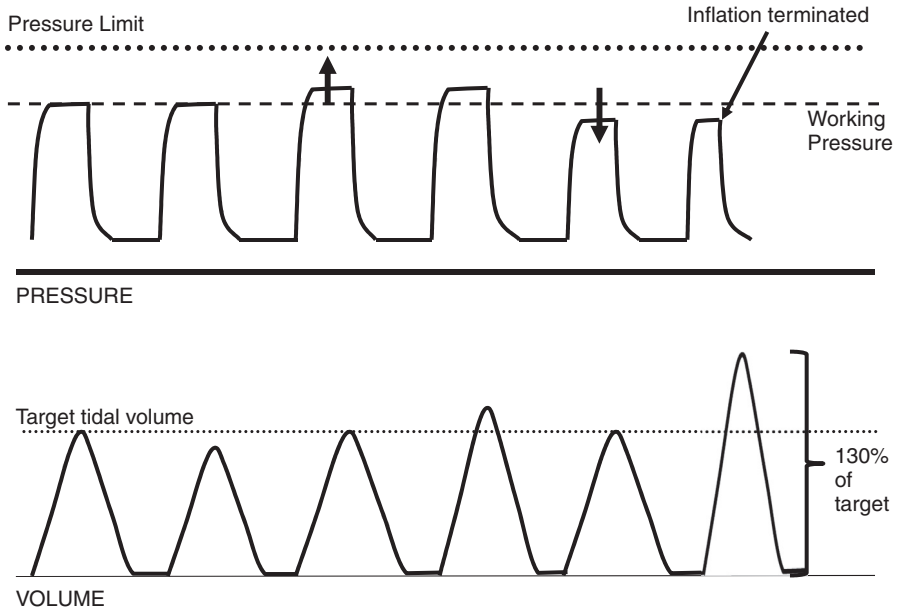

Fig. 10.10 Basic principle of volume guarantee ventilation. The upper panel shows the peak inflation pressure (PIP) and the lower panel the tidal volume (V_T). The ventilator is always looking at the previous V_T and comparing it to the set target. With the first ventilator inflation, the V_T was near the target, thus no adjustment was made to the PIP. The second V_T was below target, thus PIP was increased for the next inflation. With V_T on target, there was no change in PIP for the next cycle, but the fourth cycle resulted in V_T above the target value with consequent decrease in PIP. The last inflation resulted in a very large V_T, likely because of a strong inspiratory effort of the infant. As an important safety feature, when the inspiratory V_T exceeds the target by >30%, inflation is terminated to avoid volutrauma.

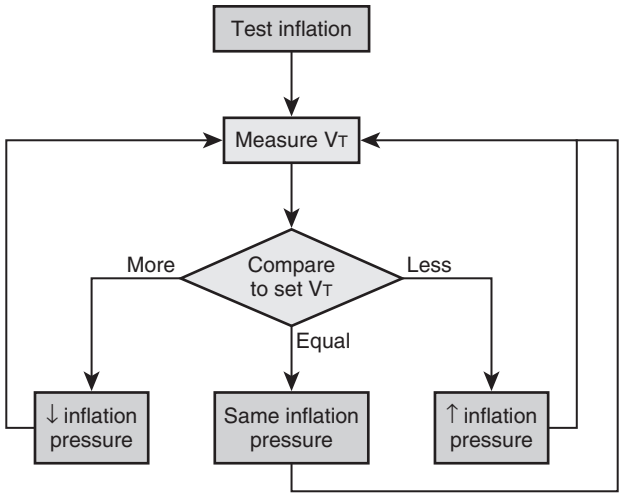

Fig. 10.11 Basic control algorithm for all current volume-targeted modes of ventilation. The exhaled V_T of the previous inflation is compared with the target value and the inflation pressure for the next inflation is adjusted up, down, or is unchanged based on that comparison. Ventilators vary in where and how the V_T is measured and how rapidly the ventilator responds. In general the change from one inflation to the next is limited to avoid overshoot.

The relationship between PIP, compliance, and V_T is the same whether the PIP is being adjusted manually or automatically. The difference is that with VTV, the V_T becomes the primary control variable and the PIP fluctuates to keep V_T stable, in contrast to pressure-controlled ventilation where the PIP is fixed and the V_T is the dependent variable that changes as lung compliance and the patient's own respiratory effort change. Because it is a form of pressure-controlled ventilation, it can cope with leak around the endotracheal tube and deliver a very small V_T accurately. Documented benefits of VTV include earlier extubation, lower rate of bronchopulmonary dysplasia, pneumothorax, hypocapnia, intraventricular hemorrhage, and periventricular leukomalacia and are listed in Table 10.2 (Klingenberg, Wheeler et al. 2017). Evidence-based initial V_T targets for various clinical conditions are shown in Table 10.3 (Keszler 2018).

CASE 3, CONTINUED

Because this is an average sized preterm infant in the early days of his disease, you chose a V_T of 4.5mL/kg, a PIP limit of 24 cmH_2O, PEEP of 7 cmH_2O, a backup rate of 40, and Ti 0.35. The infant appears comfortable, with a respiratory rate of 50 and only minimal retractions. The working PIP is fluctuating between 16 and 22, and the blood gas confirms the adequacy of your settings. You are very pleased with your initial experience, but a nagging question comes to you.

Exercise 12

Question

How do I wean this baby off mechanical ventilation?

Answer

A common misconception is that V_T needs to be lowered progressively to facilitate weaning. It is a misconception because

TABLE 10.2 Documented Benefits of Volume-Targeted Ventilation

	Relative Risk or Mean Difference	95% CI	NNTB (95% CI)
Death or BPD at 36 wk PMA	0.75	0.53–1.07	NA
BPD at 36 weeks PMA	0.73	0.59–0.89	8 (5–20)
Grade 3–4 IVH	0.53	0.37–0.77	11 (7–25)
PVL ± severe IVH	0.47	0.27–0.80	11 (7–33)
Pneumothorax	0.52	0.31–0.87	20 (11–100)
Hypocapnia	0.49	0.33–0.72	3 (2–5)
Days of mechanical ventilation	−1.35	−1.83 to −0.86	

BPD, Bronchopulmonary dysplasia; *CI,* confidence interval; *IVH,* intraventricular hemorrhage; *NNTB,* number needed to benefit; *PMA,* postmenstrual age; *PVL,* periventricular leukomalacia.
Data from Klingenberg et al, 2017. The metaanalysis contains 16 parallel studies with 977 infants and four crossover studies.

TABLE 10.3 Recommended Initial Tidal Volume Settings for Various Clinical Situations

Condition	Initial V_T	Rationale
Term, late preterm, normal lungs	4–4.5 mL/kg	Baseline
Preterm RDS 1250–2500 g	4–4.5 mL/kg	Low alveolar dead space
Preterm RDS 700–1249 g	4.5–5 mL/kg	Dead space of the flow sensor
Preterm RDS <700 g	5.5–6 mL/kg	Dead space of the flow sensor
Preterm evolving BPD	5.5–6.5 mL/kg	Increased anatomic and alveolar dead space
Term MAS with classic CXR[a]	5.5–6 mL/kg	Increased alveolar dead space
Term MAS with whiteout CXR	4.5–5 mL/kg	Alveolar dead space less of a problem
Term CDH	4–4.5 mL/kg	Normal CO_2 production requires normal alveolar minute ventilation
Established severe BPD	7–12 mL/kg	Greatly increased alveolar and anatomic dead space; lower respiratory rate due to long time constants needs larger V_T

[a]Classic CXR in MAS shows heterogeneous inflation and air trapping.
Individual patients may need slightly smaller or larger V_T.
BPD, Bronchopulmonary dysplasia; *CDH,* congenital diaphragmatic hernia; *CXR,* chest radiograph; *MAS,* meconium aspiration syndrome; *RDS,* respiratory distress syndrome.

the V_T that is appropriate for the baby's condition does not decrease—the PIP needed to achieve that V_T decreases instead, as compliance and the infant's own respiratory effort improve. One of the benefits of VG is that PIP comes down automatically, as long as the infant has a pH low enough to have a respiratory drive. Lowering V_T inappropriately can increase the work of breathing and result in a failed extubation attempt. Another benefit of VG is that very few blood gas measurements are needed, because minute ventilation and Pco_2 will remain quite stable over the course of a day. When working pressure is down to the 10 to 15 cmH_2O, Fio_2 is less than or equal to 0.30, PEEP is 5 to 7 cmH_2O, and the infant has a sustained respiratory effort, extubation should be attempted.

CHALLENGING CLINICAL SCENARIOS

CASE 4: TINY INFANT WITH RDS AND METABOLIC ACIDOSIS

You are caring for a 1-hour-old, 27-week, 560 g, growth-restricted infant with RDS. She was born by urgent cesarean delivery under general anesthesia due to acutely worsening maternal preeclampsia with no time for antenatal steroids. The mother was receiving magnesium sulfate for the preeclampsia. The infant required positive pressure ventilation in the delivery room. Surfactant was administered and she was started on AC+VG with PIP limit of 22 cmH_2O, PEEP 5 cmH_2O, inspiratory time (Ti) 0.3 sec, backup rate 40, target V_T of 5 mL/kg, and Fio_2 of 0.55. The baby is making minimal respiratory effort. An initial ABG reveals a pH of 7.22, $Paco_2$ of 54 mm Hg, PaO_2 of 63 mm Hg, and BE of −5 with a working PIP of 20 to 22 cmH_2O. Over the next few hours, the Fio_2 has increased to 0.65 and the PIP limit is increased to 24 cm H_2O because of a persistent low tidal volume alarm. Subsequent ABG shows little change.

Exercise 13

Question

Why is my patient not doing better?

Answer

The baby appears to be depressed after a difficult delivery and is likely affected by the large dose of magnesium sulfate given

to the mother for her impending eclampsia. The combination of a baby not breathing above the ventilator backup rate and an inadequate tidal volume (5 mL/kg), for a baby this size explains the high $Paco_2$ (Table 10.3). The rising Fio_2 indicates that this low V_T, coupled with inadequate PEEP has resulted in progressive atelectasis, which in turn led to worsening lung compliance, necessitating the higher PIP.

CASE 4 (CONTINUED)

You obtain a chest x-ray, which confirms the suspicion of diffuse atelectasis. Having learned this trick earlier in this chapter, you increase the PEEP stepwise to 7 cmH_2O and are pleased to see that the Fio_2 came down to 0.32 and the working pressure has dropped to 16 to 18 cmH_2O. You are in disbelief that the blood gas shows little improvement.

Exercise 14

Question

How come oxygenation improved but the CO_2 didn't come down?

Answer

You appropriately addressed the atelectasis by increasing the PEEP. Oxygenation and lung compliance improved (evidenced by a lower PIP need to achieve the target V_T), but you did not address the respiratory acidosis component. It is evident that you are still thinking as if this were pressure-controlled ventilation where the V_T rises as compliance improves. However, with VG, the primary control variable is V_T, so the PIP came down instead and the V_T remained unchanged. You are not alone; many clinicians struggle to fully grasp the consequences of the change in paradigm when V_T, rather than PIP, is fixed. Additionally, the baby is not breathing above the ventilator backup rate and the set V_T is too low for a baby of this size. Because of the increased impact of instrumental dead space in tiny babies, 5.5 to 6 mL/kg would have been more appropriate (Nassabeh-Montazami et al, 2009).

CASE 4 (CONTINUED)

While you were waiting for the blood gas and conferring with your colleague about what to do, the baby became more active and started to breathe spontaneously. The ventilator, now driven by the baby's spontaneous effort, is cycling at around 60/min, which should bring down the Pco_2. You therefore decide that no other change is needed and head to the call room to get some rest.

Over the next few hours, the baby develops moderately severe retractions and appears intermittently agitated. You inspect the ventilator screen and are puzzled by the fact that the working PIP is intermittently dropping to less than 10 cmH_2O and that the Fio_2 is increased to 0.45. You check a blood gas, which shows pH of 7.30, Pco_2 of 35 mm Hg, Po_2 of 58 mm Hg, and BE −7. While you're not quite sure what is going on, you decide to focus on the Pco_2, which is now below your goal and decide to lower the target V_T to 4.5 mL/kg hoping to allow Pco_2 to rise to the high 40s, where you believe it should be.

You hope to get some sleep now, but before long, you are summoned again by the bedside nurse, who informs you that the baby is looking even more distressed and the Fio_2 is increasing. You examine the baby and, other than moderate retractions and tachypnea, do not see anything amiss. The ventilator PIP is still occasionally close to PEEP level but then rises to the limit when the baby pauses her respiratory effort. You are still unhappy that the Pco_2 is below your target, seemingly because of the infant's excessive respiratory rate, so you prescribe a dose of morphine. The baby settles down, the PIP and respiratory rate return to close to the pressure limit and backup rate, respectively, and you return to the call room hoping for no further disturbance.

Over the next couple of hours, the Fio_2 continues to climb and your rest is once more interrupted. You struggle to clear your head, and in the meantime you order a chest radiograph and a blood gas. Other than diffuse opacification of the lung fields with seven ribs expansion, the chest film shows no abnormality. The ABG shows pH of 7.21, Pco_2 of 59 mm Hg, Po_2 of 54 mm Hg, and BE −8.

Exercise 15

Question

Why is this baby continuing to deteriorate?

Answer

Things have become a bit complicated. The good news is the baby woke up and started to breathe. Now that she is able to respond to her respiratory control center, she is trying to compensate for her base deficit and normalize her pH. Her retractions and tachypnea indicate that she is not getting sufficient support from the ventilator (at least from her perspective—babies are not very keen on permissive hypercapnia, especially in the presence of a base deficit). The working PIP had dropped to near PEEP level because the baby is spontaneously generating a larger V_T than the set 4.5 mL/kg. When the ventilator detects V_T above target, it will drop the PIP as it is programmed to do (Fig. 10.12). With the drop in PIP, the mean airway pressure has decreased, and this is the reason for the rising oxygen requirement, confirmed eventually by the diffuse microatelectasis seen on the chest radiograph.

Question

Why can't I get the baby to tolerate a higher Pco_2?

Answer

When a baby is agitated or tachypneic, the correct response is to optimize support, not give sedation, as previously mentioned. The infant's interaction with the ventilator is an important clinical sign that should not be ignored or suppressed with sedation. Not surprisingly, when the narcotic decreased the baby's respiratory drive, she looked "better," but she was not getting adequate support, hence the return to mixed acidosis and loss of lung recruitment.

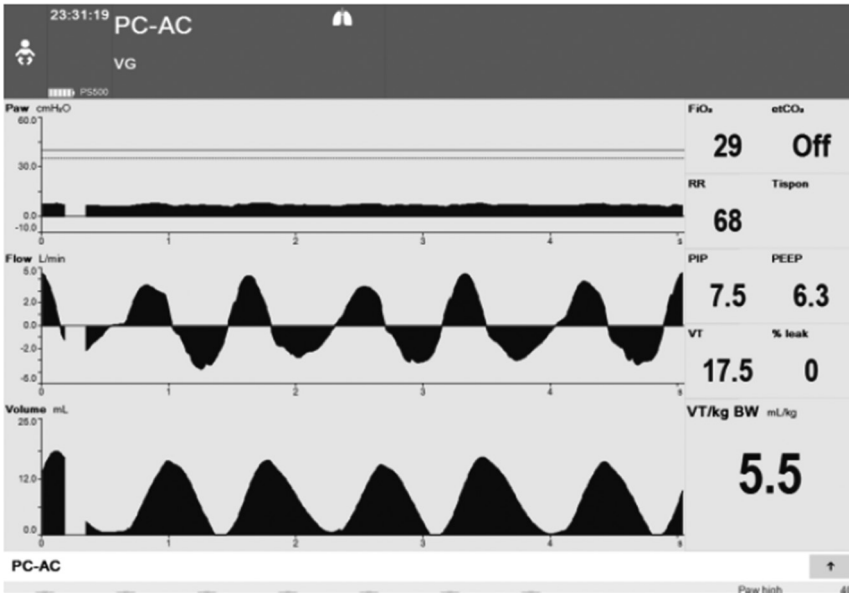

Fig. 10.12 Screenshot of a ventilator display that indicates a V_T that is insufficient to meet the infant's need. Note that the baby is not receiving any inflation pressure above PEEP, resulting in what is basically endotracheal CPAP. The clinician must decide if the infant is ready to extubate or if V_T target needs to be increased to provide adequate support.

Unfortunately, a moderate degree of metabolic acidosis is common in the extremely premature infants, who frequently exhibit some degree of bicarbonate wasting by the proximal tubule. A base deficit complicates management in these babies. It is important to appreciate that pH is the primary driver of respiratory effort and thus P_{CO_2} must always be interpreted in the context of pH.

It is appropriate to accept slightly lower P_{CO_2} values and to buffer the base deficit with acetate added to parenteral nutrition. All the neonatal literature has focused on P_{CO_2}, but cerebral vascular tone is ultimately controlled by perivascular pH (Lassen and Christensen, 1976). Although the exact safe limits of P_{CO_2} are not clearly established, it has been shown that the highest risk of severe intraventricular hemorrhage is associated with large fluctuations in P_{CO_2}, such as may occur when a baby intermittently compensates for the base deficits but then becomes exhausted and can no longer cope, which leads to rapid alterations in P_{CO_2}.

HIGH-FREQUENCY VENTILATION

CASE 4 (CONTINUED)

You've read somewhere that high-frequency ventilation (HFV) is a good way to rescue infants with severe lung disease who are not responding optimally to conventional mechanical ventilation. This is a bit beyond your comfort level, so you ask the senior neonatal fellow to explain.

She informs you that there are three basic forms of HFV: high-frequency oscillatory ventilation (HFOV), high-frequency jet ventilation (HFJV), and high-frequency flow interruption (HFFI), also known as high-frequency percussive ventilation. Of these, the first two are most widely used, and both can be used effectively to treat infants with a variety of conditions when used with an appropriate ventilation strategy.

HFOV generates a relatively high mean airway pressure with a positive and negative pressure deflection (so-called active exhalation). These pressure oscillations may be generated by a large piston or a variety of other mechanisms (Fig. 10.13). What makes a device a true oscillator is that it generates equal positive and negative pressure waveform, regardless of how that waveform is generated.

With HFJV, pulses of high-velocity gas are injected into the upper airway, and this stream of gas penetrates through the dead space gas of the upper airways (Fig. 10.14). The volume of gas injected into the airway is servo-regulated to maintain a set peak inspiratory pressure. A conventional ventilator is used in tandem to provide PEEP and optional volume-recruiting sighs.

Currently, the Bronchotron (Percussionaire Corp., Sand Point, ID) is the only flow interrupter in reasonably common clinical use as a transport ventilator. The Bunnell Life Pulse ventilator (Bunnell Inc., Salt Lake City, UT), and the SensorMedics 3100A (Wyaire Medical, Chicago, IL) are the only Food and Drug Administration approved HFJV and HFOV devices available in the United States. More sophisticated HFOV devices capable of tidal volume measurement and targeting are widely available outside of the United States.

There is no clear-cut evidence that high-frequency ventilation is superior to conventional ventilation as a first-line therapy in infants with uncomplicated RDS (Cools et al, 2010). Some centers electively use both types of HFV to initiate mechanical ventilation, whereas the majority of clinicians use HFOV and HFJV with an early rescue approach.

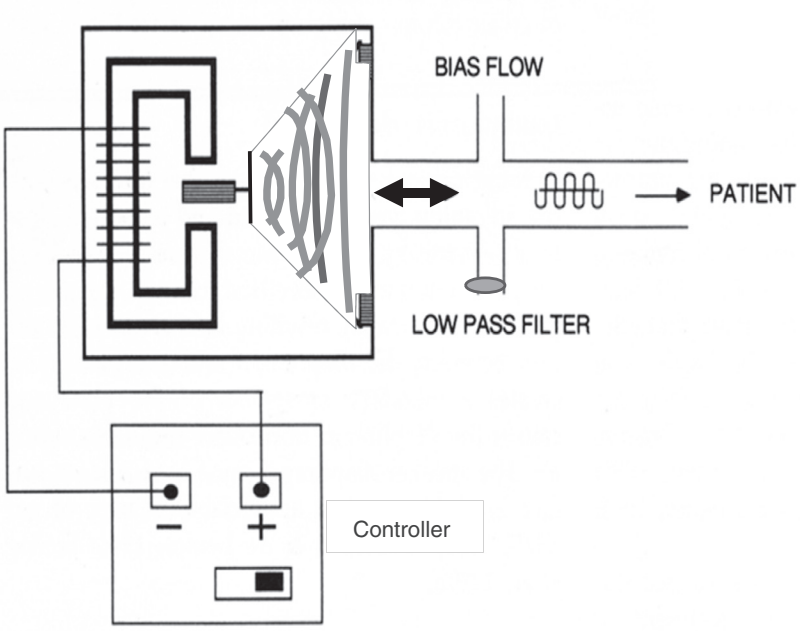

Fig. 10.13 Schematic drawing of a piston oscillator. The power applied to the electromagnet that drives the piston determines the pressure amplitude. The balance between inflow of fresh gas (bias flow) and the resistance of the low pass filter determines the mean airway pressure. The bias flow provides fresh gas and sweeps away the CO_2 as it diffuses out of the lungs.

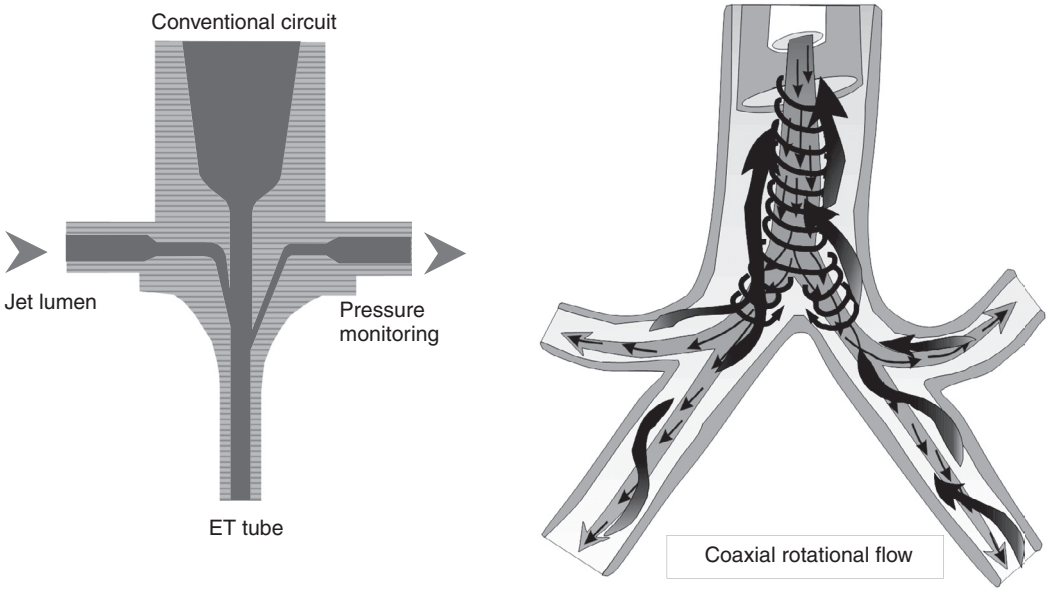

Fig. 10.14 Jet ventilation is delivered via a special endotracheal tube adaptor with a jet injector port through which the high-velocity pulses of gas are delivered and the pressure monitoring port that provides continuous feedback to the ventilator microprocessor that regulates the servo-pressure, which drives the jet pulses (left panel). The right panel shows a schematic of the unique coaxial rotational flow with simultaneous inspiratory and expiratory gas flow, which results in minimal pressure on the lateral wall of the airway.

Exercise 16

Question

If I decide to use HFOV, how do I pick my settings?

Answer

With HFOV, there are really only two primary controls. The mean airway pressure (MAP) controls oxygenation, and the pressure amplitude, also known as ΔP controls CO_2 elimination. The third setting you must choose is the frequency, measured in hertz (Hz) and the inspiratory:expiratory ratio. The choice of frequency, as with conventional ventilation, is guided by consideration of time constants. Small infants with RDS have short time constants and thus are easily ventilated with a frequency of 15Hz. In contrast, large infants with high airway resistance (e.g., term infant with MAS or a former

preemie with severe BPD) respond better to frequencies of 8 to 10Hz, occasionally even lower.

Frequency has an indirect effect on CO_2 elimination; at any given ΔP, a larger tidal volume is delivered into the lungs at lower frequency. Thus CO_2 elimination becomes more efficient at lower frequency. The inspiratory phase is normally set at 33% (1:2 I:E ratio), which results in a small pressure gradient between the ventilator circuit and the trachea, the pressure being about 2 cmH_2O higher in the circuit. This is the reason that when changing from conventional ventilation to HFOV, it is recommended to increase the MAP by 2 cmH_2O, which roughly compensates for that pressure gradient. A key element of ventilation strategy with HFOV is the use of active lung volume recruitment to achieve optimal lung inflation, improve ventilation–perfusion matching, and reduce the oxygen requirement. Though the same approach is also appropriate with conventional ventilation, in infants with severe lung disease, lung volume recruitment is more easily achieved with HFOV.

Exercise 17

The infant is switched to HFOV with frequency of 12 Hz, MAP of 10 cmH_2O, and pressure amplitude of 15 cmH_2O. The chest wall "wiggle" is adequate, but oxygen requirement remains close to 0.50. You increase MAP to 12 cmH_2O with some improvement, but a further increase to 14 cmH_2O is needed to bring the Fio_2 below 0.30. You are pleased with your success and decide to reward yourself with a cup of coffee. When you return the bedside nurse informs you that the baby's blood pressure has dropped and the capillary refill time is 3 to 4 seconds. She opines that the baby "does not like" the oscillator.

Question

Why is this baby hypotensive?

Answer

You failed to reduce the mean airway pressure once full lung volume recruitment was achieved. Remember that once the lung is recruited, it becomes more compliant because the larger radius of the adequately inflated terminal air units now requires less pressure than what was needed to reach the critical opening pressure of the atelectatic lung (LaPlace's law). The intrathoracic pressure has become excessive, leading to impedance of venous return and decreased cardiac output. The appropriate strategy is to reduce the distending pressure in small decrements until you just begin to see a fall in Spo_2 (De Jaegere et al, 2006).

CASE 4 (CONTINUED)

Unfortunately, while you were away, the respiratory therapist at the urging of the bedside nurse decided to ventilate the infant manually with a self-inflating bag to see if that would improve matters. The therapist, who was cross-covering from an adult ICU, unfortunately used no PEEP valve and, when oxygenation started to deteriorate with the hand bagging (likely due to loss of lung recruitment), compensated by generating higher inflation pressure. When you finally sort things out and obtain a chest radiograph, you see that the infant now has significant pulmonary interstitial emphysema (PIE) and therefore you decide to change to HFJV.

Exercise 18

Question

Why is HFJV preferred for air leak, and how do I use it?

Answer

HFJV has specific advantages in treating air leak likely because of its unique flow characteristics and the ability to achieve adequate gas exchange using a lower mean airway pressure. HFJV leads to faster and more frequent resolution of PIE (Keszler et al, 1991) and decreased flow through bronchopleural fistulas (Gonzalez et al, 1987) or tracheo-esophageal fistulas (Goldberg et al, 1992) and is therefore the preferred mode of HFV for these indications.

HFJV controls are more comparable to conventional ventilation. The user must select the PIP, PEEP, and rate. The inspiratory time is extremely short and is usually kept at the minimal value of 0.02. As with other forms of ventilation, the optimal rate is a function of the patient's time constants, with higher rate being appropriate for small infants with RDS and slower rate for larger infants with evolving chronic lung disease or meconium aspiration syndrome. The default rate is 420/min = 7 Hz, but rates as low as 240/min (4 Hz) may be indicated in older and larger infants with chronic lung disease. PIP is the primary regulator of CO_2 elimination, whereas PEEP (set on the tandem conventional ventilator) controls the mean airway pressure. Because of the extremely short inspiratory time of 0.02 s, the I:E ratio is very short and thus the MAP is only slightly above the PEEP level. For this reason, PEEP settings that are substantially higher than with conventional ventilation are needed to achieve and maintain lung volume recruitment. When treating an infant with RDS, a PEEP setting of 8 to 10 cmH_2O is routine. Background sighs from the conventional ventilator may be added as a means of lung volume recruitment for a limited time after initiation of ventilation or after circuit disconnection/suctioning (Keszler, 2012).

Exercise 19

Question

Are there risks to using HFV?

Answer

As with any complex intervention, the risk is mostly related to unfamiliarity with the device or use of an inappropriate strategy. Two studies, both conducted at the same time (in the mid 1990s) in a virtually identical population of preterm infants with RDS and using the same HFJV device came to very different conclusions because of the use of an inappropriate strategy in one of the studies (Wiswell et al, 1996; Keszler et al, 1997). The use of a low-pressure strategy resulted in marked respiratory alkalosis, which accounted for the increased risk of severe intraventricular hemorrhage and periventricular leukomalacia

(Wiswell et al, 1996). Because all forms of HFV are very efficient at CO_2 removal, it is advisable to use transcutaneous CO_2 monitoring when initiating HFV.

CASE 4 (CONTINUED)

Over the next couple of days, the PIE resolves and the PIP is lowered to 18 cmH_2O. You elect to change the infant back to conventional ventilation, even though you understand that is not needed and that extubation directly from HFOV or HFJV is practiced routinely in many NICUs. You place the infant back on AC+VG and make appropriate adjustment to tidal volume to support adequately the infant's respiratory effort without excessive work of breathing.

Over the next few days, the infant weans from mechanical ventilation to noninvasive respiratory support and you feel like a hero. You now understand how to ventilate a variety of infants and appreciate the fact that carefully considering the underlying cause of respiratory failure and understanding how pressure-controlled, volume-targeted, and high-frequency ventilation work is essential to achieving the best possible results.

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Abstract: Sophisticated microprocessor-based ventilators with advanced features enabling effective synchronized ventilation are now widely available. However, better technology can only improve outcomes if used with care and with optimal ventilation strategies that are appropriate for the specific condition being treated. Safe and effective respiratory support of newborn infants requires a good understanding of pulmonary physiology, familiarity with the available evidence regarding management of respiratory failure, and knowledge of the capabilities of the ventilators at one's disposal. The clinician must also recognize that individualized patient care is the best approach and that requires frequent assessment of the patient's response to treatment and regular assessment of all available information, including physical examination, assessment of patient–ventilator interaction and observation of the ventilator waveforms. Blood gas analysis and chest radiographs complete the picture but are not sufficient by themselves to provide full assessment of the adequacy of respiratory support. A good understanding of the many unique aspects of a newborn infant's respiratory physiology will help the clinician use the sophisticated tools at his/her disposal to best advantage.

Keywords: Mechanical ventilation, volume-targeted ventilation, high-frequency ventilation, ventilator-associated lung injury, respiratory failure

11

Bronchopulmonary Dysplasia

Kirsten Glaser, MD, Erik A. Jensen, MD and Clyde J. Wright, MD

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is the most prevalent and prognostically one of the most important complications associated with prematurity. In the United States, it affects 10,000 to 15,000 newborns each year, including upwards of half of all babies born weighing less than 1000 g (Jensen and Stoll; 2014). BPD predisposes infants to a prolonged initial hospitalization and increased risk for mortality and childhood morbidity (Cotten et al, 2005; Ehrenkranz et al, 2005). Chronic impairments in respiratory and cardiovascular health, poor growth, and neurodevelopmental delay are all more common in preterm infants with than without BPD (Berkelhamer et al, 2013; Bott et al, 2006; Carraro et al, 2013; Cristea et al, 2013; Doyle et al, 2006; Ehrenkranz et al, 2005).

The term bronchopulmonary dysplasia was introduced in 1967 by Northway and colleagues to describe the clinical, radiologic, and pathologic respiratory findings that developed in preterm infants following the resolution of severe respiratory distress syndrome (RDS). Ultimately, Northway described the course of 13 infants, born at approximately 32 weeks' GA and 1783 +/- 434 g born with severe RDS who were exposed to mechanical ventilation and high oxygen (80%–100%) for more than 150 hours and survived (Northway et al, 1967). With improvements in perinatal and neonatal care strategies, the babies that Northway described rarely require prolonged or aggressive ventilation in the NICU. This burden has shifted to less mature infants. Today, BPD primarily—but not exclusively—affects those born at <28 weeks gestational age. Necessarily, the definition of BPD continues to evolve, and with it, our understanding of the epidemiology, contributing factors, preventive measures, therapeutic interventions, and associated long-term outcomes.

EPIDEMIOLOGY

CASE 1

Baby H was born at $25^{5}/_{7}$ weeks' gestation and is now 36 weeks corrected. She is on 2 L high-flow nasal cannula and 21% Fio_2. She is tolerating full enteral feedings and receives approximately 70% of her required volume by nipple. Her parents have been educating themselves using the internet, and they ask you about their baby's lungs. They have read about bronchopulmonary dysplasia and they wonder if Baby H has this diagnosis.

Exercise 1

Question

You tell them the following:

A. Their baby does not have BPD.
B. More testing is required to figure out if their baby has BPD.
C. Their baby has severe BPD.
D. Their baby has moderate BPD.
E. Their baby has mild BPD.
F. Their baby has pulmonary sequelae of preterm birth, but using the currently accepted definition it is impossible classify this baby.

Answer

The correct answer is F. Using the 2000 NIH Workshop definition of BPD, is it impossible to classify this baby due to the use of 2 L high-flow nasal cannula to deliver room air. More recent proposals modify the definition so that those requiring new support modes can be classified.

Diagnostic Criteria

In 1967, Northway et al coined the term bronchopulmonary dysplasia to describe the progressive pulmonary sequelae that followed severe respiratory distress syndrome (Northway et al, 1967). The first diagnostic criteria for BPD were proposed in 1979 and classified the disease as the continued treatment with supplemental oxygen at 28 to 30 days plus the presence of specific clinical, laboratory, and/or radiographic findings (Bancalari et al, 1979; Tooley, 1979). It was hoped that having a standardized definition would allow better understanding of the incidence, pathophysiology, and natural history of this new disease. In 1988 Shennan et al demonstrated that supplemental oxygen use at 36 weeks' postmenstrual age (PMA), rather than 28 days, better predicted adverse pulmonary outcomes during the first 2 years of life (Shennan et al, 1988). This definition, which does not include additional clinical data, is the most commonly reported BPD definition (Hines

et al, 2017). A workshop sponsored by the National Institutes of Health and Office of Rare Diseases in 2000 proposed a now widely used severity-based definition of BPD (Jobe and Bancalari, 2001). This definition assesses infants for BPD at 36 weeks' PMA in those born less than 32 weeks' gestation who received supplemental oxygen for at least 28 days. (Table 11.1) BPD severity is then classified into one of three groups (mild, moderate, or severe) based on the amount of supplemental oxygen and mode of respiratory support prescribed at 36 weeks' PMA (Jobe and Bancalari, 2001).

A "physiologic definition" for BPD was proposed in 2003 to standardize the oxygen saturation threshold at which BPD is diagnosed (Table 11.2; Walsh et al, 2003). This definition uses an oxygen-reduction test to determine oxygen dependency at 36 weeks' PMA among infants receiving 30% or more Fio_2 (Walsh et al, 2003). Although the physiologic definition results in modest reductions in BPD rates and between-center variation in BPD incidence, it is not uniformly used in clinical practice or research (Hines et al, 2017; Walsh et al, 2004).

Importantly, limitations to these definitions have evolved over time. For example, it is now commonplace to administer heated and humidified high-flow nasal cannula (HHFNC) to provide some degree of positive distending pressure and minimal support (Jobe and Steinhorn, 2017). These patients are impossible to categorize using the 2000 definition. To address these limitations, various groups have offered alternative definitions. In 2015 the multicenter BPD Collaborative proposed that infants treated with HFNC at 36 weeks' PMA (along with those receiving other forms of noninvasive positive airway pressure) be defined as having type 1 severe BPD (Abman et al, 2017). They further recommended that infants receiving invasive mechanical ventilation at 36 weeks' PMA be classified as a new, type 2 severe BPD (Table 11.3; Abman

TABLE 11.1 Definition of Bronchopulmonary Dysplasia from the NICHD Workshop on BPD

Time point of assessment	36 weeks' PMA or discharge to home, whichever comes first	>28 days, but <56 days' postnatal age or discharge home, whichever comes first
	Treatment with oxygen >21% for at least 28 days **plus**	
Mild BPD	Breathing room air at 36 weeks' PMA or discharge, whichever comes first	Breathing room air by 56 days' postnatal age or discharge, whichever comes first
Moderate BPD	Need[a] for ≥30% oxygen and/or positive pressure (PPV/NCPAP) at 36 weeks' PMA or discharge, whichever comes first	Need[a] for ≥30% oxygen and/or positive pressure (PPV/NCPAP) at 56 days' postnatal age or discharge, whichever comes first
Severe BPD	Need[a] for ≥30% oxygen and/or positive pressure (PPV/NCPAP) at 36 weeks' PMA or discharge, whichever comes first	Need[a] for ≥30% oxygen and/or positive pressure (PPV/NCPAP) at 56 days' postnatal age or discharge, whichever comes first

[a]A physiologic test confirming that the oxygen requirement at the assessment time point remains to be defined. BPD usually develops in neonates being treated with oxygen and positive pressure ventilation for respiratory failure, most commonly respiratory distress syndrome. Persistence of clinical features of respiratory disease (tachypnea, retractions, rales) are considered common to the broad description of BPD and have not been included in the diagnostic criteria describing the severity of BPD. Infants treated with oxygen >21% and/or positive pressure for nonrespiratory disease (e.g., central apnea, diaphragmatic paralysis) do not have BPD unless they also develop parenchymal lung disease and exhibit clinical features of respiratory distress. A day of treatment with oxygen >21% means that the infant received oxygen >21% for more than 12 hours on that day. Treatment with oxygen >21% and/or positive pressure at 36 weeks' PMA, or at 56 days' postnatal age or discharge, should not reflect an "acute" event but should rather reflect the infant's usual daily therapy for several days preceding and following 36 weeks' PMA, 56 days' postnatal age, or discharge.

BPD, Bronchopulmonary dysplasia; *NCPAP,* nasal continuous positive airway pressure; *PMA,* postmenstrual age; *PPV,* positive pressure ventilation.

Modified from Jobe AH, Bancalari E: Bronchopulmonary dysplasia, *Am J Resp Crit Care Med* 163@:1723–1729, 2001.

TABLE 11.2 Physiologic Definition of Bronchopulmonary Dysplasia

Oxygen			**<30%**		**>30% or PPV/CPAP**
Stepwise Challenge to Room Air			Yes		No
Oxygen Saturation	<80%	80%–87%	88%–95%	≥96%	
Monitoring Duration	1 min	5 min	60 min	15 min	
Outcome	Failed	Failed	Passed	Passed	
BPD	Yes	Yes	No	No	Yes

BPD, Bronchopulmonary dysplasia; *CPAP,* continuous positive airway pressure; Min, minute; *PMA,* postmenstrual age; *PPV,* positive pressure ventilation.

Infants at 36 weeks' PMA requiring concentrations of oxygen above 30% and/or mechanical ventilation or NCPAP were defined as having BPD without a challenge test to room air. Infants at the same PMA in room air were considered not having BPD. Those newborns requiring less than 30% oxygen were challenged to a stepwise reduction of oxygen (by 2% steps every 10 minutes) until reaching room air, with continuous monitoring of oxygen saturations and heart rate. In this study, Walsh and coworkers defined as the lowest acceptable saturation a value of 88%.

Walsh MC, et al. Safety, reliability, and validity of a physiologic definition of bronchopulmonary dysplasia, *J Perinatol* 23@(6):451–456, 2003.

TABLE 11.3 BPD Definition as Proposed by the Bronchopulmonary Dysplasia Collaborative

BPD Severity	Definition (Modified from Jobe and Bancalari, 2001)[4]
None	O_2 treatment <28 days and breathing room air at 36 weeks' PMA or discharge home, whichever comes first
Mild	O_2 treatment at least 28 days and breathing room air at 36 weeks' PMA or discharge home, whichever comes first
Moderate	O_2 treatment at least 28 days and receiving <30% O_2 at 36 weeks' PMA or discharge home, whichever comes first
Severe (type 1)	O_2 treatment at least 28 days and receiving ≥30% O_2 or nasal (CPAP/HFNC at ≥36 weeks' PMA
Severe (type 2)	O_2 treatment at least 28 days and receiving mechanical ventilation at ≥36 weeks' PMA.

PMA, Postmenstrual age.
Modified from Table 1, Abman SH, et al: Interdisciplinary care of children with severe bronchopulmonary dysplasia, *J Pediatr* 181@:12–28, 2017.

et al, 2017). In 2016, the National Institute of Child Health and Human Development (NICHD) sponsored a workshop on BPD that proposed a new definition (Table 11.4; Higgins et al, 2018). Importantly, contemporary modes of respiratory support are included in this definition, including infants treated with high-flow nasal cannula. Whether either of these definitions will displace the commonly used 2000 workshop definition remains to be seen.

Of note, this proposed definition reintroduces the need for radiographic confirmation of parenchymal lung disease (Higgins et al, 2018). The need for imaging was left off the 2000 definition, as the "radiographic findings of BPD are inconsistently interpreted and not routinely available at precise ages" (Jobe and Bancalari, 2001). The radiographic findings in BPD can be quite heterogeneous. Infants with the classic radiographic features of BPD have coarse interstitial densities and cyst-like changes, hyperinflation, and emphysema (Fig. 11.1). Infants who have experienced a milder respiratory course have less severe changes found on chest radiograph and are more likely to demonstrate diffuse haziness with or without pulmonary hyperinflation (Fig. 11.2). Given the poor ability of the chest radiograph to predict clinical status and pulmonary outcomes, the utility of including radiographs in the definition remains to be determined. Whether new lung imaging techniques including computed tomography (CT)/CT angiography will perform better is unknown.

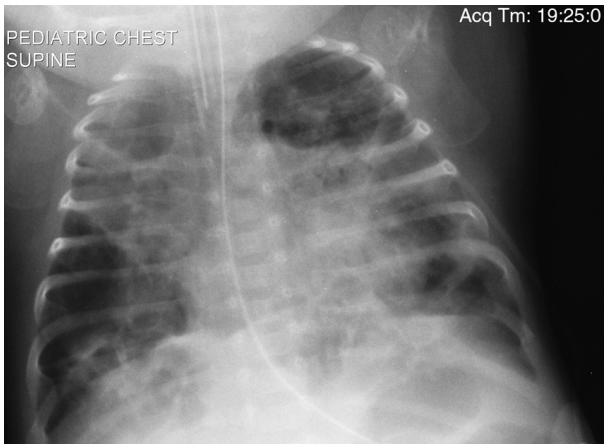

Fig. 11.1 "Old" bronchopulmonary dysplasia. Chest x-ray of an ex-28⁶/₇ weeks' gestation infant, now 38 weeks corrected, with severe bronchopulmonary dysplasia. There are patchy airspace opacities consistent with atelectasis, alternating with areas of cystic lucencies and lung overinflation. Coarse lung markings are also present.

TABLE 11.4 BPD Definition as Proposed in the Executive Summary from the NICHD Workshop on BPD

Grades	Invasive IPPV[a]	NCPAP, NIPPV, or Nasal Cannula ≥3 L/min	Nasal Cannula Flow of 1-<3L/min	Hood O_2	Nasal Cannula Flow of <1 L/min
I	–	21	22–29	22–29	22–70
II	21	22–29	≥30	≥30	>70
III	>21	≥30			
III(A)	Early death (between 14 days of postnatal age and 36 weeks) owing to persistent parenchymal lung disease and respiratory failure that cannot be attributable to other neonatal morbidities (e.g., necrotizing enterocolitis, intraventricular hemorrhage, redirection of care, episodes of sepsis).				

[a]Excluding infants ventilated for primary airway disease or central respiratory control conditions.
Values are percents.
BPD, Bronchopulmonary dysplasia; *CPAP,* continuous positive airway pressure; *IPPV,* intermittent positive pressure ventilation; *NCPAP,* nasal continuous positive airway pressure; *NICHD,* National Institute of Child Health and Human Development; *NIPPV,* noninvasive positive pressure ventilation.
A premature infant (<32 weeks' gestational age) with BPD has persistent parenchymal lung disease, radiographic confirmation of parenchymal lung disease, and at 36 weeks' postmenstrual age requires 1 of the following Fio_2 ranges/oxygen levels/O_2 concentrations for ≥3 consecutive days to maintain arterial oxygen saturation in the 90% to 95% range.
Modified from Table 1, Higgins RD et al: Bronchopulmonary dysplasia: executive summary of a workshop, *J Pediatr* 197@:300–308, 2018.

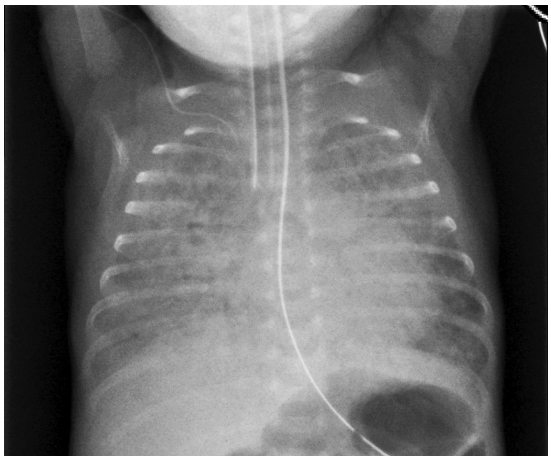

Fig. 11.2 "New" bronchopulmonary dysplasia. Anterior-posterior chest x-ray of an ex-25$^{0}/_{7}$ weeks' gestation infant, now 6 weeks old and still requiring mechanical ventilation. Notice the pulmonary hyperinflation with bilateral homogenous interstitial pattern.

Incidence of BPD

The reported incidence of BPD varies depending on the characteristics of the described population and the definition used to define the illness. Among very low birth weight infants (VLBW, birth weight <1500 g) born in Canada, Israel, and Japan, rates of BPD—defined as supplemental oxygen use at 36 weeks' PMA—ranged between 12% and 15% (Isayama et al, 2012; Klinger et al, 2013). Among VLBW infants with gestational ages of 22 to 29 weeks born in California between 2007 and 2011, the combined rate of death before 36 weeks' PMA or BPD was 45%. The rate of BPD among survivors to 36 weeks' PMA in that cohort was 33% and ranged from 81% among infants born under 750 g to 13% among those with birth weights of 1250 to 1500 g (Fig. 11.3; Lapcharoensap et al, 2015). In the NICHD Neonatal Research Network, BPD rates were as high at 68% when assessed using the NIH consensus definition because of the inclusion of infants who received supplemental oxygen for 28 days or more but were breathing in room air by 36 weeks' PMA (Stoll et al, 2010). In contrast, 42% were diagnosed with BPD based on supplemental oxygen use at 36 weeks' PMA and 40% by the physiologic definition (Stoll et al, 2010).

BPD rates can vary widely between centers. Among hospitals participating in the Vermont Oxford Network (VON), rates of BPD in 2014 ranged from 22% in the highest performing centers to 36% in the lowest performing centers (Horbar et al, 2017). At 17 NICHD Neonatal Research Network centers, rates of BPD based on the physiologic definition ranged from less than 10% to over 50% among infants born with birth weights less than 1250 g (Walsh et al, 2007). Similar variability is seen internationally (Choi et al, 2012; Payne et al, 2006a, 2006b; Rojas et al, 2012; Zeitlin et al, 2008). In 10 European regions, rates of BPD ranged between 11% and 22% for infants born less than 32 weeks' gestation (Zeitlin et al, 2008). Across all South Korean neonatal intensive care units, rates of BPD among VLBW infants varied from 5% to 50% (Choi et al, 2012). Of note, although some reports suggest that the incidence of BPD may be in decline, most indicate that BPD rates remained stable or even increased over the past two to three decades (Botet et al, 2012; Horbar et al, 2017; Smith et al, 2005; Stoll et al, 2015; Stroustrup and Trasande, 2010). This possible rise in BPD may be due, at least in part, to increased survival among the highest risk infants (Parker et al, 1992).

ANTENATAL DETERMINANTS OF BPD

CASE 2

A 34-year-old mother in her first pregnancy is admitted to the obstetric unit with contractions at 25$^{2}/_{7}$ weeks' gestation.

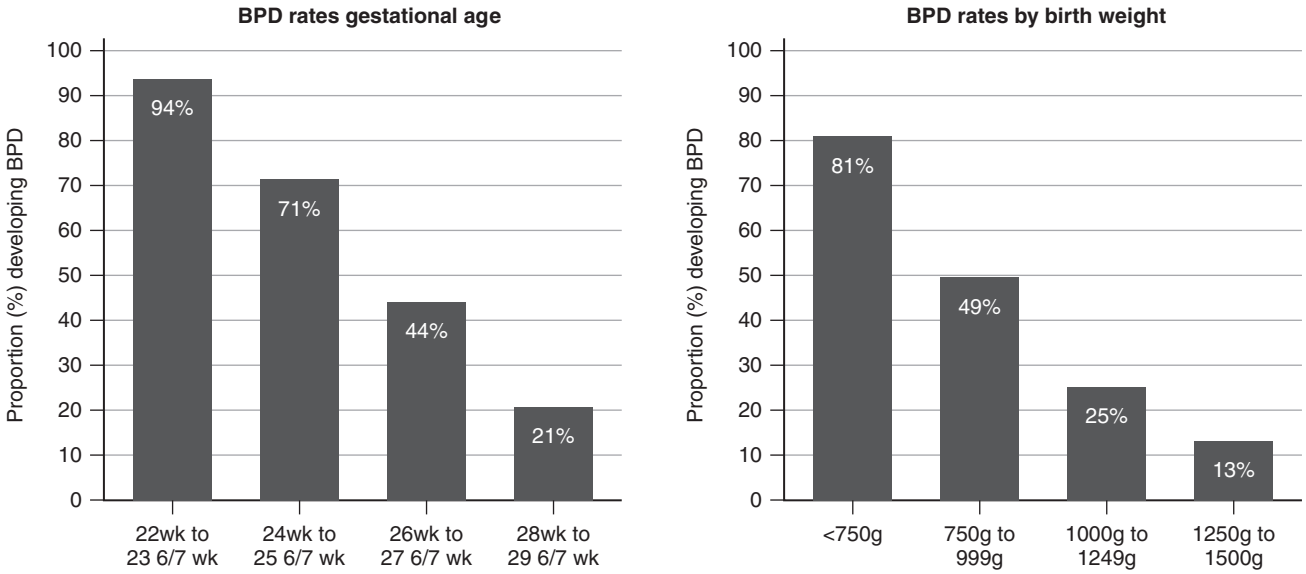

Fig. 11.3 BPD rates by gestational age and birth weight. (From Lapcharoensap W, et al: Hospital variation and risk factors for bronchopulmonary dysplasia in a population-based cohort, *JAMA Pediatr* 169[2]:e143676, 2015.)

This has been an uneventful pregnancy except for ultrasounds demonstrating fetal growth restriction (<10th percentile) of a female singleton. Maternal blood pressures have been slightly elevated; otherwise the mother has been healthy. She presents without fever on admission. However, the maternal serum CRP level is 10.2 mg/L and the WBC count 12,200/mm^3. The obstetric examination is significant for amniotic fluid leakage. It is unknown if she is colonized with group B *Streptococcus* (GBS), but vaginal swabs are taken on admission.

Exercise 2

Question

If the baby was delivered within 24 hours, what are the identifiable risk factors for developing BPD?

Answer

- Gestational age
- Fetal growth restriction
- Intrauterine inflammation
- Preterm premature rupture of membranes
- Increased maternal blood pressures
- Unknown GBS status
- Incomplete course of antenatal corticosteroids

Question

What obstetric strategies in the pregnant mother could help to reduce the infant's risk?

Answer

- Initiation of antenatal corticosteroid treatment to accelerate lung maturation
- Antibiotic therapy to prevent maternal and fetal sepsis
- Observation of the mother at a hospital with a level III NICU center

Even before delivery, adverse conditions can profoundly affect fetal lung development and susceptibility to injury. A number of antenatal risk factors have been associated with the development of BPD (Fig. 11.4) and will be discussed later. Due to complex interrelations of antenatal and postnatal events in the individual infant, however, relative contributions of injurious stimuli may vary significantly and thus do not allow for accurate estimations of prognosis. Moreover, epidemiologic data remain inconsistent, and controversy remains on the relative importance of some of these risk factors. The next section will discuss major antenatal determinants of BPD—either well acknowledged or controversial.

Intrauterine Growth Restriction and Small for Gestational Age at Birth (Table 11.5)

Intrauterine growth restriction (IUGR), defined as failure of the fetus to achieve the expected weight for a given gestational age (GA), is a major cause of preterm delivery (Morgan, 2016). Most cases of IUGR are due to pregnancy-related hypertension and preeclampsia leading to placental insufficiency (Morgan, 2016; Zeitlin et al, 2010). IUGR and prematurity have additive effects on mortality and morbidity in preterm infants (Ray et al, 2017). However, fetal growth restriction itself has been acknowledged as a major predictor of BPD. There is good evidence that IUGR and small for gestational age (SGA) birth—defined as a birth weight below the 10th percentile for a GA, constitute independent risk factors for BPD, the development of pulmonary hypertension (PH)

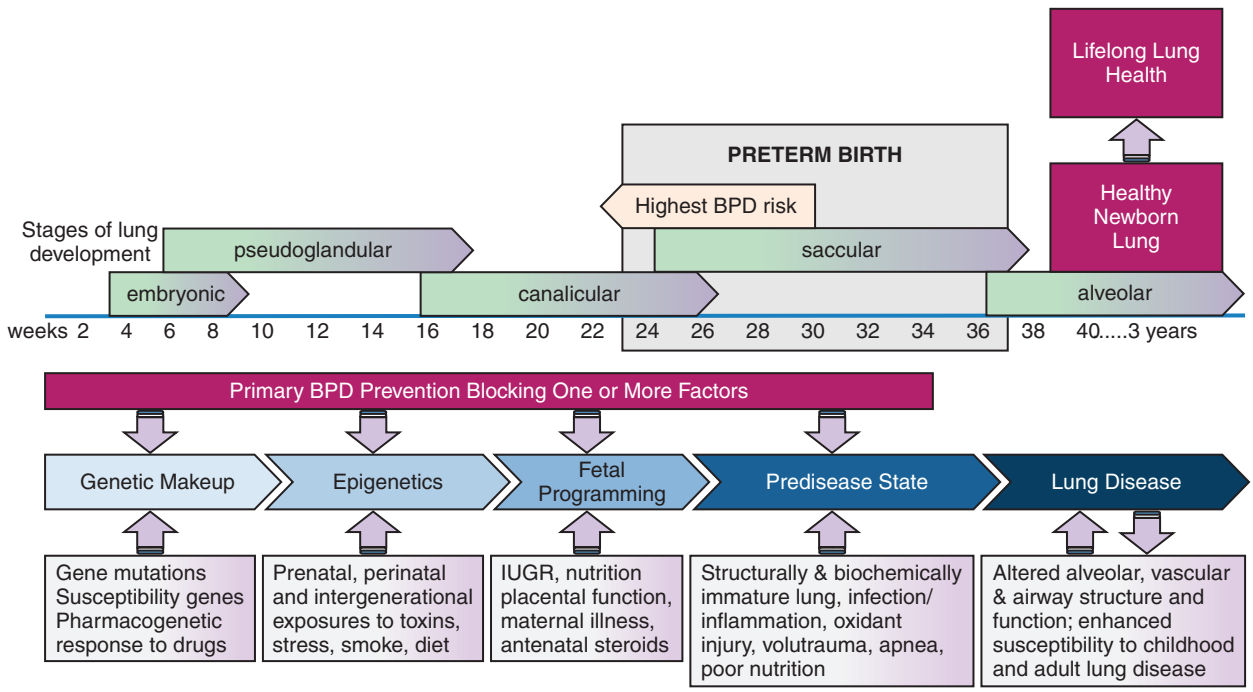

Fig. 11.4 Stages of lung development and contributors to BPD. (From McEvoy CT, et al: Bronchopulmonary dysplasia: NHLBI Workshop on the Primary Prevention of Chronic Lung Diseases, *Ann Am Thorac Soc* 11[Suppl 3]:S146–53, 2014.)

TABLE 11.5 Potential Effects of Undernutrition on the Development of BPD

Pulmonary Aspect	Impact of Undernutrition
Lung growth and development	• Decreased lung biosynthesis • Smaller alveoli, decreased surface area
Respiratory muscle function	• Fatigue of diaphragm and other respiratory muscles
Lung function	• Fewer structural proteins in extracellular matrix • Altered surfactant production • Decreased stability of chest wall
Protection from hyperoxia	• Decreased antioxidant defense systems
Susceptibility to infection	• Decreased cellular and humoral defenses
Alveolar fluid balance	• Decreased plasma oncotic pressure • Diminished alveolar fluid clearance
Control of breathing	• Diminished response to hypoxia

From Thureen P, Hay WW: Conditions requiring special nutritional management. In Tsang RC, Uauy R, Koletzko B, Zlotkin SH, editors: *Nutrition of the preterm infant: scientific basis and practical guidelines Cincinnati,* ed 2, Cincinnati, OH, 2005, Digital Educational Publishing, pp 383–411.

in preterm infants with BPD, and adverse long-term pulmonary outcomes (Bose et al, 2009; Jensen et al, 2018; Keller et al, 2017; Nagiub et al, 2017), severely impairing lung development (Bose et al, 2009; Soudee et al, 2014). Compromised fetal growth has been associated with lung dysfunction in childhood and adulthood (Davidson and Berkelhamer, 2017; van Mastrigt et al, 2017; Zeitlin et al, 2010).

The Extremely Low Gestational Age Newborn (ELGAN) study found a strong association between fetal growth restriction and BPD in infants under 28 weeks' gestation (Bose et al, 2009). Preterm infants with birth weights more than 1 standard deviation below the mean had an over threefold higher risk of BPD (Bose et al, 2009). Moreover, fetal growth restriction was identified as the risk factor most strongly associated with BPD among very immature preterm infants with little exposure to oxygen in the first 2 weeks of life (Laughon et al, 2011). Prospective multicenter studies from Israel and Germany in VLBW infants reported a 2.7-fold and 3.8-fold increased risk of BPD in infants with birth weights below the 10th percentile of GA compared with normally grown counterparts (Klinger et al, 2013; Reiss et al, 2003). A very recent retrospective study covering 6708 preterm infants born at GA less than 32 weeks found that the excess risk for neonatal morbidity and mortality, such as BPD and death and/or BPD, associated with SGA birth was correlated with low GA (Jensen et al, 2018). The risk-adjusted probability of neonatal death or neonatal morbidity among SGA infants equated to that of non-SGA matches born approximately 2 to 3 weeks less mature (Jensen et al, 2018). Data from animal models indicate that a compromised intrauterine environment leads to reduced airway growth and smaller alveoli, reduced surfactant synthesis, pulmonary vascular remodeling, and right ventricular hypertrophy (Tab 1; Liu et al, 2014; Maritz et al, 2004; Orgeig et al, 2010; Wignarajah et al, 2002). Low protein and low caloric intake appear to affect the highly integrated process of lung development by altered expression of key regulators of angiogenesis, such as vascular endothelial growth factor (VEGF), or impaired signaling (Dodson et al, 2018; Liu et al, 2014).

There is evidence that postnatal growth restriction frequently observed in very immature preterm infants (Cooke et al, 2004) and resulting from insufficient nutrient intake represents an additional risk factor for the development of BPD (Bhatia and Parish, 2009; Moya, 2014), stressing the importance of adequate nutrition in this cohort (Bhatia and Parish, 2009). Optimal nutrition and early enteral feeding, in particular, appear to be critical for normal lung growth and development, lung function and repair, and defense mechanisms (Table 11.5; Bhatia and Parish, 2009; Moya, 2014; van Mastrigt et al, 2017). It remains of interest whether this impact is attributable to caloric intake per se or to particular supplements such as lipid emulsions, amino acids, or vitamins potentially modulating molecular pathways of lung morphogenesis (Kapoor et al, 2015; Ma et al, 2017; Moya, 2014). Also of interest are recent studies demonstrating a decreased risk of BPD despite compromised postnatal growth in preterm infants fed exclusively with breast milk (Spiegler et al, 2016).

Chorioamnionitis

Controversy remains concerning the impact of antenatal inflammation and chorioamnionitis on the development of BPD. Chorioamnionitis is strongly related to premature delivery (Kim et al, 2015), contributing itself to neonatal morbidities (Ericson and Laughon, 2015; Kim et al, 2015). Chorioamnionitis is primarily a maternal inflammatory response to microbial invasion from the recto-vaginal tract (Kim et al, 2015). The histologic diagnosis refers to an inflammatory condition of the placenta involving chorion, choriodecidua, and amnion (Kim et al, 2015). The clinical syndrome comprises maternal fever, maternal and/or fetal tachycardia, elevated maternal inflammatory parameters, uterine tenderness, and foul-smelling vaginal discharge (Kim et al, 2015). However, chorioamnionitis may also be an indolent process being diagnosed only after the onset of preterm labor or preterm premature rupture of membranes (Kim et al, 2015). Whereas the diagnosis of clinical chorioamnionitis is frequently made for term or near-term labors, subclinical (histologic) chorioamnionitis appears to be the predominant manifestation in pregnancies before 30 weeks' gestation (Kim et al, 2015).

Fetuses exposed to chorioamnionitis are at high risk of developing a fetal systemic inflammatory response implicated in the development of neonatal morbidities (Hofer et al, 2013). Data from animal models suggest that exposure to antenatal inflammation may accelerate lung maturation and decrease the risk of RDS. However, chorioamnionitis may also promote inflammation, apoptosis, and adverse remodeling in fetal lungs and thus increase the risk of developing BPD (Jobe et al, 2012; Kramer et al, 2002). Epidemiologic

studies reported divergent results. Inconsistent diagnoses both of chorioamnionitis and BPD hampers the interpretation of data. Histologic chorioamnionitis appears to be associated with a lower incidence of RDS in preterm infants, indicating better lung function in infants exposed to in utero inflammation (Lahra et al, 2009b; Lee et al, 2011; Thomas and Speer, 2011). Clinical chorioamnionitis was related to poor respiratory outcomes in preterm infants in some studies and was not predictive for RDS in others (Ramsey et al, 2005; Soraisham et al, 2009; Thomas and Speer, 2011).

Similarly, previous studies have demonstrated an association of clinical and histologic chorioamnionitis with increased risk of BPD, decreased risk of BPD, or no effect (Hartling et al, 2012). A 2012 systematic metaanalysis covering most of these studies (>15,000 preterm infants) found an association between histologic chorioamnionitis—but not clinical chorioamnionitis—and BPD (Hartling et al, 2012). However, heterogeneity was substantial, and there was strong evidence of confounding effects of low GA and low birth weight and of publication bias. Adjusted results were more conservative in the magnitude of association (Hartling et al, 2012). A recent retrospective study covering 56,537 infants under 37 weeks' gestation reported a 1.23-fold risk of the composite outcome BPD and perinatal death in infants with clinical chorioamnionitis (Metcalfe et al, 2017). A prospective national cohort study in France including 2513 preterm infants under 32 weeks' gestation found no association between histologic chorioamnionitis and BPD (Torchin et al, 2017). However, a smaller cohort study in 261 VLBW infants taking into account the histopathologic findings of site and extent of inflammation documented an association with amnionitis (the final stage of chorioamnionitis) and BPD but no association of funisitis and BPD (Kim et al, 2015). Other studies evaluated the respiratory outcome of preterm infants exposed to histologic chorioamnionitis in addition to mechanical ventilation (Van Marter et al, 2002) or postnatal sepsis (Lahra et al, 2009a; Van Marter et al, 2002). The combination of histologic chorioamnionitis with each additional event (e.g., sepsis) increased the risk of BPD (Lahra et al, 2009a; Van Marter et al, 2002), indicating that antenatal and postnatal exposures interact and modulate neonatal outcomes such as BPD ("multihit hypothesis"; Van Marter et al, 2002).

Antenatal Corticosteroids (Table 11.6)

For more than 30 years, the administration of antenatal corticosteroids (ACS) to women at risk of preterm delivery at 24 to 34 weeks' gestation has been the standard of care in high-income and many middle-income countries to promote fetal lung maturation and to improve short-term neonatal outcomes, especially in high-risk infants born very premature (Jobe and Goldenberg, 2018; Liggins and Howie, 1972). Current recommendations by obstetric societies worldwide are supported by National Institutes of Health Consensus Conferences ("Antenatal corticosteroids revisited: repeat courses," 2000; "Effect of corticosteroids for fetal maturation on perinatal outcomes," 1994) and two Cochrane metaanalyses (Roberts et al, 2017; Roberts and Dalziel, 2006). ACS appears to reduce neonatal mortality and the incidence of RDS, intraventricular hemorrhage (IVH), and necrotizing enterocolitis (NEC), but there seems to be no beneficial effect of ACS on the incidence of BPD (Chawla et al, 2018; Roberts and Dalziel, 2006; Travers et al, 2018). A recent Cochrane metaanalysis covering 30 studies confirmed this finding (Roberts et al, 2017). It remains to be elucidated whether this is due to insufficient statistical power of available studies for the outcome of BPD or due to a true lack of beneficial effects of ACS on the development of BPD. A 2013 Cochrane review revealed that there is no clear evidence of particular advantages of the type of corticosteroid, such as dexamethasone or betamethasone, or the respective regimen, including dosing frequency and route of delivery (Brownfoot et al, 2013), suggesting the need to better identify the most effective corticosteroid and regimen potentially affecting BPD development.

Administration of corticosteroids to the pregnant mother leads to a thinning of the primary alveolar-capillary septa constituting the blood–air barrier, stimulates surfactant synthesis, and promotes the clearance of fetal lung fluid (Table 11.6; Kemp et al, 2016). This acceleration of fetal lung maturation has significantly contributed to neonatal survival and neonatal outcomes (Jobe and Goldenberg, 2018; Kemp et al, 2016). Undesirable effects comprise inhibition of secondary septation and impaired development of microvasculature (Jobe and Goldenberg, 2018). Data from epidemiologic studies and animal models further indicate cardiovascular and metabolic alterations years after exposure to ACS consistent with fetal programming for adult disease (Jobe and Goldenberg,

TABLE 11.6 Effects of Antenatal Corticosteroid Treatment on Fetal Lungs as Indicated by Animal Models

Pulmonary Aspect	Beneficial Effects of Antenatal Corticosteroids
Anatomy/ biochemistry	• Thinning of primary alveolar–capillary septa • Increased saccular/alveolar gas volumes • Increased antioxidant enzymes • Increased surfactant synthesis
Lung physiology	• Increased compliance • Improved gas exchange • Protection from injury during resuscitation
Interactions with exogenous surfactant	• Improved response to surfactant treatment • Improved surfactant dose-response curves • Decreased inactivation of surfactant
Short-term pulmonary outcome	• Decreased incidence of RDS • No effect on the incidence of BPD • Decreased perinatal and neonatal mortality

BPD, Bronchopulmonary dysplasia; *RDS,* respiratory distress syndrome. From Jobe AH, Kallapur SG, Kramer BW: Perinatal events and their influence on lung development and function. In Bancalari E, Polin RA, editors: *The newborn lung: neonatology questions and controversies,* Philadelphia, PA, 2012, Elsevier Saunders, pp 57–89.

2018). These late adverse side effects suggest caution for the use of ACS beyond pregnancies at 24 to 34 weeks' gestation (Jobe and Goldenberg, 2018).

ACS treatment has been expanded to periviable pregnancies before 24 weeks' gestation, mostly defined as pregnancies at $22^{0}/_{7}$ to $23^{6}/_{7}$ weeks (Jobe and Goldenberg, 2018). The Obstetric Care Consensus no. 6 for 2017 recommended the individual consideration of ACS in discussion with the family in pregnancies above $20^{0}/_{7}$ weeks' gestation (American College of Obstetricians and Gynecologists & Society for Maternal-Fetal Medicine, 2017). There is no information about the outcomes of fetuses exposed to ACS at a periviable GA but delivered at later preterm GA or at term (Jobe and Goldenberg, 2018). Another area of controversy is whether to repeat ACS if the fetus is not delivered within 1 to 2 weeks. A 2015 Cochrane metaanalysis found a reduced incidence of RDS with repeated ACS treatment but no benefits on mortality, IVH, and NEC. Therefore selective use of repeated courses of ACS was recommended (Crowther et al, 2015). The AOCG committee suggested repeated ACS treatment in women under 34 weeks' gestation at high risk of delivering preterm within 7 days and with a time interval to ACS over 14 days (American College of Obstetricians and Gynecologists' Committee on Obstetric Practice & Society for Maternal-Fetal Medicine, 2016). Repeated ACS treatment has been associated with reduced head circumference and reduced fetal growth, the latter being an independent risk factor for BPD, infant mortality, and poor neurodevelopmental outcome (Bose et al, 2009; Murray et al, 2015). In growth-restricted fetuses, questions about the benefit of ACS treatment remain (Torrance et al, 2009).

Gestational Age Dependence

Prematurity is the strongest predictor of BPD, being inversely proportional to its incidence and severity (Stoll et al, 2010, 2015). The NICHD Neonatal Research Network found an incidence of BPD of 73% in preterm infants born at 23 weeks' gestation, with severe disease in 56% of those infants (Stoll et al, 2010). At 28 weeks' gestation, in contrast, only 23% of preterm infants developed BPD, with severe disease found in only 8% (Stoll et al, 2010). The Canadian Neonatal Network reported that 28% of surviving infants under 25 weeks' gestation developed BPD in contrast to only 4% of preterm infants born at 29 to 32 weeks' gestation (Isayama et al, 2012). In an Israeli national cohort, 50% of surviving infants born at 24 to 25 weeks' gestation developed BPD, but only 4% of preterm infants born between 30 and 32 weeks did (Klinger et al, 2013). Moreover, in the same cohort, 70% of preterm infants with birth weights less than 1000 g developed BPD compared with only 29% of preterm infants with a birth weight between 1000 to 1500 g (Klinger et al, 2013). The ELGAN study of 1340 preterm infants born before 28 weeks' gestation confirmed a significant relationship of GA both with the severity of initial respiratory illness and the prevalence of BPD and severe BPD (Laughon et al, 2009; Sriram et al, 2018). A very recent cohort study in preterm infants 33 weeks' and earlier gestation with severe BPD documented that an increase in GA of 1 week was associated with higher total and normal lung volumes at 6 months corrected age (van Mastrigt et al, 2017). Reasons for variations observed in BPD outcome for infants with the same GA have not been clearly understood. Interactions of individual antenatal and postnatal events may account for the differences. Very recently, variations in epigenetic maturity of infants reflecting interindividual differences in developmental maturity were discussed as a contributing factor (Knight et al, 2018). Preterm infants who were epigenetically more mature had lower rates of BPD than matches at the same GA (Knight et al, 2018).

Genetic Factors

Twin studies pointed to an impact of genetic risk factors and heritability of BPD (Bhandari et al, 2006; Parker et al, 1996), indicating that BPD might not be an exclusively developmental disease but a disorder resulting from interactions between the immaturity of preterm lungs, adverse environmental factors, and genetic predisposition, leaving individual infants more susceptible to lung injury. Several studies have attempted to identify genetic aberrations in genes and signaling pathways associated with an increased risk of BPD (Yu et al, 2016). Genetic variations potentially involved in the development of BPD (Shaw and O'Brodovich, 2013; Wang et al, 2013) have been identified, but these findings were not replicated in other cohorts or follow-up studies (Lal and Ambalavanan, 2015; Shaw and O'Brodovich, 2013; Yu et al, 2016). Whether and to what extent each genetic variant contributes to the development of BPD remains subject to future research. Reasons for inconsistent and highly variable study results may include small sample sizes and heterogeneity in study cohorts or statistical approaches (Lal and Ambalavanan, 2015; Yu et al, 2016). Moreover, the genetic basis of severe BPD might be different from that of mild and moderate BPD, and genetic variants and pathways associated with BPD might vary by ethnicity.

Of note, recent studies described epigenetic changes and mutations in noncoding regions implicated in an increased susceptibility to BPD (Bik-Multanowski et al, 2018; Chen et al, 2017). It has been widely acknowledged that the epigenome responds dynamically to the environment (Kappil et al, 2015), and there is evidence that adverse factors such as prenatal exposure to maternal smoking or maternal obesity and postnatal exposure to hyperoxia are associated with genomic imprinting (Cassidy and Charalambous, 2018; Chen et al, 2017; Richmond et al, 2015). Epigenetic changes, such as hypermethylation of DNA, may affect the regulation of genome activity, such as by gene silencing (Cassidy and Charalambous, 2018).

Some data from epidemiologic studies and animal models suggest a sex bias in favor of male preterm infants developing BPD (Ito et al, 2017; Lingappan et al, 2016), whereas others did not confirm sex as a contributing factor (Kho et al, 2016; Nardiello et al, 2017). In the context of stem cell approaches to BPD therapy, female bone marrow–derived mesenchymal stem cells (MSCs) showed greater therapeutic efficacy than male MSCs in reducing hyperoxia-induced lung injury in neonatal rats (Sammour et al, 2016).

Other Antenatal Determinants

Additional risk factors suggested by epidemiologic research and experimental studies in animal models include maternal obesity, promoting a systemic inflammatory state with increased oxidative stress, maternal hypertension, maternal smoking (McEvoy and Spindel, 2017; Morrow et al, 2017; Yusuf et al, 2018), and placental abnormalities found with gestational hypertension, preeclampsia, and eclampsia (Torchin et al, 2016).

DELIVERY ROOM MANAGEMENT OF AT RISK NEONATES

CASE 3

Three days later, the 34-year-old mother has been treated with a complete course of betamethasone. However, labor progressed, and a 565 g female infant (birth weight 8th percentile for GA) was born via spontaneous vaginal delivery. After delayed cord clamping, the Baby H is brought to the resuscitation table. Her heart rate is 130, she is actively breathing with minimal retractions, and a preductal oxygen saturation at 2 minutes of life is 70%. A decision is made to support her work of breathing.

Exercise 2

Question

Which type of support would you choose?

A. Continuous positive airway pressure (CPAP)
B. Intubation and prophylactic surfactant
   - INtubate-SURfactant-Extubate (INSURE) versus less invasive surfactant administra/on (LISA)
C. Sustained lung inflation (SLI) followed by CPAP

Answer

Based on evidence from multiple randomized controlled trials, premature infants at high risk of developing lung injury should have a trial of noninvasive support (CPAP) before routine intubation and surfactant administration. The use of SLI is not recommended at this time, because of results from the SAIL trial (Foglia et al, 2015; Kirpalani et al, 2018). If indicated, surfactant administration should be delivered with the aim to minimize exposure to mechanical ventilation, with INSURE or LISA being appropriate options.

During a NICU course, premature infants face multiple exposures that increase the risk of developing BPD, beginning in the delivery room. Not surprisingly, many of these decisions involve the initial respiratory management of these high-risk neonates. The next section will cover supplemental oxygen in the delivery room, invasive and noninvasive respiratory support, sustained lung inflation, and surfactant treatment.

Supplemental Oxygen During Resuscitation

Use of room air versus 100% oxygen decreases the risk of mortality in asphyxiated term newborns (Saugstad et al, 2008). Thus the NRP recommends beginning resuscitation for infants over 35 weeks' gestation with room air (Weiner et al, 2016). In contrast, recommendations for how much oxygen to use in preterm infants under 28 weeks' gestation during the initial resuscitative efforts are not as clear (Oei et al, 2017). A recent metaanalysis of multiple randomized controlled trials (RCTs) comparing the use of room air versus 100% Fio_2 for resuscitation of preterm neonates demonstrated an increased risk of mortality in neonates under 28 weeks' GA initially resuscitated with room air, with no demonstrable effect on the incidence of BPD (Oei et al, 2017). However, limitations in the studies from which these conclusions are drawn urge caution with this interpretation (Foglia et al, 2017). In 2015, the International Liaison Committee on Resuscitation recommended starting resuscitation for preterm infants with a low Fio_2 concentration (21%–30%) with a call for more study (Perlman et al, 2015).

CPAP as Initial Respiratory Support

The initial respiratory support used for preterm neonates has a direct and measurable effect on their risk of developing BPD. The association between mechanical ventilation and lung injury has been known since the 1970s (Northway et al, 1967; Philip, 1975; Rhodes et al, 1975). There is no arguing that ventilators and modes of ventilation have evolved over time to become less injurious. However, once implemented, no mode of mechanical ventilation reliably protects against developing BPD compared with other modes (Wright and Polin, 2016). Given the association between mechanical ventilation and lung injury, there has been a long-standing interest in providing noninvasive respiratory support in the form of CPAP to minimize injury. Although CPAP has been used in the NICU since the early 1970s (Gregory et al, 1971), studies directly comparing CPAP to invasive ventilation as primary support for preterm neonates at high risk of developing BPD were not performed until recently. Five randomized clinical trials directly comparing nasal CPAP with intubation and surfactant have been published (Dunn et al, 2011; Finer et al, 2010; Morley et al, 2008; Sandri et al, 2010; Tapia et al, 2012). These trials enrolled subjects at high risk of developing BPD: Almost all weighed less than 1500 g, and most were less than 28 weeks' gestation. Three recent metaanalyses of these trials support the conclusion that when used as primary respiratory support, CPAP is superior to routine mechanical ventilation for preventing BPD (Fischer and Buhrer, 2013; Schmolzer et al, 2013; Wright et al, 2016).

Unfortunately, 45% to 50% of the babies at highest risk of lung injury fail noninvasive support with CPAP and require intubation in the first week of life (Dunn et al, 2011; Finer et al, 2010; Morley et al, 2008). Rates appear to be highest in the smallest babies, with rates approaching 60% at 25 to 26 weeks' gestational age (Morley et al, 2008). This rate is similar to other published observational data (Ammari et al, 2005; Dargaville et al, 2013; Fuchs et al, 2011). These data support efforts to optimize CPAP success early in the course of noninvasive support.

Sustained Lung Inflation

After birth, the newborn infant must open and aerate the lung to successfully transition to postnatal life. This process is

impaired in many extremely preterm infants because of a highly compliant chest wall, underdeveloped respiratory musculature, delayed surfactant production, and immature pulmonary epithelium (Barker et al, 1997; Heldt and McIlroy, 1987a, 1987b; Obladen, 1978). Application of nasal CPAP in the delivery room is an evidence-based strategy that aids extremely preterm infants with this transition and can help reduce BPD risk (Subramaniam et al, 2016). However, CPAP is most appropriate for the spontaneously breathing infant. Traditionally, intermittent positive pressure ventilation administered noninvasively via face mask or invasively via endotracheal tube has been used to resuscitate infants without sufficient spontaneous respirations. Sustained inflation (SI) is an alternative approach that uses a prolonged inflating pressure (10–25 cm H_20 held for 5–15 seconds) to clear lung fluid and establish functional residual capacity (FRC) (Foglia et al, 2017; Foglia and Te Pas, 2016). Several small randomized controlled trials have been published examining different SI levels and durations (Foglia et al, 2017; Schmölzer et al, 2015). Although individually these trials demonstrated favorable improvements in respiratory physiology, a metaanalysis of four studies found no differences in the rates of BPD, death, or the composite of death or BPD among those treated with SI compared with conventional therapy (Schmölzer et al, 2015). Recently the Sustained Aeration of Infant Lungs (SAIL) trial, the largest RCT examining the safety and efficacy of SI performed to date, was stopped early due to concern for harm with higher mortality rates among SI-treated infants (Foglia et al, 2015; Kirpalani et al, 2018). A planned metaanalysis inclusive of this trial's data will provide updated information about the safety and efficacy of SI.

Surfactant: Prophylactic vs. INSURE vs. LISA

(Table 11.7)

Since its introduction into clinical care in the early 1990s, surfactant replacement therapy has become the standard of care for the prevention and treatment of RDS (Owen et al, 2017; Polin et al, 2014; Sweet et al, 2017). Several randomized controlled trials and metaanalyses demonstrated that surfactant replacement reduces the severity of RDS, the incidence of air leaks and pneumothorax, and, most importantly, neonatal death (Sardesai et al, 2017). A number of animal-derived surfactants are available for the use in preterm infants with RDS, partly differing in their composition (Table 11.7; Sardesai et al, 2017; Singh et al, 2015). Development of synthetic surfactants has aimed at avoiding the use of animal-derived surfactants and improving surfactant activity (Curstedt et al, 2013). In randomized controlled trials, some second-generation synthetic surfactants were shown to be equivalent to animal-derived surfactants (Polin et al, 2014; Sardesai et al, 2017). Third-generation ("new") synthetic surfactants are being studied in a phase 1 human trial in Germany and the United Kingdom and in a phase 2 double-blinded clinical trial in the United States (Bassler et al, 2015; Curstedt et al, 2013; Pfister et al, 2007; Seehase et al, 2012; Sweet et al, 2017). Current European guidelines still recommend the administration of natural surfactants (Sweet et al, 2017).

TABLE 11.7 Animal-Derived Surfactant Preparations Licensed in the US and Europe, Respectively

Generic Name	Trade Name	Source	Dose (Volume)
Beractant	Survanta	Bovine	100 mg/kg/dose (4 mL/kg)
Bovactant	Alveofact	Bovine	50 mg/kg/dose (1.2 mL/kg)
Calfactant	Infasurf	Bovine	105 mg/kg/dose (3 mL/kg)
Poractant alfa	Curosurf	Porcine	100–200 mg/kg/dose (1.25–2.5 mL/kg)

Administration of surfactant via an endotracheal tube in a mechanically ventilated infant was the exclusive method for years. Moreover, prophylactic surfactant therapy was recommended from the 1990s onward with several clinical trials documenting advantages of early surfactant administration compared with late administration (Sardesai et al, 2017). This practice has been questioned against the background of established ACS treatment and growing evidence of the benefits of noninvasive respiratory support (Dunn et al, 2011; Finer et al, 2010; Morley et al, 2008; Sardesai et al, 2017). Large clinical trials and a Cochrane metaanalysis showed beneficial effects of selective use of surfactant versus prophylactic use on the incidence of BPD and/or death (Finer et al, 2010; Dunn et al, 2011; Morley et al, 2008; Rojas-Reyes et al, 2012). This supports a strategy of prophylactic initiation of CPAP in stabilized preterm infants in the delivery room and early selective intubation and administration of surfactant only in infants with signs of RDS (Subramaniam et al, 2016). Current North American and European guidelines both recommend this strategy (Polin et al, 2014; Sweet et al, 2017). However, if babies need mechanical ventilation because of RDS, surfactant should be given as early as possible (known as early rescue) (Bahadue and Soll, 2012; Polin et al, 2014; Sweet et al, 2017).

Aiming to reduce the need for mechanical ventilation, alternative methods of surfactant administration have evolved, combining the positive effects of surfactant and early CPAP: INSURE (INtubate-SURfactant-Extubate) and LISA (less invasive surfactant administration) (Aldana-Aguirre et al, 2017; Isayama et al, 2015; Sardesai et al, 2017; Wright et al, 2018). During INSURE, infants are intubated and receive surfactant and are supposed to be immediately extubated to CPAP again to minimize the adverse effects of mechanical ventilation (Wright et al, 2018). A metaanalysis of randomized controlled trials comparing INSURE with standard intubation followed by surfactant and mechanical ventilation reported a reduced need of ventilation and reduced risk of BPD (oxygen need at 28 days of life) in INSURE cohorts (Stevens et al, 2007). However, studies comparing prophylactic surfactant with INSURE with early CPAP treatment found no benefit of INSURE over CPAP (Dunn et al, 2011; Sandri et al, 2010).

Two metaanalyses documented that prophylactic INSURE did not lead to higher survival without BPD (Isayama et al, 2015; Rojas-Reyes et al, 2012). A retrospective cohort study in 322 preterm infants under 32 weeks' gestation in whom INSURE had been used found that 60% of study infants could not be extubated within 2 hours after the procedure (Brix et al, 2014). A modified INSURE strategy including alveolar recruitment maneuver is currently being studied (Vento et al, 2016).

The LISA approach was developed in Germany and has been widely used in Germany and increasingly in other parts of Europe (Gopel et al, 2011; Klotz et al, 2017). The procedure is embedded in a package of measures comprising ACS, early CPAP, and early caffeine treatment (Gopel et al, 2015; Mehler et al, 2012). During LISA, a fine and flexible catheter or feeding tube is inserted into the trachea of a preterm infant who is spontaneously breathing on CPAP (Gopel et al, 2011; Kribs et al, 2015). Insertion is done using a Magill's forceps under laryngoscopy (Gopel et al, 2011). As soon as the device is placed, laryngoscopy is terminated, and surfactant is administered slowly over several minutes (Gopel et al, 2011). A very similar method developed in Australia (minimally invasive surfactant treatment, MIST) uses a more rigid vascular catheter to be positioned in the trachea, again under direct laryngoscopy but without the use of Magill's forceps (Owen et al, 2017; Sweet et al, 2017). The first randomized trial of the German Neonatal Network including 220 preterm infants born at 26 to 28 weeks' gestation demonstrated a risk reduction in the need for mechanical ventilation during the first 72 hours of life and during hospital stay and reduced median days on mechanical ventilation in the LISA cohort (Gopel et al, 2011). A multicenter study from the same national network covering 37 centers and 1103 preterm infants under 32 weeks' gestation found lower rates of mechanical ventilation and BPD in infants who had received LISA compared with matched controls (Gopel et al, 2015). These findings were confirmed in a recent observational cross-sectional multicenter study conducted in Germany covering 407 VLBW infants who received surfactant via LISA or standard intubation (Langhammer et al, 2018). Preterm infants who failed LISA and needed secondary intubation were more immature, had lower birth weights, and were more likely to be SGA (Langhammer et al, 2018).

In a randomized study conducted in 200 preterm infants under 32 weeks' gestation, less invasive surfactant administration significantly reduced the need and duration of mechanical ventilation and was associated with reduced risk of BPD compared with the INSURE procedure (Kanmaz et al, 2013). Three recent metaanalyses comparing LISA/MIST with standard intubation found a reduction in BPD and/or death in preterm infants treated with LISA/MIST (Aldana-Aguirre et al, 2017; Isayama et al, 2016; Rigo et al, 2016) and reduced need for mechanical ventilation within 72 hours of birth and during hospital stay (Aldana-Aguirre et al, 2017). Some data point toward lower incidences of severe IVH in preterm infants treated with LISA compared with standard intubation and ventilation (Isayama et al, 2016; Kribs et al, 2015; Langhammer et al, 2018). Data on long-term outcomes following INSURE or LISA/MIST are missing. As far as the clinical application of less invasive surfactant administration is concerned, there is still variability regarding expertise, indications, catheter type, and redosing of surfactant (Heiring et al, 2017; Klotz et al, 2017). Moreover, premedication during placement of the catheter is not standardized, and approaches with and without premedication are common (Heiring et al, 2017; Klotz et al, 2017; Owen et al, 2017). European recommendations suggest that INSURE should be considered for infants who fail on CPAP and that LISA may be an alternative strategy to INSURE in spontaneously breathing infants (Sweet et al, 2017).

NICU MANAGEMENT OF AT-RISK NEONATES

CASE 4

By 3 days of life, Baby H is stable on CPAP 6 cm H_2O, requiring 32% to 35% oxygen to maintain oxygen saturations 88% to 92%. She is receiving trophic feeds of maternal breast milk, and total parenteral nutrition (TPN) via an umbilical venous catheter. On rounds, a medical student asks which clinical practices and NICU events contribute to lung injury and increase this baby's risk of BPD.

Exercise 4

Question

You identify the following risk factors (pick all that apply).

A. Duration of mechanical ventilation
B. Using high-frequency oscillatory ventilation instead of volume-targeted ventilation
C. Early onset sepsis
D. Late onset sepsis
E. Necrotizing enterocolitis
F. Supplemental oxygen exposure and targeting oxygen saturations of 92% to 95%

Answer

Inflammatory exposures, including early onset sepsis, late onset sepsis, and NEC, increase the risk of developing BPD. No mode of mechanical ventilation has been conclusively shown to be superior to any other for the purpose of preventing BPD. Exposure to mechanical ventilation is a major risk factor for developing BPD, and the duration of mechanical ventilation and associated ventilator-induced lung injury increases the risk of developing BPD. Oxygen alone induces lung injury and alveolar simplification in animal models, and randomized controlled trials demonstrate decreased rates of BPD when targeting oxygen saturations of 85% to 89% versus 90% to 95%. These findings suggest that oxygen toxicity contributes to the pathogenesis of BPD.

Multiple inflammatory (Balany and Bhandari, 2015; Shahzad et al, 2016; Wright and Kirpalani, 2011) and oxidant (Saugstad, 2010) insults encountered in the NICU contribute to the pathogenesis of BPD (see Fig. 11.4). Whether each of these insults acts through a unique mechanism to injure the

developing lung or whether a common pathway to injury exists is unknown. That being said, each of the exposures discussed represents an important and unique risk factor that negatively affects lung development.

Mechanical Ventilation: Ventilator-Induced Lung Injury and Modes of Ventilation

One of the strongest predictors of developing BPD is exposure to and duration of mechanical ventilation (Ambalavanan et al, 2008, 2011; Gagliardi et al, 2011; Laughon et al, 2011; May et al, 2011; Oh et al, 2005; Van Marter et al, 2000). Multiple mechanisms underlie ventilator-induced lung injury, including volutrauma, barotrauma, atelectrauma, and biotrauma (Dargaville and Tingay, 2012; Donn and Sinha, 2006). Although neonatal ventilators and modes of ventilation have improved, no single mode of invasive mechanical ventilation is clearly superior for minimizing lung injury and preventing BPD. Neither volume-targeted nor high-frequency ventilation definitively reduce the incidence of BPD in the smallest, highest risk babies (Cools et al, 2015; Klingenberg et al, 2017; Ramanathan, 2008). Although promising, neutrally adjusted ventilator assist (NAVA) has not been adequately studied in this high-risk population (Rossor et al, 2017; Stein and Firestone, 2014). These data suggest that at these early gestational ages (22–28 weeks), the developing human lung is susceptible to injury regardless of the mode of invasive mechanical ventilation used. Furthermore, prolonged ventilation is predictive of poor neurodevelopmental outcomes (Trittmann et al, 2013; Walsh et al, 2005). Every effort must be made to limit the duration of mechanical ventilation in high-risk patients.

Oxygen Toxicity

The relationship between oxygen exposure and neonatal lung injury is well established. Both clinical observations (Northway et al, 1967; Philip, 1975; Wai et al, 2016) and animal studies (Nardiello et al, 2017) implicate cumulative oxygen exposure as a significant risk factor for developing BPD. With the advent of pulse oximetry came the ability to continuously monitor and target oxygen saturations in the NICU. Observational studies suggested that targeting lower oxygen saturations (~70%–90%) was safe and associated with lower rates of BPD and ROP (Tin et al, 2001). Therefore the Neonatal Oxygenation Prospective Metaanalysis (NeOProM) was designed to test whether targeting a saturation level (SpO_2) of 91% to 95%, or a SpO_2 85% to 89% would reduce death or disability at 18 to 24 months of age in extremely preterm neonates (<28 weeks' gestation) (Askie et al, 2011). The results of the primary studies have been recently published (Australia et al, 2016; Carlo et al, 2013; Group et al, 2013; Schmidt et al, 2013; Vaucher et al, 2012), and various reviews and metaanalyses have been published using data from the primary reports of nearly 5000 randomized subjects (Askie et al, 2017; Manja et al, 2015, 2017; Saugstad et al, 2014). The data strongly support that targeting SpO_2 85% to 89% reduces the incidence of ROP, although rates of BPD were not significantly lower in that group. Importantly, neonates randomized to oxygen saturation targets of 85% to 89% had a higher risk of death at 18 to 24 months and NEC (Askie et al, 2018). These results have led some to recommend targeting oxygen saturations of 90% to 94% (Sweet et al, 2017), whereas the American Academy of Pediatrics, Committee on Fetus and Newborn are more cautious with their recommendation, stating, "The ideal physiologic target range is a compromise among negative outcomes associated with either hyperoxemia (e.g., ROP, bronchopulmonary dysplasia) or hypoxemia (e.g., NEC, cerebral palsy [CP], death). Recent RCTs suggest that a targeted oxygen saturation range of 90% to 95% may be safer than 85% to 89%, at least for some infants. However, the ideal oxygen saturation range for extremely low birth weight infants remains unknown." (Cummings et al, 2016).

Multiple studies have demonstrated that it is difficult to maintain infants within a target range. However, because care providers are more tolerant of hyperoxia than hypoxia, many infants spend considerable time with saturations over 95%. This is dependent on staffing and unit culture (Hagadorn et al, 2006; Sink et al, 2011; van Zanten et al, 2015, 2017). There are some reports that units that have increased their oxygen saturation target goals have seen increased rates of ROP with no observable decrease in mortality (Manley et al, 2016). These data stress the importance of staying within the target range selected to prevent complications associated with spending time outside of that range. Perhaps most importantly, whatever saturation targets are chosen, education for nurses, respiratory therapists, nurse practitioners, and physicians is imperative to reinforce that oxygen is a necessary drug with known toxic effects that must be precisely monitored and titrated for high-risk neonates.

Infection and NEC

Both laboratory and clinical data support a central role played by inflammation in the pathogenesis of BPD (Balany et al, 2015; Jobe, 2016; Shahzad et al, 2016; Wright et al, 2011). Multiple proinflammatory biomarkers have been identified in the serum, tracheal aspirates, or urine in babies that go on to develop BPD (Lal and Ambalavanan, 2017; Rivera et al, 2016). Furthermore, specific infections and inflammatory insults increase the risk of developing BPD. Subclinical respiratory tract colonization with *Ureaplasma* species, and postnatal cytomegalovirus (CMV) infection have been linked to BPD risk (Kelly et al, 2015; Lowe et al, 2014; Viscardi and Kallapur, 2015). Both early and late onset sepsis are independent risk factors for developing BPD (Pryhuber, 2015). In particular, *Staphylococcus epidermidis,* typically considered to be "nonvirulent," is the most common cause of late onset sepsis in the NICU and is associated with increased BPD risk (Dong et al, 2018). Both NEC and spontaneous intestinal perforation increase the risk of developing BPD (Wadhawan et al, 2014). Although these insults are unique in nature, each one represents an inflammatory stress, and they have all been independently linked with BPD. These associations support efforts to prevent infection and NEC in the NICU (Lapcharoensap et al, 2017;

Talavera et al, 2016), as these represent modifiable risk factors to prevent BPD.

PHARMACOLOGIC THERAPIES FOR PREVENTION OF BPD

CASE 5

Baby H is now 2 weeks old. On day of life 10 she required endotracheal intubation and initiation of invasive mechanical ventilation for a Pco_2 of 82 mm Hg and rising supplemental oxygen requirement (>60% Fio_2) that did not respond to increasing her noninvasive CPAP level. She is currently receiving synchronized intermittent mechanical ventilation (SIMV) with 35% Fio_2. According the NICHD Neonatal Research Network BPD Estimator, Baby H now has a 66% to 71% chance of death before reaching 36 weeks' PMA or developing BPD (supplemental oxygen requirement at 36 weeks' PMA).

Exercise 5

Question

Which of these medications reduce BPD risk in very preterm infants? (Pick all that apply.)

A. Albuterol
B. Caffeine
C. Dexamethasone
D. Furosemide
E. Inhaled nitric oxide
F. Indomethacin
G. Vitamin A

Answer

Randomized controlled trials have demonstrated that caffeine, dexamethasone, and vitamin A prevent BPD.

Several pharmacologic agents have been shown to reduce the risk for developing BPD among preterm infants. A summary of these medications and their relative effect sizes is found in the text later and in Table 11.8. Many other medications have been shown not to be beneficial for BPD prevention. A review of each of these therapies is outside the scope of this chapter, but a few are worth noting. Despite a strong association between presence of a PDA and the development of BPD, no medication (indomethacin, ibuprofen, acetaminophen) that targets ductal closure has been found to reduce BPD risk (Benitz, 2012; Fowlie et al, 2010; Ohlsson and Shah, 2018; Ohlsson et al, 2015). Diuretics may reduce pulmonary edema and provide short-term improvement in respiratory mechanics, but there are no data showing longer term benefit (Iyengar and Davis, 2015). Finally, inhaled nitric oxide (iNO), which is an effective therapy for persistent pulmonary hypertension (PPHN) in near- or full-term newborns, does not prevent BPD in preterm babies (Askie et al, 2011; Barrington et al, 2017). A recent individual patient metaanalysis using

TABLE 11.8 Medications Shown in Randomized Controlled Trials to Prevent BPD

Medication	Outcome	Trials/ Patients	OUTCOME RATES: Intervention	OUTCOME RATES: Control	RR (95% CI)	NNT (95% CI)	Comment
Noncorticosteroids							
Azithromycin (Nair et al, 2014)	BPD among survivors	3/310	50%	60%	0.83 (0.71–0.97)	10 (5–44)	Overall low quality of evidence
	Death or BPD	3/363	57%	67%	0.86 (0.77–0.97)	11 (6–55)	
Caffeine (Schmidt et al, 2006)	BPD among survivors	1/1917	36%	47%	0.76 (0.70–0.86)	10 (7–16)	Initiation in the first 3 days may be more efficacious
Vitamin A (IM) (Darlow et al, 2016)	BPD among survivors	4/886	43%	50%	0.85 (0.74–0.98)	13 (7–97)	High cost, intermittent availability in the United States has limited use
Corticosteroids							
Dexamethasone (<8 days of life) (Doyle et al, 2017a	BPD among survivors	14/1917	26%	36%	0.73 (0.64–0.83)	10 (7–17)	Early use not recommended because of increased risk for poor neuro-development
	Death or BPD	16/2581	44%	51%	0.87 (0.80–0.94)	15 (10–32)	
Dexamethasone (>7 days of life) (Doyle et al, 2017b)	BPD among survivors	6/259	56%	73%	0.78 (0.66–0.92)	6 (4–16)	Effect of late dexamethasone on long-term outcomes not well established
	Death or BPD	10/516	56%	77%	0.73 (0.65–0.83)	5 (4–8)	

Continued

TABLE 11.8 Medications Shown in Randomized Controlled Trials to Prevent BPD,—cont'd

Medication	Outcome	Trials/ Patients	OUTCOME RATES Intervention	Control	RR (95% CI)	NNT (95% CI)	Comment
Hydrocortisone (≤24 hours of life) (Baud et al, 2016)	Survival without BPD	1/523	60%	51%	1.17 (1.01–1.37)	12 (6–200)	Increased sepsis risk among infants born at 24–25 weeks treated with hydrocortisone No difference in neurodevelopment between groups
Inhaled budesonide (<2 weeks of life) (Shinwell et al, 2016)	BPD among survivors	2/749	27%	37%	0.73 (0.59–0.90)	10 (6–31)	Largest trial found higher mortality in the budesonide treated infants (RR 1.37, 95% CI 1.01–1.86) (Bassler et al, 2018)
Intratracheal budesonide + surfactant (Venkataraman et al, 2017)	BPD Death or BPD	2/381 2/381	25% 39%	44% 65%	0.57 (0.43–0.76) 0.60 (0.49–0.74)	5 (4–10) 3 (3–8)	Control arm received surfactant only All infants were receiving invasive mechanical ventilation with Fio_2 >50%–60%

BPD, Bronchopulmonary dysplasia; *IM,* intramuscular; *NNT,* number needed to treat; *RR,* relative risk.

only select iNO trials suggested iNO may reduce BPD risk among African American preterms (Askie et al, 2018). This promising finding requires validation in future studies.

