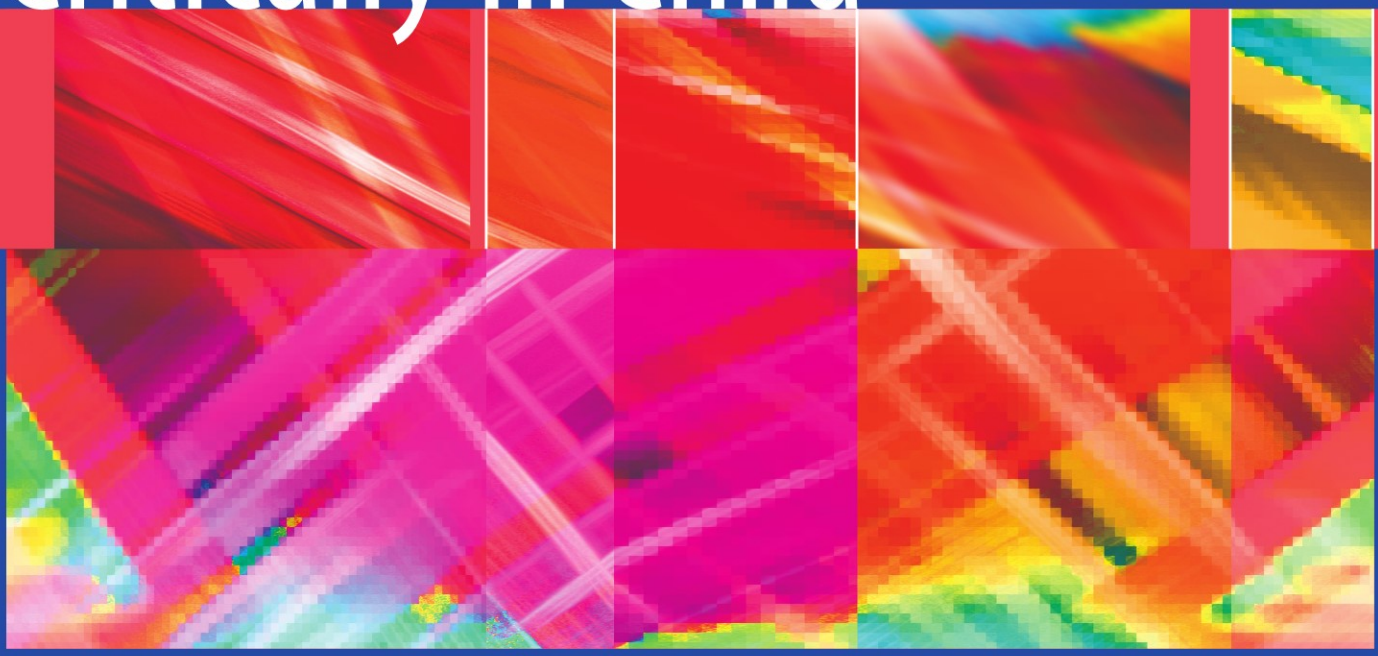
Derek S. Wheeler
Hector R. Wong
Thomas P. Shanley *Editors*

Resuscitation and Stabilization of the Critically Ill Child



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Resuscitation and Stabilization of the Critically Ill Child

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Preface

The care of the critically ill or injured child begins with timely, prompt, and aggressive resuscitation and stabilization. Ideally, stabilization should occur before the onset of organ failure in order to achieve the best possible outcomes. In the following pages, an international panel of experts provides an in-depth discussion of the early recognition, resuscitation, and stabilization of the critically ill or injured child. Once again, we would like to dedicate this textbook to our families and to the physicians and nurses who provide steadfast care every day in pediatric intensive care units across the globe.

Derek S. Wheeler
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Preface to *Pediatric Critical Care Medicine: Basic Science and Clinical Evidence*

The field of critical care medicine is growing at a tremendous pace, and tremendous advances in the understanding of critical illness have been realized in the last decade. My family has directly benefited from some of the technological and scientific advances made in the care of critically ill children. My son Ryan was born during my third year of medical school. By some peculiar happenstance, I was nearing completion of a 4-week rotation in the newborn intensive care unit (NICU). The head of the pediatrics clerkship was kind enough to let me have a few days off around the time of the delivery—my wife, Cathy, was 2 weeks past her due date and had been scheduled for elective induction. Ryan was delivered through thick meconium-stained amniotic fluid and developed breathing difficulty shortly after delivery. His breathing worsened over the next few hours, so he was placed on the ventilator. I will never forget the feelings of utter helplessness my wife and I felt as the NICU transport team wheeled Ryan away in the transport isolette. The transport physician, one of my supervising third-year pediatrics residents during my rotation the past month, told me that Ryan was more than likely going to require extracorporeal membrane oxygenation (ECMO). I knew enough about ECMO at that time to know that I should be scared! The next 4 days were some of the most difficult moments I have ever experienced as a parent, watching the blood being pumped out of my tiny son's body through the membrane oxygenator and roller pump, slowly back into his body (Figures 1 and 2). I remember the fear of each day when we would be told of the results of his daily head ultrasound, looking for evidence of intracranial hemorrhage, and then the relief when we were told that there was no bleeding. I remember the hope and excitement on the day Ryan came off ECMO, as well as the concern when he had to be sent home on supplemental oxygen. Today,

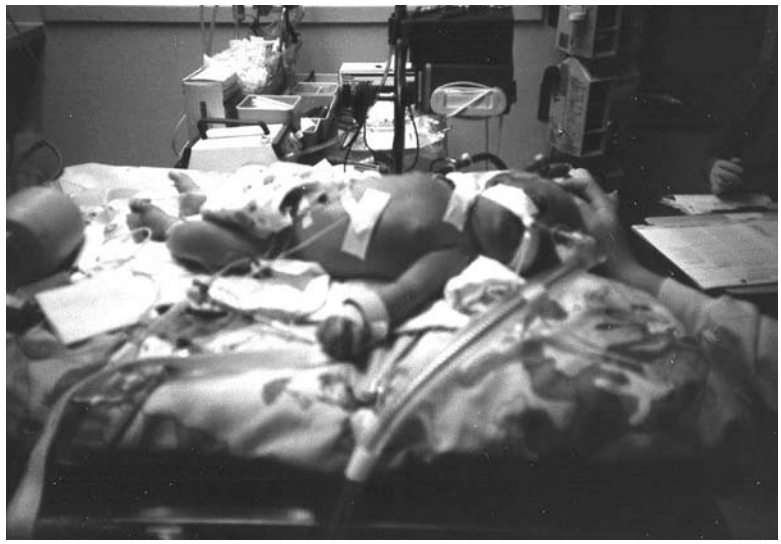

Figure 1

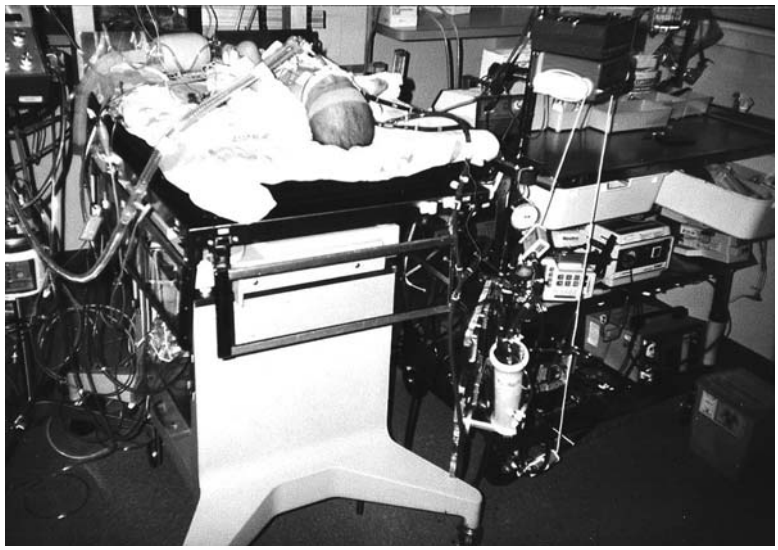

Figure 2

Ryan is happy, healthy, and strong. We are thankful to all the doctors, nurses, respiratory therapists, and ECMO specialists who cared for Ryan and made him well. We still keep in touch with many of them. Without the technological advances and medical breakthroughs made in the fields of neonatal intensive care and pediatric critical care medicine, things very well could have been much different. I made a promise to myself long ago that I would dedicate the rest of my professional career to advancing the field of pediatric critical care medicine as payment for the gifts with which we, my wife and I, have been truly blessed. It is my sincere hope that this textbook, which has truly been a labor of joy, will educate a whole new generation of critical care professionals and in so doing help make that first step toward keeping my promise.

Derek S. Wheeler

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1
Emergency Medical Services for Children

Derek S. Wheeler and Tom LeMaster

History of Emergency Medical Services for Children

The concept of a system for the emergency care and transport of critically ill and injured patients originated thousands of years ago. In fact, the first organized prehospital transport systems were developed in ancient Greece and Rome, when wounded soldiers were transported from the battlefields in chariots. During the Battle of Blenheim (1704), the Duke of Marlborough demanded that his wounded soldiers be transported safely to the rear of the battlefield *by all available wagons from the surrounding countryside* [1]. Baron Dominique-Jean Larrey, Napoleon's chief surgeon, however, is credited with developing the first organized, formal prehospital transport system during the late 18th century. He designed a system of field triage and transport, many of the concepts of which are still in use today [2]. The first organized systems of emergency care and transport of battlefield casualties in the United States were developed in the Civil War (1861–1865) [3]. The concept of air medical transport was first introduced, again by the military, during the Franco-Prussian War (1871), when 160 casualties were transported from the siege of Paris in hot-air balloons [4]. Air medical evacuation systems were further refined during the Korean and Viet Nam Wars.

Following the American Civil War, civilian systems of emergency care and transport were developed using the military systems as a model. The first civilian ambulance services were developed in Cincinnati and New York in 1865 and 1869, respectively [5]. Until that time, funeral home hearses had been the primary mode of transport. Hospital physicians staffed these first ambulances, which were horse-drawn carriages specially designed for moving the ill and injured, although in later years the physicians were replaced by volunteer rescue personnel. Two historic advances in medicine, the introduction of mouth-to-mouth ventilation in 1958 [6] and closed cardiac massage in 1960 [7], provided the firm foundation necessary for the subsequent development of the concepts of advanced life support (ALS) and emergency medical services (EMS).

The National Academy of Sciences published *Accidental Death and Disability: The Neglected Disease of Modern Society* in 1966, bringing to the forefront several major deficiencies in the emergency care system in place at that time. This report provided the impetus for the development and refinement of an organized system of emergency care. The modern EMS system as we know it was established shortly thereafter following passage of both the National Highway Safety Act of 1966 [8] and the Emergency Medical Services Act of 1973 [9]. The EMS system is composed of the following components, which are organized together to provide a comprehensive and timely response to emergencies in the community at large:

1. Prehospital transport systems capable of providing both basic life support (BLS) and ALS in the field, as well as providing timely transfer to a hospital that can provide both emergency care and definitive treatment
2. Emergency departments staffed with appropriately trained physicians, nurses, and ancillary staff
3. Hospitals providing basic and specialized inpatient care
4. Community outreach and education programs
5. Data collection and analysis and quality assurance mechanisms

For the most part, the EMS system has been successful in improving the outcome of patients suffering from trauma and cardiovascular disease. However, the needs of critically ill and injured children were largely ignored in the early planning and development of the EMS system. Children were later noted to represent a substantial proportion of the total number of patients entering the EMS system, representing 10% of all prehospital transports and nearly one-third of all emergency department visits [10,11]. Several subsequent reports documented the need for integrating emergency services for children into existing EMS systems [12–14]. In 1972, Calvin Sia, MD urged the American Academy of Pediatrics (AAP) to work toward the development of a specialized EMS system that would decrease disability and death among critically ill and injured children. Dr. Sia was later joined by Senators Daniel Inouye, Orrin Hatch, and Lowell Weicker in sponsoring the first Emergency Medical Services for Children (EMSC) legislation, which was subsequently passed in 1984.

In response to these measures, a growing interest in EMSC has developed nationwide, culminating in the development of a specialty in pediatric emergency medicine now approved by both the

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American Board of Pediatrics and the American Board of Emergency Medicine, as well as the establishment of federally funded grants to improve the entire EMSC system. Today, all 50 states, the District of Columbia, and 4 U.S. territories receive funding through the EMSC Program, which is jointly administered by the U.S. Department of Health and Human Services' Health Resources and Services Administration, Maternal and Child Health Bureau, and the U.S. Department of Transportation's National Highway Traffic Safety Administration (NHTSA). Notably, the program received over $20 million in funding in fiscal year 2003.

The EMSC program is supported by approximately $20 million in federal funding. Regrettably, at the time of this writing, the EMSC program was threatened by legislation in the 108th Congress, House bill H.R. 3999, *TRAUMA Act of 2004*. As introduced, the bill contained language that would have eliminated the EMSC program by striking the authorizing language for the program. Instead, the bill would have allowed trauma care grant funds to be used to improve EMSC, but would spread the funding among several other programs. Furthermore, the bill offered no guarantee of how much money would be dedicated solely to children's programs. Unfortunately, history has made clear that unless EMSC has distinct and dedicated authority and support, children's emergency medical needs will go unmet. After intensive lobbying efforts by the AAP and strong advocacy from emergency medicine pediatricians and others, the bill died with the congressional adjournment.

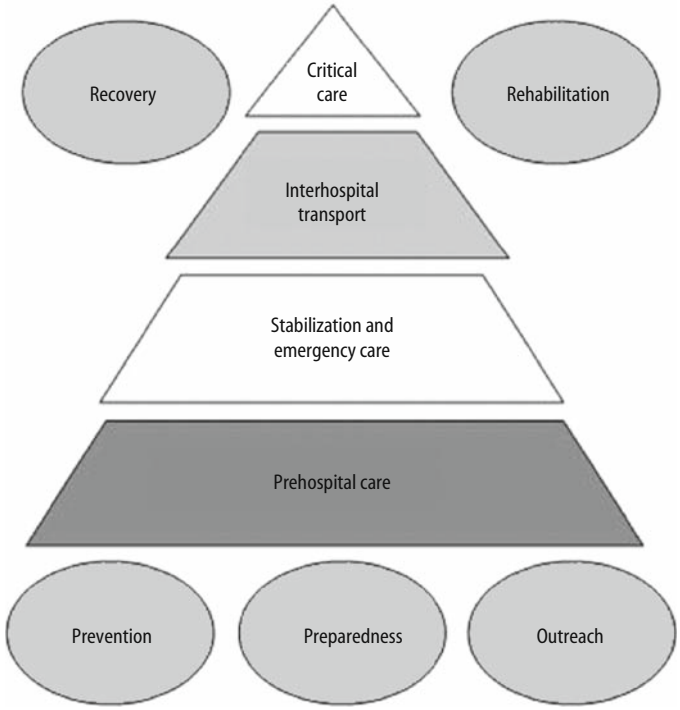


FIGURE 1.1. The emergency medical services for children pyramid. Emergency care works best when it is delivered in a vertically integrated system that ensures that a critically ill or injured child will be cared for by trained, competent personnel at all levels.

The Emergency Medical Services for Children Pyramid

Prevention, Emergency Preparedness, and Emergency Medical Services Access

The EMSC system is a vertically integrated system that ensures that critically ill and injured children will be cared for by trained, competent personnel at all levels. As illustrated in the EMSC pyramid (Figure 1.1), community outreach programs emphasizing emergency preparedness and prevention are an important facet of EMSC. All health care providers, including pediatricians, family physicians, and nurse practitioners, who care for children are in a unique position to ensure that parents and other caretakers are provided with the knowledge and instruction to prevent injuries and emergencies, recognize critically ill children, provide first aid and BLS, and activate the EMS system.

Accidental injury is the leading cause of death in children, accounting for approximately 25,000 deaths, 600,000 hospital admissions, and 16 million emergency department visits annually, with costs approaching $7.5 billion per year [15,16]. The majority of these injuries will occur at home in the presence of a parent or other care provider. A child's primary health care provider is therefore in an ideal position to provide instruction and advice on injury prevention and safety during the health maintenance visit. Unfortunately, graduating medical students and pediatric residents receive only limited instruction in injury prevention during their medical education and pediatric residency training [17,18]. Furthermore, office-based pediatricians may not provide enough information on injury prevention and safety during routine health maintenance visits. For example, one study showed that pediatricians spent an average of nearly 10 minutes with each patient, devoting only 97 seconds to anticipatory guidance for mothers with infants younger than 5 months of age. Less than 2% of this time was spent discussing issues on safety and injury prevention [19]. Pediatric health care providers need to recognize and understand that injury prevention and safety counseling is cost effective; in fact, one study estimated that every dollar spent on injury prevention counseling would save more than $13 in health care expenditures later [20].

Pediatricians and other primary care providers are the first and most important line of defense against childhood emergencies in the EMSC pyramid. Anticipatory guidance on injury prevention and safety should be included in every health maintenance visit and should be tailored to the risks prevalent for a given community, as well as the risks prevalent for a given developmental age group. Pediatricians should participate in and support the many community-wide education programs and public awareness campaigns that have documented success in improving outcome from burns, motor vehicle accidents, pedestrian injuries, and bicycle injuries [21–25]. Other educational programs offered to children and their families include Safety Fairs, Safety Outreach programs offered at school, and safety equipment such as car safety seats and bike helmets offered at a discounted price. Some emergency departments have established safety stores within the emergency department.

Unfortunately, studies have shown that EMS may be inappropriately used or underused in emergency situations [26–30]. Parents need to be educated on both when and how to access community emergency services. Studies have shown that accessing emergency care via a universal emergency access number such as *911* is more efficient than calling a physician or hospital directly [31]. Universal EMS access numbers such as 911 are easy to remember, and surveys have documented that even under the stressful conditions of an

emergency, individuals are much more likely to remember and successfully dial 911 than a seven-digit access telephone number [31,32]. The presence of a universal emergency access number such as 911 is entirely dependent on local jurisdiction and funding, however, and, unfortunately, a national survey conducted in 1992 found that only 60% of the population and 42% of the United Sates had access to emergency services through 911 [33].

Hopefully, if parents are given the proper instructions, pediatricians will rarely, if ever, encounter a critically ill child in the office setting. Unfortunately, several studies have shown that this is not necessarily the case [34–45]. A telephone survey of 51 clinics in the state of Connecticut found that a total of 2,400 emergency cases are seen annually, with a median of 24 emergencies per office practice per year. The survey also noted that, in the majority of cases, offices were generally unprepared and unequipped to handle these emergencies. Only 27% of office staff members were certified in BLS, whereas only 17% were certified in pediatric advanced life support (PALS). In several instances, important resuscitation equipment and medications were missing. Reasons cited for the disturbing lack of preparedness included (1) emergencies were rarely seen (despite evidence to the contrary; (2) pediatricians and other office personnel were too busy to obtain the necessary training and certification; (3) practices were already equipped and staffed appropriately (again, despite evidence to the contrary); and (4) emergency equipment was too costly to purchase [38].

Pediatricians need to ensure that their office personnel are appropriately trained to recognize and provide initial treatment to critically ill children. At a minimum, all office personnel should be trained in BLS, and, ideally, personnel should be trained in PALS. Appropriate care cannot be administered, even when office personnel are properly trained, if the office is not adequately equipped, although the list of equipment and medications necessary for emergencies will vary depending on the location of the office and its proximity to the hospital. However, in all cases, whether the office is located in an urban, suburban, or rural setting, a minimum set of equipment and medications should be readily available (Table 1.1) [43–50].

Having the proper equipment and medications, however, is not enough. Equipment must be periodically checked for proper functioning, and annual maintenance must be performed. Ideally, all emergency equipment and medications should be kept in a centralized, easily identified location. Finally, emergency equipment and medications should only be used for emergency situations—this will ensure that all supplies will be available if and when an emergency actually occurs. Office personnel should be oriented to the location and proper use of resuscitation equipment and medications.

Outreach programs by regional pediatric tertiary care centers may represent an effective means to improve pediatric emergency preparedness in the office setting, although further studies are required [44,45,49–53]. *Mass mail* campaigns and distribution of office emergency preparedness guidelines are probably not effective [44]. Successful outreach programs involve an active commitment and *on-site* training [45]. Ideally, an office emergency course should cover a broad range of topics, including how to recognize an emergency and choosing appropriate emergency equipment for the office. The course should provide information on staff preparation for office emergencies (including the training of *front office* reception personnel), update health care providers on basic resuscitation skills, and teach office personnel to recognize EMS providers as members of the team. Ideally, the course should be concise enough so that it can be completed during a monthly office staff meeting or in-service period.

Table 1.1. Suggested minimum pediatric office equipment and medications.

Airway/breathing
Oxygen source with flowmeter
Oxygen masks (preemie, infant, child, and adult sizes)
Bag-valve-mask resuscitators with reservoir (250 mL and 500 mL)
Suction (wall or portable)
Suction catheters (Yankauer, 8/10/12 F)
Oral airways (size 0–5)
Nasal cannulas (infant, child, and adult)
Optional for tracheal intubation:
Endotracheal tubes, sizes 2.5 to 6.0 (uncuffed) and 6.0 to 8.0 (cuffed)
Laryngoscope with spare batteries and bulbs
Laryngoscope handle with straight and curved blades
Stylets
Disposable end-tidal CO_2 detector
Circulation
Intraosseous needles (15/18 gauge)
Intravenous catheters (20/22/24 gauge)
Butterfly needles
Intravenous boards, tape, alcohol wipes, tourniquets
Intravenous fluids (0.9% saline, lactated Ringer's)
Pediatric drip chambers and tubing
Miscellaneous equipment
Blood pressure cuffs (neonate, infant, child, and adult sizes)
Sphygmomanometer
Nasogastric tubes (10/14 F)
Feeding tubes (3/5 F)
Foley catheters
Cardiac arrest board
Pulse oximeter
Portable nebulizer
Portable electrocardiographic monitor/defibrillator—may substitute automated external defibrillator
Medications
Epinephrine (1 : 1,000 and 1 : 10,000 preparations)
Albuterol
Racemic epinephrine
Activated charcoal
Lorazepam or diazepam (rapid-acting anticonvulsant)
Phenobarbital (long-acting anticonvulsant)
Fosphenytoin (long-acting anticonvulsant)
Antibiotics, parenteral
Methylprednisolone
Dextrose (25%, 50%)
Diphenhydramine, parenteral
Atropine sulfate
Sodium bicarbonate (4.2%, 8.4%)
Naloxone

Prehospital Care

The goal of prehospital care, the first tier of the EMSC pyramid, is to provide immediate medical care to ill or injured children who are outside the hospital setting and then to transport these patients to the hospital in a timely and expeditious manner. Many EMS providers have limited opportunities to maintain the skills learned during EMS training programs. Therefore, EMS providers need to maintain skills and knowledge by participating in pediatric training such as PALS and Pediatric Education for PreHospital

Professionals Course (PEPP). In addition to training, EMS professionals need to maintain proper equipment to care for the ill or injured child.

Professional, prehospital emergency care begins the moment the emergency access number (usually 911) is contacted. Dispatchers have the first opportunity to initiate emergency care through the provision of instructions to the caller at the scene. The use of pediatric-specific emergency protocols reduces the variability of information, as well as ensuring that succinct, accurate information is provided to the caller. Unfortunately, few communities utilize such protocols. Protocols should be developed so that dispatchers can properly instruct callers in pediatric BLS maneuvers, such as rescue breathing and relief of foreign-body airway obstruction [54–59]. Finally, dispatch personnel should be trained to perform telephone triage to dispatch the appropriate level of emergency care at either the BLS or ALS level.

There are three general categories of prehospital care providers, broadly designated as first responders, BLS providers, and ALS providers. A nationally standardized curriculum for first responders, emergency medical technician (EMT)-basic, EMT-intermediate, and EMT-paramedic, has been developed by the NHTSA. Currently, there is no federally mandated curriculum for the training of prehospital providers in emergency pediatrics, and the amount of training received is extremely variable from community to community. Historically, most prehospital care providers receive little education and training in the care of the critically ill pediatric patient [60–66]. However, recent studies suggest improvements are being made [67–70].

The term *first responder* refers to the prehospital care provider, regardless of credentials, who arrives first on the scene. In the context of classification of level of training, however, the term refers to a police officer, firefighter, or other health care professional who has received additional training and who possesses limited but potentially lifesaving skills. These skills typically consist of clearing the airway, bandaging and splinting, providing hemorrhage control, and administering BLS. The NHTSA First Responder curriculum consists of 40 hours of additional training, although training specific to pediatric emergencies is extremely limited.

The capabilities of BLS providers, often referred to as EMTs (encompassing both the EMT-basic and EMT-intermediate NHTSA curriculum) exceed those of the first responders. In addition to BLS skills, EMTs are trained in field triage, patient assessment, oxygen administration, automated external defibrillation, assisted ventilation, application of the pneumatic antishock garment, and transport of patients to the hospital. The EMT-basic certification requires approximately 110 hours of education and training with little to no time designated exclusively for pediatric emergency care. The EMT-intermediate curriculum includes a 3-hr module entitled *Childhood and Pediatrics* dedicated to both obstetric and pediatric emergencies.

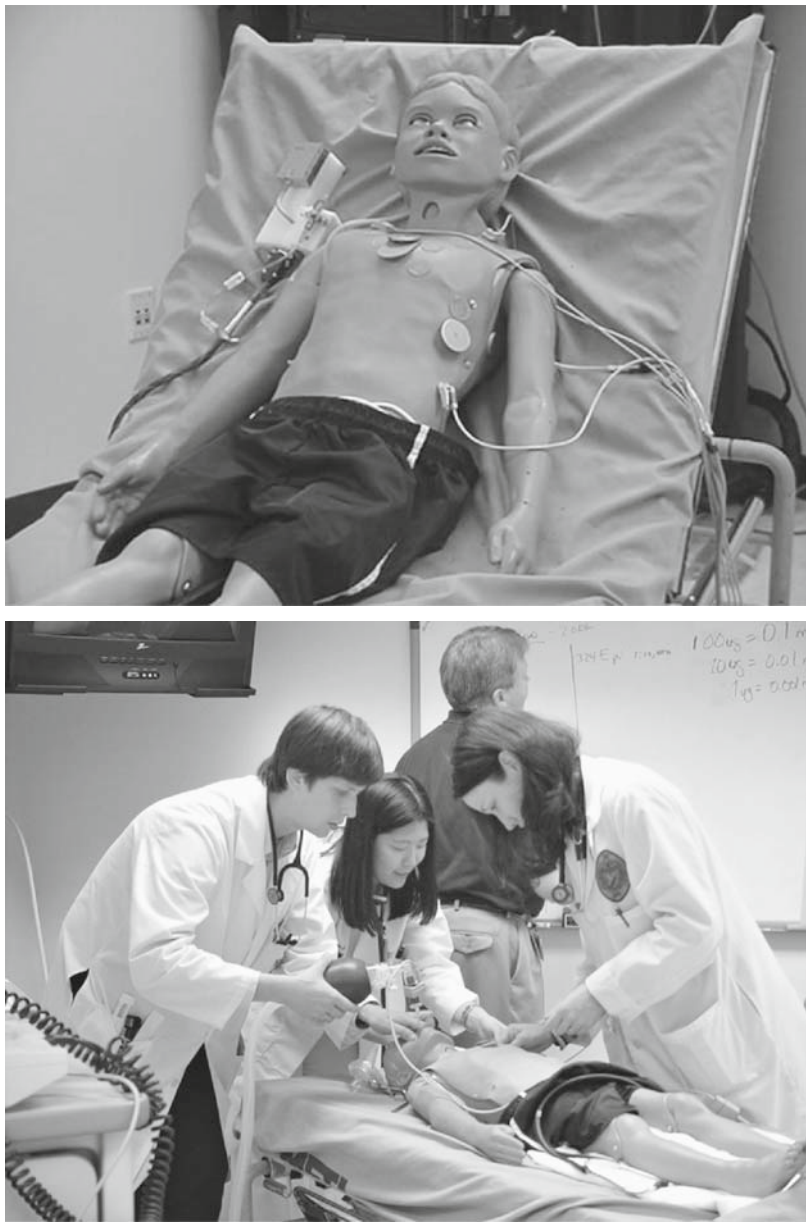
Advanced life support providers, encompassing the EMT-paramedic NHTSA curriculum, are capable of providing advanced resuscitation in the field. The EMT-paramedic is trained in advanced airway management, vascular access, medication administration, and defibrillation and cardioversion. The EMT-paramedic certification requires approximately 600–800 hours of education and training, which includes a 6-hr didactic experience and 24 hr of clinical experience in emergency pediatrics (www.NHTSA.gov).

A survey conducted in 1983 of EMT-paramedic training programs documented that 97% of the programs included some method of training in pediatric tracheal intubation in the curriculum, varying from mannequin and animal models to tracheal intubation performed in the operating room setting [71]. However, the ideal method of training has not been identified. Human simulators are now currently available that may significantly improve the education and training of paramedics, as well as physicians, in pediatric airway management and resuscitation skills. The pediatric patient simulator represents a quantum leap in pediatric emergency medical education. Until recently, one of the only ways to practice emergency medical skills for children was on a static mannequin that offered no return information. Human simulators offer health care professionals the opportunity to manage a patient in real time and see the results of their treatment.

The pediatric human patient simulator (HPS) at Cincinnati Children's Hospital Medical Center, called *PediaSim,* is approximately the size of a 7-year-old child weighing 20 kg (Figure 1.2). PediaSim simulates *real* responses to critical injury and medical interventions. He features a realistic airway and realistic pulmonary, cardiovascular, metabolic and neurologic systems and can be programmed to display a wide range of conditions and symptoms (see Figure 1.2). The HPS is computer driven, based on sophisticated mathematical models of human physiology and pharmacology. These models determine PediaSim's responses to appropriate and inappropriate medical interventions in real time, allowing students to immediately experience the effects of their treatments:

- Caregivers can assess vital signs and physical examination findings (such as blood pressure, temperature, differential pulses, heart sounds including murmurs and gallops, breath sounds including wheezing, and respiratory efforts).
- Caregivers can perform procedures in a realistic fashion (such as tracheal intubation, vascular access, hemodynamic monitoring, electrocardiographic interpretation, and defibrillation/cardioversion).
- The simulator can recognize appropriate cardiopulmonary resuscitation technique.
- PediaSim recognizes what drugs are being administered at what amounts and will react accordingly. The simulator will start to breathe once his airway receives adequate oxygenation and ventilation.

The effect of prehospital airway management on outcome has yet to be definitively established. Studies documenting a poor success rate, as well as a high incidence of associated complications, have led to some concern [72–77]. There is no question that multiple, unsuccessful attempts at endotracheal intubation in the field prolongs scene time and may adversely affect outcome. However, in certain cases, airway control and the institution of ALS in the field is quite desirable. For example, survival from respiratory arrest approaches 50% when early and appropriate resuscitation is provided [78]. In addition, early ALS in the field has been shown to improve the outcome of near-drowning victims with pulseless cardiac arrest [75,79]. Gausche et al. conducted a large, prospective, randomized trial of prehospital tracheal intubation by paramedics in children age 12 years or younger. Children were assigned to either a bag-valve-mask ventilation group (n = 410 children) or a tracheal intubation group (n = 420 children). There were no significant differences between the two groups with respect to survival or neurologic outcome [80]. Obviously, this question continues to generate significant controversy and speculation.



A

B

Figure 1.2. (A,B) Two views of the Pediatric Human Patient Simulator at Cincinnati Children's Hospital Medical Center.

Several studies have also examined the performance of intraosseous vascular access by prehospital care providers [81–87]. Intraosseous access is relatively simple and provides a route for the administration of both medications and fluids. Vascular access with this method can be reliably achieved in less than 30 seconds, even by providers with little experience [84–87]. Complications, including osteomyelitis, tibial fracture, compartment syndrome, and skin necrosis have been reported in less than 1% of patients [88–90]. Again, several authors have suggested that the increased scene time associated with on-site stabilization may be associated with adverse outcome and that prehospital care providers need to concentrate on transporting the patient as rapidly as possible to the hospital [91,92].

Appropriate prehospital care cannot be provided even with the proper training of prehospital personnel unless appropriate equipment is available. Generally, ambulance units are classified as either BLS units or ALS units. Recommended equipment lists for BLS and ALS units are provided in Tables 1.2 and 1.3. Unfortunately, again surveys suggest that many prehospital care providers are poorly equipped to deal with pediatric emergencies (see later discussion) [11,14,37,60,61].

Physicians affiliated with EMSC systems may serve in a variety of roles, from part-time medical advisors to full-time medical directors and administrators. Off-line medical supervision and direction, often referred to as *indirect medical control*, involves the development and periodic revision of protocols and standing orders, implementation of quality assurance programs, and continuing education of EMS personnel. Protocols for patient treatment, triage, and transfer should be developed. Standards for training and certification of prehospital care providers will also help to ensure quality of care.

To improve pediatric care in the community, tertiary care centers need to establish a strong communication system with the prehospital care community. Lines of communication must exist between

Table 1.2. Suggested minimum pediatric emergency equipment for basic life support ambulance units.

Airway/breathing
Oxygen source with flowmeter
Oxygen masks (preemie, infant, child, and adult sizes)
Nasal cannulas (infant, child, adult sizes)
Bag-valve-mask resuscitators with reservoir (infant, child, and adult sizes)
Oral airways
Nasal airways
Portable suction device
Suction catheters (Yankauer and 6–14 F)
Bulb suction device
Nebulizer
Miscellaneous
Blood pressure cuffs (infant, child, and adult sizes)
Sphygmomanometer
Rigid cervical collar (infant, child, and adult sizes)
Automated external defibrillator
Backboard
Extremity splints
Sterile scissors

prehospital care providers and a physician. Most systems are set up in such a manner that a base of operations exists in a centralized emergency department or other designated facility where the on-duty emergency physician provides moment-to-moment medical supervision of EMSC personnel caring for patients in the field, a system often referred to as *direct medical control*. The communication center within the pediatric medical center should receive all calls from EMS units and offer physician assistance as requested by the prehospital care provider. Physicians taking these calls will need to be knowledgeable in local EMS protocols and capabilities.

Table 1.3. Suggested minimum pediatric emergency equipment for advanced life support ambulance units.

Advanced life support units should have all the equipment listed in Table 21.2 (basic life support units), plus the following items:
Airway/breathing:
Laryngoscope batteries and bulbs
Laryngoscope handle with straight and curved blades, various sizes
Pediatric and adult Magill forceps
Stylets (child and adult sizes)
Endotracheal tubes
Uncuffed, 2.5 to 6.0 mm OD
Cuffed, 6.0 to 8.0 mm OD
Circulation:
Intravenous catheters (14–24 gauge)
Intravenous boards, tape, alcohol pads, tourniquets
Intravenous fluids (0.9% saline, lactated Ringer's)
Microdrip intravenous devices
Intraosseous needles (15 and 18 gauge)
Monitor and defibrillator
Drug dose chart or Broselow tape
Resuscitation medications
Epinephrine (1 : 1,000 and 1 : 10,000 preparations)
Atropine sulfate
Sodium bicarbonate (4.2%, 8.4%)
Naloxone
Albuterol (inhaled)
Diazepam (rapid-acting anticonvulsant that can be administered per rectum)
Dextrose (D25W, D50W)

Providing a mechanism for the prehospital care provider to communicate directly with a physician will improve the care of the child prior to arrival at the medical center and will allow the medical center emergency department to be better prepared for the patient's arrival by having necessary resources readily available. The communication center may also receive calls from other emergency departments, community physician offices, and air ambulance services. In fact, in most states medical direction of EMSC systems providing advanced care is required by law. Several investigators, however, have noted that systems of direct medical control result in prolonged out-of-hospital times [93–96]. Furthermore, in most cases, direct medical control does not result in orders for care beyond what has been dictated by field protocols. Regardless, most EMSC personnel feel that communication with a physician is helpful and desirable [93,97–99].

Outreach programs by regional pediatric tertiary care centers may represent an effective means to improve pediatric emergency preparedness in the prehospital care setting by coordinating efforts to ensure proper pediatric equipment is stocked on the rescue units. For example, the EMSC Program at Cincinnati Children's Hospital Medical Center provides community EMS providers with *pedi kits* and exchanges these kits after they have been used (Figures 1.3 and 1.4) [100]. In addition to medical equipment, outreach programs should provide medication and equipment calculation tools to community prehospital care providers in the form of cards, booklets, or length based resuscitation tapes. Finally, outreach programs should provide on-site pediatric training to community EMS services. Because of EMS budget constraints, this service is often provided at no charge. The training should include both didactic sessions and skills review and practice sessions. The outreach program must commit sufficient resources to these kinds of programs, as many of these courses must be offered in the evenings and weekends.

The entire EMSC system depends on a well-organized, well-functioning prehospital care system. Trained, adequately equipped providers need to be able to reach the critically ill or injured child, provide initial care as appropriate, and then provide transport to

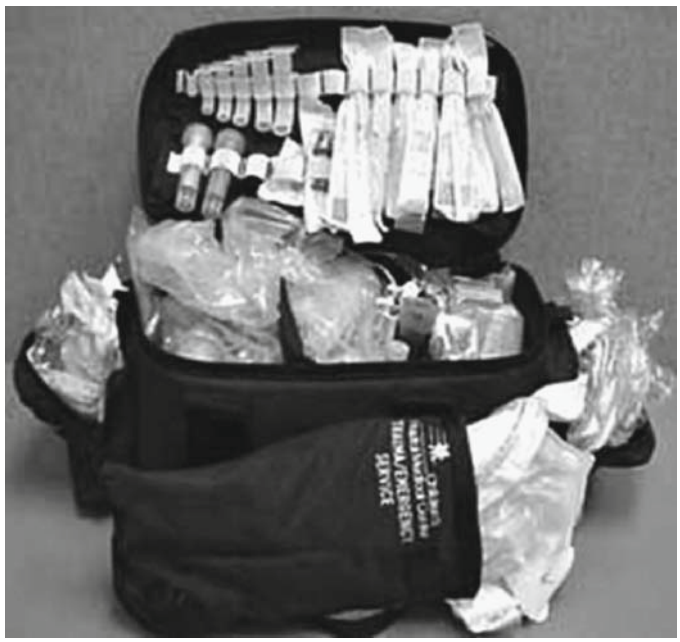
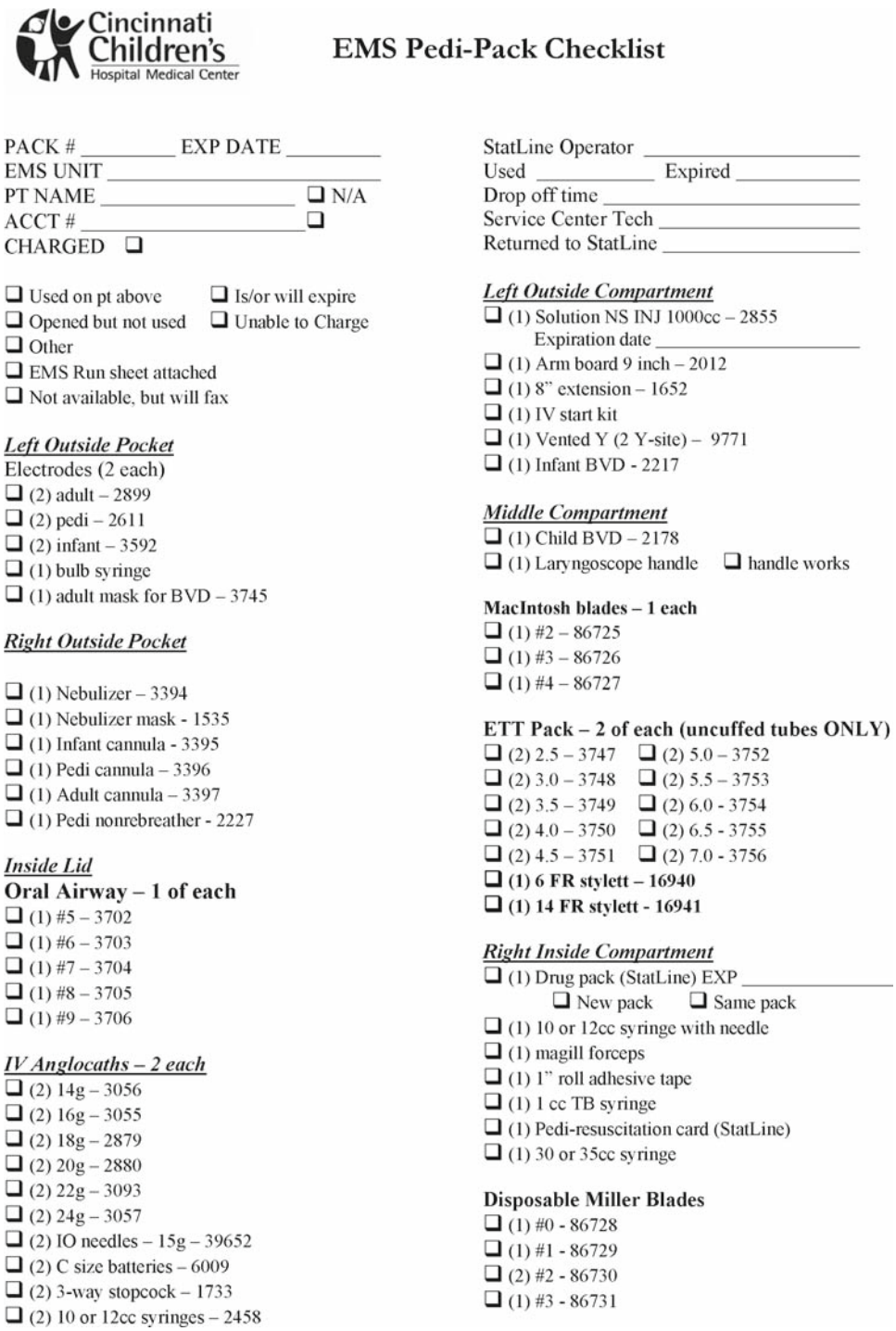


Figure 1.3. The pedi kit.



Cincinnati Children's Hospital Medical Center

EMS Pedi-Pack Checklist

PACK # _____ EXP DATE _____
EMS UNIT _____
PT NAME _____ ❑ N/A
ACCT # _____ ❑
CHARGED ❑

❑ Used on pt above ❑ Is/or will expire
❑ Opened but not used ❑ Unable to Charge
❑ Other
❑ EMS Run sheet attached
❑ Not available, but will fax

Left Outside Pocket
Electrodes (2 each)
❑ (2) adult – 2899
❑ (2) pedi – 2611
❑ (2) infant – 3592
❑ (1) bulb syringe
❑ (1) adult mask for BVD – 3745

Right Outside Pocket

❑ (1) Nebulizer – 3394
❑ (1) Nebulizer mask - 1535
❑ (1) Infant cannula - 3395
❑ (1) Pedi cannula – 3396
❑ (1) Adult cannula – 3397
❑ (1) Pedi nonrebreather - 2227

Inside Lid
Oral Airway – 1 of each
❑ (1) #5 – 3702
❑ (1) #6 – 3703
❑ (1) #7 – 3704
❑ (1) #8 – 3705
❑ (1) #9 – 3706

IV Anglocaths – 2 each
❑ (2) 14g – 3056
❑ (2) 16g – 3055
❑ (2) 18g – 2879
❑ (2) 20g – 2880
❑ (2) 22g – 3093
❑ (2) 24g – 3057
❑ (2) IO needles – 15g – 39652
❑ (2) C size batteries – 6009
❑ (2) 3-way stopcock – 1733
❑ (2) 10 or 12cc syringes – 2458

StatLine Operator _____
Used _____ Expired _____
Drop off time _____
Service Center Tech _____
Returned to StatLine _____

Left Outside Compartment
❑ (1) Solution NS INJ 1000cc – 2855
Expiration date _____
❑ (1) Arm board 9 inch – 2012
❑ (1) 8" extension – 1652
❑ (1) IV start kit
❑ (1) Vented Y (2 Y-site) – 9771
❑ (1) Infant BVD - 2217

Middle Compartment
❑ (1) Child BVD – 2178
❑ (1) Laryngoscope handle ❑ handle works

MacIntosh blades – 1 each
❑ (1) #2 – 86725
❑ (1) #3 – 86726
❑ (1) #4 – 86727

ETT Pack – 2 of each (uncuffed tubes ONLY)
❑ (2) 2.5 – 3747 ❑ (2) 5.0 – 3752
❑ (2) 3.0 – 3748 ❑ (2) 5.5 – 3753
❑ (2) 3.5 – 3749 ❑ (2) 6.0 - 3754
❑ (2) 4.0 – 3750 ❑ (2) 6.5 - 3755
❑ (2) 4.5 – 3751 ❑ (2) 7.0 - 3756
❑ **(1) 6 FR stylett – 16940**
❑ **(1) 14 FR stylett - 16941**

Right Inside Compartment
❑ (1) Drug pack (StatLine) EXP _____
❑ New pack ❑ Same pack
❑ (1) 10 or 12cc syringe with needle
❑ (1) magill forceps
❑ (1) 1" roll adhesive tape
❑ (1) 1 cc TB syringe
❑ (1) Pedi-resuscitation card (StatLine)
❑ (1) 30 or 35cc syringe

Disposable Miller Blades
❑ (1) #0 - 86728
❑ (1) #1 - 86729
❑ (2) #2 - 86730
❑ (1) #3 - 86731

FIGURE 1.4. Contents of the pedi kit. The EMSC Outreach Program at Cincinnati Children's Hospital Medical Center provides community emergency medical service providers with pedi kits and exchanges these kits after they have been used.

the emergency department best suited for that particular child's needs.

Stabilization and Emergency Care

The community emergency department represents the next tier of the EMSC pyramid. Children may be admitted to the emergency department directly, via the prehospital care network, or upon referral from a primary care provider's office. Following evaluation and care in the emergency department, children may be discharged to home, admitted to the hospital, or transferred to a tertiary care facility. In many cases, physicians and other health care personnel working in a community emergency department have only limited experience with the care of critically ill children. Significant differences in the management of critically ill children exist among emergency department physicians, depending on the level of train-

ing and specialization [101–107]. For example, in a survey of emergency department physicians practicing near a tertiary care pediatric referral center, more than 25% of physicians stated that they were not comfortable with performing potentially life-saving pediatric procedures, such as rapid sequence tracheal intubation, vascular access, chest tube placement, or intraosseous line placement [107]. Many emergency medicine physicians generally describe a certain level of discomfort with treating critically ill children compared with adults [108,109]. Subspecialty fellowship training in pediatric emergency medicine may not provide sufficient training and exposure in life-saving procedures either [110,111]. However, as pediatric emergency medicine is a relatively new subspecialty, it is anticipated that with further development and standardization of the pediatric emergency medicine fellowship curriculum this will change in the near future.

Community pediatricians who are available for consultation to the community emergency department may have limited experience in emergency pediatrics as well. Graduate medical education in pediatrics has undergone a paradigm shift in recent years, such that outpatient, ambulatory care is emphasized, often at the expense of training in critical care and emergency pediatrics [112–118]. For example, in a recent survey 33% of chief residents rated their pediatric residency program's rotation in pediatric emergency medicine as *below average* [113]. Pediatricians need to be prepared to handle emergencies in their offices, as well as in the emergency department setting. Therefore, residency training programs must recognize the importance of training in emergency pediatrics and critical care. Rotations in a pediatric emergency department should be included in the residency training curriculum. Generally, rotations with an established, formal curriculum, including a core lecture series, skills workshops, and case-by-case precepts by a pediatric emergency medicine attending physician are more likely to be worthwhile and educationally successful [113,115–118].

The guidelines for pediatric critical care training are relatively nonspecific, but training should provide residents with a basic understanding of the pathophysiology of acute, life-threatening diseases in children. In addition, residents should acquire the knowledge and skills necessary to diagnose and manage these illnesses, with special emphasis in areas such as resuscitation, initial management, and stabilization for transport [115–122]. These issues are further discussed in Chapter 8. There are also several opportunities for pediatricians to maintain their skills and proficiency in emergency pediatrics after they have finished their residency training. Ideally, certification in PALS, as taught by the American Academy of Pediatrics and the American Heart Association, should be maintained.

Every community emergency department should be able to provide the initial assessment, resuscitation, stabilization, and transport of a critically ill or injured child. The needs of a particular emergency department will depend on its location and proximity to a tertiary care referral center. The rural community-based emergency department may be placed in a situation where a critically ill child will require stabilization of the airway prior to a lengthy transport to a tertiary care facility. Unfortunately, the physicians who staff the rural community-based emergency department do not have much experience with caring for critically ill children. Regardless of their location and proximity to the tertiary care referral center, all emergency departments should have a minimum list of pediatric emergency equipment (Table 1.4).

Interhospital Transport

Most critically ill and injured children will receive their initial hospital care in the emergency department of a small community hospital, and many of these patients will ultimately require transfer to a tertiary pediatric care center (i.e., interhospital transport). Several options are available. First, the same transport team that brought the child from the scene to the emergency department (i.e., the prehospital transport team) could transport the child to the tertiary care hospital. An additional option would be to supplement the prehospital transport team with a physician or other provider with specialized skills (emergency nurse, paramedic, respiratory therapist, etc.). The final option would be to utilize a dedicated pediatric critical care transport team. Despite the longer waiting period required for the team to mobilize and travel from the tertiary care center, this is usually the safer and preferred option [123–128]. Regardless of the mode selected, transport should never diminish the level of care provided to the child, and the level of care provided during the transport should, at a minimum, be equal to that of the referring hospital. More importantly, with the advent of the concept of the *mobile intensive care unit,* the care provided during transport should be equal to that of the tertiary care center itself. Issues pertaining to both interhospital and intrahospital transport of critically ill or injured children are discussed in greater detail in Chapter 8.

Critical Care

Advances in the science and technology of critical care medicine have resulted in dramatic improvements in outcomes for critically ill or injured children. It is clear that children are different from adults and require more specialized care. It is unreasonable, however, to expect every hospital to be able to provide comprehensive care for the wide range of complex medical and surgical problems that afflict the critically ill or injured child. Several studies have documented significantly improved outcomes when children receive care in the pediatric intensive care unit (PICU) versus the adult intensive care unit [129–134].

Two additional caveats drive the need for the categorization and regionalization of pediatric critical care services. First, much of the United States is still considered "rural," and most children with emergencies are evaluated and treated in small community hospitals [135]. In the usual scenario, an injured or severely ill child is brought to the closest available hospital for emergency care, often in a remote location that is far from the nearest PICU. Second, although approximately 15% of the 3 million children hospitalized in the United States each year are admitted to free-standing children's hospitals or the inpatient pediatric wards at regional medical centers, the remainder are hospitalized in small community hospitals that may be quite varied in their ability to care for pediatric patients [136,137]. These hospitals may be perfectly capable of treating many of the routine pediatric illnesses. However, at times these children may deteriorate and require a level of care exceeding the capabilities that are available. In these instances, interhospital transport to a pediatric critical care center is required.

Guidelines for the categorization and regionalization of pediatric critical care services have been previously published [138–141], although it is evident that changes need to be made. For example, in 1997, the Division of Hazard and Injury Data Systems, U.S.

Table 1.4. Suggested minimum pediatric emergency equipment for the community-based hospital emergency department.

Airway/breathing
- Simple face masks (preemie, infant, child, and adult sizes)
- Nonrebreather face masks (infant, child, and adult sizes)
- Bag-valve-mask resuscitators, with reservoir (infant, child, and adult sizes)
- Suction catheters, flexible (sizes 5–16 F) and Yankauer
- Oral airways (sizes 00–5)
- Nasal airways (sizes 12–30 F)
- Nasal cannulas (infant, child, and adult sizes)
- Endotracheal tubes
  - Uncuffed (2.5 to 8.5 mm OD)
  - Cuffed (5.5. to 9.0 mm OD)
- Laryngoscope batteries and bulbs
- Laryngoscope handle with straight (sizes 0–3) and curved (sizes 2–3) blades
- Stylets (pediatric and adult sizes)
- Magill forceps (pediatric and adult sizes)
- Nasogastric tubes (sizes 6–14 F)
- Tracheostomy tubes (sizes 00–6)
- Chest tubes (8–40 F)
- Disposable end-tidal CO_2 detector

Circulation (Vascular Access)
- Butterfly needles (19–25 gauge)
- IV catheters (14–24 gauge)
- IV boards, tape, alcohol pads, tourniquets
- IV fluids (0.9% saline, Ringer's lactate, D5W with 0.45% saline)
- Pediatric drip chambers and tubing
- Infusion device
- Intraosseous needles (16 and 18 gauge)
- IV fluid/blood warmers
- Umbilical vein/artery catheters (3.5 and 5.0 Fr)
- Central line kits (with size 3, 4, 5 Fr catheters)

Miscellaneous equipment
- Blood pressure cuffs (neonate, infant, child, and adult sizes)
- Sphygmomanometer
- Doppler blood pressure device
- Thermometer
- Cardiorespiratory monitor (pediatric and adult electrodes)
- Pulse oximeter
- Defibrillator (0–400 J capability) with pediatric and adult paddles
- Cardiac arrest board
- Nebulizer
- Pediatric restraining devices
- Heat lamps
- Radiant warmer
- Infant and standard scales
- Oral rehydration solution
- Medication chart/Broselow tape
- Extremity splints
- Towel rolls/blanket rolls
- Cervical spine collars

Emergency medications
- Epinephrine (1 : 1,000 and 1 : 10,000)
- Albuterol
- Racemic epinephrine
- Activated charcoal
- Lorazepam or diazepam (rapid-acting anticonvulsant)
- Phenobarbital
- Phenytoin or fosphenytoin
- Parenteral antibiotics
- Corticosteroids, parenteral
- Dextrose in water (25%, 50%)
- Diphenhydramine, parenteral
- Atropine sulfate
- Sodium bicarbonate (4.2%, 8.4%)
- Naloxone
- Lidocaine
- Calcium chloride
- Dopamine
- Dobutamine
- Adenosine
- Bretylium
- Amiodarone
- Potassium chloride
- Prostaglandin E_1

Specialized, prepackaged equipment trays
- Lumbar puncture (spinal needle sizes 20, 22, 25 gauge)
- Urinary catheterization (Foley catheter sizes 5–16 F)
- Obstetric pack
- Meconium aspirator
- Tube thoracostomy
- Surgical airway
- Umbilical artery/vein catheterization
- Sterile procedure tray

Consumer Product Safety Commission surveyed the National Electronic Injury Surveillance System (NEISS) and noted some disturbing trends. Although 96% of the estimated 5,929 U.S. hospitals with emergency departments using the NEISS provided inpatient pediatric care, only 4% had both a PICU and a pediatric trauma service. Only 33% of those hospitals lacking pediatric critical care and trauma services had existing written transfer agreements with a facility able to provide such care [142]. The ideal EMSC system necessarily includes categorization of different hospitals according to their ability to provide emergency care for children. Predetermined, written transfer agreements between community-based emergency departments, community hospitals, specialized pediatric emergency departments, and tertiary care pediatric centers must exist to ensure that critically ill or injured children are rapidly transported to facilities that can provide the optimal level of care. Children deserve quality care when they are critically ill or injured. Categorization of hospitals to define the level of care provided, as well as regionalization of services to ensure access to that care, will give children the best possible outcome when an emergency occurs.

Regionalization of pediatric intensive care has only intensified the need for specialized pediatric critical care transport teams with the capability to transport the critically ill or injured child from smaller community hospitals to tertiary care centers and children's hospitals (see preceding paragraphs and Chapter 8). Although there is a large body of literature on critical care transport of adults and neonates, the interest in research on critical care transport of the pediatric patient is relatively new, and the available literature, therefore, is limited. The American Academy of Pediatrics published guidelines for the transportation of pediatric patients in November 1986, primarily to address the need for a more formalized organization of pediatric transport programs across the country [143]. These guidelines were revised further by a consensus conference made up of experts from the disciplines of pediatric emergency medicine, pediatric critical care medicine, neonatology, and trauma surgery in 1991 [144,145]. These guidelines address a

number of issues related to the organization and administration of a pediatric transport program and have been instrumental in developing and formalizing standards of care for pediatric transport medicine.

Rehabilitation and Recovery

Rehabilitation and recovery should begin as soon as a child is admitted to the hospital. Under the *medical home* model, a child's medical care should be continuous, comprehensive, family centered, and compassionate [146]. A child's pediatrician, as the primary health care provider, integrates all services and provides a continuity of care and therefore should be involved in a child's care as early as possible. Most PICUs have an assigned social worker who can be particularly useful in coordinating services with local agencies and organizations. All personnel should work closely together to ensure optimal outcomes.

Conclusion

The EMSC movement is still relatively young, and there is much work that remains to be done. A large percentage of children admitted to the PICU come from either the emergency department or referral from an outside hospital, and the ultimate outcome of a critically ill or injured child often depends to a great extent on the care that he or she receives prior to admission to the PICU. Therefore, the pediatric intensivist should take an active interest in the EMSC system and continue to advocate for efficient, high-quality pediatric emergency care.

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2
Pediatric Cardiopulmonary Resuscitation

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Introduction

Infants and children are anatomically, physiologically, and developmentally different from adults. In contrast to adults, children infrequently suffer sudden ventricular fibrillation (VF) cardiac arrest from coronary artery disease. The pathogenesis of cardiac arrest and the most common rhythm disturbances are typically respiratory in children and cardiac in adults. In addition, the characteristics and outcomes of out-of-hospital versus in-hospital cardiac arrests are very different. In either setting, the causes of pediatric arrests are diverse and are usually secondary to profound hypoxia or asphyxia caused by respiratory or circulatory failure. Prolonged hypoxia and acidosis impair cardiac function and ultimately lead to cardiac arrest. By the time the arrest occurs, multiple critical organs of the body have generally suffered significant hypoxic–ischemic insults. Thus, prevention, intervention, approach, and procedures can differ for infants and children compared with adults.

Developmental changes affect cardiac and respiratory physiology before, during, and after cardiac arrest. As an example, newborn infants transitioning from amniotic fluid-filled lungs to gaseous breathing certainly differ from adolescents. Similarly, newborns and infants have much less cardiac and respiratory reserve and higher pulmonary vascular resistance than older children. In addition, many children who experience in-hospital cardiac arrest have preexisting developmental challenges and existing or evolving organ dysfunction. Normal developmental changes create challenges for outcome assessment across the age spectrum. These developmental changes and family relationships, unique to children, create special circumstances that can be anticipated and supported.

Definition of Pulseless Cardiac Arrest

Pulseless cardiac arrest is typically defined as the documented cessation of cardiac mechanical activity, determined by the absence of a palpable central pulse, unresponsiveness, and apnea. Separation of severe hypoxic–ischemic shock with poor perfusion from the nonpulsatile state of cardiac arrest can be challenging at any age. This separation can be especially difficult in neonates and infants because of their anatomic and physiologic differences. A rescuer's ability to determine cardiac arrest by a pulse check is neither sensitive nor specific in adults [1]. Not surprisingly, the pulse check is even more problematic in children. In adults, pulses can typically be palpated until the systolic pressure is <50 mm Hg. Because the normal systolic blood pressure in neonates is generally in the 60s, a decrease in blood pressure to *nonpalpable pulse* may occur earlier in the continuum from hypoxic–ischemic shock to nonpulsatile cardiac standstill. Furthermore, the best arterial pulse to palpate in an adult is the carotid pulse; however, the short, fleshy neck of a baby with potential to compress the airway and impede respiration limits the effectiveness of carotid pulse palpation in babies.

Epidemiology of Pediatric Cardiac Arrest

The epidemiology and evidence-based approach to pediatric cardiac arrest has been limited, in part, because of diverse disease processes and pathophysiology. Until recently, many pediatric studies *lumped* all pediatric cardiac arrests, such as those secondary to sudden respiratory failure (e.g., drowning, foreign body aspiration), progressive respiratory failure from infections and/or neuromuscular diseases, trauma, SIDS, septic shock, hypovolemic shock, anaphylaxis, primary cardiomyopathy, primary arrhythmia (e.g., VF or ventricular tachycardia [VT]), and drug intoxications, together. Such *lumping* of diverse etiologies of arrest makes analysis for incremental changes in outcomes attributable to individual interventions difficult. Characterization of the process of care and outcomes following pediatric cardiac arrest events has been limited by a lack of consistent data collection and analysis [2,3]. In particu-

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lar, pediatric reports often have not clearly differentiated among respiratory arrest, near-arrests (bradycardia with pulses) treated with cardiopulmonary resuscitation (CPR), and pulseless cardiac arrest [4]. In the early 1990s, international experts developed guidelines for uniform data reporting of out-of-hospital cardiac arrests and in-hospital resuscitation, the so-called Utstein style [2,4–6]. Nevertheless, epidemiologic information regarding pediatric cardiac arrests is dominated by retrospective chart reviews with small numbers and inconsistent definitions of cardiac arrest and CPR and a few small prospective single-center studies. Importantly, the quality of CPR is generally poor and not easily accounted for in most of these studies.

Pediatric In-Hospital Arrests

The true incidence of pediatric pulseless cardiac arrest is difficult to estimate as it is complicated by inconsistent definitions and assessment of pulselessness in children. Cardiac arrests were reported in 3% of children admitted to one children's hospital, in 1.8% of all children admitted to pediatric intensive care units (PICUs) in the United States [7], in 6% of children admitted to one PICU in Finland, and in 4% of children admitted to a pediatric cardiac intensive care unit [8]. Several well-designed in-hospital pediatric CPR investigations with long-term follow-up have established that pediatric CPR and advanced life support can be remarkably effective (Table 2.1). Almost two thirds of these cardiac arrest patients were initially successfully resuscitated (i.e., attained sustained return of spontaneous circulation [ROSC]). Most of these arrests/events occurred in PICUs and were caused by progressive life-threatening illnesses that had not responded to treatment despite critical care monitoring and supportive care. Almost three quarters of survivors to discharge have good neurologic outcome. The 1-year survival rates of 10%–44% are better than reported outcomes following out-of-hospital pediatric CPR.

Only a few studies have used the more rigorous Utstein style of reporting for in-hospital pediatric cardiac arrests and CPR [9]. Two describe all CPR events at children's hospitals in Brazil [10] and Finland [11]. The most common causes of the events were progressive respiratory failure and progressive shock. Approximately two thirds of the children attained sustained ROSC, and 1-year survival was 15% and 18%, respectively.

Recently published Utstein-style reports of in-hospital pediatric cardiac arrests are derived from the American Heart Association's multicenter National Registry of Cardiopulmonary Resuscitation (NRCPR) (http://www.nrcpr.org/). The NRCPR is a prospective, multicenter observational registry of in-hospital cardiac arrests and resuscitations. The large size, scope, and quality of the NRCPR distinguish this North American database characterizing the process and outcome of pediatric in-hospital CPR events. These important characteristics are summarized in Tables 2.2 and 2.3.

In these NRCPR reports, a cardiac arrest was explicitly defined as pulseless (cessation of cardiac mechanical activity), determined by the absence of a reported palpable central pulse, unresponsiveness, and apnea. Events were excluded if the cardiac arrest began out of hospital, involved a newly born in a delivery room or neonatal intensive care unit, or was limited to a shock by an implanted cardioverter-defibrillator. Most of these arrests occurred in children with progressive respiratory insufficiency and/or progressive circulatory shock [13]. These children often had progressive underlying critical illnesses despite aggressive critical care monitoring and therapy. Therefore, 95% of these arrests were witnessed and/or monitored, and only 14% occurred on a general pediatric ward. Before the arrest, 57% of these children were mechanically ventilated, 38% had continuous vasopressor infusions, and 29% had continuous direct arterial blood pressure monitoring.

Despite the diverse and complex clinical circumstances leading to their arrests, 52% attained sustained ROSC, 36% survived for 24 hours, and 27% survived to hospital discharge. Outcomes for these children were substantially better than reported outcomes for adults in this registry (adjusted odds ratio, 2.3 [95% confidence limit 2.0–2.7]). Importantly, 65% of these children had good neurologic outcome, defined as: (1) Pediatric Cerebral Performance Category of 1, 2, or 3 or (2) no change from baseline Pediatric Cerebral Performance Category [13]. Of importance, 200 children who received chest compressions without pulselessness during this same observation period were excluded from the NRPCR cardiac arrest analysis because they did not ever completely lose their pulse during the event. Similar to the two previous Utstein-style

Table 2.1. Summary of representative studies of outcome following in-hospital pediatric cardiac arrest.

First author, year	Setting	No. of patients	ROSC	Survival to discharge	Good neurologic survival
Samson, 2006, NRCPR [12]	In-hospital CA, (initial VF/VT rhythm)	272 (104)	(70%)	(35%)	(33%)
Nadkarni, 2006, NRCPR [13]	In-hospital CA	880	459 (52%)	236 (27%)	154 (18%)
Reis, 2002 [10]	In-hospital CA	129	83 (64%)	21 (16%)	19 (15%)
Extracorporeal Life Support Organization, 2002 [unpublished]	In-hospital CA resuscitation by ECMO	232	N/A, all needed ECMO	88 (38%)	NR
Suominen 2000 [11]	In-hospital CA	118	74 (63%)	1-year survival, 21 (18%)	NR
Parra 2000 [14]	Pediatric cardiac ICU CA	32	24 (63%)	14 (44%)	8 (25%)
Chamnanvanakij, 2000 [15]	In-hospital intubated neonatal ICU patient with chest compressions for bradycardia	39	33 (85%)	CPR, 20 (51%) CA, 10%	CPR 5 (13%) (6 lost to follow-up)
Slonim, 1997 [7]	In-hospital pediatric ICU CA	205	NR	28 (14%)	NR
Torres, 1997 [16]	In-hospital CA	92	NR	1-year survival, 9 (10%)	7 (8%)
Zaritsky, 1987 [17]	In-hospital CA	CA 53	NR	CA, 5 (9%)	NR
Young, 1999 [unpublished]	Meta-analysis, in-hospital CA	544	NR	129 (24%)	NR
Lopez-Herce, 2005 [18,19]	Mixed in-hospital and OOH CA	213	110 (52%)	45 (21%)	34 (16%)
Tunstall-Pedoe, 1992 [20]	Mixed in-hospital and OOH CA	3,765	1,411 (38%)	706 (19%)	NR

Note: CA, cardiac arrest; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; OOH, out of hospital; NR, not reported; NRCPR, National Registry of Cardiopulmonary Resuscitation; ROSC, return of spontaneous circulation; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 2.2. Characteristics of pediatric in-hospital cardiac arrests from the American Heart Association's National Registry of Cardiopulmonary Resuscitation.

Characteristic	Pediatric cardiac arrest n = 880 (100%)
Age (years)	
Mean (SD)	5.6 (6.4)
Median (range)	1.8 (0–17.0)
Sex	
Male	473 (54)
Female	407 (46)
Race/ethnicity	
White	447 (51)
Black	226 (26)
Hispanic	105 (12)
Other/unknown	102 (12)
Patient type	
In-patient	750 (85)
Emergency department	121 (14)
Other (outpatient, visitor, or employee)	9 (1)
Illness category	
Medical, cardiac	158 (18)
Medical, noncardiac	402 (46)
Surgical, cardiac	150 (17)
Surgical, noncardiac	62 (7)
Trauma	91 (10)
Other[†]	17 (2)
Preexisting conditions	
Respiratory insufficiency	511 (58)
Hypotension/hypoperfusion	319 (36)
Congestive heart failure	273 (31)
Pneumonia/septicemia/other infection	259 (29)
Arrhythmia	182 (21)
Renal insufficiency	104 (12)
Diabetes mellitus	11 (1)
Metabolic/electrolyte abnormality	178 (20)
Baseline depression in CNS function	151 (17)
Metastatic or hematologic malignancy	43 (5)
Myocardial infarction	21 (2)
None[‡]	69 (8)
Hepatic insufficiency	55 (6)
Acute CNS nonstroke event	94 (11)
Acute Stroke	5 (1)
Major Trauma	97 (11)
Toxicologic problem	12 (1)

Source: Adapted from Nadkarni et al. [13].

pediatric in-hospital studies, only 82% of children who received chest compressions fit the definition of pulseless cardiac arrest. As expected, children who received chest compressions for bradycardia with pulses had a much higher survival to hospital discharge rate (60%) than those with pulseless cardiac arrest (27%, $p < 0.001$) [13].

Pediatric Out-of-Hospital Arrests

Outcomes following pediatric out-of-hospital arrests appear to be worse than after in-hospital arrests (Table 2.4). In particular, neurologic outcomes appear to be much worse among children who are out-of-hospital arrest survivors. Two diseases have especially poor outcomes: traumatic arrests and SIDS. Traumatic cardiac arrests typically result from either airway compromise and severe, prolonged hypoxia or exsanguination resulting in profound circulatory shock. Not surprisingly, chest compressions with an inadequately filled heart are not likely to provide adequate coronary and cerebral perfusion. Sudden infant death syndrome patients are typically discovered a long time before resuscitation is attempted, with understandably poor outcome. In most series of out-of-hospital pediatric cardiac arrests, more than one third of the children have the diagnosis of SIDS. For other pediatric cardiac arrests in the prehospital setting, CPR and advanced life support from emergency medical service (EMS) providers may be applied very late, after profound hypoxia and hypoperfusion of vital organs. Not surprisingly, these poor outcomes after pediatric out-of-hospital cardiac arrests are similar to the poor outcomes after adult non-VF out-of-hospital cardiac arrests.

Table 2.3. Event characteristics of pediatric in-hospital cardiac arrests from the American Heart Association's National Registry of Cardiopulmonary Resuscitation.

Characteristic	Pediatric cardiac arrest (n = 880)
Event location	
Intensive care unit	570 (65%)
Emergency department	116 (13%)
General inpatient	123 (14%)
Diagnostic area	21 (2%)
Outpatient, other, or unknown	20 (2%)
Operating room or PACU	30 (3%)
First-documented pulseless rhythm	
Asystole	350 (40%)
VF and pulseless VT	120 (14%)
VF	71 (8%)
Pulseless VT	49 (6%)
PEA	213 (24%)
Unknown by documentation	197 (22%)
Discovery status at time of event[†]	
Witnessed and/or monitored	834 (95%)
Witnessed and monitored	727 (83%)
Witnessed and not monitored	73 (8%)
Monitored and not witnessed	34 (4%)
Not monitored and not witnessed	46 (5%)
Immediate cause(s) of event	
Arrhythmia	392 (49%)
Acute respiratory insufficiency	455 (57%)
Hypotension	483 (61%)
Acute myocardial infarction or ischemia	12 (2%)
Metabolic/electrolyte disturbance	95 (12%)
Acute pulmonary edema	33 (4%)
Acute pulmonary embolism	6 (1%)
Airway obstruction	41 (5%)
Toxicologic problem	9 (1%)

Note: PACU, postanesthesia care unit; PEA, pulseless electrical activity; VF, = ventricular fibrillation; VT, ventricular tachycardia.
Data are expressed as absolute number (percentage); percentages may not all total 100 because of rounding.
Source: Adapted from Nadkarni et al. [13].

Table 2.4. Summary of representative studies of outcome following out-of-hospital pediatric cardiac arrest.

First author, year	Setting	No. of patients	ROSC	Survival to discharge	Good neurologic survival
Gerein, 2006 [21]	OOH CA, Canada	503	25 (5%)	9 (2%)	NR
Donoghue, 2005 [22]	OOH CA, systematic review	5,363	165/594 (27.8%)	647/5,363 (12.1%)	131/3,272 (4.0)
Young, 1999 [unpublished]	Meta-analysis, OOH CA	1,568	NR	132 (8%)	NR
Sirbaugh, 1999 [23]	OOH CA	300	33 (11%)	6 (2%)	1 (<1%)
Suominen, 1998 [24]	OOH CA, after trauma	41	10 (24%)	3 (7%)	2 (5%)
Suominen, 1997 [25]	OOH CA	50	13 (26%)	8 (16%)	6 (12%)
Schindler, 1996 [26]	OOH CA	80	43 (54%)	6 (8%)	0 (0%)
Kuisma, 1995 [27]	OOH CA	34	10 (29%)	5 (15%)	4 (12%)
Dieckmann, 1995 [28]	OOH CA	65	3 (5%)	2 (3%)	1 (1.5%)
Lopez-Herce, 2005 [18,19]	Mixed in-hospital and OOH CA	213	110 (52%)	45 (21%)	34 (16%)
Tunstall-Pedoe, 1992 [20]	Mixed in-hospital and OOH CA	3,765	1,411 (38%)	706 (19%)	NR

Note: CA, cardiac arrest; OOH, out of hospital; NR, not reported; ROSC, return of spontaneous circulation.

The Phases of Cardiac Arrest and Cardiopulmonary Resuscitation

There are at least four phases of cardiac arrest: (1) *prearrest*, (2) *no flow* (untreated cardiac arrest), (3) *low flow* (CPR), and (4) *postresuscitation* [29]. Interventions to improve outcome from pediatric cardiac arrest should be targeted to optimize therapies according to the timing, duration, intensity, and *phase* of resuscitation as suggested in Table 2.5. The prearrest phase represents the largest potential opportunity to impact patient survival by preventing pulseless cardiopulmonary arrest. Interventions during the prearrest phase focus on prevention. Infant safety seats and safe driving to prevent traumatic arrests, water safety programs to prevent drowning arrests, and medication safety caps to prevent drug poisoning arrests are well-known highly effective efforts to prevent cardiac arrests. Medical emergency teams (rapid response teams) are being trained to recognize and intervene when cardiac arrest is impending. Because many pediatric cardiac arrests are caused by progressive respiratory failure and shock, the main focus of the Pediatric Advanced Life Support (PALS) is the early recognition and treatment of respiratory failure and shock in children (i.e., prevention of cardiac arrest in the prearrest phase).

Interventions during the *no-flow* phase of untreated pulseless cardiac arrest focus on early recognition of cardiac arrest and beginning initiation of basic and advanced life support [30]. When there is insufficient oxygen delivery to the brain or heart, CPR should be started. The goal of effective CPR is to optimize coronary perfusion pressure and blood flow to critical organs during the *low-flow* phase [31]. Basic life support provided by continuous, effective chest compressions (characterized by push hard, push fast, allow full chest recoil, minimize interruptions, and do not overventilate) is the emphasis in this phase.

The *postresuscitation* phase is a high-risk period for brain injury, ventricular arrhythmias, and other reperfusion injuries. Injured cells can hibernate, die, or partially or fully recover function. Overventilation (hyperventilation) is frequent and can have adverse effects during and following CPR [32]. Interventions such as systemic hypothermia during the immediate postresuscitation phase strive to minimize reperfusion injury and support cellular recovery [33,34]. The postarrest phase may have the most potential for innovative advances in the understanding of cell injury and death, inflammation, apoptosis, and hibernation, ultimately leading to novel interventions. Thoughtful attention to management of temperature, glucose, blood pressures, coagulation, and optimal ventilation may be particularly important in this phase. The rehabilitation stage of postresuscitation concentrates on salvage of injured cells, recruitment of hibernating cells, and reengineering of reflex and voluntary communications of these cell and organ systems to improve functional outcome.

The specific phase of resuscitation should dictate the timing, intensity, duration, and focus of interventions. Emerging data suggest that interventions that can improve short-term outcome during one phase may be deleterious during another. For instance, intense vasoconstriction during the low-flow phase of cardiac arrest may improve coronary perfusion pressure and probability of

Table 2.5. Phases of cardiac arrest and resuscitation.

Phase	Interventions
Prearrest phase (protect)	• Optimize community education regarding child safety • Optimize patient monitoring and rapid emergency response • Recognize and treat respiratory failure and/or shock to prevent cardiac arrest
Arrest (no-flow) phase (preserve)	• Minimize interval to BLS and ACLS (organized response) • Minimize interval to defibrillation, when indicated
Low-flow (CPR) phase (resuscitate)	• Push hard, push fast • Allow full chest recoil • Minimize interruptions in compressions • Avoid overventilation • Titrate CPR to optimize myocardial blood flow (coronary perfusion pressures and exhaled CO_2) • Consider adjuncts to improve vital organ perfusion during CPR • Consider ECMO if standard CPR/ALS not promptly successful
Postresuscitation phase: short-term	• Optimize cardiac output and cerebral perfusion • Treat arrhythmias, if indicated • Avoid hyperglycemia, hyperthermia, hyperventilation • Consider mild postresuscitation systemic hypothermia • Debrief to improve future responses to emergencies
Postresuscitation phase: longer term rehabilitation (regenerate)	• Early intervention with occupational and physical therapy • Bioengineering and technology interface • Possible future role for stem cell transplantation

Note: ALS, advanced life support; ACLS, advanced cardiac life support; BLS, basic life support; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation.

ROSC. The same intense vasoconstriction during the postresuscitation phase may increase left ventricular afterload and worsen myocardial strain and dysfunction [35]. Current understanding of the physiology of cardiac arrest and recovery only enables the titration of blood pressure, global oxygen delivery and consumption, body temperature, inflammation, coagulation, and other physiologic parameters to attempt to optimize outcome. Future strategies will likely take advantage of emerging discoveries and knowledge of cellular inflammation, thrombosis, reperfusion, mediator cascades, cellular markers of injury and recovery, and transplantation technology.

Is Cardiopulmonary Resuscitation Effective for Children?

In Kouwenhoven and colleague's original report of successful resuscitation with closed chest cardiac massage [36], the initial patients were asphyxiated children in the operating room who received immediate effective resuscitation and attained excellent outcomes. When cardiac arrest is witnessed and of short duration, excellent outcomes *can* occur after various types of bystander CPR, including mouth-to-mouth rescue breathing alone, chest compressions alone, or standard chest compressions and mouth-to-mouth rescue breathing. Nevertheless, some reports question the effectiveness and advisability of prehospital pediatric CPR.

To further delineate these issues, prehospital pediatric asphyxial arrests were simulated in animal models. In the first study, asphyxia was induced by clamping of the tracheal tube of piglets until cardiac arrest occurred, defined by loss of aortic pulsation. The mean time until loss of aortic pulsations was 8.9 ± 0.4 min [37]. After loss of aortic pulsations, animals were randomized to simulated bystander CPR or no CPR until simulated EMS arrival 8 min later. After a complete cardiac arrest, 24-hr survival was clearly superior for the group who received both chest compressions and rescue breathing compared with either alone or no CPR. A similar study was performed with intervention at a slightly earlier point in the asphyxial process, when the pulse was *no longer palpable*, as defined by systolic pressure <50 mm Hg (i.e., after severe hypotension but before complete loss of aortic pulsation) [38]. After this injury without complete cardiac arrest, 24-hour survival was best when both chest compressions and rescue breathing were provided, but rescue breathing alone and chest compressions alone were individually better than no CPR at all [38]. Interestingly, most of the animals with 24-hour survival had ROSC before the simulated EMS arrival. Cardiopulmonary resuscitation was clearly not futile in these models of prehospital pediatric cardiac arrest; excellent CPR was remarkably effective when provided early enough.

Such laboratory studies put clinical reports in context. In a large, prospective study in Houston over 3.5 years, Sirbaugh and colleagues demonstrated that the outcomes from pediatric prehospital cardiac arrests were dismal: only 6 of the 300 children (2%) survived to hospital discharge, and only 1 of the 300 survived without significant neurologic deficits [23]. However, the diagnosis of cardiac arrest was determined by EMS providers when they arrived at the scene. As in most prehospital reports, children in cardiac arrest who attained ROSC after bystander CPR but before EMS arrival were excluded from analysis. Importantly, 41 children who had received bystander CPR were not in cardiac arrest at the time of EMS arrival; all 41 presumably had drowning-related cardiac arrests, and all survived with good neurologic outcomes [23]. Most exhibited evidence of significant hypoxic–ischemic injury when they arrived at the hospital, suggesting *real* cardiac arrest at the scene. In contrast, none of the other 24 children with drowning-related cardiac arrests who were still in cardiac arrest when the EMS personnel arrived survived with a good neurologic outcome.

Prospective evaluation of a decade-long, population-based study of pediatric drowning-related events in Houston demonstrated 421 children with drowning events in a population of ~2 million total and ~400,000 children (annual incidence of 10.0 per 100,000 children), and 234 required resuscitation [39]. One hundred ninety-three resuscitated children (82%) received bystander CPR, and 72% of these children were long-term survivors. Ninety-nine percent of the long-term survivors were neurologically intact. However, if the child was still apneic and pulseless when EMS personnel arrived, less than 5% were revived, and none of these subsequent survivors was ultimately neurologically intact [39]. These data and similar data from Hickey et al. [40] are consistent with the animal data, reported clinical experience, and in-hospital pediatric CPR data: CPR can be quite effective for asphyxial cardiac arrests, but timing of interventions is critically important.

In summary, animal and human data both indicate that CPR for children can be quite effective. In addition, these data support the idea that basic life support early is more important than advanced life support late. Prompt action by a citizen bystander in the prehospital setting or a provider in the in-hospital setting is generally more effective than late heroic efforts in our intensive care units.

Pediatric Ventricular Fibrillation

Ventricular fibrillation is an uncommon, but not rare, electrocardiographic (ECG) rhythm during out-of-hospital pediatric cardiac arrests. Two studies reported VF as the initial rhythm in 19%–24% of out-of-hospital pediatric cardiac arrests, but these studies excluded SIDS deaths. In studies that include SIDS victims, the frequency drops to the range of 6%–10% [41,42]. It is important to note that ECG rhythms are often not attained as promptly in children as in adults and that VF eventually converts into asystole over time. Therefore, the reported prevalence of VF is dependent on the aggressiveness and timing of monitoring and on the inclusion criteria for the report.

The incidence of VF varies by setting and age. In special circumstances, such as tricyclic antidepressant overdose, cardiomyopathy, postcardiac surgery, and prolonged QT syndromes, VF is a more likely rhythm during cardiac arrest. Commotio cordis, or mechanically initiated VF caused by relatively low-energy chest wall impact during a narrow window of repolarization (10–30 msec before the T-wave peak in swine models [43]), is reported, predominantly in children 4–16 years old. Out-of-hospital VF cardiac arrest is uncommon in infants but occurs more frequently in children and adolescents. The variance of VF by age was highlighted in a study documenting VF/VT in only 7.6% (10/131) of children in cardiac arrest 1–7 years old versus 27% of children 8–18 years old [42]. Although VF is often associated with underlying heart disease and generally considered the "immediate cause" of cardiac arrest, VF can occur secondary to asphyxia. In two studies of VF among asphyxiated piglets, the incidence of VF was 28% and 33% at some time during the cardiac arrest [37,38]. Asphyxia-associated VF is also well documented among pediatric near-drowning patients [39]. Furthermore, all VF is not the same, and VF that occurs as the initial rhythm during in-hospital cardiac arrests may be much different from VF occurring later in the arrest.

As noted above, in-hospital pediatric cardiac arrests are uncommon, but not rare, occurring in approximately 2% of PICU patients. Although the rhythms during most in-hospital cardiac arrests (in both children and adults) are asystole and pulseless electrical activity (PEA), in many arrests the rhythms are VF or pulseless VT. Among the first 1,005 pediatric in-hospital cardiac arrests in the American Heart Association's NRCPR (http://www.nrcpr.org/), 10% had an initial rhythm of VF/VT, an additional 15% had subsequent VF/VT (i.e., some time later during the resuscitation efforts), and another 2% had VF/VT but the timing of the arrhythmia was not clear. Therefore, 27% of children with in-hospital cardiac arrests had VF/VT, not an uncommon phenomenon [13]. Of note, survival to discharge was much more common among children with an initial shockable rhythm than among children with shockable rhythms occurring later during the resuscitation. Even in the setting of progressive respiratory failure and shock with an initial ECG of asystole or PEA, a substantial number of these children developed subsequent shockable VF/VT during CPR. Surprisingly, the subsequent VF/VT group had worse outcomes than children with asystole/PEA who never developed VF/VT during the resuscitation: 11% with subsequent VF/VT during resuscitation from asystole/PEA versus 27% with asystole/PEA alone. These data suggest that outcomes after *initial* VF/VT are *good*, but outcomes after *subsequent* VF/VT are substantially worse, even compared with asystole and/or PEA. Late shockable rhythms are presumed to be the result of progressive hypoxic–ischemic processes with expected poor outcomes. Traditionally, VF and VT have been considered *good* cardiac arrest rhythms, resulting in better outcomes than asystole and PEA. It is important to monitor the ECG early and repeatedly during resuscitation. Shockable rhythms of VF/VT can occur at some point in >25% of in-hospital pulseless cardiac arrests.

Termination of Ventricular Fibrillation: Defibrillation

Defibrillation (defined as termination of VF) is necessary for successful resuscitation from VF cardiac arrest. Note that termination of fibrillation can result in asystole, PEA, or a perfusing rhythm. The goal of defibrillation is return of an organized electrical rhythm with pulse. For example, prompt defibrillation provided soon after the induction of VF in a cardiac catheterization laboratory results in near-uniform successful defibrillation and survival. When automated external defibrillators (AEDs) are used within 3 min of witnessed VF, long-term survival can occur in more than 70% of victims [44]. In general, the mortality increases by 7%–10% per minute of delay to defibrillation [45,46]. Thus, provision of high-quality CPR can improve outcome and save lives. Because pediatric cardiac arrests are commonly caused by progressive asphyxia and/or shock, the initial treatment of choice is prompt CPR. Therefore, rhythm recognition in pediatrics tends to be relatively less emphasized than adult cardiac arrest situations. However, successful resuscitation from VF does require defibrillation such that the earlier that VF can be diagnosed, the more successfully it can be treated.

Determinants of Defibrillation (Termination of Ventricular Fibrillation)

Successful termination of VF (defibrillation) is achieved by attaining current flow adequate to depolarize a critical mass of myocardium. Current flow (amperes) is primarily determined by the shock energy (joules), which is selected by the operator, and the patient's transthoracic impedance (ohms). Animal studies in the 1970s with monophasic shock waveforms established that adequate electrical current flow through the myocardium led to successful defibrillation, whereas too much current flow resulted in postresuscitation myocardial damage and necrosis [47]. In addition, factors that affected transthoracic impedance were identified: paddle size, thoracic gas volume, electrode/paddle contact, and conducting paste [48]. Small paddle size increases resistance and thereby decreases current through the myocardium. On the other hand, paddles/pads larger than the heart result in current flow through extramyocardial pathways and thereby less current through the heart (consequently less flow for effective defibrillation). Poor electrode paddle contact and larger lung volumes (gas) result in greater impedance, whereas conducting paste and increased pressure at the paddle–skin contact decrease impedance. Transthoracic impedance could be decreased with multiple *stacked* shocks partly because of increased skin blood flow after electrical shocks. These studies established that current density (current flow through the myocardium) is the primary determinant of both effectiveness of the shock and myocardial damage [49].

Pediatric Defibrillation Dose

Early recommendations (1970s) for initial defibrillation doses as high as 200 J for all children were extrapolated from adult data. Despite clinical experience indicating that such doses were effective, providing these large energies to infants and children seemed potentially dangerous, with animal data demonstrating histopathologic myocardial damage at doses >10 J/kg [50,51] and suggesting 0.5–10 J/kg was adequate for defibrillation in a variety of species. Gutgesell and colleagues retrospectively evaluated the efficacy of a 2 J/kg pediatric defibrillation strategy [52]. Seventy-one transthoracic defibrillation attempts on 27 children were evaluated. These children were 3 days to 15 years old, and they weighed 2.1–50 kg. Fifty-seven of 71 shocks were within 10 J of the recommended 2 J/kg pediatric dose. Ninety-one percent (52/57) of these shocks were effective at terminating VF. The authors did not report any other outcome measures (e.g., successful termination of fibrillation to a perfusing rhythm, 24-hr survival, survival to discharge) [52]. Subsequent clinical usage suggests that the 2 J/kg dose is effective for short-duration in-hospital defibrillation [53], although this conclusion has not been rigorously evaluated.

As noted above, current density determines the effectiveness and harm of the shock. Moreover, differences in paddle size, defibrillation energy dose, and the individual's transthoracic impedance are the main determinants of current density. Therefore, Atkins and colleagues investigated the effects of paddle size, age, and weight on transthoracic impedance in children [54]. As expected, transthoracic impedance increased substantially with pediatric paddles. Based on those data, the American Heart Association recommends that *pediatric* or *small* paddles be used only for infants. More importantly, they established that the relationship between transthoracic impedance and weight is not linear [54]. The mean transthoracic impedance in their children was ~50 Ω with 83 cm^2 adult paddles and varied threefold among children. With *pediatric* or *small* pads (44 cm^2), the mean impedance was ~70 Ω in 3.8–36 kg children. The impedances of their infants were slightly lower than those of their older children, but the range of each was wide and the overlap substantial. Note that the mean transthoracic impedance in adults is typically ~60–80 Ω and also varies by more than

threefold. These data suggest that the adjustment of pediatric energy dose to weight (2–4 J/kg) requires further study.