Noncorticosteroid Therapies

Azithromycin

Azithromycin is a macrolide that exhibits both antimicrobial and antiinflammatory properties (Aghai et al, 2007; Jaffe and Bush, 2001). This class of medications has been shown to be beneficial in older children and adults with inflammatory lung diseases such as cystic fibrosis and chronic obstructive pulmonary disease (Herath and Poole, 2013; Southern et al, 2012). In preterm infants, infection with *Ureaplasma* is associated with the development of BPD (Schelonka et al, 2005; Wang et al, 1995). A metaanalysis of three small trials found a reduction in the risk for BPD and death or BPD among infants treated with azithromycin, regardless of known *Ureaplasma* colonization or infection (Nair et al, 2014). However, none of the studies individually demonstrated benefit, each used different dosing regimens, and the overall quality of evidence from these studies was low (Jensen et al, 2015; Nair et al, 2014). In addition, trials evaluating other macrolides for prevention of BPD have not shown any benefit (Mabanta et al, 2003; Ozdemir et al, 2011). At present, prophylactic use of azithromycin to prevent BPD is not recommended (Jensen et al, 2015).

Caffeine

Caffeine is a potent respiratory stimulant that increases minute ventilation, CO_2 sensitivity, and diaphragmatic activity (Dunwiddie and Masino, 2001; Julien et al, 2010; Kassim et al, 2009). The Caffeine for Apnea of Prematurity (CAP) trial showed that caffeine reduced BPD risk among infants with birth weights of 500 to 1250 g and improved neurodevelopmental outcomes at 18 to 21 months corrected age (Schmidt et al, 2006, 2007). Follow-up of trial participants through age 11 years showed that caffeine resulted in long-term improvement in motor function (Schmidt et al, 2017). Recent studies evaluating the optimal timing for caffeine initiation suggested that beginning therapy within the first 72 hours of life may result in the greatest reduction in BPD risk (Davis et al, 2010; Dobson et al, 2014; Lodha et al, 2015; Patel et al, 2013; Taha et al, 2014). In a posthoc analysis of the CAP trial, treatment with caffeine beginning on day of life 0 to 2 significantly reduced the odds of BPD by over half, while therapy initiated between day of life 3 to 10 also significantly reduced the odds of BPD, although to a lesser extent (23% reduction) (Davis et al, 2010). However, these findings may be explained by greater illness severity among the infants who were started on caffeine after 72 hours of life. Further studies are needed to determine whether early initiation of caffeine, particularly among extremely preterm infants receiving invasive mechanical ventilation, reduces BPD risk. However, initiation of

caffeine soon after birth is cautiously recommended by some experts (Jensen et al, 2015).

Vitamin A

Vitamin A is an essential nutritional supplement involved in immune regulation and growth of epithelial cells in the respiratory tract (Biesalski and Nohr, 2003; Niederreither and Dolle, 2008). A large RCT published in 1999 showed that intramuscular (IM) injections of vitamin A during the first 4 weeks of life in extremely low birth weight infants reduced rates of death or BPD and BPD among survivors (Tyson et al, 1999). However, recent observational studies showed similar rates of BPD among infants who received vitamin A and untreated controls (Gadhia et al, 2014; Tolia et al, 2014). Moreover, rates of BPD remained stable during the US vitamin A shortage despite a precipitous drop in its use (Tolia et al, 2014). Although these observational studies should not supersede the RCT data, they do raise questions about the efficacy of vitamin A to prevent BPD in the current era. Clinicians may also choose to weigh the high cost of IM vitamin A (~$12,000 per treatment course) and the need for three potentially painful injections per week during the first 4 weeks of life when deciding whether to prescribe this therapy (Jensen et al, 2015). An ongoing trial investigating enteral vitamin A supplementation for prevention of BPD may help resolve the conflict between the RCT and observational data (Meyer et al, 2014).

Corticosteroids

Dexamethasone (systemic). The strong association between lung inflammation and the development of BPD makes corticosteroids a logical therapeutic agent. Of all systemic corticosteroids, dexamethasone has been evaluated in the most RCTs. The first dexamethasone trials demonstrated earlier weaning of respiratory support and successful endotracheal extubation (Avery et al, 1985; Cummings et al, 1989; Mammel et al, 1983). Unfortunately, subsequent follow-up studies found that dexamethasone, particularly when initiated during the first week of life, carried significant risks (Barrington, 2001; O'Shea et al, 1999; Yeh et al, 1998, 2004). The most recent Cochrane review showed that although initiation of dexamethasone before 8 days of life reduced the risk of BPD, it increased the risks for gastrointestinal perforation, hypertrophic cardiomyopathy, CP, and major neurosensory disability (Doyle et al, 2017a). The combined data from trials evaluating "late" dexamethasone (initiation after the first week of life) found a reduction in BPD risk (Doyle et al, 2017b). However, it remains uncertain whether initiating dexamethasone after the first week of life results in long-term harm. Short-term adverse effects of late dexamethasone include hyperglycemia, glycosuria, and hypertension (Doyle et al, 2017b). In contrast, the risk for CP was similar among surviving infants treated with late dexamethasone and untreated controls (Doyle et al, 2017b). Importantly, the trend toward an increase in CP or abnormal neurologic examination following dexamethasone treatment is at least partially offset by a trend toward reduction in death (Doyle et al, 2017b). Importantly, none of follow-up studies were adequately powered to evaluate for differences in long-term neurodevelopment, and high rates of open label corticosteroid use among enrolled infants may mask actual treatment effects (Doyle et al, 2017b; Onland et al, 2010).

Deciding whether to use "late" dexamethasone to prevent BPD requires balancing the risks of potential neurodevelopmental impairment due to corticosteroids against those from BPD, itself a risk factor for poor neurologic outcomes (Doyle et al, 2005, 2014). A metaregression of RCTs showed that when the risk of BPD in the control population was less than approximately 33%, corticosteroids significantly increased the risk of death or CP (Doyle et al, 2014). In contrast, when the risk of BPD exceeded approximately 60%, corticosteroids reduced the risk of death or CP (Doyle et al, 2014). Therefore for many but not all, the adverse long-term effects of dexamethasone will outweigh its benefits. However, among those at high risk for BPD (such as Baby H described in the case earlier) the balance may favor dexamethasone therapy.

Hydrocortisone (systemic). The recent multicenter PREMILOC trial evaluated the utility of a 10-day course of low-dose hydrocortisone initiated within the first 24 hours of life among infants with gestational ages under 28 weeks (Baud et al, 2016). Rates of survival without BPD were higher among infants treated with hydrocortisone than placebo. However, hydrocortisone was associated with an almost twofold increase in the risk of late-onset sepsis among infants born at 24 to 25 weeks' gestation (Baud et al, 2016). Hydrocortisone in this trial was not associated with improvement in neurodevelopment at 2 years corrected age (Baud et al, 2017). Metaanalysis inclusive of PREMILOC data and the results from several smaller trials also initiating hydrocortisone in the first week of life found a reduction in the composite outcome of death or BPD but no reduction in BPD rates among survivors (Doyle et al, 2017a). Gastrointestinal perforation was more common in the hydrocortisone-treated infants (Doyle et al, 2017a). The authors of the Cochrane review called for additional RCTs evaluating long-term survival and neurodevelopment with early hydrocortisone therapy (Doyle et al, 2017a). A recently completed RCT conducted within the NICHD NRN evaluating the safety and efficacy of hydrocortisone administered to preterm infants receiving invasive mechanical ventilation at 14 to 28 days will provide additional important information (ClinicalTrials.gov Identifier: NCT01353313).

Budesonide (Onhaled)

Inhaled corticosteroids offer the theoretical benefit of reducing inflammation in the lung without the harmful short and long-term side effects of systemic corticosteroids. The efficacy of several of these agents for preventing BPD has been studied in RCTs (budesonide, beclomethasone, fluticasone, flunisolide) (Onland et al, 2017; Shinwell et al, 2016). A meta-analysis of data from all trials showed a reduction in the risk for BPD and death or BPD with inhaled corticosteroid therapy (Shinwell et al, 2016). This finding is primarily driven by the results of the multicenter NEUROSIS trial, which

randomized 863 infants born under 28 weeks' gestation to receive inhaled budesonide beginning within the first 24 hours of life or placebo (Bassler et al, 2015). Infants treated with inhaled budesonide were more likely to survive without BPD (Bassler et al, 2015). However, mortality rates were higher in the budesonide-treated infants (Bassler et al, 2015, 2018). There was no difference in rates of neurodevelopmental impairment between the groups at 18 to 22 months corrected age (Bassler et al, 2018). Although no etiology for the higher mortality in the budesonide group was identified, this concerning finding outweighs the observed benefit for BPD (Bassler et al, 2018).

Two randomized controlled trials evaluated the utility of intratracheal-administered budesonide combined with surfactant relative to surfactant therapy alone among VLBW infants with severe RDS (Venkataraman et al, 2017). The combined therapy reduced the risk for death or BPD (Venkataraman et al, 2017). Follow-up performed up to 3 years of age found no difference in motor or cognitive function between the groups (Venkataraman et al, 2017). This promising finding awaits confirmation in larger trials before widespread use is recommended.

THE DIAGNOSIS OF BPD IS MADE: WHAT DO WE DO NEXT

There is no consensus on what testing should be done or treatments should be started once the diagnosis of BPD is made. After the diagnosis is made, there are no agreed-upon or evidence-based treatments that alter disease progression. However, the clinician must keep other causes of lung disease and respiratory compromise in mind once the diagnosis of BPD is made. Flexible bronchoscopy can diagnose dynamic airway lesions frequently associated with prematurity, including tracheomalacia or bronchomalacia. Gastroesophageal reflux can be associated with aspiration and ongoing pulmonary injury. In infants with suspected microaspiration, studies to rule out reflux and aspiration (e.g., pH probe and impedance monitoring or an upper GI series) should be considered.

Importantly, guidelines and recommendations do exist that assist the clinician in anticipating complications associated with BPD. Some recommend routine echocardiographic screening "at the time of formal BPD diagnosis per current practice (36 weeks' postmenstrual age)" (Krishnan et al, 2017). These recommendations are based on the increased risk of PH in those with severe BPD. These evaluations have not been examined prospectively, and whether extending screening beyond those with severe BPD to all those diagnosed with BPD is warranted remains unknown. Comprehensive recommendations have recently been published to evaluate and manage PH in children with BPD (Krishnan et al, 2017).

Until recently, there were no specific recommendations for managing infants with severe BPD. This diagnosis is made in approximately 20% of infants born at less than 28 weeks' GA (Abman et al, 2017). These infants require a multidisciplinary approach, as they will need long-term care beyond NICU discharge. Depending on the degree of underlying injury, these infants may require tracheostomy placement and chronic ventilator support. Pharmacologic treatment must be individually tailored for each patient based on underlying pathologic contributors to disease physiology. Treatments for PH (sildenafil, bosentan), reactive small airway disease (albuterol, ipratropium, inhaled corticosteroids), pulmonary edema (diuretics), gastroesophageal reflux, and systemic hypertension may be necessary. In preparing for discharge, coordination with pulmonary, cardiac, gastrointestinal, otolaryngologist, and developmental pediatricians should be considered. Guidelines have been recently published to assist the clinician with managing these complex patients (Abman et al, 2017).

LONG-TERM OUTCOMES

CASE 6

Baby H is $40^{2}/_{7}$ weeks corrected today and is leaving the NICU with her parents. She has not needed any respiratory support for 3 weeks and has nippled every feeding for 2 weeks. Baby H receives fortified breast milk and has shown continuous weight gain along the 10th percentile. Her discharge weight is 3020 g (13th percentile). Up to 1 week ago, Baby H sporadically presented with oxygen desaturations and episodes of apnea, but the last 7 days were free of any event. Oxygen saturations are within the normal range and she breathes unlabored. H is an active baby, more and more interacting with her environment. Cranial ultrasounds are normal. However, echocardiography at discharge still documents borderline PH as assessed by tricuspid regurgitant jet velocity. Her parents are well trained in handling their baby and are happy to take her home. However, they worry about short-term and long-term morbidities and the risk of an adverse long-term outcome.

Exercise 6

Question

You tell them the following, but which of the statements are true?

A. Despite ongoing lung growth, Baby H still is likely to have altered lung development predisposing to respiratory infections, infection-related ventilator dysfunction, and rehospitalization.
B. Continuous weight gain after discharge is an important factor contributing to positive pulmonary outcome.
C. Baby H is at increased risk of pulmonary sequelae, including asthma-like symptoms and impaired exercise capacity in childhood and adolescence
D. Baby H is not at increased risk of delayed or impaired psychomotor development
E. Current echocardiographic findings need follow-up assessments
F. There is a good chance of resolution of the cardiac (echocardiographic) findings

Answer

A, B, C, E, and F are the correct answers.

Little is known about the impact of BPD on long-term neonatal outcomes. Characterization is challenging because current adult BPD survivors represent outdated neonatal care practices. However, there is growing evidence of persistent pulmonary morbidity in BPD survivors even in the postsurfactant era (Davidson and Berkelhamer, 2017; Doyle et al, 2017; Malleske et al, 2018; Urs et al, 2018). Moreover, available long-term follow-up studies raise concern for impaired neurodevelopmental outcome (Sriram et al, 2018). These long-term sequelae of BPD may represent a severe burden on each individual family and may exert a growing burden on healthcare systems also. The following section summarizes current data on long-term pulmonary and neurodevelopmental outcomes associated with BPD.

Pulmonary Outcome

See Table 11.9.

Most data on pulmonary outcomes of BPD survivors come from the presurfactant era. Only recently is information available on children and young adults who had received ACS and surfactant. Although most preterm survivors do not have ongoing oxygen dependency or respiratory distress in early childhood, they have higher rates of rehospitalization in their early years. A retrospective study in 1597 preterm infants under 33 weeks' gestation born between 1995 and 1999 found more than twofold higher rates of rehospitalization for respiratory and other reasons during the first year of life in infants with BPD (Smith et al, 2004). A recent study following 724 BPD survivors under 29 weeks' gestation confirmed BPD as a predictor of increased rates of rehospitalization for respiratory indications in the first 12 months of life (Keller et al, 2017). Data from epidemiologic studies and animal studies have raised concern for limited pulmonary recovery and persistence of altered lung structure and compromised pulmonary function into adulthood (Doyle et al, 2006; Sozo et al, 2015). A recent study in preterm infants 33 weeks' gestation or under with severe BPD reported architectural distortion of the lung (detected on CT scans) in 96% of infants and significantly impaired ventilatory function assessed by polysomnography in 74% of study patients at 6 months corrected age (van Mastrigt et al, 2017).

In a 2013 metaanalysis covering 39 studies conducted in BPD survivors born between 1964 and 2000 (Kotecha et al, 2013), forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and forced expiratory flow rate were reduced in BPD survivors compared with control teenagers or young adults. A very recent longitudinal follow-up of preterm infants under 28 weeks' gestation comparing three different periods of perinatal care and ventilatory management from 1991 to 2005 found increased rates of BPD and worsened lung function at 8 years age in the 2005 cohort compared with earlier periods—despite an increased use of less invasive ventilation over time (Doyle et al, 2017). However, significantly lower survival rates and shorter courses of mechanical ventilation were documented in the early cohort (Doyle et al, 2017), suggesting that infants at highest risk of developing BPD in this early study period did not survive long enough for BPD to develop.

Surviving infants with BPD are more likely to have asthma-like symptoms and exercise intolerance in adolescence and young adulthood (Davidson and Berkelhamer, 2017; Keller et al, 2017; Laughon et al, 2009; Malleske et al, 2018). Airflow limitation and asthma-like symptoms may demonstrate a fixed airway obstruction due to irreversible, structural airway changes and neutrophilic inflammation barely responsive to bronchodilator therapy (Joshi et al, 2013; Malleske et al, 2018). Whether this phenotype persists and has an impact on late adult pulmonary morbidity remains to be elucidated. During physical activity, children, adolescents, and adults with a history of BPD appear to be at increased risk of exercise-induced bronchoconstriction and impaired gas exchange attributed to altered lung structure or residual right ventricular dysfunction affecting cardiac output (Caskey et al, 2016; Davidson and Berkelhamer, 2017). Of note, the

TABLE 11.9 Long-Term Pulmonary Outcomes Associated With BPD

Pulmonary Outcome	Potential Mechanisms Related to BPD
Compromised pulmonary function	• Decreased FEV_1 • Decreased FVC • Decreased forced expiratory flow
Compromised pulmonary defenses	• Disrupted immunoregulatory pathways
Asthma-like symptoms	• Fixed airway obstruction and inflammation due to irreversible, structural airway changes and neutrophilic inflammation
Exercise intolerance	• Exercise-induced bronchoconstriction • Compromised gas exchange with physical activity due to long-term alterations in lung structure and/or right ventricular dysfunction
Abnormal ventilator responses	• Chemoreceptor dysfunction • Inadequate responses to hypoventilation and hypoxia
Pulmonary arterial hypertension	• Dysmorphic pulmonary vasculature • Compromised angiogenesis

FEV_1, Forced expiratory volume in 1 second; *FVC*, forced vital capacity.

EPICure study of births in the United Kingdom and the Republic of Ireland in 1995 found impaired exercise tolerance in very immature preterm infants under 25 weeks' gestation with and without BPD (Welsh et al, 2010). These findings are in accordance with other data describing increased respiratory symptoms, altered lung structure, and persistent and even declining lung function throughout childhood in survivors of preterm birth, even in the absence of BPD (Urs et al, 2018). This finding emphasizes that immaturity-related factors contribute to long-term pulmonary dysfunction with or without manifestation of BPD at 36 weeks' PMA (Malleske et al, 2018).

Impaired and dysmorphic pulmonary vascular development and compromised angiogenesis confer an increased risk of developing PHin infants with BPD (Davidson and Berkelhamer, 2017). Current studies indicate an incidence of PH of 25% to 37% in preterm infants with BPD, with rates of up to 50% in infants with severe BPD (Mourani and Abman, 2013). Infants with BPD and PH are at high risk of a PH crisis and early mortality (Berkelhamer et al, 2013). Those who survive may show resolution from manifest PH following lung growth, whereas subclinical right ventricular dysfunction often persists (Davidson and Berkelhamer, 2017). Data from animal models raise concern for an increased risk of hypoxia-induced PH in later adulthood (Davidson and Berkelhamer, 2017). There is evidence of persistent chemoreceptor dysfunction in survivors of BPD, resulting in inadequate response to hypoventilation and hypoxia (Bates et al, 2013), implying an additional risk of morbidity and mortality. BPD was described as an independent risk factor for sudden infant death syndrome by some studies, although others found no association (Davidson and Berkelhamer, 2017).

Exposure to adverse environmental factors, such as respiratory infections, tobacco, and pollution, may impair resolution of BPD and increase risks of long-term pulmonary morbidity (Davidson and Berkelhamer, 2017; McEvoy and Spindel, 2017; Morrow et al, 2017). Both epidemiologic studies and animal models have pointed toward an association of BPD and increased susceptibility to viral infections resulting from disrupted immunoregulatory pathways in affected lungs (Domm et al, 2015; O'Reilly et al, 2008). This finding seems to be additive to the increased, immaturity-related susceptibility to infection in preterm infants (Strunk et al, 2011).

Neurodevelopmental Outcome

Preterm infants, in particular those born very premature, are at increased risk of neurodevelopmental impairments and CP. Rates of moderate to severe disability have been demonstrated in about 20% of preterm infants under 28 weeks' gestation in Canada, Sweden, and France (Synnes et al, 2017; Vohr, 2014). Many determinants of BPD have been associated with delayed and impaired psychomotor development and CP, such as GA, growth restriction, systemic inflammation, and nosocomial infections (Kuban et al, 2014; Leviton et al, 2013; Murray et al, 2015; Vohr, 2014). However, several prospective studies in school-aged BPD survivors, both from the presurfactant era and more recent cohorts, identified BPD itself as an independent risk factor for lower cognitive function and higher rates of executive function limitations (Short et al, 2003; Taylor and Clark, 2016). The NICHD Neonatal Research Network reported lower head circumferences, reduced cognitive and language score and higher rates of moderate to severe CP in extremely low birth weight (ELBW) infants (birth weight $<$1000 g) born 2006 to 2007 with a history of BPD compared with matched controls (Natarajan et al, 2012).

Very recently, the Canadian Neonatal Network assessed 2340 survivors of preterm delivery less than 29 weeks' gestation at 2-year follow-up and reported a 46% incidence of neurodevelopmental impairments, but only 16.5% had significant impairments (Synnes et al, 2017). BPD was associated with neurodevelopmental impairment but not with significant neurodevelopmental impairments (Synnes et al, 2017). The recently published ELGAN study following 863 extremely preterm infants born before 28 weeks' gestation confirmed an increased risk of neurocognitive, behavioral, and social dysfunctions in 10-year-old survivors of BPD (Sriram et al, 2018). The study found children with a history of severe BPD to be more likely to have low scores on cognitive and language skills and to present with executive dysfunctions, academic achievement limitations, social skill deficits, and lower scores on assessments of health-related quality of life than children with moderate BPD or no BPD (Sriram et al, 2018).

The increased risk of impaired neurodevelopmental outcome in survivors of BPD—in particular in those with severe BPD—may be in keeping with the "multihit hypothesis" of preterm brain injury, assuming cumulative contributions of antenatal and postnatal adverse events (Korzeniewski et al, 2014; Leviton et al, 2013). Of note, a recent study following survivors of BPD until later adulthood (mean age 24.2 years) found higher rates of deficits in executive functioning relating to problem solving, awareness of behavior, and organization of environment compared with matched controls (Gough et al, 2015). Apart from neonatal strategies, early intervention strategies addressing cognitive and motor development aim to improve the neurodevelopmental outcome in preterm survivors, in particular those at highest risk of adverse outcome (Van Hus et al, 2016).

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Abstract: Bronchopulmonary dysplasia (BPD) is the most prevalent and prognostically one of the most important complications associated with prematurity. In the United States, it affects 10,000 to 15,000 newborns each year, including upwards of half of all babies born weighing less than 1000 g (Jensen and Schmidt, 2014; Stoll et al, 2015) BPD predisposes infants to a prolonged initial hospitalization and increased risk for mortality and childhood morbidity (Cotten et al, 2005; Ehrenkranz et al, 2005). Chronic impairments in respiratory and cardiovascular health, poor growth, and neurodevelopmental delay are all more common in preterm infants with than without BPD (Berkelhamer et al, 2013; Bott et al, 2006; Carraro et al, 2013; Cristea et al, 2013; Doyle et al, 2006; Ehrenkranz et al, 2005).

The term bronchopulmonary dysplasia was introduced in 1967 by Northway and colleagues to describe the clinical, radiologic, and pathologic respiratory findings that developed in preterm infants following the resolution of severe hyaline-membrane disease, or respiratory distress syndrome (RDS). Ultimately, Northway described the course of 13 infants, born at approximately 32 weeks' gestational age (GA) and 1783 +/- 434 g born with severe RDS who were exposed to mechanical ventilation and high oxygen (80%–100%) for more than 150 hours and survived (Northway et al, 1967). With improvements in perinatal and neonatal care strategies, the babies that Northway described rarely require prolonged or aggressive ventilation in the NICU. This burden has shifted to less mature infants. Today, BPD primarily—but not exclusively—affects those born at under 28 weeks' gestational age. Necessarily, the definition of BPD continues to evolve, and with it, our understanding of the epidemiology, contributing factors, preventive measures, therapeutic interventions, and associated long-term outcomes.

Keywords: bronchopulmonary dysplasia, chorioamnionitis, supplemental oxygen, mechanical ventilation, CPAP, steroids.

12

Neonatal Apnea

Ana P. Duarte Ribeiro, Elie G. Abu Jawdeh and Richard J. Martin

CASE 1

You are taking care of a 4-day-old male infant, born at 32 weeks' gestation and weighing 1750 g. He was recently transitioned from mechanical ventilation to nasal cannula. He was doing well until this morning, when you noticed a few drops in his heart rate that were accompanied by desaturations. When you spoke to the nurse, she said he had three episodes like these the day before that self-resolved, but he had already had two this morning that required some tactile stimulation.

1. What physiologic mechanisms put this infant at risk for apnea of prematurity?
2. What mode of noninvasive respiratory support could be beneficial for this patient?

COMMENTARY ON CASE 1

One of the definitions of apnea of prematurity is a cessation of breathing that lasts more than 20 seconds or a short pause in breathing that is accompanied by desaturation (Spo_2 <80%) and/or bradycardia (HR ≤80 bpm) in infants that are less than 37 weeks' gestation (Zhao et al, 2011). This is different from periodic breathing, which is also commonly seen in premature infants, and is characterized by brief and repetitive pauses lasting 5 to 10 seconds that may be accompanied by mild desaturations and bradycardia but do not require intervention.

Apnea of prematurity is a developmental disorder caused by physiologic immaturity of respiratory control and is inversely proportional to gestational age, being present in almost 100% of infants less than 29 weeks' gestational age (Eichenwald et al, 2016). There are two important physiologic mechanisms implicated in apnea of prematurity: immature respiratory control and failure to maintain upper airway patency.

The immaturity of respiratory control is manifested by impaired ventilatory responses to hypoxia and hypercapnia and an exaggerated inhibitory response to stimulation of the upper airway receptors. Hypercapnia is the major chemical stimulant of breathing and is sensed primarily centrally in the brainstem. Preterm infants have decreased response to carbon dioxide (CO_2), hence increased ventilation is not triggered until higher levels of CO_2 are achieved. Also, in preterm infants hypoxia appears to depress the response to CO_2 (Alvaro, 2018). Another physiologic mechanism related to apnea of prematurity is the CO_2 apneic threshold, which is the minimal Pco_2 required to trigger respiration. In preterm infants the apneic threshold seems to be very close to the eupneic threshold, approximately 1.5 mm Hg (Khan et al, 2005).

Chemosensitivity to hypoxia is sensed peripherally, and both enhanced and reduced peripheral chemoreceptor function of the carotid bodies may predispose to apnea, bradycardia, and desaturations in the preterm infants. The oxygen (O_2) sensitivity of the carotid body chemoreceptors *in utero* is adapted to a low Pao_2 of approximately 25 mm Hg; after birth there is a fourfold increase in Pao_2 that silences these peripheral chemoreceptors. This is followed by a gradual increase in hypoxic chemosensitivity. Exaggerated peripheral chemoreceptor stimulation may be caused by repeated hypoxic episodes and has been associated with periodic breathing. Such enhanced peripheral chemosensitivity may destabilize breathing and result in respiratory pauses secondary to hypocapnia seen after hyperventilation. Thus diminished peripheral chemosensitivity may prolong apnea while increased peripheral sensitivity may precipitate apnea (Fig. 12.1).

Stimulation of the laryngeal chemoreflexes (LCRs) by physical contact of the laryngeal mucosa can lead to apnea, bradycardia, desaturations, and hypotension, by stimulation of inhibitory airway receptors. This can be observed when deep suction is attempted during resuscitation, which can lead to bradycardia and consequently apnea. The LCR is a protective reflex inhibiting inspiration in order to avoid aspiration and will later develop into cough and swallow reflexes in more mature infants. Maintenance of functional residual capacity (FRC) is important for better oxygenation and in decreasing the degree of desaturations during brief episodes of apnea. Premature infants

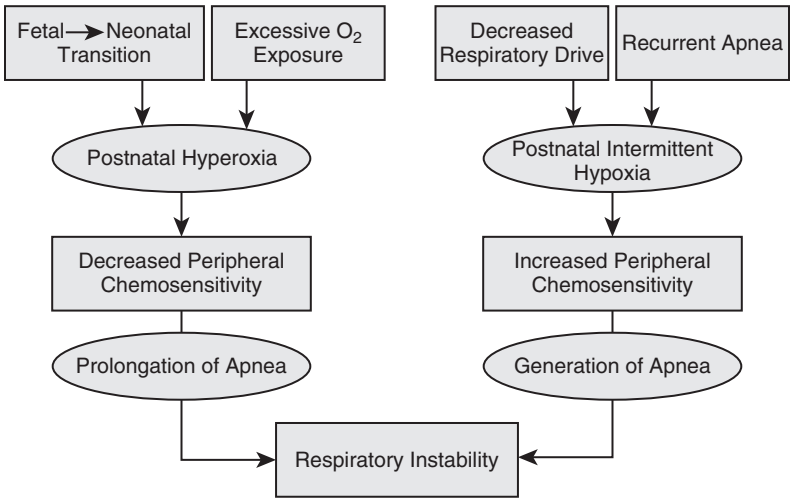

Fig. 12.1 Proposed model illustrating the effects of hyperoxia and intermittent hypoxia on carotid chemoreceptor activities and subsequent effects on respiratory instability. The fetal–neonatal transition combined with excessive O_2 exposure decreases peripheral chemosensitivity, which could prolong termination of an apneic event leading to respiratory instability. On the other hand, decreased respiratory drive and recurrent apnea result in oscillations in hypoxia during development, which may lead to a long-lasting increase in peripheral chemosensory activity (sensitization). The result could be hyperventilation and eventual apnea. (MacFarlane PM, Ribeiro AP, Martin RJ: Carotid chemoreceptor development and neonatal apnea, *Resp Physiol Neurobiol* 185:170–176, 2013).

have difficulty maintaining their FRC because of a high compliant chest wall.

Apnea of prematurity is classified into three different types: central, obstructive, and mixed, the latter being the most common. Central apnea is the total cessation of respiratory effort with a patent airway. In obstructive apnea there is respiratory effort and chest wall motion, but no nasal airflow due to an obstructed pharyngeal airway. Mixed apnea consists of respiratory efforts against an obstructed upper airway preceded or followed by central apnea.

Failure to maintain airway patency is caused by poor hypopharyngeal muscle tone leading to collapse of the airway, contribution of the inhibitory airway reflexes (LCR, mentioned earlier), and nasal obstruction and pharyngeal edema. The hypopharynx is a common site of upper airway obstruction because of its poor muscle tone, especially if the infant's neck is flexed. The larynx and trachea are more rigid structures and are less likely to contribute to the upper airway obstruction, although this can be observed when there is vocal cord dysfunction, laryngeal edema or stenosis, laryngomalacia, or tracheomalacia. The newborn trachea and larynx are relatively superiorly positioned, resulting in close proximity between the epiglottis and the soft palate, facilitating sucking. This anatomy also confers a strong preference toward nasal breathing in infants. Hence, nasal swelling can also cause obstruction of the upper airway. This can be a result of prolonged use of nasogastric tubes or nasal prongs for certain respiratory support devices, as well as constant nasal suctioning.

Continuous positive airway pressure (CPAP) may benefit this patient because most of the longer apneas observed at less than 28 weeks of age are mixed apneas, and CPAP helps by splinting the upper airway, therefore decreasing upper airway closure and/or obstruction by mechanically dilating the supraglottic airway and lowering resistance in both inspiration and expiration (Miller et al, 1990). CPAP also increases FRC, improves oxygenation, decreases respiratory frequency, and reduces the work of breathing. These effects not only help prevent apnea of prematurity but may also decrease the need for intubation.

Studies have been performed comparing noninvasive nasal intermittent positive pressure ventilation (NIPPV) and nasal CPAP (NCPAP) for management of apnea of prematurity. Some of these studies showed a reduction of apneic episodes utilizing NIPPV (Lin et al, 1998), whereas others showed CPAP superiority in preventing apnea (Pantalitschka et al, 2009). At this time there is no consensus regarding the potential benefits of one mode over the other for the treatment of apnea of prematurity.

High-flow nasal cannula (HFNC), defined as flow greater than 2 l/min, has also been used as an alternative to CPAP to treat apnea of prematurity. Its benefits are ease of administration, increased ability for parents to hold and bond with their infants, and reduction in nasal damage as shown by previous studies (Wilkinson et al, 2016). These benefits must be weighed against the uncertainty of how much pressure is being delivered by the cannula (Iyer and Mhanna, 2016).

Recent publication of a small study seems to indicate that flow-synchronized NIPPV (SNIPPV) reduces the incidence

of apneic episodes in preterm infants, <28 weeks compared with NCPAP and NIPPV (Gizzi et al, 2015). The synchronization with patients' breaths allows mechanical breaths to be delivered when the glottis is open, perhaps providing improved transmission of these breaths, ventilation, and maintenance of FRC.

Noninvasive neutrally adjusted ventilator assist (NIV-NAVA), another synchronized modality of assisted ventilation that has been used for ventilatory support of preterm infants, has shown reduction in the frequency and severity of desaturation episodes (Gibu et al, 2017). Perhaps this can be extrapolated to more oxygenation stability and fewer apneic episodes, but more studies are needed in this field.

The neonatal intensive care unit at Rainbow Babies & Children's Hospital uses NCPAP with pressures between 3 and 6 mm Hg for prevention of apnea of prematurity and low-flow nasal cannula (<2 l/min) with great success. NIPPV and HFNC (heated and humidified) are used mostly for respiratory support. The suggested utilization of HFNC in our unit is for infants older than 2 weeks of age, greater than 2 kg, and older than 34 weeks' postmenstrual age.

CASE 2

You recently admitted a female infant born at 28 weeks' gestation. She required intubation for surfactant but was immediately extubated to CPAP and did well. At 48 hours of life, she started having apneic episodes, and although she self-recovered, they increased in frequency. Upon review of her medications, you noticed she is on antibiotics for 48 hours to rule out sepsis, but you realized that she was not started on caffeine.

1. Should this infant have been started on caffeine on day of life 1?
2. What are the caffeine dosing recommendations?
3. When would be the optimal time to discontinue the caffeine?

COMMENTARY ON CASE 2

Methylxanthine therapy has been used for treatment of apnea since the mid- to late 1970s. Methylxanthines competitively inhibit adenosine receptors, resulting in stimulation of respiratory neural output. Although the basis of its beneficial effects is not completely understood, methylxanthine therapy reverses central hypoxic depression of breathing, increases minute ventilation, improves CO_2 sensitivity, enhances diaphragmatic activity, improves pharyngeal tone, and decreases periodic breathing. There may also be a dose-dependent antiinflammatory effect of caffeine.

Schmidt and colleagues published the largest randomized controlled trial of caffeine therapy for apnea of prematurity (CAP) demonstrating both respiratory and neurodevelopmental benefits for caffeine- versus placebo-treated infants (Schmidt et al, 2006; Schmidt et al, 2007). The risk of BPD was significantly reduced in the caffeine group (OR 0.63, 95% CI 0.52–0.76). At 18 to 21 months follow-up, caffeine-treated infants had less cognitive impairment (0.81, 95% CI 0.66–0.99) and decreased incidence of cerebral palsy (0.58, 95% CI 0.39–0.87). Although the 5-year follow-up suggested attenuation of these cognitive and motor benefits, follow-up at school age has revealed benefit of caffeine for developmental coordination disorder and decrease in motor impairment (Doyle et al, 2014; Schmidt et al, 2017).

Traditional indications for methylxanthine therapy initiation were treatment of apnea and facilitation of extubation. However, prophylactic use for infants at risk for apnea is now widespread. Increasing efforts to avoid intubation and mechanical ventilation have contributed to the overall shift from selective therapeutic toward widespread prophylactic use of methylxanthine therapy for apnea of prematurity. The infant in this case would be a candidate for this therapy, but data to support the practice of prophylactic methylxanthine use in preterm infants is limited (Abu-Shaweesh and Martin, 2017).

When to Start Caffeine

See Table 12.1.

Data supporting the early use of caffeine are based on retrospective analyses, such as a large Canadian cohort that showed an association between caffeine given in the first 2 days (vs later dosing) and decreased duration of invasive

TABLE 12.1 Neonatal Caffeine Therapy: Unresolved Issues

	Pro	Con
Early onset	• Improves various morbidities	• Available data are largely based on associations rather than randomized trials • How early is too early?
Prolongation of therapy	• Decreases duration of intermittent hypoxic episodes • May shorten hospitalization (if discharged on caffeine)	• May provide exposure to unnecessary medication • May prolong hospitalization (if discharged off caffeine)
Higher doses	• More strongly enhance respiratory neural output	• Adenosine receptor subtype inhibition of inflammation is variable and dose dependent, raising safety concerns • Preliminary report of cerebellar injury • Likely need for postnatal dose adjustments

and noninvasive ventilatory support (Lodha et al, 2015). Unfortunately, early caffeine prophylaxis may not significantly decrease the risk of CPAP failure and the need for invasive ventilation (Patel et al, 2017). Most recently, early caffeine also has not decreased the age of first successful extubation in ventilated preterm infants (Amaro et al, 2018).

When to Discontinue Caffeine

Widespread clinical practice is to discontinue caffeine therapy when episodes of apnea, bradycardia and desaturation are resolving, typically at around 34 weeks' postmenstrual age and corresponding to approximately 2 weeks before discharge. Extended caffeine administration does decrease the incidence of intermittent hypoxic episodes, and the potential benefit of such an approach is under investigation (Dobson et al, 2017). A related issue is whether discharge on caffeine may shorten the duration of hospitalization. In contrast, prolonged caffeine use may delay discharge if caffeine is discontinued before discharge.

What Constitutes Optimal Dosing?

This is probably the most controversial issue. Current practice constitutes a loading dose of 20 mg/kg, followed by a 5 to 10 mg/kg/day maintenance of caffeine citrate. Higher doses have been advocated but not subject to appropriately powered clinical trials, especially safety. The ability of caffeine to inhibit adenosine receptor subtypes may be dose dependent, and unanticipated adverse effects (e.g., cerebellar injury) are a possibility (McPherson et al, 2015). Recent data provide a compelling case for adjusting maintenance doses, as metabolism of caffeine increases with advancing postnatal age (Koch et al, 2017).

CASE 3

You have been taking care of a female infant since she was born at 29 weeks' gestation. She is now 30 days old, in room air, and already at full feeds orally. Today you decide to discontinue her caffeine treatment because of decreased apneic episodes over the past 7 days. When you went into her room this morning the nurse was already at the bedside because of several apneic episodes. She reported that the last one required bag-mask ventilation after tactile stimulation failed. A sepsis workup was performed and antibiotic therapy begun.

1. What are the mechanisms that lead sepsis to produce apnea?

COMMENTARY ON CASE 3

Sepsis, both viral and bacterial, frequently manifests as changes in breathing pattern and apneic episodes in preterm infants. A recent study analyzed the pattern of apneic episodes in 1211 premature infants younger than 35 weeks, showing that an acute increase of apnea, bradycardia, and desaturations can precede the diagnosis of an acute illness similar to sepsis or necrotizing enterocolitis (NEC) in the prior 24 hours before diagnosis (Fairchild et al, 2016).

So how does infection manifest as apnea in preterm infants? A local release of inflammatory mediators was suggested as a mechanism of apnea related to respiratory syncytial virus (RSV) infection, implicating IL-1β (interleukin 1 beta) as positively correlated with the severity of the disease (Lindgren, 1999). Another study published in 2007 suggested that IL-1β adversely affects the respiratory control via prostaglandin 2 (PGE_2) pathway (Hofstetter et al, 2007). During systemic inflammation or infection, IL-1β is released into the circulation and binds to its receptor (IL-1R) located on the endothelial cells of the blood–brain barrier (BBB). This activation induces synthesis of prostaglandin H_2 (PGH_2), via Cox-2 and subsequently the synthesis of PGE_2, which is released into the brain and binds its receptor (EP3R), resulting in depression of central respiration-related neurons and breathing, leading to apnea.

Corroborating the previously cited studies, in 2011 Balan and colleagues showed that injection of lipopolysaccharides (LPS) in the airway of rat pups creates an inflammatory response measured by increased expression of mRNA (messenger RNA) for IL-1β in the brainstem. This is associated with a decreased respiratory response to hypoxia (Balan et al, 2011). This suggests that cytokine-mediated mechanisms at the brainstem initiated by systemic sepsis may be implicated in apnea of prematurity and other forms of respiratory dysregulation.

In the same year, a multicenter randomized trial reported that abnormalities in heart rate patterns may serve as precursor and predictor of ensuing sepsis in the neonate (Moorman et al, 2011). This study showed a 22% relative reduction in mortality for patients randomized to have their heart rate index displayed and decreased mortality by 40% within 30 days of septicemia in blood culture–positive sepsis in these infants. If confirmed in subsequent studies, careful monitoring of cardiorespiratory patterns could be a useful contributor to determining the need for sepsis workup.

CASE 4

You are caring for a 23-day-old female infant born at 28 weeks' gestation. She is on full enteral feeds and has been stable on CPAP support for 10 days. She has increased episodes of oxygen desaturation (intermittent hypoxemia) events, often preceded by respiratory pauses and apnea. The nurse reports that the patient often requires tactile stimulation or bag-mask ventilation. Laboratory values are normal apart from a hematocrit of 24%.

1. Does anemia contribute to increased apnea, bradycardia, and intermittent hypoxemia events?
2. Would this infant's episodes benefit from red blood cell transfusion?

COMMENTARY ON CASE 4

Preterm infants with anemia are at increased risk for apnea, bradycardia, and intermittent hypoxemic events. Bell et al showed increased apneic episodes in premature infants with

lower hematocrit levels (Bell et al, 2005). Zagol et al showed that the lower the hematocrit level, the higher the probability of apnea associated with bradycardia and oxygen desaturation events (Zagol et al, 2012). In turn, red blood cell transfusions improve such events in preterm infants.

Two proposed mechanisms may explain the basis of this relationship. The first suggests that anemia decreases oxygen delivery to respiratory control centers leading to hypoxic ventilatory depression (Joshi et al, 1987; Cross and Oppe, 1952). The second underlying mechanism suggests that decrease in oxygen stores results in instability of oxygenation in the presence of apnea, leading to intermittent hypoxemic events. This is consistent with a recent model analysis showing that the rate of arterial oxygen desaturation during apnea increased with lower hemoglobin levels (Sands et al, 2009). Hence, red blood cell transfusions decrease apnea and associated bradycardia and oxygen desaturation events due to improving both oxygen delivery to the respiratory network and oxygen stores. Oxygen delivery is improved—likely due to an increase in partial pressure of oxygen from shifting the oxygen dissociation curve to the right—because of an increase in proportion of adult to fetal hemoglobin ratio after red blood cell transfusion. Oxygen stores are increased because of a rise in hematocrit. The bolus effect from volume expansion during red blood cell transfusion may play a role, but the effect is likely transient (Bifano et al, 1992).

There is ample evidence that red blood cell transfusions improve apnea frequency (Bell et al, 2005) and associated bradycardia and oxygen desaturation episodes (Zagol et al, 2012; Joshi et al, 1987; DeMaio et al, 1989; Sasidharan and Heimler, 1992; Seidel et al, 2013). However, the exact thresholds and indications for red blood cell transfusion in preterm infants remain controversial (Crowley and Kirpalani, 2010). Hematocrit levels are often the main indication for transfusion in most NICUs.

In randomized trials both Kirpalani et al and Bell et al compared maintaining a high (liberal) hematocrit level versus a lower (restrictive) hematocrit in premature infants. Bell showed possible benefit for apnea and central nervous system lesions in the liberal group (Bell et al, 2005), whereas Kirpalani showed no evidence of benefit between groups (Kirpalani et al, 2006). However, hematocrit level should not be the sole indication for red blood cell transfusion. Other factors to be considered include postnatal age, degree of respiratory support, the amount of supplemental oxygen, and intermittent hypoxemia events. Recent evidence suggests that the beneficial effects of red blood cell transfusion may vary by postnatal age (Abu Jawdeh et al, 2014). Patients on respiratory support with an increased oxygen requirement who are experiencing intermittent hypoxemic events may warrant red blood cell transfusions at a higher hematocrit threshold (Kirpalani et al, 2006; Ibonia et al, 2018). In other words, red blood cell transfusions should be strongly considered in infants with hematocrit levels of 24% or less, especially if they are receiving respiratory support (e.g., CPAP or supplemental oxygen), and who have frequent and/or severe apnea and desaturation events, as in this case (Martin, 2019).

The beneficial effect of red blood cell transfusion on apnea should be weighed against potential risks such as transmitted infections (Kaplan, 2011) and possible transfusion related adverse reactions (Sanchez and Toy, 2005; Christensen and Ilstrup, 2013). Randomized trials are ongoing to better define indications and risks in preterm infants.

CASE 5

A former 35-week-gestation male infant, now 40 weeks' postmenstrual age, was recently discharged to home. His mother found him 1 hour after a feed coughing and choking with formula in the nose and mouth. The mother reports the infant was apneic and the face turned blue. She picked him up, blew in his face, rubbed his back, gave rescue breaths, and called EMS. When EMS arrived, he appeared well. The patient was then admitted for 24-hour hospitalization.

1. Did gastroesophageal reflux (GER) precipitate this episode?
2. What workup is appropriate for this infant?
3. What are therapeutic options?

COMMENTARY ON CASE 5

Bidirectional Relationship Between GER and Apnea

This preterm infant presents a common dilemma that typically requires a short stay readmission. The approach to his management may cross multiple subspecialty disciplines, notably neonatology, pediatric pulmonology, and gastroenterology. From the infant's history, it is usually impossible to determine whether apnea or reflux/regurgitation was the precipitating event. Their interrelationship is summarized in Fig. 12.2.

The most important mechanism of gastroesophageal reflux (GER) in preterm infants is transient relaxation of the lower esophageal sphincter (LES) (Martin and Hibbs, 2019). The LES is made up of intrinsic smooth muscle of the esophagus and skeletal muscle of the crural diaphragm. Transient LES relaxation is defined as an abrupt decrease in LES pressure below the intragastric pressure. Refluxate may be acidic or nonacidic, the latter more likely soon after a feed. The laryngopharyngeal region is exquisitely sensitive to afferent stimuli, which precipitate a protective response for the airway

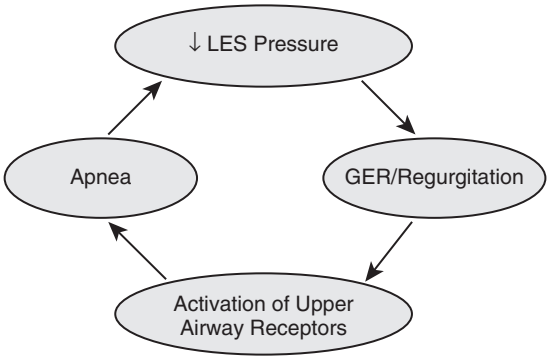

Fig. 12.2 Potential perpetuating cycle of apnea and GER.

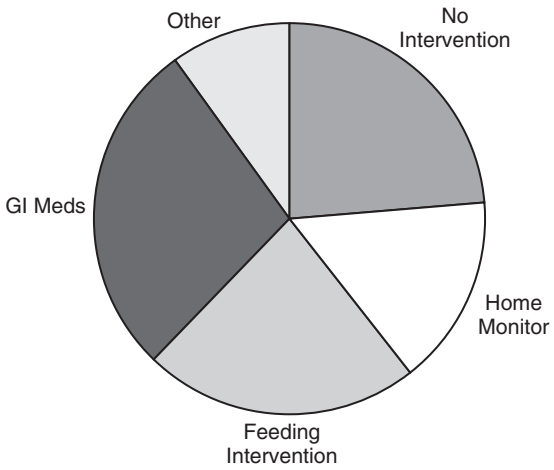

Fig. 12.3 Discharge disposition for a cohort of 100 Rainbow Babies & Children's Hospital admissions (2008–2010) with ALTE.

of preterm infants, comprising laryngospasm, apnea, and bradycardia. Therefore, if refluxate reaches as high as this region, an apneic response might result. Data suggest that nonacid—rather than acid reflux—is more likely to precipitate apnea (Corvaglia et al, 2011). Although this is theoretically possible, our data indicate that only about 3% of cardiorespiratory events (comprising apnea, bradycardia, and desaturation) are preceded by GER (Di Fiore et al, 2010).

Another possibility (see Fig. 12.2) is that apnea may be the initiating event and predispose to GER. Data from animal models and human infants have demonstrated that inhibition of respiratory neural output may be followed by a decrease in lower esophageal sphincter tone (Kiatchoosakun et al, 2002; Omari, 2009). Therefore in the clinical scenario presented earlier, it is possible that spontaneous apnea was the initiating event and a subsequent regurgitation and choking aggravated the situation.

Workup

Infants such as this are typically hospitalized at least overnight to allay anxiety and perform a minimal diagnostic evaluation. Infants with a history of multiple apparent life-threatening events (ALTE), now referred to as BRUE (brief, resolved, unexplained event), or those younger than 30 days of age are most likely to benefit from hospitalization (Claudius and Keens, 2007). Unfortunately, our ability to identify a specific etiology for such an event is limited, and there is no clear consensus on whether such an infant should receive an extensive workup. After careful history, which includes elimination of a likely seizure disorder and a thorough feeding history, we perform a simultaneous bedside evaluation for reflux and apnea.

Diagnostic evaluation for reflux comprises a probe to measure both esophageal pH and nonacidic boluses via multiple intraluminal impedance (MII). Esophageal pH measurement to detect reflux of acidic gastric contents in the distal esophagus is the most widely employed diagnostic test for GER in preterm infants. The test is performed by the transnasal passage of a microelectrode containing a pH sensor into the lower third of the esophagus. Various scoring techniques have been used to interpret the results of pH probe studies and generally include the number of acid reflux episodes, average duration of the episodes, and overall proportion of time with a pH less than 4. The reflux index (RI), which consists of the sum of the periods in which pH is less than 4 as a percent of recording time, is a widely used scoring system. It is important to note that acid may not be detected postprandially in infants because milk will buffer acid contained in the refluxate, leading to underestimation of GER.

MII uses an esophageal catheter designed to measure impedance from multiple intraluminal recording sensors. The method allows detection of GER based on changes in electrical resistance to electrical current flow between two electrodes when a liquid and/or gas bolus moves between them and can differentiate antegrade swallows from retrograde GER. The obvious advantage of MII is the ability to assess postprandial reflux, which may be masked by milk neutralizing the acid content of the refluxant when only a pH probe is used. This was illustrated in one study of preterm infants (gestational age of 23 to 37 weeks, tested at a postconceptional age between 34 to 48 weeks) that showed more episodes of reflux and less acidic reflux contents after versus before a feed (Slocum, 2009). One reservation associated with the use of MII in preterm infants remains—namely the lack of validated normative standards in neonates.

Concurrently we assess the frequency of cardiorespiratory events and attempt to relate them temporally to evidence of GER. Given the likelihood of mixed or obstructive apnea events, respiratory inductance plethysmography (RIP) provides a useful alternative to standard impedance monitoring. RIP combines a band over the rib cage and abdomen and, after appropriate calibration, provides a semiquantitative measure of airflow and tidal volume. In combination with heart rate and oxygen saturation, this provides a noninvasive assessment of cardiorespiratory events. During such an overnight study, it is possible to clearly characterize any events, although in the case of BRUE admissions, a recurrence is unlikely.

Therapeutic Options

After exclusion of any specific precipitating event by clinical history, the focus at discharge is on minimizing the risk of recurrence and protecting the infant in the face of a future episode. In our experience at Rainbow Babies & Children's Hospital, approximately 25% of these infants will be discharged without any therapeutic intervention, whereas approximately 20% will be discharged for a short period of cardiorespiratory house monitoring (Fig. 12.3). In the absence of clear diagnostic and therapeutic guidelines for these infants, these data will vary widely between centers.

As seen in Fig. 12.3, a feeding intervention such as modifying the content or pacing of feeds occurred in 23% of our ALTE infants, and another 28% were discharged on

medications for GER. A recent study reported that 47% of ALTE admissions were discharged with a diagnosis of gastroesophageal reflux disease (GERD) (Doshi et al, 2012). There is wide variation among neonatologists and pediatric specialists regarding beliefs about GERD in premature infants with pulmonologists more likely than neonatologists to report respiratory symptoms (e.g., apnea) as caused by GERD (Golski et al, 2010; Abu Jawdeh and Martin, 2013).

If GER is suspected, nonpharmacologic approaches, such as dietary change (e.g., thickened feeds) should be encouraged. Pharmacologic therapy that has been used in preterm infants includes histamine H2 receptor antagonists, proton pump inhibitors, and prokinetic agents. They have not been definitively shown to be effective in improving symptoms and may be associated with adverse sequelae; therefore they should be used sparingly and only continued in the face of documented clinical benefit (Martin and Hibbs, 2019).

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Abstract: Apnea of prematurity is one of the most common conditions in the neonatal intensive care unit (NICU). In the last three decades, our understanding of respiratory control in premature infants and its underlying neuroanatomical pathways and physiologic mechanisms has greatly improved. Some management aspects of apnea in premature infants remain debatable, with variation across centers and neonatologists. Through clinical cases, this chapter reviews the physiologic mechanisms causing neonatal apnea and the different management options while caring for patients with apnea of prematurity.

Keyword: Respiratory control, caffeine and gastroesophageal reflux.

13

Neonatal Sepsis

Thomas A. Hooven and Tara M. Randis

INTRODUCTION

Sepsis is the illness resulting from systemic bacterial or (less commonly) fungal infection. It is an ever-present threat in the NICU, accounting for approximately 10% of infant deaths under 1 month of age worldwide (GBD 2015 Mortality and Causes of Death Collaborators, 2016) and contributing significantly to long-term neurodevelopmental impairments among NICU survivors.

The clinical manifestations of neonatal sepsis are variable. The onset can be abrupt or insidious, and many of the most common signs and laboratory findings associated with neonatal sepsis are nonspecific. Although certain neonatal populations—such as very low birth weight (VLBW) and chronically instrumented infants—are at increased risk, sepsis can also strike unexpectedly in low-risk patients. Vigilance and a high index of suspicion are key to diagnosing and treating sepsis before the infection spirals out of control.

Neonatal sepsis can be categorized as early onset or late onset, with some sources using 3 days of age as the cutoff for early onset sepsis (EOS) and others using 7 days (the 3-day definition is more common). The two categories exist because early and late-onset sepsis (LOS) result from different modes of acquisition, with EOS most often caused by vertical microbial transmission during the perinatal period and LOS most often from nosocomial or other environmental sources.

The distinct modes of acquisition are reflected in differences in the organisms recovered from EOS and LOS populations, with corresponding implications for appropriate initial empiric antibiotic therapy for the two groups. A precise demarcation between EOS and LOS is therefore less important than the concept that during the first week of life a shift in the pathogenesis and pathogen profile of sepsis occurs.

This chapter addresses EOS and LOS in separate sections. Each begins with a review of pathogenesis, epidemiology, and microbiology before presenting a series of instructive cases drawn from actual patient histories.

EARLY ONSET SEPSIS

Pathogenesis

During fetal life, the innate immune system develops within the highly protected confines of the amniotic sac, defended from microbes by multiple maternal anatomic and immunologic barriers. Additionally, the fetal skin surface secretes a mixture of antimicrobial peptides into the surrounding amniotic fluid, further bolstering protection from infection (Tollin et al, 2005). Although recent evidence points to the presence of a limited placental microbiome (Aagaard et al, 2014)—whose role in fetal immunity is still unclear—there is no doubt that the perinatal period involves sudden exposure to a vast microbiological ecosystem.

The neonate has numerous adaptive responses to this abrupt transition from a nearly sterile environment. Bacterial colonization of the skin, which begins during passage through the birth canal (or immediately upon delivery for babies born by cesarean section without labor), triggers interleukin-1 (IL-1) and IL-6 release from resident macrophages at the bases of hair follicles. (This local cytokine release is clinically manifest as the benign rash of erythema toxicum neonatorum.) IL-1 and IL-6 bind hepatocyte receptors, triggering systemic release of nonspecific acute phase reactants that protect against unchecked bacteremia (Levy, 2007). At the same time, early intestinal bacterial colonization activates antiinflammatory signaling networks that promote establishment of a stable microbiome (Rakoff-Nahoum et al, 2004).

However, early exposure to a pathogenic bacterial species—often expressing cytotoxic and immune evasion virulence factors—can overwhelm the orderly process of immune adaptation to a commensal microbiome. In the absence of a robust adaptive immune response, which does not develop until later in toddlerhood, the neonate has few defenses against an expanding bloodborne bacterial population.

EOS caused by group B *Streptococcus* (GBS) exemplifies this chain of events. Perinatal mucosal exposure to maternal GBS colonization—either during passage through the birth canal or in swallowed breastmilk—allows GBS access to a

microenvironment relatively free of competing microbiota (Edwards and Nizet, 1997). As the GBS population expands, expression of the cytotoxin β-hemolysin/cytolysin permits traversal of epithelial surfaces (Whidbey et al, 2015), allowing bloodstream invasion where toxin expression is further amplified (Hooven et al, 2017).

Epidemiology

Active, population-based surveillance in the United States by the Centers for Disease Control and Prevention has revealed a stable incidence of EOS over the past 10 years, affecting 0.77 to 0.79 per 1000 live births (Schrag et al, 2016; Weston et al, 2011). Smaller studies during the same period have shown slightly higher incidence, documenting EOS rates of approximately 1 case per 1000 live births (Bizzarro et al, 2015; Stoll, 2011).

Table 13.1 lists evidence-based risk factors for EOS. The single greatest risk factor is prematurity. EOS rates are inversely proportional to gestational age, with premature infants younger than 34 weeks' gestation more than 10 times more likely to develop EOS than term infants (Schrag et al, 2016). Extremely premature, extremely low birth weight babies can have EOS rates close to 100 times greater than term neonates (Bizzarro et al, 2015).

Infectious chorioamnionitis, which is usually the result of invasion of the amnioplacental unit by vaginal microbes, can result in fetal infection and induction of labor, culminating in delivery of an acutely ill newborn (Kim et al, 2015). Historically, chorioamnionitis has been considered a key risk factor for EOS, with multiple prevention guidelines recommending empiric antibiotic therapy for all affected neonates, regardless of their clinical status (Committee on Infectious Diseases et al, 2011; National Collaborating Centre for Women's and Children's Health, 2012; Polin, 2012).

The American College of Obstetrics and Gynecology (ACOG) recently issued updated recommendations for diagnosis and management of suspected intraamniotic infection (Committee on Obstetric Practice, 2017). When chorioamnionitis is diagnosed based on multiple clinical criteria (including maternal fever, leukocytosis, tachycardia, and purulent amniotic fluid), there is good evidence that it is a significant risk factor for EOS (Wortham et al, 2016). However, recent work has called into question whether the risk extends to newborns without clinical signs of illness (Benitz et al, 2015; Hooven et al, 2018) and the consistency with which strict clinical criteria are used to diagnose chorioamnionitis. A large nationwide survey of obstetricians revealed that chorioamnionitis is often diagnosed based on fever alone (Greenberg et al, 2012), which significantly lowers its predictive power for EOS.

Recent literature has therefore suggested alternative, less stringent approaches to managing newborns following a diagnosis of chorioamnionitis (Jan et al, 2017). Several studies have demonstrated that asymptomatic late-preterm and term infants born to mothers with chorioamnionitis can be safely managed with serial examinations rather than reflexive empiric antibiotic therapy (Jan et al, 2017; Berardi et al, 2016; Berardi et al, 2015).

TABLE 13.1 Major Risk Factors for Early Onset Sepsis

Prematurity
Low birth weight
Prolonged rupture of membranes
Preterm rupture of membranes
Chorioamnionitis
5-minute Apgar score <7
Maternal GBS colonization (with no or inadequate intrapartum antibiotic prophylaxis)
Black maternal race
Maternal age ≤20 years
Multiple digital vaginal examinations
Membrane stripping
Internal fetal monitor

Microbiology

GBS and *Escherichia coli* are the most commonly isolated pathogens in EOS, accounting for approximately 75% of cases (Stoll et al, 2011). GBS is the most frequent isolate, but *E. coli* EOS is more common among VLBW infants (Stoll, 2016) and may be more common overall than GBS in certain geographic regions or single institutions (Schrag et al, 2016).

From 2005 to 2014, *Streptococcus viridans* was the next most common isolate in the CDC surveillance network (Schrag et al, 2016). The remainder of EOS is caused by a variety of mostly enteric bacteria, including *Klebsiella* spp., *Enterococcus* spp., *Haemophilus* spp., *Enterobacter* spp., and *Listeria monocytogenes.*

CASE 1

A newborn girl, born at 35⁶⁄₇ weeks' gestation, is brought to the transitional nursery at 1 hour of life after the postpartum nurse expressed concerns about her breathing. The mother is a 27-year-old primigravid woman with no significant past medical history. Her antepartum GBS screen was negative, and she received no intrapartum antibiotics. A maximum maternal temperature of 100.1°C was recorded in the setting of epidural anesthesia administration. Vaginal delivery occurred 16 hours after rupture of membranes, and the Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. The baby is pink and active without respiratory support. Her vital signs are normal except for a respiratory rate of 85 breaths per minute. The physical examination is significant for mild nasal flaring, intercostal and subcostal retractions, good bilateral air entry, and expiratory grunting. The Spo_2 is 98%.

Exercise 1

Question

How should this baby be managed?

A. Because she is still undergoing the physiologic transition to the extrauterine environment, her mild respiratory

distress is normal. Return her to the postpartum unit for routine nursery care.

B. She should be closely observed because her respiratory signs place her at increased risk of EOS. In the absence of improvement over the next several hours, she should undergo laboratory and radiographic evaluation for sepsis.

C. Her prematurity and respiratory distress, combined with maternal signs of chorioamnionitis, place her at high risk of EOS. She should have a blood culture drawn and receive empiric antibiotic therapy.

Answer

Correct answer: **B**

Sepsis evaluation and treatment decisions are usually straightforward for asymptomatic newborns with no significant EOS risk factors, who can be managed in the newborn nursery, and acutely ill newborns with clear sepsis risk factors, who must receive empiric antibiotics while EOS is ruled out.

The more challenging cases are those—like the example—where mild symptoms and a constellation of modest risk factors don't point to an obvious course of action.

A major advance in the management of possible EOS was the introduction of an online, publicly available sepsis risk calculator, based on a large clinical data set and Bayesian analysis of maternal risk factors (Puopolo et al, 2011). A subsequent refinement of the sepsis calculator included stratified risk assignments based on the newborn's clinical status, which could be characterized as well appearing, equivocal, or clinically ill (Escobar et al, 2014).

The benefit of the sepsis calculator is that it distills multiple variables—both categorical and continuous risk factors—into a single probability that the newborn is infected. Entering features of the example case into the sepsis calculator and assigning the baby to the "equivocal" clinical status reveals a risk of 9.7/1000 live births. The sepsis calculator also provides management recommendations, which are based on risk cutoffs for each clinical illness category (Escobar et al, 2014).

It is important to note that these online management recommendations are made in the absence of certain key information, such as the baby's age and overall clinical trajectory. Therefore although the calculator recommendation for the example case is to administer empiric antibiotics, the clinician may make a different decision based on additional evidence. In this instance the late-preterm baby is still within a timeframe—approximately 6 hours after birth—when it is reasonable to expect some mild respiratory distress as part of the physiologic transition. Continued observation may show that her respiratory distress is improving, which would argue strongly against sepsis; a newborn clinical examination that improves without antibiotic administration is incompatible with EOS, which is a progressive condition. If there were any clinical deterioration—or no clear improvement—within the 6-hour window, it would be imperative to draw a blood culture and start empiric antibiotics without further delay.

CASE 2

You are called to the newborn nursery to assess a 1-day-old female infant born at 36 weeks' gestation following prolonged rupture of the membranes (20 hours). There were no signs of chorioamnionitis. Although she was stable without respiratory support and feeding well throughout the day of birth, today she has been taking smaller volumes and has had intermittent tachypnea. The nurse who called you explains that she just observed an apneic episode with color change that required stimulation. The baby is pink and responsive to examination but has a respiratory rate of 70 breaths per minute and somewhat cool extremities. You decide to admit to the NICU for a sepsis evaluation, including sepsis screening laboratories.

Exercise 2

Question

Which of the following statement combinations is correct?

A.
- An immature:total (I:T) neutrophil ratio below 0.25 has a better negative predictive value than a total leukocyte count under 25,000 μL^{-1}.
- Procalcitonin peaks earlier than C-reactive protein (CRP) during infection.
- To maximize diagnostic yield, a blood culture should be greater than 1 mL.

B.
- The sensitivity of an elevated procalcitonin is greater than its specificity.
- Maternal antibiotic therapy increases the time to blood culture positivity among septic newborns.
- Up to 50% of VLBW infants (<1500 g) will have neutropenia (absolute neutrophil count (ANC) <1000 polymorphonuclear leukocytes (PMNs)/μL) during the first week of life.

C.
- CRP reaches its peak value 6 to 10 hours after infection begins.
- Newborns with signs of early onset sepsis should receive a urine culture.
- The ideal blood culture volume is greater than 0.25 mL.

Answer

Correct answer: **A**

The selection and interpretation of laboratory values is key to evaluating for EOS; it is important to understand the details of when and what various studies can reveal.

The complete blood count (CBC) can suggest but never clinch a diagnosis of EOS. Newborns' leukocyte counts are highly variable from infant to infant (much more so than older children), and the first week of a baby's life can feature significant swings in the leukocyte count and the neutrophil subset, even in the absence of infection (Fig. 13.1) (Schmutz et al, 2008). Although still relatively nonspecific, an I:T ratio greater than 0.25 is a better predictor of sepsis than a modestly elevated leukocyte count (20,000–40,000 μL^{-1}). Conversely, an I:T ratio under 0.25 (term) or 0.22 (preterm) is useful for excluding the diagnosis of EOS, with a negative predictive value of around 98% (Blommendahl et al, 2009).

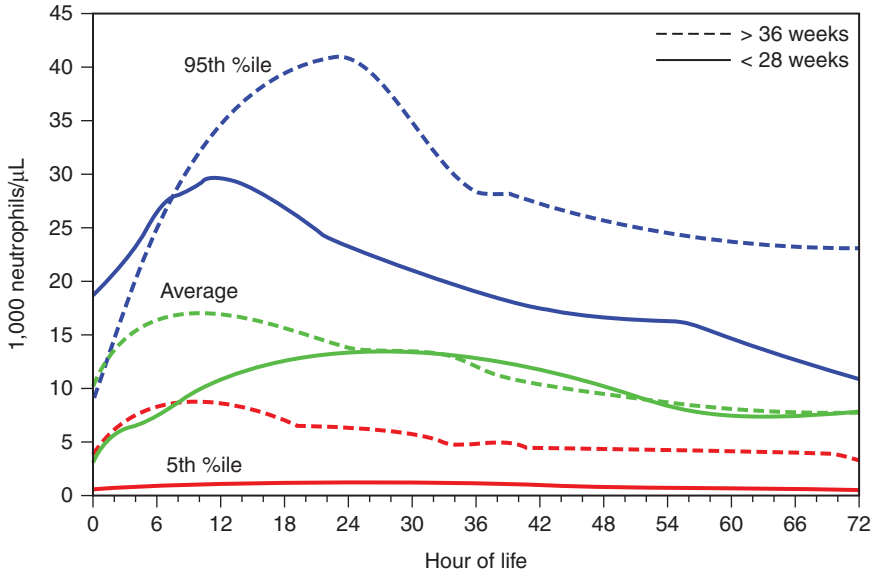

Fig. 13.1

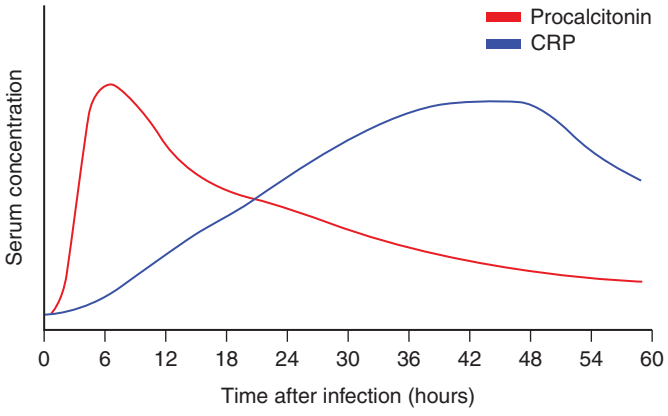

Fig. 13.2

Although around 2% of uninfected term babies will have neutropenia (often in the setting of maternal preeclampsia or other placental insufficiency), low neutrophil counts are very common in VLBW newborns, with up to 50% affected during the first week of life—many more than actually suffer from infection (Del Vecchio and Christensen, 2012).

CRP and procalcitonin are two commonly measured acute-phase reactants, whose elevation is a nonspecific indicator of an inflammatory state (i.e., the sensitivity of an elevated measurement is higher than the specificity for infection). Procalcitonin serum concentrations reach peak values within 6 to 8 hours of infection onset, while CRP continues to rise over 48 hours (Fig. 13.2) (Monneret et al, 1997). The negative predictive value of either a single normal procalcitonin measurement, performed 6 to 8 hours after birth, or two normal CRP values, performed in 8-hour intervals after delivery, is 94% to 99%, meaning that either test can reliably be used to rule out EOS (Chiesa et al, 1998; Benitz et al, 1998).

The ideal blood culture volume is greater than 1 mL, which maximizes the probability of detecting low-concentration bacteremia (Schelonka et al, 1996). There is no high-quality evidence to suggest that maternal antibiotic therapy (to treat chorioamnionitis, for instance) increases time to blood culture positivity among infected newborns (Sarkar et al, 2015).

In the absence of major congenital urogenital abnormalities that might result in early fecal contamination of bladder contents, urinary tract infection is not a cause of EOS. Therefore a urine culture does not need to be included in the standard EOS laboratory evaluation (Polin et al, 2012).

CASE 3

You have admitted a former 31-week male, born to a 25-year old gravida 3, para 2 woman who developed a fever to 102.1°F during delivery, accompanied by uterine tenderness and late decelerations prompting urgent caesarian section. After administration of positive-pressure ventilation for 30 seconds following secondary apnea, the infant cried vigorously and was initially placed on nasal continuous positive airway pressure, with an Fio_2 requirement of 30% to maintain oxygen saturations in the mid 90s. A rule-out sepsis was initiated for strong concern of maternal chorioamnionitis. The baby is now 8 hours old and has received one dose of ampicillin and gentamicin. The infant's condition has deteriorated. His Fio_2 requirement is now 80%, and you are preparing to intubate. Furthermore, his mean arterial blood pressure has fallen from the 40s to the high 20s, prompting a normal saline bolus and initiation of a dopamine drip. His tone is decreased compared with 2 hours ago.

Exercise 3

Question

What else needs to be done?

A. A surface swab from the outer ear should be sent to the laboratory to test for colonization with a pathogenic organism.
B. Blood should be ordered for a double-volume exchange transfusion.

C. The empiric antibiotics should be changed to ampicillin and cefotaxime.
D. A head ultrasound should be performed.

Answer

Correct answer: **C**

Although ampicillin and an aminoglycoside, such as gentamicin, are appropriate empiric coverage for a newborn with EOS risk factors or mild symptoms, one must remember the limitations of this combination, which covers only about 94% of EOS pathogens (Muller-Pebody et al, 2011).

Ampicillin and cefotaxime, when provided at meningitis dosages (150 mg/kg per dose for ampicillin and 75 mg/kg per dose for cefotaxime, both given every 12 hours) will reliably cover all common causes of EOS and ensure excellent penetration into the central nervous system (Muller-Pebody et al, 2011). This is appropriate in a patient who is not responding as expected to initial therapy, such as the baby in the case. However, this combination should not be used first line, due to potential later complications from multidrug resistant organism infections (Kang et al, 2005).

Although exchange transfusion has been described as a treatment for advanced sepsis, it is not evidence based, and additional stabilization and optimization steps are available for the patient in this case history (Pugni et al, 2016). Ear swabs have not been shown to provide clinically useful information and should not be performed (Polin et al, 2012). There is no indication for an urgent head ultrasound in the case, although given this preterm infant's instability, it would be appropriate to obtain one during the first week of life.

LATE-ONSET SEPSIS

Epidemiology

LOS is most frequently defined as infection occurring greater than 72 hours after birth (Dong and Speer, 2015). The incidence of LOS is inversely correlated with gestational age. Recent studies report incidences of LOS ranging from less than 0.6% to 14% of all admitted newborns (Vergnano et al, 2011; van den Hoogen et al, 2010; Shim et al, 2011; Morioka et al, 2012). Infants born extremely preterm (<29 weeks of gestation) are at highest risk, with a reported incidence of 34% (Greenberg et al, 2017). Risk factors for LOS include prematurity, the long-term use of invasive interventions (such as mechanical ventilation and intravascular catheterization), delayed enteral feeding, the need for surgery, and underlying respiratory and cardiovascular diseases (Dong and Speer, 2015).

Microbiology

The pathogens most commonly isolated from infants with LOS are shown in Table 13.2. Coagulase negative staphylococci (CONS) are responsible for the majority of cases, particularly in preterm infants. Recent studies suggest a shifting epidemiology in the pathogens responsible for LOS, including a decreased incidence of fungal sepsis and an increase in cases due to *Staphylococcus* aureus (van den Hoogen et al, 2010; Greenberg et al, 2017). Most cases of LOS are considered healthcare-associated infections (such as central-line associated bloodstream infections [CLABSI] or ventilator associated pneumonia [VAP]) because they occur while the infants are receiving treatment for other conditions in an ICU setting.

TABLE 13.2 Late-Onset Sepsis Pathogens

Coagulase-negative staphylococci
Staphylococcus aureus
Enterococcus spp.
Group B *Streptococcus*
Enterobacter spp.
Escherichia coli
Pseudomonas spp.
Klebsiella spp.
Candida spp.

Dong et al, 2015; Muller-Pebody et al, 2011.

Pathogenesis

The pathogens responsible for LOS may be acquired vertically from a colonized mother leading to initial neonatal colonization and subsequent infection. Alternatively, they may be horizontally acquired from contact with care providers, from invasive medical devices that are colonized with bacteria (central catheters, endotracheal tubes, etc.) or from environmental surfaces. Necrotizing enterocolitis, urinary tract infections, and skin and soft tissue infections may all lead to bacteremia and sepsis. Meningitis complicates LOS in approximately 5% of infants for whom a lumbar puncture is performed and may occur in the absence of documented bacteremia (Stoll et al, 2004). Recent data suggest that in low birth weight infants, LOS often results from translocation of pathogens colonizing the neonatal gut (Tarr and Warner, 2016; Carl et al, 2014).

Neonates exhibit impaired neutrophil adherence, chemotaxis, phagocytosis, and respiratory burst activity (Raymond, 2017). Furthermore, antigen presentation and pattern receptor signaling are diminished compared with that in older children. The cellular and humoral immune responses in neonates similarly contribute to increased susceptibility to infection, as there are age-related differences in toll-like receptor (TLR)–mediated cytokine production, skewing toward a Th2-type, antiinflammatory cytokine response and transient hypogammaglobinemia (Kollmann et al, 2012).

These deficiencies are exaggerated in the preterm infant, placing them at higher risk for LOS. A compromised skin barrier (absent vernix caseosa and immature stratum corneum) together with routine NICU interventions (placement of intravenous catheters and use of adhesives) provide a portal for pathogen entry (Narendran et al, 2010; Collins et al, 2018). Mucosal barriers of both the gastrointestinal and respiratory tracts in preterm infants are similarly compromised. In the

lung, there is reduced antimicrobial peptide (AMP) secretion, diminished expression of TLRs, and impaired mucociliary clearance of microorganisms (Sadeghi et al, 2007). In the intestine, AMP production is reduced in the same manner. Lack of enteral feedings and frequent exposure to antibiotics alter the immature microbiome, diminishing its ability to protect from colonization and overgrowth of potential intestinal pathogens.

Prevention

In the NICU, adherence to infection control protocols is the most effective means to prevent LOS. Minimization of ventilator days, strict hand hygiene practices, sterile suctioning and handling of respiratory equipment, and limiting respiratory circuit changes effectively decrease the incidence of VAP (Azab et al, 2015). Moreover, efforts to reduce duration of central line use, together with standardization of insertion and maintenance practices, have repeatedly been shown to reduce CLABSI rates (Schulman et al, 2015).

Other methods to prevent LOS include the implementation of early enteral feeds, use of breast milk rather than formula, and avoidance of exposure to broad-spectrum antibiotics. Recent studies examining the use of probiotics, supplementation with lactoferrin, and application of skin care antiseptics (such as chlorhexidine) in infants with indwelling catheters are promising but not have not yet yielded universal recommendations (Dong et al, 2015).

CASE 4

A 4-week-old, previously healthy, full-term male presents to the emergency department for evaluation because his mother noticed that his face suddenly turned blue. She notes that over the last 24 hours, the infant had been feeding poorly and appeared sleepier than usual.

This infant's medical history is notable for two routine visits to the pediatrician. His mother reports there were no concerns at that time. The child was born at 38 weeks' gestational age via cesarean section secondary to breech presentation without any complications. His mother is a 31-year-old G1P1 who had routine prenatal care and an uncomplicated pregnancy. Her prenatal GBS testing was positive and she was adequately treated with intrapartum ampicillin. Rupture of membranes was 20 hours.

The infant's physical examination is notable for a sleepy and lethargic appearance and sluggish capillary refill (3–4 seconds). His heart rate is elevated at 178 beats per minute. The examination is otherwise within normal limits. A sepsis evaluation was initiated and the infant was started on antibiotics. The blood culture obtained in the emergency department was positive for group B *Streptococcus*.

Exercise 4

Question

Which statement of the following statements is true?

A. Maternal intrapartum antibiotics administration reduced the risk of invasive late-onset GBS disease in this infant.
B. Maternal GBS colonization is a risk factor for early onset but not late-onset GBS disease.
C. According to most recent guidelines, this infant should have been treated with empiric antibiotics after delivery given the positive maternal GBS status and membrane rupture of 20 hours.
D. Bacteremia without a focus is the most common clinical presentation of late onset GBS disease.

Answer

Correct answer: **D**

Late-onset (LO) GBS most commonly presents as bacteremia without focal infection (65%), bone/soft tissue infections (including osteomyelitis and septic arthritis), or meningitis (27%) (Phares, 2008). Risk factors for LO GBS infection include maternal rectovaginal colonization, young maternal age, and prematurity (Pintye et al, 2016). In contrast to early onset GBS infection, there are currently no effective strategies to reduce the incidence of LO GBS disease or to target specific at-risk populations. A large prospective cohort study conducted revealed that most mothers (64%) were rectovaginally colonized with GBS at the time their infants were diagnosed with LO GBS, and 6% had GBS mastitis (Berardi et al, 2013). Notably, in that study, intrapartum antibiotic prophylaxis did not reduce the incidence of LO GBS infection but was associated both with delayed presentation of symptoms and milder disease.

CASE 5

The medical team is called to the bedside of a 21-day-old male infant who had an increasing number of desaturation episodes. The infant was born at 24 weeks' gestation with a birth weight of 621 grams. He was born to a 29-year-old woman who presented in preterm labor and was diagnosed with clinical chorioamnionitis. His history is notable for respiratory distress syndrome, for which he was intubated in the delivery room and treated with surfactant. He remains intubated on conventional ventilator support. Caffeine therapy was initiated on day of life 3. He received a 7-day course of ampicillin and cefotaxime for presumed sepsis at birth and another 5-day course of vancomycin and cefotaxime at 2 weeks of age to rule out sepsis in the setting of hypotension. All cultures were negative. He has difficulty tolerating enteral feeds and continues to require parental nutrition administered through a central venous catheter in his left lower extremity. He has mild bilateral intraventricular hemorrhages noted on his initial head ultrasound. He has no other significant past medical history.

The medical team decides to initiate another sepsis workup in this infant. After obtaining a CBC and blood and urine cultures, they begin vancomycin and cefotaxime. The infant continues to deteriorate over the next 48 hours and requires a dopamine infusion to maintain blood pressure. His CBC is notable for a white blood cell count of 5000/μL, a hematocrit of 27%, and a platelet count of 32,000/μL. The team decides to initiate empiric antifungal therapy.

Exercise 5

Question

Which of the following is not a known risk factor for invasive candidiasis in this infant?

A. Extremely low birth weight
B. Exposure to third-generation cephalosporins
C. Presence of a central venous catheter
D. Caffeine therapy
E. Presence of an endotracheal tube

Answer

Correct answer: **D**

Invasive candidiasis affects 4% to 8% of extremely low birth weight infants and is associated with 30% mortality. Death or neurodevelopmental impairment (NDI) is common, occurring in more than 70% of affected extremely low birth weight infants (Benjamin, 2006). Risk factors for invasive candidiasis are listed in Table 13.3. The use of caffeine has not been associated with an increased risk for candidiasis. Fluconazole prophylaxis in selected infants, reduced use of broad-spectrum antibacterial antibiotics, and improved care of central venous catheters have contributed to the declining incidence of invasive candidiasis in recent years.

Guidelines for the management of infants with invasive candidiasis are summarized here (Pappas et al, 2016).

- A lumbar puncture, if not already performed, is recommended in neonates with cultures positive for *Candida* species from blood and/or urine.
- A dilated retinal examination is recommended in infants with positive cultures from any sterile site.
- Computed tomographic or ultrasound imaging of the genitourinary tract, liver, and spleen should be performed if cultures are persistently positive.
- Central venous catheter removal is recommended as soon as possible. Infected central nervous system (CNS) devices, including ventriculostomy drains and shunts, should be removed if at all possible

Amphotericin B deoxycholate is the drug of choice for neonates with disseminated candidiasis. Fluconazole has activity against approximately 95% of common neonatal *Candida* isolates and is a reasonable alternative in patients who do not have evidence of CNS disease **and** have not been on fluconazole prophylaxis. Echinocandins (micafungin and caspofungin) and flucytosine should be used with caution in neonates and are generally limited to salvage therapy in neonates with persistent infections in the blood and CNS respectively. The recommended duration of therapy for candidemia without complications is for 2 weeks after documented clearance of *Candida* species from the bloodstream and resolution of signs attributable to candidemia. CNS infections should be treated until all signs, symptoms, and cerebrospinal fluid and radiologic abnormalities (if present) have resolved.

TABLE 13.3 Risk Factors for Invasive Candidiasis

Prematurity
Low birth weight
Use of broad-spectrum antibiotics (e.g., third generation cephalosporins)
Presence of central venous catheters
Use of histamine-2 receptors antagonists
Corticosteroid use
Presence of endotracheal tube
Intestinal pathology (necrotizing enterocolitis, spontaneous intestinal perforation, congenital anomalies)
Hospital site
Intravenous lipid emulsions

Benjamin and Stoll, 2010; Kelly, Benjamin, Smith, 2015.

CASE 6

You are called to the bedside to assess a 43-day-old preterm female infant who was born at 28 weeks' gestation. The infant's medical history is significant for respiratory distress syndrome, a patent ductus arteriosus, and feeding intolerance for which she continues to require continued parenteral nutrition. She has a peripherally inserted central venous catheter in her left lower extremity that was placed on day of life 7. As per the bedside nurse, the infant had deceased spontaneous activity and an increased number of apnea and bradycardia episodes over the past 24 hours. Upon hearing this scenario, you are concerned about the possibility of a central-line infection.

Exercise 6

Question

What is the most appropriate choice of empiric antibiotic therapy in this infant?

A. Ampicillin and gentamicin
B. Ampicillin and cefotaxime
C. Vancomycin and gentamicin
D. Vancomycin alone

Answer

Correct answer: **C**

CLABSIs are the most common form of healthcare-associated infections, and coagulase-negative *Staphylococcus* species (CONS) are the most commonly cultured microorganism in neonatal CLABSI (Late-onset sepsis in very low birth weight neonates, Stoll, 2002). *E.* coli, *Klebsiella pneumoniae, Enterobacter* Sp., coagulase-positive *Staphylococcus,* and *Candida* Sp. are also commonly associated with neonatal bloodstream infections. Empiric antibiotic therapy in cases of suspected CLABSI should cover most common gram-positive and gram-negative pathogens (unless there is known previous colonization or infection with a resistant organism).

Although there is not an official consensus recommendation for empiric therapy, vancomycin and gentamicin are widely used for infants when there is a central line in place. Vancomycin is effective against both CONS and methicillin-resistant *Staphylococcus aureus* (MRSA) and therefore is an appropriate choice for an infant with an indwelling central

catheter. Use of antibiotics with inadequate anti-Staphylococcal activity is associated with an increased 30-day mortality in infants with a MRSA bloodstream infection (Thaden et al, 2015) and an increased duration of bacteremia among infants infected with CONS (Ericson et al, 2015). It is worth noting that some centers choose oxacillin or other similar antistaphylococcal antibiotics for empirical therapy of LOS and reserve vancomycin when cultures are positive, whereas others may chose vancomycin for empirical therapy based upon the local prevalence of CONS and MRSA (Cotten, 2016). Empiric therapy with vancomycin alone cannot be recommended, as it does not provide gram-negative coverage. Cefotaxime may be used when there is suspicion of central nervous system infection.

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Abstract: Sepsis is the illness resulting from systemic bacterial or fungal infection. It is an ever-present threat in the neonatal intensive care unit (NICU), accounting for approximately 10% of infant deaths under 1 month of age worldwide and contributing significantly to long-term neurodevelopmental impairments among NICU survivors. Sepsis may be categorized at early onset or late onset, depending on the timing of clinical presentation, and each reflects distinct modes of pathogen acquisition. The adaptive responses of the neonatal immune system, together with the necessary and frequently invasive interventions required to care for these infants in the NICU, render this population uniquely susceptible to invasive infection. Vigilance and a high index of suspicion are paramount in reducing sepsis-related morbidity and mortality.

Keywords: sepsis, early onset, late-onset, neonatal immunity, CLABSI

14

Patent Ductus Arteriosus

William E. Benitz, MD and Shazia Bhombal, MD

While the fetus remains in utero, the ductus arteriosus is an essential component of the circulation, permitting blood to flow right to left from the pulmonary artery to the descending aorta, bypassing the fluid-filled lungs and returning to the placenta for gas exchange. At birth, the low resistance placental circulation is removed, and pulmonary vascular resistance rapidly decreases, coincident with aeration of the lungs, resulting in reversal of ductal flow, which quickly becomes predominantly left to right, from the descending aorta into the pulmonary artery and onward to the lungs. Pulmonary blood flow therefore exceeds net systemic cardiac output until the ductus closes.

In term babies, the ductus normally constricts and becomes functionally occluded by the fourth postnatal day. If the ductus does not close, hemodynamic effects of a persistent left-to-right ductal shunt may become pathologic, potentially requiring active management. Persistent ductal patency for more than a few days in a term infant is usually associated with another significant underlying pathology, such as a syndromic condition or congenital heart disease, and almost always requires a surgical or cardiac catheterization intervention. In preterm infants, however, closure of the ductus is often substantially delayed and, in some instances, may not occur at all. Prolonged ductal patency in preterm infants is associated with increased risks for numerous adverse outcomes, but this relationship may not be causal. The best strategies for evaluation and treatment are not known, so these infants often pose very difficult management dilemmas. The case studies in this chapter will present some of these challenges and suggest strategies for addressing them.

EPIDEMIOLOGY

CASE 1

An 840 g infant was delivered vaginally at 27 weeks' gestation following spontaneous onset of preterm labor at 25 weeks. Her mother had been treated with indomethacin for tocolysis and magnesium sulfate for fetal neuroprotection. She had received two doses of betamethasone more than 24 hours before delivery. The baby was vigorous at birth and responded well to support with continuous positive airway pressure by nasal mask and supplemental oxygen at an Fio_2 of 0.35.

Exercise 1

Questions

1. Which of the following most accurately reflects the probability that this infant will have a patent ductus arteriosus (PDA) at 10 days of age, in the absence of interventions intended to close the ductus?
   A. 10%
   B. 20%
   C. 33%
   D. 60%
   E. 90%
2. Which of the following features of this baby's perinatal history are associated with an increased risk of prolonged ductal patency?
   A. Estimated gestational age (EGA) <28 weeks
   B. Birth weight <1000 g
   C. Prenatal exposure to indomethacin
   D. Prenatal exposure to magnesium sulfate
   E. Treatment with antenatal steroids

Answers

1. D
2. All except E

In most healthy infants born after 36 weeks' gestation, the ductus constricts and becomes functionally closed by 72 hours of age and in all by 96 hours of age. The timing of ductal closure is related to maturity, with nearly all infants over 38 weeks' gestation achieving closure by 48 hours of age but only 50% and 60% of those born at 36 to 38 weeks. Among preterm infants, rates of ductal patency and the postnatal age at ductal closure progressively increase with decreasing gestational age at birth (Fig. 14.1). Because over half of infants born at 27 weeks still have a PDA on day 10 (Fig. 14.1), the correct answer to Question 1 is D (60%).

Early observations suggested that spontaneous ductal closure could nearly always be expected given sufficient time, but this sometimes took several months (Perloff, 1971). However, changes in practice—including widespread use of treatments to close the ductus, antenatal steroids to induce

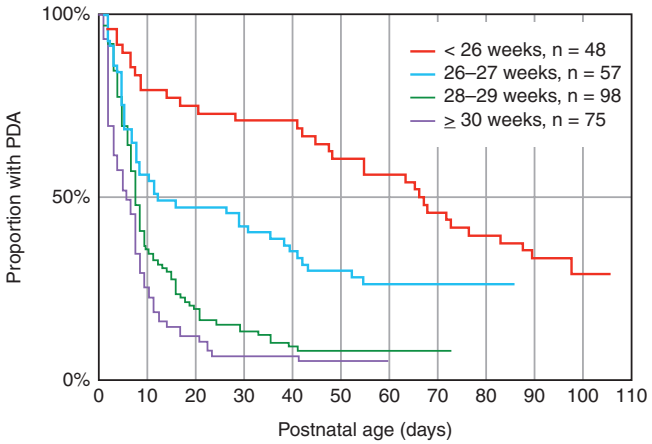

Fig. 14.1 Timing of spontaneous ductal closure in 280 VLBW infants, according to gestational age at birth. (Adapted, with permission, from Semberova J, Sirc J, Miletin J, et al: Spontaneous closure of patent ductus arteriosus in infants ≤1500 g, *Pediatrics* 140:e20164258, 2017).

lung maturity, exogenous surfactant to ameliorate respiratory distress syndrome (RDS), better strategies for respiratory support, and greatly increased survival rates among very low birth weight (VLBW) and extremely low birth weight (ELBW) infants—soon made application of those observations to practice untenable. More recent data show that the ductus closes without treatment even in preterm infants born before 28 weeks' gestation (Semberova et al, 2017). Observational data from preterm infants under 1000 g with a persistent PDA at hospital discharge suggest that the PDA will close in about 75% (Jhaveri et al, 2010) by the end of the first year. These data demonstrate that spontaneous closure of the ductus should be expected in most preterm infants.

A number of perinatal factors, in addition to prematurity and low birth weight, influence the risk of prolonged ductal patency. PDA is more common among infants who are small for gestational age, exposed to indomethacin for tocolysis before delivery, or given magnesium sulfate for neuroprotection (Katayama, 2011), and less frequent after antenatal administration of glucocorticoids. The correct answer to Question 2 is therefore "All except E," because that item (antenatal steroid exposure) is associated with a *lower* risk of PDA. A strong relationship between PDA and RDS has been recognized for many years. Although the causal nature of this association remains uncertain, PDA is consequently more common among infants who require ventilatory assistance or exogenous surfactant. This infant's requirement for support with positive airway pressure and supplemental oxygen, presumably owing to RDS, is an additional risk factor for PDA, although any causal relationship remains uncertain. The spontaneous onset of preterm labor and failure of tocolytic therapy may be signs of an intrauterine bacterial infection, another factor that would predispose to persistent PDA (Dessardo et al, 2012).

Exercise 2

Question

1. At 7 days of age, a large PDA is documented by echocardiography. Which of the following conditions are associated with persistent patency of the ductus arteriosus at age 7 days?
   A. Pulmonary hemorrhage
   B. Bronchopulmonary dysplasia
   C. Necrotizing enterocolitis
   D. Prolonged requirement for respiratory support
   E. Intraventricular hemorrhage
   F. Death

Answer

1. All except A

Delayed closure of the ductus arteriosus was first recognized more than 50 years ago as a common correlate of more severe respiratory distress in premature infants. It has subsequently

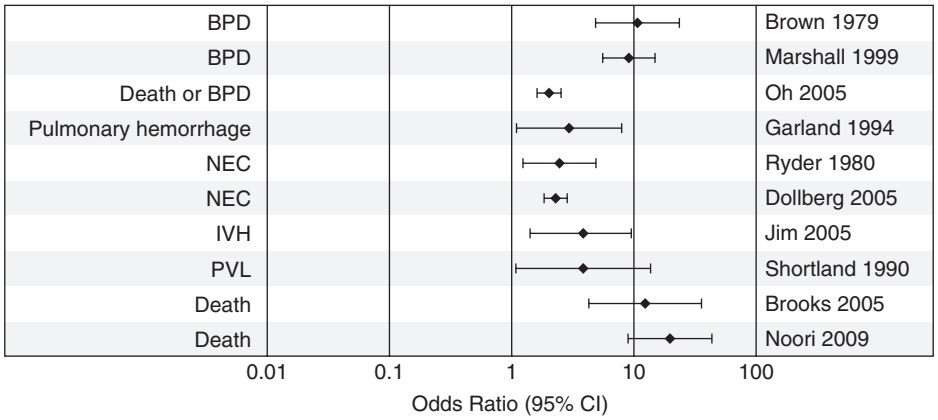

Fig. 14.2 Odds ratios for adverse outcomes associated with persistent patent ductus arteriosus. Black diamonds represent the point estimates for each odds ratio, and the error bars represent the 95% confidence interval for those estimates. None of these confidence intervals include 1, so all outcomes are statistically more likely to occur in preterm infants with persistent PDA ($P < 0.05$). Values for each odds ratio point estimate are provided in the text. (Data from suggested readings: Brooks et al, 2005; Brown, 1979; Dollberg et al, 2005; Garland et al, 1994; Jim et al, 2005; Marshall et al, 1999; Noori et al, 2012; Oh et al, 2005; Ryder et al, 1980; and Shortland et al, 1990.)

been linked to numerous adverse outcomes, including prolonged ventilation, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), impaired renal function, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), cerebral palsy, and death (Benitz, 2010). These complications are often attributed to a large left-to-right ductal shunt, resulting in excessive pulmonary perfusion and systemic organ ischemia, but the pathogenetic processes underlying these associations remain undetermined.

The strength of associations between PDA and adverse outcomes are quite impressive (Fig. 14.2). A study at two Boston hospitals in 1978 demonstrated that PDA increased the odds of BPD more than tenfold (OR 10.7) (Brown, 1979). A population-based study of preterm infants in North Carolina in 1994 found an odds ratio for BPD of 9.0 (Marshall et al, 1999), and a multicenter trial conducted between 1999 and 2001 reported an odds ratio for death or BPD of 2.0 (Oh et al, 2005). Data collected at two Boston hospitals from 1989 to 1992 revealed that ductal patency at 12 to 18 hours of age was associated with an odds ratio for early, severe pulmonary hemorrhage of 3.0 (Garland et al, 1994), but pulmonary hemorrhage after the first week was not related to persistent ductal patency. More recent data from the DETECT (Ductal Echocardiographic Targeting and Early Closure Trial) study suggest that large PDA (diameter >50th percentile for age) in the first 12 hours after birth is associated with pulmonary hemorrhage before 72 hours of age (Kluckow et al, 2014). Early treatment reduced the rate of early pulmonary hemorrhage but not the rate of all pulmonary hemorrhages or other adverse outcomes.

A multicenter study from the late 1970s demonstrated an odds ratio for NEC of 2.5 in infants with a PDA (Ryder et al, 1980), and an Israeli national analysis of NEC cases from the late 1990s found an odds ratio of 2.3 (Dollberg et al, 2005). The odds ratios for IVH (Jim et al, 2005) and that for periventricular leukomalacia (Shortland et al, 1990) have both been estimated to be 3.9. Infants in whom the ductus remains open despite treatment with indomethacin are much more likely to die before hospital discharge than those whose ductus closes without treatment. In data from a single center in Western Australia, persistent PDA after treatment was associated with an odds ratio for neonatal death of 12.3 (versus infants with spontaneous closure); after adjustment for gestational age and severity of illness, the adjusted odds ratio was still 4.0 (95% CI 1.1–14.5) (Brooks et al, 2005). A similar analysis from Oklahoma found an unadjusted odds ratio of 19.3; adjustment for perinatal factors, level of maturity, disease severity, and morbid pathologies resulted in an adjusted odds ratio of 16.8 (95% CI 6.1–46.6) (Noori et al, 2009). Confidence intervals for these odds ratios are shown in Fig. 14.2; all are statistically significant. Despite the magnitude of these associations, they do not prove a *causal* role for persistent ductal patency in production of those adverse outcomes. Nonetheless, these results (and others like them) have provided great impetus for the hypothesis that elimination of ductal patency might substantially improve long-term outcomes for preterm infants.