Pediatric Defibrillation Doses for Prolonged Ventricular Fibrillation

Of the approximately 16,000 North American children with cardiac arrest each year, only 5%–20% present with an initial rhythm VF. There are few published data regarding pediatric defibrillation doses for prolonged VF. Therefore, the approach to pediatric prolonged VF is extrapolated from adult recommendations. For adults, the same defibrillation dose is recommended after brief duration or prolonged duration VF, even though the monophasic 200 J dose is often less effective at terminating prolonged VF (~60% termination of prolonged VF compared with >90% for short-duration VF). Defibrillation is typically with biphasic defibrillators, and the 150 or 200 J biphasic adult AED dosage is nearly 90% successful at terminating prolonged VF (much better than the ~60% effectiveness with 200 J monophasic defibrillation). The presently recommended pediatric VF dose of 2 J/kg by monophasic waveform is safe, but there are limited data on effectiveness for prolonged VF. A recently published animal study regarding defibrillation after 7 min of untreated VF in 4–24 kg piglets suggests that 2 J/kg may not be adequate [55]. Twenty-four piglets were shocked with 2 J/kg, followed by 4 J/kg. The pediatric dose of 2 J/kg monophasic shocks was uniformly unsuccessful at terminating fibrillation in all 24 piglets. This should not be overinterpreted; there could be interspecies differences in defibrillation thresholds. However, a small clinical study of pediatric defibrillation attempts also confirms that a 2 J/kg defibrillation dose is often inadequate. Eleven children received 14 pediatric dose shocks for VF in the Tucson emergency medical service over a 5-year period, using the same definition as Gutgesell did in his pediatric in-hospital (i.e., brief-duration) defibrillation study (2 J/kg ± 10 J). Only 7/14 shocks (50%) terminated out-of-hospital (prolonged) VF versus 52/57 shocks (91%) in their 27 in-hospital patients ($p < 0.01$). This small series suggests that further evaluation of shock dose for prolonged VF is important.

Standard weight-based dosing strategy for pediatric defibrillation is not easily implemented in AEDs. Manufacturers have developed alternatives that attenuate pediatric dose to 50–86 J biphasic. This dosage is safe and effective in piglets after either brief or prolonged VF. In addition, the 50 J/75 J/86 J shocks were more effective than a weight-based 2 J/kg dose at initial termination of fibrillation after prolonged VF [55]. Additional piglet studies modeling prolonged out-of-hospital pediatric VF (7 min of untreated VF), adult biphasic shocks of 200 J/300 J/360 J were compared with a *pediatric* biphasic AED dose of 50 J/75 J/86 J [56]. Pediatric dosing resulted in fewer elevations of cardiac troponin T levels, less postresuscitation myocardial dysfunction (i.e., lesser decreases of left ventricular ejection fraction 1–4 hr postresuscitation), and superior 24-hr survival with good neurologic outcome [56]. These data support the use of attenuating electrodes with adult AEDs for pediatric defibrillation. It is important to remember that no shock delivery for pediatric VF is 100% lethal. Therefore, adult defibrillation doses are preferable to no defibrillation dose. A single case report in the literature demonstrated that an adult AED dose could save the life of a 3-year-old child in VF [57]. That child was defibrillated with a biphasic shock of 150 J (9 J/kg). He survived without any apparent adverse effects. In particular, he had no elevations of serum creatine kinase or cardiac troponin I and normal postresuscitation ventricular function on ECG.

Pediatric Automated External Defibrillators

Ventricular fibrillation is prolonged in nearly all children with out-of-hospital VF by the time emergency medical service personnel and defibrillators arrive. Recently, AEDs were recommended for children <8 years old [58]. Two issues had to be considered before such recommendations: (1) the safety and efficacy of the AED diagnostic rhythm analysis program in children and (2) the safety and efficacy of the AED shock dosage. An important concern was that babies and small children with sinus tachycardia or supraventricular tachycardia can have very high heart rates that might be misinterpreted as *shockable* by AEDs with diagnostic programs developed for adult arrhythmias. Fortunately, published studies regarding the rhythm analysis programs from several manufacturers have established that they are quite sensitive and specific in detecting the shockable rhythm of VF [53,59,60]. Both algorithms were less sensitive at detecting the very uncommon shockable rhythm of VT, but were quite specific (i.e., the algorithm did not misinterpret other rhythms as VT and therefore did not recommend shocking a *nonshockable* rhythm). Ideally the device should demonstrate high specificity for pediatric shockable rhythms, that is, the device will not recommend a shock for *nonshockable rhythms*. Currently the evidence is insufficient to support a recommendation for or against the use of AEDs in children <1 year of age.

Interventions During the Low-Flow Phase: Cardiopulmonary Resuscitation

Airway and Breathing

One of the most common precipitating events for cardiac arrests in children is respiratory insufficiency. Adequate oxygen delivery to meet metabolic demand and removal of carbon dioxide is the goal of initial assisted ventilation. Effective bag-mask ventilation remains the cornerstone of providing effective emergency ventilation. Effective ventilation does not necessarily require an endotracheal tube. In one randomized, controlled study of children with out-of-hospital respiratory arrest, children who were treated with bag-mask ventilation did as well as children treated with prehospital endotracheal intubation [61]. Emergency airway techniques such as transtracheal jet ventilation and emergency cricothyroidotomy are rarely, if ever, required during CPR. During CPR, cardiac output and pulmonary blood flow are approximately 10%–25% of that during normal sinus rhythm. Consequently, much less ventilation is necessary for adequate gas exchange from the blood traversing the pulmonary circulation during CPR. Animal and adult data indicate that overventilation during CPR is common and can substantially compromise venous return and cardiac output [32]. Most concerning, these adverse hemodynamic effects during CPR combined with the interruptions in chest compressions typically necessary to provide airway management and rescue breathing can contribute to worse survival outcomes.

Although *airway* and *breathing* are prioritized in the ABC assessment approach, special circumstances may impact that priority order. In animal models of sudden VF cardiac arrest, acceptable PaO_2 and $PaCO_2$ persist for 4 to 8 min during chest compressions without rescue breathing [62]. Moreover, many animal studies indicate that outcomes from sudden short-duration VF cardiac arrests are at least as good with chest compressions alone as with chest compressions plus rescue breathing. In addition, several retrospec-

tive studies of witnessed VF cardiac arrest in adults also suggest that outcomes are similar after bystander-initiated CPR with either chest compressions alone or chest compressions plus rescue breathing. A randomized, controlled study of dispatcher-assisted bystander CPR in adults found a trend toward improved survival in the patients who received chest compressions alone compared with those who received dispatcher-instructed ventilation and chest compressions [63,64]. In contrast, animal studies of asphyxia-precipitated cardiac arrests have established that rescue breathing is a critical component of successful CPR.

Because adequate oxygenation and ventilation are important for survival from any cardiac arrest, why is rescue breathing not initially necessary for VF yet quite important in asphyxia? Immediately after an acute fibrillation-induced cardiac arrest, aortic oxygen and carbon dioxide concentrations do not vary from the prearrest state, because there is no blood flow and aortic oxygen consumption is minimal. Therefore, when chest compressions are initiated, the blood flowing from the aorta to the coronary and cerebral circulations provides adequate oxygenation at an acceptable pH. At that time, myocardial oxygen delivery is limited more by blood flow than by oxygen content [65]. Adequate oxygenation and ventilation can continue without rescue breathing, because the lungs serve as a reservoir for oxygen during the low-flow state of CPR. In addition, ventilation can occur because of chest compression-induced gas exchange and spontaneous gasping during CPR in victims of sudden cardiac arrest. Therefore, arterial oxygenation and pH can often be adequate with chest compressions alone for VF arrests.

It remains important to note that, for the infant or child, forgoing ventilation may not be appropriate, because respiratory arrest and asphyxia generally precede pediatric cardiac arrest. During asphyxia, blood continues to flow to tissues; therefore, arterial and venous oxygen saturations decrease while carbon dioxide and lactate increase. In addition, continued pulmonary blood flow before the cardiac arrest depletes the pulmonary oxygen reservoir. Therefore, asphyxia results in significant arterial hypoxemia and acidemia before resuscitation in contrast to VF. In this circumstance, rescue breathing can be life saving.

Circulation

Basic life support with continuous effective chest compressions is generally the best way to provide circulation during cardiac arrest. Basic life support is often provided poorly or not provided at all. The most critical elements are to *push hard* and *push fast* [30]. Because there is no flow without chest compressions, it is important to minimize interruptions in chest compressions. To allow good venous return in the decompression phase of external cardiac massage, it is important to allow full chest recoil and to avoid overventilation. The latter can prevent venous return because of increased intrathoracic pressure.

The use of closed-chest cardiac massage to provide adequate circulation during cardiac arrest was initially demonstrated in small dogs with compliant chest walls. Based on reasonable extrapolation, these investigators felt that closed-chest cardiac massage would be effective with children but might not be with adults. Therefore, the first patients successfully treated with closed-chest cardiac massage were children [36,66]. The presumed mechanism of blood flow was direct compression of the heart between the sternum and the spine in these children with compliant chest walls. Later investigations indicated that blood can also be circulated during CPR by the thoracic pump mechanism [67,68]. That is, chest compression-induced increases in intrathoracic pressure can generate a gradient for blood to flow from the pulmonary vasculature, through the heart, and into the peripheral circulation (e.g., thoracic pump mechanism). Regardless of mechanism, cardiac output during CPR seems to be greater in children (and immature animals) with compliant chest walls than in adults with less compliant chest walls.

Circumferential Versus Focal Sternal Compressions

In adults and animal models of cardiac arrest, circumferential (Vest) CPR provides better CPR hemodynamics than point compressions. In smaller infants, it is often possible to encircle the chest with both hands and depress the sternum with the thumbs while compressing the thorax circumferentially. In an infant model of CPR, this "two-thumb" method of compression resulted in higher systolic and diastolic blood pressures and a higher pulse pressure than did traditional two-finger compression of the sternum.

Duty Cycle

Duty cycle is the ratio of time of compression phase to the entire compression–relaxation cycle. In a model of human adult cardiac arrest, cardiac output and coronary blood flow are optimized when chest compressions last for 30% of the total cycle time [69]. As the duration of CPR increases, the optimal duty cycle may increase to 50%. In a juvenile swine model, a relaxation period of 250–300 msec (a duty cycle of 40%–50% if 120 compressions are delivered per minute) correlates with improved cerebral perfusion pressure when compared with shorter duty cycles of 30%.

Open-Chest Cardiopulmonary Resuscitation

Excellent standard closed-chest CPR generates approximately 10%–25% of baseline myocardial blood flow and a cerebral blood flow that is approximately 50% of normal. By contrast, open-chest CPR can generate a cerebral blood flow that approaches normal. Although open-chest massage improves coronary perfusion pressure and increases the chance of successful defibrillation in animals and humans, surgical thoracotomy is impractical in many situations. A retrospective review of 27 cases of CPR following pediatric blunt trauma (15 with open-chest CPR and 12 with closed-chest CPR) demonstrated that open-chest CPR increased hospital cost without altering rates of ROSC or survival to discharge [70]. However, survival in both groups was 0%, indicating that the population may have been too severely injured or too late in the process to benefit from this aggressive therapy. Open-chest CPR is often provided to children after open-heart cardiac surgery and sternotomy. Earlier institution of open-chest CPR may warrant reconsideration in selected special resuscitation circumstances.

Ratio of Compressions to Ventilation

Compression/ventilation ratios and tidal volumes recommended during CPR are based on rational conjecture and educational retention theory. Ideal compression/ventilation ratios for pediatric patients are unknown. Recent physiologic estimates suggest the amount of ventilation needed during CPR is much less than the amount needed during a normal perfusing rhythm because the cardiac output during CPR is only 10%–25% of that during normal sinus rhythm. The benefits of positive pressure ventilation

(increased arterial content of oxygen and carbon dioxide elimination) must be balanced against the adverse consequence of impeding circulation.

Maximizing systemic oxygen delivery during single-rescuer CPR requires a tradeoff between time spent doing chest compressions and time spent doing mouth-to-mouth ventilations. Theoretically, neither compression-only nor ventilation-only CPR can sustain systemic oxygen delivery. The best ratio depends on many factors, including the compression rate, the tidal volume, the blood flow generated by compressions, and the time that compressions are interrupted to perform ventilations [71]. A chest compression to ventilation ratio of 15:2 delivered the same minute ventilation as CPR with a chest compression to ventilation ratio of 5:1 in a mannequin model of pediatric CPR, but the number of chest compressions delivered was 48% higher with the 15:2 ratio [72].

In adults, mathematical models of oxygen delivery during CPR performed with variable ratios of health care provider chest compressions to ventilations suggest the optimal compression to ventilation ratio is approximately 30:2 and for lay rescuers closer to 50:2. Mathematical models of compression/ventilation ratios suggest that matching of the amount of ventilation to the amount of reduced pulmonary blood flow during closed-chest cardiac compressions should favor very high compression/ventilation ratios. Babbs and Kern chose to demonstrate the effect of compression/ventilation ratio on oxygen delivery to peripheral tissues [73]. Maximizing oxygen delivery to peripheral tissues during single-rescuer CPR requires a tradeoff between the time required to compress the chest and time required to provide rescue breathing. Ignoring the amount of ventilation provided by chest compressions alone, neither compression-only nor ventilation-only CPR can sustain oxygen delivery to the periphery for prolonged periods of CPR.

The best ratio depends upon many factors, including the compression rate, the tidal volume, the blood flow generated by compressions, and the time that compressions are interrupted to perform ventilations. These factors can be related in a mathematical formula based upon physiology. These variables change as a function of the size of the patient. Such considerations may help refine the amount of ventilation recommended for both adults and children. The ratio of chest compressions to ventilations during *no-flow* and *low-flow* phases of cardiopulmonary–cerebral resuscitation remains an area of high interest, controversy, and future research. These formulas adjusted to the known physiologic variables in children have suggested the potential to simplify the compression/ventilation ratio to 15 chest compressions: 2 ventilations in children.

Intraosseous Vascular Access

Intraosseous vascular access provides access to a noncollapsible marrow venous plexus, which serves as a rapid, safe, and reliable route for administration of drugs, crystalloids, colloids, and blood during resuscitation. Intraosseous vascular access often can be achieved in 30 to 60 sec. Although a styleted, specially designed intraosseous bone marrow needle is preferred to prevent obstruction of the needle with cortical bone, butterfly needles and standard hypodermic needles have been successfully used. The intraosseous needle is typically inserted into the anterior tibial bone marrow; alternative sites include the distal femur, medial malleolus or the anterior superior iliac spine, and the distal tibia. In adult and older children, the medial malleolus, distal radius, and distal ulna are optional locations.

Resuscitation drugs, fluids, continuous catecholamine infusions, and blood products can be safely administered by the intraosseous route. Onset of action and drug levels following intraosseous infusion during CPR are comparable with those achieved following vascular administration, including central venous administration. Intraosseous vascular access may also be used to obtain blood specimens for chemistry, blood gas analysis, and type and crossmatch, although administration of sodium bicarbonate through the intraosseous cannula eliminates the close correlation with mixed venous blood gases.

Complications have been reported in less than 1% of patients following intraosseous infusion [74]. Complications include tibial fracture, lower extremity compartment syndrome, severe extravasation of drugs, and osteomyelitis. Most of these complications may be avoided by careful technique. Although microscopic pulmonary fat and bone marrow emboli have been demonstrated in animal models, they have never been reported clinically and appear to occur just as frequently during cardiac arrest without intraosseous drug administration. Animal data and one human follow-up study indicate that local effects of intraosseous infusion on the bone marrow and bone growth are minimal.

Medication Use During Cardiac Arrest

Although animal studies indicate that epinephrine can improve initial resuscitation success after both asphyxial and VF cardiac arrests, no single medication has been shown to improve survival outcome from pediatric cardiac arrest.

Tracheal Drug Administration

Intraosseous vascular access has largely replaced the need for tracheal drug administration. Important drugs could be administered via the tracheal tube before vascular access was achieved. In particular, lidocaine, atropine, naloxone, and epinephrine were commonly administered via the tracheal route. Note that sodium bicarbonate and calcium may be very irritating to the airways and lung parenchyma, so they are not recommended for tracheal administration. Absorption of drugs into the circulation after tracheal administration depends on dispersion over the respiratory mucosa, pulmonary blood flow, and the matching of the ventilation (drug dispersal) to perfusion. The small volumes of drug that remain as droplets in the tracheal tube are obviously not effective. Inadequate chest compressions resulting in poor pulmonary blood flow will also limit absorption of the drug and prevent its delivery to the heart and systemic circulation. Preexisting pathophysiologic conditions such as pulmonary edema, pneumonitis, and airway disease also affect the pharmacokinetics of tracheally administered drugs. Another confounding factor is that the vasoconstrictive effects of epinephrine may limit local pulmonary blood flow, thereby diminishing drug uptake and delivery. It is therefore not surprising that drug absorption varies greatly and that optimal drug doses have not been determined. Animal studies reveal a wide variability in plasma epinephrine levels and physiologic effects after endotracheal administration. On average, 10 times as much tracheal epinephrine is needed to attain peak plasma levels comparable to intravenous administration. Moreover, a prolonged depot effect typically occurs after tracheal epinephrine administration, which can lead to postresuscitation hypertension, tachycardia, and ventricular arrhythmias.

Vasopressors

During CPR, epinephrine's α-adrenergic effect on vascular tone is most important. The α-adrenergic action increases systemic vascular resistance, thereby increasing diastolic blood pressure, which in turn increases coronary perfusion pressure and blood flow and increases the likelihood of ROSC. Epinephrine also increases cerebral blood flow during CPR because peripheral vasoconstriction directs a greater proportion of flow to the cerebral circulation. The β-adrenergic effect increases myocardial contractility and heart rate and relaxes smooth muscle in the skeletal muscle vascular bed and bronchi, although this effect is of less importance. Epinephrine also increases the vigor and intensity of VF, increasing the likelihood of successful defibrillation.

High-dose epinephrine (0.05–0.2 mg/kg) improves myocardial and cerebral blood flow during CPR more than standard-dose epinephrine (0.01–0.02 mg/kg) and may increase the incidence of initial ROSC [75,76]. Administration of high-dose epinephrine, however, can worsen a patient's postresuscitation hemodynamic condition with increased myocardial oxygen demand, ventricular ectopy, hypertension, and myocardial necrosis. Studies indicate that use of high-dose epinephrine in adults or children does not improve survival and may be associated with a worse neurologic outcome [76,77].

A randomized, controlled trial of rescue high-dose epinephrine versus standard-dose epinephrine following failed initial standard-dose epinephrine for pediatric in-hospital cardiac arrest demonstrated a worse 24-hr survival rate in the high-dose epinephrine group (1/27 vs. 6/23, $p < 0.05$) [3]. In particular, high-dose epinephrine seemed to worsen the outcome of patients with asphyxia-precipitated cardiac arrest. High-dose epinephrine cannot be recommended routinely for initial therapy or rescue therapy.

Wide variability in catecholamine pharmacokinetics and pharmacodynamics dictate individual titration. A life-saving dose during CPR for one patient may be life threatening to another. High-dose epinephrine should be considered as an alternative to standard-dose epinephrine in special circumstances of refractory pediatric cardiac arrest (e.g., patient on high-dose epinephrine infusion before cardiac arrest) and/or when continuous direct arterial blood pressure monitoring allows titration of the epinephrine dosage to diastolic (decompression phase) arterial pressure during CPR. Nevertheless, high-dose epinephrine has not been demonstrated to improve outcome and should only be used with caution.

Vasopressin is a long-acting endogenous hormone that acts at specific receptors to mediate systemic vasoconstriction (V_1 receptor) and reabsorption of water in the renal tubule (V_2 receptor). In experimental models of cardiac arrest, vasopressin increases blood flow to the heart and brain and improves long-term survival compared with epinephrine. Vasopressin may decrease splanchnic blood flow during and following CPR. In randomized controlled trials of in-hospital and out-of-hospital arrests in adults, vasopressin had comparable efficacy to epinephrine [78]. Vasopressin did not improve outcome compared with epinephrine.

In a pediatric porcine model of prolonged VF, the use of vasopressin and epinephrine in combination resulted in higher left ventricular blood flow than either pressor alone, and both vasopressin alone and vasopressin plus epinephrine resulted in superior cerebral blood flow than epinephrine alone [79–82]. By contrast, in a pediatric porcine model of *asphyxial* cardiac arrest, ROSC was more likely in piglets treated with epinephrine than in those treated with vasopressin [83]. A case series of four children who received vasopressin during six prolonged cardiac arrest events suggests that the use of bolus vasopressin may result in ROSC when standard medications have failed [84]. Vasopressin has also been reported to be useful in low cardiac output states associated with sepsis syndrome and organ recovery in children. While vasopressin will not likely replace epinephrine as a first-line agent in pediatric cardiac arrest, there are preliminary data to suggest that its use in conjunction with epinephrine in pediatric cardiac arrest deserves further investigation [85].

Calcium

For in-hospital pediatric cardiac arrests, hypocalcemia is not uncommon. Although calcium administration is only recommended during cardiac arrest for hypocalcemia, hyperkalemia, hypermagnesemia, and calcium channel blocker overdose, it is commonly used for in-hospital pediatric cardiac arrests, especially those occurring after cardiac surgery. The administration of calcium has not been demonstrated to improve outcome in cardiac arrest. Animal studies suggest that calcium administration may worsen reperfusion injury [86].

Buffer Solutions

Cardiac arrest results in lactic acidosis from inadequate organ blood flow and poor oxygenation. Acidosis depresses myocardial function, reduces systemic vascular resistance, and inhibits defibrillation. Nevertheless, the routine use of sodium bicarbonate for a child in cardiac arrest is not recommended. Clinical trials involving critically ill adults with severe metabolic acidosis did not demonstrate a beneficial effect of sodium bicarbonate. However, the presence of acidosis may depress the action of catecholamines, so the use of sodium bicarbonate seems rational in an acidemic child who is refractory to catecholamine administration. The administration of sodium bicarbonate is more clearly indicated for the patient with a tricyclic antidepressant overdose, hyperkalemia, hypermagnesemia, or sodium channel blocker poisoning.

The buffering action of bicarbonate occurs when a hydrogen cation and a bicarbonate anion combine to form carbon dioxide and water. If carbon dioxide is not effectively cleared through ventilation, its build-up will counterbalance the buffering effect of bicarbonate. Other side effects with sodium bicarbonate include hypernatremia, hyperosmolarity, and metabolic alkalosis. Tris-hydroxymethyl aminomethane (THAM) is a noncarbon dioxide generating buffer that can be used during cardiac arrest. Note that excessive alkalosis decreases calcium and potassium concentration and shifts the oxyhemoglobin dissociation curve to the left.

Antiarrhythmic Medications: Lidocaine and Amiodarone

Administration of antiarrhythmic medications should not delay administration of a shock for a patient with VF. However, after unsuccessful attempts at electrical defibrillation, medications to increase the effectiveness of defibrillation should be considered. For both pediatric and adult patients, the first administered medication for VF is epinephrine. If epinephrine with or without vasopressin and a subsequent repeat attempt to defibrillate are unsuccessful, the antiarrhythmic agents amiodarone or lidocaine should be considered.

Lidocaine has been recommended traditionally for shock-resistant VF in adults and children. However, the only antiarrhythmic agent that has been prospectively determined to improve survival to hospital admission in the setting of shock-resistant VF when compared to placebo is amiodarone. Furthermore, patients who received amiodarone for shock-resistant out-of-hospital VF had a higher rate of survival to hospital admission than patients who received lidocaine alone [87,88]. Neither of these randomized controlled trials included children. Although there are no published comparisons of antiarrhythmic medications for pediatric refractory VF, extrapolation of the adult studies has led to the recommendation of amiodarone as the preferred antiarrhythmic agent for children.

Postresuscitation Interventions

Temperature Management

Mild induced hypothermia is the most celebrated goal-directed postresuscitation therapy for adults. Two seminal articles established that induced hypothermia (32°–34°C) could improve outcome for comatose adults after resuscitation from VF cardiac arrest [33,34]. In both randomized controlled trials, the inclusion criteria were patients older than 18 years who were persistently comatose after successful resuscitation from nontraumatic VF. The multicenter European study had a goal of 32°–34°C for the first 24 hr postarrest. The mean time until attainment of this temperature goal was 8 hr. Six-month survival with good neurologic outcome was superior in the hypothermic group (75/136 vs. 54/137 with RR of 1.40 [CI, 1.08–1.81]) [34]. Similarly, death at 6 months postevent occurred less often in the hypothermic group (56/137 vs. 76/138; RR of 0.74 [CI, 0.58–0.95]) [34]. Bernard et al. reported good outcomes in 21/43 (49%) of the hypothermic group versus 9/34 (26%) of the control group, (p = 0.046, OR 5.25 [CI, 1.47–18.76]) [33]. Importantly, hypotension occurred in over half of the patients in both groups and was aggressively treated with vasoactive infusion in the European study. Similarly, more than half of the patients in the Bernard et al. study received epinephrine infusions during the first 24 hours postresuscitation [33].

Interpretation and extrapolation of these studies to children is difficult. Fever following cardiac arrest is associated with poor neurologic outcome, and hyperthermia following cardiac arrest is common in children. It is reasonable to believe that mild induced systemic hypothermia may benefit children resuscitated from cardiac arrest. However, benefit from this treatment has not been rigorously studied and reported in children or in any patients with non-VF arrests. At a minimum, it is advisable to avoid even mild hyperthermia in children following CPR. Scheduled administration of antipyretic medications *and* use of external cooling devices are often necessary to avoid hyperthermia in this population.

Postresuscitation Myocardial Support

Postarrest myocardial stunning occurs commonly after successful resuscitation in animals, adults, and children. In addition, most adults who survive to hospital admission after an out-of-hospital cardiac arrest die in the postresuscitation phase, many due to progressive myocardial dysfunction. Animal studies demonstrate that postarrest myocardial stunning is characterized by a global biventricular systolic and diastolic dysfunction, and typically resolves after 1 or 2 days [89]. Postarrest myocardial stunning is pathophysiologically similar to sepsis-related myocardial dysfunction and postcardiopulmonary bypass myocardial dysfunction, including increases in inflammatory mediator and nitric oxide production. Postarrest myocardial stunning is worse after a more prolonged untreated cardiac arrest, after more prolonged CPR, after defibrillation with higher energy shocks, and after a greater number of shocks [90].

Optimal treatment of postarrest myocardial dysfunction has not been established. As noted earlier, this myocardial dysfunction has been treated with various continuous inotropic/vasoactive agents, including dopamine, dobutamine, and epinephrine, in both children and adults. In addition, milrinone improves the hemodynamic status of children with postcardiopulmonary bypass myocardial dysfunction and septic shock. Finally, the new inotropic agent levosimenden has also been effective in animal models of postresuscitation myocardial dysfunction. Although prospective controlled trials in animals have demonstrated that the myocardial dysfunction can be effectively treated with vasoactive agents, there are no data demonstrating improvements in outcome. Nevertheless, because myocardial dysfunction is common and can lead to secondary ischemic injuries to other organ systems or even cardiovascular collapse, treatment with vasoactive medications is a rational therapeutic choice that may improve outcome. The hemodynamic benefits in animal studies of postarrest myocardial dysfunction, pediatric studies of postcardiopulmonary bypass myocardial dysfunction, and pediatric sepsis-related myocardial dysfunction support the use of inotropic/vasoactive agents in this setting. In addition, adult studies document the common occurrence of postarrest hypotension and/or poor myocardial function "requiring" inotropic/vasoactive agents. In summary, because treatment of postarrest myocardial dysfunction with inotropic/vasoactive infusions can improve the patient's hemodynamic status, such treatment should be routinely considered and titrated to effect. Unfortunately, evidence-based therapeutic targets for goal-directed therapy are ill defined.

Blood Pressure Management

Laurent and colleagues demonstrated that 55% of adults surviving out-of-hospital cardiac arrests required in-hospital vasoactive infusions for hypotension unresponsive to volume boluses [91]. Compared with healthy volunteers, adults resuscitated from cardiac arrest have impaired autoregulation of cerebral blood flow. Hence, they may not maintain cerebral perfusion pressure in the face of systemic hypotension and likewise may not be able to protect the brain from acutely increased blood flow in the face of systemic hypertension. It is rational to presume that blood pressure variability should be minimized as much as possible following resuscitation from cardiac arrest.

A brief period of hypertension following resuscitation from cardiac arrest may diminish the no-reflow phenomenon. In animal models, brief induced hypertension following resuscitation results in improved neurologic outcome compared with normotension [92]. As retrospective human studies suggest that postresuscitative hypertension was associated with a better neurologic outcome after controlling for age, gender, duration of cardiac arrest, duration of CPR, and preexisting diseases, it seems reasonable to aggressively treat and prevent hypotension [93].

Glucose Control

Hyperglycemia following adult cardiac arrest is associated with worse neurologic outcome after controlling for duration of arrest and presence of cardiogenic shock [94–96]. In an animal model of asphyxial cardiac arrest, administration of insulin and glucose, but not administration of glucose alone, improved neurologic outcome compared with administration of normal saline [97]. Data for evidence-based titration of specific endpoints are not available.

Extracorporeal Membrane Oxygenation–Cardiopulmonary Resuscitation

Perhaps the ultimate technology to control postresuscitation temperature and hemodynamic parameters is extracorporeal membrane oxygenation (ECMO). In addition, the concomitant administration of heparin may optimize microcirculatory flow. The use of venoarterial ECMO to reestablish circulation and provide controlled reperfusion following cardiac arrest has been published [98–101], but prospective, controlled studies are lacking. Nevertheless, these series have reported extraordinary results with the use of ECMO as a rescue therapy for pediatric cardiac arrests, especially from potentially reversible acute postoperative myocardial dysfunction or arrhythmias. In one study, 11 children who suffered cardiac arrest in the pediatric intensive care unit after cardiac surgery were placed on ECMO during CPR after 20–110 min of CPR [102]. Prolonged CPR was continued until ECMO cannulas, circuits, and personnel were available. Six of these 11 children were long-term survivors without apparent neurologic sequelae [102]. Increasingly improved survival rates have been reported for pediatric cardiac patients provided with mechanical cardiopulmonary support within 20 min of the initiation of CPR. Despite these promising results, CPR and ECMO are not curative treatments; rather, they are simply cardiopulmonary supportive measures that may allow tissue perfusion and viability until recovery from the precipitating disease process can occur. Most remarkably, Morris et al. reported 66 children who over 7 years were placed on ECMO during CPR at Children's Hospital of Philadelphia [101]. The median duration of CPR before establishment of ECMO was 50 min, and 35% (23/66) of these children survived to hospital discharge. It is important to emphasize that these children had brief periods of "no flow," excellent CPR during the "low-flow" period, and a well-controlled postresuscitation phase. Potential advantages of ECMO come from its ability to maintain tight control of physiologic parameters after resuscitation. Parameters including blood flow rates, oxygenation, ventilation, anticoagulation, and body temperature can all be manipulated precisely through the ECMO circuit. As we learn more about the processes of secondary injury following cardiac arrest, ECMO might enable controlled perfusion and temperature management to minimize reperfusion injury and maximize cell recovery.

Neuropsychological Issues

Information about neurologic outcomes and predictors of neurologic outcome after both adult and pediatric cardiac arrests is limited. Barriers to assessment of neurologic outcomes of children after cardiac arrests include the constantly changing developmental context that occurs with brain maturation. Prediction or prognosis for future neuropsychological status is a complex task, particularly after an acute neurologic insult. There is little information about the predictive value of clinical neurologic examinations, neurophysiologic diagnostic studies (e.g., electroencephalographic [EEG] or somatosensory evoked potentials) [103,104], biomarkers [105], or imaging (computed tomography, magnetic resonance imaging [MRI], or positron emission tomography) on eventual outcome following cardiac arrest or other global hypoxic–ischemic insults in children. Computed tomography scans are not sensitive in detecting early neurologic injury. The value of MRI studies following pediatric cardiac arrest is not yet clear; however, MRI with diffusion weighting should provide valuable information about hypoxic–ischemic injury in the subacute and recovery phases.

Emerging data suggest that burst-suppression pattern on postarrest EEG is sensitive and specific for poor neurologic outcome [106,107]. Studies have shown that somatosensory evoked potential (SSEP) can be highly sensitive and specific in pediatric patients after cardiac arrest [108,109]. However, SSEP is not standardized in the pediatric population and is difficult to interpret. Many children who suffer a cardiac arrest have substantial preexisting neurologic problems. For example, 17% of the children with in-hospital cardiac arrests from the NRCPR were neurologically abnormal before the arrest. Thus, comparison with prearrest neurologic function of a child is difficult and adds another dimension/barrier to the assessment and prediction of postarrest neurologic status.

Biomarkers are emerging tools to predict neurologic outcome. In an adult study, serum level of neuron-specific enolase (NSE) and S-100b protein showed prognostic value. Elevated NSE and S-100b were highly sensitive and specific for poor neurologic outcome (death or persisting unconsciousness) [110]. The validation of these biomarkers in pediatric postarrest patients requires further study.

Most pediatric cardiac arrest outcome studies have not included neurologic outcomes. Investigations that include neurologic outcomes have generally used the Pediatric Cerebral Performance Category, a gross outcome scale. Many neuropsychological tests can detect more subtle, clinically important neuropsychological sequelae from neurologic insults. Neuropsychological outcomes are important issues for future pediatric cardiac arrest outcome studies.

Conclusion

Despite evidence-based guidelines, extensive provider training, and provider credentialing in resuscitation medicine, the quality of CPR and resuscitation science lacks high quality. Tremendous impact of simple, immediate actions such as "push hard, push fast, minimize interruptions, allow full chest recoil and do not overventilate" can markedly improve outcomes. Directive and corrective real-time feedback, combined with team dynamic training and debriefing, can substantially improve self-efficacy and operational performance.

Outcomes from pediatric cardiac arrest and CPR appear to be improving. Evolving understanding of the pathophysiology of events and titration of the interventions to the timing, etiology, duration, and intensity of the cardiac arrest event can improve resuscitation outcomes. Exciting discoveries in basic and applied science are on the immediate horizon for study in specific

populations of cardiac arrest victims. By strategically focusing therapies to specific phases of cardiac arrest and resuscitation and to evolving pathophysiology, there is great promise that critical care interventions will lead the way to more successful cardiopulmonary and cerebral resuscitation in children. Treatment of sudden death in children in the future requires more evidence-based and less anecdotal interventions. Timing of therapeutic interventions to prevent arrest and to protect, preserve, and promote restoration of intact neurologic survival is of the highest priority.

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3
Supplemental Oxygen and Bag-Valve-Mask Ventilation

Patricia Abboud, Jennifer Raake, and Derek S. Wheeler

Historical Perspective

"This air is of exalted nature. . . . A candle burned in this air with an amazing strength of flame; and a bit of red hot wood crackled and burned with a prodigious rapidity, exhibiting an appearance something like that of iron glowing with a white heat, and throwing sparks in all directions. But to complete the proof of the superior quality of this air, I introduced a mouse into it; and in a quantity in which, had it been common air, it would have died in about a quarter of an hour; it lived at two different times, a whole hour, and was taken out quite vigorous."

Joseph Priestley, Philosophical Transactions of the Royal Society, 1775

For over 2,000 years, people have regarded life as synonymous with breathing. For example, the Bible states that "God formed man from the dust of the ground and breathed into his nostrils the breath of life, and the man became a living being" (Genesis 2:7). The distinction between life and death has blurred with the advent of mechanical ventilation, although the fact remains that life begins and ends with breathing. A true understanding of the importance of the process of breathing would not happen, however, until a monumental discovery was made in the late 18th century.

Oxygen, the gas that Joseph Priestley called *dephlogisticated air*, was discovered in 1774. The chemists and physicists of the mid-18th century widely believed that flammable materials contained a substance called *phlogiston* (translated from the Greek word for "to set on fire") that was released during combustion. The theory held that when a candle burned, it released phlogiston into the surrounding air, and, once the air became saturated with this substance, the candle would go out. In a classic series of experiments, Priestley placed a burning candle beneath an inverted jar and tested how long a mouse would live once the flame went out. By placing a green plant in the jar and exposing it to sunlight, he was able to keep both the candle burning and the mouse alive (thereby describing the process now known as photosynthesis).

Priestley conducted his most famous experiment on August 1, 1774, when he used a magnifying lens to heat up mercury beneath an inverted glass container. The heated mercury became coated with a reddish powder, which when reheated at a higher temperature released two gases, one of which was mercury vapor. The mercury vapor condensed into drops of mercury in the glass jar as it cooled. The other gas was invisible, but Priestly knew it existed because, when he placed a smoldering splint of wood into it, the wood burst into flame and kept a mouse alive about four times as long as a similar quantity of air. Priestley called his discovery *dephlogisticated air* based on the theory that it supported combustion so well because it had no phlogiston in it and hence could absorb the maximum amount during burning.

Priestley presented his findings to the French chemist Antoine Lavoisier, who used these findings to debunk the phlogiston theory. Lavoisier argued that burning substances did not give off phlogiston but rather took on Priestley's gas, which Lavoisier called *oxygen* from the Greek word for acid-former (*oxy* meaning acid, *gen* meaning former). Less well known, a Swedish apothecary named Carl Wilhelm Scheele isolated the same gas (which he called *fire air*) and observed a similar reaction 2 years before Priestley, although his findings were not published until 1777 [1–6].

Regardless of who discovered oxygen, we now know that normal cellular function is critically dependent on oxygen, as evidenced by the relative complexity of the organ systems that evolved to transport oxygen from the surrounding environment to the cells—the cardiac, respiratory, peripheral vascular, and hematopoietic systems. Cells do not have the means to store oxygen and are therefore dependent on a continuous supply that closely matches the changing metabolic needs that are necessary for normal metabolism and cellular function. If oxygen supply is not aligned with these metabolic requirements, hypoxia will ensue, eventually resulting in cellular injury and/or death. Health care providers respond to a variety of acute life-threatening events and are bound by algorithms that begin by maintaining airway patency, optimizing gas exchange, and ensuring hemodynamic stability. Optimization of oxygen delivery is the core of what critical care physicians do on a daily basis while treating their critically patients. Oxygen delivery (DO_2) is critically dependent on an adequate cardiac output (CO), blood hemoglobin concentration (Hb), and percent oxygen saturation (SaO_2):

$$DO_2 = CO \times CaO_2$$

$$CaO_2 = (1.34 \times Hb \times SaO_2) + 0.003 \times PaO_2$$

One of the most important elements of tissue oxygen delivery is the arterial hemoglobin concentration. Although oxygen delivery from the left ventricle is linearly related to the hemoglobin

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concentration, capillary flow may be impaired at an extremely high hematocrit because of increased viscosity of the blood. The optimal hemoglobin concentration to maximize tissue oxygen delivery seems to be in the range between 10 and 13 g/dL. Whether or not transfusion to achieve these high hemoglobin levels improves outcome remains to be proven. Cardiac output is based on a number of variables, including heart rate, stroke volume, mean arterial pressure, and systemic vascular resistance, all of which can be manipulated in the pediatric intensive care unit (PICU). There are two ways to increase the percent hemoglobin saturation (SaO_2): (1) increase the fraction of inspired oxygen (FiO_2) through administration of supplemental oxygen or (2) increase the number of alveolar units participating in gas exchange with the use of positive pressure ventilation. This chapter focuses on these last two aspects of manipulating oxygen delivery in the PICU.

Administration of Supplemental Oxygen

Oxygen should be administered to all critically ill or injured children in the highest possible concentration and regardless of the measured oxygen saturation until an initial assessment of cardiorespiratory status is completed. Oxygen delivery is often compromised in critically ill children secondary to inadequate pulmonary gas exchange (ventilation-perfusion mismatching and intrapulmonary shunting), inadequate cardiac output (mixed venous desaturation), and/or maldistribution of microcirculatory flow. However, assuming normal hemoglobin, normal cardiac output, and optimal matching of ventilation with perfusion, administration of 100% supplemental oxygen will increase oxygen delivery by nearly 10% compared with room air (see later).

Air consists of a mixture of gases, and, according to Dalton's law, the total pressure exerted by a gaseous mixture (i.e., air) is equal to the sum of the partial pressures of the individual gases in that mixture:

$$P_{air} = PN_2 + PO_2 + PH_2O + PCO_2 + PH_2 + PHe + \text{etc.}$$

Therefore, the partial pressure of oxygen (PO_2) in air, given that oxygen comprises 21% of the atmosphere, may be calculated as follows:

$$P_{air} \text{ (sea level)} = 760\,\text{mm Hg} \rightarrow$$
$$PO_2 = 760\,\text{mm Hg} \times 0.21 = 160\,\text{mm Hg}$$

Inhaled air is humidified and warmed as it passes through the nose and pharynx such that the air entering the lungs is fully saturated with water vapor. As the air reaches the alveolus, it mixes with carbon dioxide. The partial pressure of oxygen in the alveolus is therefore determined by the alveolar gas equation:

$$PAO_2 = FiO_2\,(P_{air} - P_{H_2O}) - PACO_2$$

As O_2 is taken up by the lung, CO_2 is eliminated. The ratio of O_2 consumption to CO_2 production is the respiratory quotient, RQ, which is dependent on the metabolic fuels used as substrate (carbohydrates, RQ = 1.0; lipids, RQ = 0.7; proteins, RQ = 0.8). The partial pressure of CO_2 in the alveolus ($PACO_2$) can be approximated by the partial pressure of CO_2 in the arterial blood ($PaCO_2$) divided by the RQ. Under normal conditions, then, $P_B - P_{H20} = 760\,\text{mm Hg} - 47\,\text{mm Hg}$ at sea level, $PaCO_2 = 40\,\text{mm Hg}$, and RQ = 0.8. Therefore, at $FiO_2 = 0.21$ (i.e., room air), $PAO_2 = 0.21 \times (713\,\text{mm Hg}) - (50\,\text{mm Hg})$, or 100 mm Hg. CaO_2 (see earlier equation) would then equal approximately 16.4 g O_2 per liter of blood (assuming an oxygen saturation of 100% and hemoglobin 12 g/dL).

Conversely, at an $FiO_2 = 1.00$, $PAO_2 = (713\,\text{mm Hg}) - (50\,\text{mm Hg})$, or 663 mm Hg. CaO_2 would then equal approximately 17.9 g O_2 per liter, that is, an increase of nearly 10%. In other words, even though dissolved O_2 comprises a small percentage of the overall oxygen content of arterial blood, the increase associated with breathing supplemental oxygen at FIO_2 1.00 versus 0.21 may be clinically significant in the critically ill or injured child. These differences are even more clinically relevant when the hemoglobin concentration is lower than normal. For example, reducing the hemoglobin in the earlier example from 12 to 8 g/dL changes the CaO_2 from 16.4 to 11.0 g O_2 per liter of blood at $FIO_2 = 0.21$. Increasing the FIO_2 to 1.0 would then increase CaO_2 to 12.7 g O_2 per liter of blood, an increase of nearly 14%.

Humidified O_2 or air liquefies secretions and aids in clearance of secretions from the airway. Supplemental oxygen should be provided via nasal cannula or face mask (see later). In general, any child in severe respiratory distress will assume a position that maximizes oxygenation and ventilation and should be allowed to remain in this *position of comfort*. The child should be allowed to remain with his or her parents, as anxiety increases oxygen consumption and may worsen hypoxia. Supplemental oxygen should be introduced in a nonthreatening manner. For example, if the child is upset by one method, oxygen can be delivered by face tent or via the blow-by method with the mask held by a parent and directed toward the child's mouth and nose (Figure 3.1).