CLINICAL PRESENTATION AND DIAGNOSTIC EVALUATION

CASE STUDY 1 (CONTINUED)

Exercise 3

Questions

1. Which of the following physical findings on the tenth day after birth might suggest the diagnosis of persistent ductal patency?
   A. Bounding radial arterial pulses
   B. Palpable pulses in the palms of the hands
   C. Pulsus paradoxus
   D. Hyperdynamic precordium
   E. Systolic murmur
   F. Bilateral rales
   G. Hepatomegaly
   H. Cool extremities
   I. Intermittent cyanotic episodes
   J. Absent bowel sounds
2. Which of the following radiographic findings on the seventh day after birth might suggest the presence of a PDA?
   A. Cortical hyperostosis of long bones
   B. Cardiomegaly
   C. Increased lung lucency
   D. Prominent pulmonary vascular markings
   E. Pulmonary edema with a small heart
   F. Elevation of the left hemidiaphragm
3. Which of the following clinical conditions during the second week after birth might suggest the presence of a PDA?
   A. Oliguria with increasing blood urea nitrogen (BUN) levels
   B. Feeding intolerance
   C. Central apnea episodes
   D. Persistent jaundice
   E. Inability to wean respiratory support

Answers

1. A, B, D, E, G, and H
2. B and D
3. A and E

Persistent ductal patency in a preterm infant may become evident through findings on physical examination or because of signs of circulatory or respiratory impairment. A persistent PDA may first become apparent from development of the characteristic coarse systolic murmur heard best along the left sternal border. However, many infants with a large PDA may have no audible murmur despite having a large left-to-right shunt and substantial pulmonary overcirculation. The murmur may become audible or increase in intensity only as the ductus constricts, resulting in higher velocity and more turbulent shunt flow. The increased left ventricular stroke volume imposed by a large left-to-right shunt may produce a prominent precordial impulse or hyperactive precordium. Arterial pulses often are prominent, bounding, or palpable where they normally are not (e.g., in the palms).

Reduced systemic diastolic pressures with widened pulse pressures are common in preterm infants over 1000 g but lower systolic, diastolic, and mean arterial pressures without an increased pulse pressure are more typical in those under 1000 g. Congestive heart failure may be evident as rales, hepatomegaly, or peripheral edema. These findings are nonspecific, insensitive, and do not reliably predict echocardiography results (Skelton et al, 1994). Similar physical findings may be present in infants with other circulatory disorders, such as aortopulmonary window, hemitruncus, or arteriovenous malformations, or in hyperdynamic conditions, such as anemia, fever, or sepsis. Choices A, B, D, E, F, and G are correct answers to Question 1.

Pulsus paradoxus, or phasic decreases in systolic blood pressure in synchrony with respiration, should not accompany PDA. If that finding is observed in an infant with a large heart and signs of congestive heart failure, pericardial effusion and tamponade should be considered. The continuous "machinery" or "to-and-fro" murmur typical of PDA in older children is rarely found in neonates. The "runoff" effect of left-to-right ductal shunting into the pulmonary circulation is very rarely sufficient to result in overt signs of compromised systemic perfusion, such as cool extremities or lactic acidemia; such findings should suggest other causes of compromised systemic cardiac output, such as hypovolemia or sepsis. Cyanotic episodes associated with a PDA would imply periods of right-to-left shunting, which should not occur unless there is another pathologic abnormality, such as pulmonary edema, pulmonary hypertension, or compromised left ventricular output. Bowel ischemia is a potential adverse effect of the "ductal steal," but experience has shown that feedings can be continued despite ductal patency (Jhaveri et al, 2010), so loss of bowel sounds would not be expected as a sign of a PDA. Choices C, H, I, and J are therefore not correct answers to Question 1.

PDA is frequently suspected only because excessive pulmonary blood flow leads to pulmonary edema, which results in increasing oxygen requirement, decreasing lung compliance, or inability to wean the infant from supplemental oxygen, distending airway pressure, or positive pressure ventilation. Systemic hemodynamic effects include hepatomegaly and peripheral edema, as well as signs of suboptimal organ perfusion. In particular, a large ductal shunt may compromise renal blood flow, resulting in oliguria and chemical signs of prerenal renal failure (rising BUN without a proportionate increase in serum creatinine). Because of these effects, B and D are correct answers to Question 2 and A and E are correct answers to Question 3.

Cortical hyperostosis may result from prolonged administration of prostaglandin E_1 (alprostadil) to maintain ductal patency of the ductus in infants with ductus-dependent congenital heart disease but does not result from ductal patency itself. Excessive pulmonary blood flow may lead to decreased, but not increased, radiolucency of the lungs, as shown in Fig. 14.3, which also demonstrates cardiomegaly. A small heart in an infant with pulmonary edema should suggest capillary leak or pulmonary venous or lymphatic obstruction;

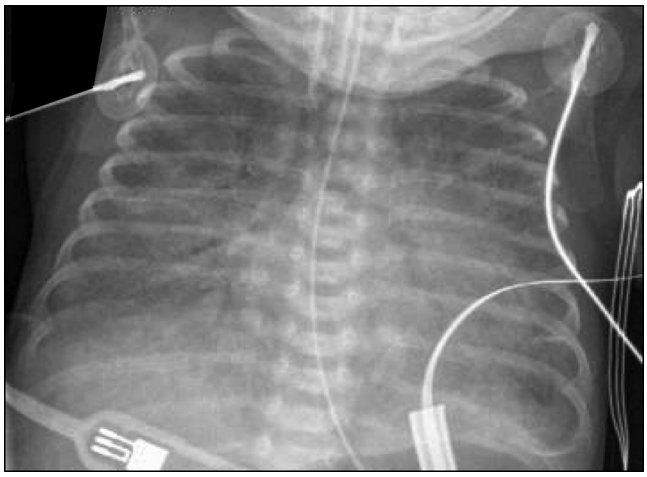

Fig. 14.3 CXR demonstrating pulmonary edema and enlarged cardiac silhouette consistent with hemodynamically significant left-to-right shunting at the ductus.

PDA is unlikely to be the cause of the lung findings. Paralysis of the left hemidiaphragm may follow surgical ligation of the ductus but is rarely associated with a PDA alone. Although feeding intolerance has been proposed as a criterion for assessment of the hemodynamic significance of PDA (Noori, 2012), a moderate PDA does not cause feeding intolerance or require discontinuation of feeding, as noted earlier. Feeding intolerance in an infant with PDA suggests a severe ductal steal resulting in either significant bowel ischemia or severe congestive heart failure with bowel edema; in either case, other clinical signs would be prominent. A PDA does not affect central nervous system or hepatic function, so central apnea or prolonged jaundice would not be expected associations. Items A, C, E, and F are therefore not correct answers to Question 2, and B, C, and D are not correct answers to Question 3.

CASE 2

Between 7 and 10 days of age, the infant described in Case Study 1 continues to require support with nasal continuous positive airway pressure (NCPAP) and exhibits a gradually increasing oxygen requirement. Her heart rate is 175 beats per minute and blood pressure is 35/18 (mean 26). She has a soft systolic murmur, full pulses, and her liver edge is palpable 2 cm below the right costal margin.

Exercise 4

Questions

1. Which of the following diagnostic studies will be most useful in determining whether the clinical findings in this infant are associated with presence of a PDA?
   A. Chest radiograph
   B. Color Doppler echocardiography
   C. Serum level of B-type natriuretic peptide (BNP)
   D. Serum level of troponin T
   E. Magnetic resonance angiography

2. Which of these diagnostic studies might be useful in assessment of the severity of the hemodynamic derangements resulting from a large left-to-right PDA shunt?

Answers

1. B
2. All except E

The definitive diagnostic test for PDA is color Doppler echocardiography, which permits direct visualization of ductal anatomy, as shown in Fig. 14.4 (panels A and B), measurement of the ductal diameter, and assessment of the direction of ductal blood flow throughout the cardiac cycle. The correct answer to Question 1 is clearly B. If the ductus is found to be patent, echocardiography may also provide useful information about its hemodynamic effects. Large shunts are associated with a ratio of left atrial to aortic root dimensions (LA:Ao ratio) greater than 2:1; ductal diameter over 3.0 mm; dilation of the left ventricle; and reduced or reversed diastolic flow in the descending aorta or in the cerebral, renal, or mesenteric arteries (Fig. 14.4C). Left ventricular dysfunction may be associated with a high velocity mitral regurgitant jet (>2.0 m/s), an increased ratio of early passive to late atrial filling (E/A >1.5), or shortening of the left ventricular isovolumic relaxation time (IVRT <40 ms). Such measurements may have utility as indicators of hemodynamic significance of a PDA (McNamara and Sehgal, 2007), particularly as components of a composite scoring system, but no individual measurement appears to be highly reliable. High composite scores incorporating nine echocardiographic measurements acquired before treatment of PDA appear to be predictive of chronic lung disease (Sehgal et al, 2013). The relationship of these measurements, or scores based on them, to other adverse outcomes potentially attributable to ductal shunting remains to be established. Nonetheless, extension of echocardiography to hemodynamic assessment—rather than only diagnosis—of PDA promises to provide better constructs for selection of subjects for clinical trials and eventually objective criteria for treatment to close a problematic ductus.

Serum biomarkers may also be useful in assessment of hemodynamic significance, guiding treatment, or prediction of sequelae of PDA. Levels of B-type natriuretic peptide (BNP) or NT-pro-BNP (an inactive byproduct of BNP synthesis) are elevated in the plasma of infants with PDA (Choi et al, 2005; Flynn et al, 2005), decrease after PDA closure (El-Khuffash

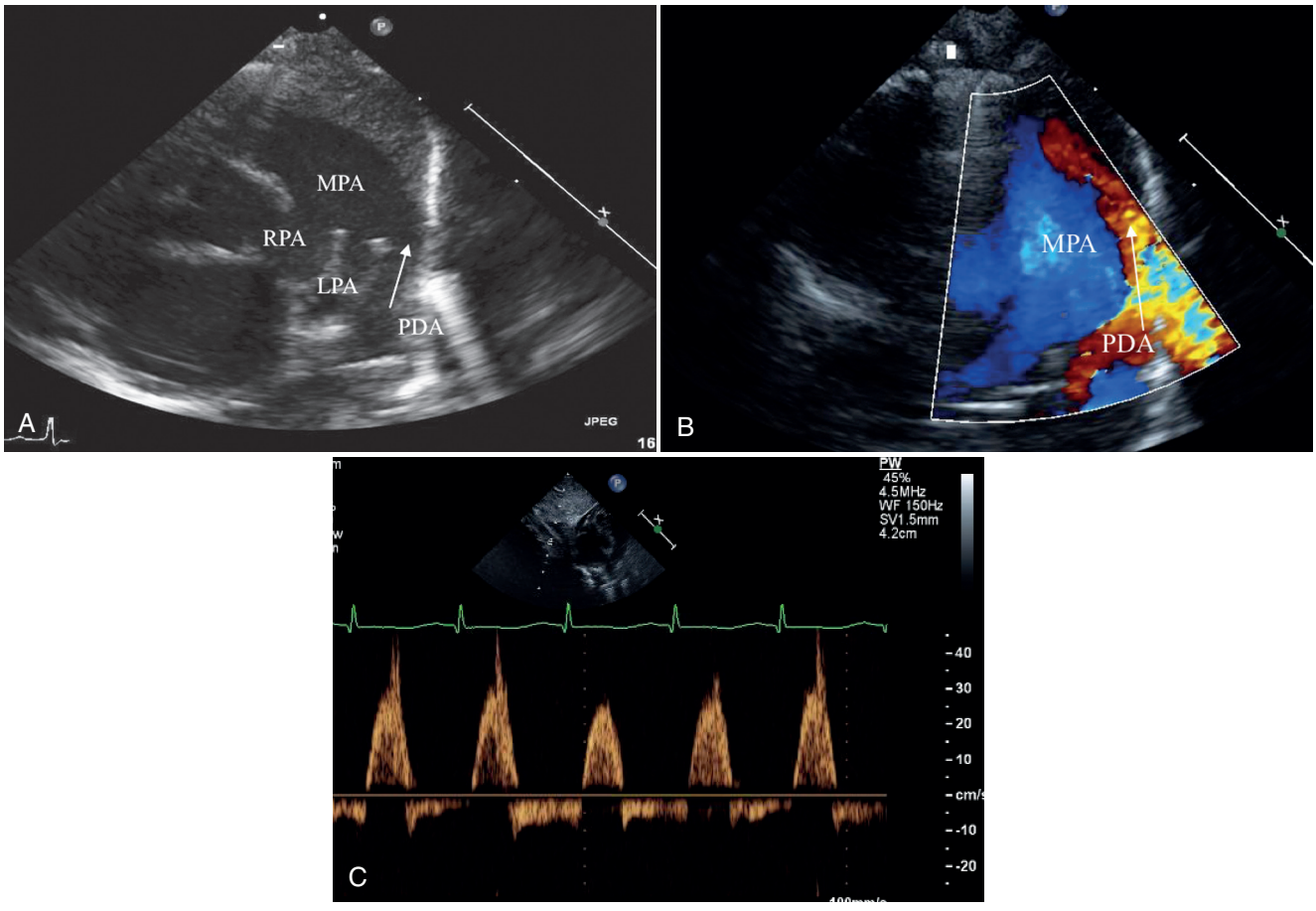

Fig. 14.4 Echocardiographic images in 2D (A) and with color Doppler (B) of a large patent ductus arteriosus *(arrow)* entering main pulmonary artery (MPA) from the descending aorta. (C) Doppler flow profiles in the descending aorta demonstrate reversal of flow throughout diastole, consistent with a hemodynamically significant duct. *LPA:* left pulmonary artery; *MPA:* main pulmonary artery; *PDA:* patent ductus arteriosus; *RPA:* right pulmonary artery. (A and C modified from Benitz WE, Bhombal S: Patent ductus arteriosus. In Martin RJ, Fanaroff AA, Walsh MC, editors: *Fanaroff and Martin's neonatal-perinatal medicine: diseases of the fetus and infant,* ed 11, Philadelphia, 2019, Elsevier, pp 1334–1342.)

et al, 2007; Sanjeev, 2005), and correlate with echocardiographic findings (El-Khuffash et al, 2007; Flynn et al, 2005; Sanjeev et al, 2005; Jeong et al, 2016). Discontinuation of indomethacin as soon as BNP levels decreased in response to treatment reduced the number of doses given but did not change other outcomes, suggesting a role in assessment of the response to or guiding duration of treatment (Attridge et al, 2009). Both severe IVH (grade III or IV) and worse neurodevelopmental outcomes are more frequent in preterm infants (<32 weeks' gestation) with PDA who had elevated levels of NT-pro-BNP at 48 hours of age (El-Khuffash et al, 2007; El-Khuffash et al, 2011). Elevated plasma troponin T levels at 48 hours of age correlate with echocardiographic findings (presence of PDA and shunt estimates) (El-Khuffash and Molloy, 2008), death or grade II–IV IVH (El-Khuffash et al, 2008), and increased risk for poor neurodevelopmental outcome at 2 years of age (El-Khuffash et al, 2011), but the role of this biomarker in clinical practice has not been established. Although these observations suggest that treatment of infants based on these biomarkers may lead to improved outcomes, that hypothesis has not been tested. Therefore these analytes are correct answers to Question 2 but not Question 1.

PDA may be associated with cardiomegaly, increased pulmonary vascular markings, or signs of pulmonary edema on chest radiographs. These signs are nonspecific and insensitive (Davis et al, 1995). Although conventional radiographs may suggest the presence of PDA, they cannot substitute for echocardiography for confirmation of the diagnosis. Heart size and the severity of pulmonary edema may help in assessment of hemodynamic significance. Choice A is therefore not correct for Question 1 but is correct for Question 2. Magnetic resonance angiography can provide excellent images of the ductus but does not provide simultaneous functional information. Although it could be used to confirm the diagnosis, bedside echocardiography remains the preferred method. Choice E is not a correct answer for either Question 1 or 2.

PROPHYLAXIS

CASE 3

A 980 g baby was born at 31 weeks' gestation after a pregnancy complicated by chronic hypertension and rapidly worsening preeclampsia. His mother received magnesium sulfate, but he had to be delivered urgently less than 12 hours after a single dose of betamethasone. He was hypotonic with poor respiratory effort and required intubation and initiation of positive pressure ventilation in the delivery room. After the initial dose of surfactant, he stabilized on moderate ventilator settings (PIP of 16 cm H_2O, PEEP of 5 cm H_2O, rate 36 breaths per minute, and Fio_2 of 0.45) with the following blood gases: pH of 7.21, $Paco_2$ of 57 mm Hg, Pao_2 of 63 mm Hg, HCO_3 of 22 mEq/L. A chest radiograph demonstrated bilateral diffuse granular lung densities and air bronchograms. A serum magnesium level was 4.5 mEq/L. Other blood chemistries and hematologic findings were unremarkable.

Exercise 5

Questions

1. Which of the following clinical outcomes would be *less* likely to occur if the ductus arteriosus was ligated on the day of birth?
   A. Early, severe pulmonary hemorrhage
   B. Severe IVH
   C. NEC
   D. BPD
   E. Neurodevelopmental impairment at age 18 to 22 months
   F. Ductal ligation
   G. Death
2. Which of the same clinical outcomes would be *less* likely to occur after treatment with indomethacin, beginning within 6 hours after birth?
3. Which of the same clinical outcomes would be *less* likely to occur after treatment with ibuprofen beginning within 6 hours after birth?

Answers

1. C, F
2. A, B, F
3. F

If persistent ductal patency is so common and the associated morbidities so severe, as described, it seems logical that intervening to close the ductus as soon as possible might be beneficial. This hypothesis has been tested extensively. In a single, small (84 subjects) trial of prophylactic ligation, infants who weighed under 1000 g at birth were randomized to either surgical ligation on the first day after birth or expectant management (Cassady et al, 1989). Not surprisingly, fewer babies in the early ligation group required subsequent surgical ligation, but there were no effects on rates of mortality, chronic lung disease (as defined at that time), IVH, severe (> grade 2) IVH, or retinopathy of prematurity (ROP). Significantly fewer infants in the early ligation group developed NEC (OR 0.20, 95% CI 0.06–0.68), possibly because initiation of feedings was significantly delayed in the surgical group. Unfortunately, that result has not been replicated in studies of ductal closure by other methods. Effects on other listed outcomes were not reported. Reanalysis of data from that trial found an increased risk of BPD, defined as a need for supplemental oxygen at 36 weeks' postmenstrual age, in the early ductal ligation group (OR 3.8, 95% CI 1.1–12.5) (Clyman et al, 2009). The answers to Question 1 are therefore C and, of course, F (although it remains uncertain whether a reduction in the risk of NEC, answer D, is a direct effect of ductal closure or is even reproducible).

Prophylaxis with indomethacin is the most extensively studied approach to accelerating closure of the ductus. In this strategy, treatment with indomethacin is initiated in all qualifying preterm infants soon after birth without waiting for confirmation of prolonged ductal patency. Two small trials of enterally administered indomethacin demonstrated efficacy in ductal closure, but no effects on mortality, chronic lung disease, IVH, or ROP. Twenty randomized controlled

trials of intravenous indomethacin enrolled nearly 3000 subjects who were randomized to either early treatment with intravenous indomethacin or placebo, typically beginning within the first 6 to 12 hours after birth. Although rate and/or severity of IVH—not PDA—was the primary outcome for about half of these trials, all reported rates of persistent PDA and other outcomes. The results are summarized in Fig. 14.5. Although indomethacin prophylaxis is associated with substantial reduction in the rate of persistent PDA (OR 0.27, 95% CI 0.23–0.32), there was no improvement in other outcomes, with the exception of lower rates of IVH, IVH above grade 2, and PVL. Despite lower rates of these neurosonographic findings, long-term neurodevelopmental outcomes were not improved. The confidence intervals for effects on the most important long-term outcomes (death, BPD, NEC, ROP, severe developmental delay, CP, and neurosensory impairment) are narrow and were not statistically different from "no effect." Data regarding effects on pulmonary hemorrhage are not included in Fig. 14.5, because the criteria for that diagnosis are not consistent among the five trials that reported that outcome (Alfaleh et al, 2008; Bada et al, 1989; Bandstra et al, 1988; Couser et al, 1996; Domanico et al, 1994). Collectively, these trials did not identify a significant effect on rates of pulmonary hemorrhage over the hospital course, but a detailed analysis (Alfaleh et al, 2008) demonstrated reduction in the frequency of early, severe pulmonary hemorrhage after indomethacin prophylaxis. That effect was not associated with a reduction in bronchopulmonary dysplasia or other long-term morbidities. The correct answers to Question 2 are therefore A, B, and F.

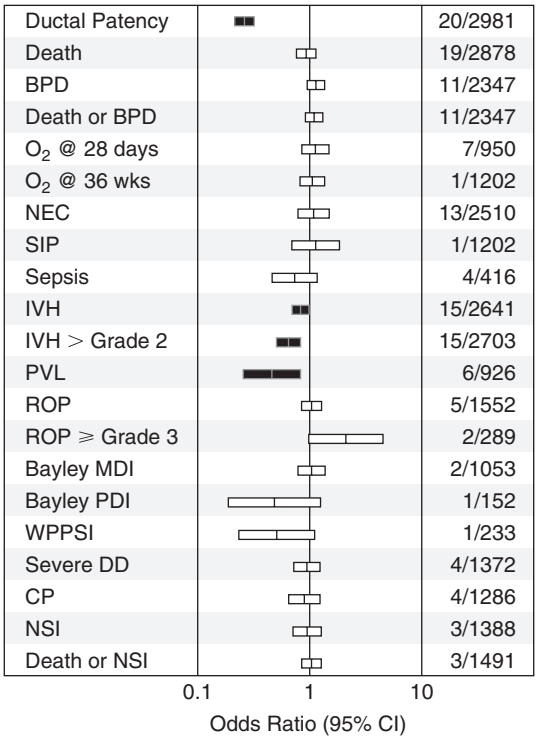

Fig. 14.5 Pooled odds ratios for outcomes observed in randomized controlled trials of indomethacin prophylaxis. Bars represent the 95% confidence intervals for each outcome; the line at the midpoint of each bar denotes the odds ratio (OR) point estimate. OR significantly different from 1 are indicated by black bars (two-tailed P <0.05). The number of trials (N) and total included subjects (n) for each outcome are shown on the right (N/n). *BPD,* Bronchopulmonary dysplasia; *CP,* cerebral palsy; *DD,* developmental delay; *IVH,* intraventricular hemorrhage; *MDI,* Mental Development Index; *NEC,* necrotizing enterocolitis; *NSI,* neurosensory impairment; *PDI,* Psychomotor Development Index; *PVL,* periventricular leukomalacia; *ROP,* retinopathy of prematurity; *SIP,* spontaneous intestinal perforation; *WPPSI,* Wechsler Preschool and Primary Scale of Intelligence–Revised. (Adapted from Benitz WE: Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis?, *J Perinatol* 30:241–252, 2010.)

There are fewer trials of ibuprofen prophylaxis, and none report long-term follow up data. The effects of prophylaxis with early initiation of ibuprofen are summarized in Fig. 14.6. Ibuprofen is effective in reducing the rate of persistent ductal patency (OR 0.24, 95% CI 0.17–0.33), but there were no significant effects on other reported outcomes. Importantly, the reduction in rates of IVH observed with indomethacin was not achieved with ibuprofen. The only correct answer to Question 3 is therefore F.

Two recent small placebo-controlled trials have evaluated prophylactic use of acetaminophen (Asbagh, 2015; Harkin 2016). Acetaminophen appears to have some efficacy for accelerating ductal closure, but other effects were not reported (Asbagh, 2015) or were not statistically significant. The role of acetaminophen for PDA prophylaxis therefore remains unestablished.

Prophylactic intervention to accelerate ductal closure in at-risk preterm infants therefore appears to be justified only by the expectation of reduction in severe IVH or severe early pulmonary hemorrhage with indomethacin prophylaxis or (possibly) in NEC with prophylactic ligation. Use of prophylaxis may be appropriate in settings where rates of these complications are high, but otherwise, these potential benefits do not appear to outweigh potential hazards (see later). Routine

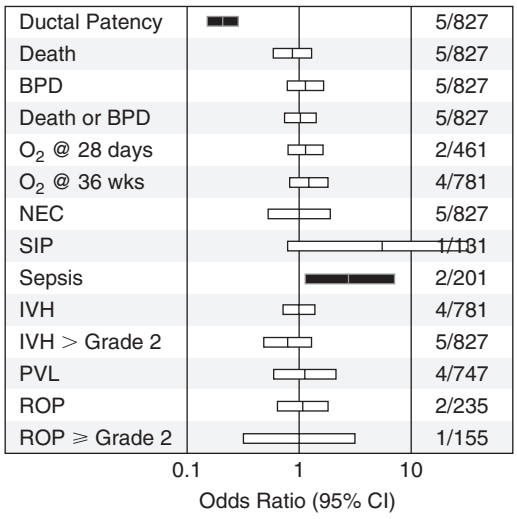

Fig. 14.6 Pooled odds ratios for outcomes observed in randomized controlled trials of ibuprofen prophylaxis. Symbols and abbreviations are as indicated for Fig. 14.5. (Adapted from Benitz WE: Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis?, *J Perinatol* 30:241–252, 2010.)

prophylactic treatment of all ELBW or VLBW neonates cannot be recommended (Hamrick and Hansmann, 2010).

TREATMENT

CASE STUDY 4

A 690 g baby was born at 27 weeks' gestation. The pregnancy had been uncomplicated until his mother presented with bulging membranes and then quickly progressed to delivery, affording no opportunity for antenatal treatments. The baby was vigorous at birth and was assigned Apgar scores of 5 and 7 at 1 and 5 minutes of age, respectively. He was initially stabilized on NCPAP with an Fio_2 of 0.40, but steadily worsening respiratory distress required intubation and administration of two doses of surfactant in the first 24 hours after birth. On the third day after birth, he continued to require positive pressure ventilation with an Fio_2 of 0.52. Vital signs included a heart rate of 165 beats per minute and transduced blood pressure of 40/24 (mean 29) mm Hg. A coarse systolic murmur was audible, and he had normal pulses and peripheral perfusion. A chest radiograph demonstrated bilateral pulmonary parenchymal densities with indistinct diaphragmatic and cardiothymic silhouettes. Echocardiography demonstrated a PDA 1.5 mm in diameter, with bidirectional but predominantly left-to-right shunting.

Exercise 6

Question

1. For which of the following treatment strategies is there evidence supporting an expectation of an improvement in long-term outcomes for this infant?
   A. Treatment with indomethacin 0.2 mg/kg/dose IV every 12 hours for three doses
   B. Treatment with ibuprofen 10 mg/kg/dose once, then 5 mg/kg/dose daily for 2 days
   C. Surgical ligation within the next 48 hours
   D. None of the above

Answer

1. D

Despite the apparent lack of benefit from universal intervention to induce early ductal closure, it is not unreasonable to hypothesize that selective intervention might be advantageous if the ductus remains open beyond the age at which closure normally occurs in term infants. There is surprisingly little empiric data that addresses this hypothesis, but it is not entirely untested. Four randomized trials—three using indomethacin (Hammerman et al, 1986; Mahony et al, 1982; Weesner et al, 1987) and one using ibuprofen (Aranda et al, 2009)—have examined the effects of treatment of infants in whom the ductus remains patent, as confirmed by echocardiography, on the third or fourth postnatal day but who do not have overt clinical signs of hemodynamic compromise (e.g., two or more of the following: bounding pulses, hyperdynamic precordium, pulmonary edema, increased heart size by chest radiograph, systolic murmur). Like prophylactic treatment, indomethacin and ibuprofen are both effective for inducing ductal closure when initiated at a few days of age (OR for persistent patency 0.23, 95% CI 0.12–0.41), but no other beneficial effects were found (Fig. 14.7). Unlike immediate prophylactic therapy, treatment delayed for even a few days, until after the period of greatest risk for IVH, does not appear to have a favorable effect on IVH or severe IVH. There have been no published trials of surgical ligation of the ductus in infants without clinical signs of significant hemodynamic effects. Because these data provide no evidence of benefit from treatment to induce ductal closure in asymptomatic infants, it is not possible to proceed with any of the listed treatment strategies with confidence that it represents the optimal course. Therefore the correct answer to Question 1 is D.

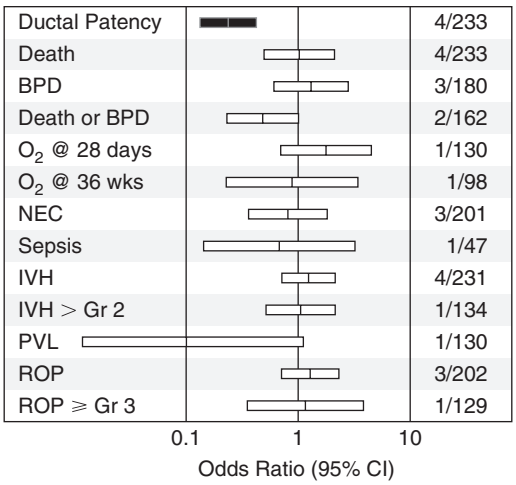

Fig. 14.7 Pooled odds ratios for outcomes observed in randomized controlled trials of ibuprofen or indomethacin treatment of asymptomatic preterm infants. Symbols and abbreviations are as indicated for Fig. 14.5.

In a similar vein, selection of infants for intervention only when clinical signs of significant hemodynamic consequences of the PDA become evident may identify a cohort for whom treatment might be beneficial. The next exercise will explore that hypothesis.

CASE STUDY 5

Echocardiography performed at 10 days of age in the infant described in Case Studies 1 and 2 confirmed the presence of a patent ductus, 2.2 mm in diameter, with continuous left-to-right flow throughout both systole and diastole. The next day, examination revealed bilateral rales, a coarse systolic murmur, and bounding radial pulses, as well as the previously noted hepatomegaly.

Exercise 7

Question

1. For which of the following treatment strategies is there evidence supporting an expectation of improvement in the long-term outcome for this infant?
   A. Treatment with indomethacin 0.2 mg/kg/dose IV every 12 hours for three doses

B. Treatment with ibuprofen 10 mg/kg/dose once, then 5 mg/kg/dose daily for 2 days
C. Surgical ligation within the next 48 hours
D. None of the above

Answer

1. D

Waiting for the effects of ductal patency to produce clinical signs does not appear to increase the likelihood that treatment will lead to measurable benefits. There is a shocking paucity of empiric data on this matter (Benitz, 2010). Two early studies of surgical ligation that enrolled and randomized a total of 56 subjects demonstrated no benefit other than ductal closure itself. Eight randomized trials of enteral indomethacin that followed up on the seminal observations that this treatment induces ductal constriction (Friedman et al, 1976; Heymann et al, 1976) were published in the early 1980s, confirming induction of ductal closure (OR 0.14, 95% CI 0.07–0.25) and suggesting a reduction in mortality (OR 0.33, 95% CI 0.15–0.74). Only one of these reported other outcomes (NEC, BPD, or death), with no evident benefit. The results of six trials of intravenous indomethacin for symptomatic PDA are summarized in Fig. 14.8. Although effective in promoting ductal closure (OR 0.17, 95% CI 0.10–0.28), no other benefits are apparent. The strength of this conclusion is limited, however, because most of these trials did not report outcomes other than ductal closure, BPD, and death. That reservation notwithstanding, the fact that beneficial effects of ductal closure have not been demonstrated with *any* treatment or prophylaxis strategy leaves little doubt that early, routine treatment to close the PDA in preterm infants is not beneficial and therefore is not indicated (Benitz, 2010). As was the case for asymptomatic babies, the correct answer to Question 1 is D.

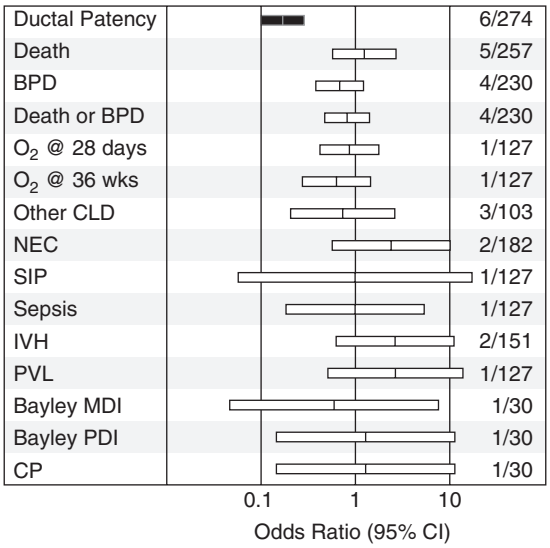

Fig. 14.8 Pooled odds ratios for outcomes observed in randomized controlled trials of intravenous indomethacin treatment of symptomatic preterm infants. Symbols and abbreviations are as indicated for Fig. 14.5. (Adapted from Benitz WE: Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis?, *J Perinatol* 30:241–252, 2010.)

The lack of long-term benefit from treatment to close a PDA may not imply that there are no short-term advantages. It is commonly believed, for example, that closing the ductus with a cyclooxygenase inhibitor or ligation reliably leads to a reduction in requirements for oxygen supplementation or mechanical support of ventilation. The next exercise will examine these possibilities.

CASE STUDY 6

An 1140 g infant was born at 31 weeks' gestation to a mother with newly recognized preeclampsia, by urgent cesarean section because of a type 3 fetal heart rate tracing and suspected placental abruption. He was flaccid at birth, responded poorly to stimulation and bag-mask ventilation, and required intubation and positive pressure ventilation before 3 minutes of age. He was given Apgar scores of 1 (HR <100), 3 (HR >100, body pink), and 5 (HR >100, body pink, some flexion, grimace) at 1, 5, and 10 minutes, respectively. Cord blood gases (arterial) were pH of 6.75, $Paco_2$ of 106 mm Hg, Pao_2 of 12 mm Hg, HCO_3 of 14.0 mEq/L, and base excess of −18.7 mEq/L. Because of concern about the perceived high risk of IVH, he was started on a course of indomethacin prophylaxis (0.1 mg/kg/dose daily for 3 days) soon after arrival in the NICU.

Exercise 8

Questions

1. Which of the following short-term effects can be expected to result from this use of indomethacin in infants similar to the one described in this case study?
   A. Earlier closure of the ductus arteriosus
   B. More use of indomethacin to close a PDA
   C. Fewer surgical PDA ligations
   D. Lower oxygen requirements from days 3 through 7
   E. Decreased requirements for mechanical respiratory support
   F. Reduced urine output
   G. Lower rates of grade III or IV intraventricular hemorrhage
2. Which of those short-term effects could be expected to result from early treatment with ibuprofen in such infants?

Answers

1. A, C, F, and G
2. A and C

Early administration of indomethacin as prophylaxis for IVH or for treatment of PDA reliably results in earlier ductal closure, and, consequently, less frequent need for subsequent treatment with indomethacin or surgical ligation. Therefore answers A and C are correct and B is not. However, such treatments fail to result in less severe respiratory disease or to reduce the requirements for supplemental oxygen or other respiratory therapies, as many had expected. On the contrary, infants treated with prophylactic or early indomethacin require more surfactant doses (Yaseen et al, 1997) as well as more oxygen (Schmidt, 2006; Van Overmeire

et al, 2001; Yaseen et al, 1997) and higher airway pressures (Van Overmeire et al, 2001) over the first 7 to 10 days after birth. Data demonstrating the latter effects are presented in Fig. 14.9. Answers D and E are therefore not correct.

Blood flow in cerebral (Austin, 1992), mesenteric (Coombs et al, 1990; Pezzati et al, 1999), and renal (Pezzati et al, 1999) arteries is reduced after treatment with indomethacin, resulting in lower cerebral oxygen saturations, decreased glomerular filtration, and decreased urine production. Choice F is therefore a correct answer. Fortunately, these hemodynamic changes apparently do not lead to more frequent complications, including BPD, NEC, bowel perforation, ROP, or neurodevelopmental impairment or to increased mortality rates (Benitz, 2010). However, there is an increased risk of spontaneous intestinal perforation if indomethacin is given to preterm infants who are also receiving hydrocortisone or dexamethasone postnatally (Stark et al, 2001; Watterberg et al, 2004). As noted previously, indomethacin prophylaxis reduces the rates of IVH and grade III or IV IVH, although the mechanism of this effect and its relationship to these local effects on cerebral blood flow remain uncertain. Choice G therefore is also a correct answer.

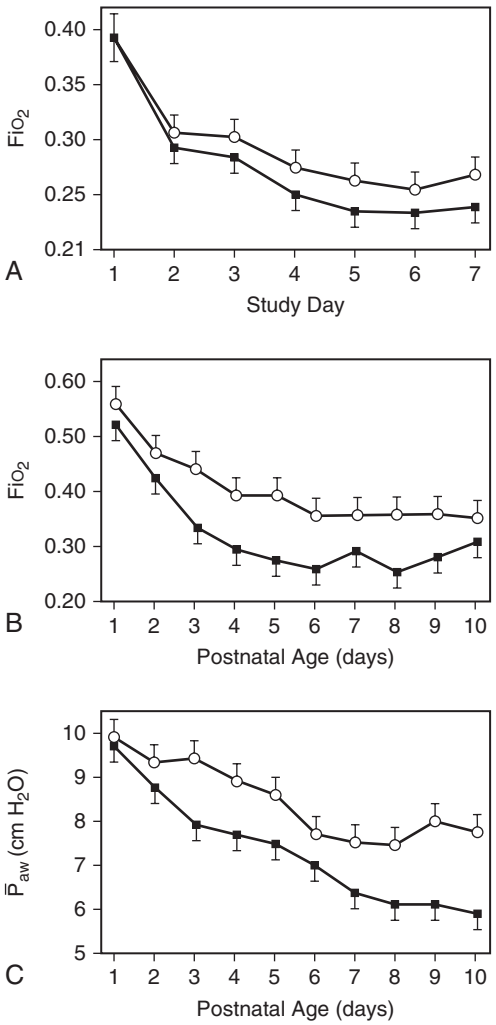

Fig. 14.9 Effects of early indomethacin on requirements for respiratory support. (A) The daily mean Fio_2 for ELBW (<1000 g) infants randomized to prophylactic indomethacin (n = 496) or placebo (n = 503) soon after birth. (B and C) Supplemental oxygen requirement (B) and mean airway pressure (C) in infants <28 weeks' gestation treated with early (day 3; n = 23) or late (day 7; n = 21) indomethacin. Data points represent mean ± standard error. All differences are significant (p <0.05) for day 3 and after. Open symbols and dashed lines represent the early indomethacin groups; filled symbols and solid lines represent placebo (A) or late indomethacin (B and C) groups. (Data in A from Schmidt B, Davis P, Moddemann D, et al: Long-term effects of indomethacin prophylaxis in extremely low-birth-weight infants, *N Engl J Med* 344:1966–1972, 2001. B and C adapted from Benitz WE: Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis?, *J Perinatol* 30:241–252, 2010.)

Ibuprofen is equally effective with indomethacin for achieving ductal closure, and its use is associated with less frequent requirements for additional treatment with indomethacin or surgical ligation. Choices A and C, but not B, are correct for this drug too. No placebo-controlled studies have examined the effects of ibuprofen treatment on requirements for respiratory support. In direct comparisons to indomethacin, ibuprofen-treated infants required slightly fewer days of ventilator support or supplemental oxygen; early effects on mean airway pressure and Fio_2 have not been reported, so there is no evidence that D and E are correct. In comparison to those associated with indomethacin, the effects of ibuprofen on cerebral, renal, and mesenteric blood flow are minimal or small. Ibuprofen may produce measurable effects on renal function, such as a slight increase in serum creatinine but usually does not cause significant oliguria. Although neither indomethacin nor ibuprofen has been associated with substantially increased or decreased rates of NEC in placebo-controlled trials, head-to-head comparisons suggest that NEC is less frequent in preterm infants treated with ibuprofen than in those who receive indomethacin (Ohlsson et al, 2013). Ibuprofen does not appear to have neuroprotective effects similar to those of indomethacin, as no reduction in IVH rates has been reported from ibuprofen trials. The possibility of an increase in the risk of neurologic injury with ibuprofen has been raised by in vitro experiments demonstrating bilirubin displacement from albumin by ibuprofen (Ahlfors, 2004), but the practical significance of those observations remains uncertain.

A handful of reports suggest that acetaminophen may be as effective as indomethacin or ibuprofen for inducing ductal closure, potentially with fewer adverse effects. Available data are not sufficient to determine whether treatment with this drug improves other outcomes, however (Ohlsson et al, 2018).

CASE STUDY 7

A 550 g baby was born at 24 weeks' gestation, 2 weeks after his mother was found to have cervical dilation and bulging membranes by regularly scheduled ultrasonography. Labor was suppressed with indomethacin, and a course of antenatal corticosteroids was completed the day before delivery. Vaginal birth followed recurrence of labor, despite tocolytic treatment with magnesium sulfate. The baby required intubation in the

delivery room because of a persistent lack of respiratory effort. He continued to require positive pressure ventilation, with slowly increasing requirements for ventilation and oxygen supplementation. By day 15 after birth, he required support with high-frequency oscillatory ventilation with an Fio_2 of 0.72 and was being treated for hypotension with hydrocortisone (3 mg/kg/day) and dopamine (18 μg/kg/min). On examination, he had a heart rate of 190 beats per minute, blood pressure of 31/17 (mean 23), a loud systolic murmur, bounding pulses, and an enlarged liver. His chest radiograph showed a large heart, shunt vascularity, and perihilar pulmonary edema. Echocardiography confirmed persistent ductal patency, with a 2.5 mm transductal diameter, LA:Ao ratio of 2.1, left ventricular distension, continuous left-to-right shunting, and reversal of diastolic low in the descending aorta.

Exercise 9

Question

1. Which of the following are *potential* short-term (within 3–4 days) consequences of immediate surgical ligation of the ductus in this infant?
   A. Resolution of hypotension
   B. Circulatory collapse
   C. Marked respiratory improvement
   D. Left diaphragm paresis
   E. Worsening pulmonary edema

Answer

1. All of the above

Surgical ligation is a relatively safe, expeditious, and reliable way to eliminate effects of a large left-to-right ductal shunt. The immediate effects of this surgery are difficult to predict, however. Elimination of the low resistance shunt into the pulmonary circulation should increase the blood pressure, and observation for that effect often provides intraoperative assurance to the anesthesiologist and surgeon that the correct vessel has been ligated. However, as many as one-third of preterm infants develop severe left ventricular dysfunction within hours of the surgery, resulting in circulatory and respiratory collapse requiring major escalations in cardiotonic and ventilatory support (Teixeira et al, 2008). This complication occurs less frequently with increasing postnatal age, so it may be preferable to defer surgery until after 1 month of age (if feasible). Some infants have substantial respiratory improvement following surgery, but this is not always the case. In the best case, elimination of excessive pulmonary blood flow leads to resolution of pulmonary edema and marked respiratory improvement. Ventricular dysfunction may produce the opposite effect, however. Paresis of the left hemidiaphragm resulting from left phrenic nerve injury is not uncommon and may greatly delay weaning from assisted ventilation. Left vocal cord paralysis, which may occur in as many as two-thirds of ELBW infants who undergo ductal ligation (Benjamin et al, 2010; Clement et al, 2008), prolongs assisted ventilation, oxygen supplementation, and hospitalization and increases the likelihood of BPD, feeding difficulties, tube feeding, and permanent voice impairment (Roksund et al, 2010). Other early complications include chylothorax, pneumothorax, and phrenic or recurrent laryngeal nerve injury (Benitz, 2011). Long-term sequelae may include increased risks of BPD (Chorne et al, 2007; Clyman et al, 2009) and neurodevelopmental impairment (Kabra et al, 2007). However, ligation was not associated with increased adjusted odds for these adverse outcomes in a more recent cohort (Weisz et al, 2017). Some adverse outcomes may result from the circumstances creating the need for surgery rather than the surgery itself, so it is not certain that they could be averted by avoidance of surgery. Because of these unpredictable and widely variable responses to surgical ductal ligation, all of the options are correct answers to Question 1.

Nearly all of the trials that provide evidence that early, routine ductal closure in preterm infants does not produce better outcomes were conducted in the first week or two after birth, and interventions to close the PDA if it persisted into the third or fourth week were common, even for subjects assigned to the placebo arms. Those data therefore do not allow the conclusion that intervention to close the ductus is not beneficial at any age in preterm infants. In fact, the consequences of large left-to-right shunts in the second half of the first postnatal month and beyond in ELBW infants are largely unknown, as are the possible indications for, potential benefits from, optimal timing of, and best method for achieving later ductal closure. If there is a benefit from later intervention, it is not apparent whether optimal management might consist of immediate ligation or a trial of cyclooxygenase inhibitor before ligation. Similarly, the possibility remains that some infants may benefit from ductal closure before 14 days of age, either because they were not well represented in prior clinical trials or by virtue of selection using echocardiographic or biomarker criteria as discussed above. It does seem likely that there are some infants, perhaps including the baby described in Case Study 7, for whom treatment benefits eventually will be demonstrated in well-designed clinical trials. Until those trials produce the evidence needed to guide care, it will be necessary to base management on individualized clinical judgment.

ALTERNATIVES TO DUCTAL CLOSURE

CASE STUDY 8

At 1 week of age, the baby described in Case Study 4 remained intubated and on positive pressure ventilation, but he had stabilized on low ventilator settings (PIP 15, PEEP 4, rate 24) with an Fio_2 of 0.28. Blood gases were pH of 7.21, $Paco_2$ of 42 mm Hg, Pao_2 of 95 mm Hg, HCO_3 of 27.4 mEq/L, base excess −3.3 mEq/L. He was receiving trophic feedings of maternal milk (2 mL every 3 hours) and parenteral nutrition with a total fluid intake at 150 mL/kg/day. His blood pressure was 44/19, his murmur persisted, and his arterial pulses were prominent. A chest radiograph showed mild cardiomegaly and pulmonary congestion. Laboratory studies were significant for the following values: creatinine 0.9 mg/dL, urea

nitrogen 43 mg/dL, albumin 1.6 g/dL, hemoglobin 7.8 g/dL, hematocrit 24.

Exercise 10

Questions

1. Which of the following summarizes the best strategy for managing the presumed PDA in this infant?
   A. Monitor for signs of decompensation without interventions.
   B. Implement measures to mitigate PDA effects.
   C. Begin a course of ibuprofen.
   D. Request ligation.
2. Excluding medical or surgical treatment to close the PDA, which of the following measures might be appropriate steps to ameliorate the potential adverse effects of the presumed PDA?
   A. Reduce the ventilator rate and/or PIP.
   B. Increase positive end expiratory pressure (PEEP) to 6 cm H_2O.
   C. Increase Fio_2 to 0.34.
   D. Restrict fluid intake to 130–150 mL/kg/day.
   E. Increase acetate content in parenteral nutrition fluid.
   F. Add albumin to the parenteral alimentation solution
   G. Transfuse red blood cells.

Answers

1. A or B
2. B, D, and G

There is little evidence to guide correct answers to these questions. Given the lack of evidence for benefit from medical or surgical closure of the ductus and the modest apparent impact that PDA is having in this infant, the correct answer to Question 1 is probably A, but measures to minimize adverse effects such as modest fluid restriction (B) may be helpful. The potential effects of PDA may be important, so it should not simply be ignored, and measures to prevent complications probably are preferable to treatment of complications after they develop. Several reports provide reassurance that adoption of less aggressive management strategies is consistent with favorable outcomes (e.g., Sung et al, 2016; Semberova et al, 2017). Management of VLBW infants with symptomatic PDA using fluid restriction to 130 to 150 mL/kg/day, diuretics, and captopril (to reduce systemic vascular resistance) decreased the need for either indomethacin or ligation (in only 1.6% and 3.6% of infants, respectively), yet produced outcomes that compared favorably with Vermont Oxford Network benchmarks (Pietz et al, 2007).

Outcomes comparable to or better than those reported to multicenter collaboratives were also achieved in ventilated infants 30 weeks' gestation or less who had a PDA demonstrated by echocardiography, using "conservative management" consisting of fluid restriction to 130 mL/kg/day, reduction of the inspiratory time to 0.35 seconds (from 0.4–0.45 seconds), and an increased end expiratory pressure (to 4.5 cm H_2O) (Vanhaesebrouck et al, 2007). The PDA closed without treatment in more than 95% of those infants. At another center, adoption of a strategy of selective rather than universal PDA ligation for infants whose ductus remained open after indomethacin prophylaxis decreased the rate of surgery in that high-risk cohort from 100% to 72% (Jhaveri et al, 2010). Therefore 28% of the babies in the latter era avoided surgery. In those infants, the ductus closed spontaneously before hospital discharge in one-third, after discharge but before 6 months of age in one-third, and remained patent or was closed by transcatheter coiling in the remaining one-third. It is worth noting, however, that ligation was considered in the latter era only for infants who developed signs of circulatory compromise. Therefore surgeries were performed at a later age, resulting in significantly more days of exposure to ductal shunting in infants who had surgery. However, prolonged exposure to the effects of PDA was not associated with any increase in adverse outcomes (BPD, sepsis, ROP, IVH $\geq$ grade III, neurologic injury, or death), and the risk of NEC was actually substantially lower (adjusted OR 0.25, 95% CI 0.07–0.95).

This favorable change in the incidence of NEC is all the more remarkable because it was also associated with continuation of feedings despite presence of a PDA, in contrast to the earlier practice of interrupting enteric nutrition under those circumstances. Another study compared outcomes of infants requiring respiratory support with moderate to large PDAs before and after adoption of selective rather than liberal criteria for treatment with indomethacin or ligation. The revised approach relied primarily on modest fluid restriction (to approximately 130–140 mL/kg/day); indomethacin or ligation was reserved for infants who could not be weaned from positive pressure ventilation or could not maintain adequate oxygenation and ventilation on NCPAP (Kaempf et al, 2012).

Despite less use of indomethacin or ligation in the second era (in 26% vs. 79% and 33% vs. 45% of infants, respectively), neither the requirements for respiratory support nor rates of multiple morbidities (BPD, IVH, PVL, NEC, etc.) were affected. However, the rate of death or BPD as a combined outcome was greater (54% vs. 40%) in the second era. In the infants discharged home with PDA, the ductus closed spontaneously in 70% within 1 year. Recent observational studies have found that marked reduction in (Semberova et al, 2017) or elimination of treatment to close the PDA in preterm infants (Sung et al, 2016) resulted in high rates of eventual spontaneous closure (Fig. 14.1) and other outcomes comparable to historical experience or contemporaneous benchmarks. Although these reports do not provide strong evidence that any of these approaches constitutes a "best practice" for PDA management, they do indicate that more tolerant approaches to preterm babies with PDA do not lead to worse outcomes. In concert with the previously described evidence that early, routine intervention to close the ductus does not improve outcomes, these observations suggest that a correct answer to Question 1 might be modest fluid restriction. However, which other measures to use remains to be determined in trials targeted to evaluate their efficacy.

Until evidence to guide management is available, judgment will have to rely on considerations of the pathophysiology of ductal shunting. The consequences of such shunting

can be categorized as follows: excessive pulmonary blood flow, compromised perfusion of other organs, and congestive heart failure. Even large left-to-right shunts may not result in pulmonary edema unless pulmonary fluid fluxes are additionally disturbed by factors such as surfactant deficiency, low serum oncotic forces, or capillary leak syndrome. When pulmonary edema develops, the alveolar-arterial oxygen gradient increases and lung compliance decreases. Systemic cardiac output and perfusion of vital organs may be compromised by the "ductal steal" of a large left-to-right shunt. Doppler ultrasound may demonstrate decreased, absent, or reversal of diastolic flow in the descending aorta and in the middle cerebral, superior mesenteric, and renal arteries (Groves et al, 2008). Early changes in cerebral blood flow velocities associated with PDA have been correlated with later development of periventricular leukomalacia (although the causal relationship is uncertain) (Pladys et al, 2001). Reduced renal blood flow correlates with impaired renal function (Vanpee et al, 1993), and changes in mesenteric artery flow may be related to development of NEC (Dollberg et al, 2005). In term infants with congenital heart disease requiring surgical correction, retrograde flow in the descending aorta during diastole is associated with an increased risk of NEC (Carlo et al, 2007). The implications of diastolic flow reversal in preterm infants with PDA have not been formally evaluated, however. These ischemic effects of large ductal shunt may be compounded by myocardial dysfunction resulting from a greatly increased volume workload on the left heart, leading to atrial and ventricular distension, echocardiographic signs of ventricular dysfunction, ST segment depression (Way et al, 1979), or elevated serum troponin levels (El-Khuffash and Molloy, 2008).

This disturbed pathophysiology can be addressed at each of those levels (Benitz, 2011). Excessive pulmonary blood flow may be mitigated by measures that increase pulmonary vascular resistance, including permissive hypercapnia, increased distending airway pressure, transfusion to increase the hematocrit, and avoidance of alkalosis, excessive supplemental oxygen, and pulmonary vasodilator agents such as nitric oxide. These measures also augment systemic cardiac output and organ perfusion. Systemic afterload reduction (e.g., captopril) and avoidance or very judicious use of systemic vasopressor drugs will reduce the driving force behind the left-to-right ductal shunt. Careful attention to support of total cardiac output through ensuring adequacy of preload and provision of inotropic support may also be helpful. When adrenal insufficiency is suspected, supplemental hydrocortisone may increase blood pressure. Standard methods for management of congestive heart failure—preload reduction through fluid restriction and diuretics, inotropic support, and afterload reduction—should be effective. Published data suggest that modest fluid restriction, to approximately 140 mL/kg/day, is sufficient in this setting.

In addition to consideration of these hemodynamic factors, management should address other factors that may directly contribute to organ compromise, prolong ductal patency, or independently influence outcomes through mechanisms not related to the PDA. Conditions that may augment development of pulmonary edema, such as hypoproteinemia or capillary leak, should be prevented or treated. Optimal nutrition is the key to prevention of hypoproteinemia but is not always sufficient. Hypoproteinemia may be corrected by administration of albumin (along with diuresis to remove the concomitant salt load); however, the administration of albumin is controversial because of safety concerns. Capillary leak should be avoided by prevention of bacterial infection using meticulous infection control methods.

Similarly, circumstances that may increase the risk of injury to the brain (infection, anemia, hypoglycemia), kidneys (hypovolemia, nephrotoxic drugs), or bowel must be minimized. Closure of the ductus may be delayed by excessive fluid administration (especially above 180 mL/kg/day), hospital-acquired bacterial infection (particularly coagulase-negative *Staphylococcus*), and possibly by therapy with furosemide. Although furosemide does not appear to interfere with ductal closure in response to indomethacin (Lee et al, 2010), it may delay closure in infants who are not treated with cyclooxygenase inhibitors (Green et al, 1983). None of these strategies have been evaluated in clinical trials, and the net effect of each may depend on the balance between conflicting actions. For example, aggressive use of furosemide may help in management of pulmonary edema and congestive heart failure but may have adverse effects if it results in hypovolemia, metabolic alkalosis, or prolonged ductal patency.

These considerations suggest that answers to Question 2 are B, D, and G. Answer B is correct, because an increase in PEEP might increase pulmonary vascular resistance and decrease the transpulmonary arteriovenous pressure gradient. Increasing the Fio_2 (C) would not be helpful, as that might reduce pulmonary vascular resistance and increase pulmonary blood flow. Because the Pao_2 is already high, a reduction in Fio_2 would be a better response. Fluid restriction (D) would be appropriate, but it is important to make sure the nutritional intake is adequate to support normal growth. Increasing the acetate content in parenteral fluids (E) would exacerbate the existing mild metabolic alkalosis, potentially increasing pulmonary blood flow. Adding albumin to the parenteral nutrition fluid (F) might help increase the serum albumin level and favor mobilization of third space fluid from the lungs and elsewhere, but that practice has safety concerns and is usually discouraged. Transfusion with red blood cells (G), with a goal hematocrit in the upper 40s or greater, may help limit excessive pulmonary blood flow (because of differential effects on systemic and pulmonary vascular rheology) and will reduce the total cardiac output required to meet metabolic demand; however, the role of this strategy in infants with PDA has not been established.

Managing patent ductus in preterm infants remains one of the most challenging tasks in neonatal medicine. Beyond the knowledge that induced early closure of the ductus does not improve long-term results, there is little empiric evidence to guide the treatment of this condition. Acceptance of ductal patency while attending to its hemodynamic consequences is increasingly accepted as the best initial approach

to management, particularly in infants over 1000 g, in whom the ductus will nearly always close without intervention. Smaller infants, particularly those with RDS, may require treatment to address ductal patency, but the indications for intervention, optimal timing, and best treatment(s) are unknown. While we seek answers to these questions, management of the preterm infant with patent ductus should be approached with humility, circumspection, and patience.

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Abstract: Constriction and closure of the ductus arteriosus, which normally occurs within 72 hours after birth in term infants, occurs much later in preterm infants. Delayed closure of the ductus is associated with several adverse outcomes, including higher rates of death and bronchopulmonary dysplasia. A causal role of prolonged left-to-right shunting through the PDA in these conditions has not been established. Although treatment using nonsteroidal antiinflammatory drugs or surgical ligation is effective in closing the ductus and eliminating left-to-right shunting, these treatments have not been shown to improve other outcomes. Data from randomized trials demonstrate that early, routine treatment is ineffective, implying that this practice should be abandoned. Observational studies indicate that reduction or elimination of treatment to close the ductus is not associated with worse long-term outcomes. Potential benefits of more selective or later treatment have not been defined. Extremely premature infants, particularly those with severe respiratory distress syndrome and evolving bronchopulmonary dysplasia, may require treatment to address ductal patency, but the indications for intervention, optimal timing, and best treatment(s) are unknown.

Keywords: Patent ductus arteriosus Preterm infants Indomethacin Ibuprofen Ductal ligation

15

Neonatal Hypotension

Tai-Wei Wu, Shahab Noori and Istvan Seri

INTRODUCTION

Hypotension of the premature newborn is a condition commonly encountered in the neonatal intensive care setting. Although no definite cut-off values exist in considering a given newborn to be hypotensive, certain blood pressure ranges will cause significant anxiety among caregivers. The goal of this chapter is to illustrate the complexity involved in the diagnosis and management of neonatal hypotension and guide the clinician in decision making using available evidence and a physiology-based individualized approach when caring for patients with neonatal circulatory compromise. We present a real case with a type of cardiovascular compromise frequently seen in the neonatal intensive care unit (NICU) and ask the reader to make clinical decisions. Along with the description of the course of the patient, we also present current evidence for and the pitfalls of the definition, diagnosis, and management of neonatal hypotension. Lastly, supplanting the case with additional information, we hope the reader arrives at a logical, reasonable, and pathophysiology-based treatment plan.

CASE 1

A 618-gram male preterm twin infant was born at $24^{5}/_{7}$ weeks' gestation via cesarean section for fetal heart rate deceleration. The pregnancy was complicated by preterm labor and maternal fever treated with antibiotics. A full course of antenatal steroid was given before delivery.

At birth, the infant emerged with weak cry and a heart rate of more than 60 beats per minute. He was intubated in the delivery room and subsequently given one dose of surfactant. Apgar scores were 3, 7, and 9 at 1, 5, and 10 minutes respectively, and the patient was transferred to the NICU of the delivery hospital. On the third postnatal day, a course of indomethacin was started for a "large" patent ductus arteriosus. On this day, a right-sided grade III peri/intraventricular hemorrhage (P/IVH) was also discovered on cranial ultrasound. Repeat cardiac ultrasound on the sixth postnatal day revealed the persistence of the patent ductus arteriosus. However, his blood pressure was reported within acceptable range and thus the patient did not receive supportive cardiovascular treatment. After completion of the indomethacin course, patient was also started on trophic feedings with breastmilk by nasogastric tube receiving 2 mL every 3 hours.

On the seventh postnatal day, the infant had multiple bradycardic events accompanied by arterial oxygen desaturations. Abdominal radiograph revealed abdominal free air, and the arterial blood gas showed a pH of 6.9, $Paco_2$ of 75 mm Hg, PaO_2 of 50 mm Hg, and a base deficit of 10 mEq/L. The infant was started on broad-spectrum antibiotic treatment and dopamine infusion at 2.5 mcg/kg/min and was transferred to a tertiary care center for provision of multidisciplinary pediatric medical and surgical subspecialty care. During transport, the infant developed progressively worsening systemic hypotension, and the dose of dopamine infusion was gradually increased to 10 mcg/kg/min. He subsequently also received 20 mL/kg isotonic saline bolus.

On arrival at the tertiary care center, he presented with a heart rate of 198 beats per minute, a respiratory rate of 40 per minute, and arterial systolic, diastolic, and mean blood pressures of 37, 12, and 19 mm Hg, respectively. On physical examination, the infant did open his eyes when stimulated but had minimal spontaneous movement. He appeared pale and mottled with a sunken fontanelle, breath sounds were equal bilaterally, and there was a loud holosystolic murmur over the heart. Abdomen was distended and appeared to have a bluish hue. He had had no urine output over the last 8 hours before admission. He remained appropriately ventilated on conventional ventilation and had a capillary blood pH, Pco_2, PaO_2, bicarbonate and base deficit of 7.02, 52 mm Hg, 36 mm Hg, 13 mEq/L, and 16.6 mEq/L, respectively. His blood lactate level was 14.3 mmol/L (normal value $\leq$2.5 mmol/L). The complete blood count revealed a WBC of $8.11 \times 10^3/\mu L$, Hgb and Hct of 9 g/dL and 27%, respectively, and a platelet count of $202 \times 10^3/\mu L$. Patient's serum cortisol concentration was appropriately elevated at 62 mcg/dL. Coagulation profiles were abnormal with a prothrombin time (PT) and partial thromboplastin time (PTT) of 20.3 and 103 seconds respectively, with a normal fibrinogen level at 176 mg/dL. Blood products were transfused to address the patient's coagulation abnormality. Following the initial emergent medical management, pediatric surgeons placed a peritoneal Penrose drain at the bedside, producing 15 mL of meconium-like fluid. Blood culture at the referring hospital

reported the growth of gram-negative bacilli. At this time, he was already on 20 mcg/kg/min of dopamine infusion with epinephrine added at 0.01 mcg/kg/min. However, patient's blood pressure continued to decline with systolic, diastolic, mean blood pressure values being very low at 22, 10, 15 mm Hg, respectively. This finding triggered the administration of two more 10 mL/kg boluses of isotonic saline.

Exercise

Question

Which of the following is the mostly likely *primary* cause of hypotension at this time?

1. Decreased systemic vascular resistance (vasodilatory shock)
2. Decreased cardiac output (cardiogenic shock)
3. Ductal steal-associated decreased postductal systemic blood flow due to the presence of a hemodynamically significant patent ductus arteriosus with left-to-right shunting
4. Adrenal insufficiency
5. Decreased intravascular volume (hypovolemic shock)

By themselves or in combination, all of these conditions can cause systemic hypotension. However, before addressing the question, it would be useful to review the determinants of blood pressure and the definition of the "normal" blood pressure range in neonates.

DETERMINANTS OF BLOOD PRESSURE

In fundamental fluid mechanics, pressure within a tube is described by Ohm's law:

$$\text{Pressure Gradient} = \text{Flow} \times \text{Resistance}$$

Applying this equation to the cardiovascular system, the equation becomes:

$$\text{Mean Blood Pressure} - \text{Right Atrial Pressure} = \text{Cardiac Output} \times \text{Systemic Vascular Resistance}$$

Thus blood pressure (the mathematically dependent variable) is the product of two independent variables: **cardiac output** and **systemic vascular resistance (SVR)**. The heart pumps a certain volume of blood per minute (cardiac output = stroke volume × heart rate) into the arterial bed, where it meets a given resistance. Stroke volume is determined by preload, myocardial contractility, and afterload whereas the heart rate is affected by a number of factors, including autonomic sympathetic–parasympathetic balance, catecholamine production and release, and temperature. Adequate circulating blood volume and ventricular compliance are necessary for appropriate filling of the heart chambers during diastole, resulting in the generation of necessary sarcomere stretch before ventricular contraction.

The Frank-Starling law describes the sarcomere length-dependent changes of cardiac contractility, where increased preload, up to a certain point, improves myocardial contractility (Fig. 15.1). During systole, SVR contributes to afterload

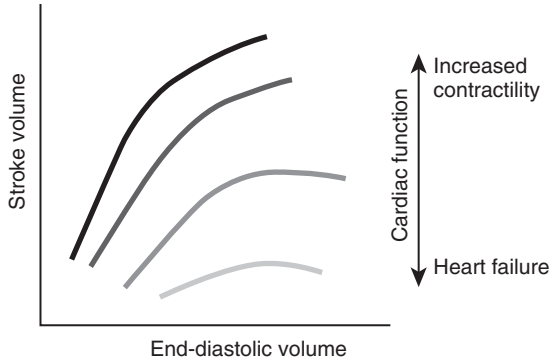

Fig. 15.1 Frank-Starling curves of the heart represented as the relationship between end-diastolic volume and stroke volume. In a normal heart (blue and green curves) stroke volume increases with increases in end-diastolic volume (sarcomere stretch). However, in a heart with depressed function, the Frank-Starling curve shifts downward and to the right and increases in end-diastolic volume only minimally augment stroke volume. (Hanft et al, 2008).

as the heart has to generate a pressure to overcome the resistance and produce forward flow. In addition to the blood pressure generated, afterload is directly determined by the diameter and is inversely related to the thickness of the left ventricle. An increase in afterload shifts the Frank-Starling curve and decreases stroke volume (Fig. 15.2). The overall resistance that is overcome to create blood flow within the vascular network is the SVR. This value is not directly measured but derived from the measurement of blood pressure and cardiac output based on Ohm's law. SVR is the mean value of the resistance to blood flow within a vascular network irrespective of the pulsatile changes in resistance throughout the cardiac cycle. Regional differences in vascular resistance exist to allow for autoregulation of end-organ blood flow within a given range of perfusion pressure (autoregulatory blood pressure range). Based on fluid dynamics and the Poiseuille's equation:

$$\text{Resistance} = 8 \times L \times \mu / (\pi \times r^4)$$

where L = vessel length, μ = blood viscosity, r = vessel radius. From this equation, we can appreciate that vessel diameter (inversely to the 4th power) is the most potent regulator of vascular resistance, because vessel length and blood viscosity usually do not change acutely. Regulation of the smooth muscle tone of the blood vessels is complex and is influenced by local, endothelial-derived substances such as nitric oxide, endothelin, and prostacyclin as well as neural and humoral factors (antidiuretic hormone, angiotensin II, catecholamines, etc.). In sepsis, inflammatory cytokines such as tumor necrosis factor, the interleukin-1 family, and prostaglandins are the most potent mediators of vasodilatory shock.

Upon understanding these determinants of blood pressure, one can realize that the different etiologies in neonatal shock correspond to a compromise in a particular determinant or a combination of determinants (cardiac output and/or SVR) without adequate compensation. The ability to identify the specific hemodynamic components and their

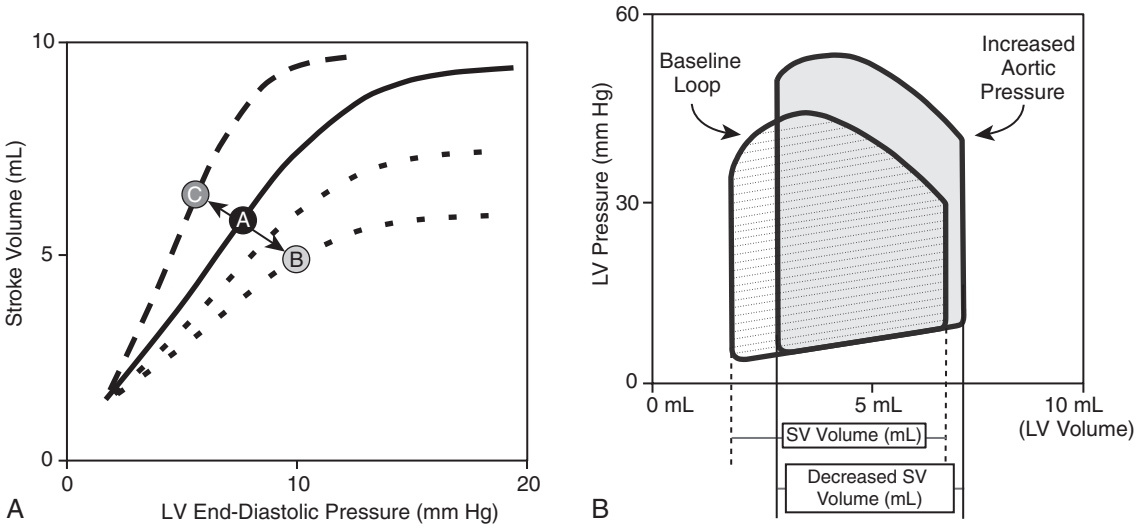

Fig. 15.2 Depiction of the effect of increasing afterload (represented by aortic pressure) on the left ventricle end-diastolic pressure–stroke volume relationship (Frank-Starling curves; A) and the left ventricle volume–pressure relationship (volume-pressure loop; B) adjusted for the neonatal heart with the heart rate, inotropy, and left ventricle wall thickness held constant. A shift in the stroke volume–LV end-diastolic pressure relationship from A to B and A to C occurs with increased and decreased afterload, respectively (A). In B, the baseline (control) volume–pressure loop is depicted by the stripes, whereas the shift in and change of the pressure–volume loop in response to the change in afterload is shown in gray. The decrease in stroke volume and the increase in end-diastolic and end-systolic left-ventricle pressure in response to the increased afterload are represented by the right and upward shift and narrowing of the pressure volume loop. (Modified from Klabunde RA: Effects of preload, afterload, and inotropy on ventricular pressure-volume loops. In Klabunde RA, editors: *Cardiovascular physiology concepts*, ed 2, Philadelphia PA, 2011, Lippincott Williams & Wilkins. http://www.cvphysiology.com/Cardiac %20Function/CF025.htm)

interplay that determine blood pressure will aid the clinician in making more appropriate management decisions, such as the choice of vasopressor-inotrope, inotrope, or lusitrope, and in deciding if volume administration is needed. The clinical components that affect blood pressure are shown in Fig. 15.3. As—in addition to heart rate—blood pressure is the most readily and accurately monitored clinical hemodynamic variable, the bedside clinician is often dependent on its measurement in the management of shock. However, the particular blood pressure value at which it is considered "too low" in a neonate is unclear.

NORMATIVE BLOOD PRESSURE DATA

A number of investigators have reported population-based normal ranges of blood pressure values based on gestational age, postnatal age, or birthweight. The majority of the data support the notion that larger and more mature infants have higher blood pressures. In addition, blood pressure also increases with postnatal age (Table 15.1) (Watkins et al, 1989). One of the common clinical practices is to consider the minimum acceptable mean blood pressure value to numerically equal the gestational age of the infant. This rather simplistic but practical approach is based on the 1992 recommendations from the Joint Working Group of the British Association of Perinatal Medicine (Development of audit measures, 1992). Of note is that a recent study of extremely

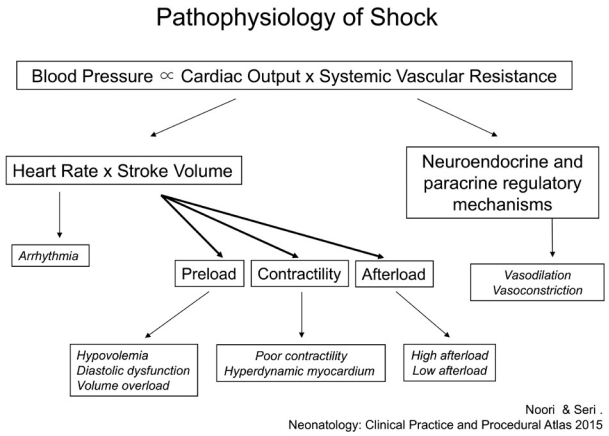

Fig. 15.3 Pathophysiology of neonatal shock. In accordance to Ohm's law, the two primary determinants of blood pressure are cardiac output and systemic vascular resistance. These two independent variables can be further broken down into the different hemodynamic variables shown. (From Noori S and Seri I, *Neonatology: clinical practice and procedural atlas,* United States of America, 2015, McGraw-Hill.)

preterm infants reported a higher survival rate without major morbidity and a lower rate of severe cerebral abnormalities when *isolated, clinically not symptomatic hypotension* (defined as the numeric value of blood pressure lower than that of the gestational age in weeks) was treated with volume, vasopressor-inotropes, and/or corticosteroids during the

TABLE 15.1 Average Mean Blood Pressure (MBP) and the 10th Percentile MBP for 131 Very Low Birth Weight Infants Throughout the First 3 days of Postnatal Life (MBP/10th percentile of MBP)

Birth Weight (g)	TIME (H) POSTNATAL AGE								
	3	12	24	36	48	60	72	84	96
500	35/23	36/24	37/25	38/26	39/28	41/29	42/30	43/31	44/33
600	35/24	36/25	37/26	39/27	40/28	41/29	42/31	44/32	45/33
700	36/24	37/25	38/26	39/28	42/29	42/30	43/31	44/32	45/34
800	36/25	37/26	39/27	40/28	41/29	42/31	44/32	45/33	46/34
900	37/25	38/26	39/27	40/29	42/30	43/31	44/32	45/34	47/35
1000	38/26	39/27	40/28	41/29	42/31	43/32	45/33	46/34	47/35
1100	38/27	39/37	40/29	42/30	43/31	44/32	45/34	46/35	48/36
1200	39/27	40/28	41/29	42/30	43/32	45/33	46/34	47/35	48/37
–	–	–	–	–	–	–	–	–	–
1400	40/28	42/29	42/30	43/32	44/33	46/34	47/35	48/36	49/38
1500	40/29	42/30	43/31	44/32	45/33	46/35	48/36	49/37	50/38

Numbers refer to average MBP/tenth percentile for MBP.
From Watkins AMC, West CR, Cooke RWI: Blood pressure and cerebral haemorrhage and ischaemia in very low birthweight infants, *Early Hum Develop* 19:103–110, 1989.

first 3 postnatal days (Durrmeyer et al, 2017). These findings suggest that in the present clinical practice, undetectable but clinically relevant changes in organ (brain) blood flow and oxygen delivery might accompany decreases in blood pressure that are considered harmless by many ("permissive hypotension").

Another approach is to use population-based norms as the accepted blood pressure range (Fig. 15.4) (Nuntnarumit et al, 1999).

Finally, based on the presumptive lower elbow of the cerebral blood flow autoregulatory curve, others have proposed the use of 28 to 30 mm Hg as the critical lower limit of acceptable blood pressure in preterm infants during the immediate transitional period (Greisen, 2012; McLean et al, 2012). Furthermore, it has been suggested that at mean arterial pressure below 28 to 30 mm Hg, the compromised and pressure passive cerebral blood flow may contribute to the development of intraventricular hemorrhage and periventricular leukomalacia (Kleinman and Seri, 2012; Munro et al, 2004). However, high level of evidence supporting this latter notion is lacking.

From these differing approaches, one can easily see why it has become extremely difficult to appropriately define neonatal hypotension (Munro et al, 2004) and to reach a general consensus on blood pressure management in the preterm neonate (Dempsey and Barrington, 2009; Noori, 2012b). The main reason for the confusion in defining neonatal hypotension is the simple fact that, aside from the heart rate, blood

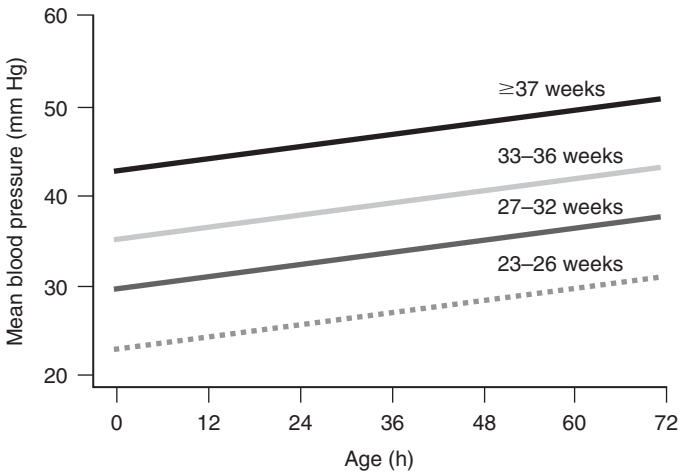

Fig. 15.4 Mean blood pressure (two-tail, 80% confidence interval) in 103 infants born at gestational ages of 23 to 43 weeks during the first 72 postnatal hours. The higher the gestational and postnatal age, the higher the mean blood pressure. (From Nuntnarumit P, Yang W, Bada-Ellzey HS: Blood pressure measurements in the newborn, *Clin Perinatol* 26[4]:981–96, 1999.)

pressure is the only continuously and routinely monitored hemodynamic variable. As blood pressure is the mathematically dependent variable in the equation determining systemic blood flow (CO = BP × SVR), a clinically relevant definition of hypotension and its treatment cannot be solely based on the blood pressure value. Indeed, with the exception of a recent large trial (Durrmeyer et al, 2017) evidence from randomized control studies is lacking on clinically relevant outcome measures of treatment of preterm infants with mean arterial pressures below gestational and postgestational age-dependent norms. However, the heterogeneity of clinical presentations and patient populations, the differences in the approach to treatment among the studies, and the differences in the patients' ability to compensate for the decreased blood pressure–associated decline in systemic and organ blood flow might, at least in part, explain why conclusive evidence could not be found to identify the lowest acceptable blood pressure range in preterm neonates in the transitional period. Importantly, this "magic" number is likely different among patients and also changes with time in the same patient due to the patient's ability to mount a successful compensatory response to maintain acceptable blood flow and oxygen delivery to the vital organs. Thus such a critical value cannot be determined for entire populations of preterm and term neonates. Rather, it will have to be defined in each patient at each point in time applying the concept of "precision medicine" (Soleymani et al, 2012).

Interestingly, a number of studies have found an association between early hypotension and subsequent peri/intraventricular hemorrhage (P/IVH) and poor neurodevelopmental outcome in premature infants (Watkins et al, 1989; Bada et al, 1990; Goldstein et al, 1995; Cunningham et al, 1999; Martens et al, 2003; Fanaroff et al, 2006; Limperopoulos et al, 2007; Batton et al, 2007; Pellicer et al, 2009). Of note, although the association between early postnatal hypotension and subsequent brain injury has been established, causation remains to be proven. On the other hand and as mentioned earlier, some studies have found blood pressure below gestational age alone did not affect neurodevelopmental outcome, possibly explained by the finding that treatment of hypotension by volume bolus or low to moderate dose dopamine did not change regional cerebral oxygen saturation significantly (Alderliesten et al, 2014; Bonestroo et al, 2011).

In summary, derangements in blood pressure are the result of uncompensated shock as also seen in our case. However, from the equation based on Ohm's law, we can also appreciate that even in the setting of cardiac dysfunction or impaired vasomotor tone, compensatory capacity even of the immature cardiovascular system might maintain blood pressure in the "normal" range. Accordingly, we can classify the hemodynamic status of a neonate into four major categories:

1. Cardiac dysfunction *with* compensatory increase in vasomotor tone,
2. Cardiac dysfunction *without* adequate compensation in vasomotor tone,
3. Vasomotor dysregulation leading to vasodilation *with* compensation in cardiac output, and
4. Vasomotor dysregulation leading to vasodilation *without* adequate compensation in cardiac output (Fig. 15.5).

Next, we turn our attention to direct and indirect hemodynamic assessments of systemic and end-organ perfusion along with the limitations of these approaches.

BLOOD PRESSURE MEASUREMENT

As discussed earlier, blood pressure has traditionally been the conventional determinant of initiating clinical intervention in the newborn with cardiovascular compromise. It is readily obtainable and frequently monitored invasively in the critical care setting. Blood pressure obtained through the umbilical arterial catheter and peripheral arterial line strongly correlate with one another with correlation values approaching of 0.98 for systolic pressure and 0.97 for diastolic pressure (Butt and Whyte, 1984). The correlation between noninvasive oscillometric measurements and invasive blood pressure measurements is also acceptable provided that appropriate cuff size is being used (0.45–0.55 cuff width-to-arm ratio), adequate pain control is provided, and there is an absence of movements or other procedures (Emery and Greenough, 1993; Dannevig et al, 2005) during the measurements.

Because hemodynamic changes can occur within seconds to minutes, different sampling frequencies of hemodynamic

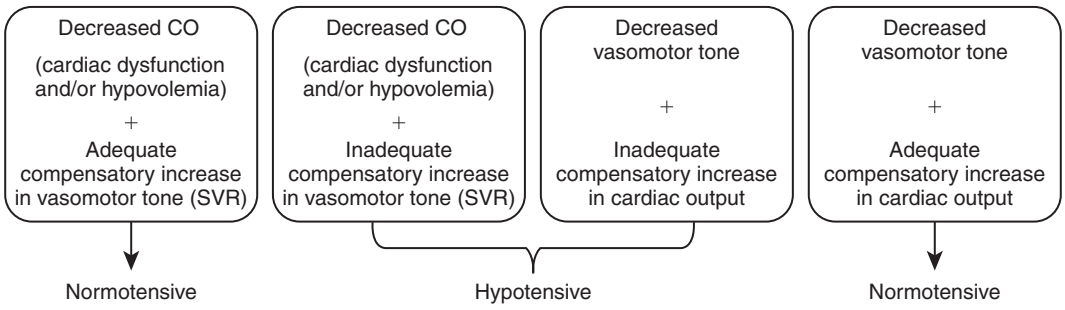

Fig. 15.5 Pathophysiology of neonatal cardiovascular compromise in primary myocardial dysfunction and primary abnormal vascular tone regulation with or without compensation by the unaffected other variable. This figure illustrates why blood pressure can remain in the "normal" range when there is appropriate compensatory increase in either vasomotor tone or cardiac output. In the hypotensive scenarios, there is inadequate compensatory increase in these variables. *CO,* Cardiac output.

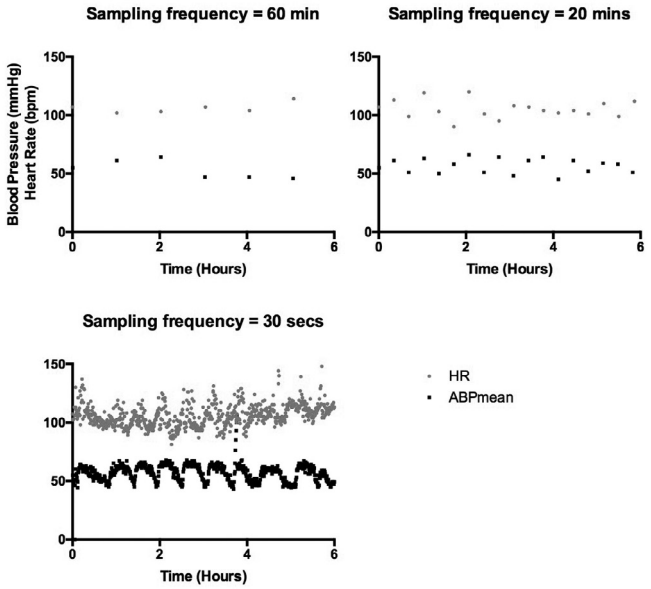

Fig. 15.6 Blood pressure and heart rate are plotted against time over 6 hours. With increasing sampling frequency (from every 60 minutes, every 20 minutes, and every 30 seconds), there is a more accurate depiction of the hemodynamic trends.

variables will alter interpretation of hemodynamic trends. Fig. 15.6 illustrates three different sampling frequencies for heart rate and blood pressure plotted against time in a term newborn with hypoxic-ischemic encephalopathy. Note the drastic differences in hemodynamic data that is derived when the sampling is increased in frequency.

SYSTEMIC BLOOD FLOW MEASUREMENT

Assessment of cardiac output is essential in critical care medicine, as it evaluates the ability of the heart to deliver a certain blood volume per unit time into the circulation, with the ultimate goal to maintain adequate oxygen delivery. Clinically, measurements by invasive means (thermodilution) are technically difficult in preterm neonates. More commonly, cardiac output measurement is obtained by echocardiography. Left ventricular output (LVO) can be derived from Doppler flow velocity measurements at the level of the aortic valve in conjunction with aortic valve diameter.

In most pediatric and adult patients, LVO measurements adequately represent systemic blood flow. However, in cases of premature neonates with a left-to-right shunt distal to the point of measurement, such as in the presence of a patent ductus arteriosus (PDA), LVO often overestimates systemic blood flow because a proportion of the blood ejected by the left ventricle is shunted to the pulmonary circulation through the ductus arteriosus. In this instance, LVO represents both pulmonary and systemic blood flow. Indeed, Kluckow and Evans found a poor correlation between mean blood pressure and LVO in preterm infants ($r = 0.14$) (Fig. 15.7A). The correlation improved only slightly in the cohort of neonates with a closed ductus arteriosus ($r = 0.38$), again illustrating the ability of the premature cardiovascular system to compensate and maintain an adequate blood pressure despite derangements in systemic blood flow (Fig. 15.7B, left upper quadrant of graph: normal MBP and low LV output) (Kluckow and Evans, 1996). Hence, studies have utilized superior vena cava (SVC) flow as a surrogate of systemic blood flow (Kluckow, 2000a; Hunt et al, 2004).

Although assessment of SVC flow has its technical limitations and thus requires a large number of patients to be included in a given study, its use as a surrogate of systemic blood flow is an intuitively reasonable approach in patients with the fetal channels open, especially when used in clinical trials (Fig. 15.8). Indeed, a significant association between low SVC flow and P/IVH (Kluckow, 2000a) and abnormal neurodevelopment at 3 years of age (Hunt et al, 2004) has been found. The same group of researchers also found no effect of treatment of low SVC flow with dopamine or dobutamine on death and neurodevelopmental disability compared with group of preterm neonates with normal SVC flow (Osborn et al, 2007). However, because the study did not include a nontreated control group with low SVC flow, used fixed doses of inotropes without titration to an optimum hemodynamic effect, and utilized SVC flow as a surrogate of systemic blood flow, the findings must be viewed with caution. Lastly, in a small cohort of premature neonates with septic shock managed by pressure-based algorithm, blood pressure improved in all patients—survivor and nonsurvivor. However, serial echocardiography to assess systemic blood flow changes revealed that there was no change in systemic blood flow despite a low SVR in survivors. In contrast, systemic blood flow decreased despite significant increases in SVR in nonsurvivors (de Waal and Evans, 2010). This further illustrates the intricacies of hemodynamic changes beyond blood pressure measurements that can only be detected by serial echocardiography or other systemic blood flow monitoring techniques (see later).

Another noninvasive method of cardiac output measurement is electrical velocimetry. Changes in red blood cell alignment throughout the cardiac cycle are detected in the form of electrical impedance and translated to blood velocity and calculated cardiac output. In hemodynamically stable infants without a PDA, there is clinically acceptable agreement in cardiac output measurements between echocardiography and electrical velocimetry (Noori et al, 2012a; Blohm et al, 2014; Torigoe et al, 2015). Its advantages include ease of use and ability to continuously monitor cardiac output. However, its use in the setting of hemodynamic instability and in presence of a PDA requires further validation. The presence of a PDA increases its bias and percent error compared with echocardiography (Torigoe et al, 2015) and should be used only to assess trend (Hsu et al, 2017) and not viewed as accurate absolute measurements of cardiac output.

INDIRECT MEASURES OF ORGAN PERFUSION

Clinical findings of hypotension and compromised organ blood flow can manifest as decreased capillary refill time (CRT), development of lactic acidosis, and/or decreased/absent urine output. These are often incorporated into routine physical examinations by the astute physician in the assessment of the hemodynamic status of the newborn.

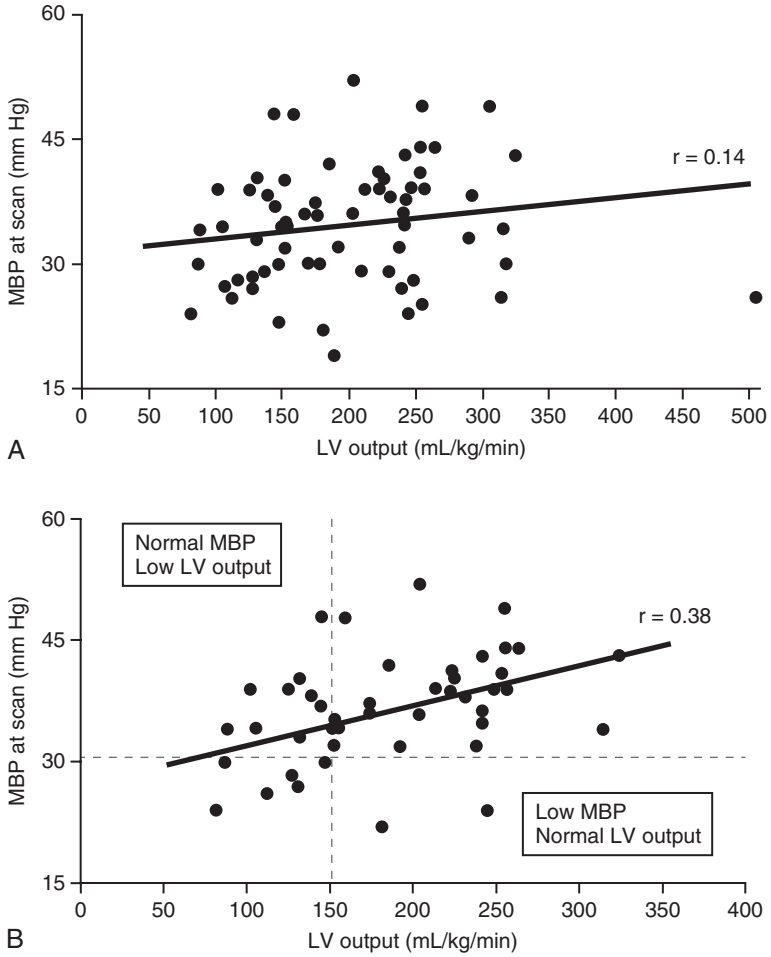

Fig. 15.7 Scatterplots illustrating the poor correlation between mean blood pressure (MBP) and left ventricular output (LVO) in 67 preterm infants requiring ventilation (Plot A) and in 45 preterm infants with closed ductus arteriosus (Plot B). (From Kluckow M, Evans N: Relationship between blood pressure and cardiac output in preterm infants requiring mechanical ventilation, *J Pediatr* 129[4]:506–12, 1996.)

Capillary Refill Time

Capillary refill time (seconds) is assessed by pressing the skin for 3 to 5 seconds and then measuring the time it takes for the capillary bed to refill and for the skin to return to its baseline color. The forehead and sternum are considered the most appropriate and reliable sites for measurement of CRT, and a value of greater than 3 seconds is generally considered as abnormal (Strozik et al, 1998; Weindling and Paize, 2010). CRT in the newborn does *not* correlate with blood pressure and has poor sensitivity and specificity in the detection of decreased systemic blood flow. Various factors are at play, including the site of assessment, duration of digital pressure, skin maturity, skin and ambient temperature, interobserver variability, presence of compensated shock, and medications. In a study of 128 infants less than 30 weeks' gestation, a CRT of 3 seconds only had a 55% sensitivity and 81% specificity in detecting low SVC blood flow (<41 mL/kg/min). The sensitivity to detect normal SVC flow improved to 78% when a CRT of less than 3 seconds was combined with a mean blood pressure of greater than 30 mm Hg (Osborn et al, 2004).

Lactic Acidosis

When organ blood flow has decreased to a critical level, tissue hypoxia occurs and anaerobic metabolism ensues, resulting in increased production of lactate. The finding of lactic acidosis (lactate levels >2.5 mmol/L and decreased pH) is thus a relatively late finding in neonatal circulatory compromise, and the associated decrease in pH must be differentiated from metabolic acidosis secondary to renal or, less frequently, enteral bicarbonate wasting of the preterm neonate. In severe circulatory collapse, lactate ion may primarily accumulate in the severely underperfused tissue bed and not be evident in the centralized systemic circulation. In that situation, the clinician might not fully appreciate the severity of acidosis initially. Thus following the resuscitation of these patients, lactic acidosis might first increase despite signs of improved tissue oxygen delivery (lactate "wash-out" phenomenon). In addition, one needs to be aware that as in the case earlier, when epinephrine is administered to manage neonatal cardiovascular compromise, lactate production will increase independent of the circulatory status and the patient's response to the treatment. This occurs because epinephrine,

via its selective beta-2 adrenoreceptor-mediated effects, enhances hepatic glycogenolysis and glycolysis. Therefore in the setting of hypotension treated by continuous infusion of epinephrine, lactate levels may become elevated and thus repeated assessment of changes in blood lactate levels can no longer serve as a reliable surrogate measure of tissue perfusion (Valverde et al, 2006).

Oliguria/Anuria

As decreases in urine output already occur during the compensated phase of shock, it often presents before lactic acidosis can be detected. As a filtering organ, the kidney receives around 20% of the cardiac output but it only requires approximately 5% to maintain cellular integrity and function. Thus in the early, compensated phase of shock the kidney is among the nonvital organs with the most significant decrease in tissue perfusion. Unfortunately, as urine output significantly decreases following delivery in every neonate, changes in urine output are difficult to use as early indirect evidence of compensated shock in the preterm neonate during the first postnatal day(s). On the other hand, as the immature renal tubules are unable to reabsorb solutes and water appropriately, the developmentally regulated glomerulotubular imbalance might result in relatively higher urine output even in the face of decreased glomerular filtration rate. Therefore, as with blood lactate measurements, repeated assessment of urine output and serum creatinine values along with a thorough understanding of developmental renal physiology are required to better understand the renal response to cardiovascular compromise in the preterm neonate.

DIRECT MEASURES OF ORGAN PERFUSION BY BEDSIDE EQUIPMENT

Assessment of systemic blood flow and organ blood flow distribution is a complex and difficult undertaking, especially because cardiovascular changes are dynamic in nature. Many factors can alter systemic and organ blood flow in seconds, including changes in tissue oxygen delivery and metabolic demand for oxygen, developmentally regulated changes in vital organ assignment, medications, volume, and type of fluid administration and so forth (Soleymani et al, 2012; Lemson et al, 2011). In addition, the physician must take into account the clinical context and the changes in the patient's condition. For a more comprehensive discussion on advanced hemodynamic monitoring, we refer the readers to reviews that discuss this matter in depth (Azhibekov et al, 2015).

CASE SUMMARY AND ADDITIONAL HEMODYNAMIC INFORMATION

Case Summary

- $24\frac{5}{7}$ weeks' gestation, 618 g preterm neonate who had received pharmacologic treatment for patent ductus arteriosus closure and subsequently developed spontaneous intestinal perforation. In addition, his blood culture was positive for gram-negative rods. Thus with the clinical presentation in mind, this patient also had a gram-negative sepsis.
- Patient could be appropriately ventilated on conventional ventilator after bedside Penrose drain insertion. However, metabolic acidosis persisted in the setting of hypotension and anuria.
- Blood pressure remained "low" despite repeated volume administration and escalating medium-to-high dose dopamine infusion with additional low-dose epinephrine treatment.

Additional Hemodynamic Information

To assess the infant's cardiovascular status more objectively and directly (Soleymani et al, 2012; Lemson et al, 2011), an echocardiogram was performed at bedside (Fig. 15.9). The study revealed adequate myocardial contractility with a shortening fraction of 48% (normal 28%–44%). In addition, both right ventricular output (RVO) and LVO were adequate at 282 mL/kg/min and 287 mL/kg/min (normal 150–300 mL/kg/min), respectively. End-organ blood flow was also indirectly assessed at the cerebral, enteral, and renal level by the use of Doppler ultrasound. Let us interpret the echocardiography findings first.

Shortening fraction (SF) is a measure of left ventricular (LV) systolic function and is calculated as follows:

$$\text{SF}\,(\%) = \frac{\text{LV end-diastolic diameter} - \text{LV end-systolic diameter}}{\text{LV end-diastolic diameter}} \times 100$$

Normal SF ranges between 28% and 44% (Eidem et al, 2010), but in extremely preterm infants, especially in early postnatal period, a value in low 20s may be acceptable (Noori, 2013). However, this measure is affected by both preload and afterload and thus values below the normal range may indicate intrinsic myocardial dysfunction and/or changes in the loading condition of the heart.

Right ventricular output may first appear to the reader as a measurement of blood flow to the pulmonary circulation. However, it is also a measure of the blood flow returning to the right side of the heart from the rest of the body. Therefore in the absence of significant atrial-level shunting, RVO also represents systemic blood flow. As previously stated, in the presence of a left-to-right shunting at the PDA, LVO becomes a measure for both systemic and pulmonary blood flow. In patients with left-to-right shunting across the PDA, assessment of right ventricular output or SVC flow (Kluckow and Evans, 2000) is thought to be a better measure of systemic blood flow. However, both techniques have their significant technical and pathophysiology-related limitations. For instance, significant left-to-right shunting through the foramen ovale renders RVO a less appropriate measure of systemic flow. The reader can better appreciate the complexity of the concept described here by looking at the schematic diagram in Fig. 15.8.