Supplemental oxygen may be administered using any of a number of oxygen-delivery devices. The choice of a particular device will be dictated by the desired concentration of oxygen and by what device

Figure 3.1. Children should be allowed to remain in their position of comfort, as this will optimize gas exchange. Supplemental oxygen should be administered in a nonthreatening manner (in some instances, a parent may need to administer supplemental oxygen). (Reprinted with permission from Foltin GL, Tunik MG, Cooper A, Markenson D, Treiber M, Phillips R, Karpeles T. Teaching Resource for instructors in Prehospital Pediatrics. New York, NY: Center for Pediatric Emergency Medicine; 1998.)

is best tolerated by the child. These devices are commonly classified as either low-flow systems or high-flow systems [7–10]. Low-flow systems entrain room air because the rate of the flow of oxygen is insufficient for the child's inspiratory flow requirements. These systems theoretically provide an FiO_2 of 0.23–0.90. In contrast, high-flow systems do not entrain room air as the flow rate is sufficient to meet all the inspiratory flow requirements. When used with an oxygen reservoir, these systems can reliably deliver close to 1.0 FiO_2 and are preferred to the low-flow systems for use in critically ill children.

Oxygen Tent

An oxygen tent is an enclosure system that consists of a clear plastic shell that is designed to enclose the child's entire body or at least the upper body. Oxygen tents require inspiratory flow rates on the order of 20–30 L/min and deliver FiO_2 0.40–0.50. There are several disadvantages to this system, however, that limit its use in the critical care setting. Most importantly, access to the child is rather limited, and room air is entrained whenever the tent is entered such that, even with a high flow of oxygen, reliable, stable oxygen concentrations are rarely achieved. For this reason, a tent should not be used if an $FiO_2 > 0.30$ is required.

Oxygen Hood

Oxygen hoods are another type of enclosure system and consist of a clear plastic shell designed to completely surround the child's head, necessarily limiting use to newborns and infants less than 1 year of age. In contrast to the oxygen tent, use of an oxygen hood allows ready access to the child's chest, abdomen, and extremities without entraining room air. By using gas flow rates of 10–15 L per minute, FiO_2 of 0.8 to 0.9 are readily attained.

Nasal Cannula

A nasal cannula consists of two prongs that extend approximately 1 cm into the child's nares and is held in place with an adjustable head strap. Generally, the delivered FiO_2 will depend on the flow rate of oxygen as well as on the child's respiratory rate, tidal volume, inspiratory flow rate, and volume of the nasopharynx, all of which determine the amount of entrained room air. As a rough guideline, the delivered oxygen concentration will increase by approximately 4% for each 1 L/min increase in the flow rate of oxygen, for example, 1 L/min flow will deliver an FiO_2 of 0.25, 2 L/min flow will deliver an FiO_2 of 0.29, and so forth, although the maximum FiO_2 that can be reliably delivered is about 0.40 (at 6 L/min flow rate) [7–10]. Excessive flow rates, however, are uncomfortable and may result in gastric distention secondary to swallowing of air. Nasal cannula devices have the distinct advantage that they are less restrictive than either the simple face masks or nonrebreather face masks described later and therefore may be potentially better tolerated by children. Importantly, nasal cannula oxygen delivery in children who are *mouth breathers* is perfectly acceptable, because inspiratory airflow through the posterior nasopharynx entrains oxygen through the nose via the Bernoulli principle [8,9].

Simple and Partial Rebreathing Face Masks

Face masks used for administration of supplemental oxygen are usually categorized as simple, partial rebreathing, nonrebreathing, and Venturi (or air-entrainment) masks. Simple face masks were first developed in 1789 and consist of a valveless oxygen inlet and a clear plastic mask designed to fit loosely over the nose and mouth [10]. Simple face masks will generate FiO_2 0.35–0.65 at approximately 6–10 L/min because of the entrainment of room air through the ports in the side of the mask or around the periphery of the mask itself. The inspiratory flow rate should always be at least 5 L/min so that the flow of oxygen into the mask exceeds the child's minute ventilation in order to prevent rebreathing of carbon dioxide. Simple face masks offer few advantages over a nasal cannula. Partial rebreathing masks, on the other hand, incorporate a simple face mask, a valveless oxygen inlet, and an oxygen reservoir bag. As the name implies, at least a portion of the child's exhaled gas reenters the reservoir bag. If the inspiratory flow rate is sufficient, this portion of gas usually comprises the anatomic dead space. As the anatomic dead space does not normally participate in gas exchange, the concentration of CO_2 in this gas is relatively negligible. As the reservoir bag fills and the pressure within the reservoir increases, the exhaled gas at the end of the normal tidal volume, which contains CO_2, is forced out through the holes at the side of the mask. Importantly, the bag should not collapse during inspiration. With inspiratory flow rates of 10 L/min or greater, an FiO_2 of 0.5–0.6 is easily achieved with this type of mask. However, as the partial rebreathing face mask is often mistaken for the nonrebreathing face mask, many experts feel that this type of mask has no place in the critical care setting.

Nonrebreathing Face Masks

A nonrebreathing face mask consists of a face mask connected to a unidirectional valve and oxygen reservoir bag. The one-way valve assembly is located on the exhalation port of the mask and allows fresh gas to enter the mask from the reservoir bag while preventing exhaled gas from entering the reservoir bag. Under ideal conditions, FiO_2 close to 1.00 may be delivered. The inspiratory flow rate must be sufficient to maintain a partially distended reservoir bag, and the mask must fit relatively snugly over the nose and mouth.

Air-Entrainment or Venturi Masks

Air-entrainment masks, also known as Venturi masks, are based on Bernoulli's principle (the velocity of the oxygen increases as it flows through a narrowed tube, generating a subatmospheric pressure around the stream of gas, which in turn entrains a specific proportion of ambient, room air). As oxygen is introduced into the device through a tapered inlet, or *injector*, room air is entrained through the side ports of the device. The large volume of entrained air (up to 100 L/min in some cases) mixes with the oxygen flowing through the injector, producing stable FiO_2 ranging between 0.24 and 0.40. More importantly, using this kind of system, the delivered FiO_2 is stable and relatively independent of the child's minute ventilation. Nebulizers that are used to deliver aerosolized medications (e.g., albuterol, racemic epinephrine) operate on much the same principle as the Venturi mask.

Bag-Valve-Mask Ventilation

For some children, establishing an airway using the techniques described is sufficient to allow for resumption of spontaneous respiration and adequate gas exchange. However, for some children positive airway pressure will be necessary to overcome obstruction

of the airway, and, hence, manual ventilation with a bag-valve-mask assembly becomes necessary. Effective bag-mask ventilation requires a good seal between the mask and the face (Figure 3.2) and is generally most effectively achieved by two providers, with one provider using both hands to maintain an open airway and an air-tight mask-to-face seal while the second provider squeezes the ventilation bag [11]. The mask should fit snugly across the nose and bony prominence of the chin, although undue pressure over the eyes, nose, and face should be avoided—generally 90% of the effort should be directed toward bringing the face into the mask, whereas the remaining 10% of the effort should actually be directed toward pushing the mask down on the child's face [12].

During bag-valve-mask ventilation, it is usually necessary to gently move the head and neck through a range of positions to determine the optimal position for adequate gas exchange. A neutral sniffing position is usually best, although excessive hyperextension of the head and neck should be avoided, especially in infants, as this may itself lead to airway obstruction. Again, all critically ill or injured children have cervical spine injury until proven otherwise, and manipulation of the head and neck should be avoided under these circumstances. The *triple airway maneuver* or placement of a nasopharyngeal airway can be quite helpful in maintaining an open airway during bag-valve-mask ventilation. If effective gas exchange (as determined by the rise and fall of the chest with each breath) still is not achieved, the head and neck should be repositioned and proper mask-to-face seal should be verified.

In general, two types of bags are commonly used in the PICU—the self-inflating bag (Figure 3.3) and the standard anesthesia bag (Figure 3.4) [13,14]. There are advantages and disadvantages to both types of bags. The self-inflating bag consists of a bag, an inlet port for oxygen, an adaptor (for either a face mask or tracheal tube), an oxygen reservoir (see earlier), and a pressure relief or *pop-off* valve. The pressure relief valve is a safety feature designed to limit excessive inspiratory pressures that could result in either volutrauma or barotrauma to the lung, and most self-inflating bags in use will *pop off* at pressures approaching 35–40 cm H_2O. However, the pressure relief valve may be bypassed in situations in which high inspiratory pressures are required to generate adequate gas exchange (e.g., the critically ill child with poor lung and/or chest wall compliance). Occlusion of the pop-off valve is easily accomplished by depressing the valve with a finger during ventilation or by twisting the valve

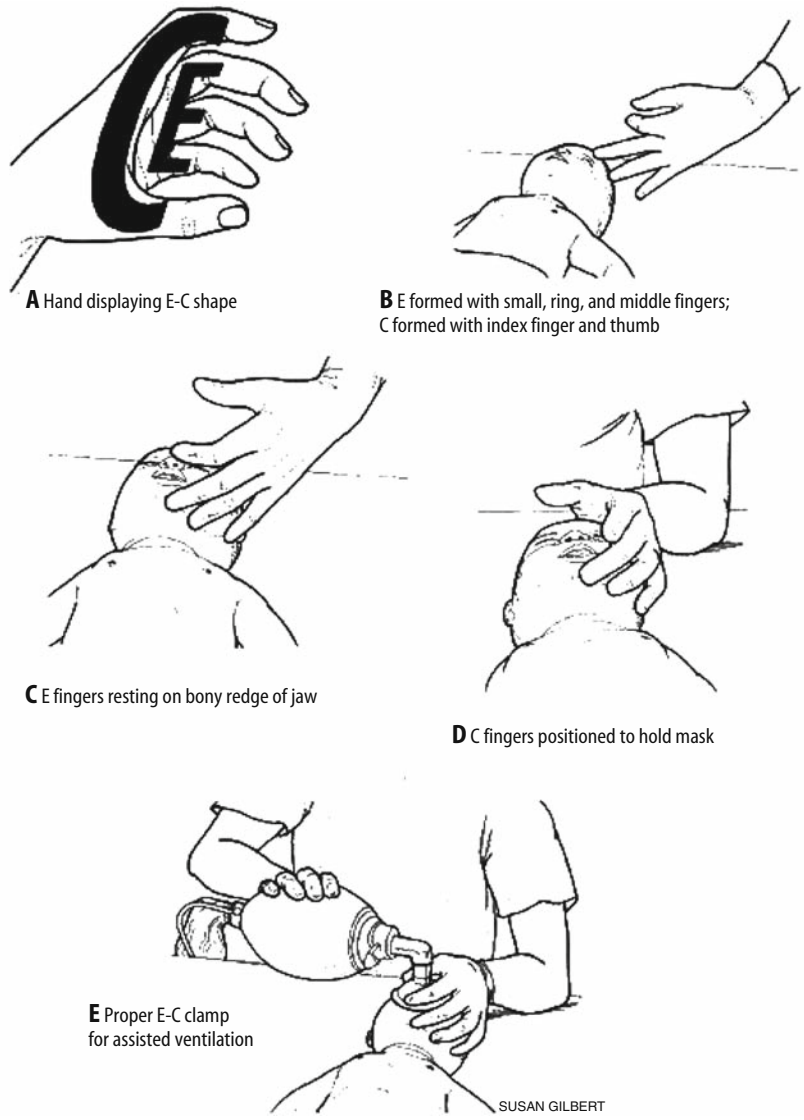

Figure 3.2. The *E-C clamp technique* achieves a good seal when placing a mask for assisted ventilation. The third, fourth, and fifth fingers are placed along the jaw to provide a chin lift (forming an E), and the thumb and index finger are placed to hold the mask on the child's face (forming a C). (Reprinted with permission from Foltin GL, Tunik MG, Cooper A, Markenson D, Treiber M, Phillips R, Karpeles T. Teaching Resource for Instructors in Prehospital Pediatrics. New York, NY: Center for Pediatric Emergency Medicine; 1998.)

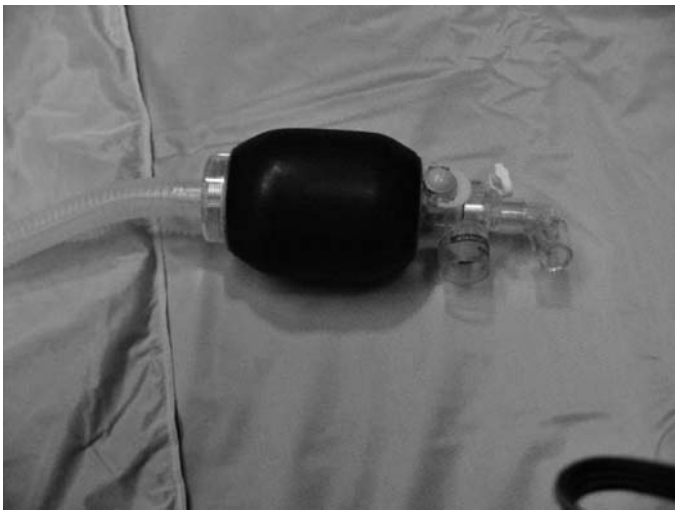

Figure 3.3. Self-inflating bag. The self-inflating bag consists of a bag, an inlet port for oxygen, an adaptor (for either a face mask or a tracheal tube), an oxygen reservoir, and a pressure relief or pop-off valve.

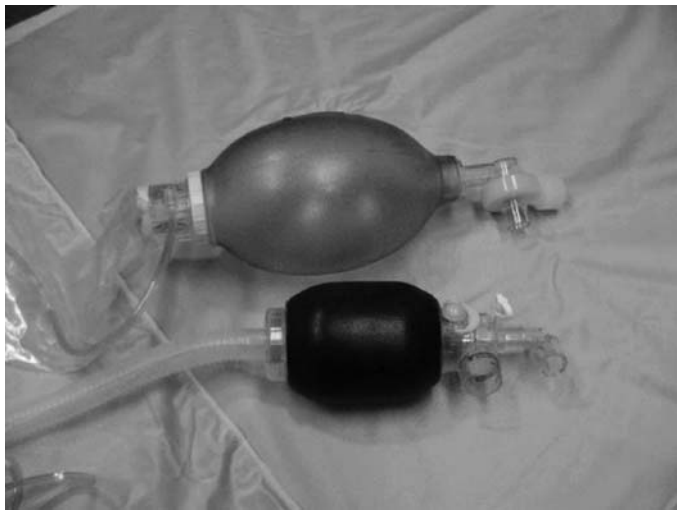

Figure 3.5. Self-inflating bags are available in various sizes: newborn (volume 450 mL); infants, toddlers, and smaller children (750 mL); and larger children and adolescents (1,200 mL).

into a closed position [14,15]. Finally, the adaptors on most self-inflating bags currently used are equipped with a one-way valve feature such that rebreathing of exhaled air is minimal. Self-inflating bags without oxygen reservoirs deliver an FiO_2 between 0.30 and 0.80 at an oxygen flow of 10 L/min, while the simple addition of an oxygen reservoir will deliver an FiO_2 between 0.60 and 0.95. Self-inflating bags are available in various sizes for newborns (volume 450 mL); infants, toddlers, and smaller children (750 mL); and larger children and adolescents (1,200 mL) (Figure 3.5). Smaller children can be ventilated with a larger bag as long as proper techniques are used, although most children will not need the entire volume of the bag to be ventilated properly. The tidal volume should be titrated to adequate rise and fall of the chest under these circumstances. The main advantage to the self-inflating bag is its ease of use, especially by inexperienced providers. In addition, the self-inflating bag provides a rapid means of ventilating a child in the event of an emergency and does not require an oxygen source, although only room air (21% oxygen) is delivered unless supplemental oxygen is provided. Unfortunately, the main drawback is that supplemental *blow-by* oxygen or mask continuous positive air pressure (CPAP cannot be administered.

In contrast to self-inflating bags, standard anesthesia bags require a constant flow of oxygen under pressure in order to expand. Similar to the self-inflating bags, anesthesia bags consist of a bag (again, in various sizes ranging from 500 mL for neonates and infants, to 1,000–2,000 mL for children, to 3,000–5,000 mL for adults) (Figure 3.6), an inlet for oxygen, an adaptor for connection to either a face mask or a tracheal tube, and a pressure-release valve. Most setups also include a manometer to monitor airway pressures. Most PICUs currently use a Mapleson D configuration

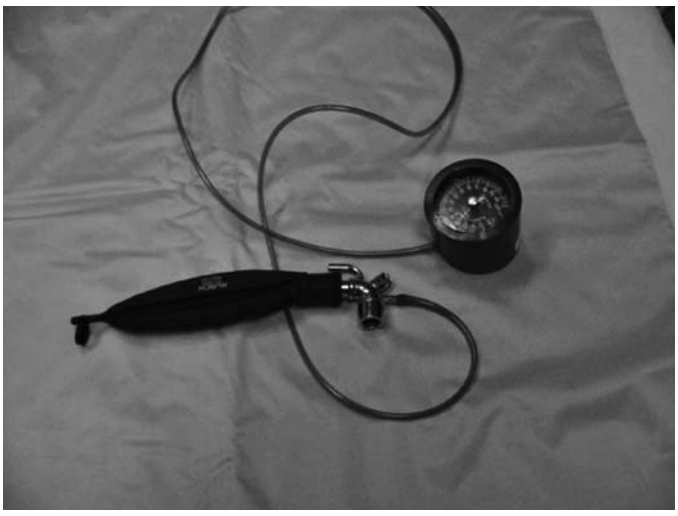

Figure 3.4. Anesthesia bag. Anesthesia bags consist of a bag, an inlet for oxygen, an adaptor for connection to either a face mask or a tracheal tube, and a pressure-release valve. Most setups also include a manometer to monitor airway pressures. Most pediatric intensive care units currently use a Mapleson D configuration in which the oxygen inlet is located just distal to the adaptor/patient connection. The pressure-release valve can be adjusted to deliver varying amounts of continuous positive airway pressure or positive end-expiratory pressure (PEEP) and hence is also commonly called a *PEEP valve*.

Figure 3.6. Anesthesia bags are available in various sizes, ranging from 500 mL for neonates and infants, to 1,000–2,000 mL for children, to 3,000–5,000 mL for adults.

in which the oxygen inlet is located just distal to the adaptor/patient connection. The pressure release valve can be adjusted to deliver varying amounts of CPAP or positive end-expiratory pressure (PEEP) and hence is also commonly called a *PEEP valve*. The main advantage to using the standard anesthesia bag is the ability to deliver either *blow-by* oxygen (because of the constant flow of oxygen through the system) or CPAP/PEEP. In addition, most providers prefer the ability to *feel* the patient's lung compliance and adjust the delivered tidal volume accordingly.

There are two main disadvantages to the anesthesia bag. First, the system may be difficult for inexperienced providers to use. Second, rebreathing of expired air is theoretically possible, although an adequate flow of oxygen (generally two to three times the patient's minute ventilation) will generally ensure adequate CO_2 elimination and prevent rebreathing of expired air [16–18]. Therefore, gas flows should be adjusted to at least 2 L/min for children <10 kg in body weight, 4 L/min for children weighing between 10 and 50 kg, and 6 L/min for children weighing more than 50 kg.

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4
Assessment and Management of the Pediatric Airway

Derek S. Wheeler, James P. Spaeth, Renuka Mehta, Suriyanarayana P. Hariprakash, and Peter N. Cox

Introduction

Respiratory failure is a common cause of cardiopulmonary arrest in children, both within and outside the hospital [1–5]. Acute airway obstruction (AAO) can cause rapidly progressive respiratory failure. Therefore it is *time critical* to recognize early respiratory compromise and prevent progression to respiratory failure and cardiopulmonary arrest, as once respiratory arrest progresses to asystolic cardiac arrest, the outcome is quite poor [6,7]. The goal of airway management is to anticipate and recognize respiratory compromise and to provide support and stabilization of the airway in a timely manner. Anatomic differences between pediatric and adult patients render children more susceptible to acute airway compromise; it is therefore important to recognize and understand these differences, as they may have an impact on the success of airway management.

Developmental Anatomy and Physiology of the Pediatric Airway

The upper airway is a vital part of the respiratory tract and consists of the nose, paranasal sinuses, pharynx, larynx, and extrathoracic trachea. The structural complexity of the upper airway reflects its diverse functions, which include phonation, olfaction, humidification and warming of inspired air, digestion, preservation of airway patency, and protection of the airways [8,9]. The pediatric airway is markedly different from the adult airway [10–13]. These differences are most dramatic in the infant's airway and become less important as the child grows—the upper airway assumes the characteristics of the adult airway by approximately 8 years of age.

Anatomic features that differ between children and adults include (1) a proportionally larger head and occiput (relative to body size), causing neck flexion and leading to potential airway obstruction when lying supine; (2) a relatively larger tongue, decreasing the size of the oral cavity; (3) decreased muscle tone, resulting in passive obstruction of the airway by the tongue; (4) a shorter, narrower, horizontally positioned, softer epiglottis; (5) cephalad and anterior position of the larynx; (6) shorter, smaller, narrower trachea; and (7) funnel-shaped versus cylindrical airway, such that the narrowest portion of the airway is located at the level of the cricoid cartilage (Figure 4.1).

The first and perhaps most obvious difference is that the pediatric airway is much smaller in diameter and shorter in length than the adult's. For example, the length of the trachea changes from approximately 4 cm in neonates to approximately 12 cm in adults, and the tracheal diameter varies from approximately 3 mm in the premature infant to approximately 25 mm in the adult [11,13]. According to Hagen-Poiseuille's law, the change in air flow resulting from a reduction in airway diameter is directly proportional to the airway radius elevated to the fourth power:

$$Q = (\Delta P\ \pi\ r^4)/(8\ \eta\ L),$$

where Q is flow, ΔP is the pressure gradient from one end of the airway to the other end, r is the radius of the airway, η is the viscosity of the air, and L is the length of the airway. Therefore, increasing the length of the airway (L), increasing the viscosity of the air (η), or decreasing the radius of the airway will reduce laminar air flow. Changing the airway radius, however, has the greatest effect on flow. Small amounts of edema will therefore have a greater effect on the caliber of the pediatric airway compared with the adult airway, resulting in a greater increase in airway resistance (Figure 4.2).

Aside from these size differences, the pediatric airway demonstrates several additional unique features as introduced earlier [10–13]. For example, the larynx is located relatively cephalad in the neck, with the inferior margin of the cricoid cartilage residing at approximately the level of C2–C3 in infants compared with C4–C5 in adults. This elevated position brings the epiglottis and palate in close proximity, thus making the infant an obligate nose breather in the first few weeks to months of life, which has potential clinical significance for various congenital abnormalities of the nasal airway. Infants are at greater risk of upper airway obstruction as nasal breathing doubles the resistance to air flow [13]. In addition,

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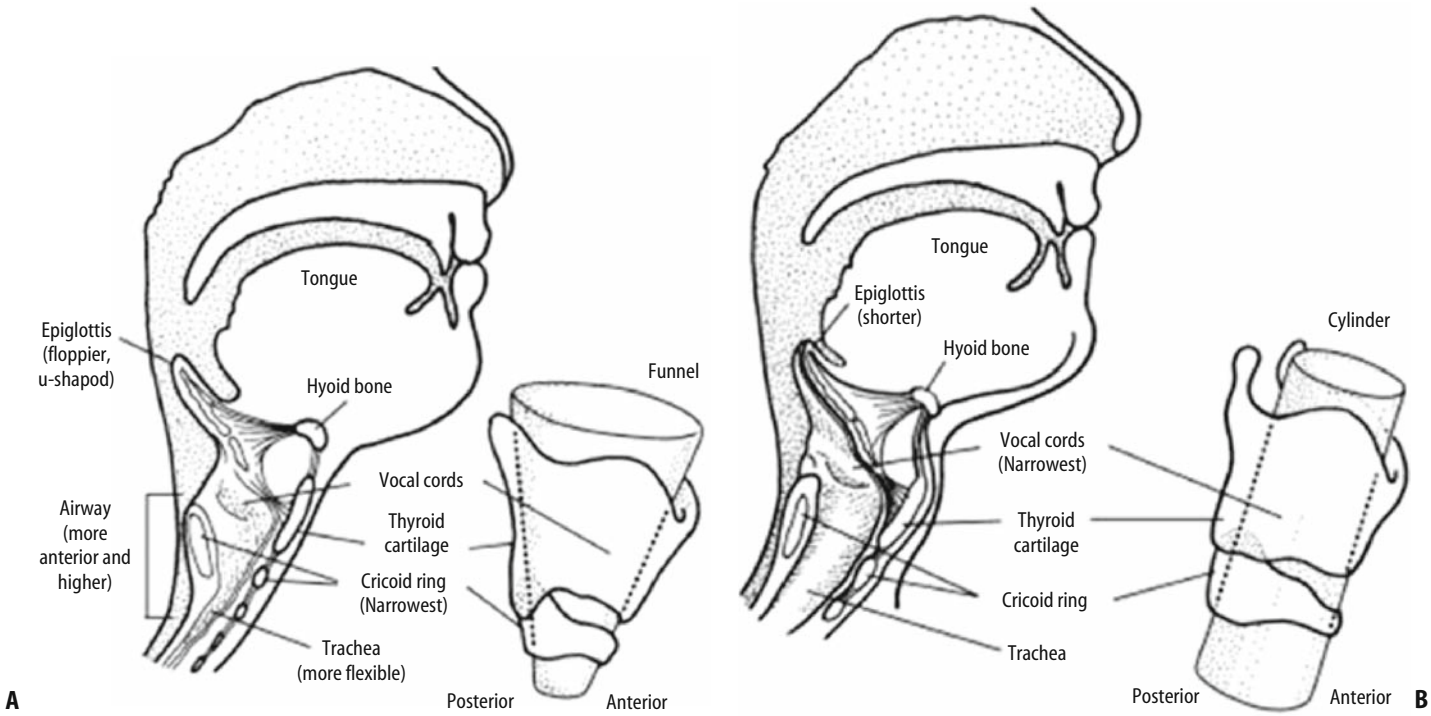

Figure 4.1. Anatomic differences between the pediatric **(A)** and adult **(B)** airway. (Reprinted with permission from Foltin G, Tunik MG, Cooper A, Markenson D, Treiber M, Phillips R, Karpeles T. Teaching Resource for Instructors in Prehospital Pediatrics. New York: Center for Pediatric Emergency Medicine; 1998.)

the nares are much smaller in children and can account for nearly 50% of the total resistance of the airways. The nares are easily obstructed by secretions, edema, blood, or even an ill-fitting face mask, all of which can significantly increase the work of breathing.

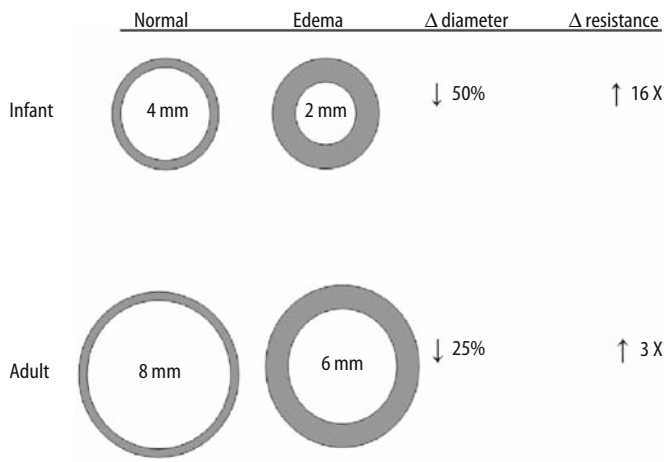

Figure 4.2. Age-dependent effects of a reduction in airway caliber on the airway resistance and air flow. Normal airways are represented on the left (top, infants; bottom, adults); edematous airways are represented on the right. According to Poiseuille's law, airway resistance is inversely proportional to the radius of the airway to the *fourth power* when there is laminar flow and to the *fifth power* when there is turbulent flow. One millimeter of circumferential edema will reduce the diameter of the airway by 2 mm, resulting in a 16-fold increase in airway resistance in the pediatric airway versus a threefold increase in the adult (cross-sectional area reduced by 75% in the pediatric airway versus a 44% decrease in the adult airway). Note that turbulent air flow (such as occurs during crying) in the child would increase the resistance by 32-fold.

The tongue, which is large relative to the size of the oral cavity, more easily apposes the palate and represents one of the more common causes of upper airway obstruction in unconscious infants and children. A jaw-thrust maneuver or placement of either an oral or nasal airway will lift the tongue and relieve the obstruction in this situation (see later).

Tracheal intubation requires the alignment of three axes: the oral axis, the pharyngeal axis, and the laryngeal axis (Figure 4.3). Normally, the oral axis is perpendicular to the laryngeal axis, and the pharyngeal axis is positioned at an angle of 45° to the laryngeal axis. Placement of a folded towel beneath the occiput will flex the neck onto the chest, thereby aligning the pharyngeal and laryngeal axes. With proper extension of the atlanto-occipital joint, that is, head extension and neck flexion (s*niff position*), these three axes are superimposed to establish the necessary line of visualization for optimal tracheal intubation. The cephalad position of the infant's larynx effectively shortens the length over which these three axes are superimposed, thereby creating more of an acute angle between the base of the tongue and the glottic opening. The glottic opening appears *anterior* such that adequate visualization may be difficult during direct laryngoscopy. The occiput is much larger in children than in adults, leading to hyperflexion of the neck on the chest. A neck or shoulder roll will facilitate adequate visualization of the glottic opening during laryngoscopy. In addition, straight laryngoscope blades are often used in infants and young children to better visualize the airway during tracheal intubation.

The epiglottis is short, narrow, and angled posteriorly away from the long axis of the trachea and may be difficult to control via vallecular suspension with a curved laryngoscope blade. A straight laryngoscope blade is preferable to a curved laryngoscope blade in this situation. The adult vocal cords lie perpendicular to the laryngeal axis, whereas the infant's vocal cords are angled in an antero-

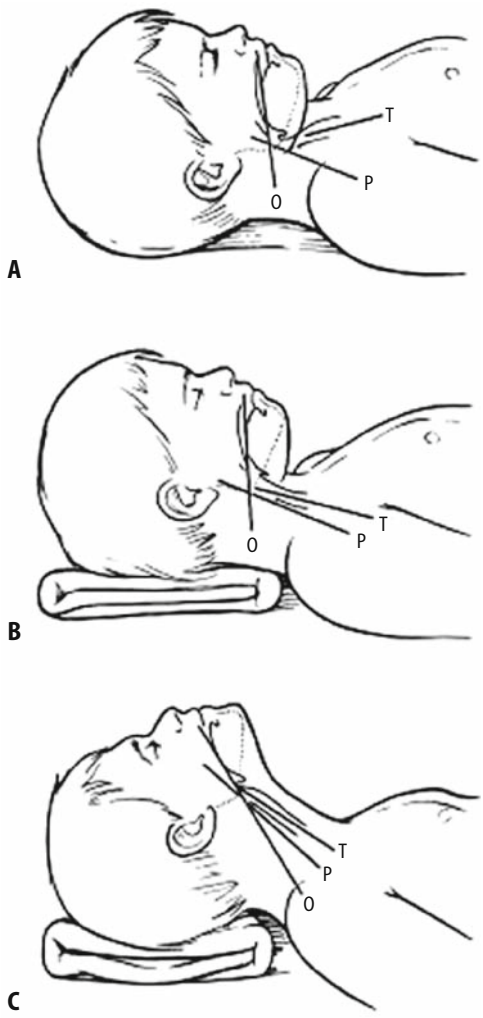

Figure 4.3. Correct positioning of the child more than 2 years of age for ventilation and tracheal intubation. **(A)** With the patient on a flat surface, the oral (O), pharyngeal (P), and tracheal (T) axes pass through three divergent planes. **(B)** A folded sheet or towel placed under the occiput of the head aligns the pharyngeal and tracheal axes. **(C)** Extension of the atlanto-occipital joint results in alignment of the oral, pharyngeal, and tracheal axes. (Reprinted from Coté et al. [11]. Copyright 1993 with permission of Elsevier.)

caudal position (the anterior attachments are more inferior than the posterior attachments). The tracheal tube can therefore become caught on the anterior commissure during passage through the glottic opening. Simple rotation of the tracheal tube will usually allow the tube to pass in this situation.

The narrowest portion of the pediatric airway is located below the level of the vocal cords at the cricoid cartilage, whereas the narrowest portion of the adult airway is at the level of the vocal cords (Figure 4.4). The pediatric airway is funnel shaped as a result compared with the cylindrical shape of the adult airway (Figure 4.5). This anatomic configuration is one reason why uncuffed tracheal tubes can be used effectively in infants and children in that an effective seal will often form between the tracheal tube and the ringlike cricoid cartilage. Conversely, in adults, the circular tracheal tube will not form a good seal through the trapezoid-shaped glottic opening, and cuffed tracheal tubes are essential to provide for adequate ventilation and protection from

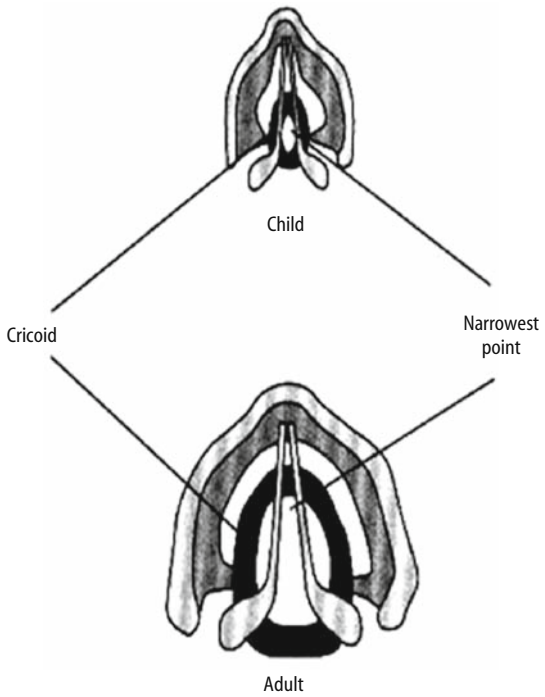

Figure 4.4. The narrowest portion of the pediatric airway is at the cricoid cartilage versus the vocal cords in the adult. (Reprinted from Coté et al. [11], with permission of Elsevier.)

aspiration. The subglottic airway is completely encircled by the cricoid cartilage and is restricted in its ability to freely expand in diameter. In addition, the subglottic airway contains loosely attached connective tissue that can rapidly expand with inflammation and edema, leading to dramatic reductions in airway caliber (see Figure 4.2). Children are at significant risk for viral laryngotracheobronchitis (croup) or postextubation stridor, especially

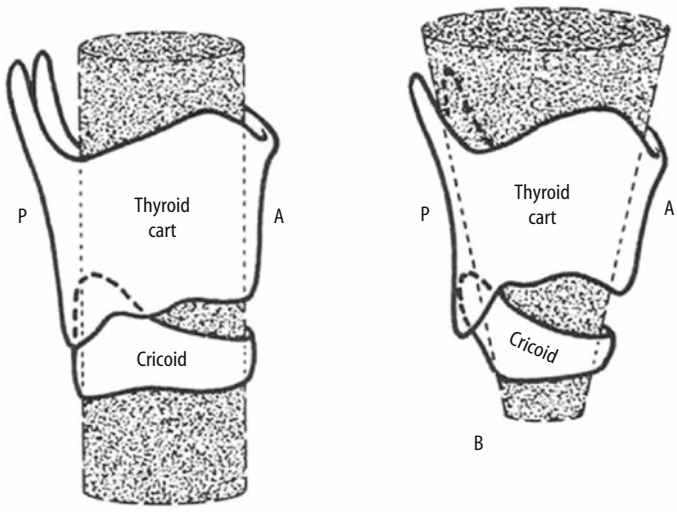

Figure 4.5. Configuration of the adult **(A)** and the infant **(B)** larynx. Note the cylindrical shape of the adult larynx. The infant larynx is funnel shaped because of a narrow cricoid cartilage. A, anterior; P, posterior. (Reprinted from Coté et al. [11]. Copyright 2001 with permission from Elsevier.)

when an oversized tracheal tube is used or the cuff is overinflated. Young children are also at risk for acquired subglottic stenosis when exposed to prolonged or recurrent tracheal intubation.

The newborn trachea is soft and six times more compliant than that of the adult trachea. The transverse muscles are arranged uniformly, but longitudinal smooth muscles vary throughout the entire tracheal length. The musculature of the lower half of the trachea is more developed and functions to preserve stability of the tracheal lumen. Tracheal growth progresses throughout childhood into puberty. After puberty, the C-shaped cartilaginous tracheal rings do not expand such that tracheal growth is the result of further growth of the tracheal musculature and soft tissue [10–13].

Acute Airway Obstruction

Children are at particular risk for AAO because of the anatomic differences between the pediatric and adult airway, as discussed earlier [13,14]. Children may appear surprisingly well despite being on the verge of cardiorespiratory collapse. Infants have a high oxygen demand because of a higher metabolic rate relative to body size and weight. Consequently, in the presence of apnea or inadequate ventilation, hypoxemia develops more rapidly in the child than in the adult, and acute decompensation of cardiorespiratory status may be swift and often difficult to reverse [14–16]. Upper airway obstruction often leads to acute respiratory failure and is an important cause of out-of-hospital cardiopulmonary arrest, in stark contrast to adults in whom primary cardiac disease commonly precipitates cardiopulmonary arrest. Once respiratory arrest progresses to cardiac arrest, outcome is dismal [17,18], and prompt recognition of AAO and appropriate, timely intervention are crucial to ensure the best possible outcome.

The pediatric airway is highly compliant and the cartilaginous support less well-developed than the adult airway and is therefore more susceptible to dynamic airway collapse in the presence of airway obstruction. The normal respiratory dynamics change significantly in the presence of upper airway or lower airway obstructions (Figure 4.6). A forced inhalation that is required to generate air flow in the presence of a partial upper airway obstruction requires a stronger contraction of the diaphragm and respiratory muscles, generating a greater decrease (i.e., more negative relative to atmospheric pressure) in intrapleural and intraluminal airway pressures. The larger gradient between atmospheric pressure and the airway pressure leads to dynamic collapse of the extrathoracic trachea just beyond the level of obstruction. Conversely, lower airway or intrathoracic airway obstruction (e.g.. aspirated foreign body, asthma, bronchiolitis) results in a ball-valve effect and subsequent air trapping. Increased respiratory effort during exhalation is required, generating an increase in intrapleural pressures and leading to dynamic compression of the intrathoracic airways.

The movement of a gas (i.e., air) through a partially closed, collapsible tube (i.e., airway) obeys the laws of physics. According to

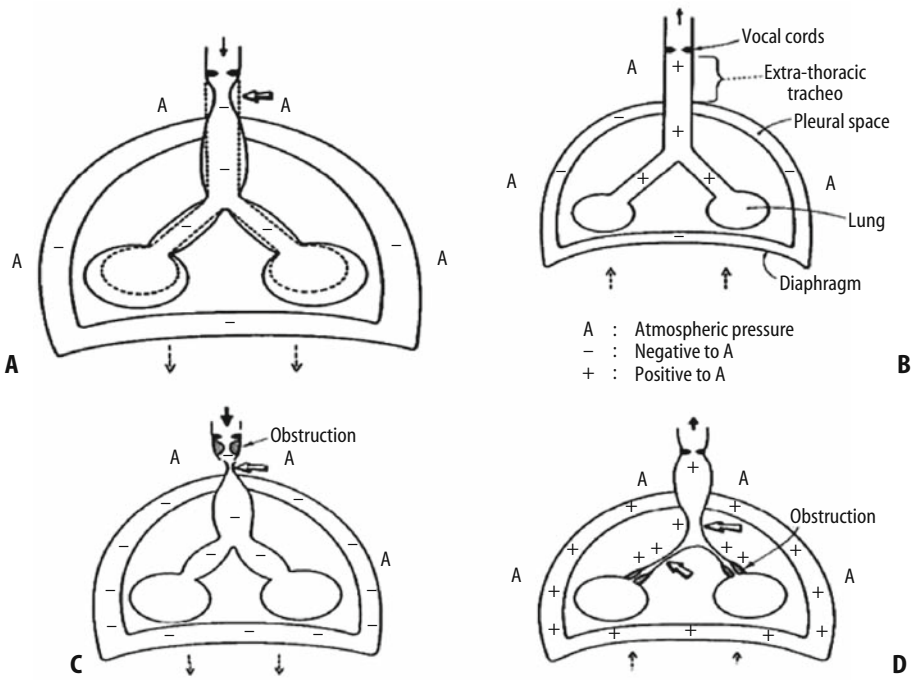

Figure 4.6. **(A)** Normal Inspiration. At end expiration, intrapleural pressure is less than atmospheric pressure, so it should maintain airway patency. In infants the highly compliant chest wall does not provide the support required. Thus airway closure occurs with each breath. Descent of the diaphragm and contraction of the intercostal muscles develop a greater negative intrathoracic pressure relative to intraluminal and atmospheric pressure. The net result is a longitudinal stretching of the larynx and trachea, dilation of the intrathoracic trachea and bronchi, movement of air into the lungs, and some dynamic collapse of the extrathoracic trachea because of the increased compliance of the trachea and the negative intraluminal pressure in relation to atmospheric pressure. **(B)** Normal expiration. Intraluminal pressures are slightly positive in relation to atmospheric pressure, so air is forced out of the lungs. **(C)** Extrathoracic obstruction (obstructed inspiration). Respiratory dynamics occurring with upper airway obstruction; note the severe dynamic collapse of the extrathoracic trachea below the level of obstruction. This collapse is greatest at the thoracic inlet, where the largest pressure gradient exists between negative intratracheal pressure and atmospheric pressure. **(D)** Intrathoracic obstruction (obstructed expiration). Respiratory dynamics occurring with lower airway obstruction. Breathing through a partially obstructed lower airway (such as occurs in bronchiolitis or asthma) results in greater positive intrathoracic pressures, with dynamic collapse of the intrathoracic airways (prolonged expiration or wheezing). (Reprinted from Coté et al. [11]. Copyright 1993 with permission of Elsevier.)

Table 4.1. Common causes of upper airway obstruction in children.

Anatomic
Altered level of consciousness (airway muscle laxity)
Postextubation airway obstruction
Tonsillar hypertrophy
Subglottic stenosis (acquired or congenital)
Macroglossia
Vocal cord paralysis
External or internal compression
Tumor
Hemangioma
Hematoma
Cyst
Papilloma
Vascular rings and slings
Infectious
Laryngotracheobronchitis (Croup)
Peritonsillar abscess
Retropharyngeal abscess
Bacterial tracheitis
Epiglottitis ("supraglottitis")
Infectious mononucleosis
Miscellaneous
Postextubation airway obstruction
Angioedema
Foreign body aspiration
Airway trauma

the *Venturi effect*, the pressure exerted by a gas (i.e., air) as it flows through a partially closed tube is equal in all directions except when there is linear movement, which creates additional pressure in the forward vector with a corresponding fall in the lateral vectors. This decrease in lateral pressure (i.e., the distending pressure keeping the collapsible tube open) causes the tube to narrow, leading to partial obstruction. In addition, according to the *Bernoulli principle*, the velocity of a gas increases as it flows through a partially obstructed tube, creating an additional decrease in intraluminal pressure and further exacerbating the obstruction. This pattern of intermittent flow produces audible sounds that are characterized (depending on the level of partial obstruction) as stertor, gurgling, stridor, wheezes, rhonchi, and rales. For example, stertor is a snoring or snorting sound that is produced by turbulence within the nasopharynx. Gurgling is produced by turbulence within the oropharynx caused by the mixture of air and secretions. Stridor is the sound produced by turbulent air flow in a partially obstructed trachea because of either intrinsic obstruction or extrinsic compression. Careful assessment of the time in the respiratory cycle in which stridor predominates may provide valuable diagnostic clues in determining the site of airway obstruction [14,19–25]. For example, partial obstruction of the extrathoracic, supraglottic airway usually manifests as inspiratory stridor (i.e., occurring during the initial phase of inspiration). Partial obstruction of the intrathoracic, subglottic airway usually manifests as biphasic (inspiratory *and* expiratory) stridor. Changes in the severity of stridor may suggest the presence of an expanding lesion, such as a papilloma or congenital cyst. Wheezing, on the other hand, is produced by partial obstruction in the smaller, peripheral airways.

The differential diagnosis of AAO is provided in Table 4.1. Initial attention should focus on the child's overall appearance and cardiorespiratory status, as this will influence subsequent decision making with respect to the necessary speed and sequence of subsequent diagnostic and therapeutic actions [14,19,20]. The child's level of consciousness should be assessed immediately, as an obtunded or unconscious child may require immediate control of the airway. Restlessness, anxiety, and diaphoresis are usually signs of *air hunger* and hypoxemia. Drooling or the inability to handle oral secretions results from an inability to swallow secondary to pain or swelling of affected tissues and is typically seen with supraglottic pathology (e.g., supraglottitis, retropharyngeal abscess). Accessory muscle use is an additional sign of increased work of breathing and is indicative of compromised gas exchange.

During quiet breathing, air flow is laminar and resistance to air flow is inversely proportional to the fourth power of the airway radius as stipulated by Poiseuille's law. When air flow is turbulent (e.g., during crying) resistance to air flow is inversely proportional to the fifth power of radius such that even a minor reduction in the cross-sectional area of the airway will result in a marked increase in air flow resistance and work of breathing. For these reasons, the infant or child with airway obstruction should be kept calm and as quiet as possible to prevent generation of turbulent air flow, increased airway resistance, and worsening respiratory distress. In general, any child in severe respiratory distress will assume a position that maximizes oxygenation and ventilation and should be allowed to remain in this *position of comfort* (Figure 4.7). For example, the child with supraglottitis will sit erect with the head tilted forward in the *sniffing position*, whereas a child with a retropharyngeal abscess will assume a head tilt or opisthotonus posture because of spasm of the muscles supporting the cervical spine [14].

Figure 4.7. The child's *position of comfort* should be maintained at all times, as excessive crying and agitation leads to airway turbulence, further compromising a partially obstructed airway. (Reprinted with permission from Foltin G, Tunik MG, Cooper A, Markenson D, Treiber M, Phillips R, Karpeles T. Teaching Resource for Instructors in Prehospital Pediatrics. New York: Center for Pediatric Emergency Medicine; 1998.)

Basic Airway Management

Stabilization of the airway is of primary importance during the initial resuscitation of the critically ill or injured child. No matter what the cause or underlying condition, further attempts at resuscitation or treatment will fail without proper control of the airway. The goals of airway management are threefold: (1) relieve anatomic obstruction, (2) prevent aspiration of gastric contents, and (3) promote adequate gas exchange.

Emergency management of the airway proceeds in a sequential order and begins with proper positioning of the head and protection of the cervical spine—all critically injured children have cervical spine injury until proven otherwise. Collapse of the tongue and soft tissues leads to obstruction of the upper airway and is the most common cause of airway obstruction in children (see Table 4.1). The *triple airway maneuver* is a simple method of relieving airway obstruction in this scenario and includes (1) proper head positioning while avoiding neck flexion (*head tilt maneuver* or *sniff position*—although the *head tilt* should be avoided whenever cervical spine injury is suspected), (2) anterior displacement of the mandible (*jaw thrust maneuver*), and (3) placement of an oral airway (Figure 4.8).

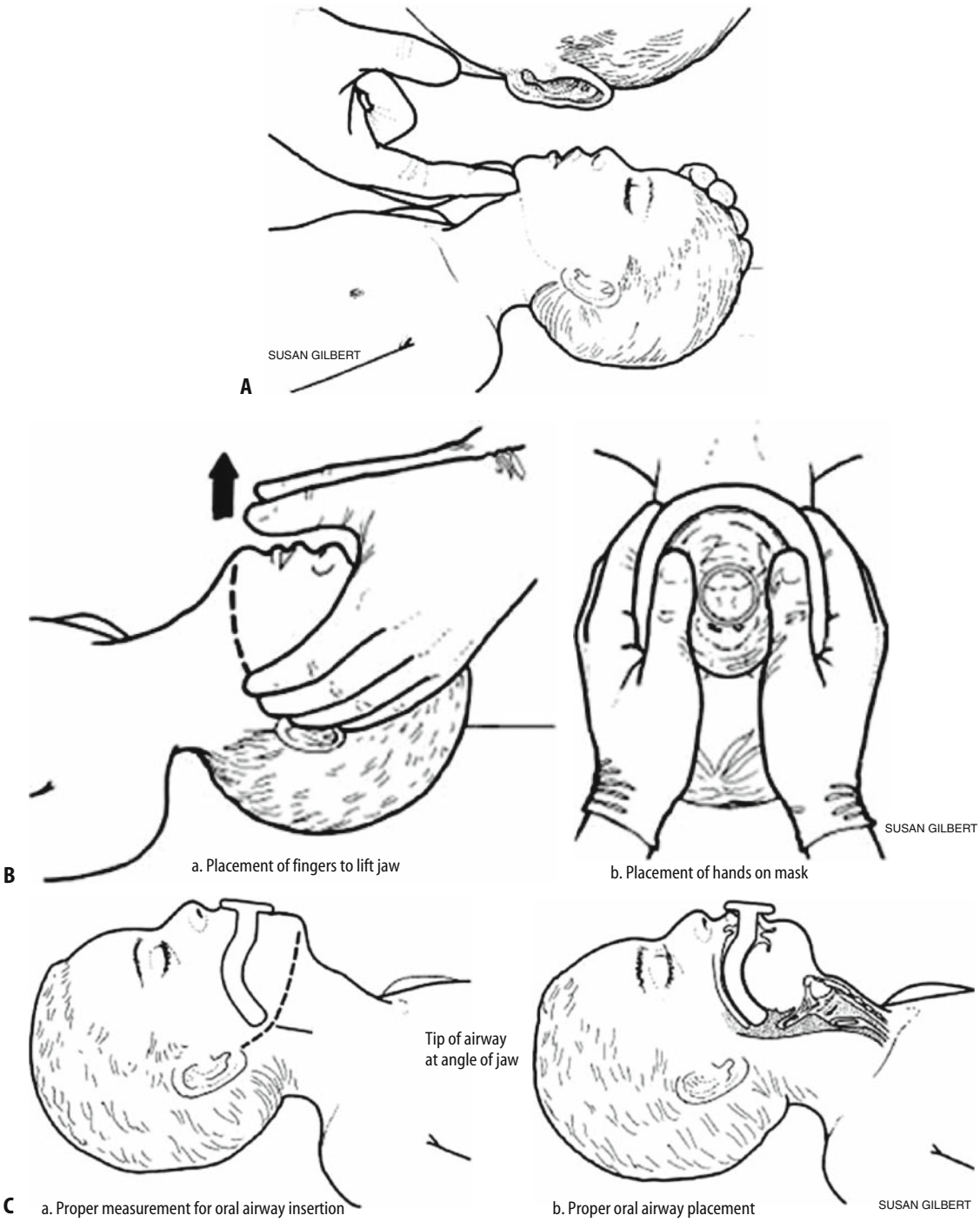

Figure 4.8. The *triple airway maneuver*. **(A)** Head tilt–chin lift maneuver **(B)** Jaw thrust maneuver **(C)** Placement of an oral airway. (Reprinted with permission from Foltin G, Tunik MG, Cooper A, Markenson D, Treiber M, Phillips R, Karpeles T. Teaching Resource for Instructors in Prehospital Pediatrics. New York: Center for Pediatric Emergency Medicine; 1998.)

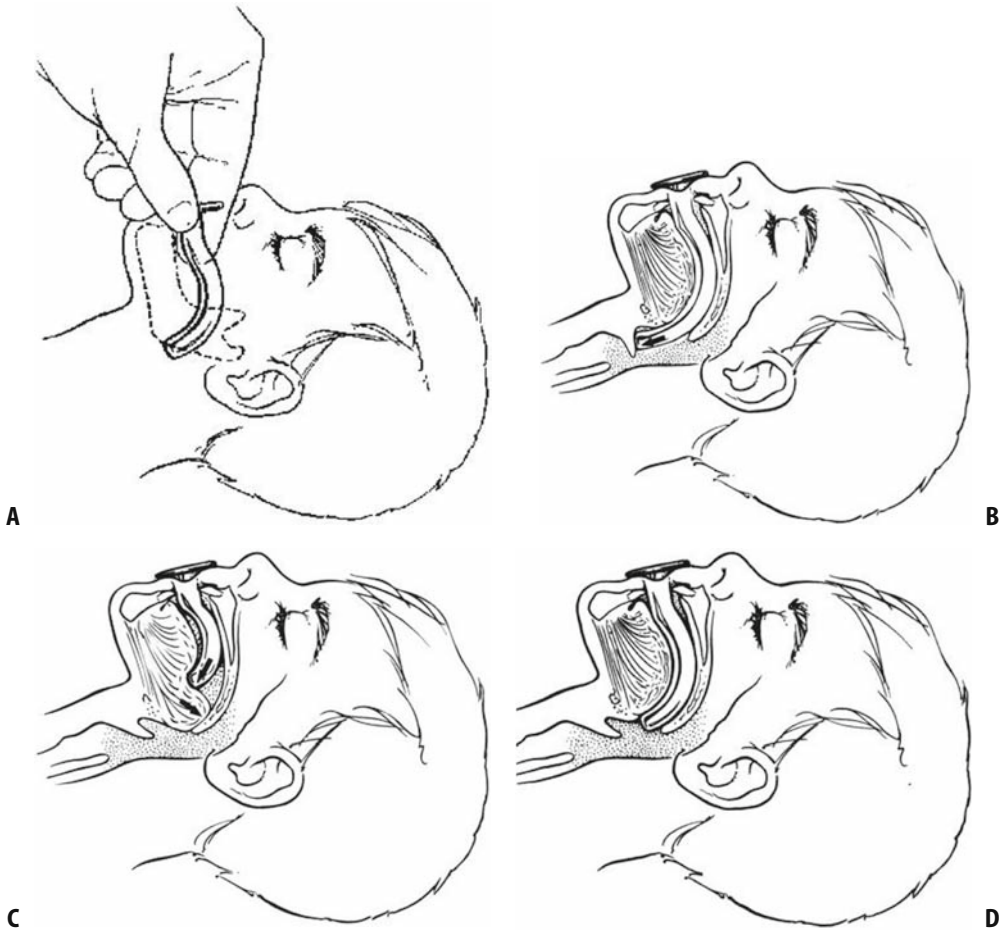

Figure 4.9. **(A)** Proper oral airway selection. An airway of the proper size should relieve obstruction caused by the tongue without damaging laryngeal structures. The appropriate size can be estimated by holding the airway next to the child's face—the tip of the airway should end just cephalad to the angle of the mandible (broken line), resulting in proper alignment with the glottic opening. An oral airway that is either too large **(B)** or too short **(C)** may exacerbate obstruction of the airway. **(D)** Conversely, a correctly sized oral airway will lift the tongue off the posterior wall of the oropharynx, relieving airway obstruction. (Reprinted from Coté et al. [11]. Copyright 1993 with permission of Elsevier.)

Airway adjuncts such as the oral airway and nasopharyngeal airway help to relieve obstruction of the airway by lifting the tongue from the soft tissues of the posterior pharynx. Oral airways consist of a flange, a short bite-block segment, and a curved body made of hard plastic that is designed to fit over the back of the tongue, thereby relieving airway obstruction and providing a conduit for air flow and for suctioning of the oropharynx. Proper sizing of the oral airway is imperative, as an incorrectly sized (either too long or too short) oral airway may exacerbate airway obstruction (Figure 4.9). Sizes generally range from 4 to 10 cm in length (Guedel sizes 000 to 4). An oral airway is inserted by depressing the tongue with a blade/tongue depressor and following the curve of the tongue. Another commonly described method in which the oral airway is inserted with its concave side facing the palate and then rotating it to follow the curve of the tongue may damage the oral mucosa and/or teeth and should be avoided. Oral airways are poorly tolerated in children with an intact gag reflex and are therefore contraindicated in awake or semiconscious children.

A nasopharyngeal airway (*nasal trumpet*) should be used if the patient is semiconscious, as use of the oral airway can lead to vomiting and potential aspiration of gastric contents in this scenario. The nasopharyngeal airway consists of a soft, rubber tube that is designed to pass through the nasal alae and beyond the base of the tongue, thereby relieving airway obstruction (Figure 4.10) and providing a conduit for air flow. An appropriately sized nasopharyngeal airway extends from the nares to the tragus of the ear and should be of the largest diameter possible—it should pass relatively easy through the nasal alae with lubrication. The

Figure 4.10. The proper nasopharyngeal airway length is approximately equal to the distance from the tip of the nose to the tragus of the ear. (Reprinted from Coté et al. [11]. Copyright 1993 with permission of Elsevier.)

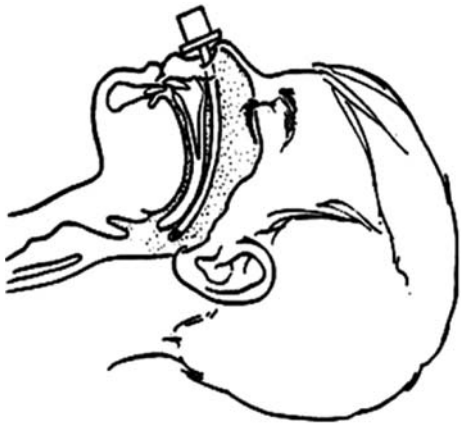

Figure 4.11. A shortened, cut-off tracheal tube may also be used as a nasopharyngeal airway. (Reprinted from Coté et al. [11], with permission of Elsevier.)

nasopharyngeal airway should not cause blanching of the nasal alae—if blanching occurs, the airway is too large. Nasopharyngeal airways are available in sizes 12 F to 36 F, with a 12-F airway (closely approximating a 3-mm tracheal tube) easily fitting through the nasal passages and nasopharynx of a full-term newborn. A shortened tracheal tube is an acceptable substitute if a nasopharyngeal airway is not readily available (Figure 4.11). The nasopharyngeal airway is lubricated and passed through the nasal passages perpendicular to the plane of the face and gently so as to avoid laceration of friable lymphoid tissue and subsequent bleeding. The use of nasopharyngeal airways is contraindicated for children with coagulopathies, cerebrospinal fluid leaks, or basilar skull fractures.

Tracheal Intubation

Indications

If all of the aforementioned measures fail to stabilize the airway, tracheal intubation should be performed in an expeditious manner (Table 4.2). The most common indication for tracheal intubation in the pediatric intensive care unit (PICU) is acute respiratory failure. Acute respiratory failure is conceptually defined as an inadequate exchange of O_2 and CO_2 resulting in an inability to meet the body's metabolic needs. Clinical criteria, arbitrarily set at a PaO_2 <60 mm Hg (in the absence of congenital heart disease) and a $PaCO_2$ >50 mm Hg, are not rigid parameters but rather serve as a context in which to interpret the clinical scenario. Failure of the anatomic elements involved in gas exchange—the conducting airways, the alveoli, and the pulmonary circulation—results in disordered gas exchange and is clinically manifested as hypoxemia (hypoxic respiratory failure). Failure of the respiratory pump—the thorax, respiratory muscles, and nervous system—results in an inability to effectively pump air into and out of the lungs, thereby leading to hypoventilation and subsequent hypercarbia (hypercarbic respiratory failure). Although there are clear consequences of dysfunction of each these components, each also interacts significantly with the other. Therefore, failure of one frequently is followed by failure of the other.

Table 4.2. Indications for tracheal intubation.

Respiratory failure (defined in terms of either inadequate oxygenation or ventilation)
Upper airway obstruction
Shock or hemodynamic instability
Neuromuscular weakness with progressive respiratory compromise
Absent protective airway reflexes
Inadequate respiratory drive
Cardiac arrest (for emergency drug administration)

Other common indications for tracheal intubation in the PICU include upper airway obstruction (e.g., epiglottitis, croup, airway trauma), neuromuscular weakness leading to neuromuscular respiratory failure (e.g., Guillain-Barré syndrome, myasthenia gravis, Duchenne muscular dystrophy), central nervous system disease, resulting in the loss of protective airway reflexes and inadequate respiratory drive (e.g., head trauma, stroke), and cardiopulmonary arrest. Importantly, tracheal intubation in the latter situation provides an avenue for administration of resuscitation medications (the medications that may be administered via the tracheal tube are easily recalled by the mnemonic *LEAN* = *L*idocaine, *E*pinephrine, *A*tropine, *N*aloxone) when vascular access is unavailable. Tracheal intubation may become necessary for children with impaired mucociliary clearance (e.g., secondary to inhalation injury, prolonged tracheal intubation) or copious, thick, tenacious respiratory secretions as a means for aggressive pulmonary toilet and frequent suctioning. Tracheal intubation may also provide a means for administration of therapeutic gases (e.g., carbon dioxide, nitrogen, inhaled nitric oxide) in order to manipulate pulmonary vascular resistance in children with pulmonary hypertension or cyanotic congenital heart disease with single ventricle physiology.

Children with hemodynamic instability (e.g., shock, low cardiac output syndrome following cardiopulmonary bypass) may also benefit from early tracheal intubation and mechanical ventilation. Agitation and excessive work of breathing increase oxygen consumption, which may lead to cardiovascular collapse in the face of an already compromised oxygen delivery. The excessive oxygen consumption often associated with the shock state has been compared by some investigators to running an 8-min mile 24 hr a day, 7 days a week [26]. For example, Aubier and colleagues [27] induced cardiogenic shock in dogs via cardiac tamponade and noted that the arterial pH was significantly lower and the lactate concentration significantly higher in dogs that were spontaneously breathing compared with dogs that were mechanically ventilated. Using the same model, these investigators studied respiratory muscle and organ blood flow with radioactively labeled microspheres in order to assess the influence of the working respiratory muscles on the regional distribution of blood flow when arterial pressure and cardiac output were lowered. Blood flow to the respiratory muscles increased significantly during cardiac tamponade in spontaneously breathing dogs—diaphragmatic flow, in fact, increased to 361% of control values—whereas it decreased in dogs that were mechanically ventilated. More importantly, although the arterial blood pressure and cardiac output were comparable in the two groups, blood flow distribution during cardiac tamponade was quite different. The respiratory musculature received 21% of the cardiac output in spontaneously breathing dogs compared with only 3% in the dogs that were mechanically ventilated. Blood flows to the liver, brain, and quadriceps muscles were significantly higher during tamponade in the dogs that were mechanically ventilated than in the dogs that were spontaneously breathing [28]. These findings have been further corroborated in experimental models of

septic shock [29] and clinical studies involving adults with cardiorespiratory disease [30] and critical illness [31,32]. Therefore, with the judicious and careful use of sedation, neuromuscular blockade, tracheal intubation, and mechanical ventilatory support, a large fraction of the cardiac output used by the working respiratory muscles can be made available for perfusion of other vital organs during the low cardiac output state [27–32].

Assessment and Preparation

Resuscitation of any critically ill or injured child is chaotic even under ideal circumstances, and emergency airway management is often fraught with difficulties. Prior preparation and appropriate training of personnel therefore assume vital importance [33]. The appropriate equipment and medications should be prepared well in advance [34]. Ideally, all of the necessary equipment for basic and advanced airway management should be readily accessible in an easily identifiable, central location in the PICU. Many PICUs keep all of the necessary airway equipment in specialized *airway carts* (similar to the *crash cart*) or *airway rolls* that can be brought to the bedside in an emergency.

The American Society of Anesthesiology defines a *difficult airway* by the presence of anatomic and/or clinical factors that complicate either mask ventilation or tracheal intubation by an experienced physician [35]. A *difficult intubation* is defined by the need for more than three tracheal intubation attempts or attempts lasting longer than 10 min [35]. Notably, this definition was developed specifically for the operating room scenario—most critically ill patients probably would not tolerate an intubation attempt lasting longer than 10 min. *Difficult ventilation* is defined as the inability of a trained physician to maintain the oxygen saturation >90% with bag-valve-mask ventilation at an FIO_2 of 1.0 [35]. Some children (e.g., children with neuromuscular disease, cerebral palsy, obstructive sleep apnea) are dependent on coordinated tone of the upper airway muscles to maintain a patent airway and are very sensitive to sedation, anesthesia, and neuromuscular blockade, resulting in significant difficulty with mask ventilation. The inability to mask ventilate has considerably more implications than does failure to tracheally intubate, as subsequent management options are limited (see later). Importantly, there is tremendous overlap among anatomic factors that predict a *difficult airway*, *difficult intubation*, and *difficult ventilation* (Table 4.3). In one study as many as 15% of difficult intubations were also associated with difficult mask ventilation [36]. Fortunately, however, difficult intubations are relatively uncommon, even in children, with an estimated incidence between 2% and 4%. Inability to mask ventilate has an even lower incidence, 0.02%–0.001% [37].

A number of quick, easy techniques have been proposed to predict a *difficult airway*. Unfortunately, a recent retrospective analysis suggested that performing this kind of airway assessment was not feasible in 70% of critically ill adults [38]. An airway assessment may be even more difficult for children, as most of the reported techniques require cooperation on the part of the patient [20,39,40]. Moreover, most studies demonstrate that these bedside techniques have both poor interobserver agreement and positive predictive value [41,42]. Regardless, whenever feasible, an airway assessment should be performed so that problems with either bag-valve-mask ventilation or tracheal intubation can be anticipated and prepared for in advance.

Table 4.3. Anatomic factors associated with a difficult airway.

Small mouth, limited mouth opening, or short interincisor distance
Short neck or limited neck mobility
Mandibular hypoplasia
High, arched, and narrow palate
Poor mandibular translation
Poor cervical spine mobility
Obesity
Mucopolysaccharidoses

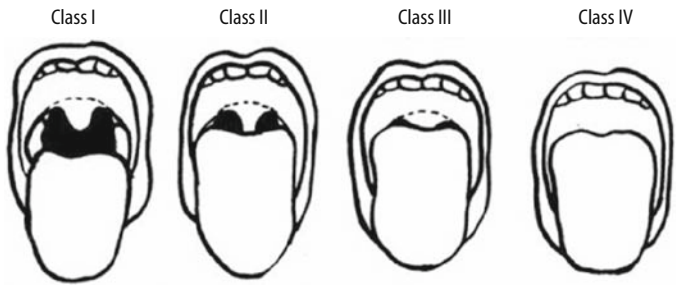

Figure 4.12. Samsoon and Young modification of the Mallampati airway classification.

Generally, in the absence of any obvious airway abnormality or specific syndrome associated with a difficult airway (see later), most difficult airways can be recognized by performing the following three maneuvers: (1) oropharygneal examination, (2) assessment of atlanto-occipital joint mobility, and (3) assessment of the potential displacement area. These three tests correctly predict a difficult airway in *adults* virtually 100% of the time. However, these three tests may not be applicable to the pediatric patient as they require cooperation on the part of the patient. The relative size of the oral cavity is assessed by asking the child to open his or her mouth. The Mallampati classification system [43], as modified by Samsoon and Young [44], classifies the degree of airway difficulty based on the ability to visualize the faucial pillars, soft palate, and uvula (Figure 4.12). A Mallampati class of I or II predicts a relatively easy airway, whereas a Mallampati class >II predicts an increased difficulty with adequate visualization of the airway during laryngoscopy. Critically ill patients with altered mental status or children may be unable to cooperate with this kind of assessment, although evaluation of the oropharyngeal airway with a tongue blade may be feasible and worthwhile [20,39,45]. Cormack and Lehane [46] proposed a classification system based on the ability to visualize the glottic opening during laryngoscopy, although this type of assessment is probably more useful as a means to facilitate communication of the degree of difficulty between providers and not as a screening tool for predicting a difficult airway at the bedside. The interincisor distance can also be assessed at this time—an interincisor distance less than two fingertips in breadth can be associated with a difficult airway [20,39]. Decreased range of motion at the atlanto-occipital joint leads to poor visualization of the glottis during laryngoscopy. Cervical spine immobilization with a C-collar may also limit atlanto-occipital joint extension, leading to a potentially difficult airway. Finally, if three fingers in adolescents, two fingers in children, and one finger in infants can be placed between the anterior ramus of the mandible and the hyoid bone, the so-called potential displacement area, adequate visualization of the glottis during laryngoscopy usually will be successful (Figure 4.13). If the *potential displacement area* is too small, excessive extension of the neck will only

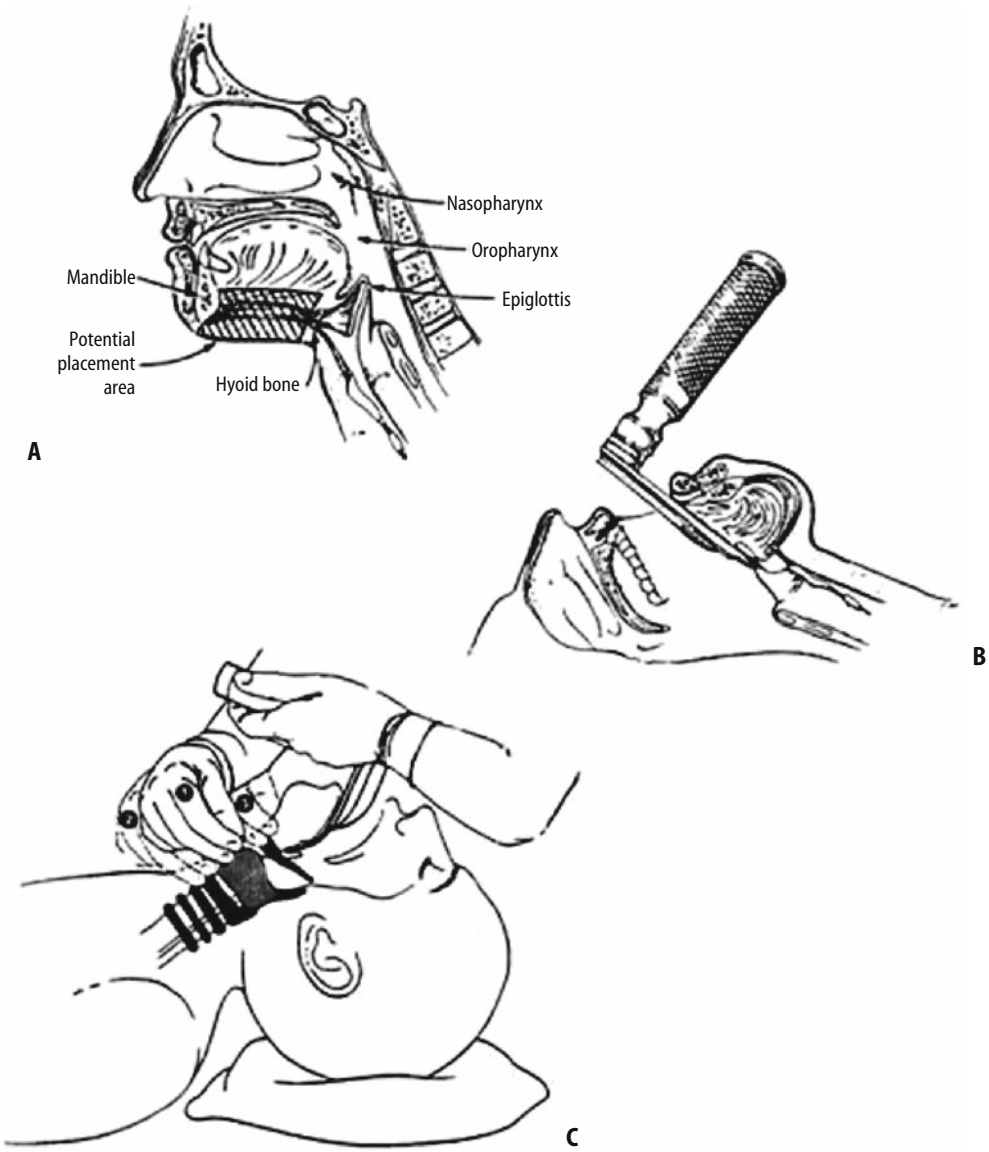

Figure 4.13. **(A)** Diagram of airway, demonstrating *potential displacement area* for tracheal intubation. **(B)** Laryngoscopy with displacement of the tongue and soft tissue into the *potential displacement area*. **(C)** The BURP maneuver, determining the optimal external laryngeal manipulation with the free (right) hand. (A, B, reprinted from Berry FA, ed. Anesthetic Management of Difficult and Routine Pediatric Patients, 2nd ed. London: Churchill Livingstone; 1990:173. Copyright 1990 with permission from Elsevier.) C, reprinted from Benumof JL, ed. Airway Management: Principles and Practice. St. Louis: Mosby-Yearbook, Inc.; 1996:268. Copyright 1996 with permission from Elsevier.)

shift the larynx into a more *anterior* position [47]. The *BURP* maneuver (*B*ack, *U*p, and *R*ightward *P*ressure on the laryngeal cartilage) displaces the larynx in three directions, (1) posteriorly against the cervical vertebra, (2) superiorly as possible, and (3) laterally to the right, and may improve visualization of the glottic opening in this situation (see Figure 4.13) [48,49].

Several malformation syndromes are associated with a difficult airway based on the presence of a few notable anatomic features:

1. *Macroglossia*: A large tongue in children with Beckwith-Wiedemann syndrome or trisomy 21 (Down syndrome) may be difficult to control and make visualization of the glottis during laryngoscopy difficult. Mask ventilation under these circumstances may also be difficult and frequently requires placement of an oral or nasal airway. A curved laryngoscope blade may be more appropriate in this scenario.

2. *Mandibular hypoplasia*: Mandibular hypoplasia is frequent in children with the Pierre-Robin sequence (see later), Crouzon disease, Goldenhar syndrome, and Treacher-Collin syndrome. Mandibular hypoplasia forces the tongue posteriorly in the oropharynx and hinders visualization of the glottis during laryngoscopy. Alternative techniques, including use of a laryngeal mask airway, light wand, or fiberoptic bronchoscope, are frequently required for these children and should be readily available.

3. *Limited cervical motion*: Limited atlanto-occipital range of motion is frequently found in children with Goldenhar syndrome and Klippel-Feil syndrome, thereby limiting an adequate line of

sight to the glottis because of failure of the three axes (discussed above) to align. Other disease processes such as juvenile rheumatoid arthritis and neuromuscular scoliosis also can result in limited cervical spine mobility. Children with Trisomy 21 or trauma, on the other hand, have atlanto-occipital instability, and cervical spine precautions should be followed.

4. *Mucopolysaccharidoses*: Children with the mucopolysaccharidoses often have difficult airways for a number of reasons.

Equipment

All the necessary equipment for airway management must be available at the bedside before any attempts at tracheal intubation are made! At a minimum, this list includes (1) a source of oxygen (either wall or tank) with the necessary tubing, ventilation bag (either a self-inflating or standard anesthesia bag, appropriately sized), and mask (appropriately sized); (2) a source of suction (either portable suction or wall suction) and appropriate suction catheters (preferably the rigid, wide-bore *tonsil tip* or Yankauer suction catheters); (3) laryngoscope and proper-sized blade with a well-functioning light; (4) tracheal tubes of the anticipated size, plus the next size largest and smallest (see below); (5) stylet; and (6) a means of securing the tracheal tube. Additional items include oral airways, nasopharyngeal airways, and a Magill forceps.

Oxygen Source

There are two types of oxygen sources commonly used in the critical care setting—wall oxygen sources and gas cylinders. Federal regulations require that wall oxygen sources utilized in hospitals in the United States provide a working pressure of at least 50 psi, thereby ensuring at least the 35 psi of pressure required by most commercially available mechanical ventilators. Oxygen cylinders are available in a variety of sizes and operate at much higher internal pressures—generally on the order of 1,800–2,400 psi. Therefore, the oxygen cylinder must be interfaced with a pressure-reducing valve in order to reduce the pressure between the oxygen source and the patient to a level that is consistent with the pressure supplied by a wall oxygen source (i.e., around 50 psi). However, an additional reduction in the driving pressure is required and is provided by a flowmeter, in which flow can be adjusted to a level that is comfortable for the patient. Importantly, the flowmeters commonly used in the PICU are equipped with a *back pressure compensation* mechanism such that the introduction of resistance distal to the valve does not result in spuriously elevated flow readings [50,51]. Finally, when using an oxygen cylinder as opposed to a wall oxygen source, a sufficient supply of oxygen should be on hand. The amount of time that a cylinder will supply oxygen can be determined using the following formula:

$$\text{Minutes of oxygen flow} = \frac{\text{Cylinder pressure} \times \text{cylinder factor}}{\text{Flow of oxygen (in liters per minute)}},$$

where the cylinder factor of a size D, E, and H tank is 0.16, 0.28, and 3.14, respectively [52].

Bag-Valve-Mask Ventilation

The advantages and disadvantages between self-inflating and standard anesthesia bags are discussed in Chapter 3.

Suction Devices

Removal of secretions, blood, or vomitus from the oropharynx, nasopharynx, or trachea is frequently necessary to achieve a patent airway. There are two sources of suction commonly used in the critical care setting—wall suction (vacuum outlet) and battery-operated, portable suction devices. Suction force should be limited to 80–120 mm Hg in order to minimize suction trauma to the airway mucosa. Both flexible, plastic suction catheters and rigid, wide-bore suction cannulas (*tonsil tip* or Yankauer) should be available. The Yankauer suction catheter is preferable for suctioning thick secretions and particulate matter in the airway, whereas the thin, flexible catheters are used to directly suction the tracheal tube. The combination of a small tracheal tube, dry gases, and airway secretions increases the risk of tube plugging and occlusion, and the instillation of 3–5 mL of sterile 0.9% saline followed by suctioning of the airway should be performed on a frequent basis. Sterile technique will minimize the risk of ventilator-associated pneumonia [53–55]. The catheter should be gently inserted into the airway just beyond the tip of the tracheal tube without applying suction; rather, suction is applied while withdrawing the suction catheter in a rotating, twisting motion. Suction attempts should not exceed 5 sec and should be preceded by a short period of ventilation with 100% oxygen in order to avoid hypoxemia. Heart rate and blood pressure should be monitored closely, as suctioning may stimulate the vagus nerve and produce bradycardia. Lidocaine (administered tracheally, 5–6 mg/kg dose diluted in 6 mL 0.9% saline 5–10 min before suctioning) may be administered in children with head trauma [56–58] before the airway is suctioned in order to blunt the increase in intracranial pressure (ICP) that may result from the suctioning [59–62].

Laryngoscopes

Laryngoscope blades are available in several different shapes and sizes but are usually classified into straight (e.g., Miller, Phillips, Wis-Hipple) versus curved (e.g., Macintosh) blades. Straight blades are preferable to curved blades for neonates, infants, and young children because of the relatively cephalad position of the glottis, the large tongue (relative to the size of the oral cavity), and the large, floppy epiglottis, which may be difficult to control with a curved blade (see earlier). Perhaps the most important consideration for selection of the laryngoscope blade is its length (Table 4.4). Shorter blades make visualization of the glottis difficult, whereas longer blades make it difficult to avoid direct pressure on the upper lip, teeth, and gums. The laryngoscope should be checked for proper functioning and adequate illumination before use.

Tracheal Tubes

The appropriate size for the tracheal tube is based on the child's age. Generally, a 3.0- or 3.5-mm tracheal tube should be used in

Table 4.4. Suggested laryngoscope sizes based on patient weight.

Child's weight (kg)	Laryngoscope
0–3	Miller 0
3–5	Miller 0, 1
5–12	Miller 1
12–20	Macintosh 2
20–30	Macintosh 2, Miller 2
>30	Macintosh 3, Miller 2

term infants, and a 4.0-mm tracheal tube should be used for infants older than 6–8 months of age. Beyond 8 months of age, the appropriate size for the tracheal tube can be determined according to the following rule:

$$\text{Tracheal tube (mm i.d.)} = \frac{\text{Age(y)}}{4} + 4$$

The outside diameter of the tracheal tube usually approximates the diameter of the child's little finger. It is important to note that this rule is only a starting guideline, and different-sized tubes (one size smaller *and* one size larger) should be readily available during attempts at tracheal intubation. The tracheal tube should pass through the glottis easily and with minimal force, and the presence of a minimal air leak heard around the tracheal tube with inflating pressures of 20–30 cm H_2O will ensure adequate perfusion of the tracheal mucosa and lessen the risk of tissue necrosis, edema, scarring, and postextubation stridor.

Historically, uncuffed tubes have been generally recommended for children less than 8 years of age. A prolonged period of tracheal intubation and a poorly fitted tracheal tube are significant risk factors for damage to the tracheal mucosa regardless of whether the tracheal tube is cuffed or uncuffed. Cuffed tracheal tubes may have significant advantages over uncuffed tracheal tubes, including better control of air leakage and decreased risk of aspiration and infection in mechanically ventilated children, and they are being used with greater frequency in this age group, especially when high inflation pressures are required to provide adequate oxygenation and ventilation in the setting of severe acute lung disease. The available data suggest that there is no difference in the incidence of postextubation stridor in children who were tracheally intubated with cuffed tubes compared with those who received uncuffed tubes [63–67]. A good rule of thumb is that whenever a cuffed tube is used, a half-size smaller tube from what would normally be used (based on the rule above) should be selected.

Stylets

A malleable, yet rigid stylet may be inserted into the tracheal tube in order to shape the tube to the desired configuration (e.g., *hockey stick*) before attempting tracheal intubation. However, the tip of the stylet must not protrude beyond the distal tip of the tracheal tube in order to minimize the potential of airway trauma. In addition, the stylet should be lubricated with a water-soluble lubricant before insertion into the tracheal tube in order to facilitate its easy removal once the tracheal tube has been placed.

Airway Pharmacology

Laryngoscopy and tracheal intubation are commonly associated with profound physiologic disturbances that may adversely affect the critically ill or injured child. In addition to pain and anxiety, laryngoscopy causes an increase in blood pressure and heart rate [59–62,68,69], although decreased heart rate and hypotension may be more common in infants as a consequence of their increased parasympathetic tone [70]. Hypoxia and hypercarbia are also common, especially in children with impending respiratory failure. Laryngoscopy and tracheal intubation increase ICP (which may exacerbate intracranial hypertension in children with head injury or lead to intracranial hemorrhage in children with coagulopathies or vascular malformations) [59–62], intraocular pressure, and intragastric pressure (further compounding the risk of regurgitation and aspiration of gastric contents) [71]. Tracheal intubation may also provoke bronchospasm, especially in children with asthma. The use of appropriate preinduction agents or adjuncts, induction agents, and neuromuscular blockade may modify these physiologic responses and lessen the potential for adverse effects related to laryngoscopy and tracheal intubation. It is extremely important to remember that attenuation of these normal responses following tracheal intubation may unmask hemodynamic instability leading to, at times, profound hypotension [72].

Preinduction Agents

Several preinduction agents are commonly used for tracheal intubation in critically ill or injured children, including cholinergic antagonists, lidocaine, opioids, β-adrenergic antagonists, and nondepolarizing neuromuscular blocking agents (NDNMBs) (Table 4.5). Cholinergic antagonists such as atropine (0.01–0.02 mg/kg intravenous [IV], with a minimum dose of 0.1 mg) and glycopyrrolate (3–5 μg/kg IV) may be administered in order to prevent bradycardia (especially in critically ill infants with high parasympathetic tone) and decrease oral secretions. Succinylcholine also causes bradycardia, especially in infants and young children [73–75]. Atropine is usually recommended when using succinylcholine in children less than 1 year of age, although the use of atropine in

Table 4.5. Preinduction agents used for tracheal intubation.

Agent	Indication	Dose	Comments
Oxygen	Prevent hypoxia during laryngoscopy	100% oxygen	
Atropine	Prevent bradycardia during laryngoscopy and administration of succinylcholine	0.01–0.02 mg/kg IV (minimum dose of 0.1 mg)	Probably not necessary for children >1 year of age
Glycopyrrolate	Prevent bradycardia and decrease oral secretions	3–5 μg/kg IV	
Lidocaine	Blunt the increase in intracranial pressure during laryngoscopy	1–1.5 mg/kg IV	Administered 3–5 min before laryngoscopy
Fentanyl	Blunt the increase in heart rate and blood pressure during laryngoscopy	2–3 μg/kg IV	
Vecuronium	Defasciculating dose	0.01 mg/kg IV	Prevents muscle soreness and pain as well as the increase in intracranial, intragastric, and intraocular pressures following succinylcholine
Rocuronium	Defasciculating dose	0.05 mg/kg IV	See above
Esmolol	Blunt the increase in heart rate and blood pressure during laryngoscopy	2 mg/kg IV (adult studies)	Rarely given to children. Use with caution in hemodynamically unstable patients. May precipitate bronchospasm

Table 4.6. Commonly used induction agents for tracheal intubation.

Agent	Dose	Onset	Recovery	Indications	Precautions
Thiopental	2–3 mg/kg IV	10–20 sec	15–30 min	Status epilepticus, isolated head trauma (with normal hemodynamics)	Bronchospasm, hypotension
Etomidate	0.15–0.3 mg/kg IV	30–60 sec	3–5 min	Trauma, shock(?)	Causes adrenal suppression, decreases seizure threshold
Ketamine	1–2 mg/kg IV	1–2 min	5–10 min	Status asthmaticus	May increase intracranial pressure
Propofol	2–4 mg/kg IV	30–60 sec	3–5 min	Isolated head trauma, status epilepticus	Hypotension
Midazolam	0.1–0.2 mg/kg IV	3–5 min	20–30 min		Hypotension
Fentanyl	5–10 µg/kg IV	30–60 sec	10–15 min		Rarely used as the sole agent; rigid chest syndrome

older children is more controversial and frequently not necessary [76–79].

Lidocaine (1–1.5 mg/kg IV) may be administered 3–5 min before laryngoscopy and tracheal intubation in order to blunt the associated hypertensive response and increase in ICP. Unfortunately, strong evidence to suggest that this practice improves neurologic outcome is not available [80–82]. Topical lidocaine may be just as effective as intravenous lidocaine in blunting the physiologic response to laryngoscopy [83], and lidocaine is probably not necessary if an induction agent such as thiopental (see later) is used.

Fentanyl (2–3 µg/kg IV) or the synthetic opioids (e.g., sufentanil, alfentanil, or remifentanil), which are all derivatives of fentanyl, have also been used to blunt the physiologic response to laryngoscopy and tracheal intubation [84–86]. Fentanyl is also commonly used as an induction agent and is discussed further below.

Esmolol is a rapid-onset, short-acting, cardioselective β-adrenergic antagonist that is frequently used in adults to attenuate the tachycardia and hypertension resulting from laryngoscopy and tracheal intubation [83,85,87]. Esmolol, either alone or in combination with fentanyl, may be more effective than either lidocaine or fentanyl [84,88–93], and the combination of fentanyl and esmolol may be particularly effective in this situation. However, caution should be exercised as there are currently no reports on the use of esmolol as a preinduction agent for tracheal intubation in children. Most adult studies use an esmolol dose of 2 mg/kg IV administered 1–2 min before laryngoscopy. Esmolol is contraindicated for children with reactive airways disease or asthma and is probably contraindicated in situations where hemodynamic instability could be anticipated.

Finally, some protocols recommend the use of a *defasciculating dose* of NDNMB before the use of succinylcholine. This is discussed further below.

Induction Agents

There are a variety of anxiolytic, analgesic, and sedative agents commonly used to facilitate tracheal intubation (Table 4.6). An ideal induction agent induces unconsciousness predictably with a rapid onset of action, short duration of action, and few side effects. Unfortunately, the ideal induction agent does not exist. Although the choice of which induction agent to use in any given situation depends primarily on individual physician preference and comfort, there are some important caveats to bear in mind. One particular agent may be appropriate in a given clinical scenario and entirely inappropriate in another. The induction agent should therefore be selected based on the particular clinical scenario with the goal of rapid induction and minimal adverse effects (Table 4.7).

Thiopental is a short-acting barbiturate with a rapid onset of action (10–20 sec) at the recommended dose of 2–3 mg/kg IV. Thiopental decreases cerebral oxygen consumption and effectively reduces ICP [94,95] and is therefore the agent of choice for children with closed head injury [96–100]. However, thiopental is a potent vasodilator (decreases systemic vascular resistance), venodilator (decreases preload in hypovolemic patients), and, at higher doses, a potent cardiac depressant and should be used with caution in the hypovolemic or hypotensive child. These effects may be minimized with a decreased rate of administration or with the use of a smaller dose (some authorities recommend decreasing the dose by half in this situation) [98]. Additional side effects include histamine release, with subsequent hypotension or bronchospasm, coughing, and laryngospasm. The barbiturates as a group may cause mild muscular movements such as tremors, hypertonus, or twitching.

Etomidate (0.3 mg/kg IV) is another agent that decreases cerebral oxygen consumption and hence ICP but without significant detrimental effects on either the heart or systemic vascular resistance, making it a good alternative to thiopental for children with closed head injury and hypotension [101]. Etomidate lacks analgesic effects and should be administered in conjunction with an opioid such as fentanyl. Etomidate does cause adrenal suppression [102–107] and should not be used for long-term sedation in the PICU. Some experts have further suggested that etomidate should not be used for induction for tracheal intubation in critically ill patients [108–112]. Etomidate appears to cause adrenal suppression for at least 12–24 hr following a single dose [106,108,113,114], although some investigators have questioned the clinical significance of these effects [115,116]. Etomidate should be used with caution in critically ill patients, although no definitive statements against its use can be made until additional evidence becomes available from randomized, placebo-controlled trials in this setting. Etomidate does cause myoclonic activity and may lower the seizure threshold in children with either central nervous system pathology or epilepsy [117].