As for our case, cardiac contractility appears normal as suggested by the adequate fraction shortening. The cardiac

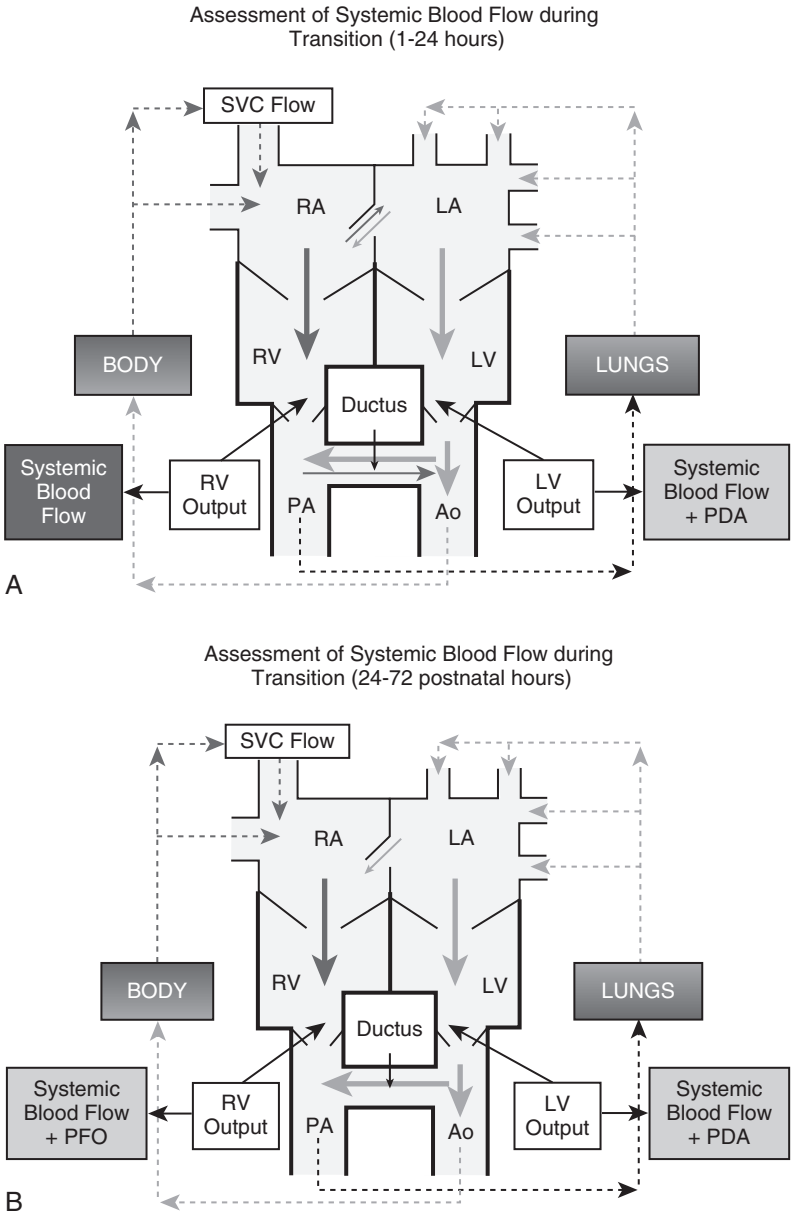

Fig. 15.8 Blood flow diagrams during 24 to 72 hours after delivery. Please note that, in the presence of a patent ductus arteriosus (PDA) and absence of significant atrial shunting, right ventricular (RV) output represents systemic blood flow and left ventricular (LV) output represents blood flow returning through the left atrium to the left ventricle and distributed between the pulmonary (via the left-to-right PDA flow) and systemic circulation.

output (both RVO and LVO) are also within normal range. Hence, we can deduce that the hypotension is not caused by myocardial dysfunction. Rather it is secondary to a significant decrease in the SVR (calculated as MBP−CVP/[LVO]=0.04 mm Hg/mL/kg/min) most likely due to a cytokine storm–induced vasodilatory shock in the setting of the gram-negative sepsis and without adequate compensatory increase of cardiac output. Furthermore, as LVO and RVO were virtually equal (282 and 287 mL/kg/min, respectively) and the diameter of the ductus arteriosus was relatively small with bidirectional shunting suggestive of near-systemic pulmonary pressure, the PDA did not play a significant role in the development of the systemic hypotension.

Aside from the assessment of systemic blood flow by functional echocardiography, surrogate measures of end-organ blood flow were also obtained by Doppler measurement of blood velocities at major arteries supplying the organ of interest. It is important to emphasize that the blood velocity (cm/second) is not equivalent to blood flow (mL/min). For our patient, there was evidence of impaired cerebral (reversal of flow during diastole), enteral (absent flow during diastole), and renal (significant reversal of flow during diastole) blood flow (Fig. 15.9).

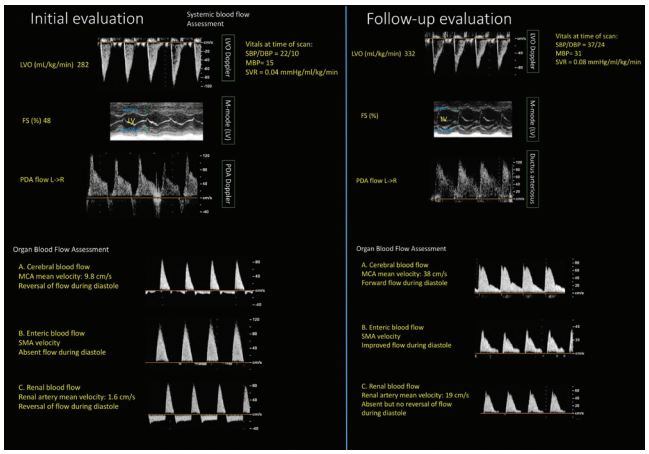

Fig. 15.9 Initial bedside echocardiography (left) of case patient and follow-up (right) 1 hour after increasing the dose of epinephrine. Left ventricular (LVO) output and fractional shortening (FS) were normal at 282 mL/kg/min and = 48%), respectively. Shunting across the PDA was left to right. Initial calculated SVR was extremely low (0.04 mm Hg/mL/kg/min). Also, indirect assessment of end-organ blood flow suggested that cerebral, enteric, and renal blood flow were compromised as Doppler velocity was either reversed or absent during diastole. After the adjustment of the dose of epinephrine, LVO increased to 332 mL/kg/min and calculated SVR doubled (0.08 mm Hg/mL/kg/min), while all organ blood flow measures improved showing more forward flow during diastole and overall higher mean velocities.

Thus we can now answer the question and claim that the *etiology* of the hypotension was a significantly decreased SVR and that the *pathophysiology* of the shock was vasodilation without an appropriate compensatory increase in cardiac output. In addition, the vasodilatory shock was in its uncompensated phase as indicated by the decrease in both vital (brain) and nonvital (kidney and intestine) organ blood flows along with the low blood pressure. The finding that cardiac output was "only" in the normal range demonstrated the patient's inability to compensate for the decrease in SVR by effectively increasing cardiac output. Our observation is that, as opposed to the more mature preterm or term neonates, very preterm neonates seldom mount an appropriate increase in their cardiac output when SVR falls. This is likely due to the developmentally regulated immaturity of their myocardium. However, and despite repeated volume administration, a potential contributory role of an inadequate circulating intravascular volume and thus preload in the less than adequate compensatory increase in systemic blood flow can only be entertained but not answered in this case. Finally, our very preterm patient did not have evidence of relative adrenal insufficiency as he presented with an appropriately elevated serum cortisol value (>60 mcg/dL).

In summary, based on the principles of cardiovascular physiology and assessment of the available data, we conclude that relying on blood pressure or blood flow *alone* cannot provide the necessary information for the clinician on which the diagnosis and treatment of neonatal cardiovascular compromise can be based. Rather, using *both* blood pressure *and* the available direct and indirect measures of systemic and organ blood flow holds the promise to facilitate the timely diagnosis and initiation of appropriate, pathophysiology-targeted treatment of neonatal shock. However, it must be emphasized that efficacy of any intervention in neonates must be assessed by *both* its short-term hemodynamic benefits *and* its impact on long-term neurodevelopmental outcome.

Question

Which of the following is a reasonable next step in hypotension management?

1. Continue current treatment and monitor signs of shock (urine output, blood lactate)
2. Start dobutamine infusion at 5 mcg/kg/min and titrate to achieve target MBP
3. Escalate the dose of dopamine infusion
4. Escalate the dose of epinephrine infusion
5. Start hydrocortisone with a 1 mg/kg loading dose followed by 0.5 mg/kg every 12 hours

Discussion of Answers

Now with the additional information confirming the clinical presentation of vasodilatory shock, let us discuss the management that best fits this infant's hemodynamic alterations.

Choice 1. Continue current treatment and monitor signs of shock (urine output, blood lactate).

This choice is inappropriate, as the infant is already in the *uncompensated phase* of shock and, as expected for this phase of shock, presents with impaired end-organ blood flow. Thus the infant is in circulatory collapse due to the inappropriately decreased SVR and requires vasoactive support to generate adequate perfusion pressure and improve organ blood flow.

Choices 2, 3, and 4. Start dobutamine (2), escalate dopamine (3), and escalate epinephrine (4) and titrate as appropriate.

Before selecting your drug of choice, it will be worthwhile to review the mechanisms of actions of each medication (Table 15.2) (Noori and Seri, 2012).

Dobutamine, the racemic mixture of its L- and D isoforms, is a synthetic catecholamine and it is classified as an inotrope due to its predominant β-adrenergic cardiac effects with less prominent β-adrenergic vascular and minimal α_1-adrenergic effects. Thus *dobutamine* significantly increases myocardial contractility while also providing some afterload relief (Eidem et al, 2010; Noori et al, 2013). However, it should be noted that, especially at higher doses, dobutamine might impair diastolic function (see later). *Dopamine* is a naturally occurring catecholamine classified as a vasopressor-inotrope. Dopamine exerts complex dose-dependent vascular, myocardial, renal, and endocrine effects and, due to developmentally regulated differences in cardiovascular adrenergic receptor expression, its dose-response curve differs in neonates from that seen in adults (Seri, 1995). At low doses, dopamine stimulates dopamine receptors (≥0.5 μg/kg/min) to induce primarily renal and mesenteric vasodilatation, direct renal tubular epithelial actions, and complex endocrine effects (Seri, 1995). At low-medium doses

TABLE 15.2 Estimated Relative Cardiovascular Receptor Stimulatory Effects of Inotropes, Lusitropes, and Vasopressors

	ADRENERGIC, DOPAMINERGIC, AND VASOPRESSIN RECEPTORS					
	α_1/α_2	β_2	α_1	β_1/β_2	DA_1/DA_2	V_{1a}
	Vascular	Vascular	Cardiac	Cardiac	Vascular/Cardiac	Vascular
Phenylephrine	++++	0	+	0	0	0
Norepinephrine	++++	+/0	++	++++	0	0
Epinephrine	++++	++++	++	++++	0	0
Dopamine[a]	++++	++	++	+++	++++	0
Dobutamine[b]	+/0	++	++	++++	0	0
Isoprenaline	0	+++	0	++++	0	0
Vasopressin	0	0	0	0	0	++++
PDE-III inhibitors	0	0	0	0	0	0
PDE-V inhibitors	0	0	0	0	0	0

Abbreviations: $\alpha_1/\alpha_2/\beta_1/\beta_2$, Subtypes of α- and β-adrenoreceptors; *DA,* dopamine; *DOB,* dobutamine; *PDE,* phosphodiesterase enzymes; *PDE-III* inhibitors used in neonates, amrinone, milrinone; *PDE-V* inhibitors used in neonates, sildenafil; V_{1a}, vasopressin reception expressed in the vasculature.

[a]Dopamine also has serotoninergic actions.

[b]Efficacy of dobutamine is independent of its affinity for adrenoreceptors.

From Noori S, Seri I: Neonatal blood pressure support: the use of inotropes, lusitropes, and other vasopressor agents, *Clin Perinatol* 39(1): 221–38, 2012.

of dopamine (≥2–4 μg/kg/min), the cardiovascular effects of vascular α-1 adrenoreceptor stimulation become apparent via increases in SVR and mild increase in myocardial contractility.

Finally, at somewhat higher doses (4–8 μg/kg/min), the drug-induced stimulation of the β-1 and β-2 adrenoreceptors results in increased myocardial contractility and heart rate; thus cardiac output increases. At even higher doses of dopamine, the α-1 adrenoreceptor stimulation induced peripheral vasoconstriction predominates. This can result in significant peripheral vasoconstriction, an increase in afterload and blood pressure with variable and, at inappropriately high doses, negative effects on systemic blood flow. Keep in mind that these dosing effects may not necessarily hold true in the critically ill premature infant, due to the immature cardiovascular system, the developmentally regulated differences in cardiovascular adrenoreceptor expression, and relative adrenocortical insufficiency (Seri, 1995). Epinephrine is a vasopressor-inotrope that has direct β-adrenergic myocardial and vascular effects at lower doses (0.01–0.1 μg/kg/min) and strong α-adrenergic effects at medium to high doses (>0.1 μg/kg/min). Thus epinephrine administration results in significant increases in myocardial contractility and cardiac output and peripheral vascular resistance and blood pressure (Noori and Seri, 2012). However, one must keep in mind that inappropriately high doses of vasopressor-inotropes (dopamine, epinephrine, and norepinephrine) might induce an overwhelming increase in SVR potentially resulting in decreased systemic blood flow. On the other hand, high doses of dobutamine, by decreasing myocardial compliance, might decrease ventricular filling and thus cardiac output (Noori and Seri, 2012).

Choice 2: Starting dobutamine infusion for its inotropic effect (Martinez, 1992; Robel-Tillig et al, 2007) is appropriate if there is evidence of cardiac dysfunction in the patient. Myocardial dysfunction is not an uncommon finding in pediatric and adult septic shock. Circulating cytokines may have direct inhibitory effects on myocyte contractility, although the precise mechanism has not been elucidated (Sevransky et al, 2007; Zanotti-Cavazzoni and Hollenberg, 2009). On the other hand, hemodynamic studies evaluating septic shock in premature infants found vasoregulatory failure to be the primary culprit, with compensatory increase in cardiac output or index (de Wall and Evans, 2010; Saini et al, 2014). In our case, functional echocardiography reveals a high fractional shortening and normal systemic blood flow. In addition, the mild peripheral vasodilatory effects of dobutamine may theoretically worsen the already depressed SVR.

Choices 3 and 4: Dopamine and epinephrine both can be helpful in improving cardiac output in patients with shock caused primarily by excessive vasodilation with or without myocardial dysfunction. However, the vasoconstrictive effects of these medications, especially at inappropriately high doses, can be counterproductive by increasing left ventricular afterload and decreasing systemic perfusion. Although there is a paucity of randomized trials to support epinephrine as the drug of choice in neonatal septic shock, epinephrine's profile makes it a desirable treatment choice. Indeed, its potent alpha-adrenergic effect is desired especially in shock secondary to vasodilatory failure. In the case, an epinephrine infusion dose of 0.01 mcg/kg/min is underdosed and can be titrated upward to reach the targeted vasoconstrictive effects. Indeed, 1 hour after stepwise titration of the epinephrine

infusion to a dose of 0.15 mcg/kg/min, systolic/diastolic (mean) blood pressure improved to 37/24 (Torigoe et al, 2015), and repeat hemodynamic assessment revealed an increase in LVO to 332 mL/kg/min, with maintenance of fractional shortening within the normal range, and a PDA with mostly left-to-right shunting. Accordingly, calculated SVR doubled to 0.08 mm Hg/mL/kg/min. Furthermore, there was an obvious improvement in end-organ blood flow at the cerebral (improved mean velocity without reversal or absent end diastolic flow), enteric (improved flow throughout diastole), and renal (improved mean velocity and no more reversal of flow) levels (Fig. 15.9). Of note is that findings of recent observational studies suggest that carefully titrated norepinephrine might also be an appropriate choice especially in cases with septic shock and enhanced pulmonary vasoconstriction (Rizk et al, 2018; Rowcliff et al, 2016).

Choice 5: Finally, a growing number of studies have found that in preterm infants with cardiovascular compromise not responding to conventional doses of vasopressor-inotropes, administration of low doses of steroids is followed by increases in blood pressure (Helbock et al, 1993; Seri et al, 2001; Ng et al, 2006) and improvement in systemic and organ blood flow (Noori et al, 2006). The genomic and nongenomic effects of gluco- and mineralocorticoids (Seri et al, 2001; Biniwale et al, 2013) and the documented high incidence of relative adrenal insufficiency of preterm infants are thought to explain these findings (Ng et al, 2004). As exposure of the preterm neonate during the postnatal first days and weeks to even low doses of dexamethasone is associated with long-term neurodevelopmental sequelae (Shinwell et al, 2000; Doyle and Davis, 2000), low-dose hydrocortisone thought to be devoid of such effects (Rademaker et al, 2007; Watterberg, 2007) has been used and perhaps overused to treat hypotension and cardiovascular compromise in very preterm neonates during the transitional period (Biniwale et al, 2013) and beyond. However, low-dose hydrocortisone is not devoid of side effects (Biniwale et al, 2013). Most concerning is the significant increase in spontaneous ileal perforations (SIPs) especially when hydrocortisone is coadministered with indomethacin or ibuprofen (Watterberg et al, 2004; Attridge et al, 2006). In the present case, as the serum cortisol level was appropriately elevated and the patient's primary condition likely contributing to the development of gram-negative sepsis, and thus septic shock was SIP, it would not be desirable to use hydrocortisone to improve the sensitivity of the cardiovascular system to catecholamines. However, if the patient's condition and hemodynamic status worsened despite the appropriate escalation of the dose of epinephrine, in addition to the use of norepinephrine (Rowcliff et al, 2016) or vasopressin (Rios and Kaiser, 2015), the administration of hydrocortisone might be considered.

CONCLUSION

As discussed in this chapter, treatment of "hypotension" and circulatory compromise in the premature newborn is complicated, and bedside functional echocardiography along with real-time, comprehensive, noninvasive, and continuous hemodynamic monitoring can help affirm the etiology of hypotension and guide management. Continuous hemodynamic assessment and trending of the response to treatment are the cornerstones of the treatment of preterm infants with cardiovascular compromise. Although the gestational- and postnatal-age dependent normal range of blood pressure is not well defined in preterm infants (McLean et al, 2012; Dempsey and Barrington, 2009), there is recently emerging evidence that treatment of even clinically nonsymptomatic neonatal "hypotension" affects clinical relevant long-term outcome measures (Durrmeyer et al, 2017). Yet clearly more data are needed before routine treatment of clinically nonsymptomatic neonatal hypotension can be recommended.

On the other hand, blood pressure in the perceived normal range can be falsely reassuring as the infant may be in the early, "compensated" phase of shock. To make matters even more complicated, "low blood pressure" does not always imply poor organ perfusion, as myocardial compensation may provide for appropriate organ blood flow even at relatively lower perfusion pressures. It is thus no wonder why no consensus exists on the diagnosis and treatment of early hypotension in the preterm infant.

Based on the available evidence and the principles of cardiovascular physiology briefly presented in this chapter, the authors advocate that both blood pressure and indirect and/or direct measures of systemic and organ blood flow be taken into consideration when decision about the initiation of treatment of suspected shock in preterm neonates is being considered. Accordingly, in routine clinical care, blood pressure should be used as one of the screening tools for cardiovascular compromise and the indirect clinical and laboratory signs of systemic and organ blood flow such as CRT, urine output, and lactic acidosis should be incorporated in assessment of cardiovascular function. Most importantly, tools such as comprehensive noninvasive and continuous hemodynamic monitoring and functional echocardiography are clearly necessary to complement the physical examination and aid in management targeted at the underlying pathomechanism.

Finally, in neonates with perinatal infection, a high index of suspicion for poor regulation of the vascular tone should be considered, as these patients might respond to carefully titrated dopamine, epinephrine, norepinephrine, or vasopressin treatment (Valverde et al, 2006; Noori and Seri, 2012; Zanotti-Cavazzoni and Hollenberg, 2009; Rowcliff et al, 2016; Rios and Kaiser, 2015). Continuous, real-time recordings of comprehensive hemodynamic monitoring systems (Azhibekov et al, 2015) and bedside echocardiograms will help to assess the underlying abnormal vasomotor tone regulation, myocardial dysfunction, intravascular volume status, or all and provide more objective information on the status of systemic and organ blood flow.

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Abstract: Systemic hypotension often occurs in the preterm neonate, especially during transition. Although there are population-based blood pressure values that raise concern among caregivers, the specific cut-off values for the individual patient requiring intervention are not known. In fact, the blood pressure values that represent decreased systemic and organ blood flow in the given patient depend on the underlying pathophysiology and the patient's developmentally regulated ability to compensate for the decrease in perfusion pressure and might even differ in different points in time. The goal of this chapter is to illustrate the complexity involved in the diagnosis and management of neonatal hypotension and guide the clinician in decision making using available evidence and a physiology-based individualized approach. This chapter describes a real clinical scenario with a type of cardiovascular compromise frequently seen and asks the reader to make clinical decisions based on the data provided. Along with the description of the case, the chapter also presents the current evidence for and the pitfalls of the definition, diagnosis, and management of neonatal hypotension.
Keywords: Neonate, preterm neonate, hypotension, myocardial function, cardiac output, systemic blood flow, organ blood flow, neonatal shock, hemodynamic monitoring, functional echocardiography

16

Congenital Heart Disease in the Newborn Period

Ganga Krishnamurthy, Veniamin Ratner, Stéphanie Levasseur and S. David Rubenstein

INTRODUCTION

Children with congenital heart disease (CHD) have structural defects of the heart and/or great vessels that are present before birth. Defects range from relatively simple lesions, which neither induce symptoms nor need therapy, to complex life-threatening lesions, which require surgery in the neonatal period.

CHD is the most common birth defect. Recent prevalence estimates for CHD range from 6 to 10 per 1000 live births. Approximately 40,000 infants are born with a congenital heart defect each year in the United States.

One of every four infants with CHD has *critical CHD* (i.e., a defect that requires either a surgical or a transcatheter procedure within the first year of life for survival). Ductal-dependent heart defects, which require the ductus arteriosus to remain patent after birth to ensure survival, are examples of critical lesions.

FETAL CIRCULATION

Before birth, the fetus is dependent on the utero-placental unit for survival. The relatively oxygen-rich blood from the placenta enters the inferior vena cava via the umbilical vein and ductus venosus. Preferential streaming of blood occurs in the right atrium between the blood returning via the superior vena cava (relatively oxygen poor) and that returning from the inferior vena cava (Rudolph, 2009). The more highly saturated blood from the inferior vena cava crosses the foramen ovale to the left side of the heart, facilitating delivery of blood with relatively high oxygen content to the fetal myocardium and brain (Edelstone and Rudolph, 1979). Deoxygenated fetal blood returning from the superior vena cava travels through the right ventricle, across the ductus arteriosus, and down the descending aorta to the placenta, where oxygen and carbon dioxide transfer occurs via simple diffusion. Both the fetal right and left ventricles are responsible for blood flow to the systemic circuit and placenta. Because the resistance in the fetal pulmonary vasculature is high, less than 15% of right ventricular output is delivered to the lungs (Rudolph, 2009). Thus the parallel fetal circulatory system promotes efficient oxygen delivery in a relatively hypoxic environment (Fig. 16.1A).

The fetal circulation is forgiving to neonates with even the most severe forms of CHD. Intra- and extracardiac shunts allow fetal circulatory adaptations to abnormal heart anatomy. For example, in neonates with severe obstruction to either ventricular outflow tract, diversion of flow into the other ventricle and great vessel occurs across the foramen ovale and the ductus arteriosus.

CASE STUDY 1

A 3.2 kg infant is born via cesarean section (due to nonprogression of labor) at 39 weeks' gestation to a primigravida woman with an unremarkable medical and obstetric history. The infant is breathing comfortably and appears pink. There are no risk factors for infection. At 5 minutes of life, the preductal saturation value in room air is 90% and the postductal value is 82%.

Exercise 1

Question

What is the best course of action for this infant?

A. Continued observation
B. Consultation with pediatric cardiology
C. Stat echocardiogram
D. Four extremity blood pressures
E. Arterial blood gas determination from the left radial artery.

Answer

A

Transitional Circulation

Most of the circulatory changes that happen in the transition from intra- to extrauterine life occur in the first few moments after birth, with additional circulatory adjustments occurring over a period of several weeks. The primary events that trigger the alteration in blood flow patterns are removal of the low resistance placental circuit and the establishment of alveolar ventilation (Rudolph, 2009). With establishment of alveolar gas volume, there is a substantial decline in pulmonary vascular resistance and a several-fold increase in pulmonary blood flow. A rise in left atrial pressure results from an increase in pulmonary venous return and allows closure of the foramen

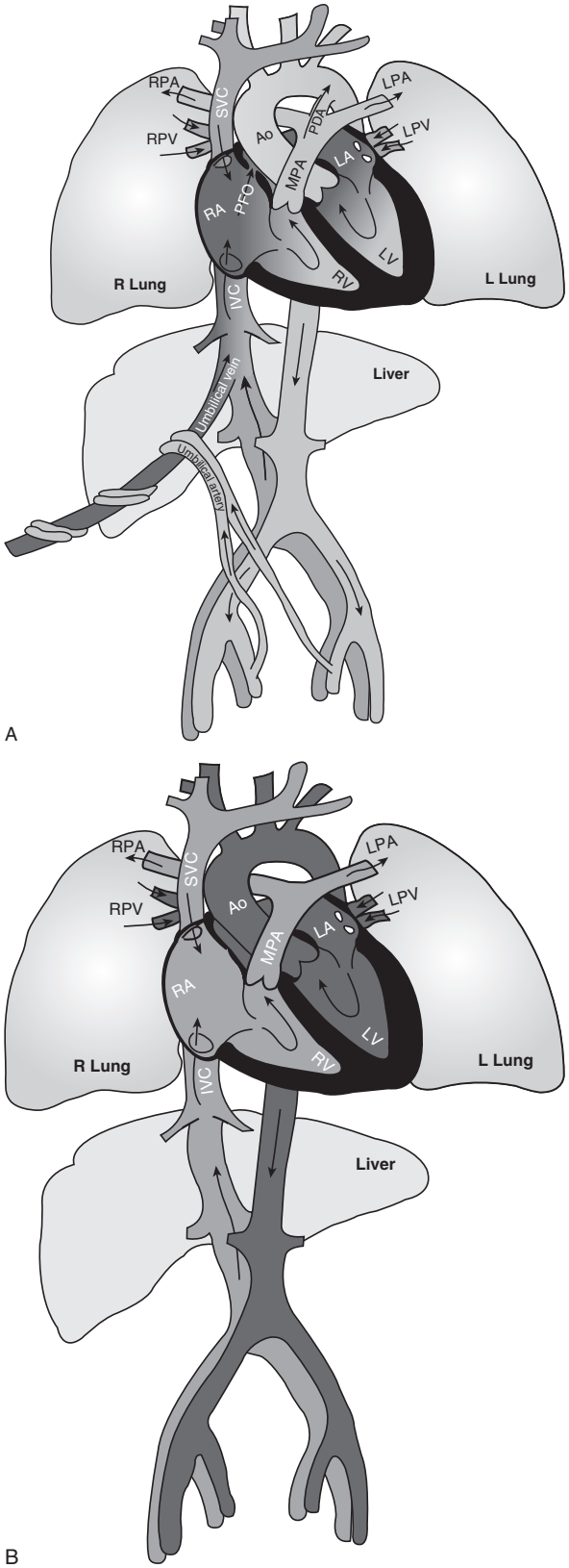

Fig. 16.1 (A) Fetal circulation. (B) Adult circulation. Arrows depict direction of blood flow. *Ao,* Aorta; *IVC,* inferior vena cava; *LA,* left atrium; *L Lung,* left lung; *LPA,* left pulmonary artery; *LPV,* left pulmonary veins; *LV,* left ventricle; *MPA,* main pulmonary artery; *PDA,* patent ductus arteriosus; *PFO,* patent foramen ovale; *RA,* right atrium; *R Lung,* right lung; *RPA,* right pulmonary artery; *RPV,* right pulmonary veins; *RV,* right ventricle; *SVC,* superior vena cava.

ovale, abolishing the atrial level shunt. The higher oxygen tension in the blood initiates postnatal closure of the ductus arteriosus, establishes complete separation of pulmonary and systemic blood flows, and leads to a circulation in series (Fig. 16.1B). In full-term infants, functional closure of the ductus arteriosus is initiated within the first hours and days following birth, and anatomic closure follows.

The switch from a parallel fetal circulation to a transitional circulation in series results in a slow rise in hemoglobin oxygen saturation in the first few minutes after birth. The median preductal oxygen saturation in healthy term newborn babies is around 90% at 5 minutes of life and increases to 98% by 15 minutes. Postductal oxygen saturation is significantly lower than the preductal oxygen saturation in the first 15 minutes of life, with oxygen saturation gradient narrowing over time. Babies born by cesarean section have lower pre- and postductal oxygen saturations in the first 15 minutes of life compared with those born vaginally. The neonate described in Case Study 1 is exhibiting a normal postnatal transition and therefore warrants only continued observation.

Postnatal closure of fetal shunts can be life threatening in babies with ductal-dependent CHD. Closure of the ductus arteriosus can lead to hypoxemia and cyanosis when there is severe anatomic obstruction to pulmonary blood flow and decreased perfusion to vital organs when there is severe anatomic obstruction to systemic blood flow. The ductus arteriosus with rare exceptions is patent at birth and hence these signs will rarely be noted in the delivery room during transition.

The transitional period can be life threatening in babies with d-transposition of the great arteries with an intact ventricular septum (d-TGA/IVS). Postnatal closure of the foramen ovale can cause severe hypoxemia in babies with this condition. In this lesion, the aorta arises from the right ventricle and the pulmonary artery arises from the left ventricle. After birth, the circulation remains in parallel and severe hypoxemia may result if the shunt at the atrial level is abolished. Only adequate mixing at the atrial level will permit a stable transition. Transition to extrauterine life may also be difficult in babies with hypoplastic left heart syndrome (HLHS) with mitral atresia and an intact or restrictive atrial septum. Because of restricted egress of pulmonary venous return, pulmonary edema quickly ensues, and hence these babies are severely hypoxemic from birth with signs of inadequate cardiac output. However, with the few exceptions described earlier, most babies with CHD should transition normally.

SCREENING METHODS FOR CONGENITAL HEART DISEASE

Although antenatal diagnosis of CHD is increasing, a significant proportion of babies with CHD are not diagnosed before birth. Postnatal diagnosis of CHD in the delivery room or the newborn nursery is possible only if signs of CHD manifest during the hospital stay or if there is a universal screening protocol utilizing pulse oximetry. In a review of 20-year trends in the diagnosis of life-threatening cardiovascular malformations, 62% of babies with such

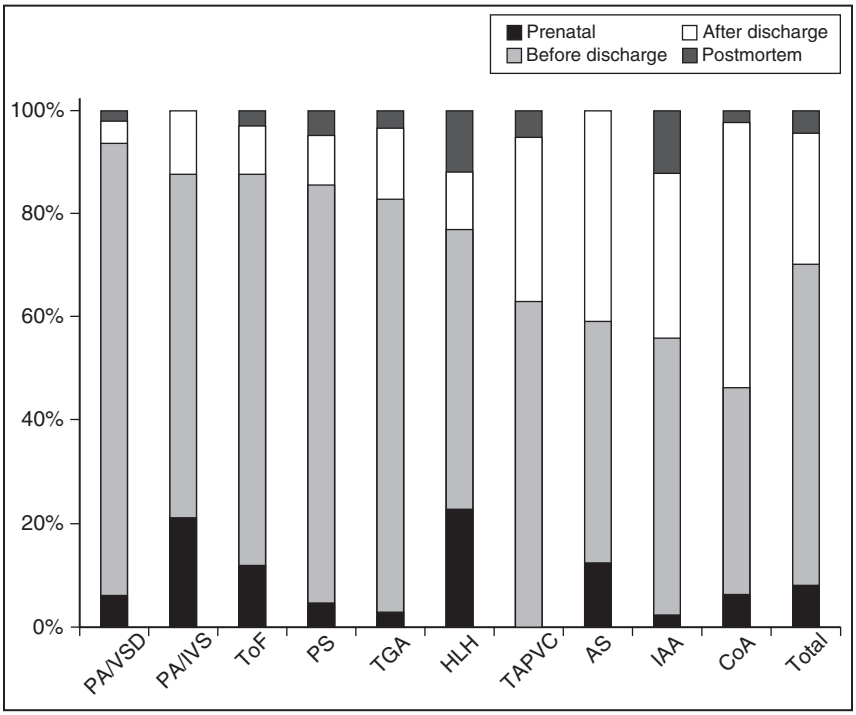

Fig. 16.2 Congenital heart disease and timing of diagnosis. *AS,* Aortic stenosis; *CoA,* coarctation of the aorta; *HLH,* hypoplastic left heart syndrome; *IAA,* interrupted aortic arch; *PA/IVS,* pulmonary atresia, intact ventricular septum; *PA/VSD,* pulmonary atresia, ventricular septal defect; *PS,* pulmonary stenosis; *TAPVC,* totally anomalous pulmonary venous connection; *TGA,* transposition of the great arteries; *ToF,* tetralogy of Fallot. (Adapted from Wren C, et al: Twenty-year trends in diagnosis of life-threatening neonatal cardiovascular malformations, *Arch Dis Child Fetal Neonatal Ed* 93[1]:F33–F35, 2008, with permission from BMJ Publishing Group Ltd.)

lesions presented before discharge from the hospital, 25% of babies with critical CHD were diagnosed after discharge from the nursery, and 5% were diagnosed at autopsy (Fig. 16.2) (Wren et al, 2008). Babies with left sided obstructive lesions such as coarctation of the aorta were more likely to be diagnosed after discharge from the nursery (Fig. 16.2), whereas those who had cyanotic CHD were more likely to be identified while still in the nursery.

Critical CHD is difficult to uncover in asymptomatic newborn infants because several congenital heart defects do not produce visible central cyanosis despite severe hypoxemia. Screening by pulse oximetry provides an opportunity to detect clinically silent hypoxemia in critical CHD. In September 2011, the U.S. Department of Health and Human Services recommended that all newborns be screened for critical CHD before discharge from the newborn nursery using pulse oximetry. This recommendation has been endorsed by several national organizations, including the American Academy of Pediatrics. Pulse oximetry has now been included in the Recommended Uniform Screening Panel for newborns across several states. The proposed newborn screening strategy is described in Fig. 16.3.

Screening by pulse oximetry is highly specific for detection of critical CHD (99.9%) and has moderate sensitivity (70%). The false positive rate is very low (0.035%) when screening occurs after 24 hours of age (Mahle et al, 2009, 2012). It is important to note that although pulse oximetry is generally a reliable screening tool, it can miss lesions, particularly those that involve obstruction to systemic blood flow.

Neonates with critical CHD may escape detection at all three stages of screening (i.e., antenatal ultrasound, routine neonatal examination in the nursery, and pulse oximetry). A high index of suspicion, along with prompt and timely recognition of babies with critical CHD, improves prognosis.

EVALUATION OF NEONATES FOR CHD

History

Most babies with critical CHD follow an ordinary transition to extrauterine life, and perinatal history is often unremarkable. The *absence* of important clinical information that would foster the consideration of an alternative diagnosis is a notable feature of CHD. For example, babies with severely obstructed totally anomalous pulmonary venous connection commonly present with respiratory distress and cyanosis within the first 24 hours of life. However, respiratory distress is a common symptom in neonates and has several etiologies. Fortunately, in most of these other disorders, the etiology is apparent from the history. Respiratory distress caused by surfactant deficiency is seen in preterm or late-preterm infants and is rarely encountered in infants born at term. Respiratory distress caused by an invasive bacterial infection is likely if there is a maternal history of prolonged rupture of membranes, a history of chorioamnionitis or maternal vaginal

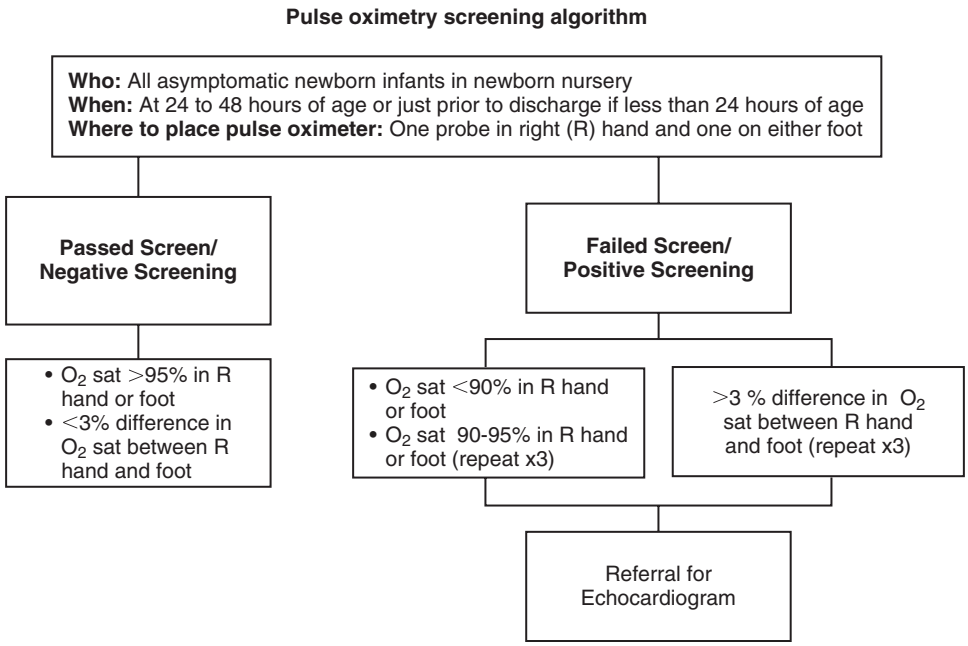

Fig. 16.3 Algorithm for pulse oximetry screening for congenital heart disease.

carriage of group B *Streptococcus*. In the presence of such historical data, a diagnosis of the usual etiologies of respiratory distress (e.g., sepsis or surfactant deficiency) is easily made. It is the *absence* of such relevant historical information that makes a diagnosis of CHD more likely.

Babies with cyanotic CHD usually present with cyanosis or cyanotic "spells." Lesions that cause obstruction to pulmonary blood flow or poor mixing often present during the initial hospital stay in the nursery. In these patients, cyanosis may not be noticed at birth because the ductus arteriosus is still patent. Parents or medical caretakers may initially note transient cyanosis during crying or feeding. As the ductus arteriosus begins to close, cyanosis becomes more apparent and persistent. Most importantly, despite the cyanosis, a history of respiratory distress with dyspnea is usually not elicited.

Parents of babies with left sided obstructive lesions may report an increase in the rate of breathing, irritability, and progressive difficulty in feeding. These symptoms emerge as systemic blood flow becomes compromised with closure of the ductus arteriosus. Infants usually present after nursery discharge, typically within the first 2 weeks of life. As circulatory failure ensues, patients may present to the emergency room in extremis.

Babies with large left-to-right shunts manifest symptoms of heart failure (e.g., rapid respirations, diaphoresis, feeding difficulties). These symptoms are subtle at first, usually appear by 4 to 6 weeks of age, and worsen over time.

PHYSICAL EXAMINATION

General Physical Examination

Anthropometric measurements: Weight, height, and head circumference should be measured. A small head circumference is noted in some babies with CHD, such as hypoplastic left heart syndrome. In babies with congestive cardiac failure who are several weeks old, comparison of current weight to birth weight may uncover inadequate interim growth.

Vital signs: Tachycardia (normal heart rate 120–160 beats/minute) in babies with CHD may be reflective of depressed ventricular function. An increased respiratory rate (normal 40–60 breaths/minute) may be caused by pulmonary edema, excessive pulmonary blood flow, or metabolic acidosis. Blood pressure should be measured in all four extremities. Normally, the measured blood pressure in the lower extremities is a little higher than that measured in the upper extremities. A blood pressure gradient of greater than 10 to 20 mm Hg between the right arm and lower extremities may indicate juxta-ductal coarctation of the aorta or interruption of the aortic arch. Systemic hemoglobin oxygen saturation should be measured using pulse oximetry. Ideally, both preductal (right hand) and postductal (any foot) hemoglobin oxygen saturation values should be recorded simultaneously. Normally, both preductal and postductal saturations are above 95% with minimal difference in measurements. Low (<95%) preductal or postductal saturation may be suggestive of cyanotic CHD especially in the absence of respiratory symptoms.

General examination: CHD often has an underlying genetic etiology with recognizable patterns indicative of a chromosomal abnormality or syndrome. Underlying hypoxemia with central cyanosis is best recognized in the buccal mucosa, lips, and tongue. Cool extremities, feeble pulses, mottled skin, and prolonged capillary refill time indicate poor cardiac output and systemic perfusion. Peripheral pulses are globally diminished when ventricular function is depressed. Disparity in both pulses and blood pressure between the upper and lower extremities suggests juxtaductal coarctation of the aorta or interruption of the aortic arch distal to the origin of the left subclavian artery.

Cardiovascular examination: The site of precordial activity should be noted. Dextrocardia should be suspected if the precordial impulse or activity is noted over the right hemithorax rather than the left. Parasternal impulse rather than an apical impulse is normal in neonates and signifies right ventricular dominance. A prominent parasternal impulse is noted with right ventricular pressure overload (right ventricular outflow tract obstructive lesions, pulmonary hypertension, and d-TGA). A diminished parasternal impulse is noted in right ventricular inflow obstruction (e.g., tricuspid atresia or tricuspid stenosis with hypoplasia of the right ventricle). Left ventricular volume overload in infants with left-to-right shunts (large ventricular septal defect, large patent ductus arteriosus) causes a prominent and hyperdynamic apical impulse.

Abnormalities of the first heart sound are rarely appreciated in newborns. Split S_1 may be seen in infants with Ebstein's anomaly. Soon after birth, when the pulmonary vascular resistance is still elevated, closure of both aortic and pulmonary valves occurs almost simultaneously. Hence, a single S_2 is commonly heard. As the pulmonary vascular resistance falls, the pulmonary valve closes after the aortic valve and a split S_2 becomes apparent. A rapid heart rate makes it difficult to appreciate physiologic splitting of the second heart sound in newborn infants. Fixed splitting of the second heart sound in newborns is heard when pulmonary blood flow is excessive, as in unobstructed total or partial anomalous pulmonary venous connection. Wide, fixed splitting of the second heart sound occurs in atrial septal defects but is not typically heard in the newborn period. A split second heart sound is also appreciated when there is right ventricular obstruction or conduction delay. A single second heart sound is appreciated when there is only one semilunar valve, as in pulmonary or aortic atresia or truncus arteriosus. A loud pulmonic component is heard in pulmonary hypertension, whereas a soft P_2 may suggest pulmonary stenosis. Stenosis of semilunar valves, a bicuspid aortic valve, or a dysplastic truncal valve (truncus arteriosus) may produce additional sounds or ejection clicks. A midsystolic click is sometimes appreciated in Ebstein's anomaly or with mitral valve prolapse.

Murmurs are often associated with structural abnormalities of the heart. Quite often, the murmurs are innocent and bear little clinical significance. It may be difficult for the inexperienced practitioner to distinguish innocent from pathologic murmurs. A systematic approach to evaluation may assist in identifying an underlying anatomic malformation causing the cardiac murmur. The intensity, quality, location, radiation, duration, and timing of the murmur should be assessed. Murmurs can occur during systole, diastole, or continuously during the entire cardiac cycle. Timing and duration of murmurs during the different phases of systole or diastole should be noted. A harsh murmur of at least grade 3 intensity—best heard in the left lower sternal border and occupying the whole duration of systole—is likely to be secondary to a ventricular septal defect. A harsh 3- to 4-grade intensity murmur with a crescendo–decrescendo configuration, best heard in the upper right sternal border and radiating to the carotids, may suggest stenosis of the aortic valve. A murmur heard continuously across systole and diastole and best appreciated in the left upper sternal border is probably due to a widely patent ductus arteriosus. Innocent murmurs are common in the newborn period. Innocent murmurs are softer, occur in systole, and do not have accompanying symptoms. It is extremely important to note that the absence of murmur does *not* rule out CHD.

Pulmonary examination: Respiratory rate, effort, quality of breath sounds, and the presence of adventitious sounds should be assessed. Babies with significant left-to-right shunts and increased pulmonary blood flow are tachypneic and show an increased respiratory effort. Most babies with cyanotic CHD exhibit normal respiratory activity despite low oxygen saturation. A *normal* respiratory examination in the presence of cyanosis *strongly* suggests CHD.

Abdominal examination: Location and size of the liver should be assessed. A left sided liver is present in situs inversus and a midline liver is often noted in heterotaxy syndromes. Hepatomegaly suggests hepatic congestion and right ventricular dysfunction or volume overload. Neonates with hepatic arteriovenous malformation and high output cardiac failure may have a bruit over the liver.

Diagnostic Tests

Chest radiograph: Characteristic chest radiographs may be useful in the diagnosis of some CHD. However, in most cases of CHD, chest radiographs are rarely diagnostic.

Electrocardiogram: A 12-lead electrocardiogram (ECG) often reveals typical ECG findings in some types of CHD. However, a normal ECG should *not* rule out the presence of a serious underlying CHD.

Hyperoxia test: Hyperoxia test is helpful in differentiating hypoxemia caused by structural heart disease from that caused by lung disease. Arterial blood gas is obtained at baseline and after exposure to 100% oxygen under an oxyhood for at least 15 minutes. Babies with structural heart disease do not show a significant increase in Pao_2 (remains less than 150 mm Hg) after exposure to 100% oxygen.

Echocardiogram: An immediate cardiology consultation should be requested when CHD is suspected. Echocardiogram is often the only definitive procedure required to confirm a diagnosis of structural heart disease.

Blood tests: Baseline blood work includes complete blood count to help rule out infection, serum chemistry to assess for electrolyte and renal function abnormalities, and an arterial blood gas with lactate level to assess gas exchange and the presence or absence of lactic acidosis.

Early Management and Stabilization

Airway, breathing, and circulation must be assessed in patients with signs consistent with pulmonary or cardiac disease. In patients presenting with severe hypoxia and increased respiratory effort, intubation and mechanical ventilation may assist in improving gas exchange. Circulation cannot be reestablished without a patent ductus

arteriosus in ductal-dependent lesions. Prostaglandin E1 (PGE-1) infusion can reopen a closing ductus arteriosus and must be initiated as soon as ductal-dependent CHD is suspected. It is not necessary to wait for an echocardiogram for confirmatory evidence before initiating a PGE-1 infusion except in cases of totally anomalous pulmonary venous connection where an infusion of PGE-1 has the potential to increase pulmonary edema, thereby worsening oxygenation. Reopening the ductus arteriosus will improve oxygen saturation in patients with ductal-dependent pulmonary circulation, and systemic perfusion will improve in patients with ductal-dependent systemic circulation after initiation of a PGE-1 infusion. Correction of hypovolemia and initiation of cardiotonic drugs to enhance inotropy may be required in patients presenting in cardiogenic shock. Metabolic derangements including hypoglycemia and hypocalcemia should be corrected. Early transfer to a cardiac center is important.

The three **major** presenting features of CHD in the newborn period are *central cyanosis, decreased perfusion to the body,* and *tachypnea.* The predominant clinical manifestation depends on the type of CHD. The following case studies provide examples of typical presentations of CHD.

EVALUATION OF THE CYANOTIC NEWBORN

CASE 2

A 32-year old gravida 2, para 1 woman delivers a male infant at 39 weeks by elective cesarean section. Routine prenatal laboratory tests are unremarkable. Normal fetal anatomy was noted on an 18-week screening ultrasound.

A term male infant with a vigorous cry is handed to you. Apgar scores of 8 and 8 at 1 and 5 minutes respectively are assigned. You provide free flow oxygen at 10 minutes of life for central cyanosis. There is minimal improvement in skin color. At 20 minutes of life, you note that the baby's face, oral mucosa, and tongue continue to have a bluish hue but the abdomen and both legs appear pinker. The baby is breathing comfortably (respiratory rate is 50 breaths/minute) with neither grunting nor subcostal retractions, that is, without dyspnea. The lungs are clear to auscultation with equal air entry. The precordium is quiet, the heart rate and rhythm are normal, and there are no murmurs heard. The second heart sound is loud. Peripheral pulses are normal. There is no hepatomegaly. A chest radiograph shows well-aerated lung fields with no focal pathology, a normal heart size, and a left aortic arch.

Exercise 2

Questions

1. Indicate whether the following statements are true (T) or false (F):
   A. Peripheral cyanosis signals underlying arterial hypoxemia.
   B. Clinical recognition of central cyanosis is easier in neonates with polycythemia than in those with a normal hemoglobin concentration.
   C. This infant's cyanosis is most likely related to lung disease.
2. What is the differential diagnosis of central cyanosis in a newborn infant?

Answers

1. **A:** F; **B:** T; **C:** F
2. See Fig. 16.4.

Because the normal systemic arterial oxygen saturation in fetal life is around 60% to 65%, generalized cyanosis at birth is a normal finding but is transient. In most babies who are born at term, skin color improves rapidly as alveolar ventilation is established. Persistent cyanosis is abnormal. Cyanosis signals the presence of elevated levels of deoxyhemoglobin in the underlying capillaries. At least 3 to 5 g/dL of deoxyhemoglobin should be present in the microcirculation for cyanosis to be apparent. Cyanosis may not be recognized if deoxyhemoglobin levels are less than this critical amount. For example, let us assume that this infant has a total hemoglobin concentration of 18 g/dL and an oxygen saturation of 83%. The calculated oxyhemoglobin concentration for this infant would be 15 g/dL (0.83×18 g/dL) and the calculated deoxyhemoglobin level would be 3 g/dL. At this absolute concentration of deoxyhemoglobin, cyanosis is likely to be apparent. In the same example, if the absolute concentration of deoxyhemoglobin were 2 g/dL, this infant would *not* appear cyanotic despite an abnormal hemoglobin oxygen saturation of 89% (oxyhemoglobin concentration = 16/18 g/dL or 89%).

It is important to note that hemoglobin concentration determines the saturation level at which cyanosis is visible and detected (Fig. 16.5). Cyanosis may not be appreciated in newborn infants with normal hemoglobin levels unless oxygen saturation falls below 85%. Cyanosis is identified at a higher level of hemoglobin saturation in newborns with polycythemia. For example, if the hemoglobin concentration were 22 grams/dL, cyanosis would be detected at a saturation of 86% (22 − 3 grams/dL = 19 grams/dL, 19/22 = 86%). Cyanosis is more difficult to detect in patients with anemia. In anemic infants, the hemoglobin saturation has to fall profoundly before cyanosis is visible. For example, with a hemoglobin concentration of 6 grams/dL, cyanosis would be noticeable only if the hemoglobin saturation fell below 50% (6 − 3 grams/dL = 3 grams/dL, 3/6 = 50%).

Other factors that affect detection of cyanosis include skin pigmentation, fetal hemoglobin concentration, and conditions that influence the position of the hemoglobin-oxygen dissociation curve.

In peripheral cyanosis, cyanosis is restricted to the periphery (e.g., nail beds, hands, and feet). Sluggish peripheral circulation associated with hypothermia, vasomotor instability, or polycythemia causes increased oxygen extraction by the tissues and elevated levels of deoxyhemoglobin in the microcirculation. However, in peripheral cyanosis, oxygen tension and saturation of hemoglobin in the systemic circulation are normal. Peripheral cyanosis is a common finding in newborn infants. It is usually innocuous unless it is associated with low cardiac output states.

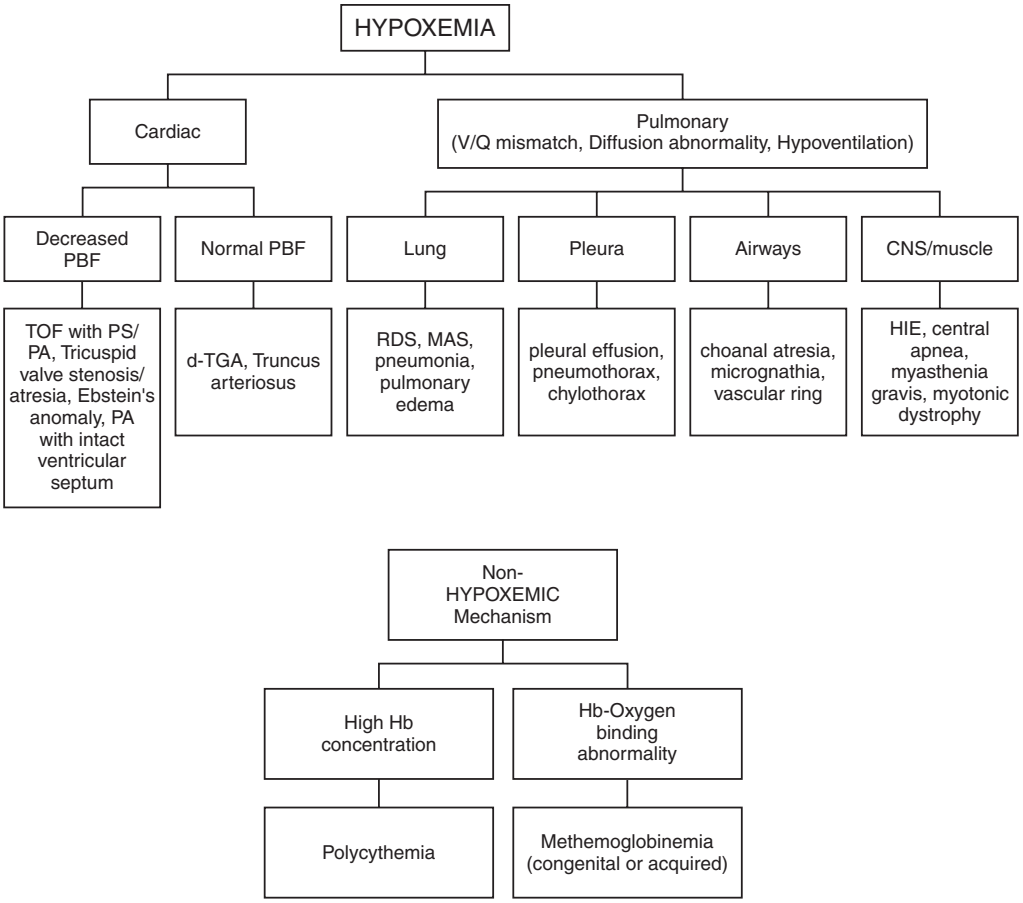

Fig. 16.4 Pathophysiologic mechanisms of and examples of conditions that can cause central cyanosis. *CNS,* Central nervous system; *d-TGA,* d-transposition of the great arteries; *Hb,* hemoglobin; *HIE,* hypoxic ischemic encephalopathy; *MAS,* meconium aspiration syndrome; *PA,* pulmonary atresia; *PBF,* pulmonary blood flow; *PS,* pulmonary stenosis; *RDS,* respiratory distress syndrome; *TOF,* tetralogy of Fallot.

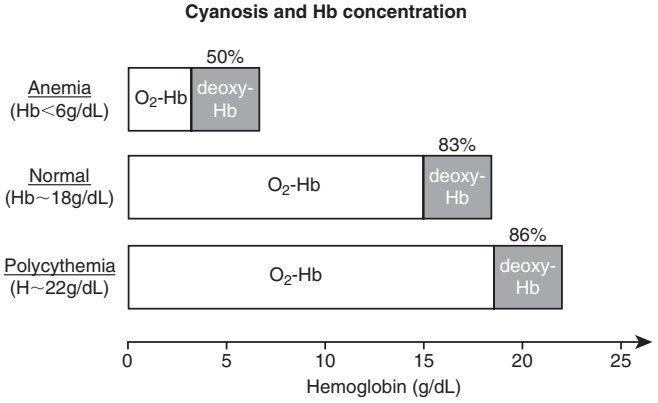

Fig. 16.5 Effect of hemoglobin concentration and cyanosis. *Hb,* Hemoglobin; *O_2*-Hb, oxyhemoglobin.

Central cyanosis is more ominous and *never* a normal finding. It is caused by elevated levels of deoxyhemoglobin and reduced levels of oxyhemoglobin in the *circulation.* Unlike peripheral cyanosis, central cyanosis is most often indicative of underlying *hypoxemia.* Hypoxemia results from two underlying pathophysiologic mechanisms: (1) reduced oxygen tension in pulmonary venous blood (and thereby in the aorta) or (2) extrapulmonary right-to-left shunting of systemic venous blood with low Pao_2 into the systemic arterial circuit.

Conditions that lead to ventilation/perfusion mismatch and intrapulmonary right-to-left shunting or those that result in impairment of oxygen diffusion across the alveolar epithelium lead to decreased oxygen tension in pulmonary venous blood. Etiologies for low oxygen tension in pulmonary veins include pulmonary (respiratory distress syndrome, meconium aspiration, pneumonia), airway abnormalities (choanal atresia), neurologic, neuromuscular or muscular (myotonic dystrophy), and skeletal anomalies (severe scoliosis, thoracic dystrophies). Extrapulmonary right-to-left shunting occurs in the setting of cyanotic CHD or persistent pulmonary hypertension. Other pathophysiologic mechanisms that may cause central cyanosis but that are not associated with hypoxemia include polycythemia (excessive hemoglobin concentration and high levels of circulating deoxyhemoglobin) and abnormalities of hemoglobin-oxygen binding (congenital or acquired methemoglobinemia). Fig. 16.4 lists conditions that cause central cyanosis in newborn infants.

It is possible to distinguish cyanosis caused by CHD from other conditions that cause hypoxemia and systemic arterial hemoglobin oxygen desaturation. Diseases involving the lung parenchyma (e.g., pneumonia, meconium aspiration) or involving the pleural space (e.g., effusion or pneumothorax) commonly affect gas exchange and oxygenation (Fig. 16.4). In these conditions, other clinical features suggestive of respiratory disease (e.g., nasal flaring, grunting, dyspnea) accompany cyanosis, as does hypercarbia. Infants born with congenital neurologic, muscular, or neuromuscular conditions may present with cyanosis and hypercarbia caused by decreased respiratory effort from hypotonia. In neonates with cyanotic CHD, cyanosis is often the *sole* clinical feature. The *absence* of respiratory distress and hypercarbia in a cyanotic infant should raise a strong suspicion of CHD.

Hypoxemia caused by extrapulmonary right-to-left shunting in CHD can be distinguished from that caused by pulmonary venous desaturation by employing the hyperoxia test.

The primary determinant of hemoglobin-oxygen association is the partial pressure of oxygen in the blood (Fig. 16.6). Oxygen binds readily to hemoglobin in the lungs where the partial pressure of oxygen is high and dissociates from hemoglobin in tissues where the partial pressure is much lower. Because of the sigmoidal properties of the hemoglobin-oxygen dissociation curve, increasing partial pressure of oxygen beyond 100 mm Hg does not produce significantly greater binding of oxygen to hemoglobin; hence, there is negligible increase in hemoglobin oxygen saturation and oxygen content when alveolar partial pressure of oxygen is increased beyond 100 mm Hg. The hyperoxia test uses the sigmoidal properties of the hemoglobin-oxygen dissociation curve to differentiate hypoxemia caused by intrinsic lung disease from that caused by cyanotic CHD. The Pao_2 from an arterial blood gas is measured at baseline and after administering 100% oxygen for at least 10 to 15 minutes. The partial pressure of oxygen in the alveolus, pulmonary vein, and aorta is reduced in babies with parenchymal lung disease. An increase in inspired oxygen concentration

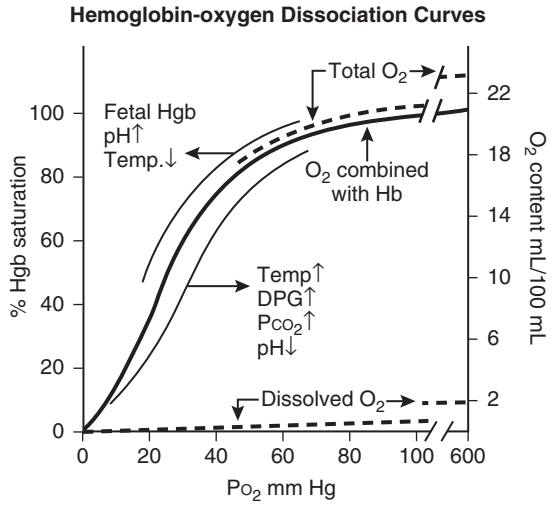

Fig. 16.6 Oxyhemoglobin-dissociation curve demonstrating the sigmoid relationship between Pao_2 of the blood and hemoglobin saturation and the linear relationship between dissolved oxygen and Pao_2.

to 100% increases alveolar partial pressure of oxygen, which in turn results in a higher pulmonary vein oxygen tension and a higher oxygen tension and saturation in the aorta. Typically, in babies with intrinsic lung disease, the Pao_2 increases to greater than 150 mm Hg after exposure to 100% oxygen for 10 to 15 minutes.

Babies with cyanotic CHD are hypoxemic primarily due to right-to-left shunting of systemic venous blood into the systemic arterial circuit. The systemic arterial circuit therefore has an admixture of pulmonary venous blood (with Pao_2 of 100 mm Hg and oxygen saturation of 100%) and systemic venous blood (with Pao_2 of approximately 40 mm Hg and oxygen saturation of approximately 70%). Administering 100% oxygen to patients with cyanotic CHD and no lung disease will increase alveolar and pulmonary venous partial pressure of oxygen (to above 600 mm Hg) but will not increase the oxygen saturation of pulmonary venous blood. As mentioned previously, due to the sigmoidal properties of the hemoglobin-oxygen dissociation curve, increasing alveolar partial pressure of oxygen beyond 100 mm Hg does not cause a significantly greater binding of oxygen to hemoglobin. As noted in Fig. 16.6, neither oxygen saturation nor the oxygen content at Pao_2 of 100 mm Hg and at 600 mm Hg is remarkably different. Hence, as administering 100% oxygen does not significantly alter the oxygen saturation and content of the pulmonary venous blood, the net oxygen saturation and Pao_2 in the arterial circuit in babies with cyanotic CHD is not changed significantly. Typically, the Pao_2 in babies with cyanotic CHD remains below 100 mm Hg despite exposure to 100% oxygen. The one exception to the rule is persistent fetal circulation where Pao_2 may remain below 100 mm Hg despite a normal intracardiac anatomy.

Examples of congenital heart lesions likely to present with central cyanosis include those that involve restriction of blood flow to the lungs, e.g., severe pulmonary valve stenosis or atresia, and tetralogy of Fallot with severe valvar and/or subvalvar pulmonary stenosis. In these lesions, a combination of right-to-left shunting of desaturated blood across a patent foramen ovale into the left side of the heart and into the aorta and decreased blood flow into the lungs cause arterial hypoxemia and central cyanosis. Typically, these defects are diagnosed when constriction of the ductus arteriosus causes further decrease in pulmonary blood flow. Defects without restriction to pulmonary blood flow but characterized by the admixture of desaturated blood in the aorta may also present with central cyanosis. These include d-TGA and truncus arteriosus, where there is a single arterial trunk. Table 16.1 lists congenital heart lesions likely to present with central cyanosis.

Exercise 3

Question

Indicate whether the following statement is true (T) or false (F):

Pulse oximetry sensor on the left hand is the ideal location to measure preductal hemoglobin oxygen saturation in infants with a left aortic arch and normal head vessel branching.

TABLE 16.1 Congenital Heart Lesions Likely to Present With Central Cyanosis

A. Right Ventricular Inflow/Outflow Abnormality	Defect
Tricuspid valve stenosis/atresia	Stenosis/atresia of tricuspid valve
Ebstein's anomaly	Inferior displacement of tricuspid valve
Pulmonary atresia with intact ventricular septum	Atresia of pulmonary valve
Pulmonary stenosis	Subvalvar, valvar, or supravalvar obstruction to pulmonary blood flow
Tetralogy of Fallot with pulmonary stenosis or atresia	Anterior malalignment of the conal septum leading to variable degree of obstruction to pulmonary blood flow, overriding aorta, ventricular septal defect, and right ventricular hypertrophy
B. Without Right Ventricular Inflow/Outflow Abnormality	**Defect**
Transposition of the great arteries	Ventriculoarterial discordance: aorta arises from the right ventricle, pulmonary artery arises from the left ventricle
Truncus arteriosus	Single arterial trunk arises from the ventricles with variable origins of the pulmonary arteries from the trunk
Totally anomalous pulmonary venous connection with obstruction	Abnormal connection of all the pulmonary veins to the systemic venous system

Answer

False. Preductal and postductal hemoglobin oxygen saturation measurements are critical in the evaluation of a neonate for CHD. A pulse oximetry sensor placed on the right hand in an infant with a presumed left aortic arch and a normal branching pattern of the head vessels measures preductal hemoglobin oxygen saturation; a sensor on either leg measures postductal hemoglobin oxygen saturation. A pulse oximetry sensor on the left hand is not an accurate reflection of preductal oxygen saturation because the origin of the left subclavian artery is close to the region where the ductus arteriosus connects to the aorta.

Exercise 4

Question

In which conditions would you expect the preductal hemoglobin oxygen saturation to be higher than the postductal hemoglobin oxygen saturation value, and in which congenital heart lesion would you expect the reverse to be true?

Answer

Preductal saturation is higher than postductal saturation with persistent pulmonary hypertension of the newborn and left heart obstructive lesions such as critical coarctation or interrupted aortic arch. Postductal saturation is higher than preductal saturation with d-TGA with pulmonary hypertension or with coarctation of the aorta.

CASE 2 (CONTINUED)

Pulse oximetry readings from the right hand and left foot are 60% and 80% respectively. The baby continues to breathe comfortably with unchanged skin color despite oxygen administration by nasal cannula at 1.5 L/minute and Fio_2 of 1.0. Peripheral pulses are normal. A baseline arterial blood gas obtained from the right radial artery shows pH of 7.32, Pco_2 of 40 mm Hg, Pao_2 of 34 mm Hg, base deficit of −2, and bicarbonate of 21 mEq/L. The Pao_2 after a hyperoxia test was 40 mm Hg.

Exercise 5

Question

What is the most likely diagnosis in Case Study 2?

Answer

d-TGA. A centrally cyanotic infant without respiratory distress and a positive hyperoxia test suggests an underlying cyanotic CHD. Reverse differential cyanosis, absent murmur but loud S_2 (anterior aortic valve in d-TGA), and a normal sized heart without oligemic lung fields, make the diagnosis of d-TGA most likely.

CASE 2 (CONTINUED)

The pediatric cardiologist confirms the diagnosis of d-TGA. The interventricular septum is intact, and concern about a restrictive foramen ovale is confirmed. The pediatric cardiologist suggests starting a PGE-1 infusion at 0.01 micrograms/kg/minute and to make arrangements for an urgent transfer to a cardiac care center where a balloon atrial septostomy may be performed to improve mixing.

In babies with d-TGA, the aorta arises from the right ventricle and the pulmonary artery arises from the left ventricle (Fig. 16.7; Video 16.1). After birth, the circulation remains in parallel and deoxygenated blood returning to the right atrium recirculates into the aorta. For survival to occur, adequately oxygenated blood from the left side of the heart must enter the systemic circulation through septal defects at the atrial or ventricular level or at the level of the ductus arteriosus. If the ventricular septum is intact and the foramen ovale becomes restrictive after birth, there are no other major venues for adequate mixing of oxygenated and deoxygenated blood.

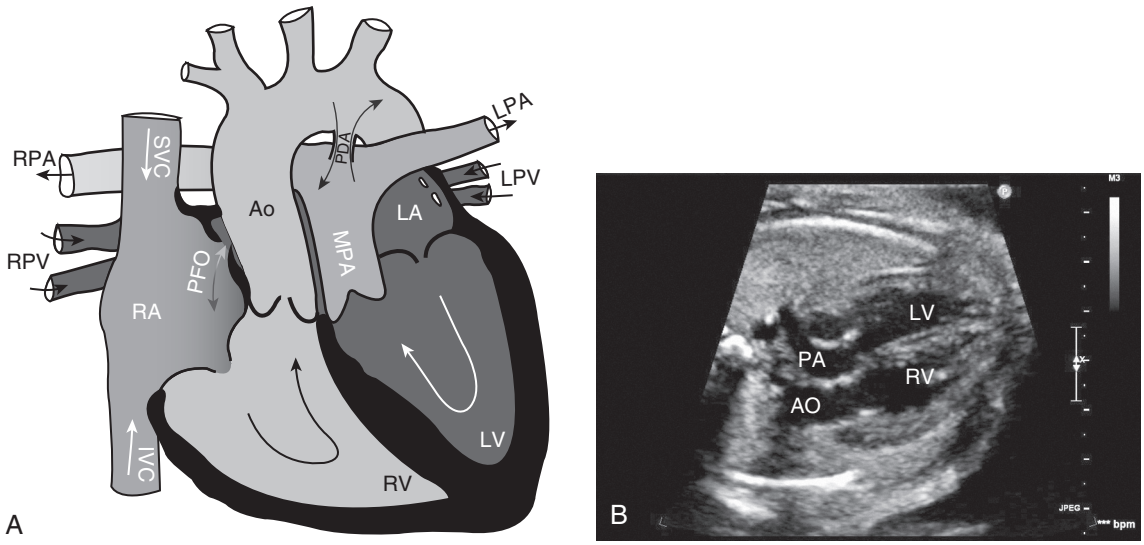

Fig. 16.7 (A) Cartoon of d-transposition of the great arteries. Arrows depict direction of blood flow. (B) Outflow tract view on echocardiogram in fetus with d-transposition of the great arteries showing the transposed relationship (LV-PA and RV-AO) of the ventricles and great vessels. *Ao,* Aorta; *IVC,* inferior vena cava; *LA,* left atrium; *LPA,* left pulmonary artery; *LPV,* left pulmonary veins; *LV,* left ventricle; *MPA,* main pulmonary artery; *PDA,* patent ductus arteriosus; *PFO,* patent foramen ovale; *RA,* right atrium; *RPA,* right pulmonary artery; *RPV,* right pulmonary veins; *RV,* right ventricle; *SVC,* superior vena cava.

Babies are consequently profoundly hypoxemic and cyanotic in the first minutes to hours after birth. Survival depends on the rapid creation of an atrial level communication through a transcatheter route. Only interventional cardiologists at cardiac centers can perform these procedures, and urgent transfer to such centers is critical.

A simple d-TGA without critical outflow tract obstruction is not a ductal-dependent lesion because there is neither restriction to pulmonary nor systemic blood flow. However, the majority of blood flow into the lungs and into the aorta is *ineffective.* Oxygenated blood in the left ventricle is pumped back into the lungs and deoxygenated blood in the right ventricle is pumped into the aorta. PGE-1 is instituted to increase effective pulmonary and systemic blood flows (Fig. 16.8). Maintaining patency of the ductus arteriosus promotes aorta-to-pulmonary-artery shunting, thereby increasing effective pulmonary blood flow (deoxygenated blood from aorta to pulmonary artery through the ductus arteriosus). The increased pulmonary blood flow will in turn increase left atrial pressure and increase effective systemic oxygenated blood flow (oxygenated blood shunts from left atrium to right atrium across the foramen ovale). Sometimes, the anticipated improvement in oxygenation does not occur after initiating PGE-1 because the foramen ovale is restrictive. An urgent balloon atrial septostomy (a bedside procedure that enlarges the foramen ovale) is required to improve mixing (Video 16.2). Once the balloon atrial septostomy is performed, systemic oxygenation usually improves dramatically. *After a few days of observation, an elective arterial switch procedure is performed.* This procedure involves switching the great vessels so that they connect to the appropriate ventricles. In addition, the coronary arteries are transferred to their new location in the neoaorta. In the current era, operative survival and long-term outcomes after the arterial switch procedure are excellent.

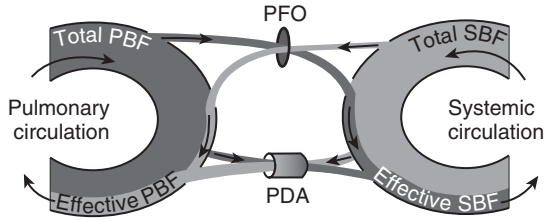

Fig. 16.8 Cartoon depicting the relative contributions of oxygenated and desaturated blood in pulmonary and systemic circulations and areas of mixing in d-transposition of the great arteries and intact ventricular septum. Effective pulmonary blood flow (PBF) denotes desaturated blood directed toward the pulmonary circulation. Effective systemic blood flow (SBF) denotes oxygenated blood directed toward the systemic circulation. *PDA,* Patent ductus arteriosus; *PFO,* patent foramen ovale.

CYANOTIC NEWBORN IN THE NEWBORN NURSERY

CASE STUDY 3

You are called to evaluate a 4-hour-old female infant in the well-baby nursery. The nurse is concerned that the baby appears cyanotic. This infant was born at 39 weeks' gestation to a 24- year-old gravida 2, para 1 woman. The mother's pregnancy was unremarkable and delivery was by elective cesarean section. Apgar scores were 8 and 9 at 1 and 5 minutes respectively. This infant's vital signs are as follows: temperature: 36.8°C, heart rate 160 beats/minute, respiratory rate 65 breaths/minute, blood pressure 73/45, pre- and postductal

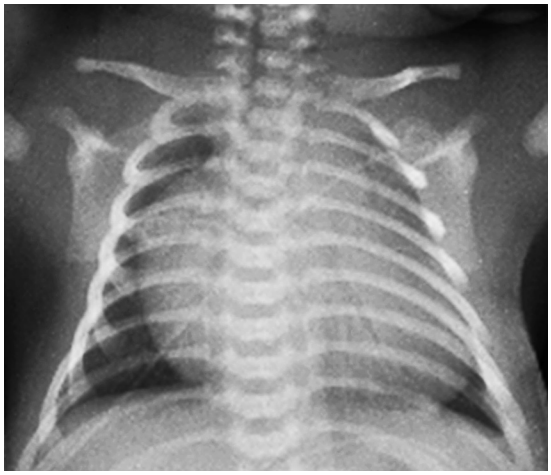

Fig. 16.9 Chest radiograph of patient described in Case Study 3.

BOX 16.1 List of Conditions That May Cause Cyanotic Spells in the Newborn Period

1. Sepsis/pneumonia
2. Hypoglycemia
3. Hypothermia
4. Gastroesophageal reflux
5. Airway obstruction
6. Congenital heart disease
7. Persistent pulmonary hypertension
8. Intracranial hemorrhage related to birth trauma
9. Apnea, seizures
10. Effects of maternal sedation
11. Hypermagnesemia
12. Inborn errors of metabolism

saturations are 60% and 62% respectively. The infant appears nondysmorphic, active, and vigorous but with central cyanosis. She is breathing comfortably. Both lung fields receive equal air entry and are clear to auscultation. Her precordium is active, multiple heart sounds are heard, and a 3/6-pansystolic murmur is heard in the lower left parasternal region. The liver is palpable 2 cm below the right costal margin. Peripheral pulses and perfusion are normal. A chest radiograph is shown in Fig. 16.9.

An ECG reveals tall P waves and right ventricular conduction delay. Arterial blood gas: pH of 7.35, Pco_2 of 32 mm Hg, Pao_2 of 36 mm Hg, HCO_3 of 22 mEq/L. Complete blood count: white blood cell (WBC) 18 $\times$ 10^9/L, hemoglobin 17 grams/dL, hematocrit 49%, platelet count 224 $\times$ 10^9/L. WBC differential includes 55% neutrophils, 35% lymphocytes, and no bands. Pediatric cardiology consult has been requested.

Exercise 6

Questions

1. Under what conditions should cyanosis be considered a normal finding in a newborn infant?
2. What is the most likely diagnosis in Case Study 3?

Answers

1. Cyanotic or "blue" spells can be seen in otherwise well babies. By definition, benign cyanotic spells are transitory and brief. These spells typically occur during crying and resolve rapidly when the baby is calm and quiet. The hemoglobin oxygen saturation measurement by pulse oximetry is normal after resolution of the cyanotic episode. There are no other symptoms or signs, and these babies are well appearing and have a normal examination (Box 16.1).
2. In this case the most likely cause of the cyanosis in this infant is incompetence of the tricuspid valve. The early auscultation of a parasternal pansystolic murmur is most likely to be related to a tricuspid regurgitant murmur. Regurgitation across the tricuspid valve can be seen in structurally normal as well as abnormal hearts. The most common cause of tricuspid regurgitation in structurally normal hearts occurs with pulmonary hypertension for a short time after birth and is generally transient. A flail tricuspid valve caused by necrosis or rupture of papillary muscle in the setting of perinatal asphyxia may result in severe tricuspid valve regurgitation. Congenital cardiac anomalies causing tricuspid regurgitation include Ebstein's anomaly and pulmonary atresia with intact ventricular septum. Other congenital abnormalities of the tricuspid valve—such as dysplasia of the tricuspid valve, abnormal chordal attachments of the tricuspid valve, unguarded tricuspid valve (where there is no valvar apparatus), or cleft tricuspid valve leaflet—are quite rare. The identification of several heart sounds, including split first and second heart sounds and third and fourth heart sounds, makes the diagnosis of a primary abnormality of the tricuspid valve—especially Ebstein's anomaly—more likely.

   Watch changes in margins. In Ebstein's anomaly, the tricuspid valve is abnormal (Fig. 16.10A,B; Video 16.3). The septal and posterior leaflets are displaced inferiorly and are usually tethered to the right ventricular wall. Mobility of the tricuspid valve is further limited by abnormal chordal attachments. Varying degrees of tricuspid regurgitation occurs, resulting in right atrial enlargement. A high right atrial pressure promotes right-to-left shunting across a patent foramen ovale or an atrial septal defect. The region of the right ventricle between the tricuspid valve annulus and the inferiorly displaced valve leaflets is called the atrialized portion of the right ventricle and has no role in right ventricular output. During systole, blood from the right ventricle regurgitates into the right atrium, especially in the setting of elevated pulmonary vascular resistance as seen in the newborn period. Pulmonary blood flow across the pulmonary valve may be minimal under these conditions. Therefore pulmonary blood flow may be dependent on the patency of the ductus arteriosus while pulmonary vascular resistance is still elevated. Hence Ebstein's anomaly is often diagnosed when the ductus arteriosus begins to constrict, further decreasing blood flow into the lungs. As a result, values of hemoglobin oxygen saturation fall, and cyanosis becomes apparent.

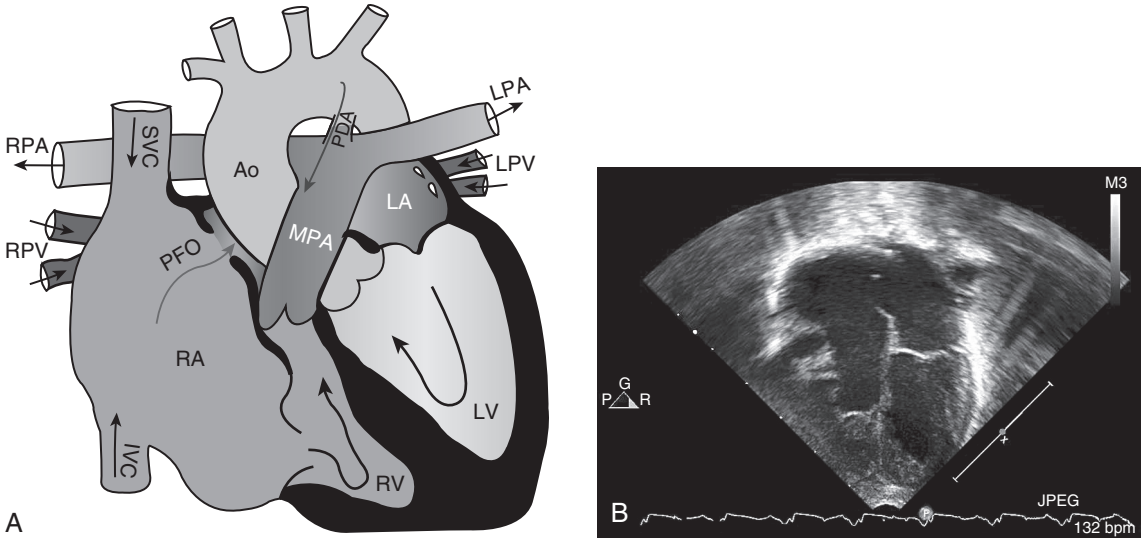

Fig. 16.10 (A) Cartoon of Ebstein's anomaly. Arrows depict direction of blood flow. (B) Four chamber view on echocardiogram of patient with Ebstein's anomaly. The displaced tricuspid valve and atrialized portion of right ventricle are clearly seen. *Ao,* Aorta; *IVC,* inferior vena cava; *LA,* left atrium; *LPA,* left pulmonary artery; *LPV,* left pulmonary veins; *LV,* left ventricle; *MPA,* main pulmonary artery; *PDA,* patent ductus arteriosus; *PFO,* patent foramen ovale; *RA,* right atrium; *RPA,* right pulmonary artery; *RPV,* right pulmonary veins; *RV,* right ventricle; *SVC,* superior vena cava.

Babies with Ebstein's anomaly and moderate to severe tricuspid valve regurgitation may have a hyperdynamic precordium due to volume overload of the right ventricle. The tricuspid regurgitant murmur is best heard along the lower left sternal border. S_1 is split due to increased flow across the tricuspid valve. S_2 is often split due to right ventricular conduction delay. Third and fourth heart sounds are often appreciated and may be related to vibrations of the abnormal tricuspid valve. Multiple heart sounds and a parasternal pansystolic murmur in a cyanotic newborn are suggestive of Ebstein's anomaly.

Exercise 7

Question

What are the causes of a large cardiothymic silhouette in the newborn period?

Answer

Chest radiograph and ECG are useful diagnostic tools in the evaluation of babies with CHD. The position and contour of the cardiovascular silhouette on chest radiographs is informative. Dextrocardia and presence of a right sided stomach bubble or a midline liver may indicate complex CHD, including heterotaxy syndromes. The presence or absence of a thymic shadow and sidedness of the aortic arch should be assessed. An absent thymic shadow (first day of life) may suggest 22q11.2 deletion syndrome and raises the possibility of a conotruncal malformation (congenital abnormalities of cardiac outflow tracts). Characteristic radiographic features are noted in some types of CHD (e.g., Coeur en Sabot or boot-shaped heart in tetralogy of Fallot, "egg on string" appearance in d-TGA). Prominence of pulmonary vasculature indicates excessive pulmonary blood flow; relatively oligemic lung fields suggest paucity of blood flow to the lungs. Pulmonary venous congestion and pulmonary edema are noted in totally anomalous pulmonary venous connection with obstruction.

Very few cardiac conditions cause a massive cardiothymic silhouette as seen on chest radiographs. Most neonatal cases of enlarged cardiac shadow on x-rays are due to an enlarged right atrium (Ebstein's anomaly, pulmonary atresia with intact ventricular septum). Other causes include cardiomegaly due to increase in myocardial mass or length (hypertrophic or dilated cardiomyopathy), enormous increase in right ventricular volume and pressure overload (large arteriovenous malformations), cardiac or mediastinal tumors, and pericardial effusions. The most common cause of massive cardiomegaly in a *cyanotic* newborn is Ebstein's anomaly, where massive right atrial enlargement results from tricuspid regurgitation.

Exercise 8

Question

What intervention(s) may improve the hemoglobin oxygen saturation in this patient?

Answer

Increase the inspired oxygen concentration and consider starting inhaled nitric oxide.

As mentioned previously, the atrialized portion of the right ventricle contributes minimally toward right ventricular output. In the neonatal period, when the pulmonary vascular resistance is elevated, the right ventricle may not be able to generate adequate systolic pressure to open the pulmonary valve. The pulmonary valve is hence "functionally" atretic, as blood does not flow across it (Fig. 16.11). During this time,

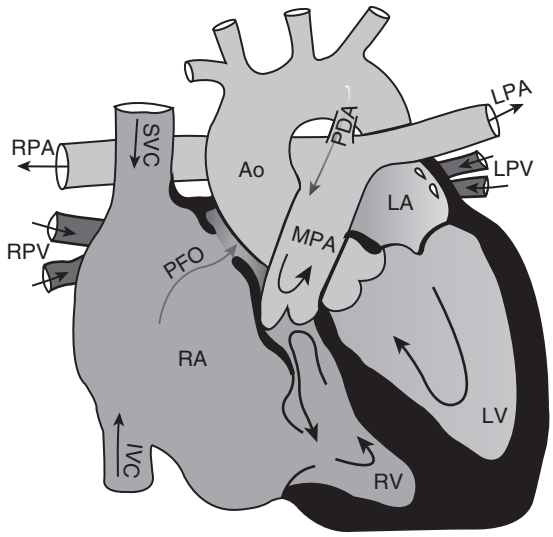

Fig. 16.11 Cartoon depicting functional pulmonary atresia in Ebstein's anomaly. Arrows depict direction of blood flow. *Ao,* Aorta; *IVC,* inferior vena cava; *LA,* left atrium; *LPA,* left pulmonary artery; *LPV,* left pulmonary veins; *LV,* left ventricle; *MPA,* main pulmonary artery; *PDA,* patent ductus arteriosus; *PFO,* patent foramen ovale; *RA,* right atrium; *RPA,* right pulmonary artery; *RPV,* right pulmonary veins; *RV,* right ventricle; *SVC,* superior vena cava.

pulmonary blood flow is dependent on the patency of the ductus arteriosus. Hypoxemia and cyanosis may worsen if the ductus arteriosus constricts or closes. Antegrade flow across the pulmonary valve in the setting of functional pulmonary atresia may be promoted by decreasing the pulmonary vascular resistance, which may be accomplished by increasing the concentration of inspired oxygen or by providing inhaled nitric oxide and by awaiting spontaneous ductal closure. Oxygen and/or inhaled nitric oxide may be weaned over the course of several days as the pulmonary vascular resistance declines, antegrade flow across the pulmonary valve increases, and right-to-left flow across the foramen ovale or atrial septal defect diminishes. In the case of anatomic obstruction, ductal patency is of course critical until an intervention to open the pulmonary outflow tract can be performed. The differentiation of functional versus true pulmonary outflow obstruction can be difficult and requires consultation with pediatric cardiology and investigation with echocardiography. The institution of PGE-1 should be delayed, if possible, until the exact physiology—anatomic versus functional pulmonary atresia is determined.

CASE 3 (CONTINUED)

The pediatric cardiologist confirms the diagnosis of Ebstein's anomaly with moderate to severe tricuspid regurgitation and functional pulmonary atresia. Inspired oxygen is increased to 50% by nasal cannula. Oxygen saturation improves steadily to above 90%. After 3 to 4 days, oxygen is weaned back to 21% and the patient is discharged home on the seventh day of life with a hemoglobin saturation of 85%.

Severity of Ebstein's anomaly varies. Patients with mild abnormalities of the tricuspid valve and minimal regurgitation may remain asymptomatic and require no intervention. Some may present with cyanosis in the newborn period as the patient described in this case study. More severe cases can present with cardiac failure and/or cyanosis in infancy and may require surgical intervention.

MURMUR IN NEONATE

CASE STUDY 4

You receive a call from a pediatrician in the well-baby nursery who wishes to transfer a 12-hour-old male infant to the neonatal intensive care unit (NICU) after a murmur was discovered in the admission physical examination. The mother is a 26-year-old primigravida. The pregnancy was uneventful. This infant was born at 39 weeks' gestation by normal spontaneous vaginal delivery. Apgar scores were 9 and 9 at 1 and 5 minutes, respectively. On examination, the infant appears comfortable, pink, and not in any apparent cardiorespiratory distress. The birth weight is 3.56 kg. Vital signs are as follows: heart rate is 150 beats/minute, respiratory rate is 50 breaths/minute, blood pressure is 68/45 mm Hg (right arm), preductal and postductal hemoglobin saturations are 86%. The baby is breathing comfortably, with neither tachypnea nor chest retractions. Precordial examination is significant for a prominent parasternal impulse. A harsh 3/6 ejection systolic murmur is best heard over the left upper sternal border. Peripheral pulses and blood pressure are normal.

Chest radiograph reveals mild cardiomegaly, left aortic arch, and mildly oligemic lung fields with no focal lung pathology. ECG reveals a normal sinus rhythm, rightward QRS axis, and right ventricular hypertrophy. Pediatric cardiology consultation is awaited.

Exercise 9

Questions

1. On a physical examination, what features are used to differentiate an innocent murmur from a pathologic murmur?
2. Which of the following statements about murmurs is true?
   A. The most common innocent murmur in the newborn period is peripheral pulmonary artery stenosis.
   B. Absence of murmur in the newborn period rules out CHD.

Answers

1. Routine newborn physical examination within 24 hours of birth and again before discharge offers a critical window during which presymptomatic infants with CHD may be detected. Reported prevalence of murmurs in term newborns is highly variable. In most large series, the prevalence of murmurs in the newborn period is less than 1%.

   Cardiac murmurs may be innocent and of no consequence or may be associated with structural abnormalities of the heart. In one large series, more than 54% of babies in whom a murmur

was noted in the newborn period had CHD (Ainsworth, et al, 1999). Certain qualities may differentiate pathologic from innocent murmurs. High grade (grade 3 intensity or higher), harsh quality, murmurs extending through systole and best noted in the left upper sternal border, and those associated with an abnormal S_2 are most likely pathologic and indicative of an underlying structural heart disease.

2. A.

The most common lesions recognized from murmurs are those with left-to-right shunts, particularly ventricular septal defects. The remaining 46% in the same series (mentioned previously) (Ainsworth et al, 1999) had either a structurally normal heart or physiologic findings that accounted for the murmur, e.g., physiologic branch pulmonary artery stenosis. Common "innocent" murmurs heard in the newborn period include peripheral pulmonary artery stenosis (PPS), a closing ductus arteriosus, or Still murmur. The typical murmur of PPS is described as a low grade, 1 to 2/6 midsystolic ejection murmur best heard in the left upper sternal area and radiating to the axilla and back. PPS murmurs generally resolve in most patients by 6 months of age. This murmur is caused by turbulence created by the relative size discrepancy between the main and branch pulmonary arteries. Still murmur is generally heard in young, school-aged children but occasionally can be heard in newborn infants. Still murmur is a low-grade systolic murmur with a musical quality and is best heard in the lower left parasternal regions.

The *absence* of a murmur *does not* rule out CHD. Many serious congenital heart lesions do not present with a murmur at all. Some may have not yet developed the physiologic changes for the murmur to be detected in the newborn nursery. In the same large series described previously, 47% of infants who were eventually diagnosed with CHD later in infancy had no murmur in the neonatal period (Ainsworth et al, 1999).

The infant in our case study has a prominent precordial impulse suggestive of right ventricular pressure overload. An ejection systolic murmur, best appreciated in the left upper sternal border, is likely related to an obstruction of the right ventricular outflow tract at the supravalvar valvar or subvalvar levels. A low hemoglobin saturation of 86% suggests right to left shunting at the atrial level. Oligemic lung fields on chest radiograph indicate reduced blood flow to the lungs.

CASE 4 (CONTINUED)

A diagnosis of critical valvar pulmonary stenosis is confirmed on echocardiogram by the pediatric cardiologist. The ductus arteriosus is restrictive. The cardiologist requests that a PGE-1 infusion be started immediately at 0.01 mcg/kg/min. The hemoglobin saturation increases to 94%. The next day, the infant undergoes a successful transcatheter balloon valvuloplasty.

One of the most common causes of obstruction to the right ventricular outflow tract is pulmonary valve stenosis

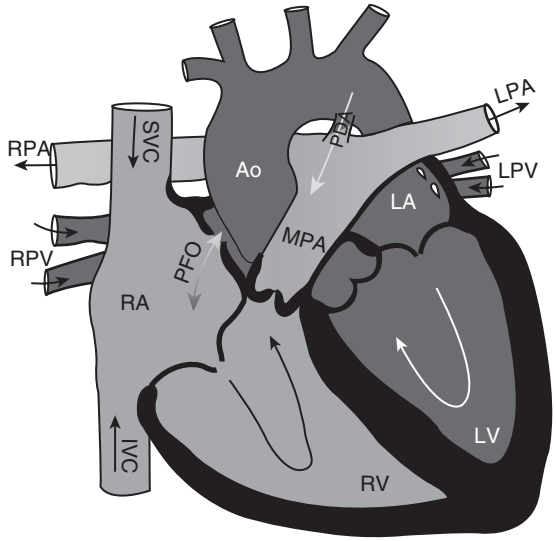

Fig. 16.12 Cartoon depicting valvar pulmonary stenosis. Arrows depict direction of blood flow. *Ao,* Aorta; *IVC,* inferior vena cava; *LA,* left atrium; *LPA,* left pulmonary artery; *LPV,* left pulmonary veins; *LV,* left ventricle; *MPA,* main pulmonary artery; *PDA,* patent ductus arteriosus; *PFO,* patent foramen ovale; *RA,* right atrium; *RPA,* right pulmonary artery; *RPV,* right pulmonary veins; *RV,* right ventricle; *SVC,* superior vena cava.

(Fig. 16.12; Video 16.4). The pulmonary valve may be domed without distinct separation into leaflets or the leaflets may be fused at the commissures. Sometimes, especially in patients with Noonan syndrome, the valve leaflets are thickened and dysplastic. Obstruction at the pulmonary valve causes right ventricular hypertrophy, particularly of the infundibulum, which may contribute to the right ventricular outflow tract obstruction.

There are varying degrees of valvar pulmonary stenosis. Mild pulmonary valve stenosis rarely progresses and usually requires no treatment. Moderate or severe obstruction to the pulmonary valve is progressive and therapy is required. Severe obstruction to the right ventricular outflow tract (critical pulmonary stenosis) can cause compromise of pulmonary blood flow and requires ductal patency to provide an alternate source of pulmonary blood flow.

Transcatheter balloon valvuloplasty is curative when obstruction is restricted to the valvar level (Video 16.5). Neonatal transcatheter balloon valvuloplasty is very successful; surgical or transcatheter reinterventions are rarely required.

After balloon valvuloplasty, PGE-1 infusion is usually discontinued. Over the course of the next 48 hours, a decline in oxygen saturations is expected as the ductus arteriosus closes. Decline in oxygen saturation is due to continued right-to-left atrial shunting in the setting of diminished right ventricular compliance caused by right ventricular hypertrophy. As right ventricular hypertrophy regresses over several weeks to months, right ventricular compliance will improve, right-to-left shunting across the foramen ovale will diminish, and the hemoglobin oxygen saturation will improve.

CYANOTIC NEWBORN WITH RESPIRATORY DISTRESS

CASE 5

A full-term male neonate is born to a 23-year-old primigravida whose prenatal laboratory tests are unremarkable, including a negative cervical culture group B *Streptococcus.* Membranes ruptured 4 hours before delivery; the amniotic fluid was clear. There is no history of maternal fever during labor. Labor was spontaneous and uncomplicated; vaginal delivery occurred at 39 weeks of gestation. Apgar scores of 9 and 9 are assigned. You are called to evaluate this infant at 12 hours of life in the newborn nursery for grunting respirations. On physical examination, you find a 3 kg nondysmorphic, centrally cyanotic male infant of term gestation with significant respiratory distress manifest by nasal flaring and subcostal and intercostal chest retractions. Air entry is equal bilaterally; diffuse rales are appreciated. On precordial examination, the second heart sound appears loud. A 2/6 systolic murmur is appreciated over the upper left sternal border. His abdomen is not distended; however, the liver is palpable 1 to 2 cm below the right costal margin. The extremities are warm and distal pulses appear fairly strong. You bring him to the NICU for further management. Vital signs: respiratory rate 85 to 90 breaths/minute, heart rate 168 beats/minute, blood pressure 76/46, hemoglobin saturation is 60% breathing room air. He is placed on nasal prong continuous positive airway pressure (CPAP), but is intubated shortly thereafter for a persistently low saturation value of 65% and continuing respiratory distress. On conventional mechanical support and inspired oxygen of 1.0, his saturation measured by pulse oximetry is 68%. Arterial blood gas: pH of 7.32, Pco_2 of 42 mm Hg, Pao_2 of 35 mm Hg, HCO_3 of 20 meq/L, base deficit of −2/Sao_2 65%.

A chest radiograph obtained on admission is shown in Fig. 16.13. Complete blood count: WBC 15 × 10^9/L, hemoglobin 18 grams/dL, platelet count 245 × 10^9/L. Differential: 54% neutrophils, no bands, and 35% lymphocytes.

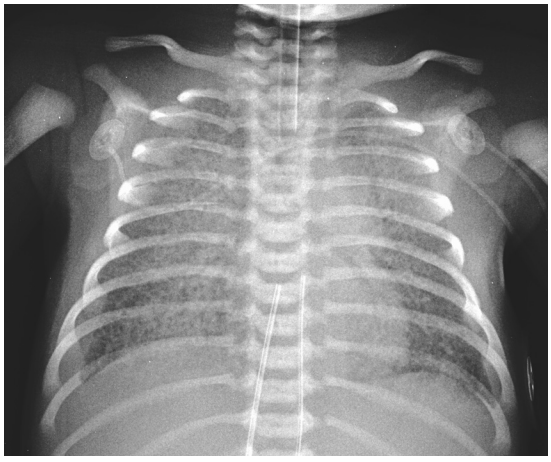

Fig. 16.13 Chest radiograph of patient described in Case Study 5.

Exercise 10

Question

Which of the following diagnoses is most consistent with this infant's clinical course and chest radiograph?

A. Transient tachypnea of the newborn
B. Respiratory distress syndrome
C. Totally anomalous pulmonary venous connection with obstruction
D. Large ventricular septal defect

Answer

C

It is not uncommon for newborn infants to have respiratory distress.

The timing of onset of symptoms, contributory information from prenatal and delivery history, and a thorough physical examination help in establishing the correct diagnosis. Respiratory distress in the term infant may have several etiologies, including transient tachypnea of the newborn (TTN), pneumonia, aspiration, or air-leak syndromes, pleural effusions, or CHD.

Excessive pulmonary blood flow occurs in lesions with an abnormal communication between the pulmonary and systemic circuit at the level of the atria, ventricles, or the great vessels. Examples of such lesions include large atrial or ventricular septal defects, atrioventricular septal defects, large patent ductus arteriosus, aortopulmonary window, truncus arteriosus, or totally abnormal pulmonary venous connection without obstruction. Typically, symptoms of increased respiratory effort manifest when there is a substantial decline in pulmonary vascular resistance and left-to-right shunt volume increases. As the pulmonary vascular resistance is still elevated after birth; the above lesions rarely exhibit symptoms of pulmonary over circulation at birth or in the first few days of life.

Some or all four pulmonary veins may not return normally to the left atrium. Instead, the pulmonary veins may establish an abnormal communication with a systemic venous channel (Fig. 16.14). If there is significant resistance to flow in the anomalous pulmonary venous pathway, pulmonary venous hypertension ensues. When the hydrostatic pressure within the pulmonary veins exceeds oncotic pressure, pulmonary edema follows. The decrease in lung compliance results in respiratory distress and the alveolar diffusion abnormality from edema results in hypoxemia and reduced hemoglobin oxygen saturation. Timing of symptoms depends on the number and degree of obstructed pulmonary veins. In isolated totally anomalous pulmonary venous connection with obstruction, symptoms of respiratory distress and cyanosis are seen within the first 24 hours after birth but are rarely noted at birth.

Finally, increased left atrial pressure may secondarily cause pulmonary venous hypertension and pulmonary edema and hence respiratory distress. Examples of lesions causing an increased left atrial pressure include hypoplastic left heart

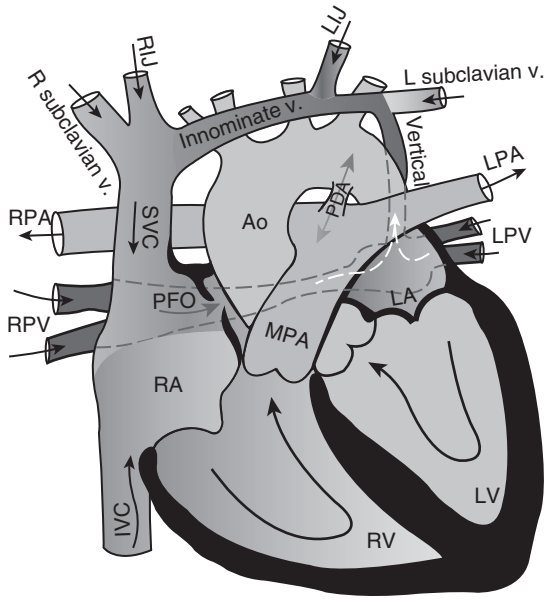

Fig. 16.14 Cartoon depicting supradiaphragmatic totally anomalous pulmonary vein connection. Arrows depict direction of blood flow. *Ao,* Aorta; *IVC,* inferior vena cava; *LA,* left atrium; *LPA,* left pulmonary artery; *LPV,* left pulmonary veins; *LV,* left ventricle; *MPA,* main pulmonary artery; ; *PDA,* patent ductus arteriosus; *PFO,* patent foramen ovale *RA,* right atrium; *RIJ, LIJ,* right and left jugular vein; *r, l subclavian v,* right, left subclavian vein; *vertical v,* vertical vein; *RPA,* right pulmonary artery; *RPV,* right pulmonary veins; *RV,* right ventricle; *SVC,* superior vena cava.

syndrome with mitral atresia and a restrictive or intact atrial septum, severe mitral or aortic valve stenosis or regurgitation, decreased left ventricular systolic or diastolic function secondary to cardiomyopathy, or obstruction to the left ventricular outflow tract. Infants with these lesions typically show signs of decreased perfusion in addition to respiratory distress.

Totally anomalous pulmonary venous connection must be excluded in term infants presenting with respiratory distress, especially when there are chest radiographic findings of pulmonary edema and a normal heart size (Fig. 16.13). Totally anomalous pulmonary venous connection may be classified into different types based on the location of drainage of the pulmonary veins. Supracardiac, cardiac, and infracardiac types reflect the areas of connection of the pulmonary veins. Totally anomalous pulmonary venous connection may be also classified based on whether they are obstructed or not. The degree of obstruction often varies, and the clinical presentation depends on the severity of obstruction. Patients with *unobstructed* total anomalous pulmonary venous connection generally present with symptoms of pulmonary over circulation and cardiac failure by 4 to 6 weeks of age.

CASE 5 (CONTINUED)

On an echocardiogram, the pediatric cardiologist makes the diagnosis of infracardiac totally anomalous pulmonary venous connection with obstruction. The four pulmonary veins join to form a confluence, which drains via a long vertical vein into the portal vein. Pulmonary artery pressure is elevated, right ventricular systolic function is mildly depressed, and the foramen ovale is not restrictive. Flow through the patent ductus arteriosus is right-to-left in systole. He recommends urgent transfer to a cardiac surgical center.

The hemoglobin oxygen saturation as measured by pulse oximetry is no higher than 70%, and he is placed on conventional mechanical ventilation with a peak inspiratory pressure of 22 mm Hg, positive end expiratory pressure of 5 mm Hg, and Fio_2 of 1.0.

Exercise 11

Question

While awaiting transport, a medical student suggests adding inhaled nitric oxide to improve oxygenation. This intervention will most likely:

A. Improve oxygenation by increasing pulmonary blood flow
B. Worsen oxygenation by increasing pulmonary blood flow

Answer

B

Totally anomalous pulmonary venous connection with obstruction is a surgical emergency. Urgent transfer to a cardiac center where surgery can be performed is critical for survival. Infants with obstructed totally anomalous pulmonary venous connection exhibit hypoxemia, the severity of which varies with the degree of obstruction. Several factors contribute to the hypoxemia: (1) pulmonary edema and the secondary diffusion abnormality lead to low oxygen tension and saturation in the pulmonary veins; (2) mixing of oxygenated and deoxygenated blood—pulmonary venous return mixes with systemic venous return; and (3) hypoxic reflex pulmonary artery vasoconstriction leads to pulmonary artery hypertension, right-to-left shunting across the ductus arteriosus, and decreased pulmonary blood flow. Pulmonary artery vasoconstriction in the setting of pulmonary venous obstruction and hypertension restricts blood flow into the lungs and protects the pulmonary bed from worsening alveolar edema. Maneuvers that decrease pulmonary vascular resistance (e.g., inhaled nitric oxide) are expected to lead to an increase in pulmonary blood flow. In the setting of fixed downstream obstruction, pulmonary edema is likely to worsen if blood flow into the pulmonary circuit is greater than that drained from it. Therefore the use of pulmonary vasodilators in an effort to improve oxygenation may be counterproductive and may be ill advised.

Exercise 12

Question

The same medical student asks if PGE-1 may be used in this patient. The most appropriate answer to this question is:

A. PGE-1 is absolutely contraindicated in *all* cases of obstructed totally anomalous pulmonary venous connection.

B. PGE-1 may be used in *some* cases of obstructed totally anomalous pulmonary venous connection.

Answer

B

The use of PGE-1 in obstructed total anomalous pulmonary venous connection is controversial. There may be a role for its use in select cases, but PGE-1 must always be used with caution. In obstructed total anomalous pulmonary venous connection, PGE-1 may be employed to off-load the failing right ventricle or when left ventricular inflow or outflow is inadequate. The latter can occur when the foramen ovale is restrictive. In total anomalous pulmonary venous connection, left ventricular preload and hence output is dependent on right-to-left shunting across the foramen ovale. If the foramen is small and restrictive, left ventricular preload or filling is reduced and hence left ventricular stroke volume is reduced. A posteriorly deviated interventricular septum (in the setting of severe pulmonary hypertension and right ventricular dilatation) can lead to encroachment of left ventricular cavity and impede left ventricular filling and output.

NEONATE WITH DECREASED PERFUSION

CASE 6

A 10-day-old female infant born at 39 weeks of gestation arrives at the emergency room of the community hospital where you are covering. She was born by normal spontaneous vaginal delivery at the same hospital and was discharged home within 48 hours. The mother's pregnancy, labor, and delivery were unremarkable. A normal neonatal admission and discharge physical examinations were documented in the hospital records. This infant was feeding and voiding appropriately while in the hospital. By parental account, their infant became progressively "fussy." She breathed faster and required a longer time for each bottle feeding. On the day of presentation, she fed no more than 1 ounce of formula and hadn't voided since the night before.

Vital signs: temperature 36.8, heart rate 190 beats/minute, noninvasive blood pressure from the right arm 78/50 mm Hg, respiratory rate 78 breaths/minute, Sao_2 from the right hand is 98%. Weight is 3.3 kg (birth weight and discharge weight are 3.5 and 3.4 kg). The infant appears alert but irritable. She is in moderate respiratory distress with nasal flaring and has subcostal and intercostal retractions. Equal breath sounds are heard bilaterally, and fine rales are heard at both lung bases. The precordium is hyperdynamic, pulmonary component of the second heart sound is loud, and no murmurs are appreciated on auscultation. The liver is palpable 4 cm below the right costal margin. Lower extremity pulses are difficult to palpate. Her feet are cool to touch. There are no skin lesions; the capillary refill is 5 seconds. CBC: WBC 15 × 10^9/L, Hct 40%, platelet count 23 × 10^9/L. Differential count 50% neutrophils, 35% lymphocytes, and no bands. Serum chemistry panel: sodium 145 mEq/L, potassium 5 mEq/L, chloride 110 mEq/L, bicarbonate 14 mEq/L, blood urea nitrogen 40 mg/dL, creatinine 1.0 mg/dL. Chest radiograph shows pulmonary edema and cardiomegaly and a left aortic arch. Blood culture is pending. Intravenous antibiotics have been administered.

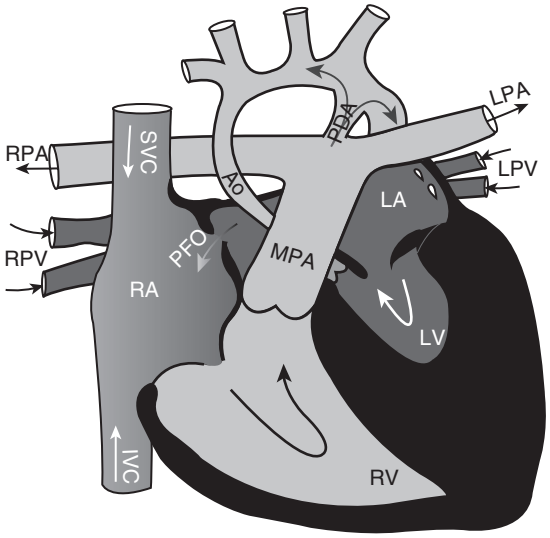

Fig. 16.15 Cartoon depicting hypoplastic left heart syndrome. Arrows depict direction of blood flow. *Ao,* Aorta; *IVC,* inferior vena cava; *LA,* left atrium; *LPA,* left pulmonary artery; *LPV,* left pulmonary veins; *LV,* left ventricle; *MPA,* main pulmonary artery; *PDA,* patent ductus arteriosus; *PFO,* patent foramen ovale; *RA,* right atrium; *RPA,* right pulmonary artery; *RPV,* right pulmonary veins; *RV,* right ventricle; *SVC,* superior vena cava.

Exercise 13

Question

This infant's clinical presentation is most consistent with a:

A. Left heart obstructive lesion
B. Right heart obstructive lesion
C. Adrenal insufficiency
D. Sepsis

Answer

A.

Newborn infants with obstruction to left ventricular output may be difficult to distinguish from those with sepsis. The clinical presentation is often similar, but careful and thorough physical examination and historical evaluation may help in establishing an accurate clinical diagnosis. Obstruction to left ventricular outflow may occur at different levels. Examples include coarctation of the aorta, interrupted aortic arch, hypoplasia of the aortic arch, and valvar or subvalvar aortic stenosis. In extreme cases, the entire left sided structures may be exceedingly small (hypoplastic left heart syndrome). Severity of obstruction to flow from the left ventricle is variable and can range from mild (coarctation with minimal obstruction) to severe (hypoplastic left heart syndrome where the minute left ventricle is ill equipped to support the systemic circulation) (Fig. 16.15).

Coarctation of the aorta refers to narrowing of the aorta, usually discrete, and in the juxtaductal region (Fig. 16.16).

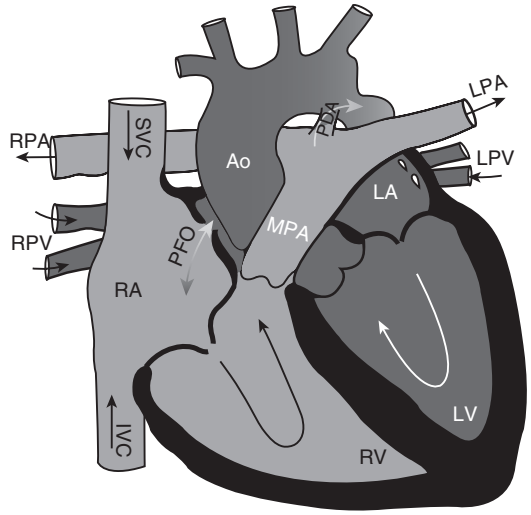

Fig. 16.16 Cartoon depicting juxtaductal coarctation of the aorta. Arrows depict direction of blood flow. *Ao,* Aorta; *IVC,* inferior vena cava; *LA,* left atrium; *LPA,* left pulmonary artery; *LPV,* left pulmonary veins; *LV,* left ventricle; *MPA,* main pulmonary artery; *PDA,* patent ductus arteriosus; *PFO,* patent foramen ovale; *RA,* right atrium; *RPA,* right pulmonary artery; *RPV,* right pulmonary veins; *RV,* right ventricle; *SVC,* superior vena cava.

CASE 6 (CONTINUED)

Femoral artery pulses are difficult to appreciate, whereas both brachial artery pulses are felt easily. You ask that noninvasive blood pressure be measured in all four extremities: right arm 78/50 mm Hg, left arm 66/40 mm Hg. After several failed attempts, blood pressure on the lower extremities is obtained: right leg 30/22 mm Hg, left leg 34/22 mm Hg. Pulse oximetry reading from sensor on the right hand is 98%; a similar sensor on the foot shows a poor tracing.

Exercise 14

Question

Of the following, the most likely diagnosis is:
A. Juxtaductal coarctation of the aorta
B. Hypoplastic left heart syndrome
C. Aortic valve stenosis
D. None of the above

Answer

A.

As described previously, obstruction to left ventricular outflow can occur at different levels. When such an obstruction is suspected, clinical evaluation and vital sign measurements may offer clues to the level of obstruction (Table 16.2). A good starting point is to palpate femoral pulses. It is generally difficult to feel femoral pulses easily in newborn infants unless hips are abducted. In this optimal position, one should be able to easily palpate femoral artery pulses. If there is difficulty in feeling both femoral pulses, comparison should be made with brachial artery pulses. If brachial artery pulses are very strong and femoral pulses are poor, the level of aortic obstruction is below the level of the left subclavian artery (if the arch is leftward) or below the level of the right subclavian artery (if the arch is rightward). If the right brachial pulse is easily felt, but the left brachial and both femoral pulses are equally diminished, the arch is likely to be interrupted proximal to the origin of the left subclavian artery. Sometimes, in severe coarctation of the aorta, the adjacent subclavian artery also may be narrowed; hence the pulse on that arm may be difficult to appreciate or may be of lower amplitude than that of the contralateral arm. When both brachial and femoral pulses are diminished and the perfusion is poor, significant depression in cardiac performance is likely. The other possibility is the presence of an aberrant right subclavian artery arising distal to the obstruction. Feeling the carotid pulses may differentiate the two. When cardiac output is severely compromised, carotid pulses are also difficult to palpate. However, in coarctation of the aorta with an aberrant right subclavian artery, the carotid pulse amplitude will be very strong. Blood pressure measurement in the four extremities should show the same differences as that revealed by pulse strength. When obstruction is more proximal, e.g., aortic stenosis or hypoplastic left heart syndrome, there is no difference in pulse amplitude or blood pressure between the four extremities.

TABLE 16.2 Level of Obstruction of Aortic Arch

Femoral Pulses	Right Brachial Pulse	Left Brachial Pulse	Possible Site of Obstruction
++	++	++	No obstruction
+/−	++	+	Juxtaductal coarctation of the aorta (left brachial pulse may be diminished due to narrowing extending into the left subclavian artery)
+/−	++	+/−	Interruption of the aortic arch proximal to the left subclavian artery (left brachial and femoral pulses are similar)
+/−	+/−	+/−	• Diminished left ventricular performance • Aortic stenosis • Hypoplastic left heart syndrome • Aberrant origin of the right subclavian artery distal to the level of obstruction

++, Normal pulse; +, palpable pulse but diminished; −, absent pulse.

Exercise 15

Question

A pediatric cardiologist is not readily available. The emergency room physician requests your assistance in the management of this infant. The best option is to:
A. Start PGE-1 infusion right away before echocardiogram and arrival of pediatric cardiologist

B. Wait for pediatric cardiologist and echocardiogram to start PGE-1 infusion

Answer

A.

PGE-1 must be started right away if critical left heart obstruction is suspected. It is not necessary to wait for a confirmatory echocardiogram if one cannot be obtained readily. Other therapeutic interventions such as volume resuscitation and inotropic therapy are rarely effective unless the ductus arteriosus is reopened and systemic blood flow is reestablished. PGE-1 is administered as a continuous infusion owing to its rapid metabolism. Low doses of PGE-1 (0.01 mcg/kg/min to 0.05 mcg/kg/min) are usually adequate to maintain patency of an open ductus arteriosus. A higher dose of PGE-1 (0.1–0.2 mcg/kg/min) may be effective in reopening a functionally closed ductus arteriosus. Once the ductus arteriosus is reopened, the dose of PGE-1 may be titrated to the lowest effective dose. PGE-1 induces several side effects, including apnea, hyperthermia, hypotension, and thrombocytopenia. These side effects are dose dependent and are usually encountered with higher doses of PGE-1.

CONCLUSION

Congenital heart disease is the most common birth malformation. Despite the numerous forms, neonates with CHD present in limited ways: cyanosis, shock, and tachypnea. A careful history and physical examination guided by a systematic approach will help formulate a clinical diagnosis without much difficulty.

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17

Persistent Pulmonary Hypertension of the Newborn and Hypoxemic Respiratory Failure

Bobby Mathew, Payam Vali and Satyan Lakshminrusimha

The fetus is in a state of physiologic pulmonary hypertension. The PaO_2 in the descending aorta of the fetus is approximately 20 to 25 mm Hg with an oxygen saturation (Sao_2) of 55% to 58% (Fig. 17.1). In spite of being "hypoxemic" (low PaO_2 levels relative to postnatal standards), the fetus can deliver adequate oxygen to its tissues and is not hypoxic. Oxygen delivery (DO_2) is dependent on cardiac output (CO) and oxygen content of the blood (CaO_2). The fetus maintains adequate oxygen delivery to its tissues by the following physiologic adaptations: (1) presence of fetal hemoglobin (HbF) with high affinity for oxygen, (2) higher hemoglobin levels in a term fetus compared with children and adults resulting in a higher CaO_2 at any given oxygen saturation level, and (3) high cardiac output (450 mL/kg/min from both ventricles). During fetal life, the placenta is the organ of gas exchange. The difference in oxygen saturation (a measure of oxygen uptake from the organ of gas exchange) between the umbilical vein (80%) and umbilical artery (58%) during fetal life (see Fig. 17.1) is similar to the difference between the pulmonary vein/aorta (95%–100%) and pulmonary artery (70%) in an adult.

Similar to the adult lung, the placenta receives approximately 40% to 45% of combined ventricular output during fetal life. The lungs receive 8% to 10% of combined ventricular output in fetal lambs and approximately 25% in near-term human fetuses (Rasanen et al, 1996). After birth and following initiation of air breathing, pulmonary blood flow markedly increases (Lakshminrusimha and Steinhorn, 1999) resolving the fetal physiologic pulmonary hypertension (Lakshminrusimha, 2012). In infants with an adverse event in utero or with abnormalities of pulmonary transition at birth, pulmonary hypertension persists into the newborn period, resulting in persistent pulmonary hypertension of the newborn (PPHN) leading to hypoxemic respiratory failure (HRF).

The following case studies discuss the presentation, clinical features, and management of PPHN and HRF.

CASE STUDY 1

A 32-year-old woman with gestational diabetes is admitted to a community hospital at $37^{3}/_{7}$ weeks' gestation following rupture of membranes. She weighs 225 pounds and has a healthy 2-year-old boy born by cesarean section. A repeat cesarean section is performed for late decelerations. The baby weighs 8 pounds and 8 ounces (3855 g) and is brought to the nursery at 2 hours of age for hypoglycemia. He is noted to be tachypneic at 82 breaths per minute. His oxygen saturation (SpO_2) is 83% in room air, and he is placed in a hood with 30% oxygen. His SpO_2 continues to be low at 85%, and the inspired oxygen concentration is gradually increased to 45% to achieve saturation values in the 90s. A chest x-ray is obtained (Fig. 17.2) and the regional perinatal center is called to request transfer.

Exercise 1

Question

What is the most likely cause for hypoxemia and tachypnea in this infant?

A. Surfactant deficiency and respiratory distress syndrome (RDS)
B. Retained fetal lung liquid and transient tachypnea of the newborn (TTN)
C. Infection with pneumonia
D. Atelectasis
E. Cardiac failure

Answer

B. This infant has several risk factors for respiratory distress at birth.

- Early term delivery ($37–38^{6}/_{7}$ weeks postmenstrual age [PMA]) is associated with a higher risk of respiratory distress and admission to the neonatal intensive care unit (NICU) (Engle, 2011). The American College of Obstetrics and Gynecology (ACOG) strongly recommends against induction and elective cesarean section before 39 completed weeks of gestation (Spong et al, 2011) and has recently updated the guidelines for medically indicated late-preterm and early term deliveries (Committee opinion no. 560: medically indicated late-preterm and early-term deliveries, 2013).
- Maternal diabetes increases the risk of surfactant deficiency and RDS.
- Delivery by cesarean section also increases the risk of respiratory distress. The additive effect of cesarean section on respiratory morbidity is higher at 37 weeks' gestation

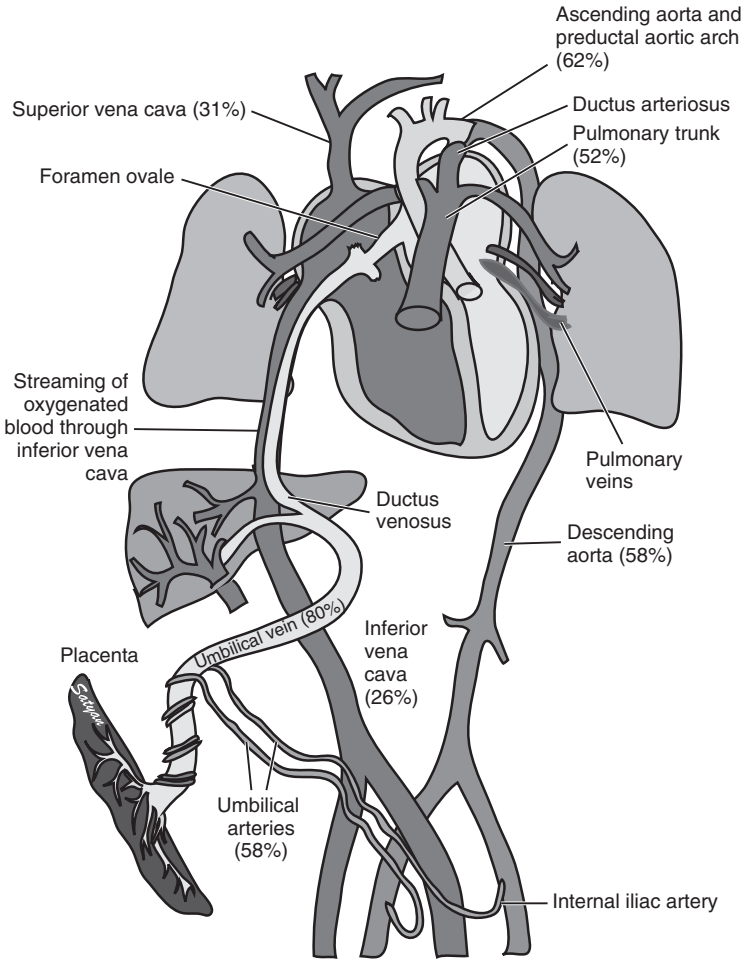


Fig. 17.1 Normal fetal circulation. The approximate oxygen saturation values in various blood vessels are shown in parentheses. Darker shade indicates lower oxygen saturation. There are three major vascular shunts that maintain the fetal circulatory pattern: (1) Ductus venosus shunts oxygenated blood from the umbilical venous circulation directly to the inferior vena cava. This oxygenated blood is preferentially streamed through the inferior vena cava and the right atrium toward the foramen ovale. (2) Foramen ovale shunts oxygenated blood from the right atrium to the left atrium. Subsequently, this blood enters the left ventricle and ascending aorta and supplies the coronaries and the brain. (3) Deoxygenated blood in the pulmonary artery bypasses the lungs through the ductus arteriosus and enters the descending aorta. (Copyright 2015 Bobby Mathew, Satyan Lakshminrusimha. Published by Elsevier Inc. All rights reserved.)

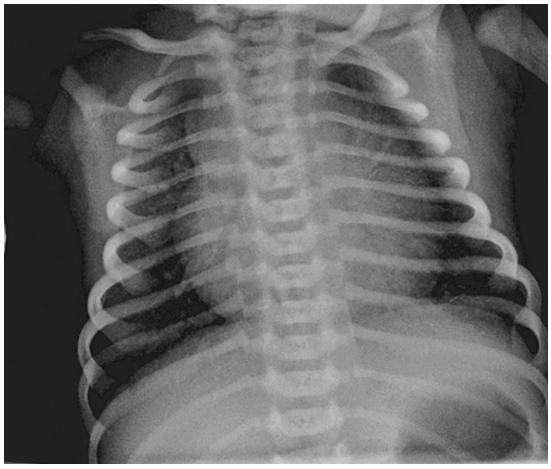


Fig. 17.2 Chest x-ray from Case Study 1 obtained at 2.5 hours of age showing 10-rib expansion and some bilateral streakiness. (Copyright 2015 Bobby Mathew, Satyan Lakshminrusimha. Published by Elsevier Inc. All rights reserved.)

compared with 39 or 40 weeks' gestation. Vaginal delivery is associated with a rapid reduction in fetal pulmonary vascular resistance (PVR) at birth. Delivery by elective cesarean section (Ramachandrappa and Jain, 2008; Sulyok and Csaba, 1986) delays the decrease in pulmonary arterial pressure (Fig. 17.3) and increases the risk for PPHN (Wilson et al, 2011). Compared with matched controls, infants with PPHN are more likely to have been delivered by cesarean section (Hernández-Díaz et al, 2007).

PULMONARY VASCULAR TRANSITION AT BIRTH

The entry of air into the alveoli with crying and breathing improves oxygenation of the pulmonary vascular bed, thereby decreasing PVR and increasing pulmonary blood flow (Teitel et al, 1990). The increase in pulmonary blood flow raises left atrial pressures above right atrial pressures,

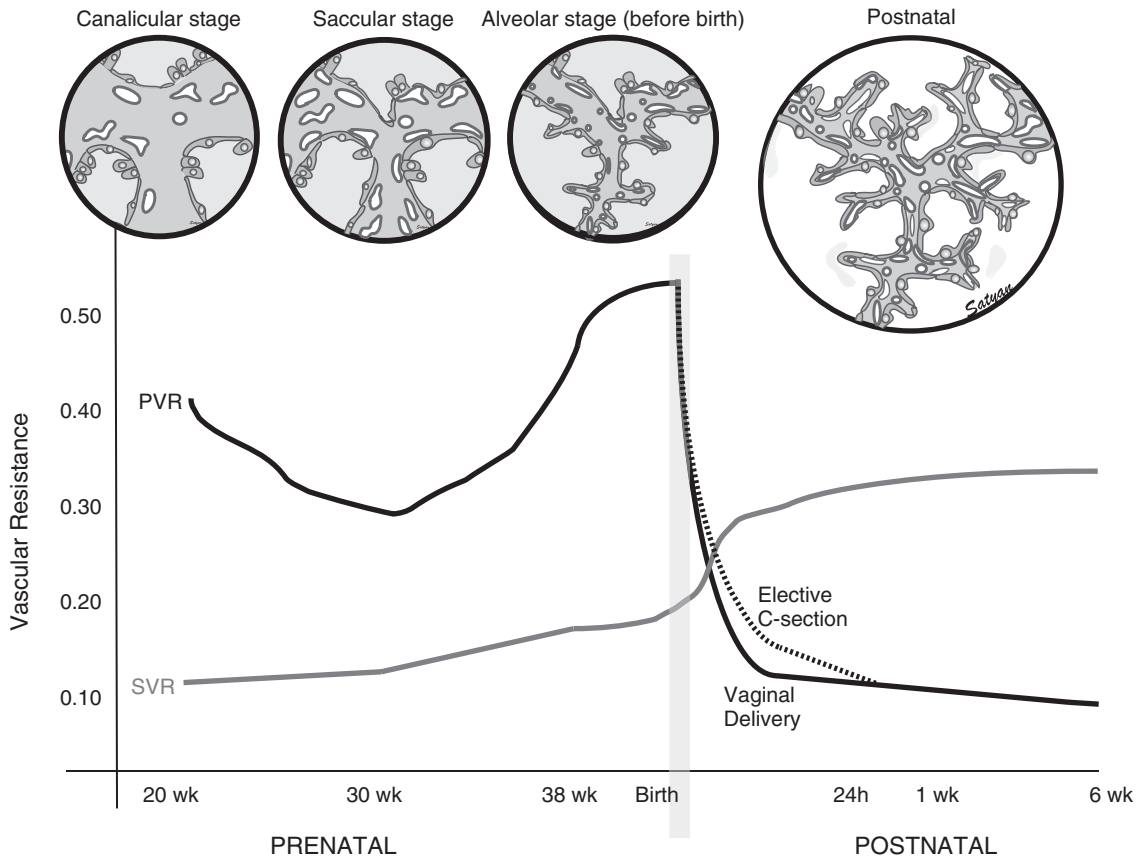


Fig. 17.3 Changes in pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR) during the last half of gestation and postnatal period. During the canalicular phase of lung development, high PVR is caused by low density of vasculature. In the saccular stage, broad intersaccular septae contain the "double capillary network" and with increasing vascular density, PVR decreases. In the alveolar phase, despite the rapid increase in the number of small pulmonary arteries, high PVR is maintained by active vasoconstriction. After birth, lung liquid is absorbed and an air–liquid interphase is established with juxtaposition of capillaries and alveolar epithelium to promote effective gas exchange. Dashed line represents the delay in decrease of PVR observed following elective cesarean section. SVR markedly increases after clamping the umbilical cord and removal of the low-resistance placental circuit from the systemic circulation.

closing the foramen ovale. Removal of the low resistance placental bed from the systemic circulation at birth increases systemic vascular resistance (SVR). PVR falls to approximately half of SVR within a few minutes after birth. As PVR becomes less than SVR, flow reverses across the ductus arteriosus and oxygenated blood flows from the aorta to the pulmonary artery. The ductus arteriosus closes in the first few hours following birth in the newborn at term, largely in response to an increase in oxygen tension and clearance of circulating prostaglandin by the lungs, thus establishing the postnatal circulatory pattern. Vasodilator mediators such as nitric oxide (NO) and prostacyclin (PGI_2) are important mediators of pulmonary vascular transition at birth (Abman et al, 1990).

CASE STUDY 1 (CONTINUED)

The transport team arrives 3 hours later. The baby's oxygen requirement has steadily increased to 95% oxygen by hood with saturations in the high 90s. Clinical examination reveals tachypnea (72 breaths/minute), grunting, and intercostal retractions. The arterial blood gas is as follows: pH 7.21, P_{CO_2} 66 mm Hg, and P_{O_2} 52 mm Hg. His chest x-ray is repeated and is shown in Fig. 17.4A. A decision is made to intubate the patient before transport.

Exercise 2

Question

What is the most likely cause of hypoxemia and respiratory distress in this infant?

A. PPHN
B. Pneumonia
C. Absorption atelectasis
D. RDS/surfactant deficiency

Answer

C. The infant is now grunting, which suggests that he is trying to maintain a normal functional residual capacity. Respiratory deterioration in this infant can be secondary to any of the choices mentioned above. However, the administration of

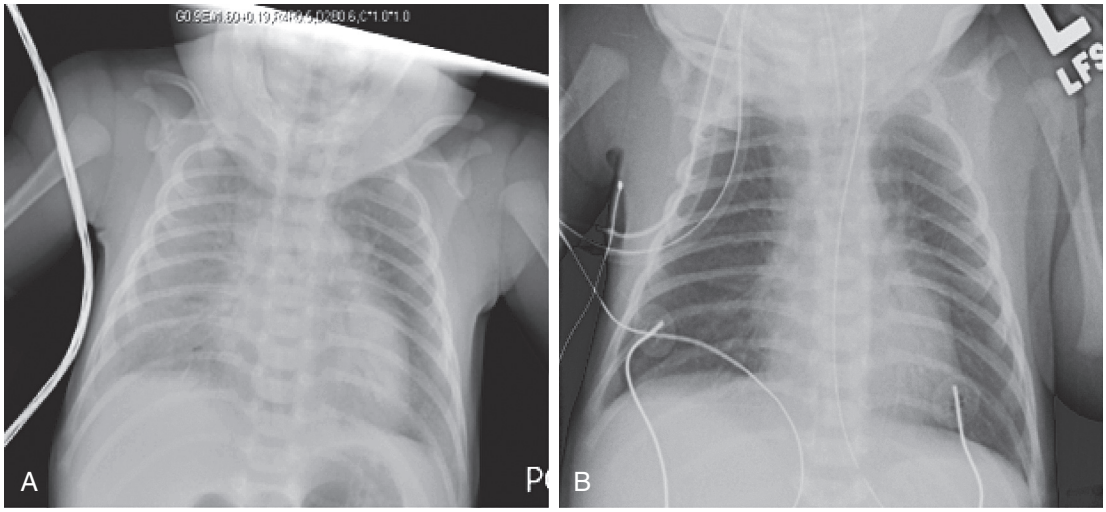


Fig. 17.4 (A) Chest x-ray obtained at approximately 5 hours of life showing 8- to 9-rib expansion with increasing parenchymal densities. (B) Chest x-ray obtained 1 hour after intubation and a dose of surfactant.

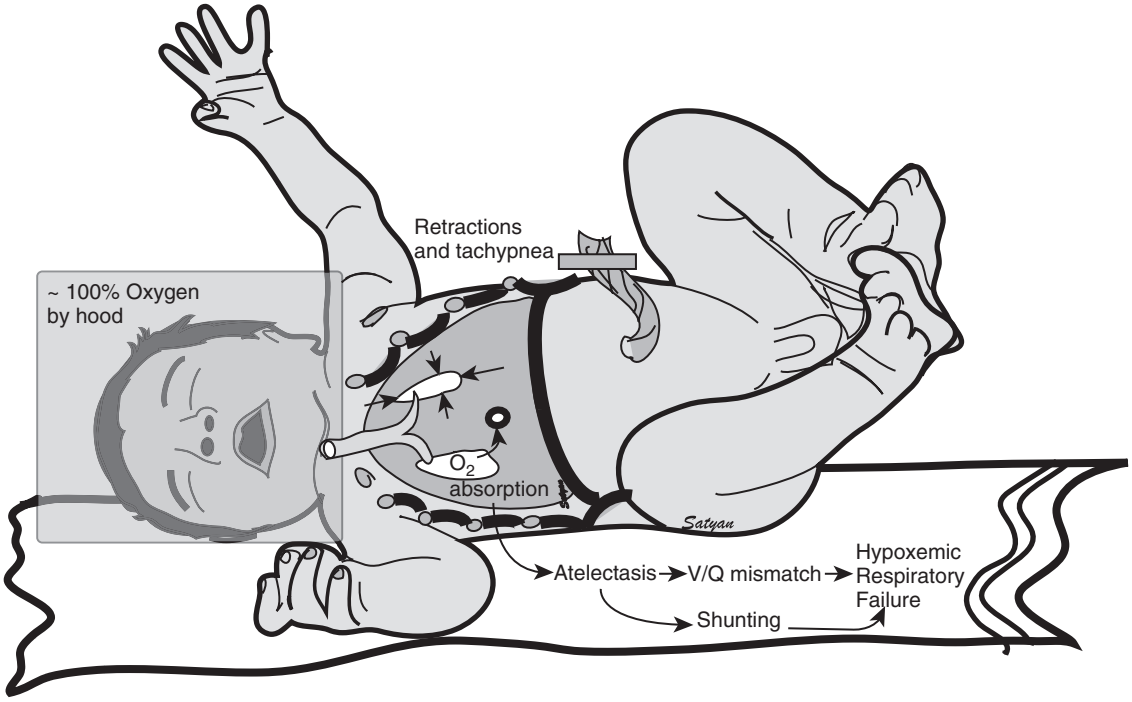


Fig. 17.5 Absorption atelectasis—administration of a high concentration of inspired oxygen without positive pressure in an infant with respiratory distress—can lead to nitrogen washout and alveolar collapse. Atelectasis can result in V/Q mismatch, shunting, and HRF with PPHN. (Copyright 2015 Bobby Mathew, Satyan Lakshminrusimha. Published by Elsevier Inc. All rights reserved.)

high ambient concentrations of oxygen without positive pressure can result in absorption atelectasis (Fig. 17.5). Unlike nitrogen (the predominant gas in room air), oxygen is easily absorbed from the alveoli into the bloodstream, leading to alveolar collapse. Because of nitrogen's low solubility, very little diffuses across the alveolar capillary interface, and most of the inspired nitrogen stays in the alveolus helping to keep it open. When high fractional inspired oxygen is used, the concentration of nitrogen in the inspired gas and in the gas within the alveolus is decreased. Oxygen absorption atelectasis leads to ventilation–perfusion (V/Q) mismatch, shunting, and hypoxemia. Therefore it is important to avoid administration of high concentrations of inspired oxygen (above 50%–60%) without positive pressure (such as continuous positive airway pressure [CPAP]) in neonates with respiratory distress.

CASE STUDY 1 (CONTINUED)

The baby is intubated by the transport respiratory therapist and placed on a conventional ventilator with a positive end expiratory pressure (PEEP) of 6 cm H_2O, and peak inspiratory pressure (PIP) of 18 cm H_2O at a rate of 35 breaths per minute. A dose of surfactant is administered. A subsequent x-ray, obtained before transfer, shows improved aeration (Fig. 17.4B). The oxygen concentration is reduced to 35% with a right upper extremity (preductal) SpO_2 of 94%. On the baby's arrival to the Children's Hospital, the echocardiogram shows normal cardiac anatomy with left-to-right shunting at the patent ductus arteriosus (PDA) and patent foramen ovale (PFO). An arterial blood gas drawn from the umbilical arterial line is as follows: pH of 7.49, $Paco_2$ of 31 mm Hg, and PaO_2 of 60 mm Hg. The ventilator rate is weaned to 30 breaths per minute and the PIP is lowered to 16 cm H_2O after delivery of adequate tidal volumes is verified. The neonatologist discusses with the transport team and the residents the importance of avoiding hypocapnia and the effect of blood gases and ventilator settings on pulmonary blood flow.

Exercise 3

Question

All of the following statements regarding the effect of pH, Po_2, and Pco_2 on pulmonary and cerebral circulation are correct EXCEPT:

A. Hypoxia causes pulmonary vasoconstriction and cerebral vasodilation.
B. Acute metabolic acidosis increases PVR and dilates the cerebral circulation.
C. Acute respiratory acidosis increases PVR and dilates the cerebral circulation.
D. Decreasing mean airway pressure (Paw) and reducing lung volume below functional residual capacity (FRC) increases PVR.
E. Marked increase in Paw reduces cardiac output and cerebral blood flow.

Answer

B. The systemic (cerebral) circulation responds to changes in blood gas parameters in a different manner compared with the pulmonary circulation (Fig. 17.6). Hypoxia constricts

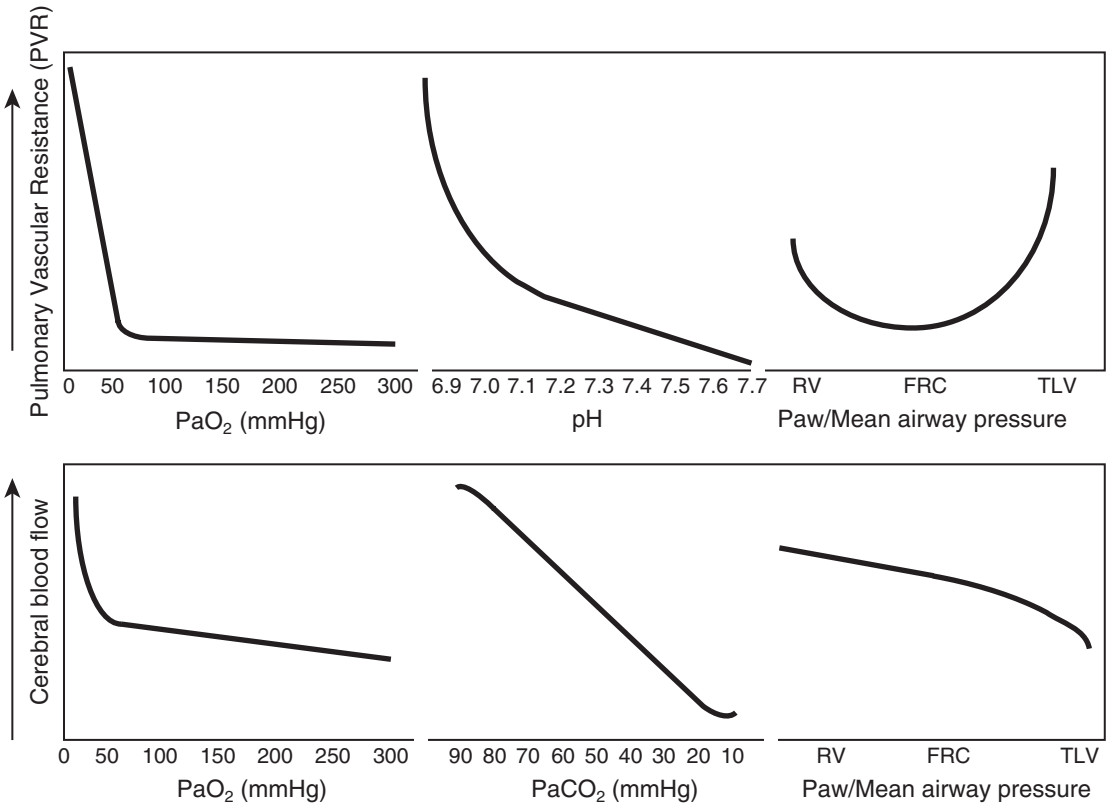


Fig. 17.6 The effect of Pao_2, pH (or $Paco_2$), and mean airway pressure (Paw) on pulmonary vascular resistance (PVR, top panel) and cerebral blood flow (bottom panel). Decrease in Pao_2 below 50 mm Hg increases PVR by hypoxic pulmonary constriction and increases cerebral blood flow. Metabolic and respiratory acidosis cause pulmonary vasoconstriction and alkalosis causes pulmonary vasodilation. Increase in $Paco_2$ increases cerebral blood flow, but acute metabolic changes in pH do not influence cerebral blood flow, as hydrogen ions do not easily diffuse across the blood–brain barrier. Extremes of Paw increase PVR. PVR is minimal at functional residual capacity (FRC). Progressive increase in Paw toward total lung volume (TLV) reduces cardiac output by impeding venous return. Very low Paw reduces lung inflation to residual volume (RV), kinks extraalveolar pulmonary vessels, and increases PVR.

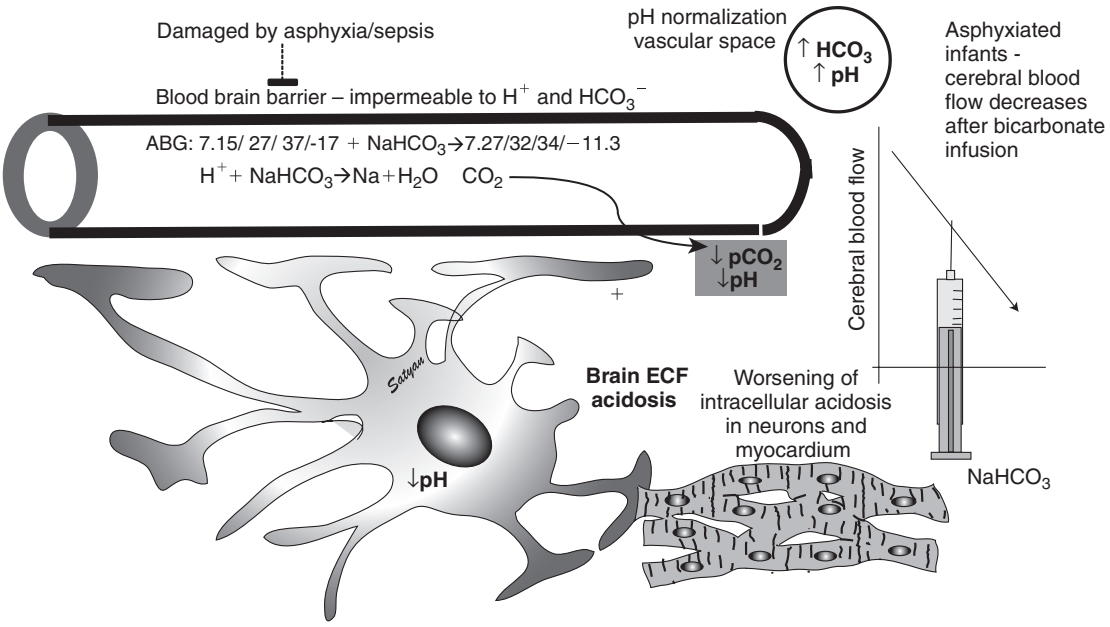


Fig. 17.7 Consequences of rapid infusion of large doses of sodium bicarbonate. The blood–brain barrier is normally impermeable to hydrogen ions and bicarbonate ions. However, CO_2 diffuses easily across the blood–brain barrier into the perivascular space. Acidosis in the perivascular extracellular fluid space in the brain causes cerebral vasodilation, and alkalosis in this space causes cerebral vasoconstriction. In conditions associated with acute metabolic acidosis with compensatory hypocapnia as seen in Case Study 6, low $Paco_2$ results in cerebral vasoconstriction. Rapid correction of intravascular acidosis with rapid, large infusions of sodium bicarbonate results in increase in plasma pH, increase in $Paco_2$, and reduction in base deficit. However, increased CO_2 diffuses across the blood–brain barrier, causing perivascular acidosis in the brain. Diffusion of CO_2 also leads to intracellular acidosis in the neuronal cells, glial cells, and cardiac myocytes. In conditions associated with damage to the blood–brain barrier (as in asphyxia, hypoxia, and sepsis/meningitis), sodium bicarbonate may pass through the blood–brain barrier causing acute perivascular alkalosis and reduction in cerebral blood flow (Lou et al, 1978). Hence, caution must be exercised during alkali therapy. If sodium bicarbonate is absolutely needed, only small doses (such as 1–2 mEq/kg) should be infused, slowly and with careful monitoring of acid–base status.

pulmonary vessels and increases PVR. Normoxia dilates pulmonary vessels and decreases PVR, but hyperoxia does not result in additional vasodilation (Lakshminrusimha et al, 2007; Lakshminrusimha et al, 2009; Rudolph and Yuan, 1966). The change point below which PVR increases is the alveolar PAO_2 that corresponds to a PaO_2 of 50 mm Hg in neonatal animals without pulmonary hypertension and 60 mm Hg in neonatal animal models of PPHN. Conversely, cerebral vasodilation occurs in response to decreased arterial oxygen content. Acidosis (both respiratory and metabolic) leads to pulmonary vasoconstriction, and alkalosis (both respiratory and metabolic) causes pulmonary vasodilation. The combination of acidosis and hypoxia results in exaggerated pulmonary vasoconstriction. Maintaining an arterial pH over 7.30 will reduce pulmonary vasoconstriction in response to hypoxia (Rudolph and Yuan, 1966).

Cerebral blood flow, on the other hand, decreases with respiratory alkalosis (approximately 4% reduction in flow per mm Hg decrease in $Paco_2$ in adults and a slightly lower degree in neonates). Changes in $Paco_2$ mediate alteration in cerebral blood flow by changing perivascular fluid pH in the brain (Fig. 17.6 and Fig. 17.7). Acute metabolic acid–base disturbances do not result in changes in cerebral blood flow, as H^+ ions do not cross the blood–brain barrier. However, in neonates with severe birth asphyxia, a rapid infusion of sodium bicarbonate causes cerebral perivascular alkalosis (owing to a leaky blood–brain barrier) and reduces cerebral blood flow (Lou et al, 1978). Increasing Paw reduces venous return, thereby decreasing cardiac output and cerebral blood flow. The effect of Paw on PVR is dependent on lung volume. At FRC, PVR is at its lowest and increases with atelectasis and hyperinflation (Fig. 17.6).

Chest x-rays are often helpful in the diagnosis of infants with HRF and some of the characteristic x-ray appearances for common neonatal respiratory disorders (Box 17.1) are described here. These descriptive terms are often used in the NICU and may provide a clue to the diagnosis (Box 17.2, Snow White and the Radiology Seven Dwarfs).

Grainy: This is a classic description of RDS caused by surfactant deficiency. Grainy, translucent appearance of the lung fields is caused by the presence of microatelectasis interspersed with areas of hyperexpansion. In the absence of surfactant, small alveoli have a tendency to collapse, owing to a higher surface tension, and inspired air empties into larger

BOX 17.1 The Differential Diagnosis of HRF and PPHN (Mnemonic: TACHyPneA)

Transient tachypnea of the newborn/retained fetal lung fluid
Aspiration syndromes (meconium, blood or amniotic fluid, and **a**sphyxia)
Congenital anomalies (congenital diaphragmatic hernia)
Hyaline membrane disease/RDS
Pneumonia or sepsis
Air leaks (and **A**ntidepressant use by mothers)

RDS: respiratory distress syndrome

BOX 17.2 X-ray Patterns in Various Respiratory Conditions Associated With PPHN (Snow White and the Seven Radiology Dwarfs)

Grainy - Respiratory distress syndrome or pneumonia
Hazy - Respiratory distress syndrome, pneumonia, pulmonary hemorrhage, or edema
Patchy - Pneumonia or atelectasis
Fluffy - Meconium aspiration syndrome
Bubbly - Pulmonary interstitial pneumonia (small bubbles) and congenital diaphragmatic hernia (large bubbles)
Blacky - Idiopathic PPHN (black-lung PPHN) and pneumothorax
Streaky - Transient tachypnea of newborn
(Snow) Whiteout - Chylothorax, pleural effusion, massive atelectasis

PPHN: persistent pulmonary hypertension of the newborn

alveoli. Large alveoli have lower surface tension and continue to get larger (Laplace's law), leading to a translucent, ground glass, or grainy appearance. The lungs are low volume (in nonintubated infants), and air bronchograms (air in large airways superimposed on a background of granularity) may be present.

Streaky: A streaky appearance is characteristic of TTN with retained fetal lung liquid. Streaky interstitial shadowing associated with fluid in the horizontal fissure is the classic appearance of TTN. The lungs are usually well expanded or have an increased volume. This is caused by peribronchial cuffing and air trapping in expiration leading to hyperexpansion of the lungs (Guglani et al, 2008).

Black lung: In "black-lung" or idiopathic PPHN without parenchymal lung disease, lung fields are dark because of decreased pulmonary vascularity. The lung fields may also appear black in infants with a pneumothorax secondary to anterior layering of lucent air in the pleural space.

Fluffy: In meconium aspiration syndrome (MAS), lung fields are overinflated with fluffy infiltrates in both lung fields. Aspirated meconium may exert a ball-valve effect leading to expiratory obstruction and air trapping.

Bubbly: Lung fields appear bubbly in pulmonary interstitial emphysema where air extravasates into the wall of the bronchi. A bubbly appearance may also be seen on the side of herniation in congenital diaphragmatic hernia (CDH) caused by the presence of air in the intestines.

Hazy: The lung fields can appear hazy in infants with pneumonia, RDS, and pulmonary hemorrhage.

Patchy: A patchy (nonhomogenous opacities) chest x-ray is suggestive of pneumonia. It is important to recognize that pneumonia caused by early onset sepsis from group B streptococcal infection and gram-negative infections such as *Escherichia coli* can mimic other neonatal respiratory disorders such as RDS or MAS.

White-out appearance: A white-out appearance may be seen in diffuse extensive atelectasis of the lung. A similar appearance may be seen in obstructed total anomalous pulmonary venous return (TAPVR). The typical "snowman in a snowstorm" appearance is caused by pulmonary edema from obstruction of the pulmonary venous return associated with a supracardiac form of TAPVR. Clinically, TAPVR may occasionally be confused with PPHN, and a chest x-ray may be helpful in narrowing the diagnosis. However, an echocardiogram is necessary to confirm the diagnosis.

SYSTEMIC OXYGEN DELIVERY

An understanding of the basic principles of gas exchange and transport is crucial to assessing severity of PPHN and HRF. Fig. 17.8 reviews the changes in oxygen levels through the process of oxygen transport from inspired gas to the mitochondria. This figure also illustrates the concept of systemic oxygen delivery (calculated by multiplying cardiac output with the difference between arterial and venous oxygen content A−V DO_2).

$$\text{Systemic oxygen delivery} = \text{cardiac output} \times [(\text{arterial oxygen content}) - (\text{venous oxygen content})]$$

$$\text{Oxygen content} = (\text{oxygen bound to hemoglobin}) + (\text{oxygen dissolved in the plasma}) \text{ in mL/dL}$$

$$\text{Oxygen content} = (\text{hemoglobin concentration g/dL} \times 1.34 \times \text{oxygen saturation}) + (PO_2 \text{ in mmHg} \times 0.003) \text{ mL/dL}$$

Question

List the factors that determine oxygen delivery to the tissues in the order of importance.
A. Dissolved oxygen
B. Hemoglobin concentration
C. Hemoglobin saturation
D. Cardiac output

Answer

D, B, C, A. The cardiac output and hemoglobin concentration are the most important factors determining systemic oxygen delivery. The essential goal of management of PPHN is to maintain adequate delivery of oxygen to the tissues.

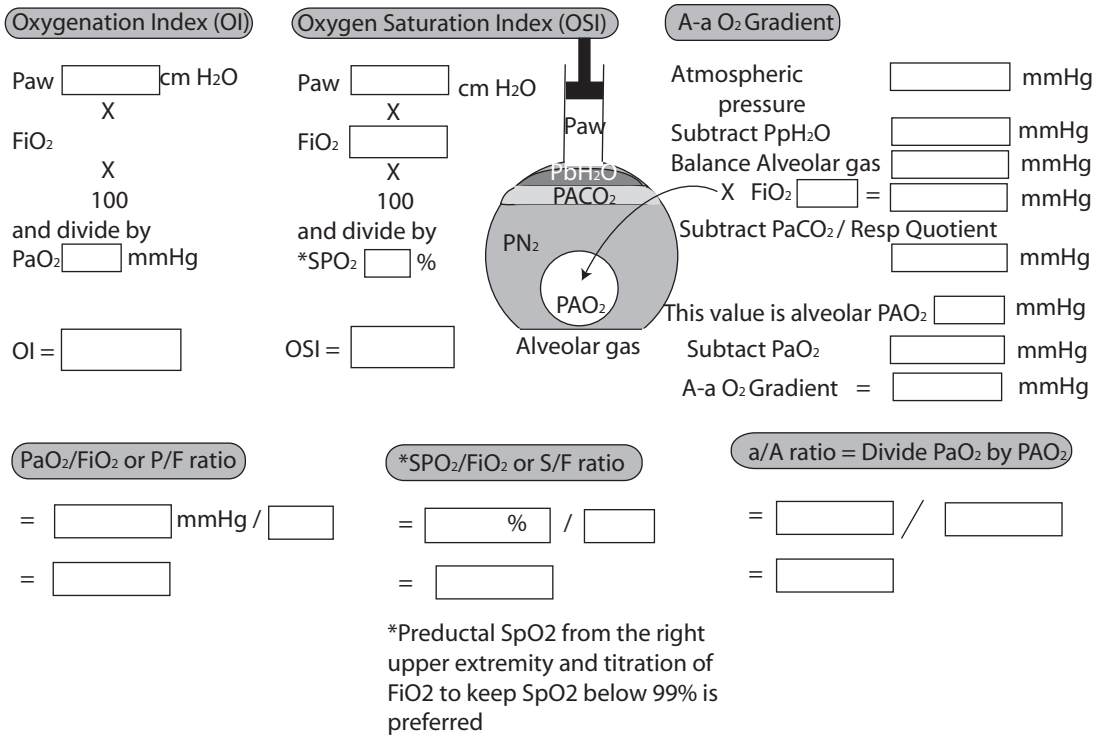


Fig. 17.8 Basics of gas exchange and transport. In this graph, the Y-axis represents P_{O_2} levels through the process of oxygen transport from inspired gas to the tissues and mitochondria. Approximate equivalent values for saturation (SO_2 in %) and oxygen content (in mL/dL assuming a hemoglobin level of 15 g/dL) are shown. The solid horizontal line shows approximate P_{O_2} values as oxygen moves from inspired gas to the alveolus. In the alveolus, oxygen is diluted by the presence of water vapor (ppH_2O), nitrogen, and carbon dioxide. There is a slight decrease in P_{O_2} as oxygen diffuses from the alveolus to the pulmonary capillary. In the left atrium, right-to-left shunt across the patent foramen ovale (PFO) decreases P_{O_2} in neonates with PPHN. A similar right-to-left shunt from pulmonary artery to aorta through the patent ductus arteriosus (PDA) further decreases the P_{O_2} in the postductal aorta. As the blood traverses the capillary, P_{O_2} decreases as oxygen diffuses into the tissues. The P_{O_2} values are low within the cell and mitochondria. The difference between arterial and venous oxygen content is called $AVDO_2$ and is expressed in mL/dL. Multiplying $AVDO_2$ with cardiac output provides systemic oxygen delivery (DO_2).

ASSESSMENT OF SEVERITY OF PPHN/HRF

The severity of PPHN and HRF and response to treatment are objectively assessed by using six indices (Figs. 17.8 and 17.9).

1. **Oxygenation index (OI):** This index includes factors that determine oxygenation (Paw and concentration of inspired oxygen) in the numerator and arterial oxygen tension in the denominator. This is one of the few indices that includes ventilator pressure and is commonly used in clinical trials to evaluate therapy in PPHN/HRF. The formula for calculating OI is given here and is illustrated in Fig. 17.9 with an example.

$$OI = FiO_2 \times MAP \times 100/PaO_2$$

Some units assess the severity of PPHN/ HRF based on OI (Golombek and Young, 2010).
Mild − OI ≤15
Moderate − OI 15 to ≤25
Severe − OI 25 to ≤40
Very severe − OI >40 (with possible need for extracorporeal membrane oxygenation [ECMO])

2. **Oxygen Saturation Index (OSI):** Many neonatal units prefer to monitor infants on invasive mechanical ventilation using noninvasive measures such as oxygen saturation by pulse oximetry (SpO_2) in the absence of indwelling arterial lines (Rawat et al, 2015). OSI is calculated as $Fio_2 \times$ Paw $\times$ 100 divided by SpO_2. Preductal SpO_2 values, preferably in the low to mid 90s (by adjusting Fio_2) will result in clinically meaningful values for OSI. High SpO_2 values (especially 100%) reduce the accuracy of OSI as the range of PaO_2 associated with 100% SpO_2 can vary widely along the top flat portion of the oxygen–hemoglobin dissociation curve. Within reasonable limits, OSI values are approximately half of OI values.
3. **Alveolar-arterial oxygen gradient (A-a gradient or A-aDO_2):** This number estimates the gradient in the partial pressure of oxygen from the alveolus (PAO_2 with an uppercase "A" to denote alveolus) to the aorta (PaO_2 with

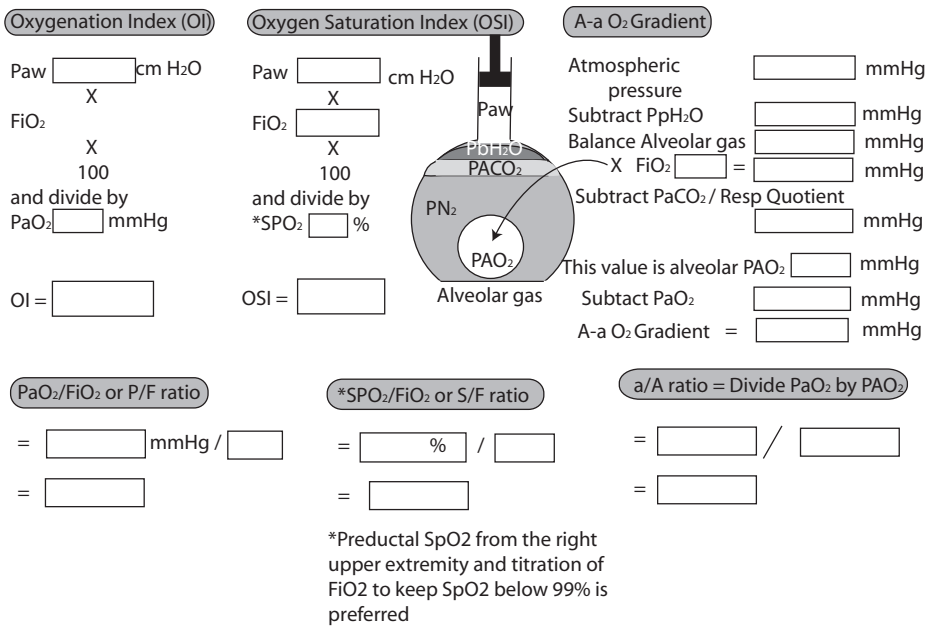


Fig. 17.9 Worksheet for calculating severity of illness in PPHN/ HRF. A full-term baby with meconium aspiration syndrome on a mean airway pressure (Paw) of 15 cm H_2O, Fio_2 of 1.0, $Paco_2$ of 50 mm Hg, and Pao_2 of 50 mm Hg is cared for at the Women and Children's Hospital of Buffalo (atmospheric pressure – 747 mm Hg).

a lowercase "a" to denote arterial) and is calculated as follows:

$$A - aDO_2 = [(FiO_2)(\text{barometric pressure } [\sim 760 \text{ mmHg}] - \text{water vapor pressure } [47 \text{ mmHg}]) - PaCO_2/R] - PaO_2$$

where R – respiratory quotient = 1 for neonates receiving glucose infusion).

Please refer to Fig. 17.9 for a detailed explanation.

4. **a/A ratio:** This is a ratio of arterial to alveolar Po_2 and is commonly used in translational studies.
5. **P/F ratio:** This is commonly used in pediatric and adult critical care units to assess severity of acute lung injury (ALI) and/or acute respiratory distress syndrome (ARDS) and is obtained by dividing PaO_2 by fraction of inspired oxygen (Fio_2). The patients are categorized based on the severity of hypoxemia: mild (>200 mm Hg to ≤300 mm Hg), moderate (>100 mm Hg to ≤200 mm Hg), and severe (PaO_2/Fio_2 ≤100 mm Hg).
6. **S/F ratio:** This index is calculated by dividing preductal SpO_2 by Fio_2. The limitations described in the section on OSI also apply to this index (see Fig. 17.9).

CASE STUDY 2

A 38-year-old woman at 34⅗ weeks' gestation with poorly controlled diabetes mellitus and a previous history of stillbirth at 36 weeks is being evaluated at the high-risk antenatal clinic. An episode of prolonged fetal bradycardia is noted, and an emergency cesarean section is performed. The baby needs CPAP in the delivery room for mild grunting and is transferred to the newborn nursery in room air. The infant is tachypneic and has preductal saturations in the mid-80s. He is given 50% oxygen by hood with improvement in saturations to the mid-90s. The initial chest x-ray shows expansion to seven ribs, bilateral haziness with mild granularity, and fluid in the horizontal fissure. The baby is transferred to the NICU for further evaluation.

Exercise 5

Question

What is/are the most likely diagnoses?

A. RDS
B. Retained fetal lung fluid and TTN
C. Early onset sepsis with pneumonia
D. Pulmonary hypoplasia

Answer

A and **B.** This is a common scenario that presents to clinicians in the NICU and well-baby nursery. This baby has clinical symptomatology that straddles both RDS and TTN. However, late-preterm gestation and maternal diabetes put this infant at greater risk of RDS. The presence of low lung volumes with granularity on chest x-ray suggests that RDS is the predominant cause of hypoxemia in this infant. This infant is born prematurely without labor and some degree of retained lung liquid should be expected.

CASE STUDY 2 (CONTINUED)

Following admission to the NICU, the baby is placed on nasal CPAP 4 to 6 cm H_2O in 40% oxygen. The initial capillary blood gas is as follows: pH 7.28, Pco_2 55 mm Hg, and Po_2 62 mm Hg.

The baby continues to be tachypneic with moderate retractions and the CPAP is increased to 6 and then to 8 cm H_2O. The oxygen requirement gradually increases to 65% to maintain SpO_2 in the mid-90s. The arterial blood gas at 4 hours of age is as follows: pH 7.22, $Paco_2$ 60 mm Hg, PaO_2 48 mm Hg, and base deficit of 4 mEq/L. The chest x-ray is repeated and shows decreased lung volumes and increased granularity. A complete blood count (CBC) with differential count and blood culture are obtained. The baby is started on ampicillin and gentamicin. The white blood cell count is 18,000/mm^3 with an immature to total neutrophil ratio of 0.11, hematocrit 55%, and platelets 246,000/mm^3. The oxygen saturation values are 92% and 82% in the right upper and lower limb, respectively.

Exercise 6

Question

What is the next step in the management of this infant?

A. Request an echocardiogram to rule out cyanotic congenital heart disease (CHD) or PPHN
B. Start inhaled NO via CPAP because this infant has clinical symptomatology consistent with PPHN
C. Endotracheal intubation and surfactant replacement
D. Maintain the current level of CPAP (6–8 cm of water) and repeat an arterial blood gas in 1 hour
E. Noninvasive positive pressure ventilation (NIPPV) via nasal cannula

Answer

C. This infant has untreated RDS as evidenced by the clinical picture of respiratory distress with elevated $Paco_2$ and increasing oxygen requirement. This infant has predisposing risk factors for RDS such as late-preterm gestation and maternal diabetes. The chest x-ray appearance confirms the diagnosis. The SpO_2 in the right upper limb is higher than that in the lower limb. This suggests shunting across the ductus arteriosus from right (pulmonary artery) to left (aorta). Preductal oxygen saturations are often obtained from the right upper extremity (the right subclavian artery always arises proximal to the ductus arteriosus, whereas the left subclavian artery occasionally can arise at or after the insertion of the ductus arteriosus; see Fig. 17.10). The presence of a lower SpO_2 in the lower limb compared with the right upper limb

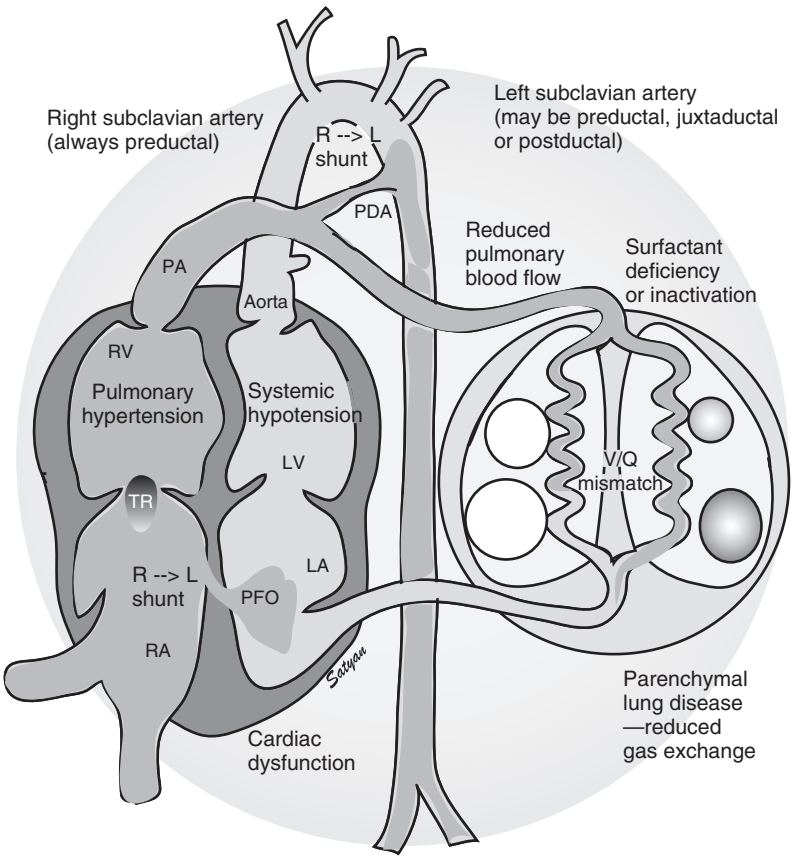


Fig. 17.10 Hemodynamic changes in PPHN/HRF. Surfactant deficiency (RDS) or inactivation (meconium aspiration or pneumonia) result in parenchymal lung disease and ventilation–perfusion (V/Q) mismatch. Increased pulmonary vascular resistance results in reduced pulmonary blood flow and right-to-left shunt through the PDA and/or PFO. Pulmonary hypertension is often associated with systemic hypotension with septal deviation to the left. Cardiac dysfunction secondary to asphyxia, sepsis, or CDH may complicate HRF. The right subclavian artery (and blood flowing to the right upper extremity) is always preductal. The left subclavian artery may be preductal, juxtaductal, or postductal. Hence, preductal oxygen saturations should be obtained from the right upper extremity. *LA,* Left atrium; *LV,* left ventricle; *PA,* pulmonary artery; *PDA,* patent ductus arteriosus; *PFO,* patent foramen ovale; *RA,* right atrium; *RV,* right ventricle; *TR,* tricuspid regurgitation.

is indicative of a right-to-left ductal shunt. An echocardiogram will be helpful if the infant does not respond to intubation, surfactant replacement, and alveolar recruitment.

CASE STUDY (CONTINUED)

The baby is intubated and receives a dose of surfactant. The initial ventilator settings are PIP of 20 cm H_2O, PEEP of 4 cm H_2O, pressure support of 12 cm H_2O, Paw of 10 cm H_2O, rate 40 breaths per minute, and inspiratory time of 0.35 seconds. There is minimal improvement in oxygen requirement following administration of surfactant. Umbilical arterial and venous lines are placed, and the blood gas at 8 hours of age has a PaO_2 of 45 mm Hg in 70% oxygen.

$$[\text{oxygenation index} = \text{Paw}\,(10) \times \text{FiO}_2\,(0.7) \times 100/\text{PaO}_2\,(45) = 15.6]$$

An echocardiogram is performed, which shows a structurally normal heart with a right ventricular systolic pressure of 55 mm Hg. Right-to-left shunting is noted both at the foramen ovale and PDA (Fig. 17.11A). Inhaled NO is started at 20 ppm. The baby is reevaluated 15 minutes following initiation of inhaled NO and noted to have a persistent oxygen requirement at 70%. A repeat arterial blood gas at 10 hours of age shows pH of 7.22, $Paco_2$ of 58 mm Hg, Pao_2 of 64 mm Hg, and a base deficit of 5 mEq/L. The chest x-ray shows poorly inflated lungs with bilateral ground-glass opacities.

Exercise 7

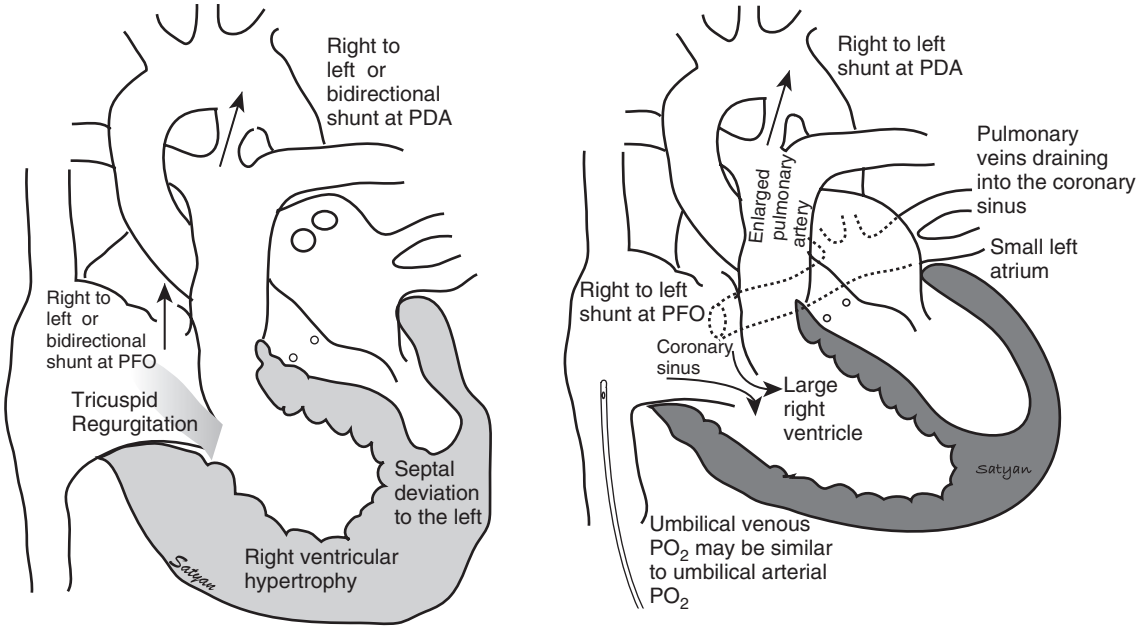
Question

What is the most likely reason for poor response to inhaled NO in this infant?

A. Missed diagnosis of cyanotic CHD
B. Inadequate alveolar recruitment
C. Surfactant protein B deficiency
D. Pulmonary venous hypertension

Answer

B. The most likely reason for not responding to inhaled NO is inadequate alveolar recruitment. The persistent underinflation on chest x-ray is evidence of inadequate respiratory support. Increasing the PEEP, PIP, or inspiratory time are common strategies to increase Paw and oxygenation during conventional ventilation. The use of high-frequency ventilation with adequate Paw can also achieve lung recruitment. It is unusual for cyanotic CHD to present with elevated $Paco_2$. Surfactant protein B deficiency is a very rare condition and



A. Echocardiographic features in PPHN

B. Total anomalous pulmonary venous return to coronary sinus

Fig. 17.11 (A) Echocardiographic features of PPHN. Infants with significant PPHN often have a right-to-left or bidirectional shunt at the level of the patent foramen ovale (PFO) and/or patent ductus arteriosus (PDA). Tricuspid regurgitation (TR) jet is often noted and is used to estimated right ventricular systolic pressure. Right ventricular hypertrophy with deviation of interventricular septum to the left is commonly present. (B) Cardiac findings in total anomalous pulmonary venous return (TAPVR) to the coronary sinus. Left atrium is small and pulmonary venous flow is diverted to the right atrium. The left atrium is filled by a right-to-left shunt across the PFO. The right ventricle and pulmonary artery are enlarged because of increased blood flow. Pulmonary arterial blood flows right to left across the PDA to the aorta. If the tip of the umbilical venous catheter is in the right atrium, Po_2 levels might be relatively high—similar to umbilical arterial sample—as oxygenated blood enters the right atrium.

presents with intractable respiratory failure in term infants. Pulmonary venous hypertension is usually secondary to obstruction to pulmonary venous drainage, mitral stenosis, or left ventricular dysfunction.

CASE STUDY 2 (CONTINUED)

The baby is placed on a high-frequency oscillator with the following settings: Paw of 12 cm H_2O, amplitude 30, frequency 12 Hz, and 50% O_2. Inhaled NO is continued at 20 ppm. A chest x-ray is repeated and shows inflation to eight ribs, symmetric bilateral opacification, and normal heart size.

For inhaled NO to be effective, it has to be delivered to the site of action (i.e., to the vascular smooth muscle cell in the pulmonary arteriole through the respiratory tree). Failure to achieve lung recruitment before initiation of inhaled NO is a common cause for failure to sustain an oxygenation response.

CASE STUDY 2 (CONTINUED)

The baby is given another dose of surfactant, and the lungs are recruited by increasing the Paw to 16 cm H_2O with prompt improvement in oxygenation. The inspired oxygen concentration is weaned to 30%. The Paw is decreased to 14 cm H_2O. A repeat blood gas is as follows: pH of 7.33, $Paco_2$ of 40 mm Hg, and PaO_2 of 98 mm Hg.

Subsequently, supplemental oxygen is weaned to 21%, and inhaled NO is weaned off over the next 20 hours. The baby is switched over to the conventional ventilator the following day and extubated 24 hours later to 30% oxygen by nasal cannula.

CASE STUDY 3

A 32-year-old gravida 2, para 0 mother is admitted in labor at 40 weeks' gestation with rupture of membranes. Meconium-stained amniotic fluid (MSAF) is noted, and induction of labor with oxytocin is commenced. Fetal tachycardia and loss of variability are observed, and an emergency cesarean section is performed.

Exercise 8

Question

What are the factors that determine the need for tracheal suctioning in infants born through MSAF?

A. Consistency of meconium
B. Duration of rupture of membranes
C. Gestational age
D. Nonvigorous state
E. None of the above

Answer

E. Following new evidence, the current neonatal resuscitation guidelines (Wyckoff et al, 2015) do not support a recommendation of routine intervention of intubation and suction for the nonvigorous newborn with MSAF. In two clinical trials of 297 term nonvigorous newborns delivered through MSAF randomized to tracheal suctioning (n = 148) and no tracheal suctioning (n = 149), there was no difference in the incidence of death (13% in suction group and 11% in no-suction group) and/or MAS (32% in the suction group and 28% in the no-suction group) (Chettri et al, 2015; Nangia et al 2016; Rawat et al, 2018). In a lamb model of meconium aspiration, tracheal suctioning did not decrease pulmonary vascular resistance, and the process of tracheal suctioning significantly delayed onset of resuscitation with positive pressure ventilation (PPV) leading to left ventricular dysfunction, elevated left atrial pressure, and pulmonary venous hypertension (Lakshminrusimha et al, 2015). Pulmonary venous hypertension can potentially lead to iNO-resistant PPHN and ECMO. Implementation of the new guidelines have led to reduced use of ECMO and deaths following ECMO among neonates with MAS (Fig. 17.12). Routine tracheal suction is no longer recommended, and prompt initiation of resuscitation with PPV is necessary in infants born through MSAF with bradycardia. However, if tracheal obstruction precludes effective ventilation of the lungs, tracheal suction may be considered.

CASE STUDY 3 (CONTINUED)

At birth this baby is apneic and limp with a heart rate of 50 beats per minute, and PPV is provided. The heart rate improves with PPV. Apgar scores are 1, 4, 5, and 7 at 1, 5, 10, and 15 minutes respectively. The cord pH is 7.02 with base deficit of 15 mEq/L. The baby is noted to have irregular gasping respirations and is placed on mechanical ventilation. Arterial blood gas at 1 hour of age is as follows: pH of 6.83, $Paco_2$ of 76 mm Hg, PaO_2 of 52 mm Hg, and base deficit of 22.8 mEq/L. The infant requires 100% oxygen to maintain preductal saturations above 92%. Postductal saturations in the lower limb are 83%. The baby is placed on high-frequency oscillator with the following settings: Paw of 18 cm H_2O, amplitude 40 cm H_2O, frequency 9 Hz, and Fio_2 of 1.0. On neurologic examination, she is noted to have poor tone, absent reflexes, dilated nonreactive pupils, and absent Moro reflex. Whole-body hypothermia is initiated for features of severe hypoxic ischemic encephalopathy (HIE) and a target esophageal temperature of 33.5°C is achieved at 2.5 hours of age.

Her chest x-ray shows fluffy infiltrates with 9- to 10-rib expansion on both sides. A dose of surfactant is administered with minimal improvement in respiratory status. Systemic blood pressure is 52/36 (mean 44 mm Hg). Arterial blood gas from an umbilical arterial catheter 2 hours after achieving hypothermia at 33.5°C is as follows: pH of 7.21, $Paco_2$ of 54 mm Hg, PaO_2 of 40 mm Hg, and base deficit at 6.1 mEq/L.

Exercise 9

Question

What is the most appropriate next step in the management of this infant?

A. Increase pH by an infusion of sodium bicarbonate
B. Induce a respiratory alkalosis by increasing the ventilator frequency
C. Increase Paw to achieve 10- to 11-rib expansion

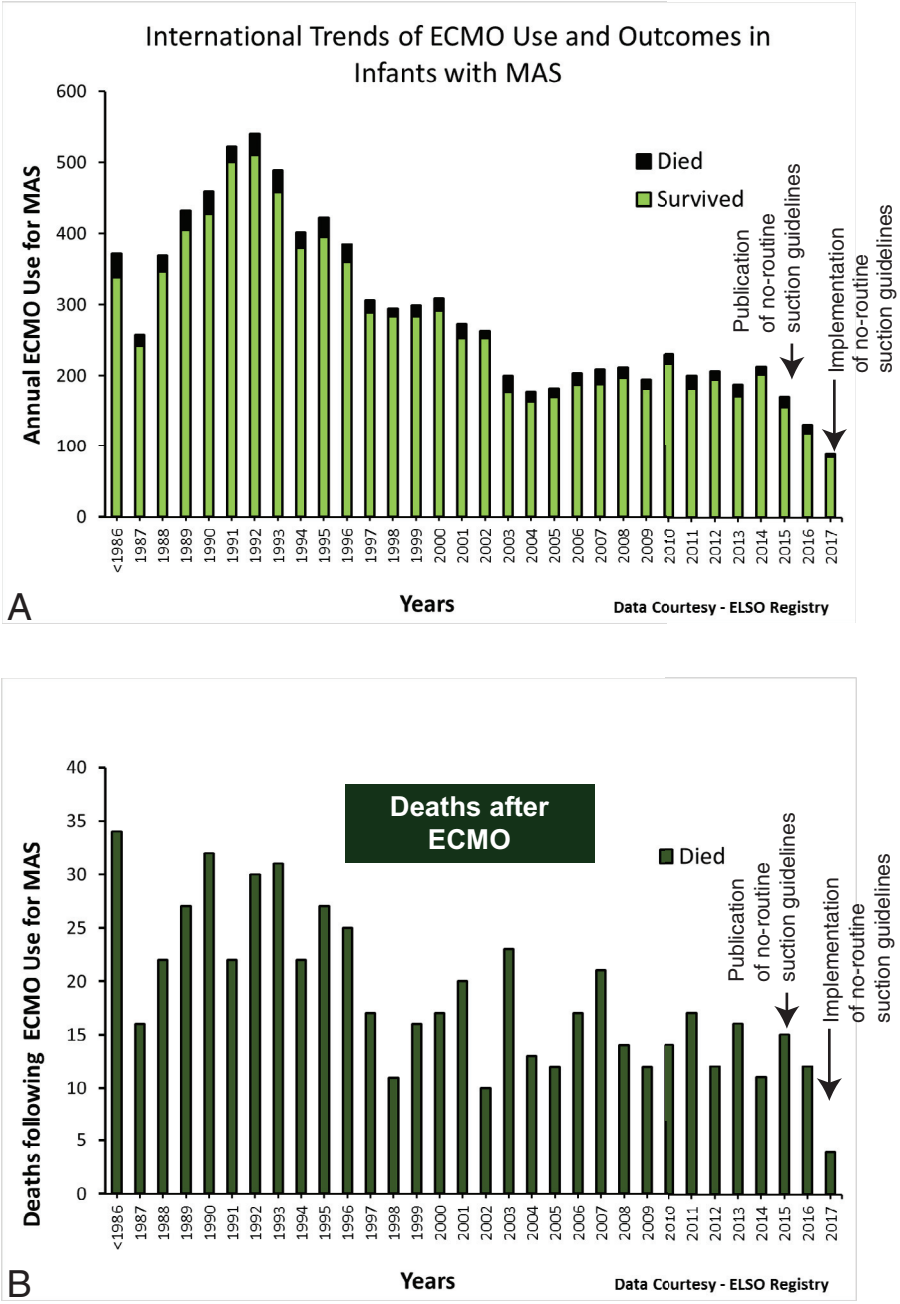


Fig. 17.12 International trends in ECMO use for neonatal respiratory indication of meconium aspiration syndrome (A) and deaths following ECMO for the same indication (B). The no-routine suction for infants born with meconium-stained amniotic fluid were published in late 2015 and implemented in 2017. (Data courtesy ELSO registry.)

D. Inhaled NO
E. Dopamine infusion

Answer

D. This baby has MAS (with HRF) and HIE. Both of these conditions predispose the infant to develop PPHN (Lakshminrusimha et al, 2018). The infant has clinical signs of PPHN with right-to-left shunting at the ductus arteriosus as evidenced by the difference in pre- and postductal saturation values. The concurrent multiple pathophysiologic processes in this infant present challenging issues in management. Metabolic acidosis is associated with pulmonary vasoconstriction and worsening of pulmonary hypertension (Fig. 17.6). In the past, induction of respiratory and/or metabolic alkalosis was the mainstay of therapy for pulmonary hypertension. Although short-term pulmonary vasodilation is achieved with hyperventilation, infants managed with respiratory alkalosis have worse neurodevelopmental outcomes with a high incidence of sensorineural deafness (Hendricks-Munoz and Walton, 1988).

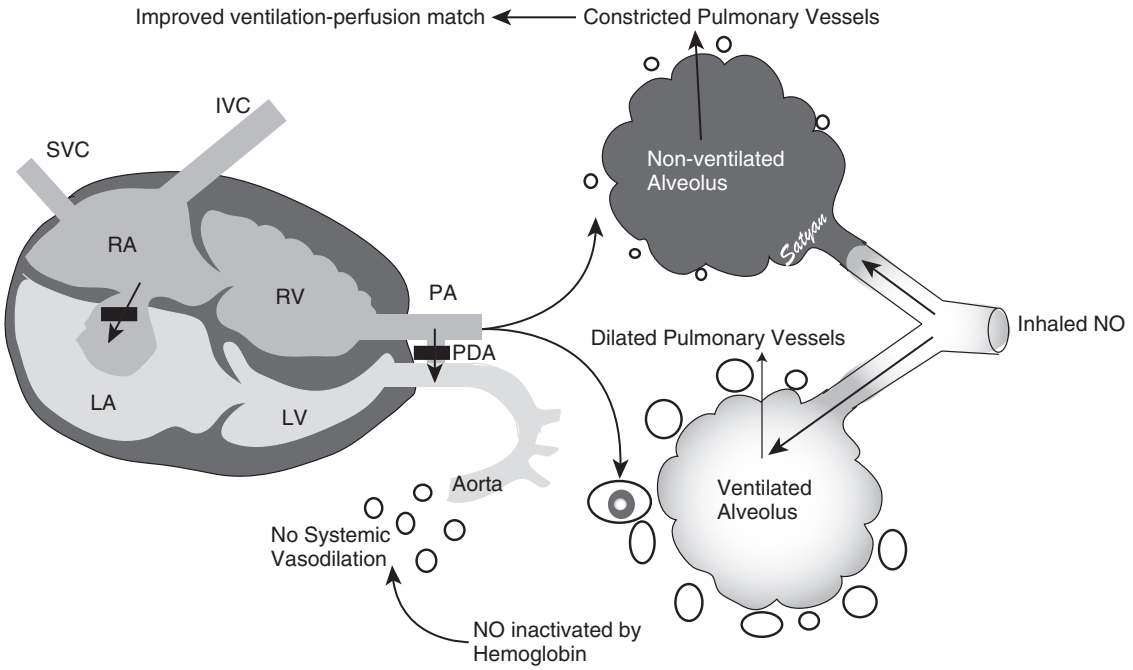


Fig. 17.13 Selective and microselective action of inhaled nitric oxide (NO). Inhaled NO is a selective dilator of the pulmonary circulation without any significant systemic vasodilation as it combines with hemoglobin to form methemoglobin. As it is an inhaled vasodilator, it selectively enters the well-ventilated alveoli, improves blood flow to these alveoli, and reduces V/Q mismatch (microselective effect). (Copyright 2015 Bobby Mathew, Satyan Lakshminrusimha. Published by Elsevier Inc. All rights reserved.)

Sodium bicarbonate infusion improves intravascular pH but may cause paradoxical intracellular acidosis in tissues and is associated with decreased cerebral blood flow in infants with HIE (see Fig. 17.7). In contrast to the conventional ventilator, increasing the frequency on the high frequency oscillator reduces tidal volume and increases $Paco_2$. Adjusting the Paw on high-frequency oscillator to optimize lung inflation is critically important for oxygenation and ventilation. However, hyperexpansion is associated with decreased venous return and increased PVR (Fig. 17.6), leading to deterioration in systemic oxygen delivery. There is no clinical indication for the use of dopamine in this infant. The mean blood pressure in this infant is within the normal limits for a newborn full-term infant. In addition, dopamine has vasoconstrictor effects both on the systemic *and* pulmonary vasculature.

In this case initiation of inhaled NO to selectively dilate pulmonary vasculature may be the most effective therapy with least side effects. Inhaled NO is inactivated by hemoglobin and has no systemic vasodilator effect. Inhaled NO also reduces intrapulmonary right-to-left shunting by preferentially dilating blood vessels that supply well-ventilated alveolar units. This is referred to as the microselective effect of inhaled NO (Fig. 17.13).

CASE STUDY 3 (CONTINUED)

Following initiation of inhaled NO, there is a transient improvement in oxygen saturation to 97%. However, within 30 minutes, preductal oxygen saturations decrease to 85%. Arterial blood gas values 2 hours after initiation of inhaled NO are as follows: pH of 7.17, $Paco_2$ of 58 mm Hg, Pao_2 of 59 mm Hg, and base deficit of 7.3 mEq/L. The chest x-ray shows increased haziness with mild cardiomegaly. An echocardiogram shows a right-to-left shunt at the level of the PDA but a left-to-right shunt through the PFO suggestive of myocardial dysfunction and poor contractility.

Exercise 10

Question

Which of the following factors contributes to poor response to inhaled NO in this patient with MAS and HIE?

A. Whole-body hypothermia results in pulmonary vasoconstriction
B. Liver dysfunction from asphyxia impairs response to inhaled NO
C. Left ventricular dysfunction with pulmonary venous hypertension
D. Coexisting acute tubular necrosis and renal dysfunction

Answer

C. Hypothermia induces both pulmonary and systemic vasoconstriction. In a recent Cochrane review, a metaanalysis of several trials (cooling 33.5°C to 34.0°C) has shown no effect of hypothermia on PPHN and no significant effect of hypothermia on the need for inhaled NO (Jacobs et al, 2013). A more recent randomized trial comparing cooling for longer (120 hours), deeper (32.0°C), or both to the current hypothermia protocol of 33.5°C for 72 hours has shown a trend toward increased PPHN

TABLE 17.1 Differential Diagnosis of Hypoxemia in a Neonate Based on the Direction of Shunt at Atrial and Ductal Level on Echocardiography

Diagnosis	Ductal Shunt	Atrial Shunt	Management
Parenchymal lung disease and V/Q mismatch and intrapulmonary shunt	L → R	L → R	Lung recruitment, specific therapy (antibiotics for pneumonia, surfactant for RDS) Inhaled NO may be beneficial by correcting V/Q mismatch
PPHN	R → L	R → L	Oxygenation, correction of acidosis, and inhaled NO
Left ventricular dysfunction (common in diaphragmatic hernia, asphyxia, and sepsis) (Kinsella, 2008; Sehgal et al, 2012	R → L	L → R	Inotropes and vasodilators (Milrinone)
Tricuspid atresia/stenosis or pulmonic atresia/stenosis	L → R	R → L	PGE_1 + Surgery
TAPVR (total anomalous pulmonary venous return) (Lakshminrusimha et al, 2009)	R → L (Large PA)	R → L (small LA and *no tricuspid regurgitation*)	Surgery

Modified from Lakshminrusimha S, Kumar VH: Diseases of pulmonary circulation. *L:* left; *LA:* left atrium; *NO:* nitric oxide; *PA:* pulmonary artery; *PGE1:* prostaglandin E1; *PPHN:* persistent pulmonary hypertension of the newborn; *R:* rigth; *RDS:* respiratory distress syndrome; *TAPVR:* total anomalous pulmonary venous return; *V/Q:* ventilation/perfusion In Fuhrman BP, Zimmerman JJ, editors: *Pediatric critical care,* ed 4, Philadelphia, 2011, Elsevier/Saunders, pp 632–656.

and statistically significant increase in inhaled NO use in the group cooled to 32.0°C (Shankaran et al, 2014). However, there is no evidence to suggest that infants undergoing hypothermia do not respond to inhaled NO.

The patient in this vignette has ventricular dysfunction. Patients with HRF and PPHN typically have a right-to-left shunt at the level of PDA and PFO (see Fig. 17.10 and 17.11A). In the presence of left ventricular dysfunction, left atrial pressures are elevated, resulting in a left-to-right shunt at the foramen ovale (Table 17.1). Elevated left atrial pressure results in pulmonary venous hypertension. Administration of inhaled NO to a patient with pulmonary venous hypertension can result in flooding of the pulmonary capillary bed and worsening of pulmonary edema resulting in clinical deterioration (Kinsella, 2008). It has been suggested that an inodilator such as milrinone may be more effective than inhaled NO in improving left ventricular function and reducing pulmonary venous hypertension (Lakshminrusimha and Steinhorn, 2013) (Fig. 17.14).

CASE STUDY 3 (CONTINUED)

With respiratory deterioration, inhaled NO is discontinued and the patient is started on a milrinone infusion at 0.33 mcg/kg/min following a loading dose of 50 mcg/kg over 30 minutes. After 2 hours, the dose of milrinone is escalated to 0.66 mcg/kg/min. A repeat echocardiogram obtained 24 hours after initiation of milrinone shows improved cardiac function. Following 3 days of therapy with milrinone, the patient is weaned from the oscillator to a conventional ventilator.

Meconium staining of amniotic fluid occurs in 5% to 25% of normal pregnancies. Risk factors for in utero meconium passage include postmaturity, placental insufficiency, fetal distress, and intrauterine growth restriction. Gasping occurs with asphyxia and causes particulate meconium to be aspirated into the airways. MAS occurs in about 5% of infants born through MSAF. The incidence of MAS has decreased in recent years due to the reduction in the number of postterm deliveries. The pathophysiology of MAS includes a combination of mechanical effects from airway obstruction, chemical pneumonitis, inflammation, surfactant inactivation, and increased PVR. The practice of suctioning of the oropharynx upon delivery of the head does not reduce the incidence or severity of MAS and is no longer recommended (Fraser et al, 2005; Vain et al, 2004). Infants with MAS are at high risk for PPHN, HRF, and air leaks.

The basic principles of management include assisted ventilation with avoidance of respiratory and metabolic acidosis, preventing hypoxia-induced pulmonary vasoconstriction, and maintaining normal blood pressure and perfusion. As surfactant inactivation occurs with meconium aspiration, surfactant replacement should be considered in severe cases. Surfactant has been shown to decrease the need for ECMO in patients with MAS (Lotze et al, 1998). With the use of surfactant, inhaled NO and high-frequency ventilation, there has been a marked reduction in patients needing ECMO for MAS. Infants who undergo ECMO for MAS have a much higher survival compared with infants with other indications for ECMO (Table 17.2).

CASE STUDY 3 (CONTINUED)

This neonate with asphyxia, MAS, and PPHN is undergoing whole-body cooling to a core temperature of 33.5°C. An arterial blood gas is drawn from the umbilical arterial line. The laboratory reports a pH of 7.41, $Paco_2$ of 35 mm Hg, and PaO_2 of 55 mm Hg at 37°C. You call the laboratory supervisor and inform her that the baby's core temperature is 33.5°C.

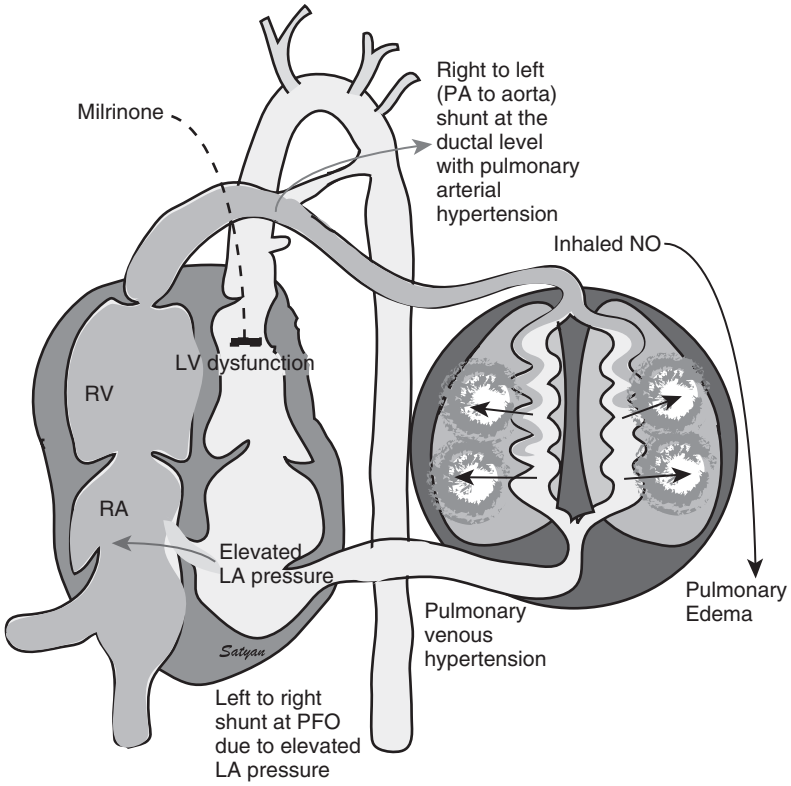


Fig. 17.14 Pulmonary hemodynamic changes in the presence of left ventricular dysfunction. Left ventricular (LV) dysfunction is occasionally associated with asphyxia, sepsis, or diaphragmatic hernia. In the presence of LV dysfunction, left atrial (LA) pressure is elevated, resulting in a left-to-right shunt at the patent foramen ovale (PFO). Pulmonary venous hypertension leads to pulmonary edema. Administration of inhaled NO dilates pulmonary arteries and increases blood flow to the lungs without improving LV dysfunction or LA pressure. This results in worsening pulmonary edema and deterioration of respiratory status. Administration of milrinone improves diastolic and systolic function of the LV and improves pulmonary venous hypertension. (Copyright 2015 Bobby Mathew, Satyan Lakshminrusimha. Published by Elsevier Inc. All rights reserved.)

TABLE 17.2 Recent Data on Neonatal Respiratory ECMO Runs by Diagnosis (5-year Period From 2013–2017)

Diagnosis	Total Runs	Survived	% Survived
Congenital diaphragmatic hernia (CDH)	1291	659	51%
Meconium aspiration syndrome (MAS)	789	731	93%
Persistent pulmonary hypertension of the newborn (PPHN)/ persistent fetal circulation (PFC)	800	589	74%
Respiratory distress syndrome (RDS)	30	23	77%
Sepsis	133	64	48%
Others	925	611	66%
Total	3968	2677	67%

Data from ELSO Registry. Accessed January 2018.

Exercise 11

Question

The laboratory supervisor corrects the blood gas results to the baby's temperature of 33.5°C. What changes do you expect with $PacCO_2$ at the baby's body temperature?

A. The $Paco_2$ decreases with hypothermia and correction to a temperature of 37°C results in a higher value (40.5 mm Hg).

B. Temperature has no effect on $Paco_2$ and no correction is necessary.

C. The $Paco_2$ increases with hypothermia and correction to a temperature of 37°C results in a lower value (31.5 mm Hg).

Answer

A. The clinician should pay particular attention to the changes in $Paco_2$ with hypothermia for HIE. $Paco_2$ decreases with hypothermia and correction to a temperature of 37°C results in an elevated $Paco_2$ level. This can compromise cerebral blood flow and hence a higher corrected $Paco_2$ should

be accepted in these patients. In a retrospective study of patients enrolled in the whole-body cooling trial, Pappas and colleagues demonstrated an association between hypocarbia and poor neurodevelopmental outcome at 18 to 22 months (Pappas et al, 2011). A delicate balance exists between improving pulmonary blood flow and gas exchange and providing adequate cerebral perfusion to optimize neurodevelopmental outcome in infants with MAS, PPHN, and HIE (Fig. 17.6).