The benzodiazepines (midazolam, lorazepam, and diazepam) are potent anxiolytics and amnestics but lack analgesic properties and are therefore commonly co-administered with a narcotic such as morphine or fentanyl (see later). Midazolam (0.1–0.2 mg/kg IV) has a relatively rapid onset of action (3–5 min) and shorter duration

Table 4.7. Suggested induction agents for specific clinical scenarios.

Status epilepticus	Isolated head trauma	Shock	Head trauma + shock	Status asthmaticus
Propofol -or- Thiopental -or- Midazolam	Propofol -or- Thiopental	Etomidate(?) -or- Ketamine	Etomidate	Ketamine

of action (20–30 min) and is more frequently used in this setting than either lorazepam or diazepam. Midazolam does have some effects on reducing ICP [118–120], although clearly thiopental and etomidate are superior in this regard. Midazolam may reduce mean arterial blood pressure (MAP), thereby lowering cerebral perfusion pressure (CPP), as CPP = MAP – ICP [119] and should be used with caution in children with hemodynamic instability [121–124]. The hemodynamic effects may be more pronounced in newborns and infants [121,123], so particular caution should be exercised in this patient population.

Morphine (0.1–0.2 mg/kg IV) causes profound histamine release and potential hypotension or exacerbation of bronchospasm and is generally not used as an induction agent for tracheal intubation [86,96–98,125,126]. Fentanyl is approximately 180 times more potent than morphine and does not cause histamine release, but it may cause chest wall rigidity when large doses are administered rapidly [127–131]. Opioid-induced chest wall rigidity may be reversed with IV naloxone or neuromuscular blockade [126,132]. Although largely devoid of significant cardiovascular side effects, hypotension can occasionally occur with the use of fentanyl [133–135]. The dose required for induction of anesthesia (doses as high as 30–150 μg/kg IV have been reported in the literature) is much higher than the dose required for analgesia alone [96–98,125,126,133,134,136], although reports on the use of fentanyl for tracheal intubation in the critically ill or injured are relatively limited [137]. For these reasons, fentanyl is probably better utilized as either a preinduction agent (see earlier) or as an adjunct to another induction agent.

Ketamine is a phencyclidine (PCP) derivative that has potent amnestic, analgesic, and sympathomimetic properties. It is generally considered a dissociative anesthetic agent and acts by selectively inhibiting the cerebral cortex and thalamus while stimulating the limbic system [125,126]. Although ketamine has direct negative inotropic effects [138,139], systemic blood pressure is preserved, primarily through increased sympathetic stimulation [96–98,125,126,140]. The hemodynamic safety of ketamine in children with congenital heart disease is well established [141–144]. Critically ill patients have rarely been known to respond to ketamine with profound hypotension caused by the depletion of endogenous catecholamines [140,145], otherwise ketamine is widely considered the induction agent of choice for hemodynamically unstable patients [96–98,125,126], including those with cardiac tamponade [146,147]. Ketamine is also a potent bronchodilator (related to its sympathomimetic effects) and has been used therapeutically in children with status asthmaticus [148–151] and is also the induction agent of choice for laryngoscopy and tracheal intubation of children with reactive airways disease or asthma. Contrary to common belief, although spontaneous ventilation is preserved in most children, larger doses may precipitate laryngospasm or apnea. Ketamine also increases cerebral blood flow and ICP and should be used with caution, if at all, in children with closed head injury and high ICP, although recently these concerns have been questioned [152,153]. Ketamine was historically thought to be contraindicated for patients with pulmonary hypertension, as it was thought that it could increase pulmonary vascular resistance and provoke a pulmonary hypertensive crisis. Recent studies, however, support the use of ketamine for this patient population [143,154,155]. Additional side effects of ketamine include hypersalivation and emergence dysphoria and/or hallucinations.

Propofol (2–4 mg/kg IV) is an induction agent with a rapid onset of action (30–60 sec) and short duration of action (3–5 min) that is frequently used for rapid sequence intubation in adults [86,126]. Propofol reduces ICP and decreases cerebral metabolism [86,126] and effectively attenuates the hemodynamic response to direct laryngoscopy and tracheal intubation [156]. Propofol is a potent vasodilator and venodilator, and to some extent it has negative inotropic effects, thereby limiting its use to patients with stable hemodynamics [86,126,156].

Neuromuscular Blocking Agents

Several excellent reviews are available on the pharmacology of neuromuscular blocking agents [86,96–98,157–161]. Nondepolarizing neuromuscular blockers act by competitively inhibiting the interaction of acetylcholine (ACh) with its receptor on the motor endplate. Neuromuscular transmission requires the binding of two ACh molecules (one ACh molecule binds to each α-subunit); thus, even if only one binding site is occupied by an NDNMB, ACh activation is effectively inhibited. However, approximately 90%–95% of the ACh receptors must be blocked before neuromuscular transmission is completely inhibited [157]. The diaphragm is more densely populated with ACh receptors than are other muscles, so the diaphragm may continue to function even after the muscles of the hands and upper airway have been effectively paralyzed [157]. The NDNMBs (Table 4.8) are all highly water-soluble, positively charged quaternary ammonium compounds commonly subdivided into two main classes. The benzylisoquinolones include mivacurium, atracurium, cis-atracurium, doxacurium, and d-tubocurarine. All of these compounds, with the exception of mivacurium, are degraded by a nonenzymatic chemical process called Hofmann elimination at physiologic pH and temperature and are therefore commonly used in children with renal insufficiency or liver failure. Mivacurium, on the other hand, is metabolized by plasma cholinesterase. The

Table 4.8. Neuromuscular blocking agents used for tracheal intubation.

Agent	Class	Dose	Onset	Recovery	Comments
Succinylcholine	DNMB	1–2 mg/kg IV 2–4 mg/kg IM	60 sec 3–4 min	5–10 min	See adverse reactions (Table 4.9)
Atracurium	NDNMB	0.6 mg/kg IV	2–3 min	20–30 min	Hofmann degradation, histamine release
Cis-atracurium	NDNMB	0.1 mg/kg IV	2–3 min	25–40 min	Hofmann degradation
Rocuronium	NDNMB	0.6 mg/kg IV	60 sec	25–35 min	Hepatobiliary excretion
Mivacurium	NDNMB	0.1 mg/kg IV	2–3 min	15–30 min	Degraded by plasma cholinesterase
Vecuronium	NDNMB	0.1 mg/kg IV	60–120 sec	20–40 min	Hepatobiliary and renal excretion
Pancuronium	NDNMB	0.1 mg/kg IV	2–3 min	60–120 min	Tachycardia common

Note: DNMB, depolarizing neuromuscular blocker; NDNMB, nondepolarizing neuromuscular blocker.

aminosteroids include pancuronium, vecuronium, and rocuronium (the newest aminosteroid, rapacuronium, was removed from the market because of concerns regarding its associated side effects of severe bronchospasm). These compounds are metabolized in the liver and excreted in the urine and bile. Duration of neuromuscular blockade may therefore be prolonged in patients with either renal or hepatic disease. The choice of which NDNMB to use in any given situation depends primarily on individual physician preference and comfort. However, caution should be exercised when using the longer acting NDNMBs if a difficult airway and/or difficult intubation is anticipated—these drugs should not be given to children who may be difficult to ventilate with bag-valve-mask ventilation.

Succinylcholine (SCh), the only depolarizing NMB currently available for clinical use, was introduced into clinical practice in 1951. Succinylcholine consists of two acetylcholine molecules joined together. Succinylcholine binds to the ACh receptor (AChR) and produces initial depolarization and muscle contraction, which is observed clinically as fasciculations. However, the AChR remains in an inactive state and muscle relaxation occurs (phase I block). Neuromuscular blockade persists until SCh is hydrolyzed to succinate and choline by plasma pseudocholinesterase, which occurs much more slowly than the breakdown of ACh by true AChE. Further exposure of the neuromuscular junction to SCh may result in a prolonged state of muscle relaxation that cannot be reliably reversed pharmacologically (phase II block). The duration of blockade may also be increased if there is a decrease in endogenous pseudocholinesterase (e.g., familial pseudocholinesterase deficiency, hepatic disease). Succinylcholine has numerous side effects that have limited its use in routine clinical settings (Table 4.9). In addition to the receptors localized to the neuromuscular junction, SCh will also occupy other nicotinic, cholinergic receptors located throughout the body. For example, administration of SCh to infants may produce vagally mediated bradycardia, and for this reason most clinicians will administer atropine before SCh in this patient population. Succinylcholine also produces initial contraction of the extraocular muscles, which may lead to increased intraocular pressure. Similarly, SCh may also produce increased ICP.

Many physicians recommend the use of a *defasciculating dose*, or one-tenth of the intubation dose of an NDNMB such as vecuronium before administering SCh [86,96–98,125,126]. Theoretically, the use of a *defasciculating dose* prevents the muscle soreness and pain, as well as the increase in intracranial, intragastric, and intraocular pressure following administration of SCh. However, the available evidence that such a protocol improves outcome is limited [162].

Table 4.9. Succinylcholine, its side effects and relative contraindications.

Side effect	Mechanism
Muscle soreness/pain	Fasciculations caused by initial depolarization of the NMJ (may be prevented with the use of a defasciculating dose, typically one-tenth dose of an NDNMB, e.g., 0.01 mg/kg vecuronium)
Hyperkalemia	Succinylcholine will typically raise serum K^+ 0.5–1 mEq/L because of initial depolarization of the NMJ (serious and life-threatening hyperkalemia may occur with renal failure or when extrajunctional acetylcholine receptor are upregulated [crush injury, burns, disuse atrophy, muscular dystrophy]) *Contraindications:* 1. Preexisting hyperkalemia 2. Acute renal failure or chronic renal insufficiency 3. History of trauma, burns, crush injury (at-risk period occurs between 48 hr and 120 days postinjury) 4. Disuse atrophy, neuromuscular diseases (e.g., Duchenne's muscular dystrophy)
Malignant hyperthermia (syndrome characterized by unremitting muscle rigidity, hyperthermia, hypercapnia, and metabolic acidosis)	Mechanism not completely understood *Contraindicated* for patients with family history of malignant hypertension
Increased intraocular pressure	Contraction of extraocular muscles during initial depolarization of NMJ (may be prevented with "defasciculating dose") *Contraindications:* 1. Glaucoma 2. Open globe injury
Increased intracranial pressure	Fasciculations and muscle rigidity (may be prevented with "defasciculating dose") Use with caution in patients with head injury
Increased intragastric pressure	Contraction of abdominal muscles (may be prevented with "defasciculating dose") Use with caution in patients with full stomach (increased risk of aspiration)
Prolonged neuromuscular blockade	Plasma pseudocholinesterase deficiency (liver disease, pregnancy, h/o oral contraceptive use, familial pseudocholinesterase deficiency)

Note: NDNMB, nondepolarizing neuromuscular blocker; NMJ, neuromuscular junction.

Oral Tracheal Intubation

Oxygen should be administered to all critically ill and/or injured children in the highest possible concentration and regardless of the measured oxygen saturation until an initial assessment of cardiorespiratory status is completed. Breathing 100% oxygen for 2–3 min creates a nitrogen washout that will fill ventilated alveoli with oxygen, and under most conditions an alveolar oxygen tension of 663 mm Hg yields an adequate reservoir to provide sufficient oxygen delivery following the onset of apnea that occurs following sedation and neuromuscular blockade [163,164]. This oxygen reservoir theoretically permits adequate oxygenation of blood circulating through the pulmonary blood vessels for up to 3 or 4 minutes following the onset of apnea [165]. However, infants and young children, in particular, have a high metabolic rate or oxygen consumption (7 mL/kg/min in children compared with 3 mL/kg/min in adults) [163,165] and will develop hypoxia faster than adults. Once this oxygen reservoir is used up, arterial oxygen saturation will decrease precipitously after the onset of apnea.

Heart rate, blood pressure, and oxygen saturation should be monitored continuously during attempts at tracheal intubation, as mechanical stimulation of the airway may induce bradyarrhythmias, particularly in neonates and infants (see above). If either hypoxemia or bradycardia occurs, tracheal intubation should be interrupted and the child should be ventilated at FIO_2 1.00 via

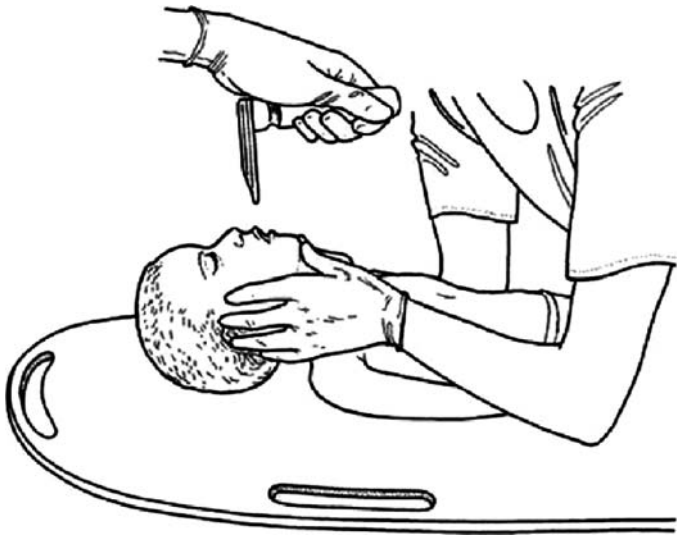

Figure 4.14. Manual in-line stabilization of the cervical spine during tracheal intubation. (Reprinted with permission from Foltin G, Tunik MG, Cooper A, Markenson D, Treiber M, Phillips R, Karpeles T. Teaching Resource for Instructors in Prehospital Pediatrics. New York: Center for Pediatric Emergency Medicine; 1998.)

bag-valve-mask ventilation. Immediately before laryngoscopy, the child is positioned (*sniff position* as described earlier, with manual cervical spine stabilization if cervical spine injury is suspected) (Figure 4.14), and preinduction medications are administered, as clinically indicated. Once all preparations have been made, the appropriate induction agents and NMB are administered. The laryngoscope is held in the left hand, and the blade is inserted into the right side of the mouth following the natural contour of the pharynx to the base of the tongue (Figure 4.15).

Control of the tongue is achieved by sweeping the proximal end of the blade to the midline, thereby moving the tongue toward the middle of the mouth, providing a channel along the right side of the mouth for visualization of the airway and passage of the tracheal tube. The tip of a curved blade is inserted into the vallecula, thereby lifting the epiglottis and visualizing the glottis by vallecular suspension. In contrast, the tip of a straight blade is used to lift the epiglottis directly in order to visualize the glottis (Figure 4.16). Once the blade is positioned correctly, traction is exerted in the direction of the long axis of the laryngoscope handle—the laryngoscope blade must not be used as a lever, and the teeth/gums are not to be used as the fulcrum! It is frequently helpful to have a second provider place a slight amount of traction on the corner of the mouth to enable better visualization of the airway. The BURP maneuver [48,49] may be used to further facilitate visualization of the glottic opening (see Figure 4.13). However, the BURP maneuver may worsen visualization of the glottic opening when used in

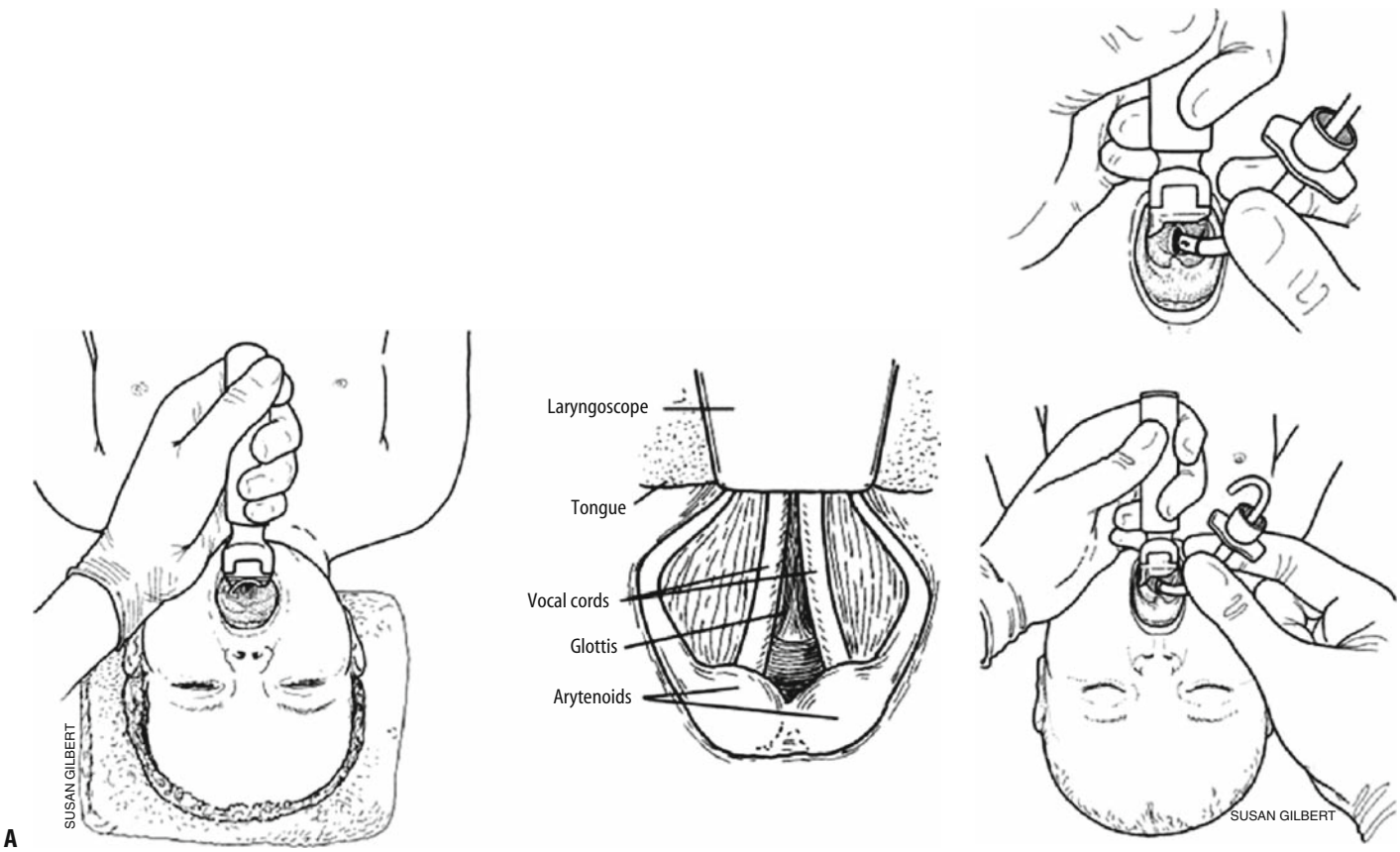

Figure 4.15. Operator's view of the glottis during laryngoscopy **(A)** with subsequent placement of the tracheal tube **(B)**. (Reprinted with permission from Foltin G, Tunik MG, Cooper A, Markenson D, Treiber M, Phillips R, Karpeles T. Teaching Resource for Instructors in Prehospital Pediatrics. New York: Center for Pediatric Emergency Medicine; 1998.)

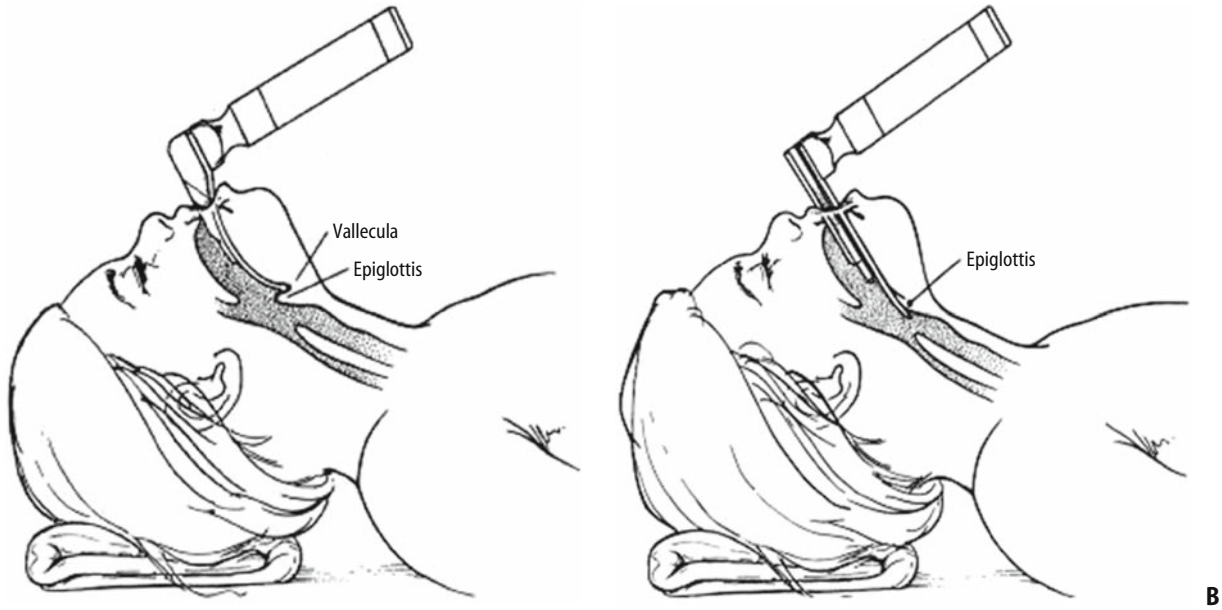

Figure 4.16. Position of laryngoscope blade when using a curved blade versus a straight blade. A straight blade may also be used in the same manner as a curved blade, that is, its tip is placed in the vallecula. This is a matter of preference and experience. **(A)** The tip of the curved laryngoscope blade is positioned in the vallecula and is used to *lift* the epiglottis via vallecular suspension in order to visualize the glottic opening. **(B)** The tip of the straight laryngoscope blade is used to directly *lift* the epiglottis in order to visualize the glottic opening. (Reprinted with permission from Foltin G, Tunik MG, Cooper A, Markenson D, Treiber M, Phillips R, Karpeles T. Teaching Resource for Instructors in Prehospital Pediatrics. New York: Center for Pediatric Emergency Medicine; 1998.)

conjunction with cricoid pressure [166]. Alternatively, a laryngeal lift [167] or mandibular advancement [168] maneuver can be performed to better visualize the glottic opening. The utility of cricoid pressure has recently been questioned, as undue or improperly applied force may cause complete loss of adequate visualization of the glottis [169–171]. The tracheal tube is inserted from the right corner of the mouth and not down the barrel of the laryngoscope blade. The tracheal tube is then passed through the vocal cords under direct visualization. The black glottic marker of the tube is placed at the level of the vocal cords. Alternatively, when a cuffed tracheal tube is used, the cuff is placed just below the vocal cords. The depth of insertion of the tracheal tube is also commonly estimated either by multiplying the inside diameter of the tube by 3 or by using the following formula:

$$\text{Depth of insertion} = \frac{\text{Age(y)}}{2} + 12$$

Immediately following tracheal intubation, the correct position of the tracheal tube is confirmed by observation for symmetric chest movements, auscultation of equal breath sounds over each axilla and not over the abdomen, and documentation of end-tidal CO_2 [172–174]. Capnometry/capnography is the most reliable and most valid way to confirm tracheal intubation [172] and is now widely viewed as the standard of care. A chest radiograph should be obtained to document proper position with the distal tip of the tracheal tube above the carina in the midtrachea (Figure 4.17).

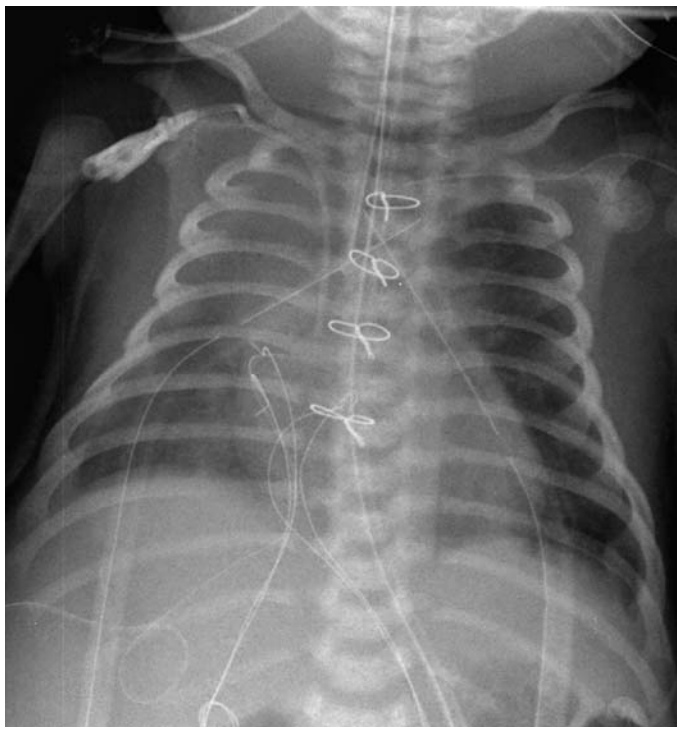

Figure 4.17. Chest radiograph demonstrating proper position of the tracheal tube, with the tip located midway between the thoracic inlet and the carina.

Nasal Tracheal Intubation

Under the vast majority of circumstances, oral tracheal intubation is preferred for emergency management of the airway. However,

nasotracheal intubation is generally more comfortable for semiconscious children, causes less stimulation of the gag reflex, and is more easily secured, especially in children with copious oral secretions or saliva. In addition, oral tracheal tubes are more easily kinked or bitten. Nasotracheal tubes appear to be safe for use in neonates, infants, and children [175–178], although some studies suggest an increased risk of nosocomial sinusitis and pneumonia associated with nasotracheal intubation [179–181]. Anecdotally, we have found that the use of nasotracheal tubes decreases the risk of unplanned or accidental extubation, which in and of itself may be associated with an increased risk of nosocomial pneumonia [182–185]. The available literature appears to support this contention [186–188]. Nevertheless, nasotracheal intubation is technically more challenging than orotracheal intubation and may be more time consuming. For these reasons, whenever nasotracheal intubation is preferred in a critically ill infant or child, it should generally follow orotracheal intubation in order to facilitate adequate oxygenation and ventilation until a nasotracheal airway is established. The nasotracheal route is contraindicated in the presence of a coagulopathy, maxillofacial trauma, and basilar skull fractures.

A topical vasoconstricting agent such as 0.25% phenylephrine or 0.05% oxymetazoline may minimize the risk of bleeding. The nare is anesthetized and lubricated with lidocaine jelly, and a tracheal tube the same diameter as the oral tube is gently passed through the nare and advanced along the floor of the nasal cavity into the nasopharynx. The oral tracheal tube is placed in the left-hand corner of the mouth while an assistant continues applying positive pressure ventilation. The oral and nasal tracheal tubes are visualized with the laryngoscope; the orotracheal tube may need to be moved away from the nasotracheal tube using the Magill forceps. The tip of the nasotracheal tube is grasped with the Magill forceps and positioned directly above the cords, anterior to the orotracheal tube. As the assistant removes the orotracheal tube, the nasotracheal tube is gently advanced through the vocal cords; the Magill forceps should not be used to advance the tracheal tube through the vocal cords, as this may cause trauma to the glottis. Several methods of estimating the depth of insertion of nasotracheal tubes have been described [189–191], although the following formula [190] works well for children up to 4 years of age:

$$\text{Depth of insertion (in cm)} = 10.5 + (\text{weight, in kg})/2$$

Complications of nasotracheal intubation include bleeding, adenoid injury, sinusitis, and trauma to the nasal turbinates, nasal septum, or nares (e.g., pressure necrosis) [177,192].

Rapid Sequence Intubation

Unlike elective tracheal intubation performed in the operating room suite, critically ill or injured children should be assumed to have a full stomach and are at risk for regurgitation and aspiration of gastric contents. Trauma, pain, anxiety, and critical illness all reduce gastric emptying, such that regardless of when the child last ate, he or she is still considered to have a full stomach. Rapid sequence intubation (RSI) should be performed to decrease the risk of aspiration in these situations. The keys to successful RSI can be easily recalled by the *six Ps*: *P*reparation, *P*reoxygenation, *P*remedication, *P*aralysis, *P*assage of the tracheal tube, and *P*ostintubation care [126]. Preparation is paramount to a smooth, safe, and successful tracheal intubation. If possible, an *AMPLE* (*A*llergies, *M*edications, *P*ast medical history, *L*ast meal, *E*xisting circumstances) history is obtained. A directed physical examination should be performed, with particular attention to the anatomy of the upper airway. All the necessary medications and equipment are assembled at the child's bedside (see earlier).

Preoxygenation or nitrogen washout is performed by the administration of 100% oxygen via a tight-fitting face mask *without* positive pressure ventilation. Preoxygenation creates a reservoir of oxygen in the lung that limits hypoxemia during subsequent attempts at tracheal intubation (see earlier). Premedication consists of the administration of both premedication (e.g., lidocaine, atropine) and induction agents, and the combination of medications should be tailored specifically to the clinical circumstance (see Table 4.7). Sellick's maneuver (cricoid pressure) is employed immediately before sedation and neuromuscular blockade in order to compress the upper esophagus between the cricoid cartilage and the cervical vertebral column and should be maintained until proper placement of the tracheal tube is confirmed [193]. Sellick's maneuver prevents the passive regurgitation of gastric contents [194–196], although excessive cricoid pressure may worsen airway obstruction or interfere with visualization of the glottis during laryngoscopy [reviewed in 125].

A rapid-acting, short-duration NMB is administered next. Succinylcholine provides safe and effective neuromuscular blockade for the majority of patients, although rocuronium or high-dose vecuronium (0.25–0.3 mg/kg) is an acceptable alternative if there are contraindications or concerns regarding the use of succinylcholine. Pretreatment with a defasciculating dose of an NDNMB may prevent the muscle fasciculations (and the subsequent pain and soreness that result) associated with succinylcholine, although the available evidence is limited [85,162,197–200]. Typically, one-tenth of the normal dose of an NDNMB is administered 1–3 min before administering succinylcholine (e.g., vecuronium, one-tenth of 0.1 mg/kg/dose = 0.01 mg/kg defasciculating dose). Priming, on the other hand, entails the administration of a smaller dose (again, typically one-tenth the normal dose) of an NDNMB administered 3–5 min before the full dose of the same NDNMB. Priming is thought to shorten the time of onset of neuromuscular blockade, although again evidence suggesting any real clinical benefits or improvements in outcome is limited.

Once the child is relaxed, laryngoscopy and intubation are performed (see earlier). If laryngoscopy is not immediately successful and the child's oxygen saturation begins to fall, assisted ventilation is administered via bag-valve-mask ventilation with cricoid pressure. Tracheal intubation is confirmed by direct visualization of the tracheal tube passing through the glottis, auscultation of the chest and abdomen (breath sounds auscultated in both axilla and not the epigastric area), and detection of end-tidal CO_2. A chest radiograph is the final method of verification of proper placement of the tracheal tube and should be obtained with the head and neck in the midline, neutral position (Figure 4.17). Flexion and extension of the neck moves the tracheal tube toward the carina (flexion, *chin moves down*) and away from the carina (extension, *chin moves up*), respectively [201,202]. After proper placement of the tracheal tube is verified, a long-acting sedative should be administered.

The importance of RSI should be emphasized. Rapid sequence intubation, when performed properly, provides superior, safer intu-

bating conditions compared with either nasotracheal or oral tracheal intubation performed with sedation alone [98,100]. However, RSI is not necessary and provides no additional advantages for children with cardiopulmonary arrest. Finally, RSI should be performed with caution, if at all, in children who are dependent on their own upper airway musculature to maintain adequate airway patency. In these cases, neuromuscular blockade may impair the ability to visualize the airway during laryngoscopy, and, more important, it may impair or even preclude the ability to provide adequate oxygenation and ventilation with bag-valve-mask ventilation.

Complications of Tracheal Intubation

Complications following tracheal intubation are variable. Excluding failed tracheal intubation, right main bronchus intubation, and esophageal intubation, immediate complications include hemodynamic derangements in response to laryngoscopy (described earlier), such as bradycardia, dysrhythmias, and hypertension, as well as hypoxia, aspiration, subluxation of the cervical spine (especially in children with either a congenital deformity of the cervical spine or traumatic injury to the cervical spine), loss of teeth, injury to the lips and gingivae, and injury to the airway.

Positive pressure ventilation, especially application of positive end-expiratory pressure (PEEP), often improves gas exchange by opposing the forces causing airway collapse. Postobstructive pulmonary edema (POPE) frequently occurs following the relief of upper airway obstruction [203–212]. Postobstructive pulmonary edema, also known as negative pressure pulmonary edema, is believed to result from the excessive negative pressures required to inhale against an upper airway obstruction, resulting in increased venous return, increased right ventricular preload, and increased pulmonary blood volume. In addition, the negative intrathoracic pressure during inspiration leads to increased left ventricular afterload. These factors tend to favor the development of pulmonary edema [206,207,210,211]. Although frequently asymptomatic, POPE may cause hypoxia, increased work of breathing, and shortness of breath. Treatment, although rarely required, includes administration of supplemental oxygen, positive pressure ventilation, and diuretics. Once the child is initially stabilized, further management depends upon the degree of obstruction and the etiology. The child should be admitted to the PICU where constant supervision and airway intervention can take place immediately, if required [210,212].

Most late complications of tracheal intubation (e.g., postextubation stridor and, in rare instances, acquired subglottic stenosis) occur because of incorrect tracheal tube size [213,214], traumatic or multiple intubations [215], and inadequate sedation/analgesia resulting in excessive up and down movement of the tracheal tube [213,216–218]. The *air-leak test* is a poor predictor of extubation success, although it may predict the presence of postextubation stridor with some degree of accuracy [219,220]. The use of corticosteroids in the prevention and/or treatment of postextubation stridor is advocated by many pediatric intensivists, although there is very little evidence to support the universal use of corticosteroids at this time [220]. The most serious late complication of tracheal intubation is acquired subglottic stenosis, although several studies support the safety of tracheal intubation (rather than early tracheotomy) for children requiring long-term ventilatory support because of burns, botulism, acute lung disease, and prematurity [221–223].

Tracheal Extubation

A trial of extubation is appropriate when the conditions that resulted in tracheal intubation are no longer present. However, extubation failure is associated with significant morbidity, including an increased incidence of ventilator-associated pneumonia [224], an increased length of stay in both the ICU and hospital [224,225], and an increased risk of mortality [224–226]. Specific, concrete guidelines and objective criteria regarding when to attempt tracheal extubation are lacking, and, unfortunately, adult weaning indices based on direct measurements of pulmonary function have been applied to children with only varied success [227–236]. General recommendations include (1) reversal of the disease process that prompted tracheal intubation (e.g., resolution of hypoxemic respiratory failure, improvement in mental status); (2) presence of an intact cough and gag reflex (i.e., ability to maintain and protect the airway); (3) acceptable oxygenation and ventilation on minimal mechanical ventilatory support; (4) appropriate neurologic status (generally, either a Glasgow Coma Score >8 or spontaneous eye opening and the ability to follow simple commands); and (5) hemodynamic stability. Additional criteria that are commonly listed, although infrequently used in the clinical setting, include a negative inspiratory force (NIF) of 25–50 cm H_2O and a forced vital capacity of 15 mL/kg [51]. In children who were tracheally intubated secondary to upper airway obstruction, the presence of an audible leak around the tracheal tube is also a criterion for extubation. Finally, adequate reversal of neuromuscular blockade must be present—adequate reversal is generally assumed by the ability to sustain a head lift or, in an infant, a leg lift. Although the use of pharmacologic agents to reverse either sedation or neuromuscular blockade may be occasionally necessary (Table 4.10), reliance on these medications to *make a child ready for extubation* is fraught with danger and should be summarily avoided.

It is a common practice to hold nasogastric feedings for 4–6 hours before an attempt at extubation, although a recent study showed that continuous transpyloric feeding during tracheal extubation was safe and improved the delivery of more optimal nutrition [237]. Sedation during weaning from mechanical ventilation toward extubation may be difficult. For example, the need for continued sedation to prevent an uncontrolled or accidental extubation often conflicts with the desire to decrease sedation to the point where a child is awake enough to attempt extubation. Anecdotally, we and others have found that the use of a short-acting agent such as propofol or dexmedetomidine facilitates opioid or benzodiazepine withdrawal during the periextubation period (Wheeler,

Table 4.10. Reversal agents.

Agent	Dose	Onset	Duration
Neostigmine	0.025–0.1 mg/kg IV	3–5 min	1–2 hr
Pyridostigmine	0.1–0.25 mg/kg IV	3–5 min	2–3 hr

Note: These agents should be administered either in conjunction with (neostigmine) or after (pyridostigmine) atropine, 0.01–0.02 mg/kg IV (minimum dose of 0.1 mg), or glycopyrrolate, 3–5 μg/kg IV.

unpublished data) [238–241]. Typically, dexmedetomidine or propofol is initiated as the dosage of opioid and benzodiazepine infusions are rapidly deescalated, usually approximately 6–12 hr before a trial of extubation. Children are then generally extubated shortly after the propofol or dexmedetomidine is discontinued. We have also extubated children while maintaining a *plane of sedation and analgesia* with low-dose dexmedetomidine (Wheeler, unpublished data). Finally, corticosteroids (dexamethasone, 0.5 mg/kg/dose IV every 6 hr, beginning 12 hr before extubation and continued for the first 12 hr following extubation) are occasionally administered during the periextubation period in an attempt to minimize postextubation stridor.

The Difficult Airway

The Difficult Airway Algorithm

The American Society of Anesthesiology (ASA) Task Force on Management of the Difficulty Airway published *Practice Guidelines for Management of the Difficult Airway* in 1993 [35]. These guidelines were revised to incorporate the laryngeal mask airway (see later) in 2003 [242] and should be familiar to pediatric anesthesiologists, emergency medicine physicians, and intensivists alike. These guidelines were developed specifically for use in the operating room suite and may not necessarily apply directly to the practice of pediatric intensive care. However, the guidelines serve as a framework for management of the difficult airway in the intensive care setting (Figure 4.18). It is important to note that an otolaryngologist or pediatric surgeon should be available at the bedside whenever a difficult airway is encountered should the need for an emergency surgical airway arise. Pediatric intensivists must optimize their first attempt at tracheal intubation but should be facile with at least one alternative device for securing the airway. Several alternatives to laryngoscopy exist, although their use in the PICU has not been adequately studied. The following specialized techniques are available when the situation calls for their use.

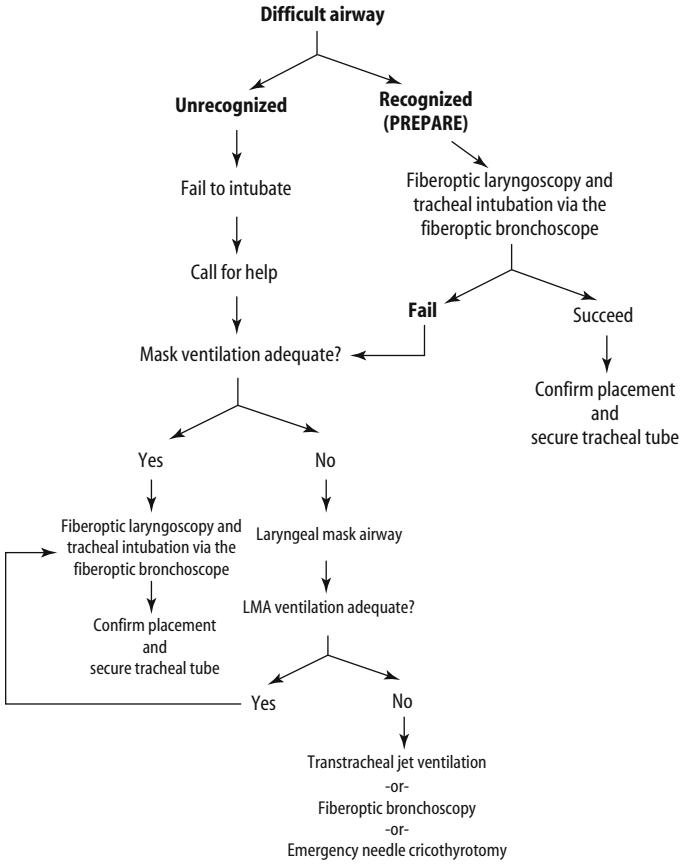

Figure 4.18. Proposed difficult airway algorithm for use in the pediatric intensive care unit.

Laryngeal Mask Airways

The British anesthesiologist Archie Brain designed the first laryngeal mask airway (LMA™, LMA North America, San Diego, CA) in 1988, and since that time the LMA has had a profound impact on management of the difficult airway. The original purpose of the LMA, however, was more or less to serve as an intermediately invasive, artificial airway, bridging the gap between the use of bag-valve-mask ventilation and tracheal intubation [243]. Regardless of its original intended use, the LMA is now considered a primary option for the management of the difficult and failed airway [242,244,245]. The LMA consists of a semirigid tube and an inflatable mask that is designed to be placed into the hypopharynx and advanced over the glottic opening (Figure 4.19A). When fully inflated, the mask cuff provides a tight seal around the glottic opening, thereby providing a conduit into the airway (Figure 4.19B). The LMA is available in both pediatric and adult sizes (Table 4.11) and provides more effective ventilation than bag-valve-mask ventilation alone, as bag-valve-mask ventilation frequently requires two hands to maintain an adequate mask seal around the face [246].

Successful placement of the LMA (Figure 4.20) is unaffected by Mallampati score, Cormack score, or the presence of either manual inline cervical spine stabilization or a rigid cervical collar [247–250]. Laryngeal mask airways have even been placed successfully in patients in the prone position [251–253]. The LMA is not designed to prevent aspiration of gastric contents and therefore should not

Table 4.11. Laryngeal mask airways.

LMA™ size	Minimum i.d. (mm)	Maximum ett size	Maximum FOB size	Patient size (kg)	Maximum cuff inflation volume (ml; air)*
1	5.3	3.5	2.7	Neonates <5	4
1.5	6.1	4.0	3.0	Infants 5–10	7
2	7.0	4.5	3.5	Children 10–20	10
2.5	8.4	5.0	4.0	Children 20–30	14
3	10.0	6.0 cuffed	5.0	Children 30–50	20
4	10.0	6.0 cuffed	5.0	Adolescents 50–70	30
5	11.5	7.0 cuffed	5.5	Adults 70–100	40
6	11.5	7.0 cuffed	5.5	Adults >100	50

*These are maximum clinical volumes that should never be exceeded. It is recommended that the cuff be inflated to 60 cm H_2O intracuff pressures.

Note: ETT, tracheal tube size (i.d.); FOB, flexible bronchoscope; i.d., internal diameter in millimeters.

Source: Adapted from LMA™ Airway Instruction Manual. San Diego, CA: LMA North America; 2005.