CASE STUDY 4

A 19-year-old mother with poor prenatal care is admitted in labor a week before her expected date of delivery. A quick sonogram reveals that the fetus has a left sided diaphragmatic hernia. A 3245 gram male infant is born by spontaneous vaginal delivery. On examination, he has mild respiratory distress and a heart rate of 140 beats per minute. Auscultation reveals absence of breath sounds on the left with heart sounds shifted to the right. A Replogle suction tube is passed into the stomach. He is intubated with a 3.5 mm tracheal tube. An umbilical arterial line is placed, and an arterial blood gas is drawn while the infant is on conventional ventilation with the following settings: PIP of 23 cm H_2O, PEEP of 5 cm H_2O, Paw of 13 cm H_2O, rate of 40 breaths/minute, and inspired oxygen concentration of 70%. The preductal oxygen saturation is 70%. The arterial blood gas is as follows: pH 7.27, P_{CO_2} 57 mm Hg, and P_{O_2} 29 mm Hg. To assess the severity of his illness, calculate his oxygenation index and oxygen satuation index using the formula given in Fig. 17.9.

Exercise 12

Question

What is the oxygenation index in this patient?

A. 13
B. 26
C. 31
D. 36
E. 45

Answer

C

Question

What is the oxygen saturation index (OSI) in this patient?

A. 13
B. 26
C. 31
D. 36
E. 45

Answer

A

CASE STUDY 4 (CONTINUED)

The chest x-ray shows herniated abdominal contents in the left hemithorax. There is mediastinal shift to the right. The right lung is expanded to nine ribs. Because of low oxygen saturations, the inspired oxygen concentration is steadily increased to 100%. His preductal and postductal saturations are 86% and 68% respectively. Therapy with inhaled NO at 20 ppm is initiated with no significant improvement in oxygenation.

Exercise 13

Question

What is (are) the causes of poor response to inhaled NO in this patient?

A. Decreased cross-sectional area of pulmonary vasculature
B. Muscularization of arteries and "fixed" pulmonary hypertension
C. Left ventricular dysfunction
D. Enzyme abnormalities in the NO pathway
E. Elevated levels of vasoconstrictors such as endothelin

Answer

All of the above. Infants with CDH have pulmonary hypoplasia and PPHN secondary to impaired pulmonary vascular development and increased muscularization of the pulmonary arterioles. Abnormalities of enzymes in the NO pathway (de Buys Roessingh et al, 2011) have been observed in animal models of CDH (Karamanoukian et al, 1996). Many infants with CDH also have abnormalities in left ventricular structure and function that can lead to pulmonary venous hypertension and may contribute to poor response to inhaled NO. Elevated endothelin (a powerful vasoconstrictor, Fig. 17.15) levels have been observed in patients with CDH (Keller et al, 2010). The only randomized control trial evaluating the use of inhaled NO in CDH showed a higher need for ECMO in patients that received NO (Inhaled nitric oxide and hypoxic respiratory failure in infants with congenital diaphragmatic hernia. The Neonatal Inhaled Nitric Oxide Study Group [NINOS], 1997). Infants with CDH need frequent echocardiographic assessment of ventricular pressure and function during therapy. Corrective surgery is usually performed following adequate control of pulmonary hypertension.

ROLE OF ECHOCARDIOGRAPHY IN INFANTS WITH HRF

Hemodynamic profile assessed by functional echocardiography is extremely useful to diagnose, manage, and follow the changes with therapy in infants with HRF (El-Khuffash and McNamara, 2011). Pulmonary arterial pressure is estimated from the tricuspid regurgitation jet velocity. Using the modified Bernoulli equation, systolic right ventricular pressure (mm Hg) is estimated as $4(v^2)$ + right atrial pressure, where "v" is the maximal velocity of tricuspid regurgitation jet in meters/second on continuous-wave Doppler echocardiogram (Yock and Popp, 1984). Right ventricular dysfunction caused by excessive afterload appears to be a major risk factor for poor outcome in HRF (Lapointe and Barrington, 2011) and may influence the velocity of the tricuspid regurgitation jet. Echocardiographic assessment of atrial and ductal level

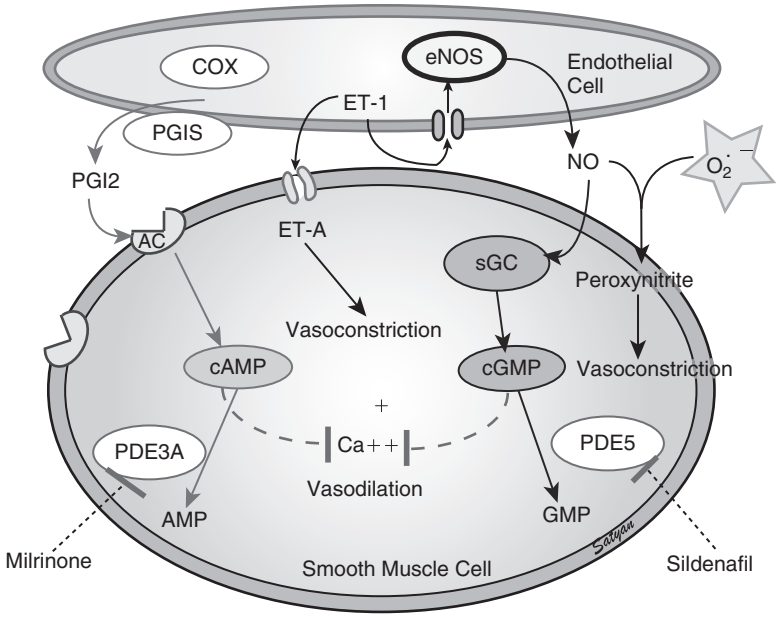


Fig. 17.15 Endothelium-derived vasodilators: prostacyclin (PGI_2), nitric oxide (NO), and vasoconstrictor (endothelin, ET-1). The enzymes, cyclooxygenase (COX), and prostacyclin synthase (PGIS) are involved in the production of prostacyclin. Prostacyclin acts on its receptor in the smooth muscle cell and stimulates adenylate cyclase (AC) to produce cyclic adenosine monophosphate (cAMP). Cyclic AMP is broken down by phosphodiesterase 3A (PDE 3A) in the smooth muscle cell. Milrinone inhibits PDE 3A and increases cAMP levels in pulmonary arterial smooth muscle cells and cardiac myocytes, resulting in pulmonary (and systemic) vasodilation and inotropy. Endothelin is a powerful vasoconstrictor and acts on ET-A receptors in the smooth muscle cell and increases ionic calcium concentration. A second endothelin receptor (ET-B) on the endothelial cell stimulates NO release and vasodilation. Endothelial nitric oxide synthase (eNOS) produces NO, which diffuses from the endothelium to the smooth muscle cell and stimulates soluble guanylate cyclase (sGC) enzyme to produce cyclic guanosine monophosphate (cGMP). Cyclic GMP is broken down by PDE 5 enzyme in the smooth muscle cell. Sildenafil inhibits PDE5 and increases cGMP levels in pulmonary arterial smooth muscle cells. Cyclic AMP and cGMP reduce cytosolic ionic calcium concentrations and induce smooth muscle cell relaxation and pulmonary vasodilation. NO is a free radical and can avidly combine with superoxide anions to form a toxic vasoconstrictor, peroxynitrite. The bioavailability of NO in a tissue is determined by the local concentration of superoxide anions. Hyperoxic ventilation with 100% oxygen can increase the risk of formation of superoxide anions in the pulmonary arterial smooth muscle cells and limit the bioavailability of NO.

shunts assists in diagnosis and optimal management of a newborn presenting with hypoxemia (see Table 17.1).

Exercise 14

Question

Which of the following disorders associated with PPHN has the highest mortality following ECMO?

A. Air-leak syndromes
B. CDH
C. MAS
D. Surfactant deficiency leading to respiratory distress syndrome (RDS)
E. Idiopathic "black-lung" PPHN

Answer

B. Of the various causes of PPHN listed in Box 17.1, CDH is associated with a high requirement for ECMO. Recent data from the Extracorporeal Life Support Organization (ELSO) registry shows that survival following ECMO is only 51% with CDH (compared with 93% with MAS).

CASE STUDY 4 (CONTINUED)

In spite of maximal support with conventional ventilation and inhaled NO, this baby continues to exhibit hypoxemia. The arterial blood gas from the umbilical arterial line is as follows: pH of 7.15, $Paco_2$ of 80 mm Hg, and PaO_2 of 27 mm Hg. The baby is switched to the high-frequency oscillator. The parents are approached regarding the risks and benefits of ECMO. A head ultrasound, echocardiogram, PT, PTT, fibrinogen, and blood products are ordered.

Exercise 15

Question

Which of these findings would be considered a contraindication to ECMO?

A. Echocardiogram showing evidence of biventricular dysfunction
B. The presence of liver in the thorax on x-ray
C. PT of 17.5 seconds and PTT of 100 seconds with a fibrinogen of 250 mg/dL from a heparinized umbilical arterial line

TABLE 17.3 Differences Between Venovenous (VV) and Venoarterial (VA) Extracorporeal Membrane Oxygenation (ECMO)

Criteria	VV ECMO	VA ECMO
Relationship between "artificial" lung and native lung	In series and replaces part or all of native lung function	In parallel with the native lungs and replaces part or all of both heart and lung function
Carotid artery ligation	Not necessary—results in better cerebral hemodynamics	Required—alters cerebral hemodynamics (reduced cerebral blood flow velocities and decreased cerebral oxygenation during right carotid cannulation and impaired autoregulation)
Embolic strokes	Minimal risk of embolic strokes (the risk is nonexistent if there is no interatrial communication)	Risk of embolic strokes
Indication	Preferred mode for neonatal respiratory failure	Primary cardiac dysfunction for providing partial or complete circulatory support, secondary cardiac failure from profound respiratory failure (some centers prefer VV ECMO for this indication), inability to place a 12 Fr double lumen cannula (because of size or mediastinal shift), shock/severe hypotension
Pressure in cerebral circulation	Normal	High, increasing the risk of reperfusion injury
Risk of reperfusion injury	Low	High risk of hyperoxic and hypocarbic reperfusion injury
Pulmonary blood flow	Maintained with well oxygenated blood	Decreased pulmonary blood flow
Systemic flow	Preservation of pulsatile arterial flow	Potential loss of pulsatile arterial flow (pulsatile flow can be maintained with partial bypass and good cardiac function)
Pao_2	45–80 mm Hg	60–150 mm Hg
Cardiac effects	Negligible (no change in RV preload or LV afterload)	Decreased LV preload and increased LV afterload
Coronary blood flow	Derived from LV/ascending aorta blood (oxygenated)	Derived from LV poorly oxygenated blood (before arterial catheter) and retrograde flow from the arterial cannula
Recirculation	Occurs secondary to single cannula flow dynamics and cannula position	Chance of recirculation is eliminated
Rate of stabilization	Slow stabilization	Instant stabilization

D. A grade III intraventricular bleed on head ultrasound
E. Single umbilical artery observed during umbilical catheterization

Answer

D. ECMO is prolonged cardiopulmonary bypass for neonates with reversible respiratory or cardiac failure who are unlikely to survive in spite of maximal medical management. Ventricular function assessment on echocardiogram is important in deciding the appropriate mode of ECMO (venovenous vs. venoarterial, see later and Table 17.3). Biventricular dysfunction is not a contraindication for ECMO. Prolonged PTT is likely related to contamination from heparin, and this sample needs to be repeated with a sufficient "waste" draw. A grade III intraventricular hemorrhage is likely to expand and deteriorate with anticoagulation, and ECMO is contraindicated in this context (Fig. 17.16).

CASE STUDY 4 (CONTINUED)

In this patient with CDH, the echocardiogram suggests severe PPHN as evidenced by right-to-left shunting through a patent foramen ovale and ductus arteriosus and a slightly decreased ejection fraction. Dopamine is started at 5 mcg/kg/min with normalization of systemic blood pressure. The head ultrasound is normal. An arterial blood gas on a Paw of 15 cm H_2O, rate = 8 Hz and 100% oxygen is as follows: pH of 7.13, $Paco_2$ of 55 mm Hg, and PaO_2 of 30 mm Hg. The atmospheric pressure in this NICU is 747 mm Hg.

Exercise 16

Question

Based on these findings, which of the following statements is TRUE?

A. OI is >40 and $AaDO_2$ is >600 and the patient is a candidate only for VA ECMO.
B. OI is >40 and $AaDO_2$ is >600 and the patient is a candidate for VV ECMO.
C. OI is <40 and $AaDO_2$ is <600 and the patient is not a candidate for VA or VV ECMO.
D. OI is >40 and $AaDO_2$ is <600 and the patient is a candidate for VA ECMO.

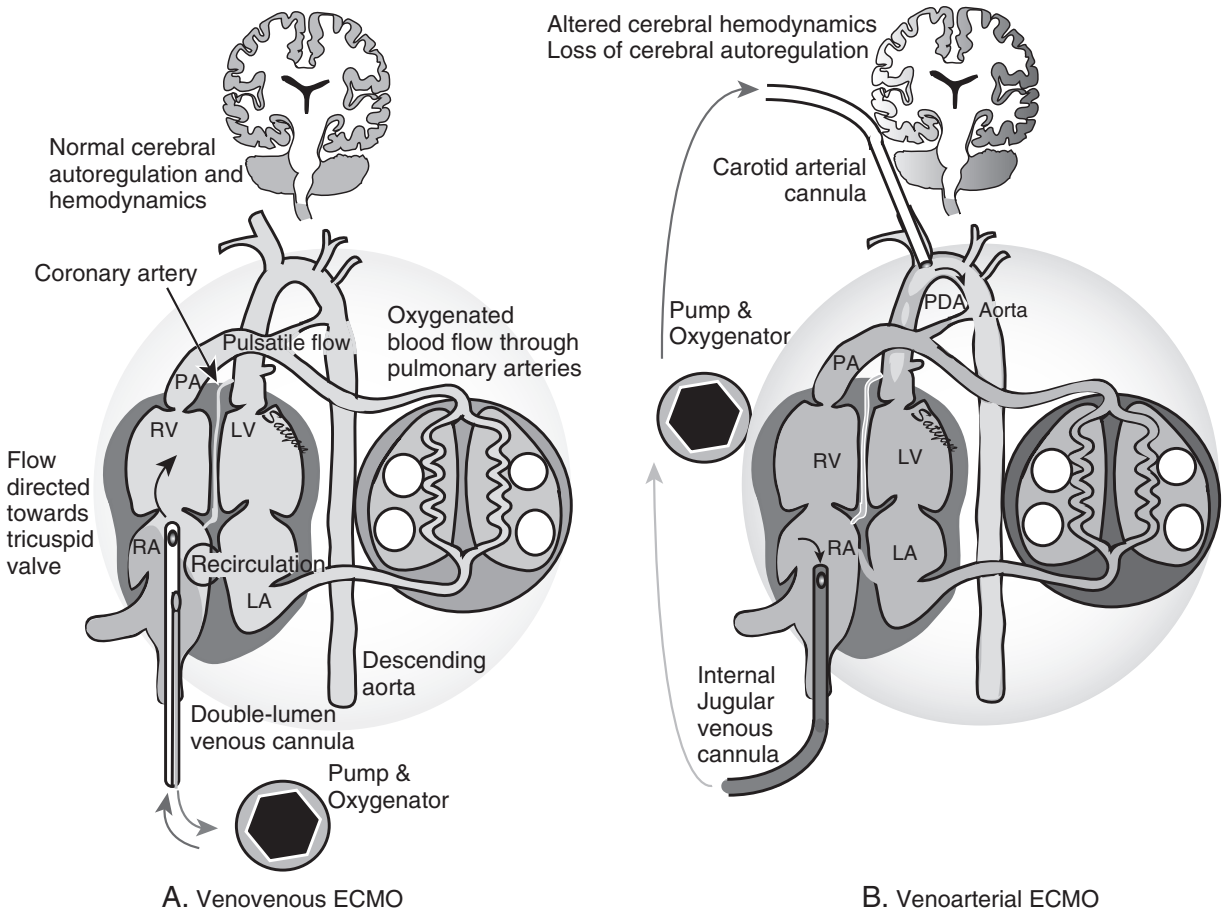


Fig. 17.16 Diagram of circulatory pattern and oxygenation of blood during venovenous VV (A) and venoarterial VA (B) ECMO. In VV ECMO, a double-lumen venous cannula is placed. Blood is drawn from the right atrium and pumped back into the right atrium with the flow directed toward the tricuspid valve. Because both input and output are through the same cannula, there is a risk of recirculation. Oxygenated blood perfuses the lung and returns to the left heart and the systemic circulation. Cerebral hemodynamics are preserved in VV ECMO. In VA ECMO, blood drains from the right atrium and is oxygenated and pumped back into the arch of aorta. The presence of a carotid arterial cannula results in disruption of cerebral autoregulation. The lung is perfused with deoxygenated blood.

E. This patient has CDH and has high mortality in spite of ECMO and hence ECMO is contraindicated.

Answer

B. To be eligible for ECMO, neonates should be greater than 34 weeks' PMA (birth weight >2000 grams), ventilated for less than 10 days (i.e., less likely to have irreversible chronic lung disease), have a reversible pulmonary or cardiac disease, and be at high risk for dying. To predict which infants with respiratory disorders are at high risk of dying, OI and A-aDO_2 (Fig. 17.9) are used to quantitate the degree of respiratory failure. An OI >40 (for >2 hours in 3 of 5 serial arterial blood gases) is predictive of a 60% to 80% risk of death (Engle et al, 1993; UK collaborative randomized trial of neonatal extracorporeal membrane oxygenation, 1996). Similarly, A-aDO_2 ≥630 for longer than 4 hours is predictive of about an 80% risk of death. Many neonatal units prefer to cannulate patients for ECMO before the onset of severe cardiopulmonary decompensation in an attempt to improve outcome.

CASE STUDY 5

An estimated ex-25-week small-for-gestational age baby girl is born to a 20-year-old mother with no prenatal care. The infant delivered precipitously and the mother did not receive antenatal steroids. The patient was intubated shortly after birth and placed on a conventional ventilator. She had RDS (Fig. 17.17A) and received a total of three doses of surfactant. Her initial course was complicated by progressing respiratory distress and pulmonary hypertension. She was switched to high-frequency ventilation, and her PPHN responded to inhaled NO, which was weaned off within 3 days. She had a brief period of improvement with a decrease in Fio_2 and low ventilator settings, however, at about 2 weeks of age her chest x-ray

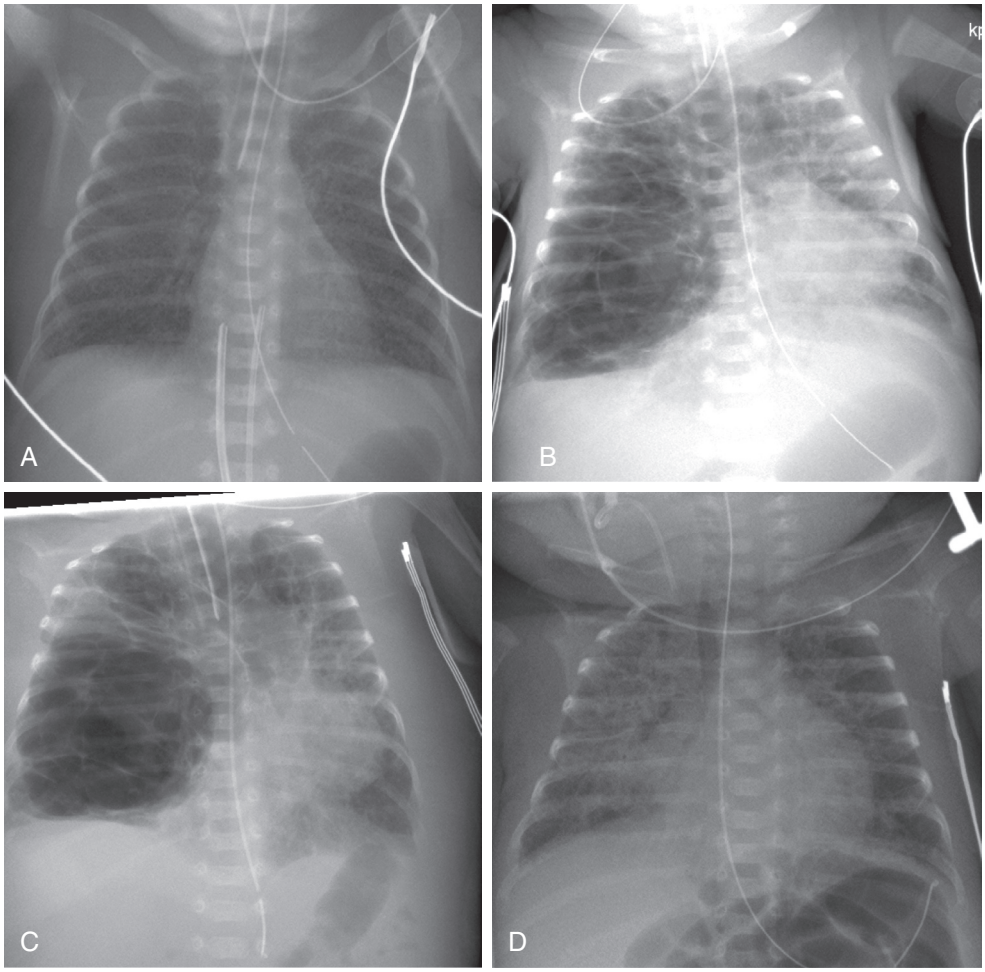


Fig. 17.17 Chest radiographs (CXR) of an extremely premature, extreme low birth weight baby girl. CXR on day 1 of age shows findings consistent with RDS following two doses of surfactant (A). CXR on day 15 of age shows pulmonary interstitial emphysema (B). CXR on day 25 of age shows large pneumatocele with mediastinal shift (C). CXR on day 30 shows resolution of PIE following low-dose dexamethasone course (D).

demonstrated evidence of pulmonary interstitial emphysema (PIE) (Fig. 17.17B).

Exercise 17

Question

Which of the following statement(s) is/are correct?

A. PIE typically presents following prolonged mechanical ventilation (>2 weeks)
B. PIE results in overdistention of the lung and increased compliance
C. The interstitial air may compress airways and increase airway resistance
D. Pneumopericardium may present as a complication of PIE

Answer

C and **D.** PIE arises from the disruption of the basement membrane of the alveolar wall allowing for air entry into the interstitial space; air traps in the perivascular tissues of the lung. PIE usually affects mechanically ventilated extremely low birth weight infants, may involve one or both lungs, and tends to occur within 96 hours after birth. PIE is associated with decreased compliance and overdistention of the affected lung(s). The interstitial air, also, compresses the airways, resulting in increased airway resistance. Furthermore, the dissection of air in the perivascular sheath can lead to pneumothorax, pneumomediastinum, pneumopericardium, and increased pulmonary vascular resistance.

CASE STUDY 5 (CONTINUED)

In an attempt to minimize the risk of air leaks and limit overdistention of the affected lung, the Paw is slowly decreased and the frequency increased (to attenuate the amplitude). Over the course of the next few days, the patient becomes hypotensive and has decreased urine output. The chest x-ray shows a large pneumatocele with mediastinal shift (Fig. 17.17C). An echocardiogram shows poor cardiac function caused by decreased venous return to the heart. Dopamine and dobutamine infusions are started to improve cardiac output and blood pressure.

Exercise 18

Question

What treatment option(s) can you consider in managing this patient with severe PIE?

A. Position the infant with the affected side down
B. Attempt selective bronchial intubation of the unaffected side
C. Surgical resection of the affected lung

Answer

All of the above. Management of PIE is supportive. In infants affected by unilateral PIE, placing the infant in the lateral decubitus position with the affected side down may reduce aeration of the lung with PIE and promote gas exchange in the unaffected lung (Swingle et al, 1984; Cohen et al, 1984). In severe unilateral cases of PIE where supportive care provides no improvement, collapse of the affected lung by selective bronchial intubation of the contralateral lung or occlusion of the bronchus of the affected lung using a Swan-Ganz catheter may promote decompression and healing in the lung with PIE (Brooks et al, 1977; Rastogi et al, 2007). In severe cases, surgical resection may also be considered.

CASE STUDY 5 (CONTINUED)

The pediatric pulmonologist was consulted to attempt selective intubation under bronchoscopy, which was unsuccessful, as the patient did not tolerate the procedure. The pediatric surgeons who were also consulted did not recommend any surgical intervention because of the critical state of the patient. The decision to start dexamethasone was made, and the patient was started on the DART (Dexamethasone: A Randomized Trial) protocol (Doyle et al, 2006). The patient responded well to the steroid course and was extubated to noninvasive positive pressure ventilation within a week. A repeat chest x-ray shows resolution of the PIE (Fig. 17.17D).

Her hospital course was further complicated by a left sided grade 3 IVH, a PDA that was surgically closed on day 28, and necrotizing enterocolitis with perforation. At 38 weeks PMA, she has severe bronchopulmonary dysplasia (BPD) and requires respiratory support with CPAP of 6 to 8 cm H_2O and an Fio_2 of 0.45.

Exercise 19

Question

What are the underlying pathophysiologic mechanisms for persisting CPAP and oxygen requirements in this infant?

A. Pulmonary hypoplasia secondary to oligohydramnios
B. Impaired alveolarization
C. Tracheo/bronchomalacia
D. Increased airway reactivity
E. Pulmonary hypertension

Answer

All of the above. With improved survival of extremely preterm infants, morbidities such as pulmonary hypertension are increasingly seen in this group of infants. Pulmonary hypertension is observed in 15% to 20% of extremely preterm infants (and approximately 25%–37% of infants with BPD) (An et al, 2010; Slaughter et al, 2011). Prolonged duration of ventilation, intrauterine growth restriction, and oligohydramnios are risk factors associated with development of pulmonary hypertension. The pathophysiology of pulmonary hypertension in these infants is a combination of pulmonary hypoplasia and impaired vascular development. BPD is associated with a reduced cross-sectional perfusion area, decreased arterial density, and abnormal muscularization of peripheral pulmonary arteries.

CASE STUDY 6

A 3-hour-old term male infant (birth weight of 3925 grams) born to a 32-year-old gravida 2, para 1 mother with adequate prenatal care develops respiratory distress with tachypnea and desaturations needing supplemental oxygen. The mother's antenatal culture for group B *Streptococcus* (GBS) was positive, and rupture of membranes occurred 8 hours before delivery. There was no maternal pyrexia in labor. He is transferred to the NICU and is placed in a hood with 60% oxygen; saturation values are in the mid-90s. He is started on antibiotics after obtaining a blood culture. A chest x-ray shows bilateral haziness with increased pulmonary vascularity and enlarged cardiothymic silhouette. Vital signs reveal temperature of 37.3°C, heart rate of 162 beats/minute, respiratory rate of 80 breaths/minute, and BP of 59/40 (mean 47) mm Hg. An arterial blood gas is obtained, and the results are as follows: pH of 7.27, $Paco_2$ of 42 mm Hg, PaO_2 of 45 mm Hg in 60% oxygen. No murmur is audible on auscultation of the precordium. He appears comfortable but is tachypneic with mild intercostal retractions.

Exercise 18

Question

What is the most appropriate next step in the management of this infant?

A. Intubation and administration of surfactant
B. Nasal CPAP
C. Increase inspired oxygen concentration to 100%
D. Echocardiogram

Answer

B, C (for hyperoxia test), and **D.** The differential diagnosis for the infant includes: (1) parenchymal lung disease such as pneumonia and early-onset sepsis; (2) idiopathic PPHN; and (3) cyanotic CHD, as is outlined in Table 17.4. Appropriate antibiotic therapy should be started for suspected sepsis. In spite of mild respiratory distress and tachypnea, the infant has a normal $Paco_2$ and severe hypoxemia. This picture is more suggestive of PPHN or cyanotic CHD. A normal antenatal sonogram does not rule out the possibility of CHD. Although abnormalities such as hypoplastic left heart, septal defects, and single ventricle are commonly diagnosed antenatally, abnormalities of the vessels such as transposition of the

TABLE 17.4 Differential Diagnosis of Hypoxemic Respiratory Failure in a Newborn Infant

	Lung Disease	PPHN	Cyanotic CHD
Respiratory distress	Present	Often present	Usually absent
Oxygen saturation (pulse oximetry) Spo_2	Improves with supplemental O_2	Labile, postductal Spo_2 may be lower than preductal Spo_2	Low fixed Spo_2 with minimal increase with supplemental O_2
$Paco_2$	Elevated	Often elevated (except in "black lung" PPHN)	Usually normal/low
Hyperoxia test	Pao_2 often >150 mm Hg	Pao_2 often >100 mm Hg	Pao_2 often <100 mm Hg
Hyperoxia–hyperventilation	Pao_2 often >150 mm Hg	Pao_2 improves with hyperventilation	Pao_2 often <100 mm Hg
Echocardiography	Normal	Structurally normal heart; RV hypertrophy, tricuspid regurgitation, bowing of interventricular septum to left, R→L or bidirectional shunt at PFO and/or PDA	Abnormalities in cardiac anatomy
Chest x-ray	Often associated with parenchymal densities	Depends on primary respiratory disease; reduced pulmonary vascularity in "black-lung" or idiopathic PPHN	Usually normal at birth; may be associated with abnormal cardiac silhouette and altered pulmonary vascularity

L: left; *PDA:* patent ductus arteriosus; *PPHN:* persistent pulmonary hypertension of the newborn; *R:* right; *RV:* right ventricle

great vessels, coarctation of the aorta, and anomalous pulmonary venous return may be missed.

CASE STUDY 6 (CONTINUED)

The infant is placed on nasal CPAP with 100% inspired oxygen to minimize respiratory distress and to perform a hyperoxia test. His blood pressure and perfusion are normal. An arterial blood gas is obtained from the right radial artery 30 minutes after placing on CPAP. The results are as follows: pH of 7.25, $Paco_2$ of 46 mm Hg. PaO_2 of 62 mm Hg, with a base deficit of 7.3 mEq/L.

Exercise 19

Question

How would you interpret the results of the hyperoxia test and what is the appropriate next step in management of this hypoxemic infant?

A. The results are suggestive of severe parenchymal lung disease, and the baby should be intubated and placed on mechanical ventilation.
B. Hyperoxia test results confirm the presence of PPHN; intubation and inhaled NO should be administered.
C. Hyperoxia test results are suggestive of PPHN or cyanotic CHD. Intravenous prostaglandin E_1 (PGE_1) therapy should be initiated. An echocardiogram should be ordered.
D. Current management with nasal CPAP and 100% oxygen is appropriate as the PaO_2 is above 60 mm Hg.

Answer

C. A right radial arterial PaO_2 of under 150 mm Hg in 100% oxygen with CPAP is highly suggestive of cyanotic CHD or severe PPHN. It is important to immediately confirm these possibilities by an echocardiogram. Intravenous PGE_1 therapy should be initiated to maintain ductal patency because ductal dependent CHD is a possibility. This agent also has pulmonary vasodilator effect and may be beneficial in PPHN. Common side effects of PGE_1 include pyrexia, apnea, and hypotension.

CASE STUDY 6 (CONTINUED)

The baby is placed on intravenous PGE_1 at 0.05 mcg/kg/min. Apneic spells are observed, and he is intubated and placed on conventional ventilation. The echocardiogram shows a large right ventricle, large main pulmonary artery, right-to-left shunt at the PFO and PDA, and a small left atrium. An estimate of pulmonary arterial pressure cannot be determined, as a tricuspid regurgitation jet is not observed. Based on these findings, severe PPHN is suspected. Intravenous PGE_1 infusion is stopped, and inhaled NO is administered at 20 ppm. An hour later, a repeat arterial blood gas from the umbilical arterial line is as follows: pH of 7.15, $Paco_2$ of 27 mm Hg, PaO_2 of 37 mm Hg, and base deficit of 17 mEq/L. The metabolic acidosis is "corrected" with sodium bicarbonate ($0.3 \times$ base deficit $\times$ weight in kg $= 0.3 \times 17 \times 3.9 = 20$ mEq diluted 1:1) infused over 30 minutes.

Exercise 20

Question

Treatment to induce rapid alkalinization of the blood may be complicated by which of the following?

A. Intracellular acidosis
B. Rapid fluctuation in cerebral blood flow
C. Decrease in intravascular pH
D. None of the above

Answer

A and **B.** Many infants with PPHN and HRF have a metabolic acidosis. Acidosis causes pulmonary vasoconstriction. In the

past, it was a common practice to induce metabolic alkalosis, but this strategy was associated with an increased need for ECMO (Walsh-Sukys et al, 2000). Rapid infusion of sodium bicarbonate is associated with fluctuations in cerebral blood flow and serum sodium levels. In addition, the CO_2 produced as a result of interaction between $NaHCO_3$ and acid diffuses across the blood–brain barrier and cell membranes resulting in perivascular acidosis in the brain and intracellular acidosis in neuronal cells and cardiac myocytes (Fig. 17.7). Caution should be exercised during bicarbonate therapy (Aschner and Poland, 2008).

CASE STUDY 6 (CONTINUED)

The patient continues to remain hypoxemic despite correction of pH and inhaled NO. A repeat echocardiogram is obtained in preparation for ECMO. The cardiologist confirms earlier findings but cannot clearly track pulmonary veins to the left atrium. A computed tomography (CT) angiogram is performed, and the diagnosis of anomalous drainage of pulmonary veins into the coronary sinus is confirmed (Fig. 17.11B). After surgical correction, he is discharged home at 20 days of age.

Infants with TAPVR mimic parenchymal lung disease (especially if obstructed) and PPHN. There are many clinical and echocardiographic features common to both conditions. Patients with TAPVR or PPHN can present with hypoxemia and respiratory distress. The chest x-ray may show coarse opacities. An echocardiogram shows a dilated pulmonary artery and right ventricle with right-to-left shunting at the foramen ovale and ductus arteriosus in both conditions. The presence of fixed hypoxemia (as opposed to labile hypoxemia in PPHN), presence of a small left atrium without draining pulmonary veins, and *absence* of tricuspid regurgitation should alert the physician to the possibility of TAPVR. Patients with TAPVR do not generally respond to an infusion of PGE_1, although some cases of infradiaphragmatic TAPVR associated with a closed ductus venosus respond with improved oxygenation.

This case illustrates the importance of continuous assessment and multidisciplinary evaluation of patients with PPHN and HRF.

OVERVIEW OF MANAGEMENT OF PPHN/HRF AND PULMONARY VASODILATOR THERAPY

The pathophysiology of PPHN involves abnormalities in the lung, pulmonary vasculature, and cardiac function. Hence therapy should address general supportive measures, optimal lung recruitment, cardiac support, and pulmonary vasodilation.

- PPHN and/or HRF with underlying parenchymal lung disease is a common problem in neonatal units. Appropriate diagnostic workup and specific therapy targeting the underlying lung disease such as pneumonia is important.
- Minimal stimulation, sedation, and analgesia are crucial to avoid episodes of hypoxemia. Labile hypoxemia is a characteristic feature of PPHN, and excessive stimulation can precipitate hypoxic pulmonary vasoconstriction.
- Surfactant therapy is beneficial in patients with RDS and in conditions associated with surfactant inactivation, such as MAS (Lotze et al, 1998).
- Maintaining optimal oxygen levels and avoiding hypoxemia and hyperoxemia is vital during management of PPHN/HRF. Maintaining the PaO_2 in the 60 to 80 mm Hg range and preductal oxygen saturation in the 90% to 97% range is recommended.
- Gentle ventilation to maintain $Paco_2$ in the 40s to low 50s and avoiding acidosis (pH $<$7.30) has been associated with better outcomes.
- If it is not possible to maintain adequate ventilation and oxygenation with conventional ventilation, and if a high PIP ($>$25 cm H_2O) is required to keep $Paco_2$ in the 40s to low 50s, many centers recommend switching to a high-frequency oscillator or jet ventilator. Some centers prefer to use high-frequency ventilation as the primary mode of ventilation in the management of PPHN/HRF.
- Infants with clinical or echocardiographic evidence of PPHN (Fig. 17.10 and 17.11A) and infants with moderate to severe HRF benefit from pulmonary vasodilator therapy. Inhaled NO is currently the only FDA-approved specific pulmonary vasodilator for infants. The typical starting dose is 20 ppm when the OI exceeds 20 to 25. Optimal lung recruitment with the use of adequate PEEP, Paw, and/or surfactant is crucial for adequate and sustained response to inhaled NO. If inhaled NO results in improvement in systemic oxygenation, the Fio_2 should be gradually weaned, maintaining the Spo_2 in the 90% to 97% range. Inhaled NO is weaned in steps when the Fio_2 is 0.6 or under and PaO_2 is 60 mm Hg or greater or preductal Spo_2 is 90% or higher as shown in Fig. 17.18.
- Cardiac support with adequate volume infusion to avoid hypovolemia and inotropic support is essential. Deteriorating right ventricular and left ventricular function is a common cause for failure of medical management and need for ECMO in PPHN. It is important to remember that inotropes such as dopamine are not selective to the systemic circulation and can result in pulmonary vasoconstriction.
- Intravenous sildenafil and/or intravenous milrinone (Fig. 17.15) are not currently approved by the FDA. These promising therapeutic strategies are used by clinicians and centers with expertise in pulmonary vasodilator therapy.
- If PPHN/HRF does not respond to conventional medical management, early referral to an ECMO center is important.

CONCLUSION

Advances in respiratory management and pulmonary vasodilator therapy have reduced the need for ECMO for neonatal respiratory disorders. However, 20% to 40% of patients with PPHN/HRF fail to respond to conventional therapy,

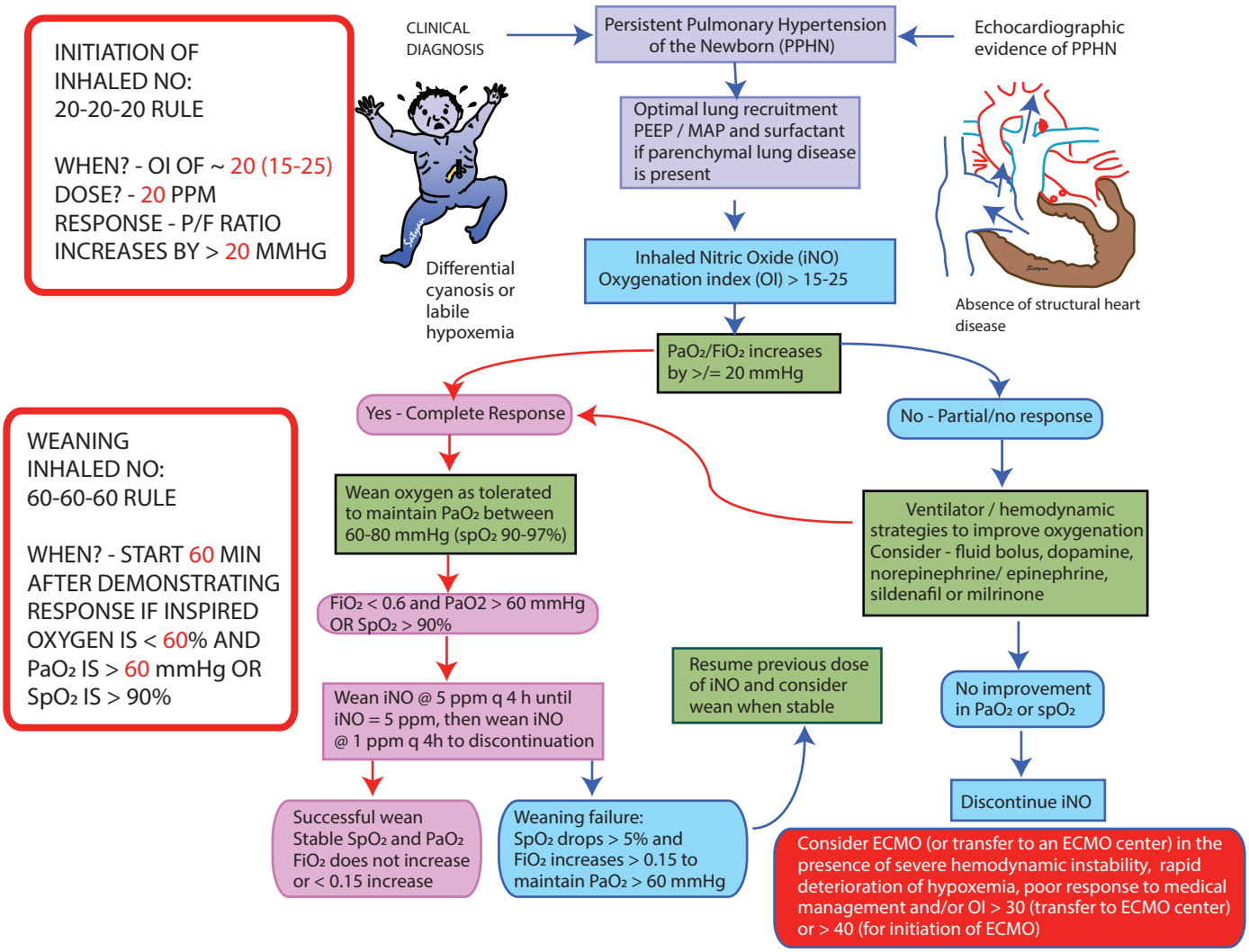


Fig. 17.18 Protocol for initiation and weaning of inhaled nitric oxide use at Women and Children's Hospital of Buffalo. (Adapted from Lakshminrusimha S, Kumar VH: Diseases of pulmonary circulation. In Fuhrman BP, Zimmerman JJ, editors: *Pediatric critical care,* ed 4, Philadelphia, 2011, Elsevier/Saunders, pp 632–656. Copyright 2015 Bobby Mathew, Satyan Lakshminrusimha. Published by Elsevier Inc. All rights reserved.)

and this failure rate is based on the primary underlying disease. Pulmonary hypertension associated with conditions such as CDH and BPD responds poorly to treatment, and further studies are required to improve outcome in these conditions.

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Abstract: Persistent pulmonary hypertension of the newborn (PPHN) is often associated with hypoxemic respiratory failure (HRF) and is a common cause of morbidity and mortality in the neonatal intensive care unit. Perinatal asphyxia, meconium aspiration syndrome, sepsis, bronchopulmonary dysplasia (BPD), and congenital diaphragmatic hernia (CDH) are common causes of PPHN. Advances in respiratory management and pulmonary vasodilator therapy have reduced the need for extracorporeal membrane oxygenation (ECMO) for neonatal respiratory disorders. However, 20% to 40% of patients with PPHN/HRF fail to respond to conventional therapy, and this failure rate is based on the primary underlying disease. Pulmonary hypertension associated with conditions such as CDH and BPD responds poorly to treatment, and further studies are required to improve outcome in these conditions.

Keywords: hypoxemia, pulmonary vascular resistance, acidosis, hypothermia

18

Renal Failure in Neonates

Kimberly J. Reidy and Fangming Lin

The etiology of neonatal renal failure encompasses both chronic conditions such as congenital defects of the kidney and urinary tract and acute insults such as hypoxia, ischemia, or drug toxicity leading to acute kidney injury (AKI) (Moghal et al, 2006). AKI in the neonate has been difficult to define, especially in the setting of prematurity, as standard definitions for both adult and pediatric patients rely on changes in serum creatinine and urine output (Fortenberry et al, 2013). During fetal development, the placenta provides renal-like clearance of plasma waste products. For the first day after birth, the newborn's creatinine predominantly reflects maternal renal function. Glomerular filtration rate is relatively low in newborn infants and changes rapidly over the first few weeks of life. Nephrogenesis continues in the normal fetus until 34 to 35 weeks' gestation, and thus a "normal" serum creatinine is difficult to define for infants born before 34 weeks' gestation. In addition, neonatal AKI can present with severe oliguric or anuric renal failure that requires renal replacement therapy (RRT) but can also present with nonoliguric AKI, especially in the setting of injury from nephrotoxic medications. Thus given that there is no standard definition for neonatal AKI and because nonoliguric AKI may be unrecognized by clinicians, it is challenging to determine the true incidence of neonatal AKI. Whereas early studies of neonatal AKI often used a serum creatinine of 1.5 mg/dL or blood urea nitrogen (BUN) over 20 mg/dL as a cutoff indicating AKI for infants greater than 34 weeks' gestation, more recent studies use a modified KDIGO (Kidney Disease: Improving Global Outcomes) definition for neonates that includes a rise in serum creatinine of 0.3 mg/dL or more from the lowest previous value, a 50% rise in serum creatinine from the lowest previous value, and/or urine output of less than 1 mL/kg/hour (Fortenberry et al, 2013; Jetton and Askenazi, 2012.)

A retrospective multinational multicenter study, Assessment of Worldwide Acute Kidney injury Epidemiology in Neonates (AWAKEN), has given new insights into the incidence of AKI and its complications (Harer et al, 2018; Jetton et al, 2016, 2017; Kraut et al, 2018). Overall, 30% of neonates developed AKI (Jetton et al, 2017). AKI risk varied by gestation, and there was a U-shape risk curve with youngest and oldest infants at highest risk. Not surprisingly, AKI affected the greatest percent of extremely premature (22–28 weeks' gestation) infants, with almost one-half (48%) developing AKI. Infants with AKI were more likely to have hypoxic ischemic encephalopathy, congenital heart disease, and necrotizing enterocolitis (Jetton et al, 2017). Neonatal hypertension was more common in infants with AKI (Kraut et al, 2018) Early caffeine administration to preterm infants may be protective against AKI in the first 7 days of life (Harer et al, 2018).

It has been increasingly recognized that neonatal AKI can lead to adverse long-term consequences. Neonatal AKI results in fourfold higher odds for mortality in the NICU and is associated with increased mortality following NICU discharge (Koralkar et al, 2011). In addition, studies suggest that low birth weight, prematurity, and neonatal AKI may lead to increased risk for microalbuminuria, hypertension, and chronic end-stage kidney disease later in life (Carmody and Charlton, 2013; Hoy et al, 2005).

CASE STUDY 1

A baby boy is born to a 29-year-old gravida 3, para 2 mother at 35 2/7 weeks' gestation. The pregnancy was complicated by oligohydramnios and a concern for right renal agenesis, left renal dysplasia, and preterm labor. Maternal testing: rapid plasma reagin (RPR) negative, hepatitis B surface antigen negative, group B *Streptococcus* (GBS) colonization negative, and human immunodeficiency virus (HIV) negative. Amniocentesis demonstrated a normal male karyotype. He was born via vaginal delivery (VD). His Apgar scores were 6/7/8, and his birth weight was 2510 g.

Exercise 1

Question

What is the initial diagnostic test that should be performed?

A. Kidney and bladder ultrasound
B. Measurement of serum creatinine
C. Voiding cystourethrogram

Answer

A. In the first 24 hours of life, a newborn's serum creatinine will reflect maternal creatinine and thus is not useful for diagnosis of renal failure. This infant has a history of oligohydramnios and bilateral renal anomalies. Thus a kidney–bladder

TABLE 18.1 Causes of Neonatal Acute Kidney Injury

Prerenal	Intravascular volume depletion Reduced renal perfusion, such as with heart failure
Intrinsic Renal	Nephrotoxic medications Acute tubular necrosis secondary to hypoxia/ischemia/asphyxia Sepsis Hypotension Renal agenesis or hypodysplasia Cystic kidney disease Vascular: renal arterial or vein thrombosis
Postrenal	Posterior urethral valves

ultrasound is the best initial diagnostic step. The infant's urine output should be monitored. No bladder abnormalities were described prenatally, but posterior urethral valves would be on the differential diagnosis of this infant's anomalies. Posterior urethral valves involve obstruction at the level of the prostatic urethra. The initial management is relieving the obstruction by placement of a Foley catheter. Dilation of the prostatic urethra during voiding on a voiding cystourethrogram (VCUG) confirms the diagnosis of posterior urethral valves but would not be the initial diagnostic approach for the patient in this vignette (Table 18.1).

CASE STUDY 1 (CONTINUED)

The patient was admitted to the NICU. A renal ultrasound showed a small, mildly echogenic right kidney (2.12 cm) without hydronephrosis and a slightly larger mildly echogenic left kidney (2.62 cm) with dilatation of the left renal pelvis without caliectasis. The bladder appeared normal. A VCUG revealed bilateral grade 3 vesicoureteral reflux and he was started on amoxicillin prophylaxis (Fig. 18.1). The BUN is 13 mg/dL and the creatinine is 2.2 mg/dL.

Exercise 2

Question

Which of the following electrolyte abnormalities is most likely to occur in this infant?

A. Hypokalemia
B. Hyponatremia
C. Hypophosphatemia

Answer

B. There are three types of acute renal failure: prerenal, intrinsic renal, and postrenal failure. This infant likely has intrinsic renal failure due to bilateral renal hypodysplasia. Infants with abnormal kidney development and renal failure may exhibit polyuria or oliguria/anuria. Hyponatremia can be observed with both extremes of urine output. Many infants with polyuric renal failure and hyponatremia require water and sodium supplementation; studies have demonstrated improved linear growth with sodium supplementation. Despite the polyuria, hyperkalemia and hyperphosphatemia, rather than hypokalemia or hypophosphatemia, is likely to occur in infants with renal failure. The kidneys are the major sites for phosphorus excretion. In the setting of renal insufficiency, phosphorus excretion decreases and the elevations in serum phosphorus stimulate secretion of parathyroid hormone. Secondary hyperparathyroidism and reduced formation of the active form of vitamin D (1,25-$[OH]_2$-vitamin D) due to decreased 1-hydroxylation that occurs in the kidney can lead to chronic kidney disease related mineral bone disease (CKD-MBD). In turn this leads to defective bone mineralization (renal rickets) and long-term cardiovascular complications due to deposition of calcium and phosphorus in the vasculature. Both breast milk and Similac PM 60/40 have lower potassium, calcium, and phosphorus content, making these better choices for neonates with renal insufficiency. High-calorie-containing formulas and breast milk fortifiers contain higher levels of potassium, calcium, and phosphorus and can lead to hyperkalemia and hyperphosphatemia in neonates with renal failure. In addition, following ablation of posterior urethral valves, many neonates will never recover function of the collecting ducts, which are the segments responsible for water reabsorption and will become polyuric. These infants require additional free water intake to compensate for water loss in their diluted urine; thus concentrated formulas (e.g., 22–24 kcal/oz versions) should be avoided in infants with persistently high urine volumes and low urine specific gravity.

NEONATAL HYPERKALEMIA AND MANAGEMENT

Hyperkalemia (K >6.0 mEq/L) can be a life-threatening complication of neonatal AKI. Premature neonates have lower GFR and relative resistance to aldosterone, limiting their ability to excrete potassium. Therefore reducing potassium intake by lowering potassium from total parenteral nutrition (TPN) or intravenous fluid (IVF) and/or use of low potassium formula (Similac PM 60/40 or breast milk) is an important precaution in the management of neonatal AKI. Administration of sodium polystyrene resins can be used to achieve the exchange of potassium for sodium, but direct oral or rectal administration might carry risks in neonates as it has been reported to cause intestinal ischemia, obstruction, and perforation. Potassium intake can be further decreased by premixing sodium polystyrene with Similac PM 60/40 or breast milk allowing the potassium to precipitate out. After allowing the precipitate to settle, the supernatant is decanted for oral/gastric administration (so that there is no direct administration of the resin).

For acute management of hyperkalemia, an electrocardiogram (ECG) should be performed to evaluate the effects of hyperkalemia on the heart's electrical activity. Calcium gluconate should be administered in the presence of ECG changes. As concomitant acidosis will drive potassium out of cells and elevate the serum potassium, sodium bicarbonate should be administered to treat acidosis but is not used when metabolic acidosis is not present. Administration of IV

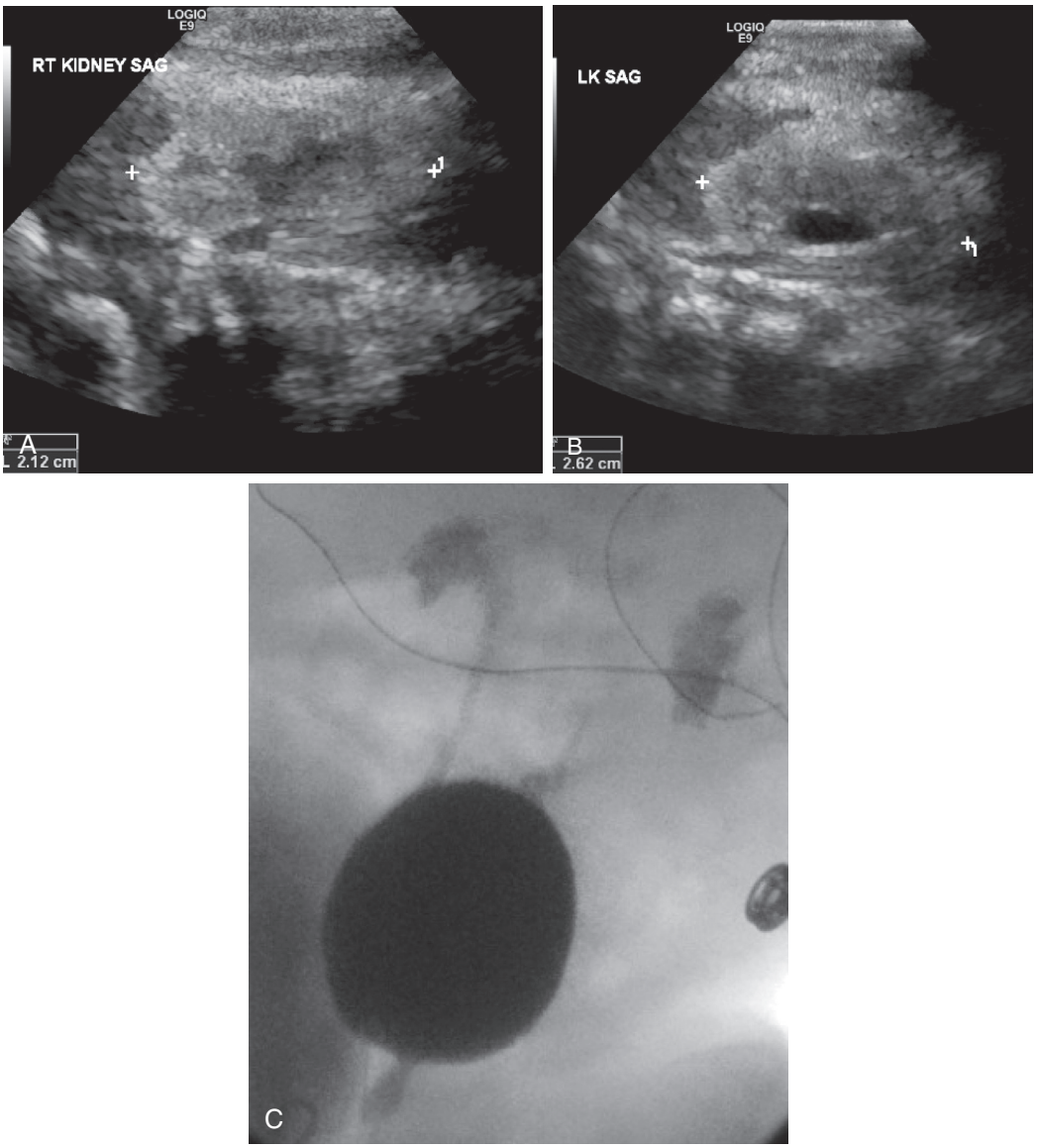

Fig. 18.1 Renal (**A** and **B**) and VCUG (**C**). A renal ultrasound shows small, mildly echogenic right kidney (2.12 cm) without hydronephrosis and a slightly larger mildly echogenic left kidney (2.62 cm) with dilatation of the left renal pelvis. VCUG demonstrates bilateral grade 3 vesicoureteral reflux.

glucose and insulin can be used in the acute setting to stimulate potassium entry into cells and temporarily lower serum potassium. However, insulin and glucose will not enhance excretion of potassium. In the nonanuric patient, IV furosemide can be administered to increase potassium excretion but is not an evidence-based intervention. More recently, inhaled albuterol (salbutamol) has been used to treat infants with elevated serum potassium values. Small randomized clinical trials indicate the drug is effective, but it has not been evaluated in a large randomized trial. If medical management fails, dialysis is indicated for potassium removal.

CASE STUDY 1 (CONTINUED)

On further questioning, it is discovered that the patient has an older sibling with a renal transplant for congenital kidney disease.

Exercise 3

Question

Which of the following is the next BEST diagnostic approach?

A. Echocardiogram to assess for associated heart malformation
B. Ophthalmic examination to assess for associated optic malformations
C. Genetic testing

Answer

C is the preferred answer.

Precision medicine using high throughput technologies has increasingly been integrated into CAKUT diagnosis and management. To date, about 40 monogenic causes have been reported. However, they account for less than 20% of the patients with CAKUT, suggesting that more genetic and perhaps environmental factors contributing to the diseases

have yet to be identified (van der Ven et al, 2018). Among genes mutated in CAKUT, some are transcriptional factors important for the development of kidney and urinary tract as well as other organs, which explains multiple organ malformations in a subset of CAKUT patients presenting with a syndrome. For mutations to be considered pathogenic, functional studies including experiments in animal models are required to establish the causality. The discovery of CAKUT-causing genes has been changing because of variable expressivity in individuals with the same mutations and incomplete penetrance that occurs in individuals with the mutation but who are otherwise well. It is expected that more pathogenic genetic defects will be identified and confirmed with advanced genomic and molecular technology. In addition, copy number variations (CNVs) that are generally defined as gain or loss of germline DNA ranging from 1 kilobases to several megabases have been shown to cause the CAKUT phenotype (Sanna-Cherchi et al, 2018). These gene-disrupting CNVs frequently involve more than one gene and are likely to be responsible for multiple organ defects. For example, CNV disorders detected in patients with renal hypodysplasia have also been associated with developmental delay or neuropsychiatric diseases (Sanna-Cherchi et al, 2012). Thus, discovering these CNVs provides a precise molecular diagnosis and guides multidisciplinary managements including early interventions for neurocognition.

EMBRYONIC KIDNEY DEVELOPMENT

The kidneys are derived from the intermediate mesoderm. There are three sets of embryonic kidneys during embryogenesis: the pronephros (at 3 weeks' gestation), mesonephros (at 4 weeks' gestation), and metanephros (at 5 weeks' gestation) (Fig. 18.2). The pronephros and most of the mesonephros degenerate. The mesonephric duct (Wolffian duct) gives rise to epididymis, vas deferens, seminal vesicles, and ejaculatory ducts in males. The mature human kidneys develop from the metanephros. The ureteric bud, which is an outgrowth of the mesonephric duct in both males and females, invades the metanephric mesenchyme and undergoes sequential branching morphogenesis to form the collecting ducts. The tips of the ureteric bud induce nephron formation in the mesenchyme. Thus the number of ureteric bud branches will influence nephron number. Defects in the budding, migration, and branching of ureteric bud can lead to congenital abnormalities of the kidneys (e.g., renal aplasia, hypoplasia, dysplasia) and urinary tract deformities such as ureteral pelvic junction (UPJ) or ureteral vesical junction (UVJ) obstruction and vesicoureteral reflux.

The inductive signals originating from the ureteric bud stimulate mesenchymal to epithelial transition, and spheres of epithelial cells known as renal vesicles are the earliest form of the developing nephron. The developing nephrons go through a series of morphologic changes, forming a comma- and then S-shaped bodies. Segments of the S-shaped body will differentiate into the distal tubule, proximal tubule, and glomerular podocytes. Endothelial cells migrate into the cleft

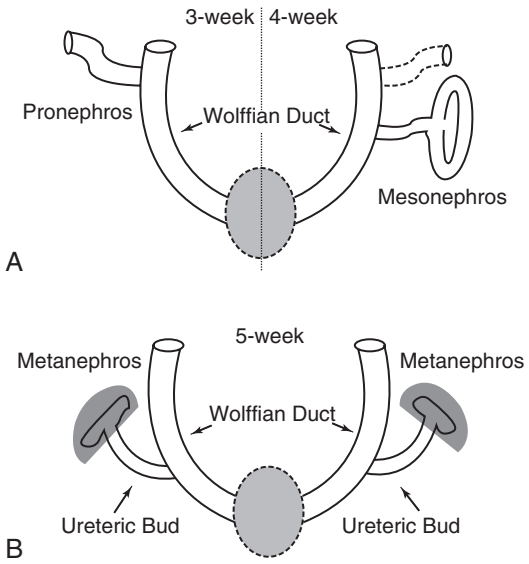

Fig. 18.2 Embryonic kidney development. (**A**) The pronephros develops at 3 weeks' gestation and degenerates at about 4 weeks when the mesonephros forms. The mesonephros has transient secretory function, but the majority of its structures also degenerate. (**B**) The metanephros that forms at 5 weeks' gestation subsequently develops into the mature kidney when the ureteric bud invades and induces nephrogenesis.

of the S-shaped body to form the glomerular endothelial cells of the capillaries. The molecular signals that drive nephrogenesis require reciprocal interactions between the ureteric bud and surrounding metanephric mesenchyme. Genetic defects in the signaling pathways can result in congenital anomalies of the kidney and urinary tract (CAKUT).

The first glomeruli form by 9 weeks, and nephrogenesis continues until 34 to 35 weeks' gestation. The ureters and bladder form around the same time as the metanephric kidney. Glomerular filtration begins at the gestational age of 9 to 10 weeks. Fetal urine is the major source of amniotic fluid from approximately 16 weeks' gestation onward. Thus obstruction of urinary outflow (as may occur in posterior urethral valves) or renal aplasia/severe dysplasia leads to low urine production and will present with oligohydramnios during the pregnancy. Oligohydramnios is associated with poor fetal lung development as the lack of sufficient amniotic fluid diminishes fetal breathing and thoracic movements that are required for proper lung maturation.

CAKUT are the leading causes of end-stage renal disease (ESRD) in children in North America. Obstructive uropathy from posterior urethral valves, followed by renal hypoplasia/aplasia/dysplasia, are the most common causes of children requiring dialysis in infancy.

Posterior urethral valves are membranes at the junction of the prostatic and bulbar urethra. Although the pathophysiology of this condition is not fully understood, these membranes are thought to form during normal development. However, failure to recanalize during urethral development leads to bladder outlet obstruction. In the face of high-pressure obstruction, bladder differentiation is impaired and a thick-walled bladder

develops. The dilation of the prostatic urethra can lead to the classic keyhole sign on a fetal ultrasound. The exposure of the developing kidneys to obstruction results in varying degrees of renal dysplasia.

CAKUT may be associated with both syndromes (e.g., Trisomy 21) and monogenic defects (Uy and Reidy, 2016). Monogenic causes of CAKUT often have extrarenal manifestations. For example, PAX2 mutations are associated with renal colobomas. The renal coloboma syndrome is an autosomal dominant disorder associated with optic nerve colobomas or dysplasia and renal defects (including hypodysplasia with or without VUR). As discussed earlier, advanced genetic technologies can help discover genetic mutations that underlie these malformations. Identifying the underlying defect allows for appropriate studies and consultations to identify and manage extrarenal disease.

CASE STUDY 1 (CONTINUED)

The clinical course over the next week was remarkable for fever with hemodynamic instability and a low urine output of 0.25 mL/kg/hour. He required multiple fluid boluses and was started on broad spectrum antibiotics. Table 18.2 lists other pertinent laboratory data and clinical information.

Physical Examination

Length 52 cm, weight 3.75 kg, HC 33.5 cm
T 37.1°C, HR 149/minute, RR 60/minute, BP 81/58, O_2 sat 97%
General: Alert
HEENT: periorbital edema
Chest: bilateral decreased air entry, no retractions
Cardiovascular: normal S1, S2, and no murmur
Abdomen: soft, distended, nontender, liver 1 cm palpable at RCM
Genitourinary: Tanner 1 male, scrotal edema
Extremities: well perfused, edema bilaterally
Neurologic: normal

Exercise 4

Question

The most appropriate next step in care for this infant is:
A. Additional normal saline bolus to increase urine output
B. Palliative care
C. Placement of a peritoneal dialysis catheter

Answer

C. This infant has normal blood pressure and perfusion and does not appear to be volume depleted; instead, the infant is edematous and likely volume overloaded. A normal saline bolus should be avoided. Fluid overload is associated with increased mortality in children, and net positive fluid balance is associated with prolonged mechanical ventilation in neonates (Arikan et al, 2012; Askenazi et al, 2012; Basu et al, 2015; Goldstein et al, 2001; Heung et al, 2017; Selewski et al, 2018; Sutherland et al, 2010; Webb et al, 2017). This infant has substantial fluid overload (weight gain of 1 kg) and thus dialysis is indicated.

Indications for dialysis include:
1. Fluid overload that results in congestive heart failure, pulmonary edema, and severe hypertension
2. Intractable acidosis
3. Hyperkalemia
4. Uremic complications (hemorrhage, encephalopathy, etc.)
5. Fluid removal to optimize nutrition and medication administration

The ethics of providing dialysis to neonates should always be a consideration, because this could indicate the potential need for lifelong renal replacement therapy (RRT) and ultimately renal transplantation. This infant was able to be extubated, suggesting that the degree of pulmonary hypoplasia was not life limiting. Furthermore, the infant appears to be neurologically intact without significant comorbidities. Thus the infant would be a candidate for dialysis. Neonatal survival at 1 year for those started on dialysis in infancy is close to 85%, although there is a slightly worse prognosis for anuric infants. The most common causes of death are from

TABLE 18.2 Major Laboratory and Clinical Findings

Day	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	HCO_3 (mEq/L)	BUN (mg/dL)	Creatinine (mg/dL)	Calcium (mg/dL)	PO_4 (mg/dL)	Fluid intake (mL)	Fluid output (mL)	Other treatments
0	132	4.4	106	21	8	1.6	7.7		186	12	Hypotensive required fluid boluses and pressors
1	133	3.6	104	20	17	2	8.2		378	22	
2	129	3.4	91	25	37	3.3	9.1	3.4	297	98	
3	130	3.6	94	24	45	3.7	9.2	3.7	250	135	Furosemide started for fluid overload
4	132	3.3	94	29	50	3.8	10	3.2	281	177	
5	138	5.7	96	32	55	4.2	10.3	2.8	251	156	
6	150	6.5	98	34	64	4.9	10.3	4.1	240	80	

cardiopulmonary causes and infection in this age group (North American Pediatric Renal Trials and Collaborative Studies or NAPRTCS reports, 2014).

CASE STUDY 2

This is a 1-day-old girl born at 26 weeks' gestation via a spontaneous vaginal delivery 2 days following premature rupture of membranes. Her birth weight was 750 g and her Apgar scores were 5 and 6 at 1 and 5 minutes of life. She was intubated and given surfactant. After a blood specimen was drawn for culture, she was started on ampicillin and gentamicin and given maintenance intravenous (IV) fluid. She fails to pass urine in the first 24 hours after birth, and her blood pressures are persistently low at 30/20 mm Hg.

Exercise 6

Questions

1. When should newborns pass the first urine after birth?
2. What should you do first to evaluate and treat this infant?
3. Is she at risk for gentamicin toxicity?

Answers

1. Studies have shown that almost 100% of newborns have the first void within 24 hours after birth and nearly half of them void 8 hours after birth (Clark, 1977). Although very few infants of less than 32 weeks' gestation were documented in these studies and the time of the first void varies considerably, failing to pass urine beyond 24 hours should prompt the physician to evaluate and intervene for newborns of any gestational age.
2. She required resuscitation at birth and has a persistently low blood pressure that may be limiting perfusion of vital organs, including the heart and kidneys. Prolonged hypotension could serve as a prerenal etiology for acute ischemic and hypoxic injury to the kidney and should be corrected immediately. A normal saline infusion at 10 mL/kg (over 30 minutes) can be given at this time, and a repeated dose with the same volume could be considered if there is no significant improvement in the blood pressure. A renal ultrasound is also recommended. She needs frequent monitoring of respiratory, cardiac, and fluid status. Placement of a Foley catheter is recommended to drain the urine from the bladder and for subsequent monitoring of urine output. If the blood pressure remains low despite the fluid boluses, consideration should be given to use of a pressor such as dopamine.
3. Aminoglycosides are frequently used to treat infants with the possibility of sepsis due to their fast bactericidal effect, synergy with β-lactam antibiotics, and low cost. However, they can accumulate in tissues such as the kidney and the ear, causing nephrotoxicity and ototoxicity. Gentamicin is one of the most nephrotoxic and best-studied aminoglycosides (Lopez-Novoa et al, 2011). The kidney excretes gentamicin, which can be toxic to all compartments of the kidney. The incidence of gentamicin nephrotoxicity ranges from 10% to 25%. Risk factors contributing to its toxicity include reduced renal mass, intravascular volume depletion, long duration and high dose of treatment, and concomitant use of other nephrotoxic medications. Gentamicin causes apoptosis and necrosis of renal tubular cells, especially epithelial cells of the proximal tubules, by complex mechanisms including phospholipidosis, reduced ATP production in the mitochondria, and increased oxidative stress. Death of tubular cells results in tubular obstruction and increased hydrostatic pressure in the tubular lumen and the Bowman capsule, leading to a reduced filtration pressure gradient and a low glomerular filtration rate (GFR). Cell death is accompanied by interstitial inflammation. Injury to epithelial cells interferes with ion transport and may result in nonoliguric or polyuric renal failure. Excessive delivery of water and solutes to the distal nephron triggers tubuloglomerular feedback (tubuloglomerular feedback is one of several mechanisms the kidney uses to regulate glomerular filtration rate) further reducing GFR. In addition, gentamicin can cause direct functional alterations in the glomerulus and increase resistance of renal vasculature, thus reducing renal blood flow. Because its toxicity is usually related to blood concentration and duration of treatment, close monitoring of drug levels is required before subsequent administration, especially when renal compromise is suspected. In this case the patient has an increased risk for gentamicin toxicity because of low nephron numbers from prematurity, possible higher drug levels from decreased blood flow to the kidneys, and renal hypoperfusion secondary to the low blood pressure. Improving her systemic circulation with fluid and inotropic agents, if indicated, may help reduce renal injury.

MEASUREMENTS OF RENAL FUNCTION IN PREMATURE INFANTS

Serum creatinine is the net result of its generation from muscle metabolism and its excretion by the kidney. Clinicians use it to estimate renal function under steady state conditions. At birth, an infant's serum creatinine level reflects the maternal creatinine level (Quigley, 2012). Serum creatinine declines after birth to a new steady state level in about 2 weeks in full-term infants. However, premature infants can have an initial increase in serum creatinine and have a slower decline in creatinine level, which may take 5 to 6 weeks before reaching a steady state level (Thayyil et al, 2008). The initial increase in creatinine is largely due to its reabsorption of creatinine by renal tubules as a result of immature tubular function and does not always indicate AKI. For these reasons, serum creatinine in premature newborns cannot truly reflect GFR. The estimated GFR for a full-term infant is about 26 mL/min/1.73M^2 and doubles by 2 weeks of age.

The postnatal increase in GFR is mainly due to postnatal hemodynamic changes resulting in increased renal blood flow by the mechanisms of reduction of renal vascular resistance and elevation of systemic blood pressure and redistribution of renal blood flow from the medulla to the cortex. Because GFR is determined by the filtration rate at each

nephron and premature infants (<35 weeks' gestation) have decreased numbers of filtering nephrons, premature infants have a lower GFR value. A prospective study of infants born at 27 to 31 weeks' gestation showed that the GFR slowly increased over the first month of life and that the increase of GFR was inversely correlated to the gestational age (Vieux et al, 2010). At 7 days and 28 days after birth, infants born at 27 weeks' gestation have a median GFR of 13.4 and 21.0 mL/min/1.73M^2, respectively. Risk factors for decreasing GFR in premature infants include the use of nephrotoxic medications, systemic hypotension, hypovolemia, perinatal asphyxia, sepsis, and intrauterine growth restriction.

Compared with term infants, premature infants exhibit a higher fractional excretion of urinary sodium (FeNa) and higher serum potassium values. FeNa can be as high as 5%, thus making it less useful in differentiating prerenal versus intrinsic renal disease. The principal cells of the collecting duct are the final regulators for urinary sodium reabsorption and potassium excretion. In the preterm infant, the epithelial sodium channels (ENaC) of the principal cells are less responsive to aldosterone and exhibit reduced sodium transport. The cause of the higher serum potassium levels is unclear but is likely due either to diminished excretion of potassium by the kidney or decreased levels of Na^+/K^+ ATPase allowing potassium to leak out of the intracellular space.

Urine concentrating ability is limited in newborns due to low response to antidiuretic hormone (ADH) in the collecting ducts, lower medullary concentration gradient, and shorter loops of Henle. Premature infants have a significantly lower GFR and less mature tubular transport function than full-term neonates. Although neonates can excrete diluted urine with an osmolality of 50 mOsm/kg water, which is comparable to adults, they are only able to concentrate the urine to 600 mOsm/kg water, which is about half of the concentrating ability in adults (Calcagno et al, 1954). Urine-concentrating ability reaches adult level by 2 years of age. In addition, neonates have increased amounts of insensible water loss through the skin, especially when they are placed under radiant warmers. The daily fluid requirement in neonates is greater when calculated based on body weight.

It is important to note that in neonates, the low GFR can also limit the ability to excrete free water. Human milk is low in sodium, but neonates are able to excrete a sufficient amount of free water absorbed from the milk. Hyponatremia can result when formula is diluted because neonates will drink larger volumes to meet their caloric needs. The proximal tubules in neonatal kidneys have lower rates of bicarbonate reabsorption, and therefore the serum bicarbonate level will be lower in a neonate compared with an adult. Similarly, glucose reabsorption in the proximal tubules is low. It is common to have renal glycosuria in infants born before 30 weeks' gestation. In contrast, neonates have more active phosphate reabsorption than adults, leading to a higher serum phosphorus concentration and a positive phosphorus balance needed for growth.

In summary, neonatal kidneys undergo functional maturation after birth. Full-term infants have more complete kidney development, but premature infants born before 34 weeks have incomplete nephrogenesis (Hughson et al, 2003). One should bear in mind premature infants' unique renal physiology when administering medications and managing fluids, electrolytes, and nutrition.

CASE STUDY 2 (CONTINUED)

The infant's blood culture was negative at 48 hours, and antibiotics were discontinued. By 72 hours of life, her urine output increased to 1 mL/kg/hr and the serum creatinine value was 1.5 mg/L. She remained on a ventilator and had bounding pulse, an active precordium, and a loud continuous murmur. An echocardiogram shows a 3 mm PDA with left-to-right shunt and retrograde diastolic aortic flow. The care tem is considering using a nonsteroidal antiinflammatory drug (NSAID) to close the ductus arteriosus.

Exercise 7

Questions

1. Can a large PDA affect renal perfusion?
2. Which NSAID has the least effect on renal function when it is used for PDA closure?

Answers

1. PDA is a common complication in premature infants and is associated with increased risk for intraventricular hemorrhage, bronchopulmonary dysplasia, necrotizing enterocolitis, and death (Hamrick and Hansmann, 2010). A significant left-to-right shunt increases pulmonary blood flow and can contribute to a continued need for respiratory support. A reversal of diastolic blood flow from the descending aorta can result in compromised blood flow to organs distal to the descending aorta such as the kidney and the intestinal tract. In the renal arteries, the velocity of diastolic blood flow can be affected and, in some cases, retro-diastolic blood flow can be observed (Bömelburg et al, 1989). Low renal perfusion limits the excretion of metabolic products generated in underperfused organs, which contributes to a systemic metabolic acidosis.
2. All prostanoids (PGD2, PGE2, PGF2, PGI2, and thromboxane A2) are synthesized in the kidney by the action of cyclooxygenases (COX1 and COX2). Prostaglandin E2 is the main renal prostanoid and plays an important role in regulating renal vascular tone (hemodynamic effect) and salt and water excretion (tubular effect). Under stress conditions, such as dehydration, hypotension, and cardiac failure, vasoconstrictors (angiotensin II, endothelin and catecholamines) are highly activated. It is essential that the vasodilatory PGE2 and PGI2 oppose the action of vasoconstrictors to maintain the glomerular filtration rate by dilating afferent arterioles. Newborn kidneys have high pre- and postglomerular vascular resistance. They are more dependent on vasodilatory prostaglandins for normal renal function and therefore are more sensitive to adverse effects of nonsteroidal antiinflammatory drugs on the kidney (Antonucci and Fanos, 2009). NSAIDs including indomethacin and ibuprofen inhibits PGE2 synthesis and can be used to constrict an open PDA,

leading to functional closure. Although studies on low birth weight infants have shown that ibuprofen is as effective as indomethacin in closing a PDA and may have a better safety profile relating to impaired renal, gastrointestinal, and cerebral blood flow, it is important to remember that all NSAIDs can precipitate acute renal failure especially when other risk factors are present. In general, adverse renal effects induced by NSAIDs are usually reversible.

CASE STUDY 2 (CONTINUED)

As a result of her hemodynamically significant PDA, she received two doses of ibuprofen. Her urine output decreased to 0.3 mL/kg/hr. Her serum creatinine increased to 1.8 mg/dL in the next 24 hours and continued to increase to 2.2 mg/dL 72 hours after ibuprofen was given. She appears puffy but does not require higher ventilator support. An echocardiogram shows closure of the PDA.

Exercise 8

Question

Does this infant have AKI?

Answer

Serum creatinine does not increase until renal function is reduced by 25% to 50%. However, serum creatinine levels in very preterm infants normally increase in the first few days after birth before declining and reaching a steady state over the next 5 to 6 weeks. Often neonatal AKI results in polyuric renal failure (urine output >1 mL/kg/hr), making urine output an unreliable measurement for renal function. Although there is no universally accepted definition for AKI in premature infants, the fact that her urine output has decreased from 1 mL/kg/hr to 0.3 mL/kg/hr while creatinine has progressively increased to 2.2 mg/dL makes the diagnosis of AKI (and renal failure) undisputable.

Risk factors for AKI in this case include low perfusion pressure for the kidney from her PDA, use of NSAIDs, and prematurity.

CASE STUDY 2 (CONTINUED)

Repeat laboratory tests reveal Na 132 mEq/L, K 5.9 mEq/L, Cl 102 mEq/L, CO2 15 mEq/L, BUN 30 mg/dL, creatinine 1.2 mg/dL

Exercise 9

Question

What is the next best step for management of this infant's electrolytes?

A. Calcium chloride
B. Sodium bicarbonate
C. Sodium polystyrene sulfonate (Kayexalate) by mouth
D. Albuterol by inhalation

Answer

B. A serum potassium concentration of 5.9 mEq/L is unlikely to induce electrocardiographic (ECG) changes and by itself is not an indication for any intervention. IV calcium is indicated in the setting of hyperkalemia but only when there are ECG changes. Treatment of acidosis with sodium bicarbonate will likely drive the potassium into cells and decrease the serum potassium concentration. Alternatively, acetate can be added to the intravenous solution as sodium acetate. Following the addition of acetate, bicarbonate levels should increase over several days. Oral administration of sodium polystyrene sulfonate is generally avoided in neonates because of potential intestinal complications and should not be used. Inhaled albuterol is an effective intervention when a reduction in serum potassium values is urgently needed. That is not required in this case.

CASE STUDY 2 (CONTINUED)

The infant's urine output improved to 1 mL/kg/hr and serum creatinine decreased to 0.8 mg/L at 3 weeks of age and 0.4 mg/dL at 5 weeks of age. She was weaned off mechanical ventilation by day 21. She is tolerating feeds and gaining weight appropriately. Her mother is expecting her to go home soon.

Exercise 10

Question

What will you tell the family about her kidney condition?

Answer

Her daughter had an AKI and her kidney function is recovering to the level that allows her to excrete fluid and metabolic wastes. However, she has an increased risk for chronic kidney disease (CKD) and can develop hypertension. She should have long-term follow up with a pediatric nephrologist after being discharged from the NICU.

LONG-TERM RENAL CONSEQUENCE IN CHILDREN WITH PREMATURE BIRTH

With advancements in neonatal intensive care, most premature infants survive and are discharged safely from the NICU. However, it is clear that these survivors have unique requirements in their healthcare. Long-term kidney care is no exception. Clinical research and observational data indicate that premature birth and low birth weight are associated with an increased risk for CKD. As kidney formation does not complete until 34 to 35 weeks of gestation and the most robust nephrogenesis occurs in the third trimester, premature birth results in low nephron numbers and immature kidneys in both structure and function. Human autopsies from cases that include infants, children, and adults have shown that there is a more than eightfold difference in glomerular numbers ranging from 220,000 to 1,825,000.

A linear relationship exists between low birth weight and total glomerular number (Fig. 18.3) (Hughson et al, 2003). Each kilogram increase in birth weight is predicted to increase the total glomerular number by 257,000. Autopsy studies in infants with birth weights of less than 1000 g show

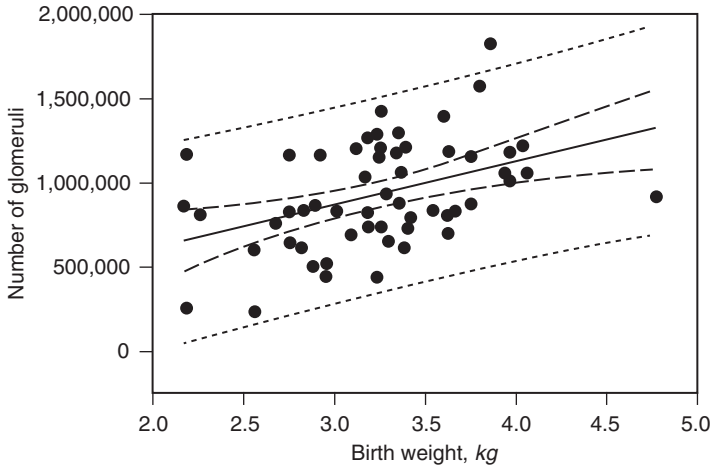

Fig. 18.3 The relationship between birth weight and total glomerular number among all cases that includes infants, children, and adults. Symbols are (•) N_{glom} vs. birth weight; (——) N_{glom} vs. birth weight regression; (—) 95% regression CI; (……) regression prediction interval. The regression coefficient predicts a gain of 257,426 glomeruli per kg increase in birth weight, $r = 0.423$, $P = 0.0012$, $N = 56$.

no evidence of new nephron formation 40 days after birth. Extrauterine insults including nephrotoxic medications, infection, and hypotension can impair kidney development further. Infants who experienced AKI have even lower glomerular numbers. Furthermore, the volume of glomeruli is larger (oligomeganephronia) in children with premature birth. Hyperfiltration occurs in the small number of nephrons that have larger glomeruli, which may lead to secondary focal glomerular sclerosis (FSGS). Proteinuria and hypertension can develop rapidly, which accelerates the progression of CKD and contributes to further declines in renal function. Systematic reviews indicate that adults born with low birth weight have a 70% increase in developing CKD and highlights the necessities of long-term renal care for children with premature birth (Carmody and Charlton, 2013).

It is worth noting that most infants discharged from the NICU have normal serum creatinine values, but the serum creatinine level does not reflect GFR accurately. Because of functional compensation, a loss of half of the nephron number leads to only a 20% to 30% decrease in GFR. At this time, there is neither a sensitive method to screen for renal impairment nor a general guideline for long-term renal care for NICU graduates. Collaborations among neonatologists, pediatricians, and nephrologists are crucial in identifying children at risk and for implementing long-term care plans. Prematurity and a history of AKI warrant a nephrology clinic follow-up. A simple urine test for albuminuria may detect glomerular lesions. Hypertension could be a sign of salt and water retention from low numbers of functional nephrons. Impaired linear growth can also be seen in children with CKD. Although there are no treatments to regenerate damaged nephrons or prevent the development of CKD, early identification of children with CKD may help to reduce CKD-associated complications such as anemia, growth failure, renal osteodystrophy, neurocognitive dysfunction, and poor quality of life. Parents can be educated to avoid nephrotoxic medications such as NSAIDs and obesity, both of which could adversely affect kidney function. As the children grow into adolescence, when stressful conditions exist, close monitoring and preparation for transition to adult nephrology services become an integral part of the long-term care.

CASE STUDY 3

A male term infant with a postnatal diagnosis of hypoplastic left heart syndrome is 1 day postoperative following a stage 1 Norwood repair. He was unable to wean from bypass and is on extracorporeal membrane oxygenation (ECMO). Preoperative laboratory testing revealed a BUN 6 mg/dL and creatinine 0.4 mg/dL. A preoperative ultrasound showed that the right kidney measured 3.8 cm in length and the left kidney 4.0 cm in length. Both kidneys have normal echotexture. There is no hydronephrosis or shadowing renal stones. His BUN is 15 mg/dL and creatinine 0.9 mg/dL. Despite furosemide injections, Urine output continues to be low at 0.4 mL/kg/hour and he is net positive 1 liter of fluid.

Exercise 11

Question

What is the next best step in managing this patient's fluid overload?

A. Initiate continuous renal replacement therapy (CRRT)
B. Begin a high dose furosemide infusion
C. Place a peritoneal dialysis (PD) catheter

Answer

A. A PD catheter may be placed at the time of major congenital heart repair in anticipation of high risk for AKI, oliguria, and fluid overload. Indeed, a randomized study comparing furosemide drip to initiation of PD for oliguria demonstrated decreased fluid overload with PD (Kwiatkowski et al, 2017).

However, the infant in our case study did not have a PD catheter placed and is on ECMO. High-dose furosemide drip is unlikely to increase urine output sufficiently to address the marked fluid overload. Thus the best option is to provide continuous renal replacement therapy (CRRT) via the ECMO circuit.

AKI is common in infants and children on ECMO. Multicenter studies indicate that over 90% developed AKI, with almost 50% requiring renal replacement therapy (Elella et al, 2017; Fleming et al, 2016). For fluid removal, some centers place a hemofilter in-line with the ECMO circuit. The filter inlet is connected after the pump and outlet is reconnected to the ECMO circuit before the oxygenator. However, this approach does not allow one to closely control net fluid removal. Alternatively, CRRT machines may be placed in series with ECMO (Cavagnaro et al, 2007; Murphy et al, 2018; Santiago et al, 2009; Sutherland et al, 2012). The CRRT machine inlet line is connected after the centrifugal pump and its outlet line before the oxygenator. To account for the highly negative return pressure of the ECMO circuit, the CRRT machine alarm settings may need to be adjusted (when able) or the return pressure modified (e.g., using clamps) (Ostermann et al, 2018).

CASE 3 (CONTINUED)

The infant was successfully decannulated; however, he remains oliguric with fluid overload.

Exercise 12

Question

Which of the following vascular accesses is the preferred route for initiating CVVH in the neonate?

A. Two 5F umbilical arterial and venous catheters (UAC/UVC)
B. Femoral double lumen 7F catheter
C. Internal jugular double lumen 7F catheter
D. Subclavian double lumen 7F catheter

Answer

B or **C.** Vascular access is often the major limiting factor when performing CVVH in neonates, especially in the setting of anasarca (Bunchman et al, 2008; Goldstein, 2011). Vascular resistance is inversely proportional to the fourth power of the radius of the catheter; thus, the smallest catheters will have the highest resistance to blood flow. The shortest, widest catheter that can be placed is desirable. Smaller catheters and the small size of neonates may limit blood flow rates, increasing the risk of clotting the circuit. Although using 5F catheters for CVVH in the umbilical artery and vein has been reported, it is often unsuccessful, and many clinicians advocate for double lumen 7F catheters as the better alternative.

CASE STUDY 3 (CONTINUED)

The severe anasarca and history of prior ECMO access precluded placement of a vascular access catheter. A PD catheter was placed and acute PD was initiated with 35 cc exchange volumes and 40 min dwell time. Ultrafiltration was successful, and the infant became less edematous and more alert. He was weaned off ventilator support. However, he remained oliguric and a permanent PD catheter was placed. He was started on Similac PM 60/40 to enhance nutrition. However, after a few days, the PD became less effective (less ultrafiltrate was observed) and the infant developed worsening edema.

Exercise 13

Question

The next intervention is to:

A. Increase the dextrose concentration in the dialysate
B. Decrease the dextrose concentration in the dialysate
C. Administer furosemide

Answer

A. The dextrose concentration in the dialysate drives the osmotic gradient to enable ultrafiltration and fluid removal, so the recommended step would be to increase the dextrose concentration. Decreasing the dextrose concentration will decrease the osmotic gradient, leading to less ultrafiltration. However, dextrose concentrations higher than 1.5% in the dialysate should only be used for a short period, as a high concentration (e.g., 4.25% dextrose-containing PD solutions) can lead to peritoneal membrane damage, resulting in dialysis failure. In oliguric and anuric infants with severe acute tubular necrosis, additional furosemide is unlikely to result in diuresis and sufficient fluid removal.

CASE STUDY 3 (CONTINUED)

After the dextrose concentration is raised to 2.5% in the dialysate, fluid removal was increased and the patient became less edematous over the next few days.

Exercise 14

Question

Of the study options below, which one may help to assess the likelihood of this infant's renal recovery?

A. Serum creatinine
B. Renal ultrasound
C. Doppler ultrasound of renal arteries

Answer

C. Recovery from AKI with acute tubular necrosis and interstitial inflammation can take weeks to months. Severe ischemic injury can also result in cortical necrosis and poor renal perfusion, which may be identified by examination of renal arterial blood flow by Doppler ultrasound. Increased echogenicity on renal ultrasound may be present in both reversible and irreversible renal failure and cannot alone be used to determine renal prognosis. As creatinine is cleared by PD, changes in creatinine while on PD may not reflect intrinsic renal function. In addition to renal blood flow studies, increased urine output can be a useful indicator of returning renal function for a neonate on dialysis.

CASE STUDY 3 (CONTINUED)

A repeat renal Doppler ultrasound demonstrated good arterial blood flow to both kidneys. Over the course of the following week, urine output increased to 2 mL/kg/hr and dialysis was discontinued. Serum creatinine gradually decreased to 0.2 mg/dL. After discharge, the patient received long-term follow up in the outpatient nephrology clinic as epidemiology and experimental animal studies demonstrate that his acute renal injury increased the risk for CKD and hypertension.

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Abstract: Neonates, especially those with premature birth, face distinct challenges in renal clearance and fluid balance. Kidney failure creates additional complexity in the management of fluid and electrolytes and the excretion of waste products. This chapter discusses the clinical presentation, pathogenesis, and treatment of common types of acute kidney injury resulting from nephrotoxic medications and renal ischemia. Information on embryonic kidney development is provided to help understand the histopathology of congenital anomalies of the kidney and urinary tract (CAKUT) and the low renal reserve in underdeveloped kidneys of premature infants. Standard dialysis modalities and the state-of-the-art treatment using continuous renal replacement therapy (CRRT) via the extracorporeal membrane oxygenation (ECMO) circuit are discussed. Furthermore, the application of genetic testing in the diagnosis of CAKUT is introduced to help with precise molecular diagnosis and guide multidisciplinary managements, including early intervention of other developmental defects.

Keywords: acute kidney injury, congenital anomalies of the kidney and urinary tract (CAKUT), end-stage renal disease, fluid and electrolytes, renal replacement therapy

19

Neonatal Seizures

Tristan T. Sands and Cigdem I. Akman

INTRODUCTION

Seizure incidence is at its highest in the neonatal period, estimated at 1 to 3 per 1000 term neonates and 10 times higher for preterm/low birth weight newborns (Vasudevan and Levene, 2013). Most cases are considered acute symptomatic seizures, result from acute brain injury, and occur in its immediate aftermath (Fig. 19.1). The underlying etiologies for acute symptomatic seizures in neonates include hypoxic ischemic encephalopathy (38%), ischemic stroke (18%), and intracranial hemorrhage (12%). Transient metabolic derangements (4%) and central nervous system infection (4%) are other less common etiologies. Epilepsy, defined as recurrent unprovoked seizures, is responsible for less than 15% of newborns with seizures (Shellhaas et al, 2017b). However, early identification carries important prognostic and therapeutic implications because the evaluation and management of neonatal-onset epilepsies is distinct from that of acute symptomatic seizures (Cornet et al, 2018). Neonatal epilepsy is largely genetic in origin, including dominantly inherited neonatal epilepsy (15%), epileptic encephalopathy (46%), and malformations of cortical development (39%), which often result from somatic mutations (Glass et al, 2016).

The timing of seizure onset in newborns may hint at the cause. Hypoxic ischemic encephalopathy often presents with seizures in the first 12 to 24 hours after birth. Seizures resulting from central nervous system infection or hemorrhage can present later, even weeks after birth. With perinatal stroke, seizures commonly present within 24 to 48 hours following birth (Kirton et al, 2011) but may occur later in infancy. Seizures secondary to intraventricular hemorrhage in preterm neonates usually present in the first week of life.

Intracranial hemorrhage can present with seizures in newborns depending on the location and type of intracranial hemorrhage. Epidural hemorrhage is rare in newborns but always follows a traumatic event. Subdural hemorrhage is the most common type of intracranial hemorrhage in neonates; it is caused by traumatic delivery but does not usually present with seizures unless there is injury to the underlying cortex (Sirgiovanni et al, 2014). Cerebral parenchymal hemorrhage involving cortical and/or subcortical gray matter commonly presents with seizures.

Metabolic derangements such as hyponatremia, hypocalcemia, and hypoglycemia can also result in acute seizures within the first days of life. Although most of these are transient in nature, all metabolic derangements should be investigated to make sure there are no congenital or acquired liver, renal, or endocrine abnormalities.

Central nervous system infection is less common than it had been in the past. Seizures associated with central nervous system infections may present as late as several weeks of age and can result from bacterial, fungal, or viral infections (e.g., herpes simplex virus, parechovirus, etc.).

Although insufficient by itself for diagnosis, the clinical manifestation of seizures—the seizure semiology—can provide clues regarding etiology that may complement the clinical history, examination, electroencephalography (EEG), and neuroimaging (Table 19.1). For example, perinatal ischemic stroke in neonates is relatively common at 1 to 2 per 1000 live births, most often affects middle cerebral artery territory (left more often than right), and may present as contralateral focal-clonic seizures. Stroke is thought to result from embolism from the umbilical cord or placenta; the majority of babies do not have a coagulopathy and are at low risk for recurrence. Newborns with stroke do not manifest hemiparesis, as corticospinal tracts are not yet used for movement, and the baby is often otherwise well appearing with seizures as the only symptom of brain injury.

Acute symptomatic seizures in neonates are focal in onset, and seizure spread to adjacent locations or rest of the brain is uncommon. Because they may not propagate sufficiently to result in any clinical manifestation, the clinical diagnosis of the seizures is limited. Moreover, when medication is used to treat seizures it often results in an uncoupling, in which the electrographic seizure continues even after clinical manifestation ceases, a phenomenon referred to as electroclinical dissociation. For these reasons, surveillance in populations at high risk for seizures represents a major indication for continuous EEG monitoring. Patients are considered high risk either because they have known or suspected brain injury (e.g., hypoxic–ischemic encephalopathy, etc.) or because they are at high risk for brain injury (e.g., on an extracorporeal membrane oxygenation [ECMO] circuit) (Table 19.2). For example, approximately 50% of patients undergoing therapeutic hypothermia for hypoxic ischemic encephalopathy

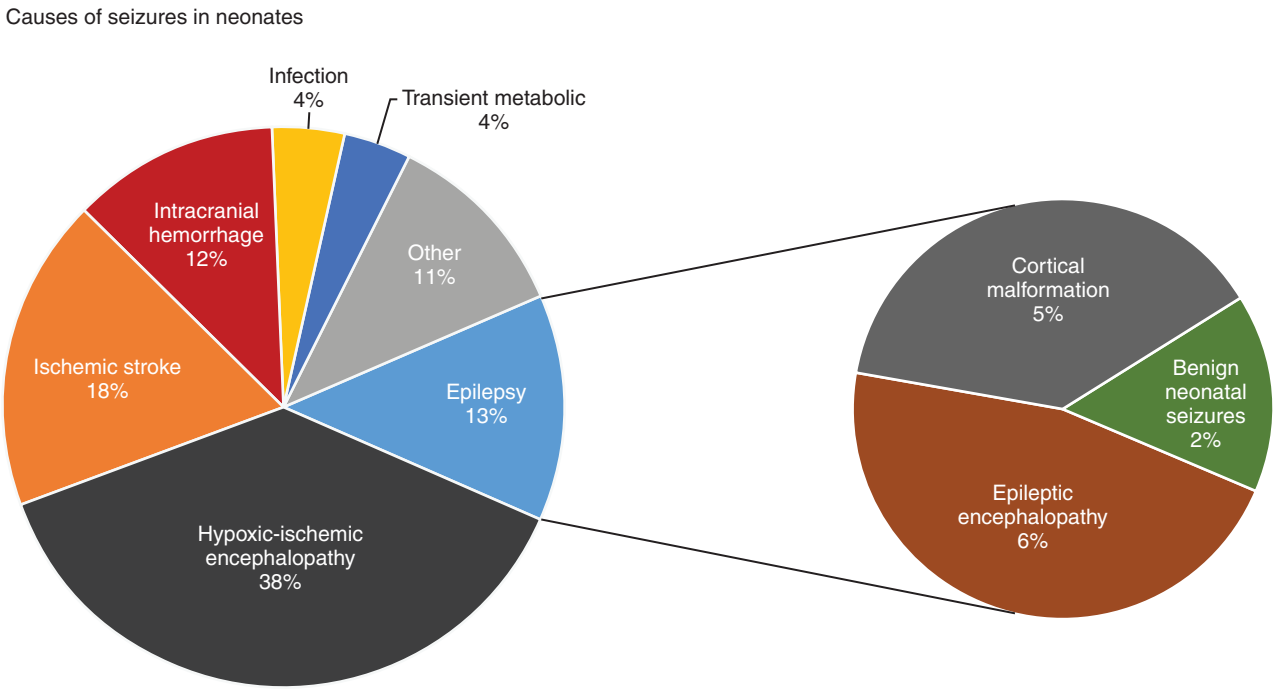


Fig. 19.1 Causes of seizures in neonates. The etiology of seizures for most neonates is acute brain injury with hypoxic–ischemic encephalopathy and ischemic and hemorrhagic stroke accounting for the majority. A sizeable minority, however, represent neonatal-onset epilepsies associated with cerebral malformations and/or genetic causes.