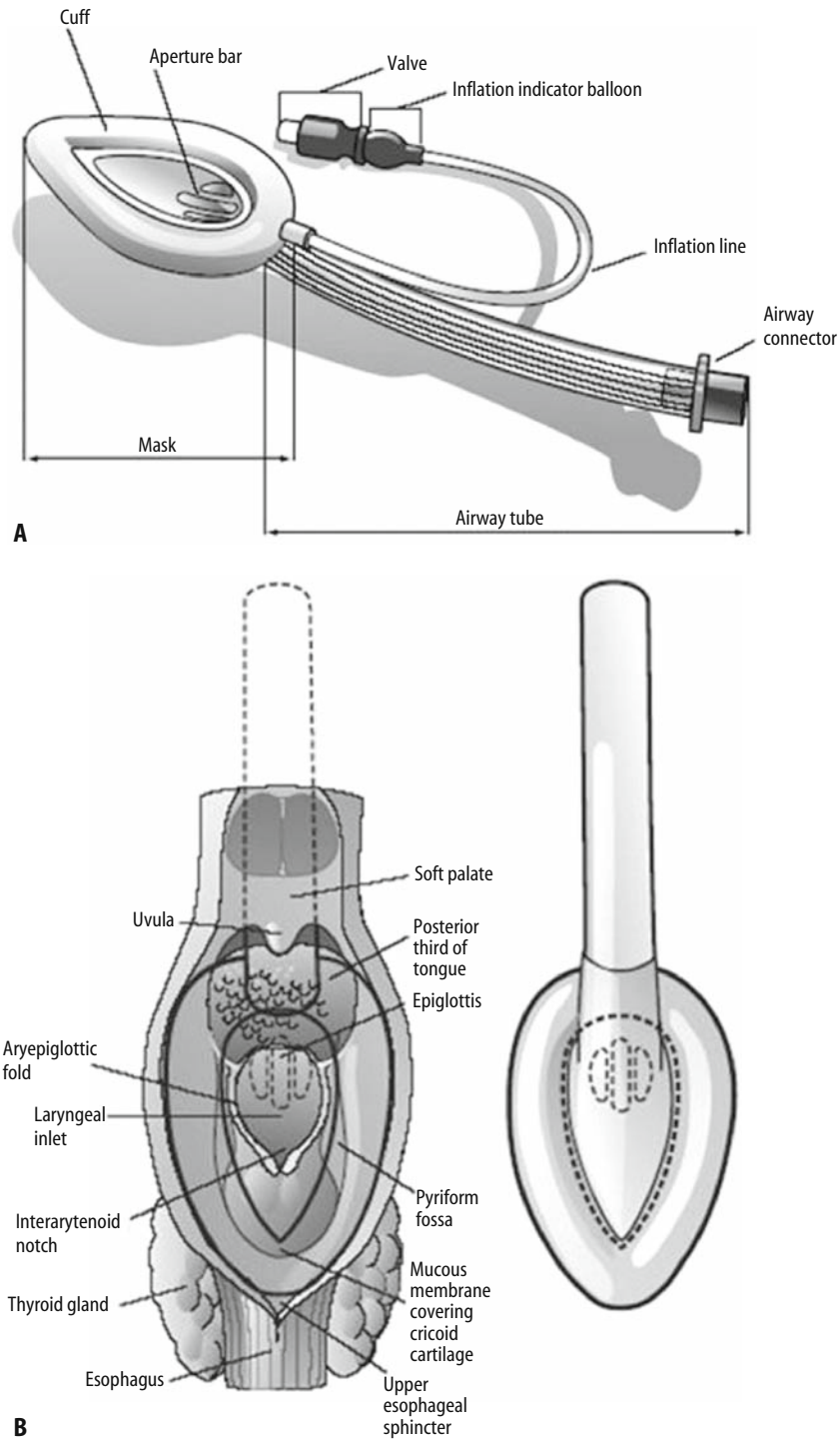

Figure 4.19. **(A)** The laryngeal mask airway. **(B)** Dorsal view of the laryngeal mask airway, showing position in relation to pharyngeal anatomy. (Reprinted with permission from LMA™ Airway Instruction Manual. San Diego, CA: LMA North America; 2005.)

be used for elective, nonemergent management of the airway in children with either a full stomach or decreased gastric emptying. Another relative contraindication for the LMA is the need for high pulmonary inflation pressures caused by poor lung compliance or increased airways resistance. Finally, the LMA can be used as a conduit for passing a tracheal tube with the use of a flexible bronchoscope (see later) [12,13,254–258]. An intubating LMA (LMA-Fastrach™, LMA North America) is available for use in children >30 kg and in adults. The intubating LMA is reviewed elsewhere [259].

Fiberoptic Laryngoscopy and Tracheal Intubation

The use of fiberoptic laryngoscopy and fiberoptic tracheal intubation was historically limited by the lack of fiberoptic bronchoscopes appropriately sized for use in children. However, this hindrance

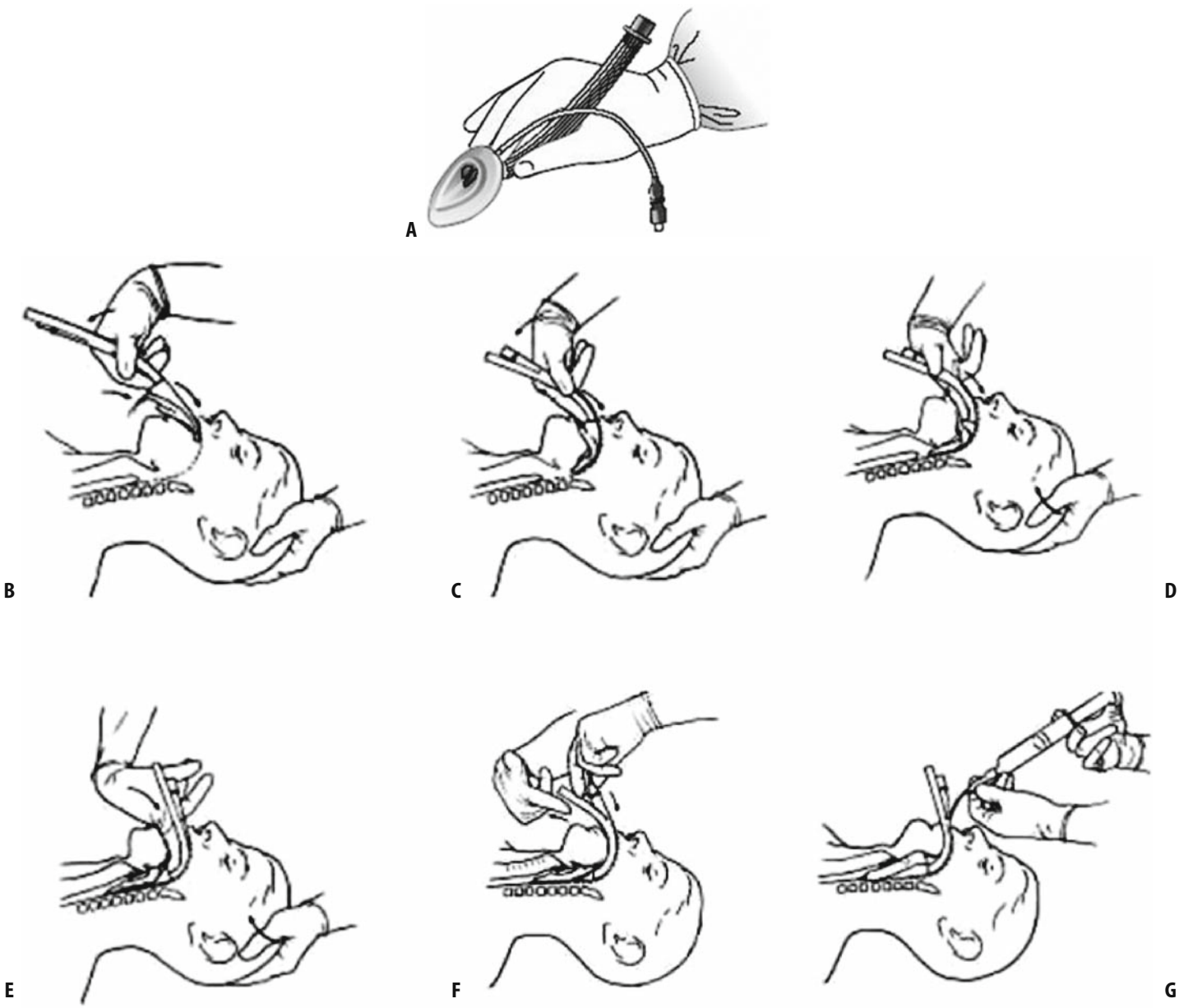

Figure 4.20. Placement of the LMA™. **(A)** The LMA™ airway is held tightly like a pen with the index finger at the cuff–tube junction. In order to position the LMA™ airway correctly, the cuff tip must avoid entering the valleculae or the glottic opening and must not become caught up against the epiglottis or the arytenoids. **(B)** Under direct visualization, the LMA™ is inserted into the mouth, and the tip of the cuff is pressed upward against the hard palate. The cuff must be deflated in the correct wedge shape and should be kept pressed against the patient's posterior pharyngeal wall. To avoid contact with anterior structures during insertion, the inserting finger must press the tube upward (cranially) throughout the insertion maneuver. **(C)** As the index finger passes further into the mouth, the finger joint begins to extend. The jaw should not be held widely open during this movement as this may allow the tongue and epiglottis to drop downward, blocking passage of the mask. **(D)** Using the index finger, the mask is pressed backward toward the other hand, which exerts counterpressure, although excessive force should not be used. **(E)** The LMA™ is advanced into the hypopharynx until a definite resistance is felt. Depending on patient size, the finger may be inserted to its fullest extent into the oral cavity before resistance is encountered. **(F)** Before removing the index finger, the nondominant hand is brought from behind the patient's head to press down on the airway tube. This prevents the LMA™ airway from being pulled out of place when the finger is removed. It also permits completion of insertion in the event that this has not been achieved by the index finger alone. At this point the LMA airway should be correctly located with its tip firmly pressed up against the upper esophageal sphincter. **(G)** After insertion, the tubes should emerge from the mouth directed caudally. The cuff is inflated with just enough air to achieve an intracuff pressure of 60 cm H_2O. Note that the cuff inflation volume listed in Table 4.11 (as well as directly on the airway tube itself) is the *maximum* clinical inflation volumes and should not automatically be considered the recommended inflation volumes. Frequently, only half the maximum volumes are sufficient to obtain a seal and/or achieve 60 cm H_2O intracuff pressure. The cuff should never be overinflated, and intracuff pressures greater than 60 cm H_2O should be avoided. (Reprinted with permission from LMA™ Airway Instruction Manual. San Diego, CA: LMA North America; 2005.)

has been dramatically improved with introduction of smaller fiberoptic bronchoscopes. The thinnest fiberoptic bronchoscopes with flexible angle are 2.2 mm, although these do not have a suction port (Olympus BF-N20, Olympus Corp.; and Machida ENT-30 F III, Machida Endoscopy Co., Ltd.). The 1.4-mm multipurpose fiberoptic bronchoscope may also be a choice for tracheal intubation in special cases (e.g., intubating an infant with a 2.5-mm i.d. tracheal tube). Fiberoptic tracheal intubation can be performed either awake or with sedation, the latter being preferred for infants and young children because of a lack of cooperation. Topical anesthesia assists in blunting the afferent response associated with instrumentation. It should be stressed that fiberoptic bronchoscopic intubation in the hands of inexperienced personnel is potentially hazardous. However, we strongly feel that pediatric intensivists should be facile with the use of the fiberoptic bronchoscope for tracheal intubation.

Light Wand or Lighted Stylets

A light wand consists of a handle containing a switch and a battery, connected by a flexible tube to a distal light bulb. Several devices are currently available. The lighted stylet or wand is lubricated and positioned within a standard tracheal tube (with the light bulb at the distal end of the tracheal tube). The tracheal tube is then placed blindly into the back of the mouth at the midline and slowly advanced until the light is visualized at the thyroid prominence. The tracheal tube is then advanced until the light disappears just below the sternal notch and the stylet or wand is removed. Proper placement of the tracheal tube within the trachea is then verified via standard means (see above). This technique requires training and is no longer a popular alternative for management of the difficult airway. In addition, a tutorial on the use of the light wand (as well as many of the other devices listed here) may be found at www.simanest.org.

Bullard Laryngoscope

The Bullard Laryngoscope® (Circon ACMI Corp, Southborough, MA) is a rigid fiberoptic laryngoscope designed to be used when a conventional laryngoscope may be difficult. The Bullard Laryngoscope aids with visualization of the glottic opening even when there is an inability to align the oral, pharyngeal, and laryngeal axes, and, compared with conventional direct laryngoscopy, the Bullard Laryngoscope only requires minimal head manipulation and positioning. The Bullard Laryngoscope is available in both pediatric and adult sizes and should be a part of every difficult airway cart.

Combitube

The Combitube® (Kendall-Sheridan Catheter Corp, Argyle, NY) is a blindly inserted, double-lumen tube designed specifically for management of the airway during cardiopulmonary resuscitation and represents a vast improvement from its early predecessor, the esophageal obturator airway. The Combitube is inserted blindly into either the trachea or esophagus and is designed specifically for use by individuals who are unskilled in airway management. For this reason, the Combitube is frequently used in the prehospital setting. The main drawback to the Combitube is that it is not currently available in sizes appropriate for children.

Gum Elastic Bougie

The gum elastic bougie consists of a semirigid, yet malleable device designed to facilitate tracheal intubation when visualization of the glottis is poor or impossible. The bougie is placed while visualizing the epiglottis via standard laryngoscopy and is used more or less as an introducer for subsequent placement of the tracheal tube. The smallest tracheal tube that the standard bougie can accommodate, however, is a 6.0-mm tube, thereby limiting its use to adolescents and adults.

Retrograde Tracheal Intubation

Retrograde tracheal intubation is an invasive technique that involves the percutaneous passage of either a wire or an epidural catheter cephalad through the cricothyroid membrane. A tracheal tube is then advanced into the trachea over the guidewire, and the guidewire is removed through the proximal end of the tracheal tube. Retrograde intubation has been a popular technique in the past [260]; however, with the advent of thin fiberoptic bronchoscopes, it is now infrequently used.

Airway Exchange Catheters

Airway exchange catheters (e.g., the Cook airway exchange catheter, Cook, Bloomington, IN) are occasionally used in the critical care setting whenever a tracheal tube needs to be changed (up-sized or down-sized) for a patient with a known difficult airway. Several reports have described the use of airway exchange catheters during a trial of extubation in children with known difficult airways who are at risk for a difficult reintubation [261–264], although these devices are by no means foolproof. The use of these devices requires that a tracheal tube is already in place, although they are mentioned here as part of the difficult airway armamentarium.

Percutaneous Needle Cricothyrotomy

Needle cricothyrotomy is rarely necessary, although it may facilitate adequate oxygenation and ventilation in children with complete upper airway obstruction caused by a foreign body, severe maxillofacial injuries, or laryngeal fracture (Figure 4.21). Further data are needed on the use of this potentially life-saving, but highly invasive modality in critically ill or injured children.

Transtracheal Jet Ventilation

If tracheal intubation or ventilation by any means described above is impossible, the patient requires emergency tracheostomy or transtracheal jet ventilation (TTJV). A large-bore intravenous catheter (14 to 20 gauge, depending on the size of the trachea) should be inserted through the cricothyroid membrane, and the catheter should be connected to a jet ventilator. If a jet ventilator is not available (which may be the case, as these devices are no longer frequently used in the PICU), a high-pressure oxygen source can be used. Intermittent insufflation of high-flow oxygen may be adequate as a temporizing measure because of the potential hazards associated with the jet ventilator if the tip of the catheter is not in the lumen of the trachea (e.g., pneumothorax, pneumomediastinum, subcutaneous emphysema).

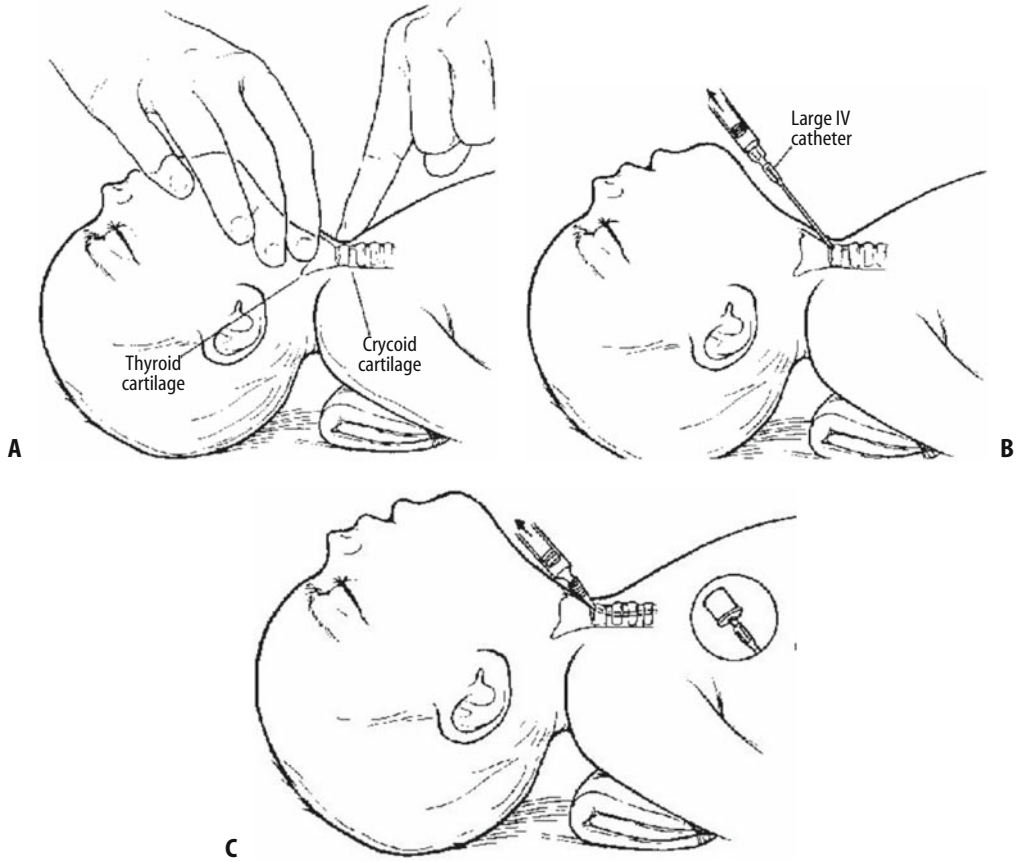

Figure 4.21. Percutaneous needle cricothyrotomy. **(A)** The head is placed in the midline position with a rolled towel or folded sheet beneath the shoulders. The anterior portion of the neck is cleansed and prepped in a sterile fashion. The trachea is stabilized with the right hand, and the cricothyroid membrane is palpated with the index fingertip of the left hand between the thyroid and cricoid cartilages (this space is very narrow, approximately 1 mm, in infants and only a fingernail will discern it). **(B)** A small-bore (20 or 22 gauge) needle is used as a *finder needle* and is introduced while pulling back on the syringe. If air is aspirated, a large-bore cannula (12 or 14 gauge) is inserted via the same technique, directed toward the midline caudally and posteriorly at a 45° angle. Intraluminal placement of the needle is again confirmed when air is aspirated. **(C)** The needle is slowly withdrawn as the cannula is advanced into the tracheal lumen. The adaptor from a 3.0 mm i.d. tracheal tube is connected to the cannula, and ventilation can then be administered via transtracheal jet ventilation. Alternatively, 100% oxygen can be administered using either a self-inflating bag or an anesthesia bag. (Reprinted from Coté et al. [11]. Copyright 1993 with permission of Elsevier.)

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5
Vascular Access

Jennifer Kaplan and Richard J. Brilli

Introduction

Percutaneous central venous access is a common procedure performed in emergency departments and intensive care units (ICUs). In adults, in the United States, approximately 3 million central venous catheters (CVCs) are placed annually, resulting in 15 million CVC days in ICUs each year [1,2]. Like adults, critically ill children often require CVC placement. These catheters are used as a reliable source for fluid and drug administration, cardiovascular monitoring, emergency vascular access during crisis situations, intermittent blood removal for laboratory analysis, plasmapheresis/hemodialysis, and long-term chemotherapy [3–7]. For example, in a retrospective review of emergency department admissions over 5 years, Chiang and Baskin [5] reported that among all patients who required placement of a CVC, 20 of 121 patients (17%) had the catheter placed as a result of a cardiac or respiratory arrest, 78 patients (64%) had catheters placed for lack of peripheral access, and 23 patients (19%) had catheters placed for inadequate or unstable peripheral access. Multiple sites and varied techniques have been described for obtaining central venous access in children. Each site and access method has associated risks and benefits.

This chapter will provide an overview of choices for central venous access sites, describe standard techniques for central venous catheterization, and delineate associated risks and complications. Other methods of venous access, such as intraosseous access, venous cut down, or peripherally inserted central catheters, will not be part of this review because they are well outlined in other standard references [7]. In addition, catheter-related bloodstream infections and catheter-related thrombosis are the subject of other chapters in this textbook and are only briefly discussed here.

Choice of Site and Type of Catheter

There are multiple sites available for central venous catheterization in children. These sites include the femoral, subclavian, internal jugular, external jugular, and axillary veins. Recently, peripherally inserted central catheters have been used more frequently to obtain central venous access. These catheters are usually inserted into the basilic or cephalic veins and then advanced into the central circulation. Decisions regarding the *best* site for cannulation depend on multiple patient-specific clinical variables, risk of complications, operator experience, and projected length of time the catheter will remain in place [8–11]. The femoral vein is the most common site for central venous access in children, especially in the emergency setting [5,8]. This site may have the lowest insertion risk profile and a high degree of operator experience across multiple specialties, hence its frequent use. In a cohort of 121 emergency department patients who required central venous access, 101 (83%) had the CVC placed in the femoral vein, 12 (10%) had the catheter placed in the subclavian vein, and 7 (6%) had the catheter placed in the internal jugular vein [5].

Clinical variables that may impact the choice of site for cannulation include the coagulation status of the patient, whether the patient is breathing spontaneously or via mechanical ventilation, and the severity of the patient's respiratory illness. For example, patients with a significant coagulopathy may be at greater risk from inadvertent arterial puncture, especially if the access site does not easily allow for direct pressure to the artery. This could make subclavian venipuncture a higher risk than the femoral approach. For patients breathing spontaneously (less likely to hold still for the procedure) or those requiring high settings on mechanical ventilation, the risk of an unplanned pneumothorax associated with the subclavian or internal jugular approach could make the femoral vein the preferred site. Subclavian and internal jugular sites may have lower catheter maintenance risks (primarily lower infection rates) compared with the femoral vein and thus may be preferred when central venous access is performed electively and the duration of cannulation is expected to be prolonged [2].

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Femoral Venous Catheterization

Demographic and Historical Data

Studies from the 1950s reported high complication rates from femoral vein cannulation, and as a result femoral venous access fell out of favor [12]. Today, femoral vein catheterization is frequently used for critically ill children because of its relatively low-risk profile and high insertion success rate in a variety of clinical settings.

Indications and Contraindications for Placement

Femoral veins are excellent central venous access sites in critically ill children. The femoral veins are attractive because they are perceived as a simple site for percutaneous insertion, especially by inexperienced operators, and the cannulation can often be performed with minimal supplemental sedation. This may be particularly important for children who are not receiving mechanical ventilation at the time of catheter placement. In addition, risks of life-threatening complications at the time of insertion are reduced because of easy compressibility of local vessels (femoral artery) and the remote location from the lung. The femoral vessels are also preferred if there are relative or absolute contraindications to accessing the jugular or subclavian veins. For example, for patients at risk for intracranial hypertension, placement of CVCs in the jugular or subclavian vein may precipitate vascular thrombosis, which could create obstruction to cerebral venous drainage and potentially life-threatening increases in intracranial hypertension. In this clinical setting, a femoral venous catheter may be preferred [8]. In addition, patients with severe respiratory failure who require high mechanical ventilatory pressures may be at increased risk should a pneumothorax develop during the placement of a cervicothoracic CVC. In this setting the femoral site may be preferred as well.

Finally, for patients with a recognized coagulopathy, the femoral site is preferable because direct compression of the femoral vessels can be performed, especially in the event of inadvertent puncture of the femoral artery [8]. Multiple studies demonstrate that femoral vein catheterization is a rapid and safe route for obtaining intravenous access in patients requiring massive intravenous fluid infusions or following cardiac arrest [4,13,14]. Furthermore, the femoral artery provides an easily recognized landmark to facilitate straightforward catheter insertion. Certain clinical situations may warrant placement of CVCs at sites other than the femoral vein. Trauma to the lower extremity, pelvis, or inferior vena cava is a relative contraindication for femoral vein catheterization [8]. In addition, bulky abdominal tumors, inferior vena cava, common iliac, or femoral thrombosis, abdominal hematomas, venous anomalies and prior pelvic radiation are associated with increased risk of complications from femoral venous catheter placement [15].

In adult patients, practitioners have traditionally avoided femoral CVC placement because of concerns about the risk of deep venous thrombosis, excess infectious risks compared with other sites, and potentially inaccurate central venous pressure measurements derived from the femoral vessels [16–19]. Although the jury may still be out in the adult critical care community regarding the use femoral catheters, evidence with children suggests a safer risk profile for femoral catheters than is observed for adults, especially when catheters are used for short periods of time [20,21]. Perceived ease of insertion combined with a low insertion risk profile often makes the femoral vessels the preferred site for children [21,22]. For adults and children, there is a wide range of reported rates for venous thrombosis associated with CVCs (1%–60%); however, the thrombosis rates for children are not significantly different for the femoral vessels and the cervicothoracic vessels [23,24]. Furthermore, for children, infectious complications associated with femoral venous catheters are similar to, and in one report less than, that reported for cervicothoracic CVCs [25–27]. Finally, multiple studies have demonstrated that, in the absence of elevated intraabdominal pressures, central venous pressure measurements derived from femoroiliac veins are similar to those measurements obtained from cervicothoracic veins and may accurately predict right atrial pressures [28–31].

Anatomy

The femoral vein lies in the femoral sheath, medial to the femoral artery immediately below the inguinal ligament (Figure 5.1). The femoral triangle is an anatomic region of the upper thigh, with the boundaries including the inguinal ligament cephalad, sartorius muscle laterally, and adductor longus muscle medially. The contents of the femoral triangle from lateral to medial are the femoral nerve, femoral artery, and femoral vein. The femoral sheath lies within the femoral triangle and includes the femoral artery, femoral vein, and lymph nodes. The femoral vein runs superficially in the thigh, approaching the inguinal ligament in the femoral triangle. The vein dives steeply in a posterior direction, superior to the inguinal ligament, as it becomes the iliac vein. The femoral vein lies medial to the femoral artery in the femoral sheath inferior to the inguinal ligament. In patients with a palpable pulse, the femoral vein can be located just medial to the femoral arterial pulse inferior to the inguinal ligament. In pulseless patients, the femoral artery

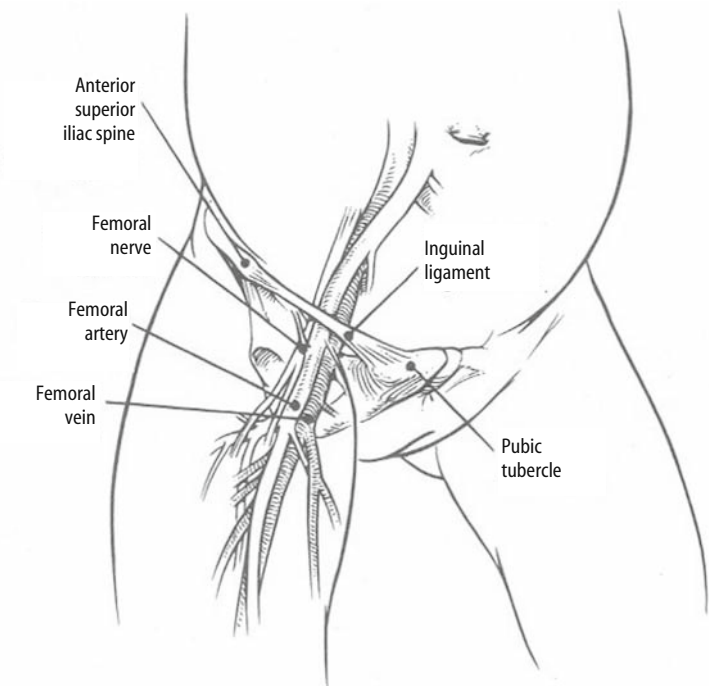


Figure 5.1. Femoral vein anatomy. (Pediatric Advanced Life Support Manual, American Heart Association. Copyright 1997. Reprinted with permission.)

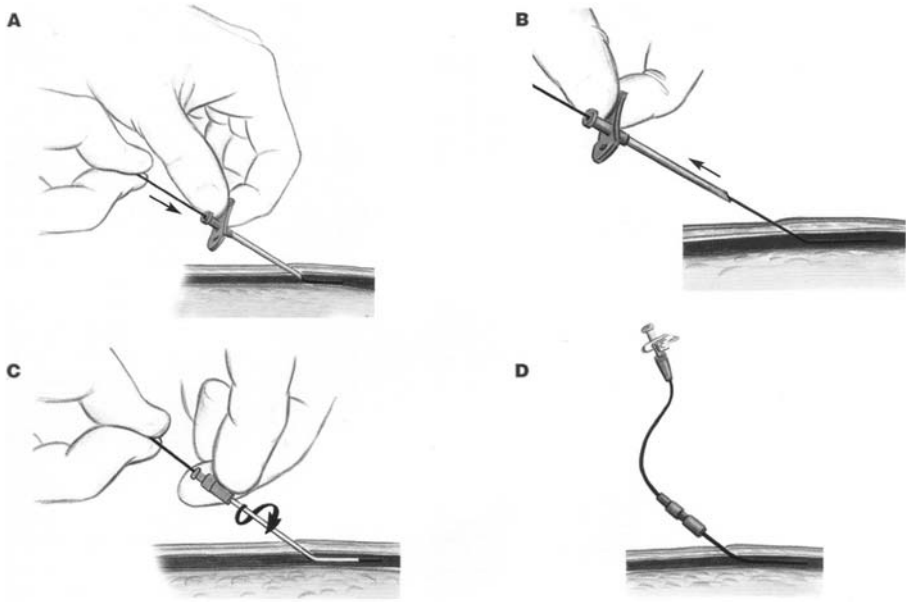


Figure 5.2. Seldinger technique for central venous catheter insertion. **(A)** Insertion of wire. **(B)** Removal of needle while wire remains in place. **(C)** Passage of catheter over wire. **(D)** Catheter in position. (PALS Provider Manual, American Heart Association, Copyright 2002. Reprinted with permission).

can be assumed to be at a point half-way along a line drawn from the pubic tubercle to the anterior superior iliac spine, at a level 1–2 cm inferior to the inguinal ligament. The femoral vein is located 0.5–1.5 cm medial to the center of the femoral artery, depending on the size of the patient [32].

Insertion Technique

Femoral vein insertion should be performed using a standard procedure, preferably using the Seldinger technique [33]. The Seldinger technique was first described by Sven Seldinger in 1953 and enabled practitioners to insert a large-sized catheter over a guidewire that was placed in the vein by venipuncture with a small-sized needle (Figure 5.2). The femoral site should be prepared and draped as for any surgical procedure and in nonemergent clinical situations, using a full sterile barrier (Figure 5.3) [34]. The optimal position of the leg can vary according to the preference of the operator; some prefer slight external rotation at the hip, whereas others prefer full *frog leg* external rotation. The location of the femoral vein is 0.5–2 cm inferior to the inguinal ligament, just medial to the femoral artery. Because the overlying skin in the inguinal region, especially in neonates and infants, is often slack and redundant, it can be important to develop a method to maintain traction on the skin while palpating for the arterial pulse and then maintaining this traction while inserting the needle (Figure 5.4).

Figure 5.3. Full sterile barrier during elective insertion of central venous catheter.

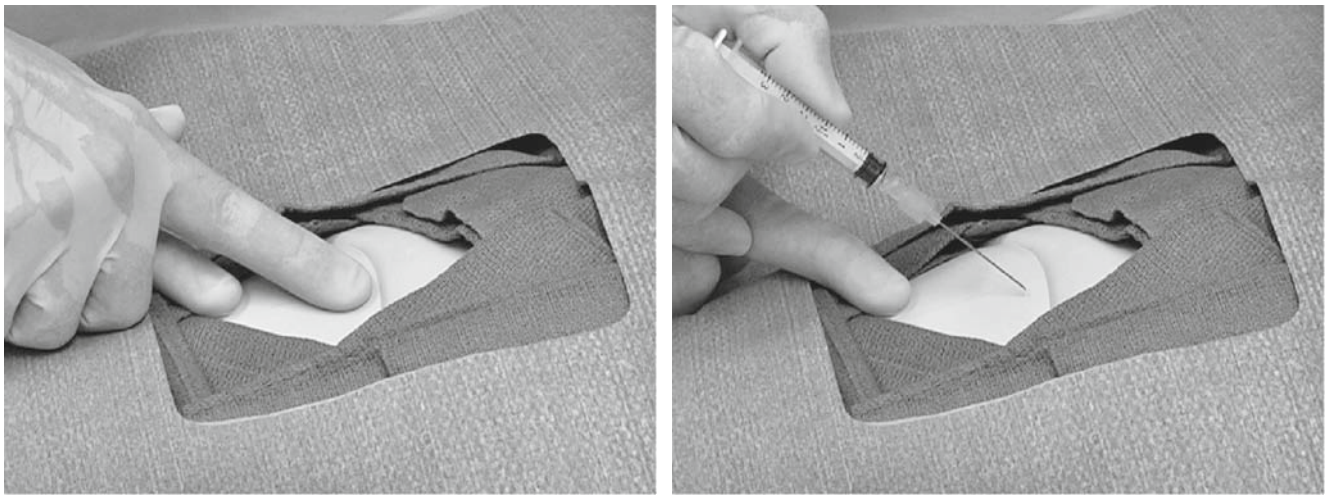


Figure 5.4. **(A)** Palpation of femoral pulse with traction on redundant skin. **(B)** Skin traction is maintained as initial skin puncture occurs. The needle is advanced through the vessel and venous flashback occurs as the needle is withdrawn using negative pressure on the syringe.

The syringe should be held at a 30°–45° angle from the skin, aimed cephalad over the femoral vein site. Some operators approach the vessel from the side, maintaining traction on the skin and palpating the pulse with the opposite hand (Figure 5.5), whereas others approach the vessel directly (see Figure 5.4B). Most operators locate the vein and obtain venous blood flashback by advancing the needle/syringe at a 30° angle toward the ischial ramus while withdrawing the syringe plunger, creating negative pressure within the syringe (see Figure 5.5). If venous blood is not returned, the needle/syringe should be slowly withdrawn, pulling back constantly on the plunger. If the vein is not located, the needle should be redirected, searching from medial to lateral until the vein is located. To avoid lacerating the vessels, the needle should be withdrawn to the skin surface before changing direction. Puncture of the vein is indicated by blood return (flashback in the syringe) while advancing or slowly withdrawing the needle.

An alternative method to locate the vein is to advance the needle/syringe over the vein site toward the ischial ramus to a depth of 1–2 cm without negative pressure in the syringe and then withdraw the needle, applying negative pressure to the syringe, thus obtaining venous blood flashback on the withdrawal of the needle. The advantage of this method is that it allows the operator to firmly rest the hand on the thigh during needle/syringe withdrawal, which allows the operator to freeze when venous blood flashback occurs. This is especially important in small infants where the cross-sectional area of the needle and that of the vein are similar in size, and as a result it is easy for the needle to move outside the lumen of the vessel as the syringe is gently removed from the needle. By freezing the operator's hand in position, this method allows for greater success with guidewire placement (Figure 5.6).

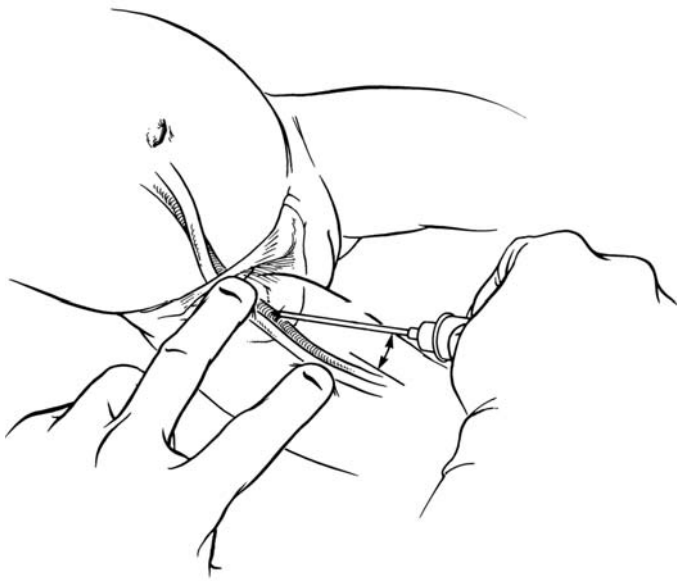


Figure 5.5. One approach to the femoral vessel. The needle and syringe are advanced at a 45° angle to the skin. (Pediatric Advanced Life Support Manual, American Heart Association. Copyright 1997. Reprinted with permission.)

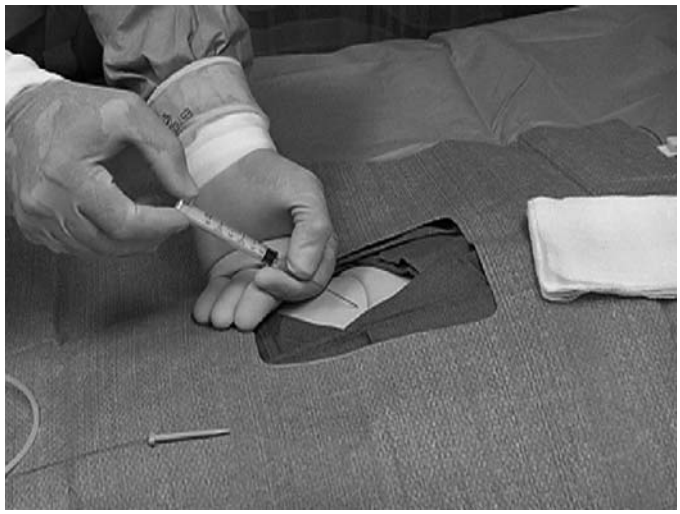


Figure 5.6. The operator's hand rests on the infant's thigh, which allows the hand to freeze when venous flashback occurs.

Kanter et al. [35] demonstrated by use of ultrasound that the location that had the greatest probability of successful puncture of the femoral vein was located 4–5 mm medial to the femoral artery pulse. In addition, if it is assumed that entry into the central half of the vein will result in successful catheterization, successive attempts 5 mm and 6 mm medial to the pulse would result in cumulative successful insertions in 53% and 61%, respectively, with no arterial punctures. A third attempt 4 mm medial to the pulse further increases cumulative success to 78%, but the arterial puncture rate would increase to 3%. Ultrasound-guided central venous puncture is becoming a common practice for adults and may increase insertion success rates and reduce insertion complication rates, especially for inexperienced operators or for difficult access patients such as obese patients, patients with poor arterial pulses, or those with partial vessel thrombosis [36].

As described by Seldinger, after observing blood return, the syringe is disconnected from the needle hub and the guidewire is advanced through the needle and into the vein. It is important to leave part of the wire in view at all times. The advancement of the wire should be smooth without meeting any resistance. If resistance occurs during guidewire advancement, it is possible that the wire is meeting a previously unrecognized thrombus, is advancing into the subcutaneous tissue, or most likely is advancing into the ascending lumbar veins that drain into the common iliac veins proximal to the femoral vein. Once the wire is in good position, the needle is removed over the wire, holding the guidewire in place. A small 0.25 to 0.50 cm skin incision is then made at the site of entry of the guidewire into the skin, making certain that the bevel of the scalpel blade is directed away from the guidewire. The dilator is held near its tip and is advanced over the guidewire into the femoral vein. The dilator should be advanced using a gentle boring motion. The guidewire is held in place, and the dilator is removed while applying light pressure to the femoral site, as bleeding is likely to occur when the dilator is removed. The catheter is placed over the guidewire and inserted into the femoral vessel. Once the catheter is inserted, the guidewire is removed and blood is aspirated through the catheter to ascertain placement and patency of the catheter. The catheter is secured in place and covered with a sterile dressing.

Important warnings to consider during cannulation of the femoral vein include the following: (1) puncture of the femoral artery requires application of direct pressure for 5–10 min or until hemostasis is achieved; (2) never push the guidewire or catheter against resistance—properly placed guidewires float freely; (3) the guidewire can be sheared off if pulled out of the needle against resistance—if resistance is met on withdrawal of the guidewire, pull out the needle and the guidewire simultaneously; and (4) the guidewire should remain in view at all times, because guidewires have remained in vessels or have floated into the central circulation when not properly monitored (Figure 5.7).

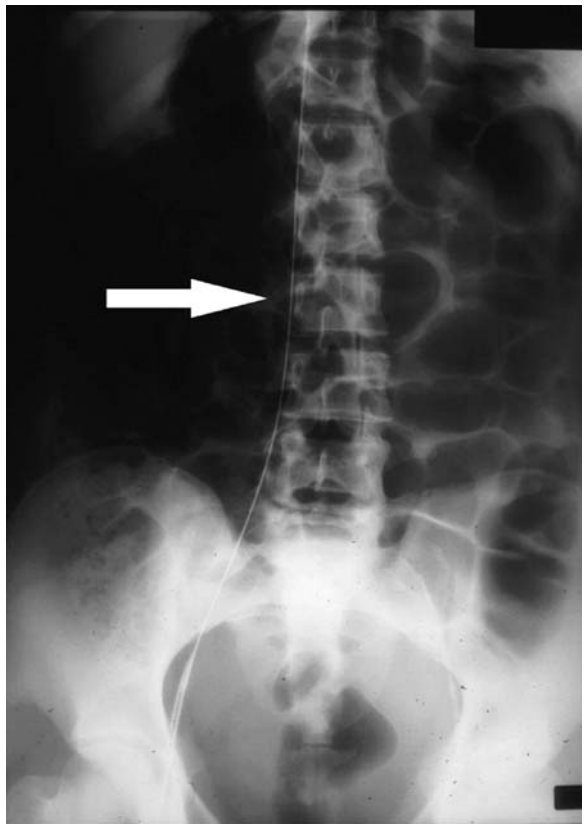


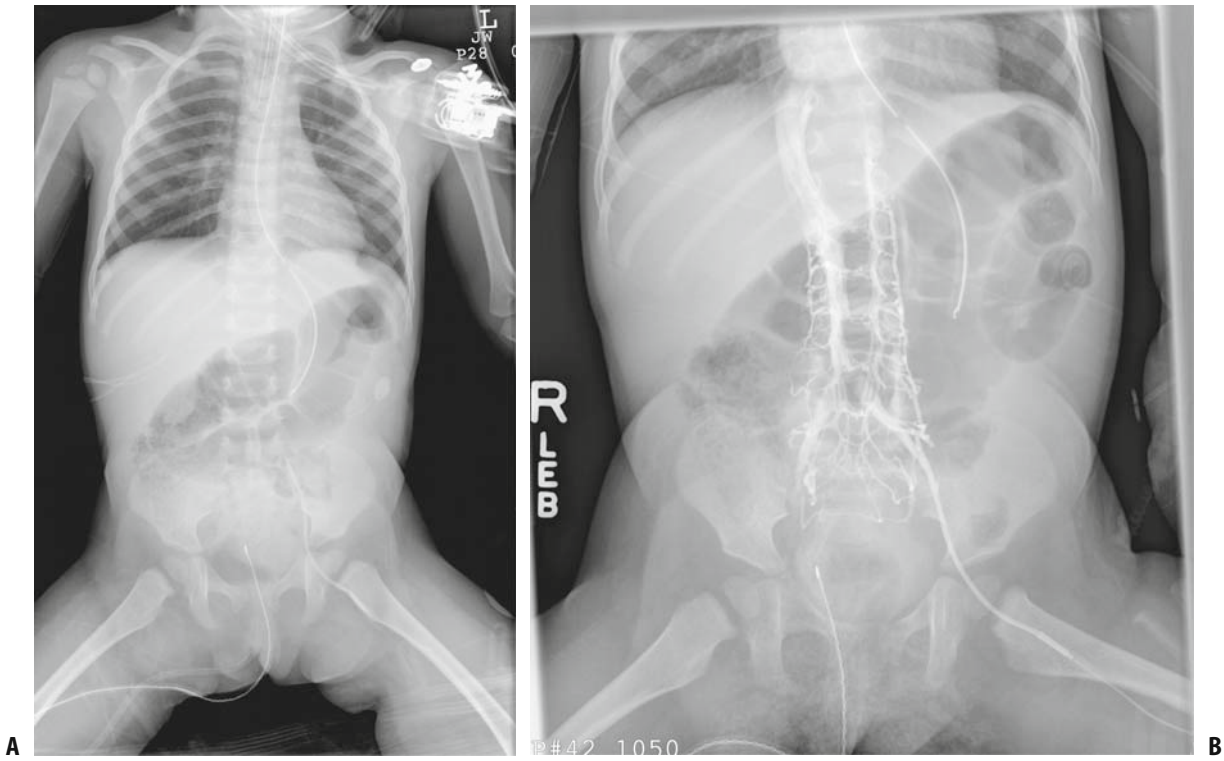
Figure 5.7. Guidewire left in right femoral vein hemodialysis catheter.