TABLE 19.1 Select Typical Clinical Patterns

Diagnosis	Seizure Type	Clinical Examination	EEG Background
Ischemic stroke	Unilateral focal clonic seizures	Normal	Mildly abnormal
Hypoxic-ischemic encephalopathy	Multifocal subclinical seizures	Moderate to severe encephalopathy	Moderately to severely abnormal
Ohtahara syndrome (e.g., due to hemimegalencephaly)	Tonic spasms	Moderate to severe encephalopathy	Burst suppressed
Early myoclonic encephalopathy (e.g., due to glycine encephalopathy)	Myoclonic seizures	Moderate to severe encephalopathy	Burst suppressed
Benign neonatal seizures	Asymmetric tonic seizures	Normal	Mildly abnormal
KCNQ2 Encephalopathy	Asymmetric tonic seizures	Moderate to severe encephalopathy	Severely abnormal

(HIE) have seizures (Glass et al, 2014). These seizures are typically subclinical or become so during the clinical course (Nash et al, 2011). Congenital heart disease is another high-risk group, with approximately 10% of this population affected by (mostly subclinical) seizures (Naim et al, 2015).

Although we have dichotomized acute symptomatic seizures and neonatal-onset epilepsy, it is important to realize that acute brain injury can, and indeed may be relatively more likely to, occur in the setting of encephalopathy related to other causes resulting in a dual diagnosis. Caution is urged as well in settling on a diagnosis when the history is not entirely consistent or definitive, as false attribution is common. Many patients with epileptic encephalopathies are initially diagnosed with HIE.

The temporal evolution of acute symptomatic seizures in newborns is not uniform. Seizure burden often reaches a peak at around 23 hours after birth in newborns with HIE. The median time from first recorded seizure to maximum seizure burden is 5.9 hours (Lynch et al, 2012). Individual neonatal seizures are rarely prolonged. Most neonatal

TABLE 19.2 Indications for Monitoring With Continuous Video-EEG (Electroencephalography)

Indication	Example
Paroxysmal spells of uncertain nature	2 day-old full-term boy with recurrent unexplained episodes of apnea
Neonatal encephalopathy of unknown etiology	34-week female with unremarkable prenatal course and delivery, but with Apgar scores of 1 and 8; examination notable for encephalopathy with poor visual attention, hypotonia, and reduced spontaneous movements
Congenital heart disease	10-day-old boy with hypoplastic left heart syndrome, status post Norwood procedure
Extracorporeal membrane oxygenation (ECMO)	2-week-old girl with truncus arteriosus, status post repair complicated by cardiac arrest and now on veno-arterial ECMO
Hypoxic–ischemic encephalopathy	37-week male child undergoing therapeutic hypothermia after birth by emergency C-section for nonreassuring fetal heart tracings in the setting of placental abruption
Stroke (ischemic infarction or intracranial hemorrhage)	Female neonate born at 29 weeks, found on screening ultrasound during the first week of life to have a left-sided periventricular hemorrhagic infarction (Grade IV intraventricular hemorrhage)
Meningoencephalitis suspected/known	Febrile neonate, alternately lethargic and irritable with episodes of opisthotonic posturing and blood cultures positive for gram-negative rods
Genetic disorder associated with epilepsy suspected/known	Male newborn born at 37 weeks with antenatal imaging notable for multiple cardiac rhabdomyomas concerning for Tuberous Sclerosis Complex
Cortical malformation	38-week male neonate born without complications; antenatal course concerning for lissencephaly, confirmed on fetal MRI

seizures last less than 90 seconds. Therefore neonatal status epilepticus is defined as the presence of electrographic seizures during at least 50% of a 1-hour EEG epoch.

CLINICAL HISTORY AND NEUROLOGIC EXAMINATION

The diagnostic workup should include investigation of the maternal and family history (e.g., previous pregnancy losses, family history of neonatal seizures), prenatal course (e.g., reduced fetal movements, substance abuse), the events surrounding labor and delivery (e.g., sentinel events such as placental abruption), and the immediate postnatal clinical course (e.g., Apgar scores, need for and duration of resuscitation). The general examination should note vital signs; growth parameters including head circumference, length, and weight; palpation *and* auscultation of the anterior fontanelle; a thorough skin inspection; and cardiovascular examination. Careful attention to the presence of dysmorphic faces, malformations affecting the digits, and genitals is also required.

Seizures localize to the cerebral cortex, but the neurologic examination of newborns rostral to the brainstem is very limited because of developmental considerations (e.g., motor movements are not directly cortically generated in the newborn period). Abnormal functioning of the cerebral cortex in neonates may manifest on examination in the following ways:

- Encephalopathy (excessive irritability, poor visual attention, lethargy, stupor, or coma) assessed by responses to sensory stimuli (visual cues, sound, touch, pain) and elicitation of sucking response and other primitive reflexes
- Abnormal tone is an additional sensitive but indirect and nonspecific sign of nervous system dysfunction; it may be reduced overall or extensor tone may be abnormally high compared with flexor tone (e.g., opisthotonic arching in an irritable baby with kernicterus or meningitis)
- Spontaneous movement is often reduced with injury to the cerebral cortex in the acute setting, though asymmetry and true weakness point to peripheral nervous system involvement

INITIAL DIAGNOSTIC TESTING FOR SUSPECTED NEONATAL SEIZURES

The Role of Polygraphic Continuous Video-EEG Monitoring

Seizures in newborn infants can be the first sign of serious neurologic disease or systemic illness. Abnormal paroxysmal events in a neonate should prompt an emergent evaluation. It is important to note, however, that although most neonatal seizures are subclinical and can only be diagnosed accurately by electroencephalography (EEG), it is also true that *most abnormal neonatal movements have no EEG correlate and thus are not seizures.* Even the most experienced clinicians may misdiagnose unusual paroxysmal events as seizures. Even if not seizures, abnormal episodes may reflect CNS dysfunction (e.g., opisthotonic posturing is not a seizure but is very abnormal). Accurate differentiation of neonatal seizures and nonseizure events is critical, both to ensure adequate treatment for infants with seizures and to avoid administering anticonvulsants to those whose events are not seizures.

Before the era of continuous EEG monitoring, seizures were identified clinically and categorized as tonic, clonic, myoclonic, or subtle (e.g., bicycling, apnea, abnormal eye movements) (Volpe, 1989). Subsequently, it has been shown that clinical observation used in isolation to diagnose seizures is inadequate because of:

- Poor specificity, as many paroxysmal behaviors in newborns are unaccompanied by electrographic correlate on EEG (Mizrahi and Kellaway, 1987)
- Poor sensitivity, as seizures are very often subclinical, lacking consistent clinical features (Murray et al, 2008)
- Poor agreement between observers (Malone et al, 2009)

CASE 1

A 3500 g male infant was delivered at 39 weeks' estimated gestational age to a 28-year-old primigravida mother after a pregnancy complicated only by maternal group B streptococcal colonization. His mother received antibiotic prophylaxis with clindamycin during labor because of an allergy to penicillin. The infant was delivered vaginally and appeared healthy, with a normal physical examination. He was cared for in the well-baby nursery and discharged to home with his mother after 36 hours.

One week later, he developed unusual episodes characterized by brief, sudden, jerking movements of his arms and legs. These occurred in clusters lasting between 1 and 5 minutes while he was sleeping. Between events, he fed normally.

At his pediatrician's office, the baby was slightly lethargic and weighed 3600 g. His head circumference was 35.5 cm and his vital signs were normal. While he was sleeping in his mother's arms, he suddenly developed a tonic stiffening of his left arm, followed by arrhythmic movements of his left leg and then the right arm. The pediatrician lifted him to the examination table and undressed him. The infant cried and the movements ceased, but he exhibited brief periods of apnea.

CASE 2

A 30-week gestational age infant was transferred from a referring hospital for evaluation of intraventricular hemorrhage. He has depressed mental status and is intubated and sedated. A brain magnetic resonance imaging (MRI) is scheduled in 2 hours.

CASE 3

A 39-week gestational age infant was delivered to a 30-year-old multiparous mother who admits to polysubstance abuse during the pregnancy. The infant is now 2 days old and she is jittery and has frequent episodes of full-body stiffening and crying. Blood and cerebrospinal fluid (CSF) cultures are negative.

Exercise 1

Options for diagnosis of neonatal seizures include bedside (clinical) observation, routine-length electroencephalography (EEG), conventional video-EEG monitoring, and amplitude-integrated EEG.

Question

For each of the preceding cases, decide if the infant is having seizures and which (if any) electrodiagnostic test (conventional [routine length] EEG, amplitude integrated EEG, or video-EEG) is indicated.

Answer

1. The infant in Case Study 1 is at very high risk for sepsis and meningitis, which raises concern for acute symptomatic seizures. Clindamycin is not considered adequate intrapartum prophylaxis. The episodes of apnea could be ictal or could be unrelated to seizures. The episode of tonic stiffening of the left arm may be a focal seizure. The depressed mental status could be accentuated by subtle or subclinical seizures. The best, most appropriate testing for this neonate is conventional video-EEG monitoring. If no seizures are recorded, and the EEG background remains stable, then monitoring can be discontinued after 24 hours. If seizures are identified on the EEG, then monitoring should continue until the infant remains seizure-free for 24 hours.
2. The neonate in Case Study 2 is at high risk for seizures due to the intracranial hemorrhage. He has depressed mental status, which raises concern for subclinical status epilepticus. However, he will need to be transported to MRI in 2 hours and cannot have EEG leads in place during the MRI scan, because the leads contain metal. In this case using amplitude-integrated EEG to screen for status epilepticus before he is transported to MRI is a reasonable option. Conventional EEG monitoring can begin after the MRI.
3. The infant in Case Study 3 likely has neonatal abstinence syndrome. Although this raises the risk for neonatal seizures, the events of concern are not focal, which lessens the chances that they represent seizures. The episodes are occurring very frequently, so they are likely to be captured during a conventional EEG. If several (three or four) typical events are recorded and are not seizures, and the EEG background is normal or nearly normal, then the EEG may be discontinued.

The diagnosis of neonatal seizures is made based on clinical findings and EEG. When seizures are suspected, multiple facets of evaluation and treatment must occur simultaneously: (1) accurate diagnosis of the events of concern (e.g., seizure versus nonepileptic paroxysmal event), which is most accurately characterized by EEG; (2) determination of the etiology of the events of concern (e.g., sepsis, electrolyte abnormalities, acquired or congenital brain abnormalities); and (3) empiric treatment of the most likely etiologies (e.g., antibiotics, adequate hydration). Here, we discuss characterization of the events of concern first, but in clinical practice an additional diagnostic evaluation and treatment occur in tandem.

Continuous video-EEG monitoring in neonates is polygraphic and records cerebral activity from the scalp (Fig. 19.2),

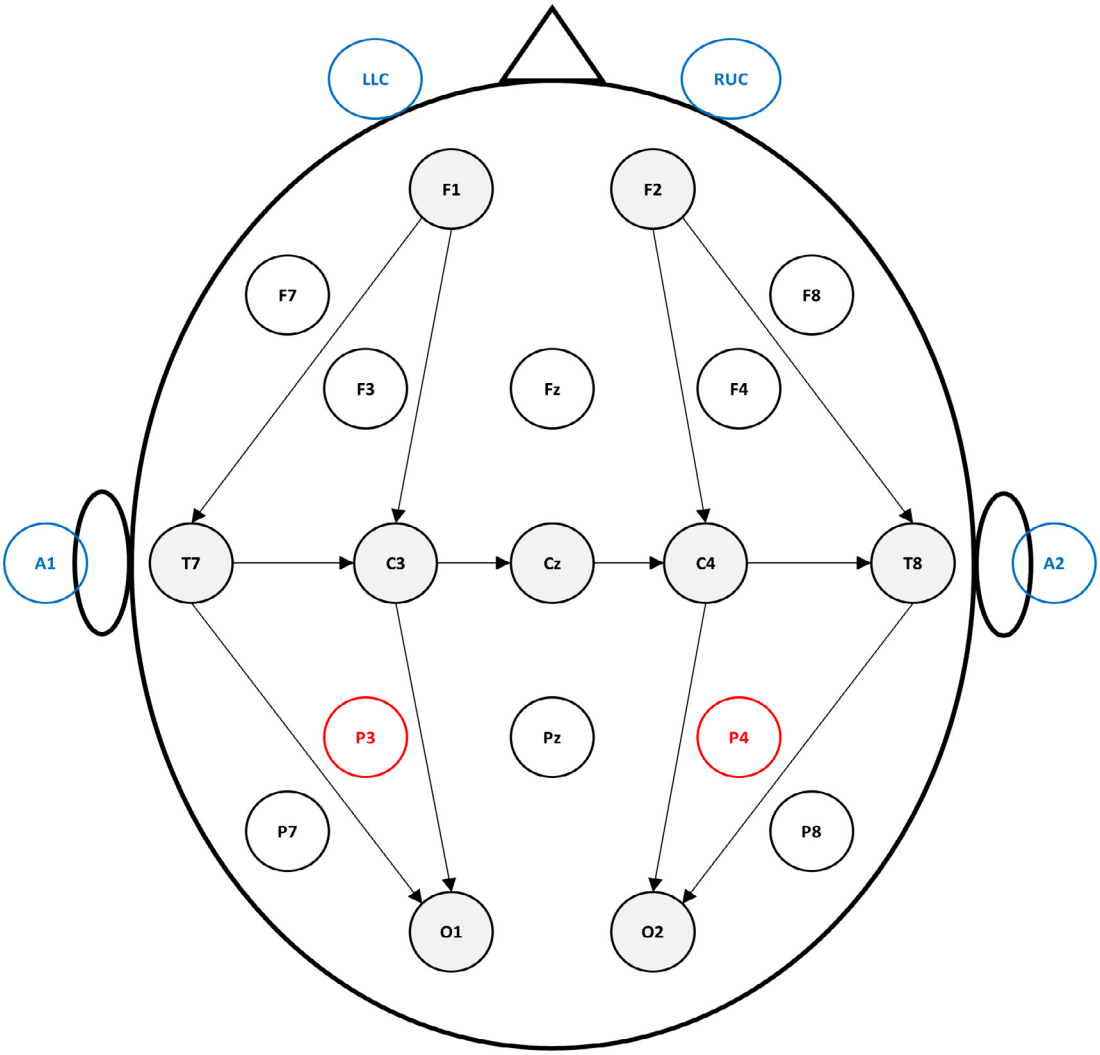


Fig. 19.2 The international 10 to 20 system for EEG electrode placement, modified for neonates. EEG electrodes are placed in the positions indicated. Odd numbers indicate the left side of the head, even numbers the right, and Z indicates the midline. Shaded electrodes are included in recordings of neonates. The parietal electrodes (checkered) represent the typical locations selected for amplitude-integrated EEG. Noncerebral electrodes (speckled) to record eye movements (left lower canthus, *LLC*, and right upper canthus, *RUC*) and as reference electrodes placed on the ears (A1 and A2) are also shown. Not shown, a respiratory channel and single-channel electrocardiogram are required for accurate interpretation of the study.

the heart (electrocardiogram, ECG), eye (electrooculogram, EOG), muscle (electromyogram, EMG), and respiration for the purposes of recording common sources of noncerebral artifacts and determination of behavioral state. The rationale for detecting electrographic seizures rests on the assumption that detection and treatment will ultimately lead to improvement in clinical outcome. Conventional (routine length) EEG remains the gold standard for seizure detection in neonates. Most acute symptomatic seizures (50%–80%) in neonates are subclinical—they have no externally apparent manifestations. Subclinical seizures are discrete electrographic events, distinct from the EEG background, that evolve in location, morphology, and/or frequency, *lasting at least 10 seconds* (Fig. 19.3). An electroclinical seizure is an abnormal electrographic change time locked to clinical features. Episodes that have no associated correlate on EEG should not be considered seizures.

As inaccurate diagnosis is expected to lead to untreated seizures on the one hand and inappropriate use of antiepileptic drugs on the other, the World Health Organization's Guideline on Neonatal Seizures strongly recommends that all clinical seizures be confirmed by EEG where available (World Health Organization, 2011). Characterization of paroxysmal events in neonates is one of the major indications for video-EEG monitoring. In addition to capturing any clinical features associated with seizure activity, video can assist with the

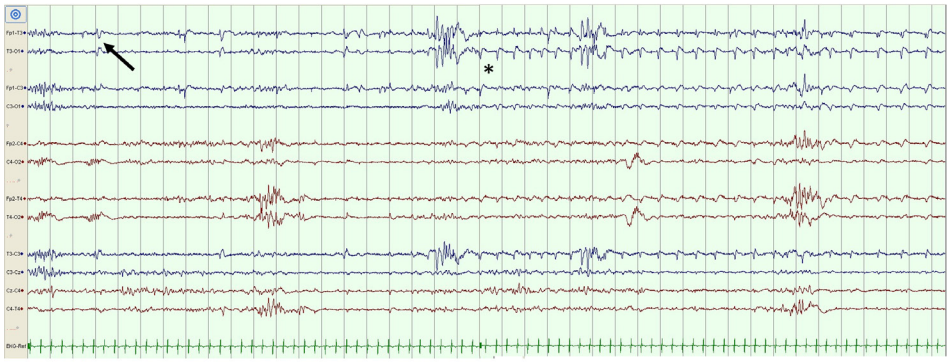


Fig. 19.3 Subclinical seizure arising in the left posterior quadrant (*) in a term neonate with an ischemic stroke. Periodic sharp waves *(arrow)* precede the seizure at T3 (same as T7).

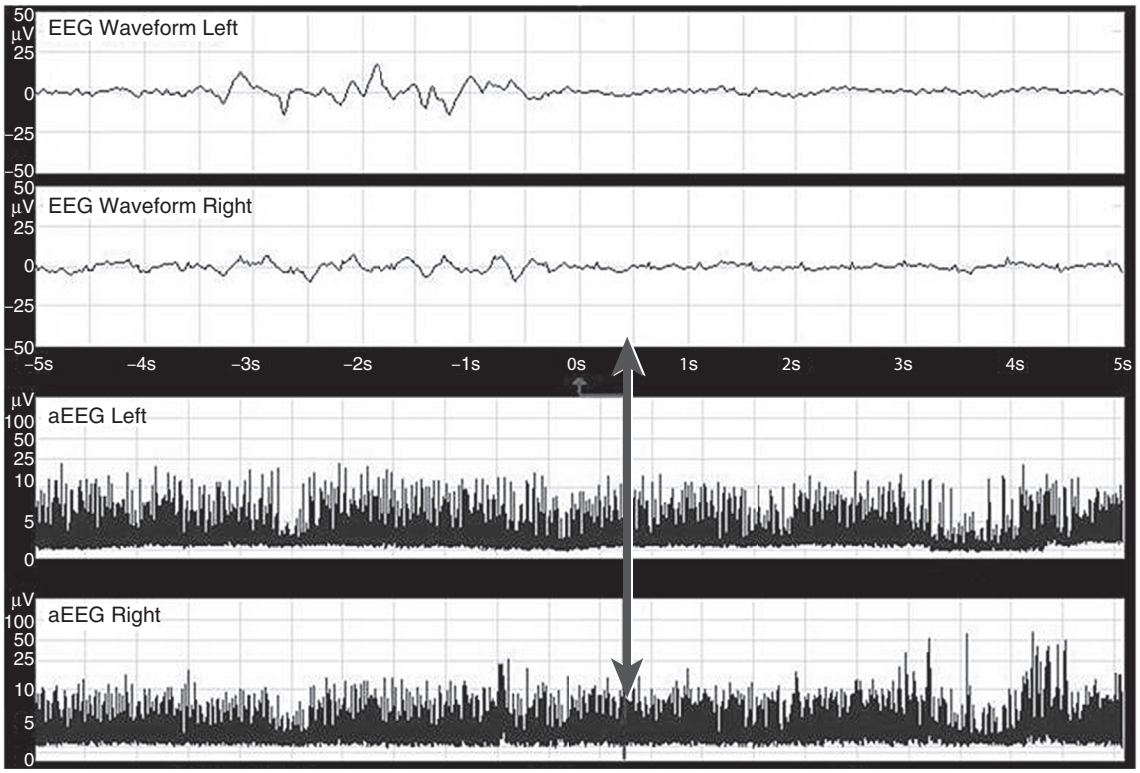


Fig. 19.4 Dual channel amplitude-integrated EEG (aEEG) recorded from a full-term infant. The top two panels display 10 seconds of "raw" EEG, whereas the bottom two panels display 3 hours of aEEG. The *arrow* indicates the point on the aEEG that corresponds to the raw EEG panels.

diagnosis of other benign or abnormal phenomena (e.g., sleep myoclonus, jitteriness, opisthotonos) or other neurologic diagnoses (e.g., hyperekplexia, paroxysmal extreme pain disorder).

Amplitude-integrated EEG (aEEG) displays a transformed signal from a 2 to 15 Hz frequency window usually recorded with two electrodes, typically parietal (Figs. 19.3 and 19.4), on a compressed timescale. The aEEG provides monitoring that can be interpreted at the bedside at a sacrifice of sensitivity, given coverage and technical limitations (Boylan et al, 2013; Rakshasbhuvankar et al, 2015; Shellhaas et al, 2007). There is also the potential for false positives, as artifact is more likely to successfully masquerade as seizures in the absence of polygraphic recording (Fig. 19.5). Seizures suspected on aEEG should be confirmed with conventional EEG recording.

A recently published expert commentary suggests that prolonged conventional video-EEG provides the best opportunity for the correct identification of seizures and is essential for the detection of the neonatal seizures (Boylan et al, 2013). With aEEG the chance to detect seizures accurately remains at only 12% and sensitivity increases with the longer seizure

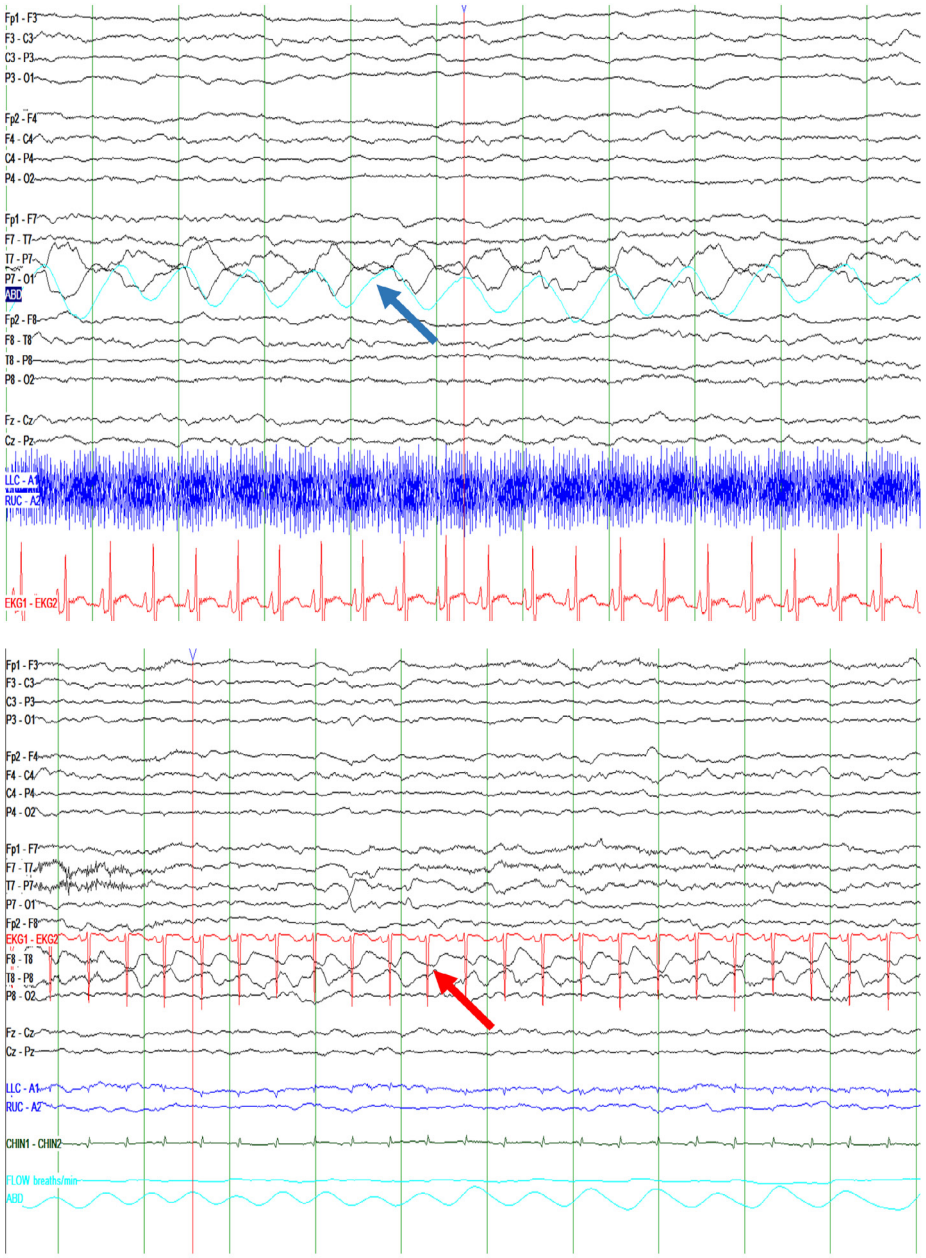


Fig. 19.5 Polygraphic recordings permit correct identification of artifact. The top panel shows apparent focal rhythmic activity in the left parietal region at P7. Overlay of the respiratory belt in gray demonstrates it to be artifact related to breathing. The bottom panel shows apparent focal rhythmic activity in the right temporal region at T8. Overlay of the electrocardiogram in gray demonstrates it to be artifact caused by pulse. In each case, the rhythmic activity could be mistaken for seizure without the benefit of the noncerebral electrodes.

duration (Rakshasbhuvankar, 2017). For instance, if a seizure duration is less than 2 minutes, the sensitivity of aEEG for seizure detection is only 13%. However, it is 65.5% for a duration between 5 to 10 minutes and 81% for seizures lasting more than 10 minutes. The limited ability to detect seizures using aEEG is because seizure durations are often short, seizure amplitudes are lower, seizure location may not be close to the aEEG leads, and of inadequate training of aEEG readers.

In addition to characterization of paroxysmal events and detection of subclinical seizures in at-risk populations, the EEG itself provides a quantitative measure of cerebral cortical dysfunction (i.e., encephalopathy) to complement the clinical assessment of mental status and may even highlight specific areas of injury (Box 19.1). In sedated and/or paralyzed patients, EEG may provide the only means of examining central nervous system function. In addition, the EEG background and its evolution over time may be predictive of outcome in

BOX 19.1 Neonatal Electroencephalography (EEG) Terms and Significance

The neonatal EEG is characterized by quantitative and qualitative features that evolve from week to week across a continuum of pre- and postnatal development. A given finding may be normal or abnormal depending on the gestational age, and inaccuracies in dates can affect interpretation.

Discontinuity – Higher voltage "bursts" interrupted by periods of lower amplitude, "interburst intervals" (IBIs); discontinuity is a normal feature of neonatal EEG with burst and IBI duration, voltage and synchrony characteristic for different states at different gestational ages; discontinuity is abnormal if in excess of these parameters for age (i.e., "dysmature")

Voltage – The normal EEG background is symmetric, with characteristic amplitude ranges in different states at different gestational ages; voltage may be low diffusely or focally in the setting of cortical injury or artificially reduced by any process that increases the distance between the brain and recording electrodes (e.g., scalp edema, subdural hemorrhage); persistent low voltage without variability or normal features is a severely abnormal background

Variability – Normal changes in the EEG over the recording period; spontaneous variability includes state changes; reactive variability refers to changes provoked by stimulation (auditory, tactile, etc.)

Burst suppression – Severe invariant discontinuous EEG background with long flat IBIs and bursts lacking identifiable graphoelements

Activité moyenne – Continuous low-moderate voltage activity of the waking EEG in term and late preterm neonates

Tracé alternant – Alternating high and moderate amplitude voltage epochs during quiet sleep of term neonates

Tracé discontinu – Normal discontinuous background EEG of premature neonates

Graphoelements – Normal named patterns of the neonatal EEG (e.g., temporal theta, delta brushes, encoches frontales, anterior dysrhythmia); abnormal if deviating from characteristic abundance in different states at a given gestational ages

Sharp waves – Surface negative waves seen in the central and temporal regions with a characteristic abundance and morphology; abnormal if excessive and/or seen in a multifocal distribution, signifying cerebral dysfunction (NB: not specifically indicating a risk for seizures as in older children and adults)

Positive sharp waves – Abnormal surface-positive waves seen at the vertex and in the central regions in association with white matter injury (e.g. grade IV intraventricular hemorrhage)

Brief rhythmic discharges (BRDs) – Abnormal short rhythmic runs <10 seconds without clinical correlate and so too brief to meet criteria for electrographic seizure; entails abnormal irritability and high risk of seizures in the region of occurrence

Electrographic seizure – Abnormal evolving rhythmic run ≥ 10 seconds and ≥ 2 uV in amplitude; occurs without clinical correlate in subclinical seizures and with a clinical correlate in electroclinical seizures

Status epilepticus – Seizure activity cumulatively present for $\geq 50\%$ of a 1-hour epoch of EEG

Adapted from Tsuchida TN, Wusthoff CJ, Shellhaas RA, et al: American clinical neurophysiology society standardized EEG terminology and categorization for the description of continuous EEG monitoring in neonates: report of the American Clinical Neurophysiology Society critical care monitoring committee, *J Clin Neurophysiol* 30(2):161–173, 2013; Mizrahi EM, Hrachovy RA: *Atlas of neonatal electroencephalography,* ed 4, New York Demos, 2016, Medical Publishing.

the setting of acute brain injury. For example, in the setting of HIE, a severely abnormal EEG background (e.g., burst suppression, extreme low voltage) is predictive of adverse neurodevelopmental sequelae (Awal et al, 2016), whereas normalization of the EEG within the first 36 hours is a positive prognostic indicator (Nash et al, 2011). Amplitude-integrated EEG can be a useful screening tool for detecting background abnormalities.

DIAGNOSTIC EVALUATION FOR SUSPECTED OR CONFIRMED NEONATAL SEIZURES

CASE 4

A 2900 g male infant was delivered by cesarean section at 39 weeks' gestation to a 32-year-old primigravida mother after a labor complicated by maternal fever and suspected chorioamnionitis. The mother was negative for group B streptococcal colonization at 36 weeks' gestation. Positive pressure ventilation is needed for 2 minutes after birth. Apgar scores are 4 and 8 at 1 and 5 minutes of life. The cord pH was 7.18 with a base excess of −9. By 10 minutes of life, the infant is well appearing, but at 2 hours of life he exhibits opisthotonic posturing and tonic-clonic movements of the left upper extremity. An aEEG confirms frequent seizures.

Exercise 2

Question

What other diagnostic tests are indicated?

Answer

- Blood culture, white blood count, and differential count
- Lumbar puncture for cells protein and glucose
- Serum chemistries ($Na+$, $K+$, $Cl-$ and HCO_3-) and serum glucose, calcium, and magnesium levels

For any infant in whom a diagnosis of neonatal seizures is being considered, a full sepsis evaluation is strongly recommended (to include cultures of blood, urine [for late-onset sepsis], and CSF) and antibiotics should be administered until the cultures are proven to be negative. Electrolyte and glucose levels should also be measured emergently and corrected if abnormal. A lumbar puncture should also be performed to assess the CSF for bacterial culture, cells, protein, and glucose. If a lumbar puncture is not feasible, then the infant should be

treated presumptively for bacterial meningitis with ampicillin and an antibiotic effective against gram-negative microorganisms that penetrates the CSF well. In the proper clinical circumstances, the infant can also be treated for presumed herpes simplex virus (HSV) encephalitis, and an HSV polymerase chain reaction (PCR) should be sent from the CSF if herpes simplex is suspected. Serum liver and kidney function tests should be assessed, because they can provide hints at the underlying diagnosis and may influence treatment decisions (e.g., one might choose to avoid high-dose phenobarbital if the infant has significant hepatic dysfunction).

If the etiology of the seizures is not immediately obvious, after the laboratory evaluation described earlier is complete, then testing for metabolic disorders is warranted (e.g., lactate, pyruvate, ammonia, plasma amino acids, urine organic acids, and sometimes CSF for neurotransmitters, lactate, and amino acids). Genetic testing (e.g. epilepsy gene panel, chromosomal microarray) should be considered if neonatal-onset epilepsy is suspected.

NEUROIMAGING

In most emergency departments and NICUs, it is fairly easy and quick to obtain a cranial ultrasound at the infant's bedside. Although ultrasound cannot provide detailed brain imaging, it can be used to assess for obvious hemorrhage or hydrocephalus. Generally, computed tomography (CT) of the head is not undertaken in newborns because of concerns about radiation and very limited information provided on the state of the brain parenchyma. Instead, MRI is the preferred neuroimaging test for neonates with seizures. Diffusion-weighted imaging can be particularly informative during the first days after ischemic brain injury, but if the MRI must be deferred, one must avoid imaging during the phase of pseudonormalization. The timing of pseudonormalization will vary, depending on the injury and the use of therapeutic hypothermia, but is typically 6 to 8 days for normothermic and 11 to 12 days for cooled infants. MRI is also essential to delineate the extent of congenital brain malformations.

TREATMENT OF ACUTE SYMPTOMATIC SEIZURES

CASE 5

A 38-week gestational age female, weighing 3000 g, has confirmed bacterial meningitis. Your clinical team monitors her with conventional video-EEG because of her high-risk clinical scenario and concurrent depressed mental status. The EEG confirms the presence of subclinical focal seizures arising from multiple locations.

Exercise 3

Question

What is your first-line agent for infants with definite seizures? What will you prescribe if your first treatment does not control the seizures?

Answer

Phenobarbital is generally the first-line anticonvulsant medication. Often an algorithm such as that outlined in Fig. 19.6 is followed.

Low quality evidence exists to guide the choice of agent in the treatment of acute symptomatic seizures in neonates. Phenobarbital and phenytoin have the best basis as first-line agents, having been used in the two randomized controlled trials enrolling the largest number of neonates. However, the efficacy of these agents was poor, with less than 50% of seizures controlled (Painter et al, 1999; Pathak et al, 2013). Despite this disappointing result, phenobarbital remains the first-line treatment for neonatal seizures. Typically, the infant is given a bolus loading dose of 20 to 30 mg/kg. The treatment response is assessed and additional loading doses may be administered, depending on side effects and efficacy, before a maintenance dose of 4 to 6 mg/kg/day is initiated. Because of risk of significant local toxicity in the setting of phenytoin extravasation, the prodrug fosphenytoin is used instead for intravenous administration. Of the two agents, phenobarbital tends to be preferred because maintaining therapeutic levels of fosphenytoin through the treatment period is challenging, given its rapid metabolism in neonates.

Lidocaine infusion consistently performs well in clinical trials (Boylan et al, 2004; Lundqvist et al, 2013; Weeke et al, 2016) but can have serious cardiac side effects. Adverse events may be relatively uncommon, however, and are primarily associated with unstable potassium levels, concurrent use of phenytoin, or baseline cardiac dysfunction (Weeke et al, 2015). Other antiseizure medications are used as second-line therapies without much evidence and some, such as levetiracetam, are actively being investigated for treatment of seizures in neonates. Midazolam infusion (or another benzodiazepine therapy) is often used as a second- or third-line agent. Doses of antiseizure agents typically used in neonates are listed in Table 19.3.

Acute symptomatic seizures typically start within 24 hours of brain injury and resolve over the subsequent 2 to 4 days, providing a limited temporal window for intervention (Lynch et al, 2012). Often seizure burden is high and status epilepticus is relatively common (Glass et al, 2016). Given concern that seizure burden affects outcomes, that the opportunity for treatment is relatively brief, and that the efficacy of medications used for acute symptomatic seizures is suboptimal, some advocate for an aggressive approach to limit the seizure burden. Conversely, once the storm has passed, EEG monitoring and antiseizure medications can be safely discontinued. Guidelines recommended by American Academy of Clinical Neurophysiology suggest at least a 24-hour long EEG monitoring after the last recorded seizure (Shellhaas et al, 2011). Although the optimal duration of treatment is unknown, it is probably safe to discontinue antiseizure medications as early as 72 hours of seizure freedom, and it is common practice at some centers to stop treatment before discharge (Fitzgerald et al, 2017; Hellström-Westas et al, 1995; Shellhaas et al, 2017a). This is important, given concerns for deleterious effects of antiseizure drugs typically

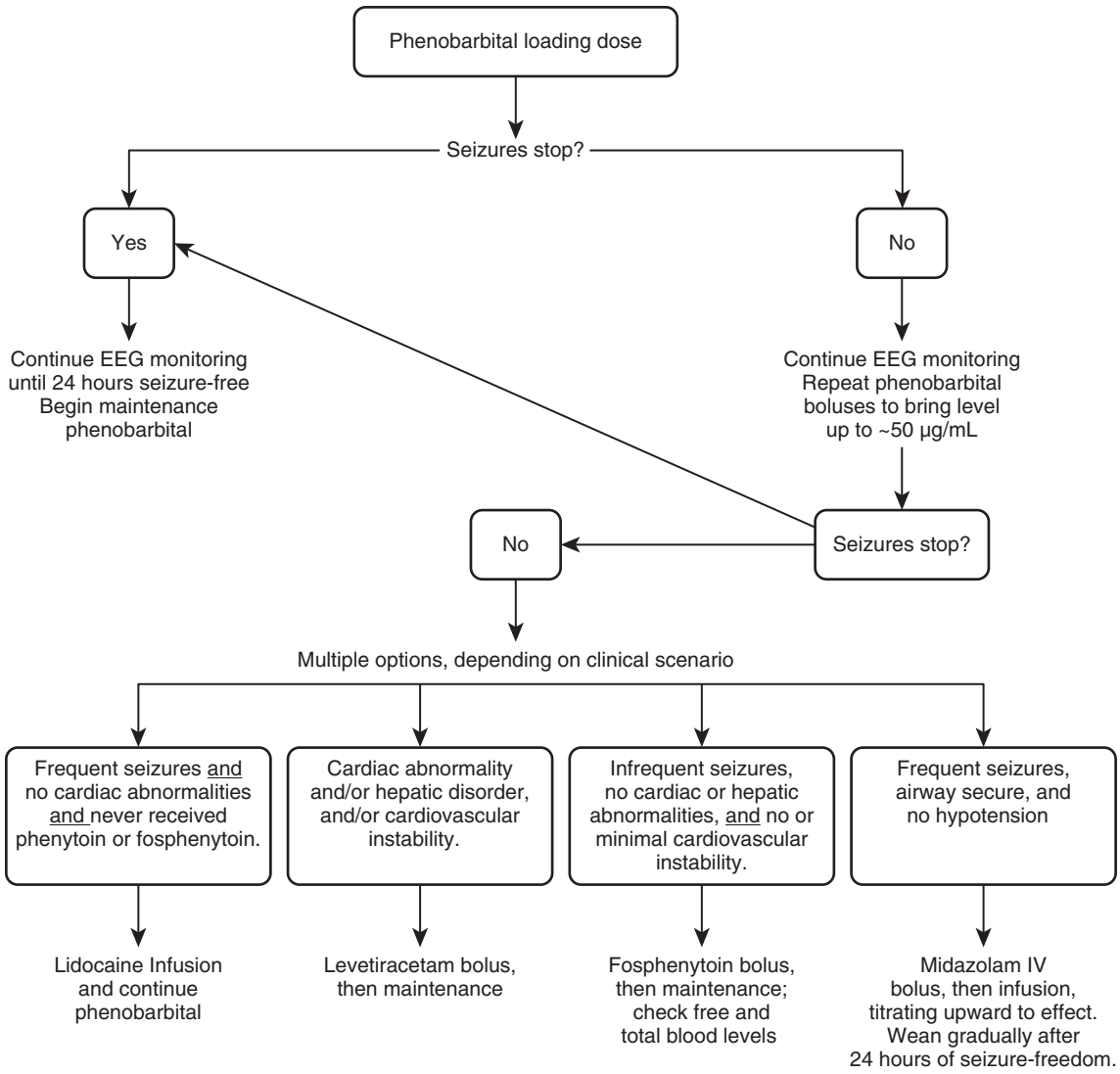


Fig. 19.6 A treatment algorithm for acute symptomatic seizures in neonates. Phenobarbital is typically used as first-line treatment. If there is an delay in obtaining phenobarbital or any of the second- or third-line medications, and the infant is having frequent seizures, a dose of lorazepam (0.1 mg/kg) may be administered in the interim. See Table 19.3 for dosing.

TABLE 19.3 Medications Used for Seizures in Neonates

Medication	Loading Dose	Initial Maintenance Dose
Phenobarbital	20–40 mg/kg IV	3–5 mg/kg/day divided bid for term neonates 5–7 mg/kg/day divided bid for preterm neonates
Fosphenytoin	20–30 mg/kg IV (phenytoin equivalents)	4–8 mg/kg/day divided bid or tid
Levetiracetam	40–60 mg/kg IV	30–60 mg/kg/day divided tid
Midazolam	0.1–0.3 mg/kg IV (max rate 4 mg/min)	0.05 mg/kg, increasing by 0.05 mg/kg q15min to 1 mg/kg/hr
Lidocaine	2 mg/kg IV over 10 min	7 mg/kg/hr for 4 hours, then weaning by 50% q12h
Pyridoxine (B6)	100 mg, may repeat	15–18 mg/kg/day divided bid May supplement with 2.5 mg bid folinic acid
Pyridoxal 5′-phosphate (P5P)	NA	40 mg/kg/day divided qid
Carbamazepine	NA	10 mg/kg/day divided bid

used for neonatal seizures on the developing brain (Bittigau et al, 2002; Ikonomidou, 2009). Of course, early discontinuation of therapy is not appropriate in scenarios in which there is recurrent injury or risk for recurrent injury, and it is important to realize that epilepsy related to prior brain injury can begin within weeks in some cases.

Disappointment with the limited efficacy of first-line agents led to the first attempts at targeted treatment of seizures based on neonatal physiology. On the supposition that seizures in neonates are refractory to standard agents in part due to altered reversal potential for chloride resulting in paradoxical depolarizing effects of GABAergic neurotransmission, bumetanide was investigated as add-on therapy to phenobarbital in a limited study that was terminated early out of concern for abnormal rates of hearing loss in the treated group (Pressler et al, 2015).

DURATION OF ANTICONVULSANT THERAPY

CASE 6

Exercise 4

Question

Once an infant's seizures are well controlled, how long should anticonvulsant medications be continued? What factors should play roles in your decision-making process?

Answer

The duration of treatment depends on several factors: etiology, ease of attaining seizure control and number of anticonvulsant medications required, and overall goals of care.

Most neonatal seizures are acute symptomatic seizures. As such, they often flare for several days and then resolve. Whether the seizures would have stopped spontaneously or were controlled because of medications is often uncertain. Equally uncertain, in many cases, is the appropriate duration of anticonvulsant therapy. Several factors are important in the decision-making process:

- What is the etiology of the seizures?
- How difficult were the seizures to control?
- What are the anticipated risks and benefits for continued treatment?

TREATING NEONATAL SEIZURES IN THE CONTEXT OF THERAPEUTIC HYPOTHERMIA

CASE 7

A 2.8 kg infant is born via emergency cesarean section resulting from placental abruption. The infant's Apgar scores are 1, 2, and 5 at 1, 5, and 10 minutes of life respectively. She has lip-smacking movements concerning for seizures at 30 minutes of life and is moderately lethargic upon arrival in your NICU. You determine that she meets clinical criteria for whole-body hypothermia as a neuroprotective strategy.

Exercise 5

Questions

1. Is therapeutic hypothermia effective for seizure treatment?
2. Are there special considerations required for dosing of anticonvulsant medications during therapeutic hypothermia?

Answers

1. Seizure control remains similar in the neonates treated with hypothermia compared with the ones without hypothermia treatment. However, in neonates undergoing hypothermia treatment, the seizure duration is often shorter and the mean age of electrographic seizure onset spans a longer time range (from 35 hours to 95 hours with the latest seizure onset). Recurrent seizure has also been reported during the rewarming period.
2. Hypothermia does not affect the pharmacokinetics or concentrations of most antiepileptic drugs. Therefore initial dosing of phenobarbital or benzodiazepines do not require adjustment during hypothermia. Hypothermia does affect the clearance of lidocaine and a modification of lidocaine dosing is recommended.

WHEN CONVENTIONAL TREATMENT DOESN'T WORK

CASE 8

A 36-week gestational age infant presented on the first day of life with frequent focal seizures, manifest as apnea with occasional focal clonic limb movements. The interictal EEG is markedly abnormal, with high-amplitude multifocal spikes and no normal patterns. The brain MRI and initial tests of infection and electrolyte disturbances are all normal. Treatment with phenobarbital, fosphenytoin, levetiracetam, and midazolam has not controlled the seizures.

Exercise 6

Question

What is your approach when the usual anticonvulsant medications fail to control the seizures?

Answer

In this case refocusing on identifying the underlying seizure etiology is essential. Once the etiology is known, it will direct your management.

NEONATAL-ONSET EPILEPSY

The management of seizures resulting from neonatal-onset epilepsy is different from the treatment of acute symptomatic seizures. Because the seizures are the result of an ongoing predisposition (e.g. genetic change, brain lesions), treatment selection is guided in part by the particular etiology and will continue beyond the neonatal period. Neonatal-onset epilepsies include inborn errors of metabolism, cerebral malformations,

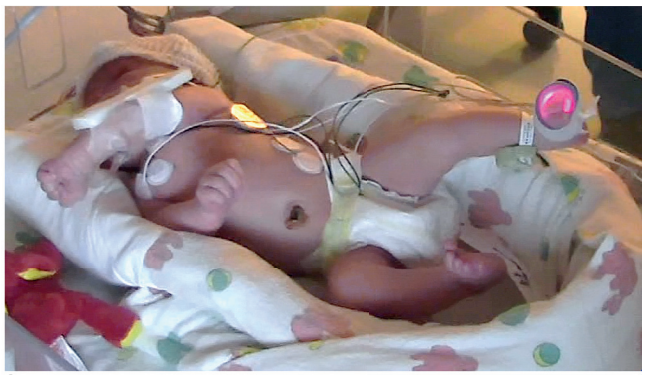
benign neonatal seizures, and epileptic encephalopathies. We highlight some conditions with practical treatment implications, recognizing that there are many genetic causes of epilepsy in newborns (Cornet et al, 2018).

Inborn errors of metabolism represent a very rare cause of neonatal encephalopathy and seizures. Pyridoxine-dependent epilepsy (PDE) is a recessive condition that presents with frequent seizures (clonic, myoclonic, and tonic) and encephalopathy in the first days of life or even in utero. *ALDH7A1* encodes antiquitin, an enzyme critical for lysine catabolism. Alpha aminoadipic semialdehyde, a metabolic intermediate, accumulates and causes the pyridoxine deficiency. It can be detected in the urine. If the condition is considered, 100 mg of pyridoxine is administered empirically (intravenously) and this dose may be repeated in the absence of response. Response may be accompanied by apnea and results in immediate seizure cessation followed by gradual normalization of the EEG. This classic response, however, may be absent in about 15% of cases and importantly does not rule out the diagnosis. Furthermore, a positive response does not confirm the diagnosis (Bok et al, 2010; Cirillo et al, 2015; Mills et al, 2010). Therefore, if the condition is suspected, pyridoxine therapy should be continued until the disorder is ruled out. Folinic acid–responsive seizures are now known to represent the same metabolic disorder (Gallagher et al, 2009). PNPO (pyridoxine 5'-phosphate oxidase) deficiency, even more rare, requires treatment with pyridoxal 5′-phosphate (P5P) (Hoffmann et al, 2007; Mills et al, 2005). As PDE can be treated with P5P as well, some providers treat all suspected pyridoxine-related conditions with P5P until the diagnosis is clarified.

Cerebral malformations that cause epilepsy in the neonatal period may be acquired, due to in utero brain injury, or may be genetic in etiology (e.g., porencephaly, polymicrogyria, lissencephaly, hemimegalencephaly, focal cortical dysplasia, cortical tubers). Somatic mutation occurring during development and affecting a subset of cells is believed to be a major genetic mechanism contributing to the formation of such lesions (Jamuar et al, 2014). In the neonatal period, epilepsy related to malformations may present with a range of phenotypes, from otherwise normal-appearing newborns with subclinical focal seizures to Ohtahara syndrome (encephalopathy with burst suppression and tonic spasms). Although many genes responsible for cortical malformation are part of the MTOR (Mechanistic Target Of Rapamycin) pathway (D'Gama et al, 2015; Mirzaa and Poduri, 2014), there is not yet demonstrated efficacy of MTOR inhibitors in newborns. Many of these children may ultimately benefit from epilepsy surgery to remove or disconnect the damaged or malformed portion of the brain, but the risks of neurosurgical intervention for epilepsy are high in the neonatal period, and surgery is typically deferred for minimum of a 2 months.

Genetic epilepsies may be either inherited or sporadic, resulting from a de novo variant. Benign familial neonatal epilepsy (BFNE) is a dominantly inherited epilepsy with incomplete penetrance caused by variants in *KCNQ2* and *KCNQ3,* which encode heteromers of a voltage-gated potassium channel important in regulating neuronal excitability. Otherwise-well babies develop tonic seizures in the first days of life characterized by asymmetric posturing evolving to unilateral, or asynchronous bilateral, clonic movements. The tonic seizures may be frequent and are accompanied by apnea. The seizures are poorly responsive to phenobarbital but exquisitely responsive to carbamazepine (Fig. 19.7) and perhaps to other sodium channel blockers (Sands et al, 2016).

Whereas inherited alterations in *KCNQ2* are responsible for the majority of BFNE (with *KCNQ3* accounting for a smaller proportion), de novo *KCNQ2* variants cause KCNQ2 encephalopathy, a major cause of neonatal epileptic encephalopathy, accounting for up to one-third of cases (Shellhaas et al, 2017b). The phenotype is characterized by profound neonatal encephalopathy with severe, frequent, intractable seizures that resemble the convulsions of BFNE (Numis et al, 2014; Weckhuysen et al, 2012, 2013). Whereas mutations that lead to BFNE result in mild reductions in potassium current, the de novo variants that cause KCNQ2 encephalopathy cause more profound channel dysfunction, such as through a dominant negative effect. As with BFNE, the seizures in KCNQ2 encephalopathy respond to sodium channel blockers



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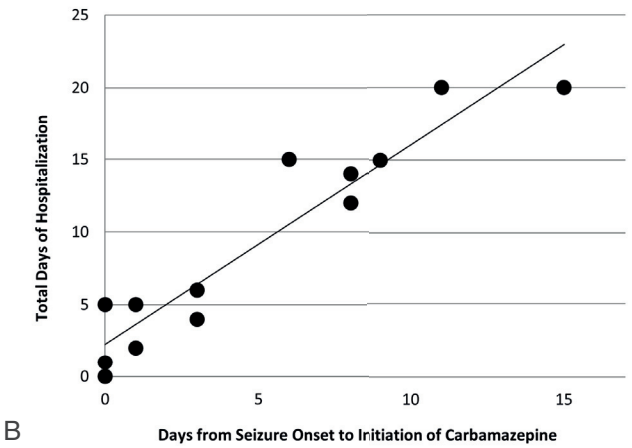

B

Fig. 19.7 Benign familial neonatal epilepsy. Clinically, seizures consist of asymmetric tonic posturing accompanied by apnea (a), followed by asynchronous clonic jerking. Recognition and appropriate treatment with carbamazepine or oxcarbazepine can help limit the hospitalization of these otherwise well newborns.

(Pisano et al, 2015). Few other neonatal-onset epilepsies have been shown to respond to particular treatments, but epilepsies associated with sodium channel genes, *SCN2A* and *SCN8A,* that present in the neonatal period may also respond particularly well to sodium channel blockers. Empiric trial of a sodium channel-blocking agent such as carbamazepine is therefore reasonable when there is clinical suspicion for a genetic epilepsy.

CASE 9

Baby girl BG is born at 38 weeks without prenatal concerns or postnatal complications. On the second day of life, she is observed by her mother to stiffen and turn to the side with one arm raised and shaking. The event repeats itself twice later in the day. In between episodes, the baby appears normal and well. The fourth event is observed by a nurse, who becomes concerned about seizures. The child is given a load of 20 mg/kg of phenobarbital and transferred to the intensive care nursery. A video EEG is placed.

Exercise 6

Questions

1. What is the differential diagnosis for the events of concern?
2. What is the utility of video-EEG monitoring in this setting?
3. What should the workup include if seizures are confirmed, and what etiologies are most likely in this case?

Answers

1. Paroxysmal movements in neonates may represent electroclinical seizures or may represent other normal or abnormal phenomena. Apart from seizures, report of tonic stiffening in a newborn could represent anything from straining associated with stooling to opisthotonos associated with meningitis. Less common causes include cramped-synchronized general movement sequences in a baby with prior brain injury and paroxysmal extreme pain disorder, a peripheral nervous system channelopathy presenting in the newborn period that results in bouts of pain with stiffening and apnea. The possibility of seizures should be investigated with video-EEG monitoring.
2. Video-EEG should be continued until the events of concern are recorded with sufficient clarity to determine whether they are seizures. Even if they are not seizures, the video component provides a way for the events to be repeatedly inspected for their characteristics and associations. In addition, the EEG provides information on brain functioning. Each of these aspects may assist in the diagnosis of conditions other than seizures resulting in paroxysmal episodes in newborns.
3. If seizures are confirmed, evaluations for acute brain injury are warranted. In addition to HIE and stroke as the most common causes, infection and metabolic derangement should be investigated thoroughly, as they represent potentially reversible conditions. Because the baby in this case is otherwise very well appearing, it makes missed HIE very unlikely. High on the differential in this case for causes of seizures include stroke and benign neonatal seizures. Family history is an important part of the workup.

CASE 9 (CONTINUED)

While monitored on EEG in the intensive care nursery, the baby continues to be well appearing and the neurologic examination is normal. The child has another episode recorded on video-EEG (Video 19.1). The video reveals asymmetric tonic posturing led from the left followed by asynchronous clonic jerking. The EEG shows diffuse attenuation at the onset, followed by rhythmic spike and wave over the centrotemporal regions. Before the seizure, the EEG background is noted to have an excess of sharp transients in the central and temporal regions but is otherwise normal. The child is given another 20 mg/kg IV load of phenobarbital. The blood level of phenobarbital is 42 μg/mL.

After the seizure and medication, the child has poor visual attention and impaired reactivity on examination, and the EEG shows mild excessive discontinuity for age. Laboratory studies on serum, urine, and CSF reveal no abnormal findings and raise no concern for infection. A head ultrasound is negative, and an MRI is ordered. The neurologist reading the EEG reported that the seizure type is typical for a genetic epilepsy. A family history of seizures in infancy is denied by mother and father. A "rapid" epilepsy gene panel including genes associated with neonatal epilepsies is ordered with a turnaround time of 2 weeks. The child has another electroclinical seizure, this time involving the right arm first, a mirror image of the first recorded seizure. Seizures become frequent, occurring every 15 minutes.

Exercise 7

Questions

1. What are the diagnostic considerations at this point?
2. Are there implications for management?

Answers

1. Genetic epilepsy is at the top of the differential diagnosis at this point, given tonic seizures and the negative workup for other acute causes. Stroke remains a possibility, as the head ultrasound is not sufficiently sensitive to rule it out and the MRI is still pending. However, unless bilateral, strokes cause unilateral seizures that may manifest clinically as clonic movements contralateral to the stroke. The fact that this child has dramatic electroclinical seizures that shift laterality supports the presence of a genetic epilepsy. Given how relatively normal the baby and EEG background were before medications, the presentation is suggestive of benign neonatal seizures. An apparently negative family history does not rule it out because 1) there is incomplete penetrance and so there may be no affected first degree relations, 2) a parent may be unaware that they had seizures as a neonate, and 3) owing to stigma and the fact that the epilepsy resolves after the first months

of life, families may not openly discuss a history of seizures. An epileptic encephalopathy is still possible, as some presentations may be milder at the outset and so prognosis in this case should be guarded.

2. Genetic epilepsies associated with tonic seizures as in this case include a few common etiologies that have been shown to respond to sodium channel blockers. Test results will not confirm the genotype for 2 weeks, and an empiric trial of carbamazepine is reasonable. Carbamazepine is an oral medication, but the response is rapid. Fosphenytoin is another sodium channel blocker that may be effective and could be used initially with subsequent transition to carbamazepine maintenance. Oxcarbazepine may also be effective but is less studied in this scenario.

CASE 9 (CONTINUED)

Carbamazepine is started at 10 mg/kg/day divided in two doses. After the first dose, there is one final seizure, then cessation. As the phenobarbital wears off, the child regains a normal examination and the EEG improves. The maternal grandmother comes to visit and reports that the child's maternal aunt had seizures in the newborn period. Two weeks later a pathogenic stop-gain variant in KCNQ2 is reported, and further testing confirms maternal inheritance.

NEURODEVELOPMENTAL PROGNOSIS AFTER NEONATAL SEIZURES

Exercise 8

Question

You are about to have a family meeting with the parents of a newborn infant with acute symptomatic seizures. They want to know their baby's prognosis. What are you going to tell them?

Answer

The risk of death or significant neurodevelopmental disability can be difficult to estimate, but it is the parents' most important concern. Although one can never be absolutely sure about the prognosis of any particular neonate, there are some data that can help with the discussion. Discussions of predicted outcome must be informed by the infant's gestational and postmenstrual ages, the etiology of the seizures, how easily the seizures are controlled with medications, and EEG and neuroimaging data. The risk for adverse outcomes is quite high and depends on the underlying cause.

Historically, there has been some debate regarding the clinical importance of neonatal seizures. In animal models, there is evidence that neonatal seizures accentuate underlying brain injury with long-term adverse consequences. Although outcome is primarily dictated by etiology, treatment of acute symptomatic seizures is predicated on the concern that seizures result in additional damage to the developing brain (Srinivasakumar et al, 2015). Acute symptomatic seizures are known to be associated with poor neurodevelopmental outcomes and future epilepsy at a rate of approximately 20% (Pisani and Spagnoli, 2016).

The EEG background activity provides important information to predict the clinical outcome in neonates diagnosed with seizures. In general, the presence of normal or mildly abnormal EEG background is associated with favorable outcomes. In contrast, EEG backgrounds with a low voltage or burst suppressed pattern portend adverse outcomes. However, if neonates with HIE show recovery of the EEG background within 24 to 36 hours, they may avoid adverse outcomes. Therefore serial monitoring of the EEG background over time improves prognostic accuracy.

CONCLUSION

Seizures in neonates are relatively common, but they are difficult to diagnose. Clinical observation lacks sensitivity and specificity, and EEG confirmation is recommended. Conventional video-EEG monitoring remains the gold standard for seizure diagnosis in neonates but can be complemented by amplitude-integrated EEG in certain circumstances. A concerted effort to search for and treat the underlying cause of the seizures is mandatory. The first-line treatment for acute symptomatic seizures is usually phenobarbital, with second- and third-line treatments selected based on the clinical scenario. Neonatal-onset epilepsies are less common but important to recognize given prognostic and therapeutic implications. Collaborative partnership with neonatal neurologists can add value to care of newborns with neurologic conditions in the intensive care unit. The underlying etiology and response to treatment are crucial predictors of long-term neurodevelopmental outcome.

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Video 19.1 Benign Neonatal Seizure

20

Intraventricular Hemorrhage

Shahab Noori

Intraventricular hemorrhage (IVH) is a major complication of prematurity. Despite the term referring to hemorrhage within the ventricle, it encompasses hemorrhage confined to the germinal matrix (grade I), extension to lateral ventricles without (grade II) or with (grade III) ventricular dilatation, and periventricular parenchymal hemorrhage (grade IV). Although periventricular hemorrhage (grade IV) may be considered as a separate entity (Inder et al, 2017), for the purpose of this chapter, the original definition of IVH is used for all the four grades (Papile et al, 1978). IVH affects approximately one-third of extremely preterm infants (<28 weeks' gestation) (Stoll et al, 2010) and is a major risk factor for cerebral palsy, neurodevelopmental impairment, hydrocephalus, and mortality among these patients (Adams-Chapman et al, 2018; Mukerji et al, 2015).

Although IVH also occurs in term infants, preterm infants are particularly vulnerable due to structural and functional immaturity of the brain. In preterm infants, the site of hemorrhage is the germinal matrix (Figs. 20.1 through 20.3). This is the site of active proliferation of future neuronal and glial cells and as such is a highly vascularized and metabolically active tissue (Bassan, 2009). Several characteristics of this vascular bed predispose it to hemorrhage. The capillary network consists of thin-walled, poorly supported fragile vessels (Ballabh, 2010). It lies within an arterial end zone, which makes it particularly vulnerable to hypoperfusion–reperfusion injury (du Plessis, 2008). The confluence of medullary, choroidal, and thalamostriate veins forms the terminal vein, which makes a U-turn going through the germinal matrix as it drains into internal cerebral vein, making it prone to congestion in case of large germinal matrix hemorrhage (Bassan, 2009; Hambleton and Wigglesworth, 1976). This venous congestion increases the risk of periventricular hemorrhagic infarction (grade IV, Figs. 20.4 and 20.5). Until its involution between 28 and 36 weeks' gestation, the germinal matrix remains vulnerable to hemorrhage (Bassan, 2009; Hambleton and Wigglesworth, 1976).

In addition to structural immaturity, the brain of preterm infants is also functionally immature. Cerebral blood flow (CBF) autoregulation, the ability to maintain CBF relatively constant despite fluctuations in blood pressure, is less robust in preterm infants and the autoregulatory plateau is quite narrow (Soul et al, 2007; Vesoulis et al, 2016; Wong et al, 2008). Therefore the brain of extremely preterm infants is prone to hypo- and hyperperfusion. Indeed, impairment of CBF autoregulation has been implicated in development of IVH among preterm infants (O'Leary et al, 2009; Vesoulis et al, 2016). Another functional immaturity of the brain that has recently been proposed is that the forebrain (including cortex, thalamus, and basal ganglia) does not have high-priority vascular bed in extremely preterm infants (Noori et al, 2009). Therefore unlike the hindbrain, which vasodilates in case of hypoxia or low perfusion pressure, the forebrain of these patients may vasoconstrict. This immaturity of the forebrain vasculature can predispose the germinal matrix to hypoperfusion–reperfusion injury, which often precedes IVH.

Although vulnerability of immature brain is the key factor, pathogenesis of IVH is multifactorial and involves immaturity and/or maladaptation during the transitional period of other organs such as the heart and lungs. In addition, interventions aimed at supporting preterm infants surviving extrauterine life can increase the risk of IVH (see later). Further discussion of etiology, risk factors, pathophysiology, and clinical outcome of IVH is done through a case of twins born at 26 weeks' gestation.

CASE

A set of Caucasian male twins was born at 26 weeks' gestation via cesarean section due to breech presentation and premature labor. The mother was a healthy 30-year-old female with uncomplicated pregnancy. She received a course of betamethasone 2 days before delivery. There was no premature rupture of membrane, and no delayed cord clamping or cord milking was performed. The Apgar scores were 7 at 1 minute and 8 at 5 minutes for both twins. The newborns received continuous positive airway pressure (CPAP) for increased work of breathing and then were intubated in the delivery room for persistent respiratory distress. They both received a dose of surfactant and were put on conventional mechanical ventilation.

Exercise

Questions

1. What is the incidence of IVH in preterm infants born at 26 weeks' gestation?

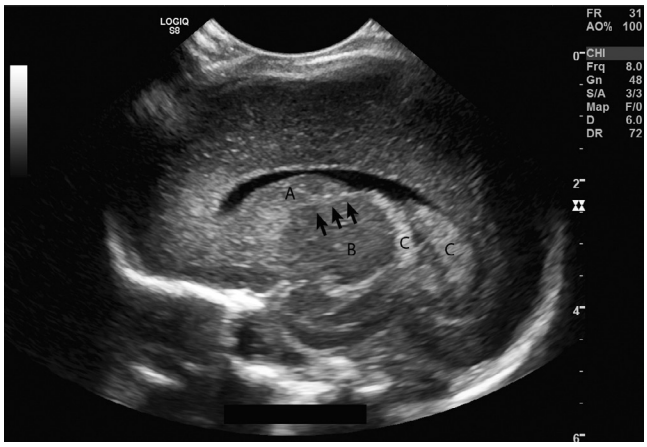


Fig. 20.1 A head ultrasound image of a 2-day old preterm infant born at 25 weeks' gestation. This is a left lateral sagittal view of the brain showing the caudate nucleus (A), thalamus (B), and choroid plexus (C). The arrows point to the caudothalamic groove. The absence of increased echogenicity anterior to the caudothalamic groove indicates absence of germinal matrix hemorrhage.

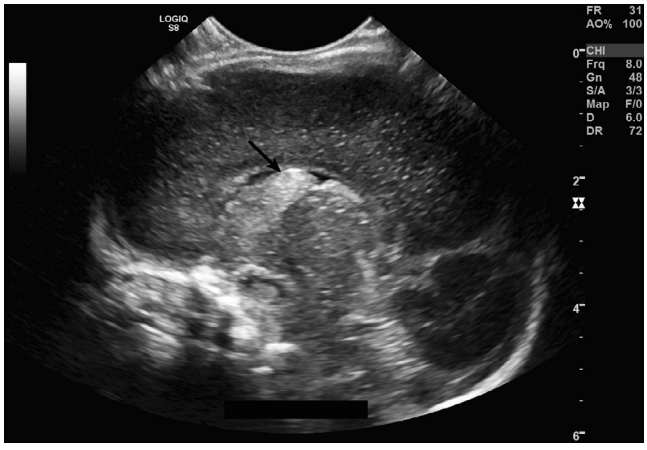


Fig. 20.2 A head ultrasound image of a 2-day-old preterm infant born at 25 weeks' gestation (same as in Fig. 1). This is a right lateral sagittal view of the brain. The arrow points to an increased echogenicity anterior to the caudothalamic groove consistent with grade I IVH.

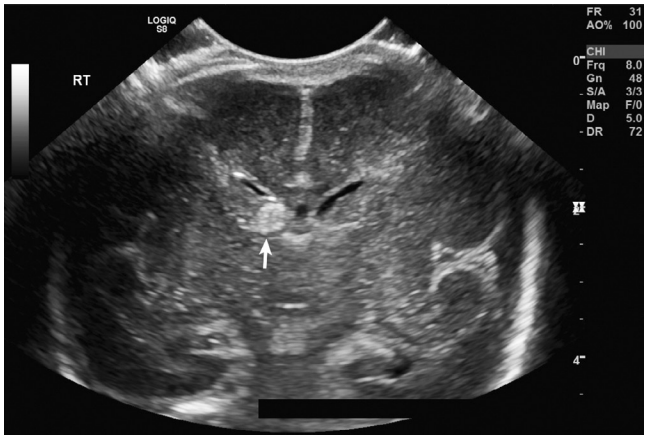


Fig. 20.3 A head ultrasound image of a 2-day-old preterm infant born at 25 weeks' gestation (same as in Fig. 1). The arrow points to right grade I IVH.

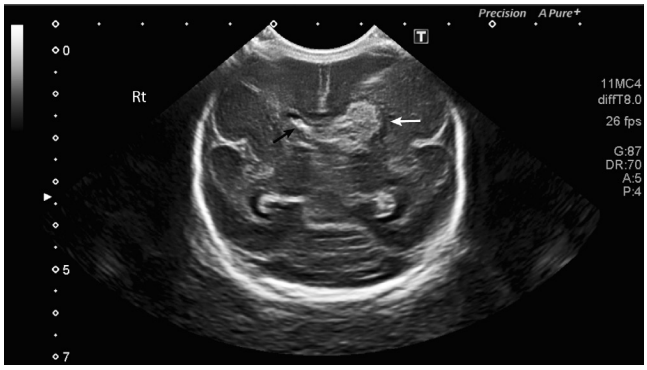


Fig. 20.4 A head ultrasound image of a 1-day-old preterm infant born at 25 weeks' gestation. This is a coronal view of the brain. The black arrow shows a right subependymal hemorrhage with possible extension hemorrhage into ventricular space without ventriculomegaly (likely grade II IVH). The white arrow points to germinal matrix hemorrhage with extension to left ventricle and possible periventricular involvement (likely grade IV).

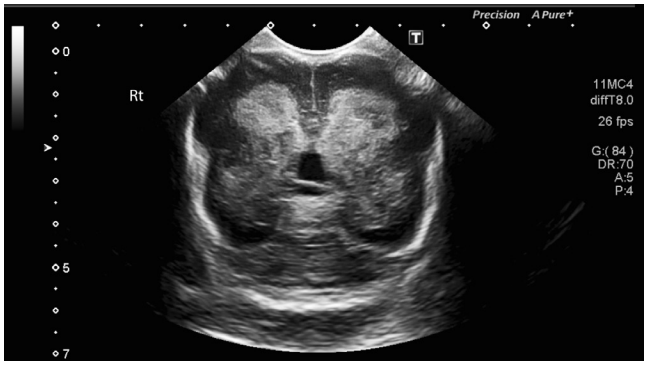


Fig. 20.5 A head ultrasound image of a 1-day-old preterm infant born at 25 weeks' gestation (same as in Fig. 4). This is a follow up coronal view on the 6th postnatal day. The bilateral periventricular echogenicity is consistent with hemorrhagic infarction (grade IV).

2. In the case presentation, what factors increase the risk of developing IVH?
3. In the case presentation, what factors are protective against developing IVH?

Answers

1. What is the incidence of IVH in preterm infants born at 26 weeks' gestation?

Approximately one-quarter and one-third of very low birth weight (VLBW, <1500 g) and extremely low birth weight (ELBW, <1000 g) infants develop IVH, respectively. Despite continued progress in neonatal medicine and increased survival of the ELBW infants, the incidence of IVH has not changed in the last decade. In the National Institute of Child Health and Human Development (NICHD) network, the incidence of IVH among infants born at 26 weeks was 33% (Stoll et al, 2010). The incidence is much higher at the threshold of viability (Table 20.1). The overall incidence of

TABLE 20.1 Incidence of All Grades IVH Among Preterm Infants ≤28 Weeks' Gestation Who Survived >12 Hours

Gestational Age (Week)	Incidence
22	64%
23	56%
24	48%
25	40%
26	33%
27	28%
28	22%
All	34%

From Stoll BJ et al: Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network, *Pediatrics* 126:443–456, 2010.

severe IVH (grade III and IV) among infants 28 weeks or shorter gestation is 16%, and this rate has not changed over the last decade (Stoll et al, 2010; Adams-Chapman et al, 2018).

2. In the case presentation, what factors may increase the risk of developing IVH?

The factors that increase the risk of IVH are extreme prematurity, male gender, and respiratory distress syndrome with the need for mechanical ventilation. Another factor that has recently been shown to increase the risk of IVH is absence of placental transfusion. Delayed or physiologic clamping of the umbilical cord facilitates transition from the fetal to postnatal life. Several studies have reported lower rates of IVH with delayed cord clamping, prompting the current recommendation of delaying clamping of the umbilical cord for at least 30 to 60 seconds in vigorous preterm infants (Baenziger et al, 2007; Committee Opinion No. 684, 2017; Ghavam et al, 2014; Rabe et al, 2008; Sommers et al, 2012). Despite this recommendation, little is known about the underlying protective mechanisms. The more gradual rather than abrupt increase in systemic vascular resistance may reduce left ventricular dysfunction seen in a subset of preterm infants who later develop IVH. Animal studies indicate an increase in pulmonary blood flow if the animal is breathing and still attached to the placental circulation (Bhatt et al, 2013). This increase in pulmonary blood flow in turn augments the left ventricular output and systemic blood flow. Therefore the protective effect may at least in part be related to mitigation of cerebral hypoperfusion, which is prevalent in preterm infants at greatest risk of IVH.

Indeed, most but not all human studies have shown higher indices of CBF in preterm infants who received delayed cord clamping (Baenziger et al, 2007; Popat et al, 2016; Sommers, 2012). The observation of similar hemodynamic benefits and reduction in IVH with cord milking (Hosono et al, 2009; Katheria et al, 2015; Takami et al, 2012) suggests that placental transfusion (higher circulating volume) may play a more significant role than other potential mechanisms (Noori and Seri, 2015). Although both delayed cord clamping and cord milking appear to be beneficial, questions remain regarding the most effective ways to conduct the two procedures. Indeed, the finding of a recent large randomized control trial (RCT) of no reduction of the combined outcome of death or major morbidity (including severe IVH) with delayed compared with immediate cord clamping highlights this point (Tarnow-Mordi et al, 2017).

3. In the case presentated, what factors are protective against developing IVH?

Several factors in the presented case decrease the risk of IVH. The twins received a full course of antenatal steroid, an intervention that has consistently been shown to be effective in reducing the incidence of IVH. Cesarean section may have provided some protective effect as well. Indeed, vaginal delivery and prolonged labor have been associated with an increased risk of IVH (Leviton et al, 1991; Shankaran et al, 1996), presumably due to increased cerebral venous pressure (Inder et al, 2017). However, this association is not a consistent finding, especially in more recent studies (Bhatta, 2011; Riskin et al, 2008). The twins had good Apgar scores, which indicate that they were born in a favorable physiologic state. Low Apgar score and need for delivery room resuscitation increase the risk of IVH (Riskin et al, 2008). Babies with low Apgar score in general—and those requiring chest compressions in particular—are at high risk for myocardial dysfunction, hypotension, poor cardiac output, impaired CBF autoregulation, pulmonary hypertension, and hypoxia, all of which contribute to pathogenesis of IVH.

CASE

Twin A was weaned to CPAP at 24 hours after birth. On the other hand, Twin B was switched to high-frequency oscillation at 44 hours due to significant carbon dioxide (CO_2) retention. Both twins were considered to be hemodynamically stable and did not receive vasopressors/inotropes. However, Twin B had mean blood pressure under 26 mm Hg (23–25 mm Hg) for several hours during the first day of life. The capillary refill time and urine output were normal. Neither of the twins had hypernatremia or hyperglycemia during the first week of life. Similarly, no thrombocytopenia or coagulopathy was noted. Twin A had a 3.5 mm patent ductus arteriosus (PDA) with a left-to-right shunt at age 18 hours, which was unchanged at 41 hours and therefore he was started on an indomethacin. Twin B had a 3.5 mm PDA with right-to-left shunt at age 18 hours. The PDA size was unchanged, but the shunt became left to right by 41 hours after birth. The PDA was not treated at that time and constricted to 1.8 mm at 76 hours after birth. However, the PDA became larger and was associated with hemodynamic instability several days later and was closed with indomethacin. Twin B was noted to have a unilateral grade I IVH on the head ultrasound at 41 hours of age, which extended to an ipsilateral grade IV hemorrhage by 51 hours after birth. Twin A did not develop IVH. The twins were being closely monitored as part of an observational study. Fig. 20.6 shows cerebral regional oxygen saturation ($CrSO_2$) as measured by near-infrared spectroscopy (NIRS) and the calculated cerebral fractional

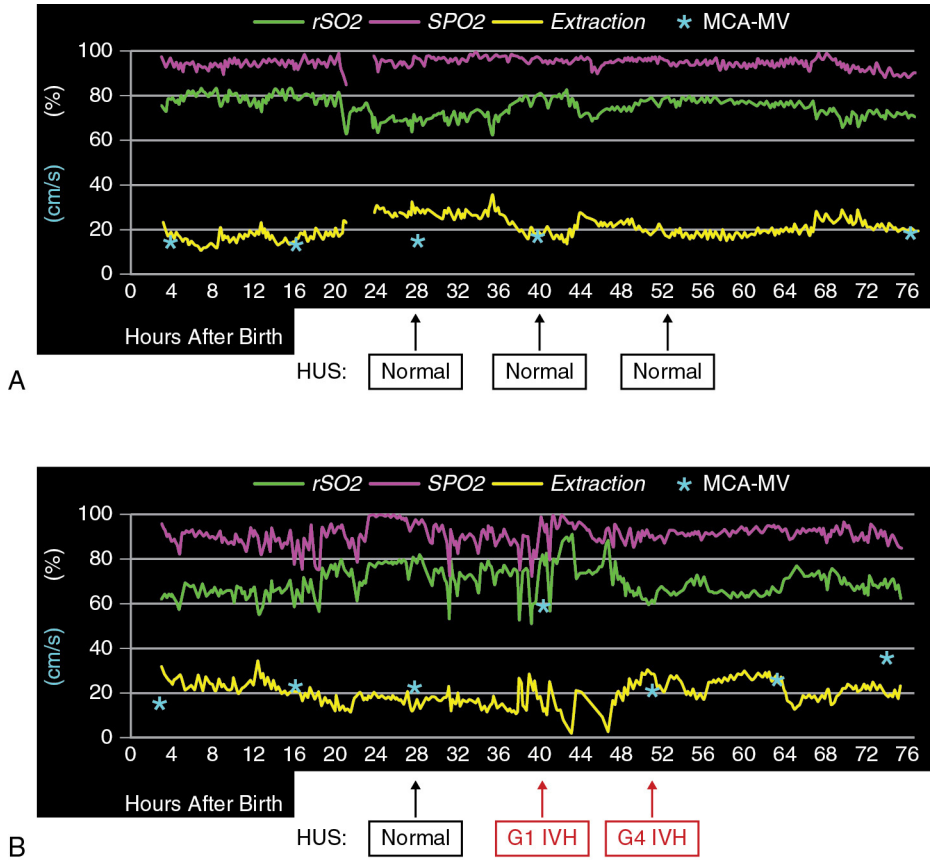


Fig. 20.6 Changes in cerebral regional oxygen saturation (rSO_2, *green*), arterial oxygen saturation (SPO_2, *pink*), cerebral fractional oxygen extraction (extraction, *yellow*), and middle cerebral artery mean velocity (MCA-MV, *blue asterisks*) in Twin A (A) and Twin B (B) during first 76 hours after birth. See text for details. *HUS*, Head ultrasound.

oxygen extraction (CFOE) in relation to head ultrasound findings in the twins during the transitional period.

Exercise

Questions

1. What does Fig. 20.6 tell us about the physiologic events leading to IVH?
2. Does hypotension increase the risk of IVH?
3. Did the PDA contribute to development of IVH in Twin B?
4. Did switching to high-frequency ventilation or the high CO_2 lead to IVH?
5. What are the chances of Twin B developing hydrocephalus?

Answers

1. What does Fig. 20.6 tell us about the events leading to IVH?

Fig. 20.6 displays the changes in surrogates of CBF during the first 3 days after birth, a period where more than 90% of IVH are detected in preterm infants. With advances in technology, NIRS has become available for clinical applications and has increasingly been used both in clinical settings and research in the neonatal intensive care units. Using light in the infrared spectrum, tissue at a depth of approximately 2 cm is interrogated. As oxyhemoglobin and deoxyhemoglobin absorb light at different wavelengths; relative concentration can be calculated and displayed as percent oxygen saturation by the NIRS device. Because most of blood in tissue is in the venous system (70%–75%), the measured oxygen saturation primarily reflects the venous saturation. Measuring arterial oxygen saturation (SPO_2) by pulse oximetry allows for calculation of CFOE as ($SPO_2 - CrSO_2$) / SPO_2. If oxygen delivery decreases, the tissue will extract more oxygen as a compensatory mechanism. In other words, an increase or decrease in CBF will result in a reduction or increase in CFOE, respectively. This inverse relationship has been used as an index to assess changes in CBF. However, this proposition is only valid when other determinants of oxygen delivery (hemoglobin, SPO_2, partial pressure of oxygen in arterial blood) and consumption (metabolism) remain stable and the ratio of venous to capillary and arterial blood in tissue is unchanged.

The other surrogate of CBF displayed in the figure is the middle cerebral artery mean flow velocity (MCA-MV). To determine blood flow through a vessel, flow velocity and vessel diameter are needed. Given the inaccuracy in measuring small vessel diameter, MCA flow measurement is impractical. However, in the absence of a significant change in vessel diameter, changes in MCA-MV can be used as a surrogate for changes in CBF. Finally, both CFOE and MCA-MV are more useful indices of changes in rather than absolute value of regional CBF. Fig. 20.6 shows that the patterns of changes in CFOE and MCA-MV are different in the twins. Twin B starts with a higher CFOE and has more variability and larger

swings in CFOE than Twin A. The high initial CFOE suggests that CBF was low after birth and the decrease in CFOE afterward indicates an improvement in CBF. Following the improvement in CBF, a grade I IVH was detected by head ultrasound (HUS) at 36 hours after birth. There was a further drop in CFOE and an increase in MCA-MV, suggestive of a further increase in CBF after which a grade IV IVH was seen on HUS at 44 hours.

Assessment of CBF surrogates using different technologies has shown that preterm infants with low CBF shortly after birth have higher risk of developing IVH (Kluckow and Evans, 2000; Meek et al, 1999). Using intermittent measurement of $CrSO_2$ and calculating CFOE with NIRS, some have reported the low CBF to persist in this population for over a week (Verhagen, 2010). In contrast, others using the same technology in the first few days after birth have described higher CBF (lower CFOE) during the 24-hour period preceding detection of IVH (Alderliesten et al, 2013). The inconsistency between these two nested studies may be related to the duration and timing of monitoring (Noori and Seri, 2015). When cerebral oxygenation was continuously and prospectively monitored and timing of IVH occurrence was assessed by frequent HUS in preterm infants <28 weeks' gestation, evidence emerged for a two-phase injury (i.e., ischemia–reperfusion) preceding development of IVH (Noori, 2014). Patients who later developed IVH had a period of hypoperfusion/ischemia in the first postnatal day as evidenced by low $CrSO_2$ and high CFOE (Fig. 20.7). This period was followed by an increase in $CrSO_2$ and

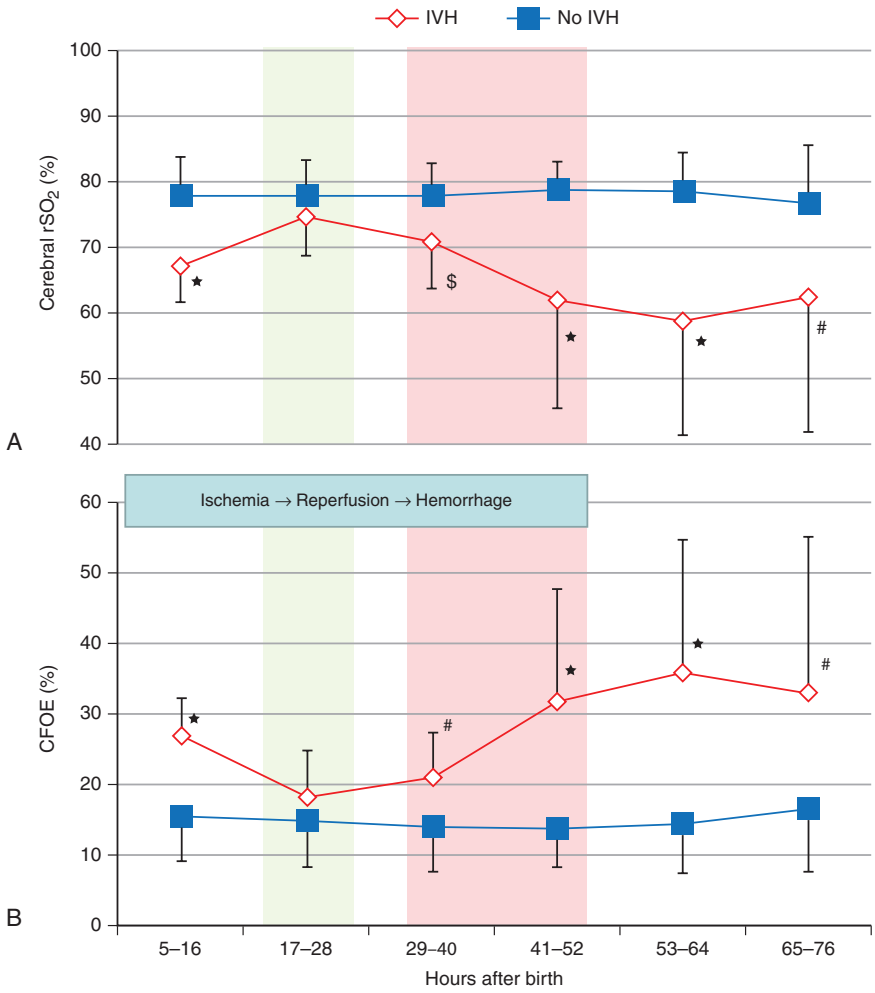


Fig. 20.7 Changes in cerebral regional oxygen saturation (rSO_2) and cerebral fractional oxygen extraction (CFOE) in two groups of very preterm neonates presenting with *(black)* and without *(blue)* intraventricular hemorrhage (IVH) during the first 3 postnatal days. The no-IVH group exhibited stable cerebral rSO_2 (a) and CFOE (b) values, whereas the IVH group presented with a characteristic pattern of changes. The IVH group had lower cerebral rSO_2 and higher CFOE during the first 12 hours of the study, followed by normalization of these parameters (highlighted in gray) just before the two study periods when IVH was detected (highlighted in blue). These findings suggest that initial cerebral hypoperfusion is followed by a period of reperfusion before the occurrence of the IVH. After the second study period, cerebral rSO_2 decreased and CFOE increased, suggesting a decrease in CBF during and after the development of IVH. Statistically significant differences between the two groups: * $p<0.005$, # $p<0.04$, and \$ $p<0.05$. The values represent the mean ±SD of the data obtained in each 12-hour data collection period. (From Noori S, McCoy M, Anderson MP, et al: Changes in cardiac function and cerebral blood flow in relation to peri/intraventricular hemorrhage in extremely preterm infants, *J Pediatr* 164:264–270.e1–e3, 2014.)

decrease in CFOE suggestive of normalization of CBF (i.e., reperfusion) by the end of first day and during second postnatal day after which IVH was detected (Noori, 2014). Therefore from a cerebral hemodynamic standpoint, there are two distinct phases in pathogenesis of IVH: an early postnatal hypoperfusion followed by a later reperfusion phase on the second postnatal day. As discussed earlier, perinatal factors and certain events during transitional period can accentuate hypoperfusion and reperfusion phases (also see below).

2. Does hypotension increase the risk of IVH?

Hypotension has long been recognized as a risk factor for IVH (Pellicer et al, 2009; Watkins et al, 1989). Hypotension can predispose to IVH by decreasing CBF and therefore contributing to the ischemic phase of the pathogenesis of IVH (see earlier). However, it is unclear what constitutes hypotension in extremely preterm infants, especially during the transitional period. Mean blood pressure less than the gestational age in weeks is the most widely used definition of hypotension (Stranak, 2014). However, this arbitrary cutoff definition does not take into account the CBF autoregulatory, functional, and ischemic thresholds (Noori et al, 2018). In addition, the impact of other coexisting factors is not incorporated in this definition. This is important, as factors such as hypoxia (Low et al, 1993), metabolic acidosis (Goldstein et al, 1995), and hypercarbia (via attenuation of CBF autoregulation) (Kaiser et al, 2005; Noori, 2014) can increase the risk of brain injury when they are concomitantly present with hypotension.

The decision on how to manage hypotension poses another dilemma. Although vasopressors/inotropes, if titrated, can improve CBF in hypotensive preterm infants (Pellicer, 2005), they have the potential to accentuate the reperfusion phase. As the hypotensive preterm infants have pressure-passive CBF, inadequate titration of the medication leading to a significant increase in blood pressure will result in hyperperfusion (Munro et al, 2004). Therefore hypotensive preterm infants who likely have low CBF if treated with inappropriately high doses of a vasopressor/inotrope would be at a very high risk for IVH as both phases of ischemia-reperfusion are accentuated. Although the threshold may be different, hypotension is almost always treated. This poses a major challenge in quantifying the contribution of hypotension itself, the treatment employed, and the underlying cause of hypotension to the observed increased risk of hypotensive preterm infants developing IVH. Recently the French national prospective population-based cohort study of preterm infants under 29 weeks found that the treatment of isolated hypotension (defined as mean blood pressure less than gestational age in weeks and without other clinical signs of inadequacy of cardiovascular function) during the transitional period was associated with higher odds of survival without major morbidity including IVH (Durrmeyer et al, 2017). The finding of an even stronger association with lower blood pressure (i.e., hypotension defined as mean blood pressure less than gestational age in week minus 5) increases the possibility of causality.

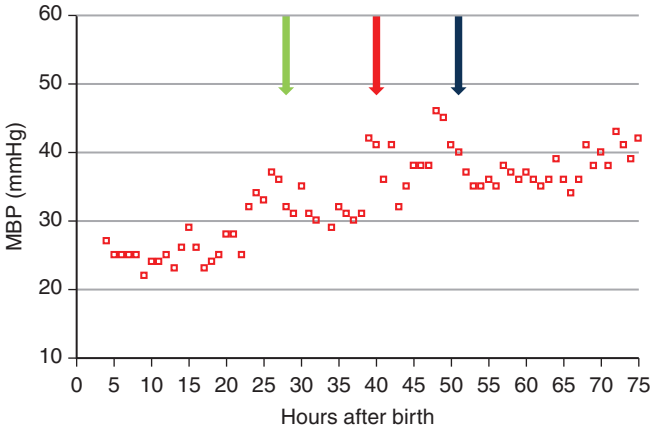


Fig. 20.8 Changes in mean blood pressure (MBP) in Twin B during the first 3 days after birth. MBP was below gestational age in weeks (26) for a few hours in the first postnatal day. Green, red, and purple arrows represent the timing of head ultrasound showing no IVH, grade I, and grade IV IVH, respectively. See text for details.

In the case presented, Twin B did have hypotension for several hours in the first postnatal day (Fig. 20.8), which coincided with higher CFOE. Therefore it is possible that the low blood pressure contributed to cerebral hypoperfusion phase. Twin B was not treated with vasopressor/inotrope, as the clinician felt there was no evidence of inadequate cardiovascular function. Although presence of clinical and/or laboratory evidence of circulatory compromise would certainly increase the risk associated with hypotension (Batton et al, 2007; Dempsey et al, 2009), duration of hypotension also appears to be important, at least as a predictor of the long-term outcome (Goldstein et al, 1995; Hunt et al, 2004).

Finally, although there is evidence for hypotension increasing the risk of IVH and some evidence that appropriate and timely treatment may attenuate the potential adverse effects of hypotension on the brain (Pellicer et al, 2009; Vesoulis, 2016), firm conclusions can only be reached with well-designed prospective randomized control trials. Unfortunately, due to several reasons, including challenges with obtaining consent and the clinician's bias in favoring treatment, such a trial is currently not feasible (Batton et al, 2012). However, several ongoing studies evaluating different thresholds for treating low blood pressure will hopefully shed light on this clinical dilemma.

3. Did the PDA contribute to development of IVH in Twin B?

As pulmonary vascular resistance drops precipitously during the first few minutes of birth, the PDA shunt becomes progressively left to right (Noori et al, 2012). By 4 hours after birth, 95% of preterm infants have a complete or predominantly left-to-right shunt (Kluckow and Evans, 2000). Although unproven, it is possible that in a subset of preterm infants, inadequate compensation for the shunt results in cerebral hypoperfusion. Most but not all studies have shown high CFOE (i.e., low CBF) in the presence of a significant PDA and normalization of CFOE with closure of the ductus (Chock et al, 2016; Lemmers, 2008, 2016). If a PDA does play

a role in cerebral hypoperfusion, the most critical time appears to be during early transitional period. Indeed, a large PDA during the first postnatal hours is found to be an independent predictor of low superior vena cava flow, a surrogate for CBF (Kluckow and Evans, 2000). This notion is supported by effectiveness of prophylactic indomethacin in reducing the incidence of IVH and PDA. However, effect and interaction of PDA and indomethacin on CBF and IVH are more complex, as the protective effect of indomethacin may not primarily be through closure of the PDA. Indeed, despite similar efficacy in closing the PDA, prophylactic ibuprofen has no effect on the incidence of IVH. Nevertheless, the strong relationship between a significant PDA and low CBF does suggest that PDA may be a contributing factor to the ischemic phase preceding the development of IVH.

Despite the large PDA diameter in Twin B, in this case the ductus did not contribute to cerebral hypoperfusion, as the ductal shunting was right to left in the first day. However, the elevated pulmonary vascular resistance associated with a more severe respiratory distress syndrome in Twin B may have contributed to cerebral hypoperfusion by decreasing the left ventricular preload and output. As a PDA serves as a "pop-off valve" for elevated right ventricular pressure, appropriately, no treatment aiming at closure of PDA was initiated.

4. Did switching to high-frequency ventilation or the high CO_2 lead to IVH?

Positive pressure ventilation can significantly affect cardiovascular function. Alterations in CBF with positive pressure ventilation have been linked to pathogenesis of IVH (Perlman et al, 1983). Animal studies indicate that with increasing positive airway pressure, systemic venous return decreases and pulmonary vascular resistance increases (Cheifetz et al, 1998; Polglase et al, 2005). These changes can compromise oxygenation and systemic blood flow. Although the findings of limited studies in human neonates are inconsistent, most have shown similar but milder effects than in the animal model (Abdel-Hady et al, 2008; Beker et al, 2014; de Waal et al, 2007; Hausdorf and Hellwege, 1987). The lung compliance appears to be the most important factor in determining the extent of the effects of positive airway pressure on cardiovascular function. With more compliant lungs, the intrathoracic pressure is more readily transmitted to the vasculature. Therefore, if the mean airway pressure is excessive for the degree of lung disease and reduced compliance, it is more likely to result in systemic hypoperfusion, decreased CBF, and increased venous pressure, which contribute to pathogenesis of IVH. In Twin B, the mean airway pressure was appropriate for the degree of lung disease and therefore unlikely to have played a role. High-frequency ventilation was initially associated with increased incidence of IVH (N Engl J Med, 1989; Wiswell et al, 1996) and was partially attributed to impaired venous return and rapid CO_2 changes (N Engl J Med, 1989; Clark et al, 1996). However, subsequent studies did find any association between high-frequency ventilation and IVH (Clark et al, 1996; Cools et al, 2015).

CO_2 has a potent effect on cerebral vasculature especially after the first postnatal day (Levene et al, 1988; Noori, 2014; Pryds et al, 1989; Tyszczuk et al, 1998). Hypocapnia leads to vasoconstriction and reduction in CBF. Conversely, hypercapnia vasodilates cerebral vasculature and leads to increase in CBF. Therefore hypocapnia and hypercapnia can accentuate hypoperfusion and reperfusion injury, respectively, and theoretically increase the risk of IVH. However, hypocapnia has not been associated with IVH even though it is clearly linked to ischemic brain injury. The absent or weak effect of CO_2 on cerebral vasculature during the first postnatal day when the hypoperfusion phase of IVH usually occurs may explain the lack of association between hypocarbia and IVH (Levene, 1988; Noori, 2014; Pryds et al, 1989; Tyszczuk et al, 1998). On the other hand, epidemiologic studies have described an association between IVH and both hypercapnia and significant swings in CO_2 (Ambalavanan et al, 2015; Fabres et al, 2007; Kaiser et al, 2006; McKee, 2009). Aside from increasing CBF, hypercapnia attenuates CBF autoregulation, which could further potentiate reperfusion injury (Kaiser et al, 2005; Noori, 2014). Preliminary findings suggest that a partial pressure of CO_2 above the low 50s (in mm Hg) has more significant effect on CBF in extremely preterm infants during the first 3 postnatal days (Fig. 20.9) (Noori, 2014). Although a cause-and-effect relationship has not been established, the epidemiologic findings and biological plausibility are strongly suggestive of hypercapnia role in pathogenesis of IVH. The twins had different CO_2 values during the first 3 days (Fig. 20.10). Twin B had greater fluctuations and more extremes of CO_2 (Figs. 20.10 and 20.11). In addition, very high CO_2 values preceded progression of IVH from grade I to IV, which may have contributed to development of IVH.

5. What are the chances of Twin B developing hydrocephalus?

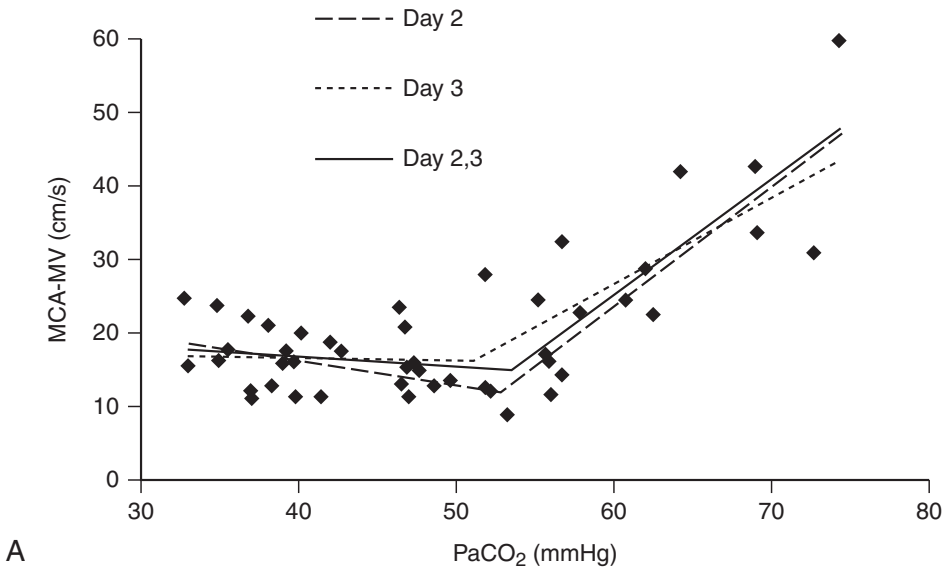
With extension of IVH and spread of blood into ventricular system, blood clot formation and obliterative arachnoiditis can occur, leading to obstructive hydrocephalus (Fig. 20.12 and 20.13). The incidence of hydrocephalus increases with higher grade IVH. With grade 4 IVH (as in the case presentation), the incidence of posthemorrhagic hydrocephalus is 28% with about one-third of these patients requiring permanent shunt placement (Christian et al, 2016).

CASE

Twin B developed an obstructive hydrocephalus for which he received a ventriculoperitoneal shunt. Otherwise the hospital course was uncomplicated, and he was discharged home at 37 weeks' postmenstrual age (PMA) in room air. Twin A had an episode of staphylococcus aureus sepsis, and he was discharged home in room air at 38 weeks' PMA. The family moved to another state where long-term follow-up was provided.

CONCLUSION

The case of twins illustrates the complexity of pathogenesis of IVH and the interplay between cardiovascular and respiratory systems on a backdrop of a vulnerable immature brain. Although they had the same prenatal risk factors and were born seemingly in the same condition at birth, their



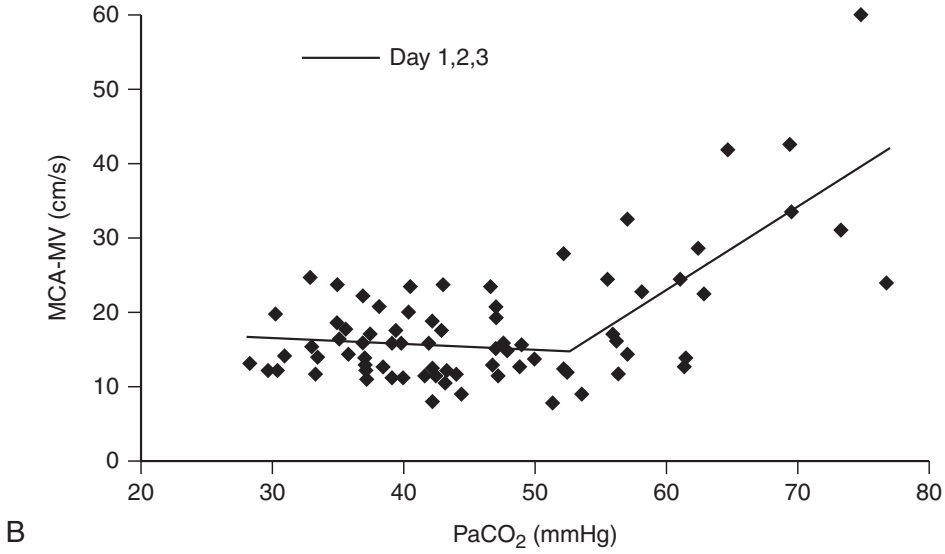


Fig. 20.9 Relationship between carbon dioxide and index of CBF. The graphs depict piece-wise bilinear regression identifying a breakpoint in the MCA-MV - $Paco_2$ relationship. Graph A shows the breakpoints at a $Paco_2$ value of 52.7 mm Hg for day 2 (broken line, $R^2 = 0.74$, $p < 0.0001$), 51.0 mm Hg for day 3 (dotted line, $R^2 = 0.60$, $p < 0.034$), and 53.2 mm Hg for days 2 and 3 combined (solid line, $R^2 = 0.66$, $p < 0.0001$). Graph B shows the breakpoint at $Paco_2$ of 51.7 mm Hg ($R^2 = 0.49$, $p < 0.0001$) for all data points, including postnatal day 1. *MCA-MV*, Middle cerebral artery mean flow velocity; $Paco_2$, partial pressure of arterial carbon dioxide. (From Noori S, Anderson M, Soleymani S, et al: Effect of arterial CO_2 on cerebral blood flow in preterm infants during the early postnatal transition, *Acta Paediatr* 103:e334–9, 2014.)

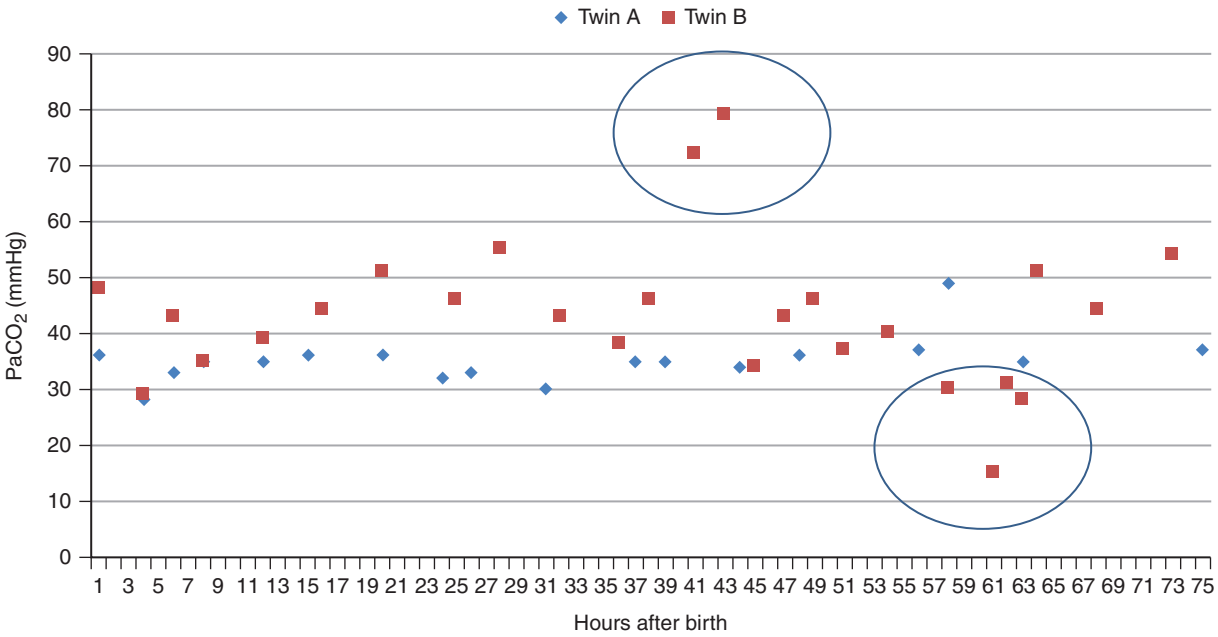


Fig. 20.10 Changes in partial pressure of arterial carbon dioxide ($Paco_2$) in Twin A (blue diamonds) and Twin B (red squares) during first 3 days after birth. Note the greater fluctuations and more extreme values in Twin B. See text for details.

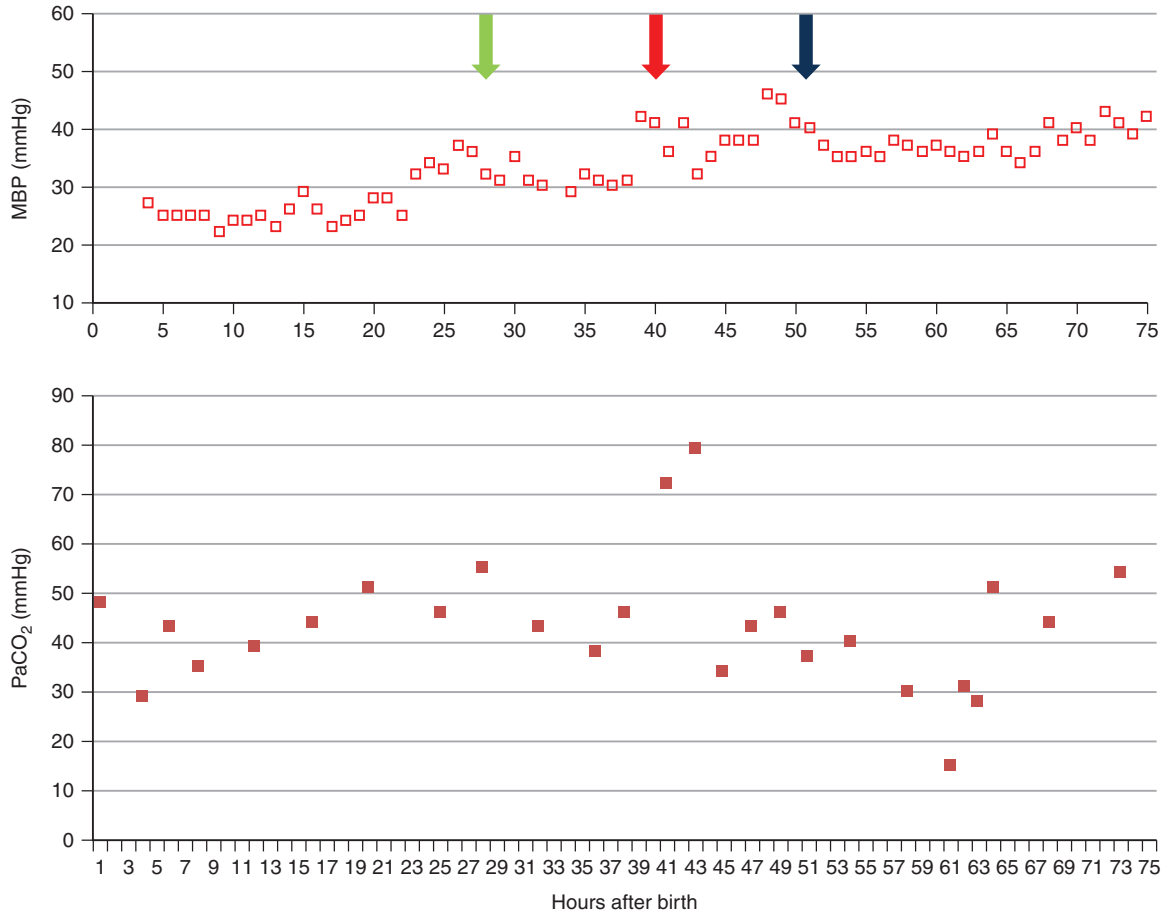


Fig. 20.11 Changes in mean blood pressure (MBP) and partial pressure of arterial carbon dioxide ($Paco_2$) in Twin B. Green, red, and purple arrows represent the timing of head ultrasound showing no IVH, grade I, and grade IV IVH, respectively. The high $Paco_2$ when MBP was high is especially concerning, as the cerebral blood flow autoregulation is progressively attenuated with increasing $Paco_2$ above normal value. This can accentuate reperfusion injury. Development of IVH and progression to grade 4 coincided with this period.

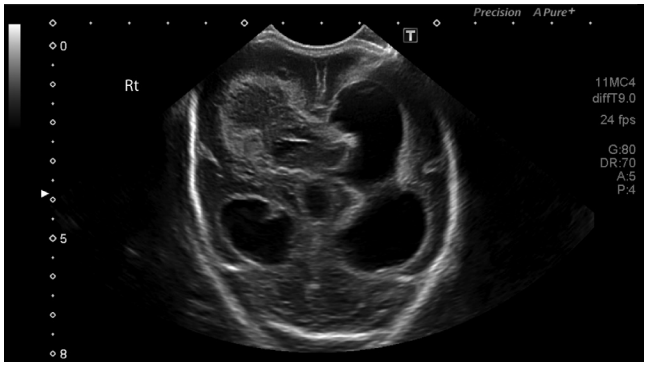


Fig. 20.12 A head ultrasound image of a 20-day old preterm infant born at 25 weeks' gestation. This is a coronal view of the brain, demonstrating posthemorrhagic hydrocephalus.

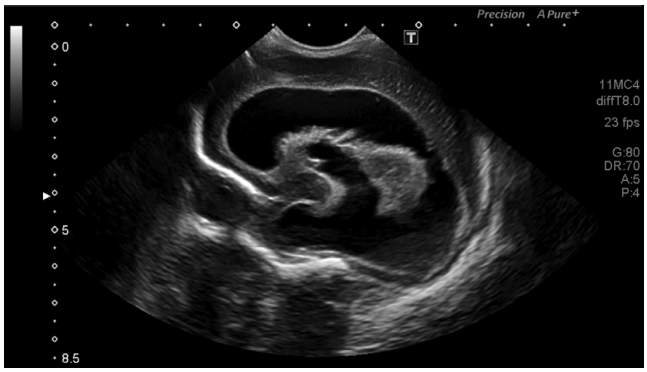


Fig. 20.13 A head ultrasound image of a 20-day old preterm infant born at 25 weeks' gestation (same as in Fig. 12). This is a sagittal view of the brain, showing posthemorrhagic hydrocephalus.

clinical courses diverged in the first postnatal day. Whereas the respiratory status of Twin A improved and he was successfully extubated by the end of first postnatal day, the respiratory support of Twin B escalated in the first day with subsequent change to HFV toward the end of second day. There were also differences in the cardiovascular status including blood pressure, CBF, and PDA flow patterns, which were undoubtedly affected by the differences in respiratory condition. Although both twins are at risk of neurodevelopmental impairment, Twin B is at much higher risk given the grade IV IVH and progressive hydrocephalus necessitating a close follow up.

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Abstract: Despite advances in the care of preterm infants, intraventricular hemorrhage (IVH) occurs with a relatively high incidence, especially among those at the threshold of viability. There are tremendous challenges in minimizing disturbances to the highly vulnerable brain while providing adequate cardiovascular, respiratory, and other organs support to sustain extrauterine life of an extremely preterm infant. Use of new bedside technologies such as near-infrared spectroscopy and increased use of point of care ultrasonography by the neonatologists have recently contributed to a better understanding of the events leading to IVH. In this chapter, a case of a set of twins born at 26 weeks' gestation with one developing IVH is reviewed, and some of the protective and risk factors, pathophysiology, and outcome of IVH are discussed.
Keywords: Autoregulation, carbon dioxide, cerebral blood flow, hypotension, infarction, ischemia, reperfusion

Surgical Emergencies in the Newborn

Ariela Zenilman, Vincent Duron and Steven Stylianos

This chapter discusses common presentations of surgical emergencies in the newborn. Frequently encountered scenarios are presented as a descriptive case followed by a discussion and explanation of the disease process and treatment options. Necrotizing enterocolitis (NEC) is the most commonly encountered abdominal emergency in the premature newborn and is discussed in further detail in a separate section of this book.

EMERGENCIES OF THE TRACHEA, ESOPHAGUS, AND THORAX

CASE 1

Within a few hours of birth, a newborn full-term male is noted to have excessive salivation. Upon feeding, he experiences choking and gagging. A feeding tube is attempted but cannot pass beyond 10 cm. The mother was found to have polyhydramnios during pregnancy, which was otherwise uncomplicated. A chest x-ray reveals the orogastric tube coiled in the proximal esophagus (Fig. 21.1).

Exercise 1

Questions

1. Upon diagnosis, what is the next appropriate step?
   A. Immediate intubation for airway protection
   B. Nothing by mouth (NPO) with initiation of total parenteral nutrition (TPN)
   C. Replace orogastric tube under endoscopic guidance for abdominal decompression
   D. Repeat physical examination
2. Which of the following prenatal findings may be associated with this diagnosis?
   A. Abnormal cardiac anatomy
   B. Abnormal renal anatomy
   C. Abnormal volume of amniotic fluid
   D. Absence of gastric bubble
   E. All of the above
3. Based on the information given and the chest x-ray shown, what is the most likely diagnosis?
   A. Isolated esophageal atresia
   B. Esophageal stenosis
   C. Esophageal atresia and distal Tracheo-esophageal fistula
   D. Esophageal atresia and proximal TEF
4. Which of the following is crucial to obtain before surgery?
   A. Echocardiogram
   B. Repeat plain abdominal films
   C. Renal sonogram
   D. Formal upper GI barium contrast study

Answers

1. **D**
2. **E:** EA/TEF is associated with other anomalies in 50% of cases, most commonly cardiac (25%), genitourinary (20%), and gastrointestinal (20%). Many of these anomalies can be suspected antenatally.
3. **C:** Presence of air in bowel confirms distal fistula.
4. **A:** An echocardiogram is useful to determine side of aortic arch, which may influence surgical approach. It also details presence of congenital heart defects, which is crucial in surgical and anesthetic planning.

The incidence of congenital tracheoesophageal malformations is about 1 in 2500 to 3000 births. Infants with esophageal atresia and TEF typically become symptomatic within the first few hours of life. Prenatal ultrasonography can suggest EA/TEF by demonstrating a small or absent stomach bubble in association with maternal polyhydramnios, but definitive prenatal diagnosis occurs less than 50% of the time (Arensman, 2009). After birth, a child with EA presents with excessive salivation, mucus coming out of the mouth or nose, and noisy breathing with episodes of choking or cyanosis. Inability to pass a nasogastric or orogastric feeding tube strongly suggests esophageal atresia. An anterior-posterior and lateral x-Ray ("babygram") that includes the neck, chest, and abdomen reveal the tube coiling within the proximal esophageal pouch (Fig. 21.2). An x-ray is crucial for many reasons:

- Presence of abdominal gas confirms the diagnosis of esophageal atresia with distal fistula, which is present in 85% of cases. A gasless abdomen, conversely, suggests a pure or isolated EA, which may require a staged or delayed surgical approach.
- Vertebral and other structural anomalies can be identified.
- Cardiac malformations can be detected.
- Abdominal gas pattern can differentiate esophageal atresia from duodenal atresia.
- Lungs can be assessed for other conditions and pneumonia (Mattei, 2011).

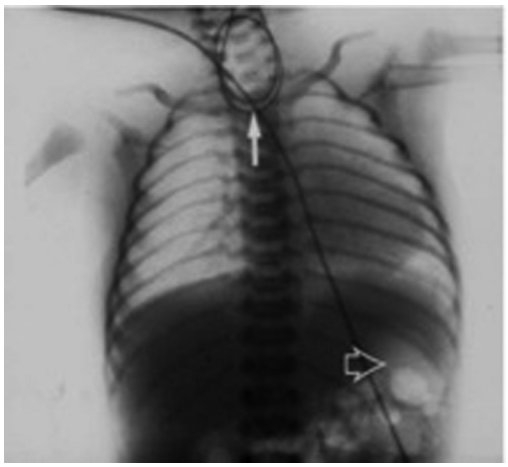

Fig. 21.1 Newborn with intolerance of initial feeding and inability to pass nasogastric tube (NGT), chest x-ray (CXR) shows tube coiled in proximal esophagus with presence of distal bowel gas. (From Arensman R: *Pediatric surgery.* ed 2, Austin, TX, 2009, Landes Bioscience.)

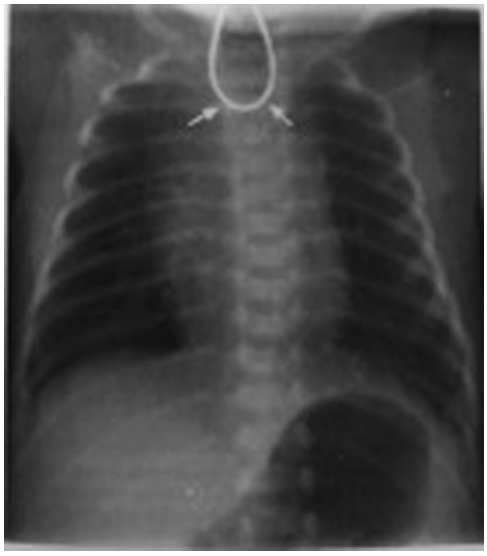

Fig. 21.2 Esophageal atresia; chest x-ray (CXR) with coiling of nasogastric tube (NGT) in the esophageal pouch. (From Coran A: *Pediatric surgery,* ed 7, Philadelphia, 2012, Elsevier Saunders.)

Once the diagnosis is made, a physical examination is necessary to identify associated anomalies. EA/TEF may be part of the VACTERL association (vertebral, anal, cardiac, tracheoesophageal, renal, and limb) so it is important to survey for these abnormalities. Spinal and renal ultrasounds are indicated, but an echocardiogram is the most important and is time sensitive as it is useful to determine location of aortic arch, which influences the surgical approach. The presence of congenital heart defects affects outcome as well.

There are five types of tracheoesophageal anomalies that are described with type C, or EA with distal TEF, being the most common (Fig. 21.3). An infant that has choking and coughing with feedings and repeated pneumonia, especially of the right upper lobe, suggests an isolated H type anomaly

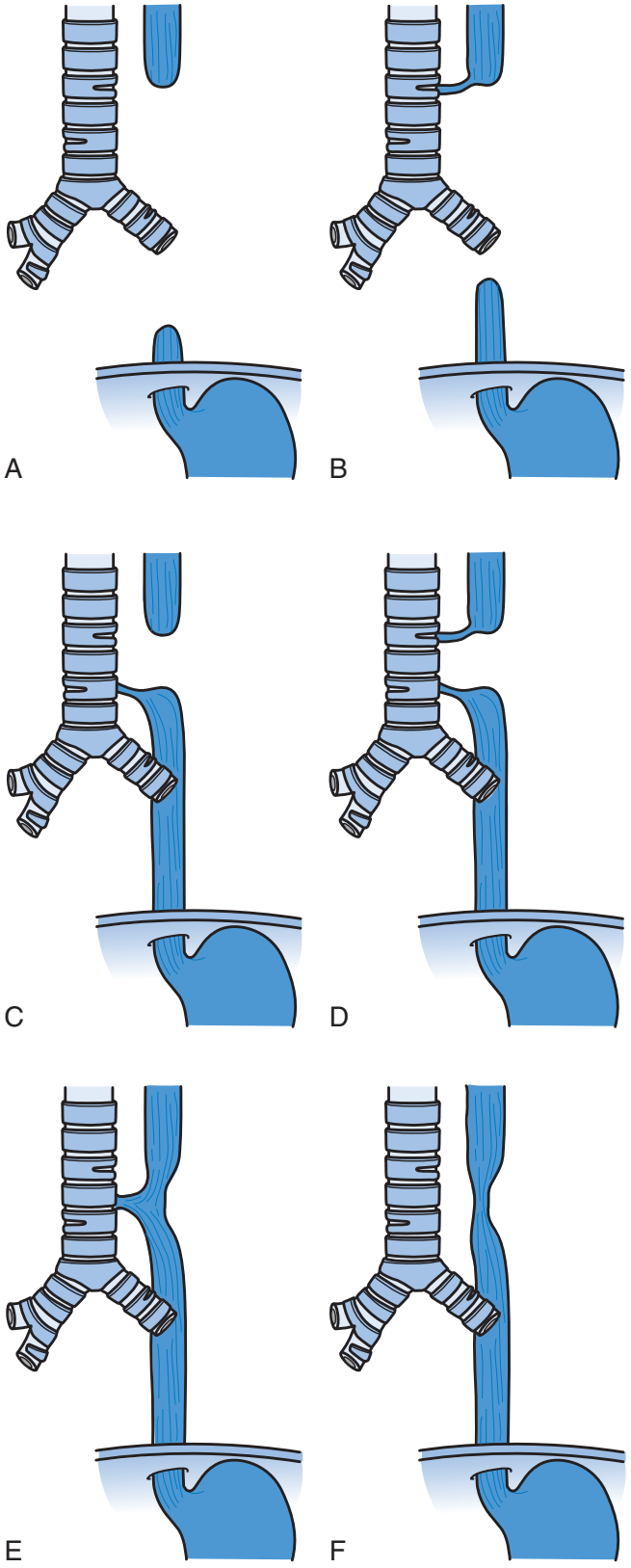

Fig. 21.3 Gross classification of anatomic patterns of esophageal atresia. **(A)** V atresia without TEF, associated with "long gap." **(B)** Atresia with proximal TEF. **(C)** Atresia with distal TEF, the most commonly encountered form. **(D)** Atresia with a double fistula, proximal and distal. **(E)** TEF without atresia; H type fistula. **(F)** Esophageal stenosis. (From Coran A: *Pediatric surgery,* ed 7, Philadelphia, 2012, Elsevier Saunders.)

(Mattei, 2011). These patients need further imaging, such as a contrast esophagram to establish the diagnosis.

The surgical approach to tracheoesophageal anomalies depends on the type of anomaly and the status of the newborn. The initial treatment in these infants involves preventing aspiration and pneumonitis. The Replogle is positioned to continuously aspirate saliva and the infant is positioned upright to minimize reflux and aspiration. H-2 blockers and broad spectrum antibiotics are initiated empirically. Intubation is typically avoided, as positive pressure ventilation may cause gastric dilation and worsening respiratory distress secondary to abdominal distension, as much of the tidal volume will enter the stomach via the fistula if present. When intubation is necessary, such as in preterm infants with respiratory distress and EA/TEF, emergent intervention to ligate the fistula is employed and is frequently lifesaving (Arensman, 2009).

Operative repair of EA/TEF involves an esophageal anastomosis and closure of the TEF through a right thoracotomy or thoracoscopy. Overall survival is 85% to 95%, but those associated with other major anomalies, especially cardiac, have a poorer prognosis. Very low birthweight neonates (<1500 g) pose a major risk factor for surgery as well. Postoperative complications are common but manageable. Leaks are not infrequent (15%) and can typically be treated nonoperatively. Most leaks seal spontaneously. Strictures can be treated with balloon dilatation.

CASE 2

A newborn term male born without complications is tachypneic, grunting, cyanotic, and pale. On examination, you notice a scaphoid abdomen (Fig. 21.4), absent breath sounds on the left, and decreased breath sounds on the right.

Exercise 2

Questions

1. What is the next step in management?
   A. Initiate empiric antibiotics for concern for aspiration
   B. Intubation and placement of a nasogastric tube
   C. Obtain echocardiogram
   D. Placement of a left thoracostomy tube
2. What is the most appropriate initial diagnostic test?
   A. Echocardiogram to assess for congenital heart defect
   B. Chest and abdomen plain film
   C. Ultrasound of the chest
   D. Chest computed tomography (CT)
3. Upon manipulation of the infant, the preductal saturation reads 88% with postductal saturation of 65%. Fio_2 on the ventilator is increased to 100%. The next step in management is:
   A. Surgical consultation for urgent operative repair
   B. Extracorporeal membrane oxygenation (ECMO)
   C. Muscle paralysis to aid in adequate ventilation
   D. Gentle mechanical ventilation without paralysis

Answers

1. B
2. B
3. D

Congenital diaphragmatic hernia (CDH) is a relatively common cause of neonatal respiratory distress, occurring in 1 in 2000 to 4000 births, with posterolateral defects accounting for 85% to 90% of occurrences (Coran, 2012); 80% to 90% of CDH occur on the left side. Diagnosis is typically made on prenatal ultrasound, which aids in predicting outcome by estimating the severity of pulmonary hypoplasia and allowing for a planned delivery at an appropriate center. At birth, respiratory symptoms are determined by the degree of pulmonary hypoplasia and reactive pulmonary hypertension (Coran, 2012). The severity of pulmonary hypoplasia depends on the duration and timing of visceral herniation into the chest. The most severely affected develop respiratory distress at birth, while a majority declare themselves within the first 24 hours of life. Classically, the infants have a scaphoid abdomen with an asymmetrically distended chest, and chest radiography reveals intestines in the chest cavity (Fig. 21.5).

Lung hypoplasia is most severe on the ipsilateral side of the hernia but occurs on both sides due to mass effect exerted by intrathoracic viscera. Alveoli in the lungs of infants

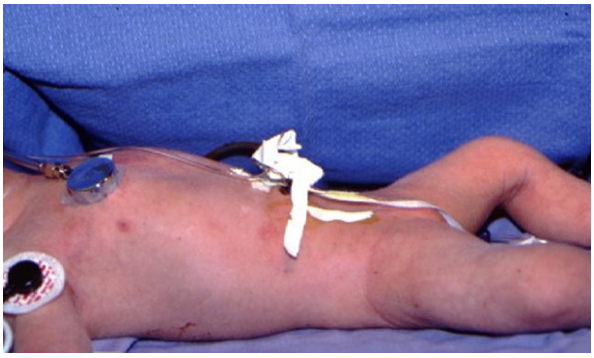

Fig. 21.4 Appearance of a scaphoid abdomen can aid in the diagnosis of CDH.

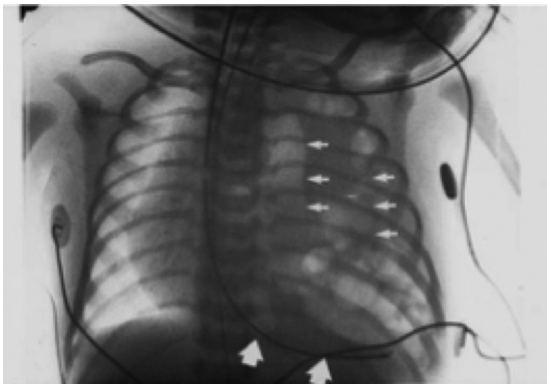

Fig. 21.5 CXR of neonate with left sided CDH; loops of bowel in the chest are outlined as well as an NGT above the diaphragm. (From Mattei P: *Fundamentals of pediatric surgery,* New York, 2011, Springer International Publishing.)

with CDH are immature, and gas exchange is limited by fewer bronchial divisions, immature alveoli, and surfactant deficiency. The pulmonary vasculature has increased muscularization, which contributes to pulmonary hypertension. With pulmonary hypertension, deoxygenated blood is shunted into the systemic circulation via a foramen ovale and the patent ductus arteriosus, leading to a gradient in the preductal and postductal pulse oximetry (Arensman, 2009). Some infants require a pulmonary vasodilators, although nitric oxide may be contraindicated when there is left ventricular dysfunction. Those that are refractory to medical treatment may require ECMO as a bridge to lung maturation and normalization of pulmonary arterial pressure (Mattei, 2011).

All newborns with CDH require operative intervention. Surgery does not immediately lead to reexpansion of the hypoplastic lung and actually often worsens respiratory status in the short term. As such, treatment protocols have evolved from emergency surgery at birth to stabilization of the infant and a semiselective repair. Optimal timing of repair is not known with certainty but is typically delayed once there is evidence of recovery or resolution of pulmonary hypertension. Monitoring of pre- and postductal oxygen saturations is useful in this regard. Immediate interventions at birth include respiratory support and decompression of the gastrointestinal tract.

ABDOMINAL WALL DEFECTS

CASE 3

You are contacted by a community hospital pediatrician where a 32-week gestation, 1900 g male newborn has a large amount of intestine outside the baby's abdomen. He describes the bowel as thick, stiff, and leathery (Fig. 21.6). He cannot visualize the size of the defect under the loops of exposed intestine. The only other notable finding on physical examination is undescended testes.

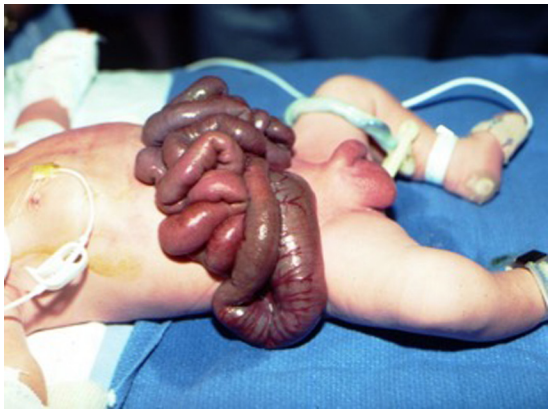

Fig. 21.6 Exposed bowel without any membrane covering, demonstrating inflammatory reaction and thickening of the bowel serosa in gastroschisis. (From Arensman RM: *Pediatric surgery*, ed 2, Texas, 2009, Landes Bioscience.)

Exercise 3

Questions

1. Based on the description given to you from the referring hospital, what kind of abdominal wall defect is described?
   A. Ruptured omphalocele
   B. Omphalocele
   C. Gastroschisis
   D. Pentalogy of Cantrell
   E. Epigastric hernia
2. What is the next step in management?
   A. Immediate transfer for surgical evaluation
   B. Placement of nasogastric tube
   C. Placement of moistened gauze dressing and a bowel bag
   D. Attempt immediate reduction to prevent further damage to the exposed viscera
   E. B and C
3. Gastroschisis is associated with cardiovascular defects such as tetralogy of Fallot, atrial septal defect (ASD), and ventricular septal defect (VSD)
   A. True
   B. False
4. The child arrives at your hospital and is being considered for primary closure of the defect by the surgery team. What is the appropriate preparation to ensure optimization for surgery?
   A. Endotracheal intubation
   B. Secure IV access for fluid resuscitation
   C. Ensuring a warm environment
   D. Identifying bowel congestion and kinking of the mesentery
   E. All of the above
5. In the postoperative period, the infant is found to have decreasing urine output, worsening abdominal distension and firmness, and new lower extremity edema. What is the next step in management?
   A. Fluid challenge
   B. Lasix bolus to relieve urinary retention postop
   C. Reopening of the abdomen
   D. Abdominal ultrasound to rule of IVC clot

Answers

1. C
2. E
3. B
4. E
5. C

The major abdominal wall defects seen in neonates are omphalocele and gastroschisis. Both defects can be seen on prenatal ultrasound and give the neonatologist and surgeon time to plan the perinatal and postnatal care.

Gastroschisis

Gastroschisis is an isolated, full-thickness, typically small defect in the abdominal wall to the right of the umbilical cord. It is typically associated with young maternal age and smoking. At birth, the eviscerated bowel is edematous

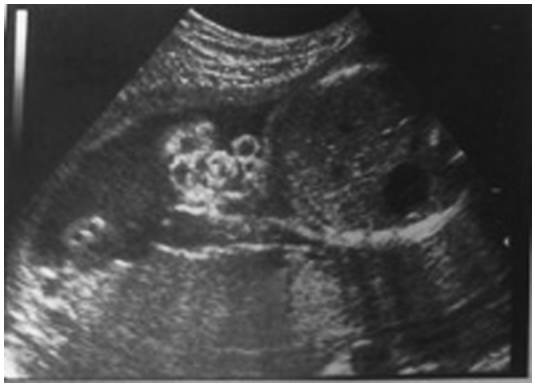

Fig. 21.7 Gastroschisis on prenatal US image demonstrating loops of intestine floating in amniotic fluid. (From Bianchi D, Crombleholme T, D'Alton M: *Fetology. Diagnosis and management of the fetal patient,* ed 2, New York, 2000, McGraw-Hill.)

and thick, described as a characteristic "peel." The peel is thought to be due to an inflammatory reaction of the bowel serosa following exposure to amniotic fluid (Fig. 21.7). At delivery, efforts should be made to minimize heat and fluid losses. Exposed bowel significantly increases the evaporative fluid losses of a neonate; it should be handled in a sterile fashion and covered with moist, warm gauze sponges. The infant's lower body to the nipple level should also be placed immediately in a clear plastic "bowel bag" and positioned in lateral decubitus to facilitate venous return from the bowel. Efforts should be made to secure the bowel in a position that avoids kinking of the mesenteric vessels to minimize swelling.

Fluid loss in these patients can be significant, so the infant's fluid status should be carefully monitored and IV access should be secured. Placement of a nasogastric tube is recommended to prevent aspiration and further bowel dilation. The infant should be placed in a warmer to maintain thermal homeostasis as exposed bowel cools the body temperature and can result in neonatal hypothermia and coagulopathy. Whereas concomitant anomalies are more highly associated with omphaloceles, gastroschisis is associated with intestinal atresia (10%), and all patients have an anomaly of intestinal rotation and fixation.

Surgical approach involves either primary closure or a staged silo reduction with delayed closure (Fig. 21.8). The first stage of surgical intervention should occur soon after birth. The infant will continue to require an increased fluid intake in the postoperative period due to ongoing sequestration of fluid into the abdominal cavity. Nutrition is supported by parenteral nutrition via a peripherally inserted central catheter line or Broviac catheter. With replacement of intestinal contents into the abdomen, the size of the abdominal cavity may not accommodate the previously herniated viscera. Abdominal compartment syndrome occurs when intraabdominal hypertension leads to end-organ insufficiency, such as impaired venous return, decreased renal perfusion, and abnormal respiratory mechanics. Therefore, particular attention should be paid to urine output, systemic perfusion (and lactic acidemia), lower extremity edema, abdominal distention, and P_{CO_2}.

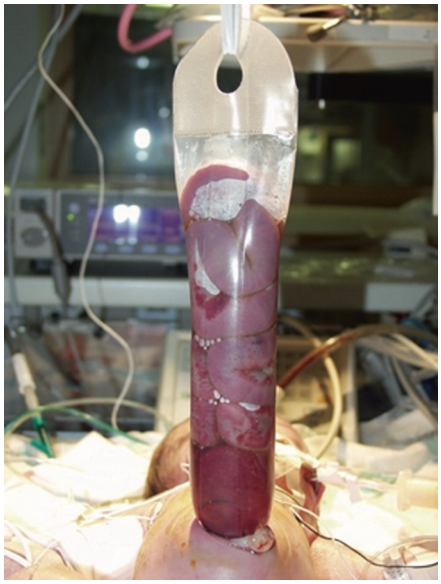

Fig. 21.8 Placement of bowel in silo allows for visualization of viable and well-perfused bowel without much tension at the level of the defect. (From Mattei P: *Fundamentals of pediatric surgery,* New York, 2011, Springer International Publishing.)

In infants with an abdominal compartment syndrome, reopening of the abdomen may be necessary to relieve intraabdominal pressure (Bianchi et al, 2000).

Omphalocele

In contrast to gastroschisis, omphalocele is a defect in the ventral abdominal wall covered by a membrane that consists of peritoneum and amnion (Fig. 21.9). Because a membrane is present, the bowel is protected, and infants do not experience the initial evaporative heat and fluid losses experienced with gastroschisis. They are also less frequently premature. There is, however, a high incidence of associated anomalies in patients with omphalocele. Up to 45% will have cardiac anomalies, 20% chromosomal defects, and 30% neural and genitourinary and gastrointestinal anomalies. Pentalogy of Cantrell is characterized by the following combination of

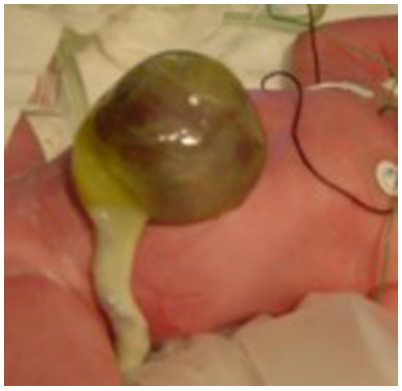

Fig. 21.9 Photo of an omphalocele defect; the ventral abdominal wall is covered by a membrane that consists of peritoneum and amnion.

defects: omphalocele, anterior diaphragmatic hernia, sternal cleft, pericardial defect, and intracardiac defect. A thorough cardiovascular workup, including an echocardiogram, is necessary in these infants.

Omphaloceles are separated into small and giant omphaloceles. Small omphaloceles can often be closed at birth, whereas giant omphaloceles, which are characterized as containing liver in the sac and with a fascial defect larger than 4 to 6 cm, are a separate entity that are quite challenging to address. A "paint and wait" approach has become the preferred approach, in which the hernia sac undergoes epithelialization and repair is undertaken weeks to months later.

CASE 4

An ex-30-week male is brought in by his parents for increased fussiness, unwillingness to feed, and inconsolable crying. The baby had an uneventful previous NICU course. The child appears visibly uncomfortable and on examination you notice a bulge in the right groin with overlying erythema.

Exercise 4

Questions

1. What is the most likely diagnosis?
   A. Hydrocele
   B. Left inguinal hernia
   C. Incarcerated right inguinal hernia
   D. Undescended testes
2. What is the most likely cause of the baby's problem?
   A. Missed duodenal atresia diagnosis
   B. Telescoping of the intestine into itself
   C. Failure or incomplete closure of the processus vaginalis
   D. In utero mesenteric defect
3. After making the diagnosis, you are able to successfully reduce the hernia. What is the next step in management?
   A. Observe in the hospital until the patient has a bowel movement
   B. Discharge home as the defect will spontaneously close with age
   C. Schedule for operative intervention within 48 hours
   D. Emergent operative intervention
4. A few hours later you are called by the nurse that the hernia is bulging again. On reexamination you are unable to reduce its contents. What is the next step in management?
   A. Place a nasogastric tube for abdominal decompression
   B. Emergency operative intervention
   C. Continued observation until surgery in the morning
   D. Fluid resuscitation and reattempt in 4 to 6 hours

Answers

1. C
2. C
3. C
4. B

Inguinal hernias are common and are due to a patent processus vaginalis; 60% of indirect inguinal hernias occur on the right side, and premature infants are at increased risk for inguinal herniation. Incarceration, in which intraabdominal contents are unable to be reduced, is an even higher risk in this group. Development of an inguinal hernia in an infant is managed as an urgent problem even if it is reducible at presentation (Coran, 2012). A child with an inguinal hernia typically presents with an obvious bulge at the external ring or within the scrotum (Fig. 21.10). Vomiting in a premature newborn with the physical findings of a groin mass that cannot be reduced suggests an incarcerated inguinal hernia. A tender, edematous, erythematous bulge or a previously reducible hernia that is no longer reducible is concerning for incarceration. Inguinal hernias do not heal spontaneously and must be surgically repaired.

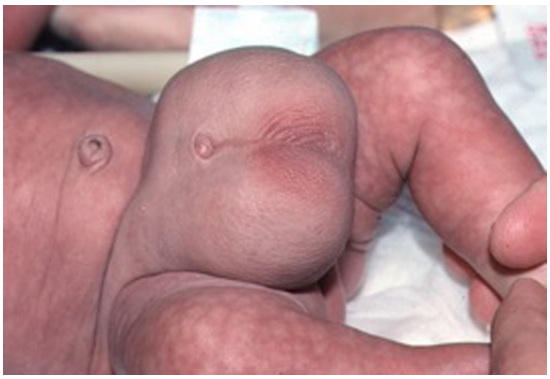

Fig. 21.10 Large hernia with concerning symptoms; erythematous changes of the skin overlying the hernia and peripheral mottling.

When there is concern for incarceration, reduction should be attempted as soon as possible, as the hernia may contain bowel, bladder, omentum, or an ovary in a female. A surgeon should be contacted with this concern as well. Reduction should be attempted with gently constant pressure in the direction of the inguinal ring. In cases where reduction is successful, the hernia should be repaired within 48 hours due to its high risk of recurrent incarceration. When the hernia is not reduced, even with sedation attempts to relax the abdominal muscle, urgent operative repair is indicated (Arensman, 2009).

GASTROINTESTINAL EMERGENCIES

CASE 5

A 2.5 kg infant is born at 32 weeks' gestation. Pregnancy was notable for polyhydramnios but otherwise uncomplicated. On the first day of life the infant had bilious emesis with no abdominal distension. A plain film was obtained and is shown in Fig. 21.11.

Exercise 5

Questions

1. Bilious emesis can be associated with which of the following?
   A. Intestinal stenosis
   B. Hirschsprung disease

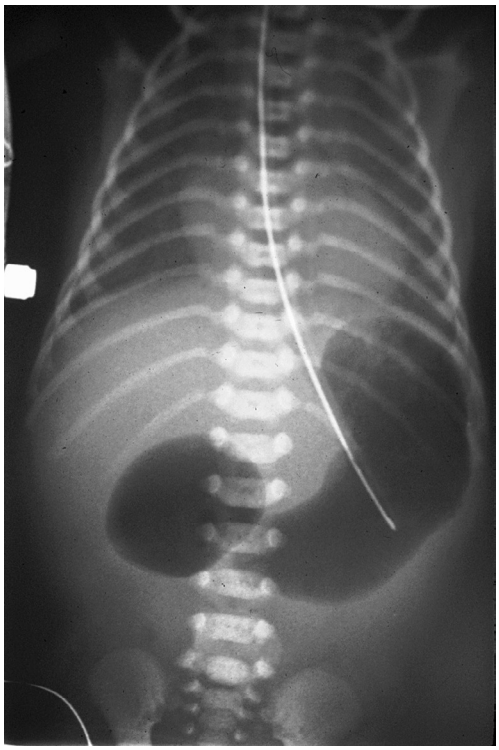

Fig. 21.11 Duodenal atresia; plain abdominal radiograph showing a double bubble sign.

C. Malrotation with volvulus
D. Duodenal obstruction
E. All of the above

2. What is the next step in management?
   A. Emergent operative intervention
   B. Immediate nasogastric decompression
   C. Serial XR to monitor for resolution of obstruction
   D. Replacement of nasogastric fluids in a "volume for volume" fashion
   E. Answers B and D
3. This condition is associated with which of the following?
   A. Trisomy 21
   B. Congenital heart disease
   C. Annular pancreas
   D. All of the above

Answers

1. E
2. E
3. D

CASE 6

A 1-week-old previously healthy infant has sudden onset of bilious emesis after feeding. Previous bowel movements have been normal as well. He is tachycardic but otherwise stable. On physical examination, his abdomen is full but with no marked abnormality. A nasogastric tube is placed with return of bilious fluid.

Exercise 6

Questions

1. What is the appropriate next step in this case?
   A. Perform an abdominal ultrasound paying close attention to the pylorus
   B. Perform upper GI contrast study
   C. Change to soy-based formula
   D. Start proton pump inhibitor for gastroesophageal reflux
2. The most likely diagnosis for this patient is:
   A. Pyloric stenosis
   B. Malrotation with midgut volvulus
   C. Colonic atresia
   D. Superior mesenteric artery (SMA) syndrome

Answers

1. B
2. B

CASE 7

A 2.7 kg male has abdominal distension and bilious emesis noted within the first few hours of life. He has not passed meconium yet. Initial x-ray excludes malrotation but shows dilated loops of bowel.

Exercise 7

Questions

1. After 48 hours the child has still not passed meconium. What is the next radiographic test to obtain?
   A. Abdominal CT
   B. Barium enema
   C. Abdominal ultrasound
   D. No further testing; he requires operative intervention
2. Imaging was obtained and is shown in Fig. 21.12. Based on the clinical scenario and radiographic finding, what is the most likely diagnosis?

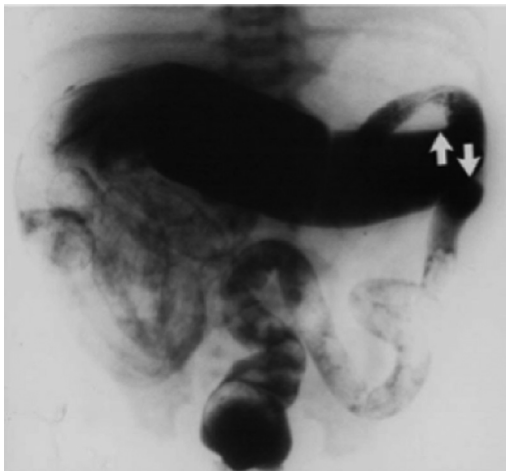

Fig. 21.12 Hirschsprung's disease: Contrast enema reveals transition zone, demonstrating bowel with ganglionic cells to aganglionic distal segment. (From Arensman RM: *Pediatric surgery*, ed 2, Texas, 2009, Landes Bioscience.)

A. Hirschsprung's disease
B. Duodenal atresia
C. Imperforate anus
D. Volvulus

3. If the barium enema demonstrated an unobstructed microcolon, and the infant began stooling shortly after administration of the enema, what would this suggest?
A. Constipation that will resolve with growth
B. Meconium plug syndrome
C. Jejunoileal atresia
D. None of the above

Answers

1. B
2. A
3. B

The presence of bilious vomiting in a newborn is indicative of a pathologic process. The first step in evaluating a newborn with history of bilious emesis is to exclude malrotation, as this could be a potentially life threatening condition. Bilious emesis occurs in a patient with an obstructing lesion distal to the ampulla of Vater. Abdominal distension and failure to pass meconium suggest intestinal obstruction as well. Causes of intestinal obstruction in a newborn are intestinal atresia, malrotation with volvulus, meconium ileus, meconium plug syndrome, Hirschsprung disease, and imperforate anus. The first step to diagnosis is a complete history and physical examination, including a prenatal history and an abnormal ultrasound finding.

The first step in management of these patients is insertion of a nasogastric tube for decompression. Chest and abdominal plain films are indicated, but the radiographic study of choice is an upper GI contrast study to evaluate for malrotation. The combination of bilious emesis, a scaphoid abdomen after decompression, and hemodynamic instability necessitates a prompt immediate surgical exploration. When there are no signs of shock and malrotation is considered, an upper GI (UGI) is obtained, which will reveal the duodenum and proximal jejunum unfixed to the left of midline spiraling in a corkscrew configuration (Fig. 21.13) (Coran, 2012). Malrotation is not always complicated by volvulus, but the combination warrants emergent surgical intervention (Mattei, 2011).

Infants with duodenal atresia, a relatively common cause of intestinal obstruction, typically present with bilious emesis and difficulty feeding, but because of a proximal obstruction, abdominal distension is less common. After birth, with swallowing of air, abdominal plain films reveal the pathognomonic "double bubble sign" delineating a dilated stomach and duodenum with absence of distal gas (see Fig. 21.11). Operative repair is not emergent and can be delayed to allow for workup and management of associated anomalies such as congenital heart defects. Gastric decompression and volume resuscitation is indicated until surgical repair begins.

Lower GI abnormalities are better evaluated with a retrograde contrast enema, which evaluates the size of the colon and the presence of a transition zone. A contrast enema can often be diagnostic in Hirschsprung disease, as a transition may be identified demonstrating ganglionic and aganglionic segments of colon (see Fig. 21.12). Even with the presence of a transition zone on contrast enema, a rectal biopsy is still necessary to confirm the diagnosis. Contrast enema may also reveal a small, unused colon, or a microcolon, which is associated with small bowel atresia and meconium ileus. Meconium ileus is the earliest sign of cystic fibrosis in 20% of patients with the condition (Di Sant'Agnese and Davis, 1976). Contrast enema in patients with meconium ileus reveals a small caliber colon, "soap suds" or "ground glass" like filling defects corresponding to inspissated meconium, and a dilated proximal bowel (Fig. 21.14). Treatment for simple meconium ileus

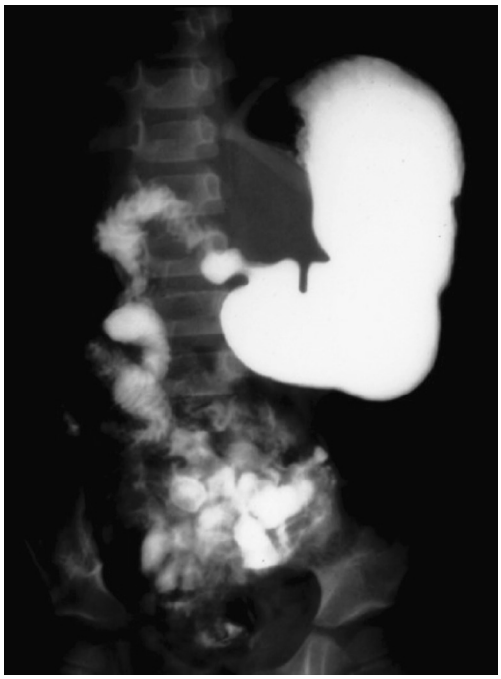

Fig. 21.13 Midgut volvulus: UGI showing duodenum and proximal jejunum unfixed to the left of midline spiraling in a corkscrew configuration. (From Coran A: *Pediatric surgery,* ed 7, Philadelphia, 2012, Elsevier Saunders.)

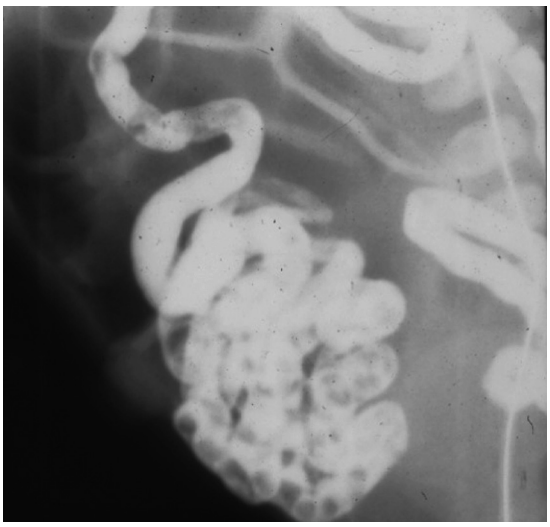

Fig. 21.14 Meconium ileus: contrast enema revealing a small caliber colon with filling defects corresponding to meconium pellets and a dilated proximal bowel. (From Mattei P: *Fundamentals of pediatric surgery,* New York, 2011, Springer International Publishing.)

involves N-acetylcysteine or Gastrografin enemas. However, meconium ileus may present as an intestinal obstruction or in utero perforation leading to peritonitis. This is termed complicated meconium ileus, which usually requires an operative intervention.

In contrast, meconium plug syndrome is a relatively common cause of colonic obstruction, which presents with bilious emesis at 24 to 48 hours of age after tolerating initial feeds. In this case the contrast enema is both diagnostic and therapeutic, in that the large meconium plug in the rectosigmoid portion of the colon is often passed during the procedure. In meconium plug syndrome, the symptoms usually resolve in 24 hours and feeds can be resumed without other interventions.

CASE 8

A 28-week gestation newborn infant, weighing 850 g born via emergent C-section, is placed on continuous positive airway pressure (CPAP) for respiratory distress and was also noted to have a distended abdomen. On physical examination, the abdomen is tender and bowel sounds are present. After obtaining appropriate laboratory results, you suspect NEC and obtain plain abdominal films, including a cross-table lateral, shown in Fig. 21.15.

Exercise 8

Questions

1. What is the next step in management?
   A. Repeat abdominal films in 4 hours to monitor for progression of disease
   B. Adjust respiratory support to decrease positive pressure that may be contributing to abdominal distension
   C. Obtain surgical consultation
   D. All of the above

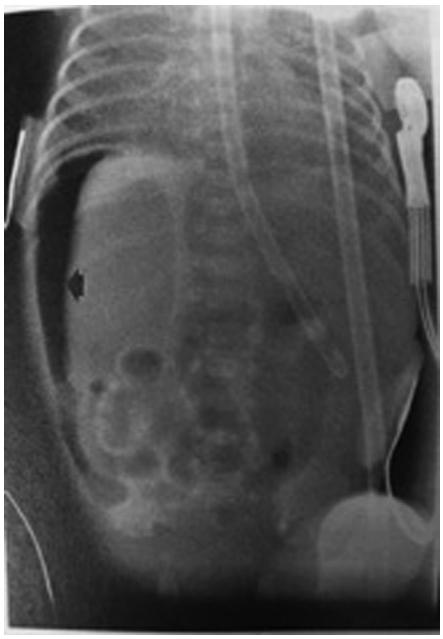

Fig. 21.15 Pneumoperitoneum. (From Polin R: *Workbook in practical neonatology,* ed 3, 2001, Elsevier Health Sciences Division.)

2. What is the major cause of significant long-term morbidity in infants with NEC who require surgical intervention?
   A. Development of short bowel syndrome
   B. Radiation exposure due to the need for repeated abdominal films
   C. Gastroesophageal reflux disease (GERD)
   D. Need for multiple platelet transfusions

Answers

1. **C**
2. **A**

Necrotizing enterocolitis (NEC), spontaneous intestinal perforation, and gastric perforation are the most frequent causes of pneumoperitoneum in a premature newborn. NEC is the most common cause of intestinal perforation. It is associated with varying levels of inflammation and hemodynamic instability. Treatment options range from bowel rest, antibiotics, and serial examinations to emergent decompressive surgery for abdominal compartment syndrome. Spontaneous intestinal perforation is usually associated with a less severe inflammatory state and is seen in infants of very low birth weight who receive postnatal steroids and indomethacin. Gastric perforation is often linked to an antecedent nasogastric tube manipulation, but it can also occur spontaneously. Like all newborn emergencies, management begins with ABCs—evaluating airway, breathing, and circulation—and obtaining adequate IV access for resuscitation. The presence of massive pneumoperitoneum, as seen in the film obtained (see Fig. 21.15), prompts an immediate surgical consultation.

Surgical intervention in this case is mandatory, but the intervention performed will be dependent on the infant's hemodynamic stability. In an infant with marked cardiorespiratory compromise who is unable to undergo laparotomy or a very small infant, peritoneal drain placement may be performed instead to allow air and fluid to evacuate and temporize the situation. Once the neonate stabilizes, a definitive procedure can be considered. In cases with no pneumoperitoneum or in larger infants, laparotomy may be indicated. Every effort is made to preserve as much bowel as possible, but NEC is associated with short bowel syndrome—a major cause of long-term morbidity in which the remaining bowel may be inadequate to absorb nutrients and support growth.

CASE 9

A prenatal ultrasound reveals a mass protruding from the sacral region. There are no signs of hydrops, and family is referred for prenatal counseling.

Exercise 9

Questions

1. When counseling the patient, what is important to discuss regarding care for their baby?
   A. Potential need for abdominal delivery
   B. Potential for heart failure
   C. Given her age at presentation, the high risk of malignancy
   D. A and B
   E. All of the above

Answer

2. D

Sacrococcygeal teratomas (SCTs) are the most common extragonadal tumor in neonates, accounting for up to 70% of teratomas in childhood. Cardiovascular shunting can lead to fetal hydrops, which is associated with a high mortality. Sacrococcygeal teratomas generally present in two ways: a neonate with a predominantly external lesion detected in utero or at birth (Fig. 21.16) or an older infant with a primarily hidden pelvic tumor. When diagnosed on prenatal sonography, masses over 5 cm generally undergo abdominal delivery to avoid rupture and dystocia. Polyhydramnios, placentomegaly, and gestational age under 30 weeks are associated with poor prognosis. Appropriate counseling and planning can take place, and survival rates are over 90% when diagnosed in utero (Coran, 2012). Complications of SCTs include high output heart failure, disseminated intravascular coagulopathy, tumor rupture, or bleeding.

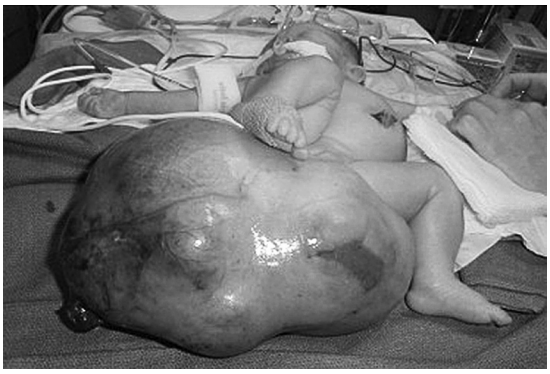

Fig. 21.16 Photo of infant born with SCT.

Sacrococcygeal teratomas are classified based on the location of the lesion (Fig. 21.17). Type III and IV lesions have no external component and are entirely presacral; malignancy rates in these hidden tumors are higher. The degree of pelvic and abdominal involvement should be assessed preoperatively with imaging—ultrasound, computed tomography, or magnetic resonance imaging—which may also characterize vascular supply to the mass. Resection of the mass is typically done in the newborn period when the infant is medically fit.

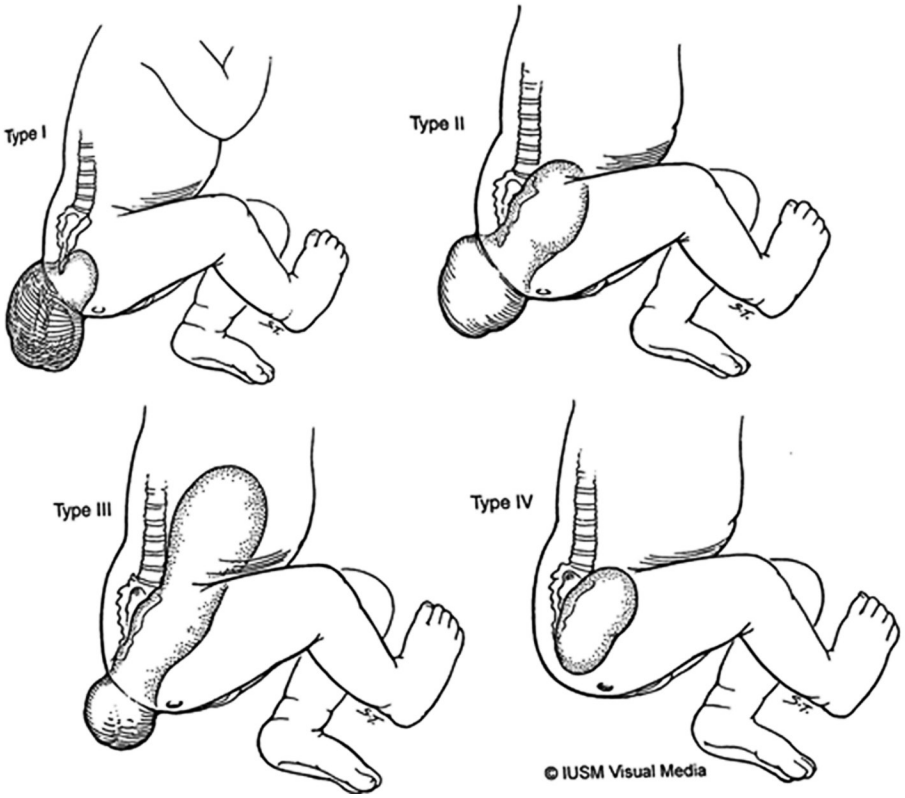

Fig. 21.17 Classification of sacrococcygeal teratomas. I: predominantly external, II: external with external extension, III: visible external but predominantly pelvic/abdominal, IV: entirely presacral. (From Coran A: *Pediatric surgery,* ed 7, Philadelphia, 2012, Elsevier Saunders, IUSM Visual Media.)

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Abstract: This chapter discusses common presentations of surgical emergencies in the newborn. Frequently encountered scenarios are presented as a descriptive case followed by a discussion and explanation of the disease process and treatment options. Necrotizing enterocolitis is the most commonly encountered abdominal emergency in the premature newborn and is discussed in further detail in a separate section of this book.

Keywords: Neonatal, surgery, gastroschisis, omphalocele, hernia, malrotation, volvulus

22

Necrotizing Enterocolitis

Lauren Astrug, MD and Erika Claud, MD

INTRODUCTION

Infants in the neonatal intensive care unit (NICU) are faced with several debilitating diseases that significantly increase the rates of morbidity and mortality. Many of these illnesses are not greatly understood, and many theories have been postulated in terms of pathogenesis and diagnostic and treatment approaches. One of these diseases is necrotizing enterocolitis (NEC), which largely affects premature infants by causing intestinal gut necrosis. There is a strong relationship with gestational age and birth weight, where younger gestational ages and extremely low birth weight (ELBW) neonates are at the highest risk of developing NEC. The disease occurs in approximately 7% of neonates with a birthweight between 500 and 1500 g (Neu, 2014). Mortality from NEC is dependent on the amount of bowel involved, the severity of the disease, and associated comorbidities (Lin, 2006). There is a spectrum of diagnostic criteria and treatment options based on the severity of the disease. Infants who survive are at an increased risk for poor neurodevelopmental outcomes in addition to morbidities, such as short gut syndrome, requiring long-term intravenous nutrition (Sharma and Hudak, 2013). Due to the continued poor understanding of NEC across the world, much research has been devoted to dissecting NEC and determining ways to prevent the disease.

CASE 1

Baby boy MD (1400 g) was born at 27 week's gestation via cesarean section due to preterm premature rupture of membranes for 4 days and concern for placental abruption. Pregnancy was complicated by maternal history of immune thrombocytopenia, factor V Leiden heterozygosity, smoking, mild asthma, and gestational diabetes. The mother received latency antibiotics and a complete antenatal steroid course before delivery. Apgar scores were 5 and 9 at 1 and 5 minutes of life respectively. At the time of the delivery, he had respiratory failure requiring intubation. He was admitted to the NICU for prematurity, respiratory distress syndrome, evaluation for sepsis and nutritional support. He received three doses of surfactant and 2 days of antibiotics; blood cultures for initial sepsis evaluation remained negative. Respiratory support was weaned over 2 weeks, but he remained on oxygen between 30% to 40% via a high-flow nasal cannula. Enteral trophic feeds of breast milk, 20 mL/kg/d, were started on day of life 2. Feeds were slowly advanced over the course of 2 weeks, reaching full feeds of breast milk fortified with human milk fortifier to reach 24 kcal/oz at 150 mL/kg/d.

On day of life 14, he developed abdominal distension, tenderness, and firmness on physical examination. The abdominal circumference increased by 4 cm within a 6 hr period. He had one episode of nonbilious, nonbloody emesis and hypoactive bowel sounds.

Exercise 1

Question

1. What should be the next steps to evaluate the neonate's signs and symptoms?
   A. Abdominal ultrasound
   B. Electrolyte panel
   C. Upper GI series
   D. Abdominal x-ray

Answer

D. Abdominal x-ray should be obtained next to evaluate the gut. The abdominal x-ray is time efficient and illuminates changes within the bowel, including bowel dilation, thickening bowel wall, and free air under the diaphragm. Abdominal x-ray is the gold standard imaging to identify pneumatosis, which is highly suggestive for NEC.

CASE 1 (CONTINUED)

Enteral feeds were held, a sepsis evaluation was completed, and an abdominal plain film was obtained. The laboratory studies revealed a white count of 13,600/mm^3 with 25% mature neutrophils and 29% band forms. The hemoglobin concentration was 12 g/dL and platelets 332 × 10^3/L. The C-reactive protein (CRP) remained under 3 mg/L. A blood culture was obtained and vancomycin and gentamycin were started. Arterial blood gas, lactate, and serum electrolytes were within normal limits. The abdominal plain film x-ray revealed abnormal diffuse bowel dilation, pneumatosis within the right and left lower quadrants with portal venous gas (Fig. 22.1). With these findings, he was made NPO, gastric decompression was begun with a nasogastric tube to

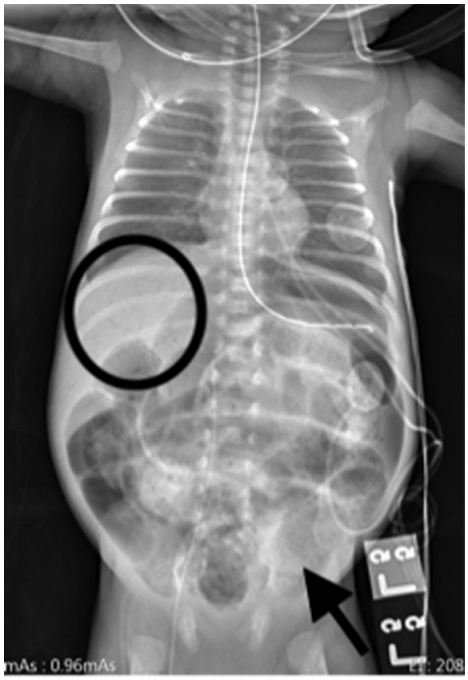

Fig. 22.1 Abdominal plain film x-ray revealing abnormal diffuse bowel dilation, pneumatosis within the right and left lower quadrants with portal venous gas *(circled).*

low intermittent suction, and surgery was consulted for an evaluation.

Exercise 2

Question

2. What clinical scenario is most concerning for NEC?
   A. A 5-day-old 23-week gestational age infant with bilious nasogastric output who has never initiated enteral feeds
   B. A 2-day-old term infant with abdominal distension and tenderness with no stool output
   C. A 3-week-old 28-week gestational age infant with abdominal distension and discoloration, recent history of multiple small episodes of nonbilious emesis, with normal stools
   D. A 5-week-old 24-week gestational age infant with respiratory failure, significantly decreased urine output, hypotension, and a history of previous urinary tract infections

Answer

C. Necrotizing enterocolitis typically presents in premature infants initiated on enteral feeds. Clinically they may start to show signs of poor tolerance of feedings and changes in the abdominal examination. Stools may become bloody, but in the setting of NEC, stools may remain normal. NEC presents with several different signs and symptoms, not limited to the gastrointestinal system, which can make the diagnosis difficult. Early detection is important, and an investigative workup should be initiated when there are any concerns for NEC.

CASE 1 (CONTINUED)

Despite rapid intervention, including holding enteral feeds and starting intravenous nutrition, gastric decompression, antibiotic coverage, and serial abdominal x-rays, 2 days after the diagnosis of NEC, the infant developed recurrent episodes of apnea with persistent desaturations requiring an initial increase of respiratory support to continuous positive airway pressure (CPAP) then to full ventilator support requiring intubation. Just before intubation, an arterial blood gas was notable for significant mixed respiratory and metabolic acidosis (pH 6.98, Pco_2 62, PaO_2 47, HCO_3- 14.6, base excess −17). Other laboratory studies were significant for thrombocytopenia (platelets 36 × 10^3/L), a decrease in hemoglobin concentration to 10 g/dL with leukopenia (3400/mm3), mature neutrophils of 35%, and bands increasing to 32%. On physical examination after intubation, the abdomen appeared bluish in color with significant distension, and no active bowel sounds. An abdominal x-ray demonstrated a persistent fixed loop of bowel (Fig. 22.2). Due to this clinical decompensation, he underwent an exploratory laparotomy. Patchy necrotic bowel was identified within the mid-small bowel and terminal ileum. Both segments were resected and a jejunostomy was created allowing the infant time to heal.

Exercise 3

Question

3. Which of the following clinical signs is due to increased abdominal distension secondary to NEC?
   A. Episodes of apnea, desaturations, and decreased urinary output
   B. Temperature instability and no stool output
   C. Recurrent episodes of emesis, bloody stools
   D. Increased urinary output, hypotension

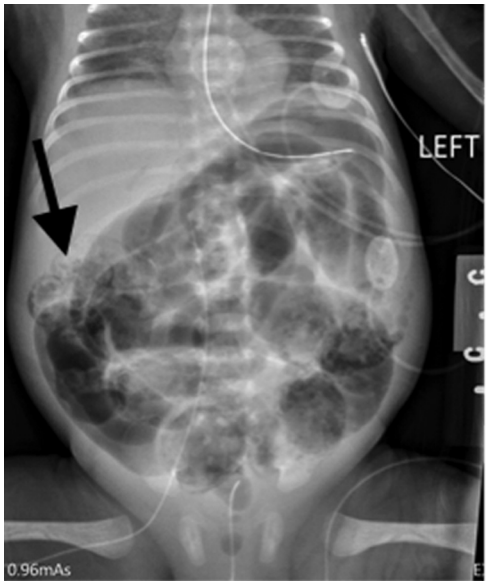

Fig. 22.2 Abdominal plain film x-ray revealing persistent bowel dilation, abnormal gas pattern, pneumatosis *(arrow),* and now multiple fixed bowel loops.

Answer

A. Abdominal distension can lead to increased pressure on the diaphragm, decreasing a neonate's lung volume and leading to respiratory failure. With worsening abdominal distension, abdominal compartment syndrome can develop leading to a decrease in urine output.

CLINICAL PRESENTATION

Timing of NEC presentation varies with gestational age. NEC tends to have a later onset in the most immature infants with a peak presentation at around 29 to 32 weeks' postmenstrual age (Patel et al, 2017). NEC can present in various ways, making the diagnosis difficult on clinical presentation alone. Radiologic findings can help aid the diagnosis. Neonates can manifest a broad range of signs such as apnea, desaturations, and temperature instability to complete clinical decompensation. More specific gastrointestinal signs include abdominal distension and/or discoloration, feeding intolerance, and bloody stools (Lin and Stoll, 2006; Sharma and Hudak, 2013; Patel et al, 2017; Palleri et al, 2017). Many times symptoms are nonspecific and require further investigation. During the early stages of NEC, subtle signs can make it difficult for the clinician to identify a specific diagnosis of NEC, and radiographic evaluation should be considered (Patel et al, 2017). The disease process is multifactorial and not well understood, but the gastrointestinal mucosal lining undergoes injury and inflammation develops, leading to disruption of the mucosal barrier and bowel necrosis (Palleri et al, 2017).

In the 1970s, a surgeon developed a way to characterize the disease based on its clinical severity and coined the term Bell's criteria. This was aimed at helping the clinician at the bedside to determine when surgery was warranted (Bell et al, 1978). Bell's criteria classify clinical findings into a level of severity based on systemic signs, physical intestinal signs, and radiographic findings (Lin and Stoll, 2006; Bell et al, 1978). It has been used for several years, but with higher rates of premature infant survival, too many neonates were classified within the first Bell's category without actually having NEC (Bell et al, 1978). The first stage includes physical signs of apnea, bradycardia, or desaturations. These findings are quite common in the neonatal period and not always associated with NEC. The approach has been modified once, yet still does not make the actual diagnosis of NEC easier (Walsh and Kliegman, 1986). Neonates with any concerning signs should be evaluated, as NEC can rapidly lead a stable neonate to death over a short period.

CASE 2

Baby LW (500 g) was born at 23 weeks by cesarean section due to preterm labor with advanced cervical dilation and breech presentation. The pregnancy was otherwise unremarkable. The infant's mother received a course of antenatal steroids and penicillin for group B *Streptococcus* (GBS) unknown status. Rupture of membranes occurred at time of the delivery; Apgar scores were 4 and 7 at 1 and 5 minutes respectively. He required intubation at time of birth due to respiratory failure and received three doses of surfactant over the first few days of life. On day of life 6, he developed frank bloody output from the endotracheal tube with worsening respiratory distress and received epinephrine for the pulmonary hemorrhage. He clinically improved within 24 hours and ultimately weaned off respiratory support over a 2-month period.

He was started on enteral feeds with breast milk on day of life 3; however, over several weeks he continued to have poor tolerance of feeding advancements. He exhibited several bouts of abdominal distension accompanied by emesis, but he never developed pneumatosis during those episodes.

At 90 days of age, he developed another episode of abdominal distension and this time appeared lethargic. His abdominal circumference increased from 32 to 37 cm, and the abdomen was tender and firm. He was intubated because of multiple episodes of apnea and bradycardia requiring positive pressure ventilation. Laboratory studies revealed leukopenia of 3300/mm^3, bands 9% with platelets of 371 $\times$ 10^3/L, and hemoglobin concentration of 10 g/dL. The CRP was under 3 mg/L and blood cultures were obtained. Abdominal x-rays of both anterior–posterior view and cross-table lateral revealed a significant amount of free air under the diaphragm (Fig. 22.3 and 22.4). The anterior–posterior view demonstrated pneumoperitoneum with pneumatosis and complete bowel dilation. The infant was made NPO and the medical team initiated gastric decompression, began antibiotics, and consulted surgery.

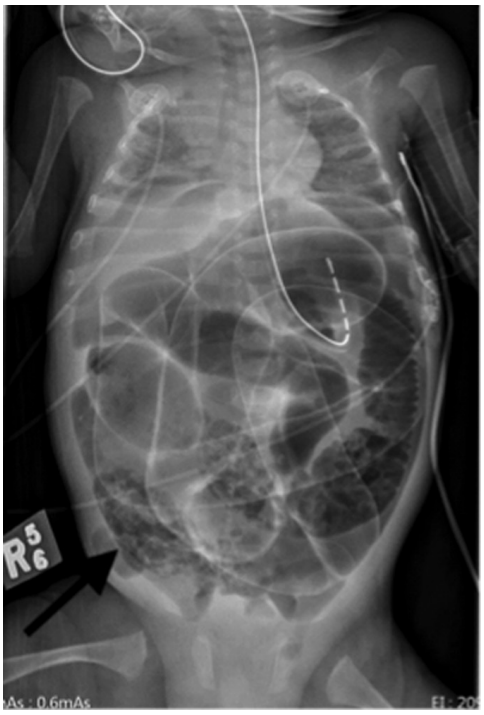

Fig. 22.3 Abdominal plain film x-ray revealing significantly dilated and elongated bowel loops, thickened bowel walls, and pneumatosis *(arrow).*

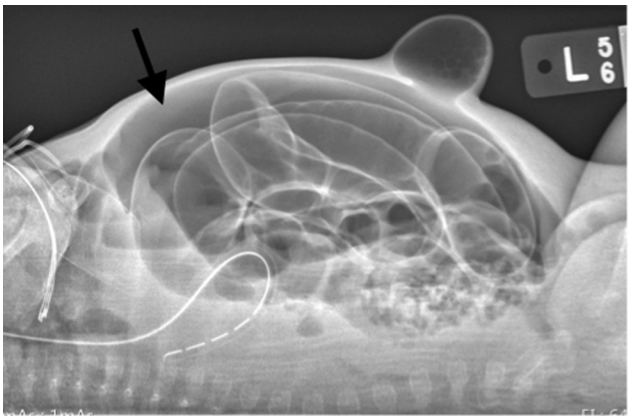

Fig. 22.4 Cross-table lateral abdominal x-ray notable for significant amount of free air within the peritoneal cavity *(arrow),* dilated loops of bowel with pneumatosis.

Exercise 4

Question

4. What laboratory studies may help guide the diagnosis of NEC?
   A. Electrolytes, blood urea nitrogen (BUN), creatinine
   B. Complete blood count (CBC)
   C. Arterial blood gas
   D. Lactate, CRP
   E. All of the above

Answer

E. Laboratory findings can be nonspecific in setting of NEC. All of the above-listed laboratory options can help provide clinical data in addition to physical examination and imaging. The electrolytes, BUN, and creatinine can provide information regarding fluid status and renal function and help with fluid resuscitation and management. When NEC develops, neonates can exhibit leukopenia or leukocytosis, a significant decrease in hematocrit and/or thrombocytopenia. These are all secondary to the inflammatory and/or infectious environment. Arterial blood gases may be significant for metabolic acidosis secondary to a lactic acidemia due to necrotic bowel, or poor systemic perfusion blood gases may also reveal respiratory acidosis, which can be secondary to significant abdominal distension, preventing the diaphragm from full movement leading to respiratory insufficiency. The CRP is a nonspecific inflammatory marker, which may be elevated when NEC is present. However, in this case, the CRP was within normal limits.

No laboratory results are specific for NEC, but they can aid in diagnosing NEC and direct supportive care for the critically ill neonate.

RADIOGRAPHIC EVALUATION

Radiographic findings range from nonspecific focal changes to widespread abdominal involvement. The pathognomonic sign of NEC is intramural gas, or pneumatosis intestinalis, that develops when mucosal damage is present (Battersby et al, 2017). Healthy bowel appears with a distinct mosaic pattern of gas throughout the bowel. It is concerning when this pattern disappears and bowel loops become elongated, especially when coupled with abnormal abdominal physical signs (Siegle et al, 1976). Bowel elongation and dilation can be focal or involve a large portion of bowel; often it is related to gut ileus. The amount of involved dilated gut can correlate with the severity of NEC (Daneman et al, 1978).

When the bowel gas pattern becomes asymmetric and the dilated loops become "fixed" or appear similar in serial images without changes in position, gut necrosis has likely occurred (Epelman et al, 2007). Bowel dilation alone is not a specific sign of NEC, whereas pneumatosis is a confirmatory sign of NEC. Pneumatosis develops from weakened and inflamed bowel lining allowing intraluminal air to become trapped within the submucosa level of the bowel walls. The intramural gas can then extend into the bowel wall veins and travel to the portal venous system, which can be identified as portal venous gas on abdominal plain film imaging (Siegle et al, 1976; Daneman et al, 1978; Epelman et al, 2007).

In severe cases of NEC, the necrotic bowel perforates and intraluminal air fills the peritoneal cavity (Nowicki, 2005). This escaped free air can be identified best on a left lateral decubitus abdominal image near the liver or be seen as a "football" sign on a plain film, where the air illuminates the falciform ligament, peritoneal cavity, and region below the diaphragm (Yajamanyam et al, 2014; Faingold et al, 2005; Lok et al, 2018). Obtaining serial images every 6 to 8 hours is recommended as bowel involvement can rapidly change and new signs can be radiographically identified. Serial radiographic images and ominous signs can identify this progression of NEC. The hope is to identify NEC as early as possible and prevent the continued progression to full bowel necrosis.

Abdominal films have been the gold standard for diagnosing necrotizing enterocolitis when those radiographic signs are present. More recently, there has been an interest in using abdominal ultrasonography for aiding in diagnosis. The first study evaluating neonatal bowel viability with color Doppler sonography was published in 2005. Faingold et al identified gastrointestinal features in healthy neonates including bowel wall thickness, bowel echogenicity, peristalsis, and perfusion of healthy bowel (Faingold et al, 2005). A more current study in 2015 by Staryszak et al using ultrasound in neonates with NEC helped identify areas of sick bowel by observing altered levels of wall echogenicity, changes in wall thickness, pneumatosis, portal venous air, pneumoperitoneum, and fluid within the peritoneal cavity. They also identified areas of disrupted intestinal wall perfusion (Faingold et al, 2005; Staryszak et al, 2015).

Locating these specific regions of involved bowel can aid in the surgical treatment of NEC (Staryszak et al, 2015). The downfall of using abdominal ultrasound is that images can be hindered by significant amount of intraluminal gas, inexperienced technician (s), and/or the inability to obtain a proper ultrasound in relation to timing and the clinical status of the patient (Lok et al, 2018). Currently abdominal radiography

continues to be the standard approach, but other modalities may continue to arise with continued research.

CASE 2 (CONTINUED)

The medical emergency of pneumoperitoneum required immediate surgery. Due to the appearance of complete bowel dilation and clinical decompensation, an exploratory laparotomy was performed. Multiple areas of ileal perforation distal to an internal hernia were discovered. A total amount of 32 cm of bowel was excised in hopes of salvaging the remaining unaffected bowel. The bowel was placed in a silo and the infant received volume resuscitation in the NICU.

Postoperatively the infant continued to require significant resuscitation including volume, blood products, and pressors. The bowel within the silo became discolored and cyanotic. Surgeons took down the silo and found more necrotic bowel. Unfortunately no bowel was salvageable during the second procedure.

Exercise 5

Question

5. What feature identified on abdominal x-ray indicates the need for surgery?
   A. Pneumatosis
   B. Bowel wall thickness
   C. Total bowel dilation
   D. Free air under the diaphragm

Answer

D. Free air under the diaphragm indicates bowel perforation from necrotic bowel. Without surgical intervention, the bowel will continue to leak air and worsen the pneumoperitoneum. The neonate will develop abdominal compartment syndrome and clinically decompensate. The free air needs to be released and the healthy bowel salvaged.

Question

6. What places an infant at higher risk of developing NEC?
   A. Formula feedings
   B. Requiring prolonged respiratory support
   C. Delivery via cesarean section
   D. Birth weight

Answer

D. Birth weight. There is much discussion regarding who is at risk for developing NEC. Birth weight is a major risk factor. The lower the birth weight, the higher risk of NEC development. Low birth weight associated with earlier gestations increases the risk of NEC, as the disease is associated with intestinal immaturity. Infants with intrauterine growth restriction (IUGR) are at a high risk of NEC development. IUGR occurs in utero from placental dysfunction that leads to changes in the fetal cardiac output to support the brain, adrenal glands, and heart. This can predispose the baby postnatally to have impaired gut function (Bozzetti et al, 2013).

PATHOGENESIS

As the diagnosis of NEC can vary, understanding the development of the disease can be quite difficult and multifactorial. The most common NEC presentation is a neonate under 32 weeks' gestational age who is already a few weeks old and receiving enteral feeds (Gordon et al, 2012). Prematurity is the greatest risk factor, as immaturity of the gut in association with underdeveloped cardiac, respiratory, and immune systems lead to hypoxic–ischemic injury to the mucosa (Esposito et al, 2017). These factors can lead to a higher chance of developing an inflammatory cascade and ultimately necrotic bowel (Lok et al, 2018; Bozzetti et al, 2013; Gordon et al, 2012; Esposito et al, 2017). The immature gut at baseline already has reduced peristalsis, thin mucosal layers, and a primitive immune system resulting in a "leaky" gut without a strong barrier. The lack of a protective gut barrier allows gut bacteria to penetrate out of the lumen (Esposito et al, 2017; Oddie et al, 2017). Many believe the introduction of enteral feeds plays a strong role in the development of NEC, as the disease does not occur in utero and cases are rare before initiating enteral feeds (Esposito et al, 2017).

Introduction of feeds may also alter the neonatal microbiome. The volume and rate of feeds have been highlighted as playing a role in the development of NEC; however, a Cochrane review in 2017 evaluated the effects of slow advancements of enteral feeds and the incidence of NEC, as well as neonatal morbidity and mortality. Ultimately the available data did not provide evidence that daily increments of 15 to 20 mL/kg reduced the risk of NEC or death in extremely premature infants (Oddie et al, 2017). Many neonatal units have focused on improving their feeding protocols to optimize nutrition in neonates by starting small amounts of enteral feeds within the first few days of life to optimize growth and to reach full enteral feeds within 2 to 3 weeks of life. Many centers have seen a decrease in the incidence of NEC, especially when initiating feeds with mother's breast milk (Patel et al, 2017; Talavera et al, 2016). This may aid in supporting the beneficial bacteria within the microbiome and building the neonatal gut immune system (Talavera et al, 2016).

The gut microbiome is the balance of good and bad bacteria within the bowel that live in symbiosis creating a healthy environment. It is thought when the microbiome is altered, dysbiosis occurs and creates an unbalanced environment. Many theorize NEC arises from a state of bacterial dysbiosis within the neonatal gut leading to inflammation weakening the gut barrier (Patel and Underwood, 2018). Dysbiosis may occur from the introduction of feeds, formula usage, antibiotics, and acid-altering medications (Talavera et al, 2016; Patel and Underwood, 2018; Jilling et al, 2006). The microbiome has been noted to vary between preterm and term infants. Term infants have an abundance of beneficial commensal bacteria, for example *Bifidobacteria,* whereas preterm infants have less abundant beneficial bacteria (Patel and Underwood, 2018; Jilling et al, 2006). When the microbiome is not in symbiosis or

undergoes constant change, pathogenic bacteria overgrow, leading to a favorable environment for NEC to occur (Underwood et al, 2015). Much research continues today evaluating the microbiome and its strong role in NEC development. A preventive measure to sustain or improve the premature microbiome by use of probiotics is a hot topic now in neonatology, which we will discuss later.

TREATMENT

The development of NEC can vary among neonates. Treatment is dependent on clinical status, the severity, and the amount of bowel affected. During the early stages of NEC, the subtle signs can make it difficult to diagnose NEC initially, possibly delaying treatment. Clinicians will opt for bowel rest and decompression, antibiotic coverage, and management of metabolic disturbances and hemodynamic compromise (electrolyte abnormalities, need for volume resuscitation, respiratory support) (Thompson and Bizzarro, 2008). With physical findings and radiographic changes, medical treatment typically includes 10 to 14 days of bowel rest with supplemental intravenous nutrition and antibiotic coverage. Neonates should be monitored closely for any increase in abdominal distension, discoloration, decreased urine output, electrolyte abnormalities, and new respiratory symptoms, including apneas and/or desaturations (Gupta and Paria, 2016). Typically clinicians will obtain radiographic imaging frequently during the acute stages of NEC to make the diagnosis, evaluate bowel involvement, and identify pneumoperitoneum. When neonates do not respond to conservative medical management or pneumoperitoneum is present, surgical intervention is considered. Surgery is indicated when pneumoperitoneum occurs and certainly with worsening clinical status of the neonate (Thompson and Bizzarro, 2008; Downard et al, 2012).

Surgical NEC is severe gastrointestinal findings that lead to surgical resection of necrotic bowel aiming at maximizing the length of viable intestine. The only absolute criterion for surgical intervention is pneumoperitoneum from perforated bowel, which can be identified by radiography (Shulhan et al, 2017). If a patient presents with clinical decompensation despite all medical efforts, surgery may also be indicated. This involves either placement of a peritoneal drain or exploratory laparotomy (Siggers et al, 2011). The use of a peritoneal drain is controversial. A Penrose drain is placed within the peritoneal cavity to evacuate enteric contents and free air, decompressing the abdominal cavity and preventing compartment syndrome (Henry et al, 2005). Many times this procedure can be performed at the bedside. Many view this as a temporary intervention before moving forward with an exploratory laparotomy to stabilize critically ill neonates (Hackam et al, 2010).

On the other hand, exploratory laparotomy aims at actually removing necrotic bowel. Surgical intervention is greatly dependent on the extent of the disease. The disease can range from focal bowel perforation to multifocal disease involving less than 50% of the intestine to NEC totalis with necrosis of 75% or more of bowel (Papillon et al, 2013). When complete involvement of bowel occurs, no medical or surgical treatment can heal necrotic bowel, and withdrawal of care should be considered (Kim and Albanese, 2006; Papillon et al, 2013). Despite an initial exploratory laparotomy, the disease can be progressive. Many times additional bowel becomes involved, and neonates undergo secondary resections to remove other sections of necrotic bowel (Papillon et al, 2013). Antibiotic coverage is continued postoperatively. Currently there are no trials evaluating the appropriate time of reinitiating enteral feeds postoperatively; the decision to reinitiate feedings depends on the infant's clinical status and overall bowel improvement. Even with all medical and surgical efforts, the morbidity and mortality of NEC remain high (Robinson et al, 2017).

NEONATAL OUTCOMES

NEC is quite a devastating disease and greatly influences neonatal growth and development. Neonates with NEC will have longer hospitalizations and higher incidence of death before discharge than neonates without NEC (Lin and Stoll, 2006; Robinson et al, 2017; Blakely, 2005; Pike et al, 2012). The disease has high morbidities, including postoperative complications such as infections, wound dehiscence, and intestinal strictures. These lead to prolonged periods of bowel rest, delaying the initiation of enteral feeds, longer healing time, and difficulty reaching full enteral feeds due to intestinal strictures affecting overall neonatal growth (Blakely et al, 2005; Pike et al, 2012). Currently with more investigative research and higher survival rates of neonates, long-term outcomes have revealed a higher incidence of neurodevelopmental delays in infants with a history of NEC. In 2012, a large ORACLE Children's study followed neonatal graduates and found children with history of NEC during their neonatal period were at a higher risk of developing functional impairment compared with those who did not have NEC (Ostlie et al, 2003). If neonates survive NEC, they are still at a high risk of several comorbidities.

CASE 3

Baby OL (2.5 kg) is a 40-week diamniotic–dichorionic twin born by uncomplicated vaginal delivery. The pregnancy was uncomplicated. Apgar scores were 5 and 9 at 1 and 5 minutes respectively. The infant remained with mother and started breastfeeding. At 9 hours of life, infant had two large episodes of green-tinged emesis with noticeable increase in abdominal girth with distension.

Exercise 6

Question

7. A term infant presents with bilious emesis. What is the next step?
   A. Obtain blood culture
   B. Upper GI study
   C. Exploratory laparotomy
   D. Begin antibiotics

Answer

B. Upper GI study. A term infant presenting with bilious emesis is a medical emergency. Bilious emesis can be a sign of gastrointestinal obstruction, most commonly from intestinal malrotation with or without volvulus. Gut malrotation with volvulus can immediately lead to gut necrosis and bowel death; therefore an evaluation needs to occur quickly. An upper GI utilizes contrast to highlight the gastrointestinal tract to determine whether malrotation is present. Other concerns for a term infant with emesis are gut atresias, duplication cysts, abdominal masses, and necrotizing enterocolitis. Clinically gastric decompression with an orogastric tube, NPO, and IV fluids should be initiated.

Feedings were held and the infant was started on intravenous nutrition. An abdominal x-ray revealed minimal gas within the distal colon. Laboratory results identified a white count of 26,000/mm^3 with 70% mature neutrophils and 6% band forms. The hemoglobin concentration was 16 g/dL and platelets 320 $\times$ 10^3/L. The C-reactive protein was under 1 mg/L, and electrolytes were within normal limits. A nasogastric tube was inserted for gastric decompression. An upper GI was intended to rule out malrotation, but a repeat abdominal film revealed diffuse pneumatosis (Fig. 22.5). Blood cultures were obtained, and ampicillin and gentamicin were started.

With this new finding of pneumatosis, serial plain and left lateral decubitus films were performed demonstrating continued presence of the pneumatosis without pneumoperitoneum. Surgery was consulted. Conservative management was continued. On day of life 3, the pneumatosis resolved on abdominal imaging. The infant received a total of 10 days of antibiotics and remained NPO for 14 days. Feedings were initiated after this course and advanced slowly.

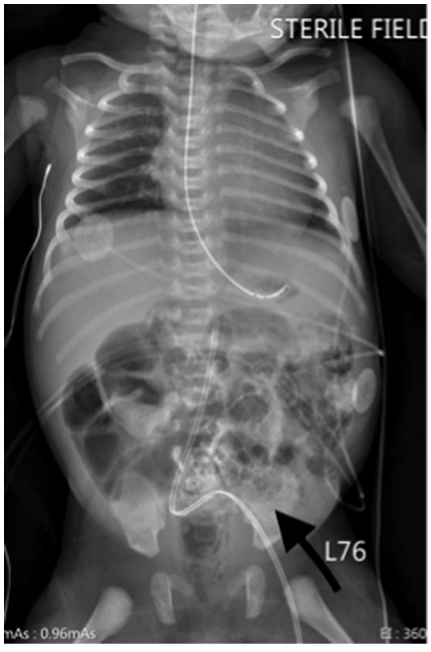

Fig. 22.5 Abdominal x-ray with persistent pneumatosis within the left upper and lower quadrants *(arrow)*.

TERM INFANTS WITH NEC

The development of NEC in term infants can be quite different from NEC in preterm infants. NEC presents much earlier in term infants, typically within the first few days to first week of life (Bozzetti et al, 2013; Lambert et al, 2007). Of all NEC cases, 10% are found in term infants. It is believed to occur from mesenteric bowel ischemia that triggers a cascade of inflammatory events leading to complete bowel necrosis or NEC. Triggers for bowel ischemia include hypoxic–ischemic events either *in utero* or during the delivery process, chorioamnionitis, polycythemia, congenital heart disease (especially left heart obstructive lesions), the advancement of feeds quickly, or feeding volumes that are excessive (Lambert et al, 2007; McClure and Newell, 1999). Clinical signs at the time of NEC development may vary from those found in preterm infants. At times, poor tolerance of feeds or abdominal distension may be the only clinical sign found in a term infant with NEC (Lambert et al, 2007). The mortality is much lower in comparison to preterm infants and does not occur as frequently as NEC in premature infants (Lambert et al, 2007; McClure and Newell, 1999). Term infants typically respond well to conservative management and few require surgical intervention (McClure and Newell, 1999). Despite its rate of occurrence, NEC in a term infant should be considered whenever they present with concerning signs and symptoms for possible NEC.

PREVENTION

With multiple theories of the pathogenesis of NEC, many studies have researched ways of prevention. Cautious feeding strategies, implementing the use of breast milk over formula, and probiotics are among some of the most controversial topics in neonatology. Initiating feeds early on in very low birth weight neonates has aimed at enhancing the neonatal gut by improving the activity of digestive enzymes, enhancing digestive hormones, increasing intestinal blood flow, and improving neonatal gut motility (Morgan et al, 2011). Many studies have shown timing of feeds, enteral volume, and the rate of advancement do not have a significant effect on the development of NEC (Schanler et al, 2005). The use of breast milk and/or donor breast milk has been associated with reduced incidences of NEC in comparison to formula (Donovan, 2006). Breast milk has protective components, such as immunoglobulins, prebiotics, and probiotics, which may overall enhance the neonatal intestinal flora (Berrington et al, 2014). More detailed studies are needed to prove these theories, as many studies have not been truly optimal, and breast milk alone will not eliminate NEC (Donovan, 2006; Berrington et al, 2014).

The microbiome, as mentioned before, plays a strong role in supporting a dynamic intestinal environment. When the microbiome equilibrium of bacteria is altered, neonates might be at a higher risk of developing NEC. Bacteria behave in symbiosis with a balance of beneficial and pathogenic bacteria. The gut microbiota is colonized with over 100 trillion

organisms, with the majority within the distal ileum and colon (Chassard et al, 2014). The microbes are ever changing over the life course, altered by exposure to enteral feedings, nutritional diet, medications, illness, and other exposures (Madan et al, 2012). When the environment is affected by certain influences (e.g., antibiotics), pathogenic flora can take over the gut.

Much research has been devoted to the dysbiosis of the neonatal gut microbiome increasing the risk of NEC. Microbiomes of neonates have been compared with term microbiomes, and striking differences have been found (Madan et al, 2012; Gritz and Bhandari, 2015). Even the infant's mode of delivery (vaginal versus cesarean section) leads to different bacterial gut colonization. *Lactobacillus* and *Prevotella* species have been identified in infants born vaginally, whereas infants born by cesarean section have a higher concentration of *Clostridium, Staphylococcus,* and *Corynebacterium* (Gritz and Bhandari, 2015; Repa et al, 2015). Furthermore, premature guts have decreased peristalsis, lack mature immune systems, and undergo a variety of adverse neonatal exposures including antibiotics, delayed initiation of enteral feeds or periods of no enteral feeds, and healthcare-associated infections, creating a unique microbiome different from healthy term infants (Repa et al, 2015). This diversity may result in dysbiosis of pathogenic bacteria, leading to an unhealthy environment of inflammation, interrupting the gut barrier, and possibly leading to the development of NEC (Madan et al, 2012; Gritz and Bhandari, 2015; Repa et al, 2015; Blackwood et al, 2017). Continued research is needed to understand the makeup of the neonatal microbiome and the steps leading to development of NEC.

With the idea that an unbalanced microbiome may lead to NEC, many believe prevention of the disease may be dependent on keeping the microbiome in a state of symbiosis using beneficial bacteria. *Lactobacillus acidophilus* and *Bifidobacterium* are both beneficial bacteria that have been found in high concentrations within the gut microbiome of healthy neonates; probiotics are postulated to overall support the gut health by improving motility, enhancing gut immunity, and preventing the overpopulation of pathogenic bacteria (Martin and Walker, 2008). Enteral probiotics may populate the developing neonatal gut microbiome and benefit the host and improve gut health (Martin and Walker, 2008; Lau and Chamberlain, 2015).

Multiple studies have been performed and offer evidence of such theories, but direct probiotic exposure can be harmful to the immune deficient neonate. Administering live bacterial probiotics in a neonatal setting may lead to cross contamination with other neonates in the unit, which can lead to higher morbidity and mortality across the entire unit (Lau and Chamberlain, 2015). The exact concentration of particular probiotic strains also varies among manufacturers, which can be quite harmful to neonates (Martin and Walker, 2008; Lau and Chamberlain, 2015). More research is needed to determine the exact concentration, best strains, and timing of administration that overall play a strong role in populating a healthy microbiome and decreasing the incidence of NEC.

CONCLUSION

The practice of neonatology continues to evolve with advancements in scientific and clinical research, but many diseases remain poorly understood. Over the years, the incidence of NEC has declined, yet it still remains with high morbidity and mortality. It can be difficult to diagnose, as symptoms and signs can be quite subtle and the disease can occur rapidly, leaving neonates acutely in an extremely critical status. Despite identification of NEC in its early stages and rapid medical and/or surgical interventions, some neonates still do not survive the disease. Studies of disease pathogenesis, the importance of the neonatal gut microbiome, and the use of probiotics to prevent the development of NEC continue to be key areas of research. Further studies are needed before altering the standard of care and implementing probiotics, which despite their benefits, may also be quite harmful to an immune deficient neonate.

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Abstract: Necrotizing enterocolitis (NEC) is a devastating disease acquired in the neonatal intensive care unit (NICU) and highly associated with younger gestational ages and low birth weights. Despite continued research, much is not known about NEC. The following reviews the theories of NEC pathogenesis, diagnostic features, treatment options, and prevention are guided by a spectrum of cases in the unit.

Keywords: Necrotizing enterocolitis, Pneumatosis, Pneumoperitoneum, IUGR, Probiotics