Confirmation of Placement

Confirmation of proper CVC position is required after placement of all CVCs. A postprocedure x-ray is the initial and usually only confirmatory test needed after femoral vein catheter insertion [37]. Some have questioned the value of confirmatory x-rays for uncomplicated placement of femoral venous catheters, although unsuspected catheter tip placement in the ascending lumbar veins can occur with potentially serious consequences, especially if such placement is unrecognized [38]. Several clinical variables can alert the clinician to possible improper femoral catheter placement: (1) a guidewire that meets resistance during advancement—suspect ascending lumbar placement or thrombosis; (2) bright red blood or arterial pulsation when vessel puncture takes place—suspect arterial placement; (3) catheter tip on x-ray that points too cephalad—suspect ascending lumbar placement (Figure 5.8); (4) catheter tip on x-ray that crosses the midline from the right groin position or tip that is too cephalad from the left—suspect arterial placement (Figure 5.9). If the location of the catheter tip is in question, a dye study should be performed to confirm proper placement in the vascular bed (Figures 5.8B and 5.9B). Placing a transducer on the end of the catheter or sending blood from the catheter for blood gas determination may help distinguish arterial from venous placement.

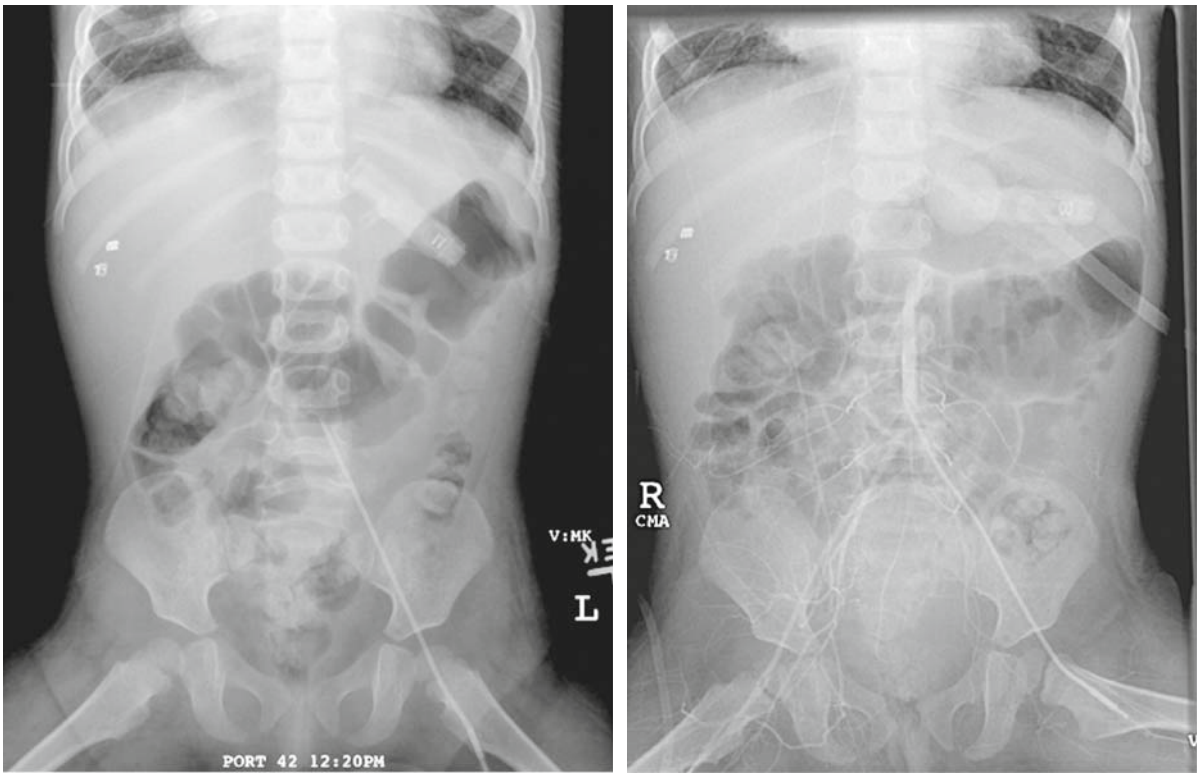
Complications and Risks

Femoral venous catheterization in children is generally regarded as safe, but, as with all CVCs, complications do occur. In a prospective study evaluating femoral vascular catheterization in children, Venkataraman et al. [6] reported that 74 of 89 (83%) femoral venous catheterizations had no complications during catheter insertion, and the other 15 (17%) had either minor bleeding or hematomas at the insertion site. During 13 of these femoral vein catheterizations, there was inadvertent puncture of the femoral artery. Overall catheterization success rate was 94.4%. Less experienced operators required significantly more attempts (2.6 ± 1.5) to attain success than experienced operators (1.5 ± 0.5). Forty-five (51%) patients were ≤1 year of age. The median duration of catheterization was 5 days, with 21% as ≤3 days' duration, 43% as 4–7 days, 26% as 7–14 days, and 10% as >14 days. Long-term complications were



A B

Figure 5.8. **(A)** Left femoral venous catheter tip pointing cephalad. **(B)** Dye confirmation of ascending lumbar catheter placement.



A B

Figure 5.9. **(A)** Left femoral catheter considered venous in patient with low blood pressure and marginal oxygenation. **(B)** Dye study (aortogram) confirming unexpected arterial placement.

uncommon. Sixty-eight patients had no long-term complications, 8 had leg swelling (all <1 year of age), and 11 patients had either suspected or confirmed catheter-related blood stream infection.

Kanter et al. [8] also examined the safety and effectiveness of femoral CVC insertion. This prospective observational study included 29 pediatric patients who underwent attempted percutaneous femoral venous catheter placement. Femoral catheterization was successful in 86% of patients attempted. Arterial puncture was the only significant complication of insertion, occurring in 14% of patients, and was not associated with adverse sequelae. The most significant complication associated with indwelling femoral CVCs was leg swelling or documented thrombosis, which occurred in 11% of 74 critically ill patients during a 4-year period of observation. Lastly, Stenzel et al. [27] prospectively reviewed complication rates over a 45-month period for percutaneously placed femoral and nonfemoral CVCs. Of the 395 catheters placed during this time period, 41% were femoral. The mean duration of catheterization was 8.9 days. No complications occurred during femoral catheter insertion. Of the 162 femoral catheters, 9 noninfectious complications occurred, which included 4 thromboses, 1 vessel perforation, 1 embolism, 1 catheter discontinuity, and 2 bleeding episodes. Stenzel et al. [27]concluded that *femoral venous catheterization offers practical advantages for central venous access over other sites. The low incidence of complications in this study suggests that the femoral vein is the preferred site in most critically ill children when central venous catheterization is indicated.*

Subclavian Vein Catheterization

Demographic and Historical Data

The infraclavicular approach to subclavian vein catheterization was originally introduced in 1952 [39]. Supraclavicular approaches to the subclavian vein have been described but have not gained wide popularity as the primary approach for subclavian vein catheterization, although complication rates between the two approaches are similar [40]. Groff and Ahmed [41] were among the first to describe their experience with subclavian vein catheterization in children. They reported on 28 patients all less than 1 year of age (20 newborns plus 8 infants less than 6 months of age). Complications included one hemothorax, one pneumothorax, and two hydrothoraces. They concluded that subclavian catheterization in children was safe.

More recently, Venkataraman et al. [42] described their experience with infraclavicular subclavian catheterization placement by nonsurgeons in 100 consecutive patients. One-third of their patients were less than 1 year of age. The overall success rate was 92%, and even under emergency conditions the success rate was 89%. Minor complications were few and included bleeding at the site, hematomas, and self-limited premature ventricular beats. There were six major complications: four pneumothoraces and two catheter-related bloodstream infections. Others have concluded that subclavian vein catheterization in children, even under emergency conditions, is safe and is associated with few major complications, especially when performed by experienced operators [43–45].

Indications

In adult patients, internal jugular and subclavian vessels are preferred sites for central venous catheterization because the rates of infection and deep venous thrombosis appear less than those found with femoral central venous catheterization; however, for children these differences are less clear [2]. Furthermore, for children, operator experience and the need for minimal sedation when placing femoral catheters are important drivers of the decision process regarding which vessel is preferred. For long-term central venous access, the subclavian vein has long been the preferred route for central venous access in children because it is easily inserted via the tunneled approach, is well tolerated, and is associated with few complications [46]. For elective or emergency percutaneous central venous access in children, the subclavian vein can be catheterized safely, as described previously; however, some specific clinical situations may further guide the decision to use this vessel. In obese or edematous patients, the clavicle can act as an easily identifiable landmark to assist in vessel cannulation, thus making the subclavian vein the preferred approach [47]. In patients with shock, the subclavian vein may be preferred because it is less likely to collapse than the internal jugular vein. The subclavian approach is not ideal for uncooperative patients (especially some nontracheally intubated children), patients with abnormal chest anatomy, patients with previous clavicular fracture, or those with bleeding diathesis [48]. In the event of unplanned subclavian artery puncture during catheterization attempts, patients with significant coagulopathy may be at greater risk because it is difficult to apply direct compression to the artery. Finally, some report that the technique for subclavian vein catheterization is not enhanced using ultrasound guidance, whereas femoral and internal jugular vein catheterization success rates and complication rates can be improved using ultrasound guidance [49,50]. Using ultrasound guidance, Gualtieri et al. [51], were able to demonstrate increased success rates for subclavian vein catheterization, especially for less experienced operators, with no reported major complications.

For cervicothoracic central vein catheterization, controversy exists regarding which vessel is preferred—internal jugular or subclavian veins. No pediatric-specific data exist that compare the rates of success and complications for these two approaches, although a recent systemic review has been published for adult patients [52]. Pooled data from 17 reports from 1982 to 1999 were analyzed, which included nearly 2,000 jugular catheters and 2,500 subclavian catheters. Despite the many potential problems routinely associated with such a large data aggregation from multiple reports, some conclusions can be derived. Arterial punctures occurred with greater frequency with the internal jugular approach; however, catheter malposition was significantly more common with subclavian vein catheterization. If rapid and correct catheter tip position is required (patient in shock requiring inotropes or hemodynamic monitoring), the jugular approach is preferred. There were no differences in the incidences of hemothorax, pneumothorax, or vessel occlusion between the two approaches. Data were too disparate to draw firm conclusions regarding comparative catheter-related infection rates. Operator success rates were not reported in this review.

Anatomy

The subclavian vein begins as a continuation of the axillary vein at the lateral border of the first rib, crosses over the first rib, and passes in front of the anterior scalene muscle (Figure 5.10). The anterior scalene muscle separates the subclavian vein from the subclavian artery. The vein continues behind the medial third of the clavicle where it is immobilized by small attachments to the rib and clavicle. At the medial border of the anterior scalene muscle and behind the sternocostoclavicular joint, the subclavian vein

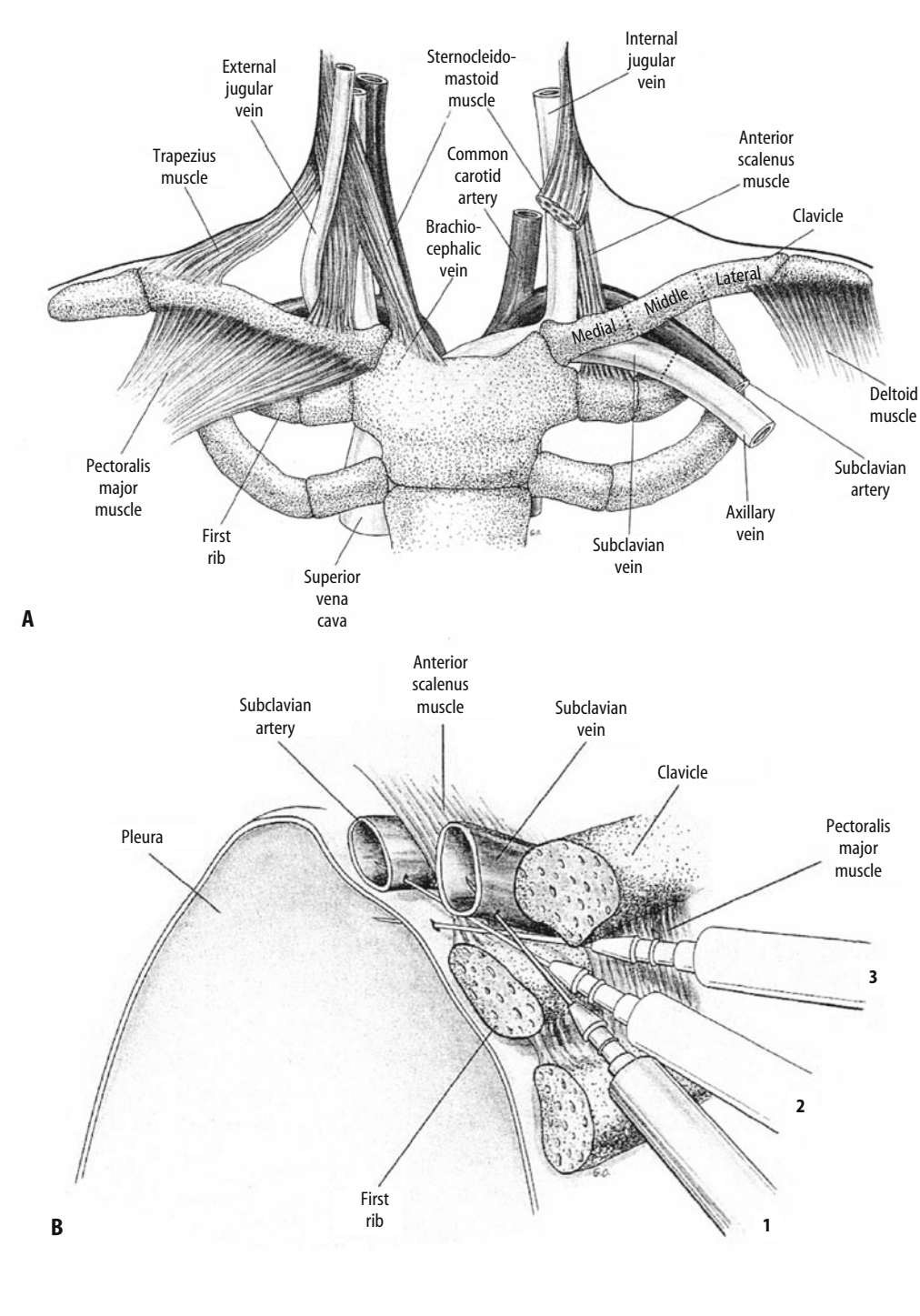
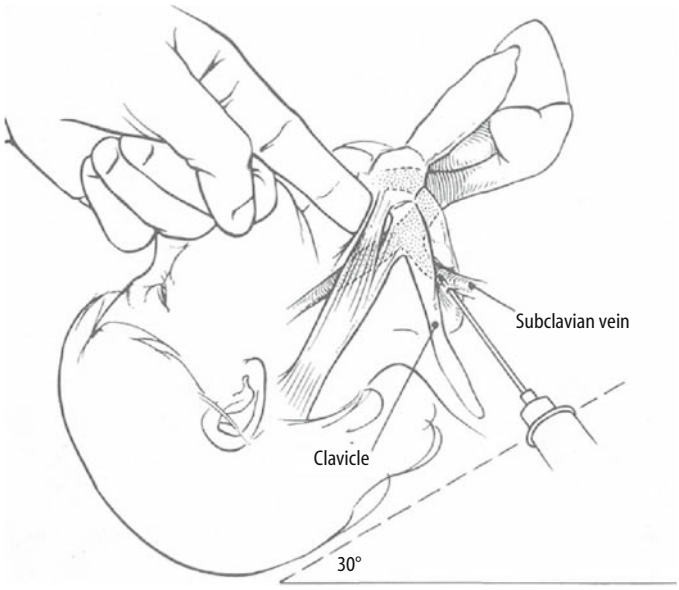


Figure 5.10. **(A)** Clavicular landmarks and vascular anatomy. **(B)** Sagittal view: course of subclavian artery and vein between boney structures and anterior scalenus muscle. (From Novak and Venus [47].) Reprinted with permission from Lippincott Williams & Wilkins.)

combines with the internal jugular to form the innominate or brachiocephalic vein.

Insertion Technique

The patient is positioned in a supine, head-down position of at least 15°–30°. A rolled towel or sandbag is placed under the shoulders longitudinally between the scapulae. Jung et al. [53] demonstrated that tilting the head toward the catheterization side appears to reduce the incidence of catheter malposition during the right infraclavicular subclavian approach in infants. The needle is introduced 1 cm below the junction of the middle and medial thirds of the clavicle (Figure 5.11). The sternal notch acts as a landmark to direct insertion of the needle. The syringe and needle should be held



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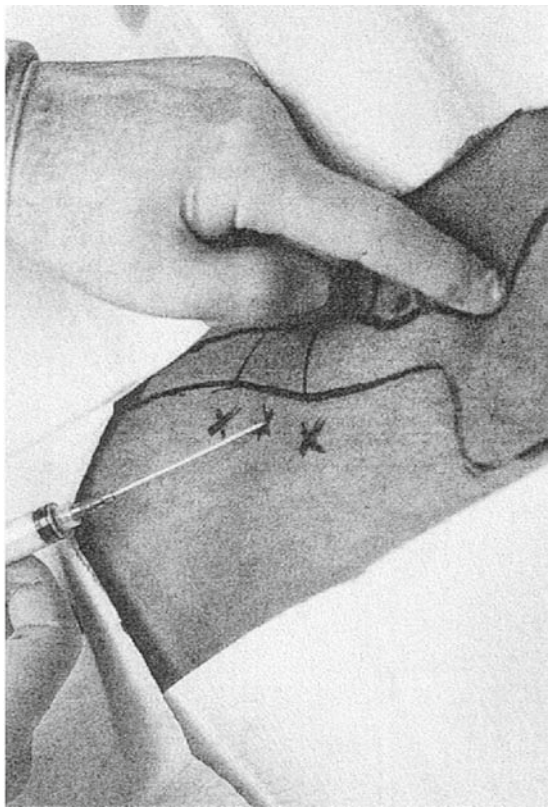


B

Figure 5.11. (A) Subclavian vein anatomy—infraclavicular approach. (From Pediatric Advanced Life Support Manual, American Heart Association. Copyright 1997. Reprinted with permission.) **(B)** Medial infraclavicular approach. (From Novak and Venus [47]. Reprinted with permission from Lippincott Williams & Wilkins.)

parallel to the frontal plane just beneath the posterior aspect of the clavicle or *marched down* the clavicle to avoid puncturing the pleura or subclavian artery. The bevel of the needle should be oriented caudally as the vein is entered to minimize catheter tip malposition. In children, especially infants, blood *flashback* into the syringe may occur during either advancement or withdrawal of the needle/syringe; therefore, it is important to withdraw the needle slowly and always with negative pressure exerted on the syringe hub. Upon entering the subclavian vein, using the Seldinger technique, a guidewire is placed through the needle to lie in the anticipated area of the superior vena cava. The catheter should be appropriately anchored to the skin and a sterile dressing placed over the site.

Proper patient position, especially in children, is an important factor that can impact successful subclavian vein catheterization. Land [54] demonstrated that when the shoulder is in neutral position the subclavian vein is overlapped by the medial third of the clavicle, thereby allowing this segment of the bone to serve as a landmark for insertion. These results were confirmed by Tan et al. [55], who demonstrated through anatomic dissection that infraclavicular subclavian venipuncture should be performed with the shoulders in a neutral position and slightly retracted. Hence the vertical placement of a small towel or sandbag between the scapulae will allow the shoulders to fall back into a proper position and facilitate vessel cannulation.

Confirmation of Placement

Significant morbidity and mortality exist with malposition of CVCs. Case reports demonstrate cardiac tamponade and perforation secondary to CVC insertion and catheter migration [56,57]. A retrospective case review of children demonstrates a mortality rate of 34% for CVC-related pericardial effusions [58]. Furthermore, the Food and Drug Administration (FDA) states that *the catheter tip should not be placed in or allowed to migrate into the heart* and recommends that CVC tips be positioned outside of the right atrium, preferably in the distal superior vena cava [1]. Andropoulos et al. [59] describe a formula for catheter insertion length that predicts positioning of the catheter tip above the right atrium 97% of the time. Their derived the formula by analyzing 452 right internal jugular and subclavian catheterizations in infants undergoing open heart surgery. The correct length of catheter insertion (cm) = (height in cm/10) − 1 for patients ≤ 100 cm in height; and (height in cm/10) − 2 for patients >100 cm in height. We have had anecdotal success in predicting proper catheter tip placement by using a *paper tape measure* to determine the distance on the chest sur-face from the proposed insertion site to the sternal–manubrium junction, which approximates the superior vena cava–right atrial junction.

After subclavian vein catheterization, confirmation of catheter tip placement is usually done by chest radiography, although controversy exists regarding the necessity for postprocedural chest radiographs following cervicothoracic CVC placement. McGee et al. [60] described the results of a prospective, randomized, multicenter trial with adults and found that, with conventional insertion techniques, the initial position of the catheter tip was in the heart in 47% of 112 catheterizations. Gladwin et al. [61] demonstrated that the incidence of axillary vein or right atrial catheter malposition from internal jugular venous catheterization was 14%. The positive predictive value of a decision rule based on a questionnaire designed to detect potential mechanical complications and malpositioned catheters was 15%. The sensitivity and specificity of the decision rule for detecting complications and malpositions was 44% and 55%, respectively. This suggests that clinical factors alone do not reliably identify malpositioned catheters. Others report that chest radiography may not be necessary to confirm proper catheter placement if (1) the procedure is performed by an experienced operator; (2) the procedure is *straightforward*; and (3) the operator

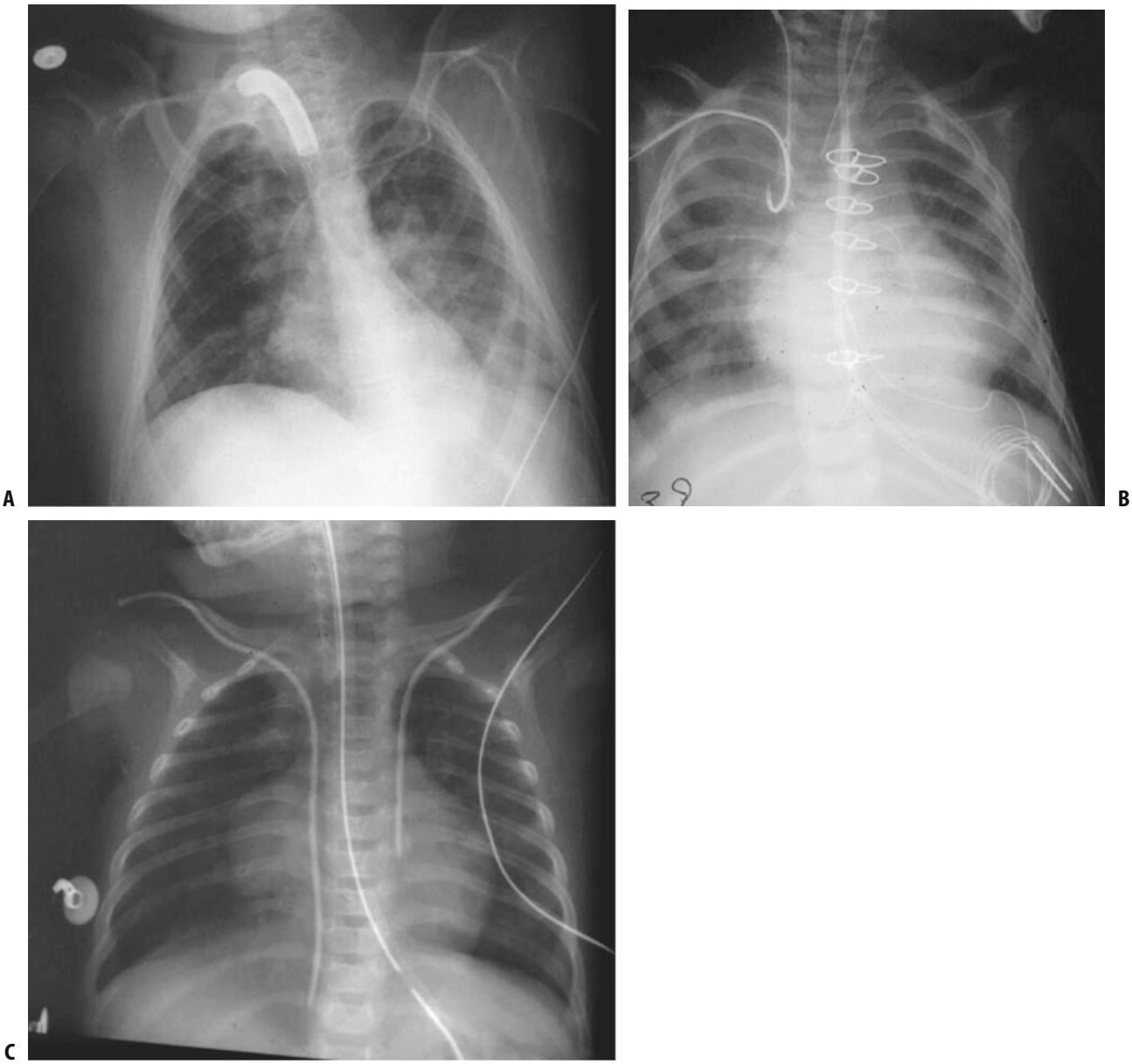


Figure 5.12. Malpositioned subclavian catheters. **(A)** Catheter tip against lateral wall of superior vena cava. **(B)** Catheter curled in superior vena cava. **(C)** Catheter through right atrium into inferior vena cava in patient with bilateral vena cava.

requires fewer than three or four needle passes to access the vessel [62–64]. In children, no current *official* data-driven recommendations exist regarding postprocedure chest radiography; however, we have observed many unexpected catheter tip placements, even in straightforward procedures, such that postprocedure chest radiography seems warranted. Figure 5.12 depicts several catheters wherein the malposition was not clinically evident and was discovered only at the time of confirmatory chest radiograph.

Complications and Risks

Reported complications from subclavian venipuncture include failure to locate the vein, puncture of the subclavian artery, catheter misplacement, pneumothorax, mediastinal hematoma, hemothorax, and injury to adjacent nerve structures. The incidences of these complications vary from 0.5% to 12% [49,52,65,66]. In general, life-threatening mechanical complications (tension pneumothorax, hemothorax) are uncommon in adults and children, occurring in <3% of catheter insertions [17,42,43,49]. In the report by Mansfield et al. [49], complications occurred in more than 25% of those patients wherein catheterization was unsuccessful. For adults, the overall failure rate of subclavian vein catheterization ranges from 10% to 19% and is primarily dependent on operator experience [67]. Controversy exists regarding the impact of ultrasound guidance on the rate of successful subclavian vein catheterization [49,51].

Internal Jugular Vein Catheterization

Demographic and Historical Data and Indications for Placement

English et al. [68] were the first to describe the safety and efficacy of internal jugular vein (IJV) catheterization in children. They reported on a series of 85 infants and children and found a 91% success rate of catheterization and few complications using the medial approach to the vein. Prince et al. [69] expanded on the IJV experience with children and reported an overall catheterization success rate of 77% and three patients with local hematomas at the site of insertion when the carotid artery was punctured. They attributed their low rate of complications to the use of a small-gauge *finder needle* to locate the vein and avoid unnecessary probing for the vein location (see Figure 5.16, later). Hall and Geefhuysen [70] described their success with two approaches (posterior and medial) to IJV catheterization in children. Successful catheterization occurred in >90% of attempts, and multiple attempts did not increase complication rates. The only complications were three arterial punctures. In this series, the IJV approach was used successfully in 20 patients who required resuscitation.

Internal jugular vein catheterization is associated with a high rate of successful catheter placement. Nonemergent catheterizations are successful in more than 90% of patients. Use of the IJV for emergency catheterization during cardiopulmonary resuscitation is more difficult primarily because management of the airway, including tracheal intubation and bag ventilation, make access to the neck less available and identification of surface landmarks for catheter insertion more difficult to assess. Internal jugular vein cannulation is often considered when other central vascular approaches are less desirable, such as in the presence of coagulation abnormalities or chest trauma. The low incidence of pneumothorax makes the IJV preferable in patients with significant pulmonary disease and lung hyperinflation (pleural dome elevated in the thorax), such as patients receiving high levels of positive pressure mechanical ventilatory support to treat respiratory failure. In addition, for patients with significant coagulation dysfunction, the IJV is favored because local compression of the vein or carotid artery is possible, whereas this is not an option with subclavian vein catheterization. The right IJV is also an optimal insertion site during emergency transvenous pacing, because it facilitates passage of the pacemaker through the tricuspid valve. In addition, the right IJV may be preferred because of the position of the pleural dome, the absence of the thoracic, and the less acute angle at the junction of the IJV and innominate vein [47]. Cervical trauma with swelling or anatomic distortion at the insertion site may make IJV catheterization difficult or relatively contraindicated [71]. In adults, significant carotid artery disease is a relative contraindication to IJV catheterization.

Anatomy

The IJV emerges from the base of the skull through the jugular foramen and enters the carotid sheath anterior and lateral to the carotid artery (Figure 5.13). The IJV usually runs beneath the triangle formed by the sternal and clavicular heads of the sternocleidomastoid muscle (SCM) as it approaches the underside of the clavicle. The caliber of the IJV increases as it approaches the clavicle. The vein is closer to the skin surface at the level of the clavicle as well. Beneath the clavicle the right IJV joins the subclavian vein to form the innominate vein, which continues in a straight path to the superior vena cava. The left IJV joins the left subclavian vein at nearly a right angle; consequently, any catheter inserted into the left IJV must negotiate this turn [72] (see Figure 5.19D, later). The carotid artery usually lies medial and posterior to the IJV in the carotid sheath. The stellate ganglion and the cervical sympathetic trunk lie medial and posterior to the IJV. Near the junction of the IJV and the subclavian vein is the pleural dome, with the left pleural

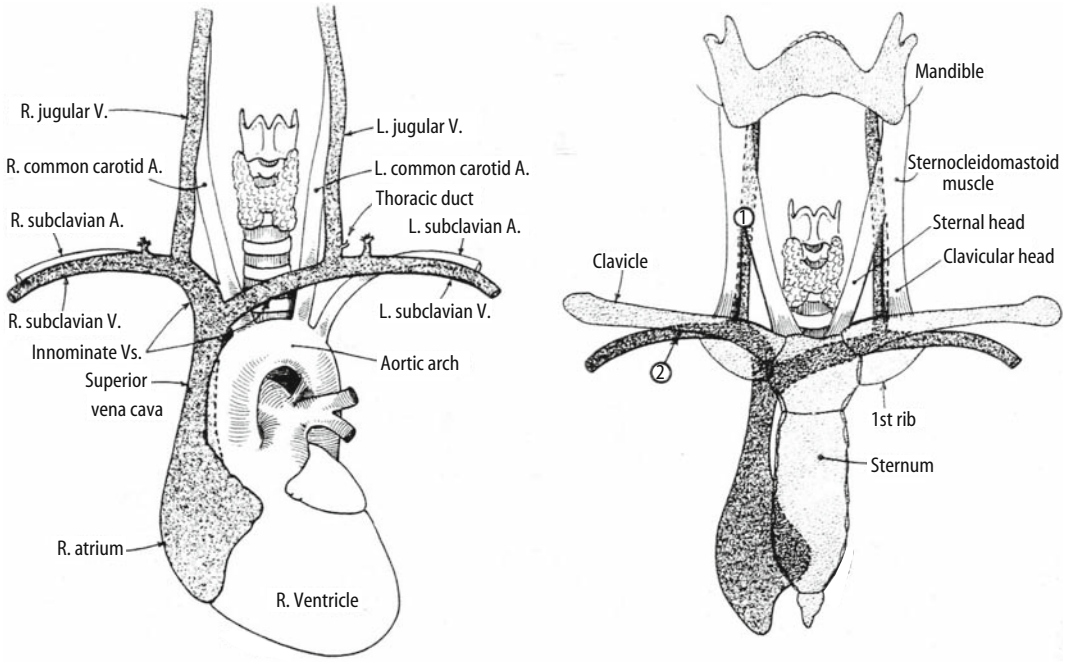


Figure 5.13. Internal jugular vein related structures and surface anatomy. (From Todres D, Cote C. Procedures. In: Cote C, Ryan J, Todres D, Goudsouzian N, eds. A Practice of Anesthesia for Infants and Children, 2nd ed. Philadelphia: WB Saunders; 1993:508. Copyright 1993 with permission from Elsevier.)

dome slightly more cephalad than the right. The lymphatic duct is adjacent to the junction of the left IJV and innominate vein.

Anatomic variation of the IJV is common, and clinical maneuvers can significantly affect vessel dynamics (vessel caliber). These variations can have an important impact on success rates for IJV catheterization. Using ultrasound, Mallory et al. [73] determined that palpation of the carotid artery decreases the IJV lumen cross-sectional area. They suggest that when attempting IJV cannulation, a mental note should be made regarding the position of the carotid artery; however, the artery should not be palpated during actual needle/syringe insertion. Maneuvers that increase the cross-sectional area and internal diameter of the IJV include (1) a Trendelenburg position with a 15°–30° of head-down tilt; (2) the valsalva maneuver; and (3) retracting the skin over the vein in a direction opposite to the direction of the advancing needle. In addition, clinical conditions that increase right atrial pressures also increase the vessel lumen cross-sectional area. Another report locating the position of the IJV by ultrasound demonstrated, in adults, that in 3% of patients studied the IJV lumen did not increase in response to a valsalva maneuver, in 1% the IJV lumen was >1 cm lateral to the carotid artery, in 2% the IJV was positioned medially over the carotid artery, and in 5% the IJV was positioned outside the area that is predicted by surface landmarks [74].

Insertion Technique

The patient is placed in the Trendelenburg position (unless contraindicated, such as with elevated intracranial pressure) with the head down 15°–30°. For the medial approach (Figure 5.14) the two bellies of the SCM should be palpated by placing the index finger in the triangle created by the clavicle and the sternal and clavicular bellies of the SCM. The skin is retracted cephalad to the insertion site before inserting the needle into the skin. This may increase the vessel lumen cross-sectional area. During actual venipuncture, avoid trying to retract the carotid artery medially and away from the IJV as this is likely to decrease the IJV lumen diameter. For the medial approach, the approximate insertion site is approximately one half the distance along a line from the sternal notch to the mastoid prominence. The needle/syringe is inserted at an angle about 20°–30° above the plane of the skin and is advanced while applying slight negative pressure on the syringe. Venous flashback indicating venipuncture may occur during needle advancement or withdrawal; therefore, if unsuccessful during advancement, then the needle should be withdrawn slowly. The needle should be completely removed from the skin before redirecting to avoid vessel laceration. This is particularly important for small infants. Before attempting to place the guidewire (Seldinger technique), it is important to demonstrate free flow of *blue* blood into the syringe. Attempts at placing the guidewire should not be attempted if blood cannot be easily withdrawn, if the blood in the syringe is pulsating, or if the blood is obviously *red*. The syringe is gently twisted off the needle hub, maintaining the needle in the same position and always occluding the needle hub with the finger to prevent air aspiration.

The guidewire should be advanced without meeting any resistance. Resistance to wire advancement usually means that the lumen of the needle is now outside the vessel. In this case, the wire can be removed and needle position slightly adjusted. If in trying to remove the wire resistance is encountered, this can mean that the wire is bent near the needle bevel. In this case, the wire and needle should be removed together. This reduces the risk of shearing the end off the wire. Once the guidewire is successfully advanced, the needle can be removed while holding the guidewire

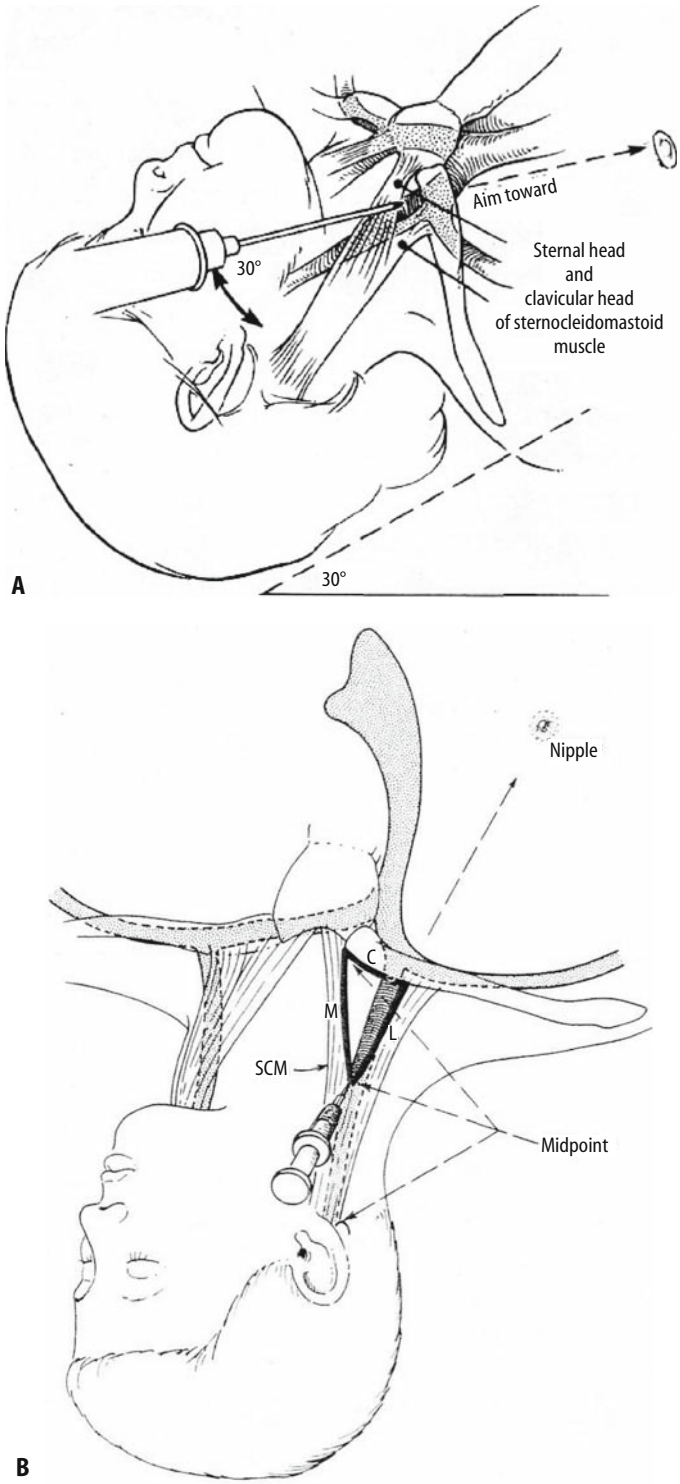


Figure 5.14. Internal jugular vein anatomy. **(A)** Medial approach. (From Pediatric Advanced Life Support Manual, American Heart Association. Copyright 1997. Reprinted with permission.) **(B)** Medial approach with triangle between bellies of sternocleidomastoid muscle. (From Todres D, Cote C. Procedures. In: Cote C, Ryan J, Todres D, Goudsouzian N, eds. A Practice of Anesthesia for Infants and Children, 2nd ed. Philadelphia: WB Saunders; 1993:508. Copyright 1993 with permission from Elsevier.)

in place. The guidewire should not be advanced to its full length, as cardiac arrhythmias may occur. A small 0.25 to 0.50 cm skin incision is made at the site of entry of the guidewire into the skin, making certain that the bevel of the scalpel blade is away from the

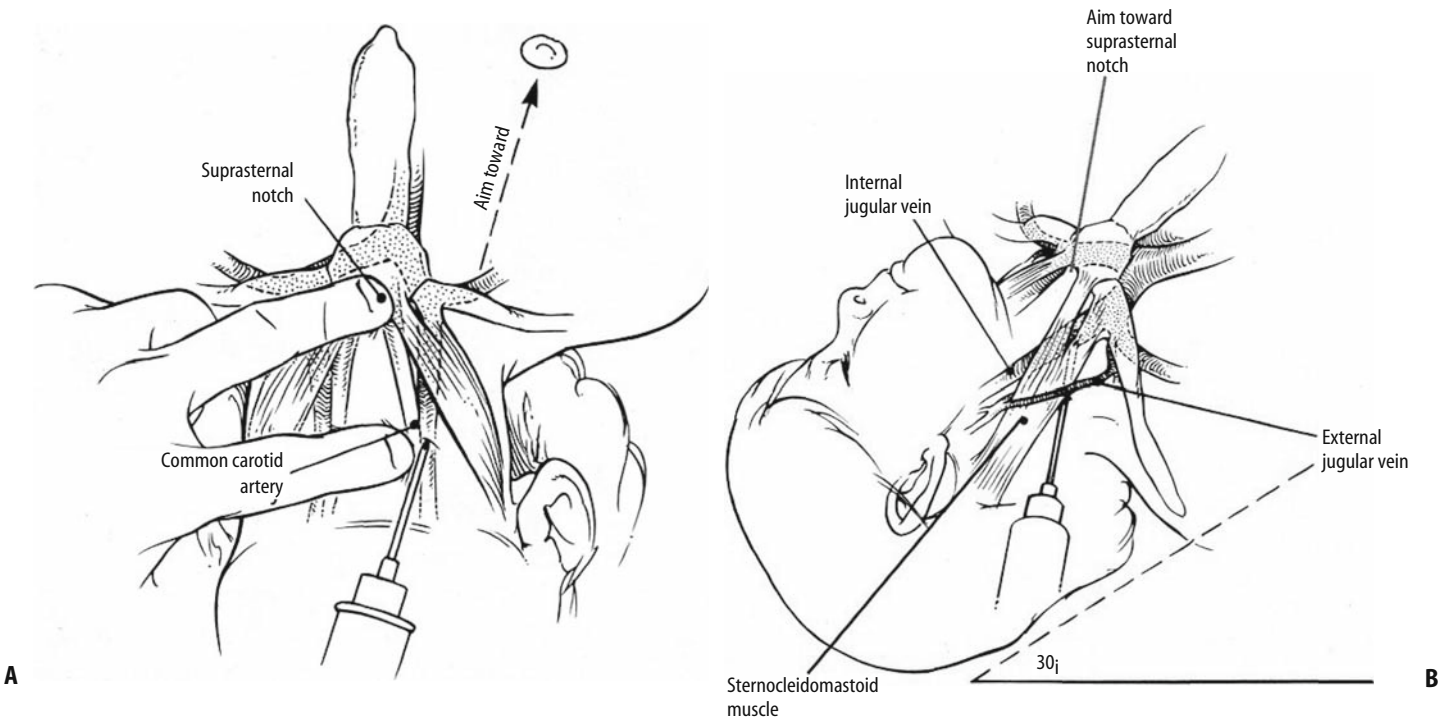


Figure 5.15. Alternative approaches to internal jugular vein catheterization. **(A)** Anterior. **(B)** Posterior. (From Pediatric Advanced Life Support Manual, American Heart Association. Copyright 1997. Reprinted with permssion.)

guidewire. The dilator is held near its tip and advanced over the guidewire into the IJV. The dilator should not be fully advanced, as its purpose is to dilate the subcutaneous tissue and make a hole in the vessel. Holding the guidewire in place, the dilator is removed while applying light pressure to the site. The catheter is then placed over the guidewire and inserted into the IJV. Once the catheter is inserted, the guidewire is removed and blood is aspirated through the catheter to ascertain placement and patency of the catheter. The catheter is secured in place using silk suture.

Posterior and anterior approaches to the IJV can also be used. These have similar success rates for cannulation, and, because the insertion sites are higher (more cephalad) in the neck, these approaches may carry lower risk of pneumothorax. Figures 5.14 and 5.15 depict all three approaches. Some have suggested that using a *finder needle* to locate the IJV reduces the incidence of carotid artery puncture. Furthermore, if inadvertent arterial puncture occurs, the smaller bore *finder needle* will cause less damage to the arterial wall and will reduce the sequelae that might occur from carotid artery hematoma. Figure 5.16 demonstrates first finding the IJV with a small-bore needle and then advancing the larger bore needle along the same trajectory as the *finder needle*. Alternatively, the finder needle can be removed and the large-bore introducer needle advanced in the same plane as the initial finder needle. This technique may be most useful for obese patients with poor surface landmarks or patients with coagulopathy wherein puncture of the artery may be more problematic than usual.

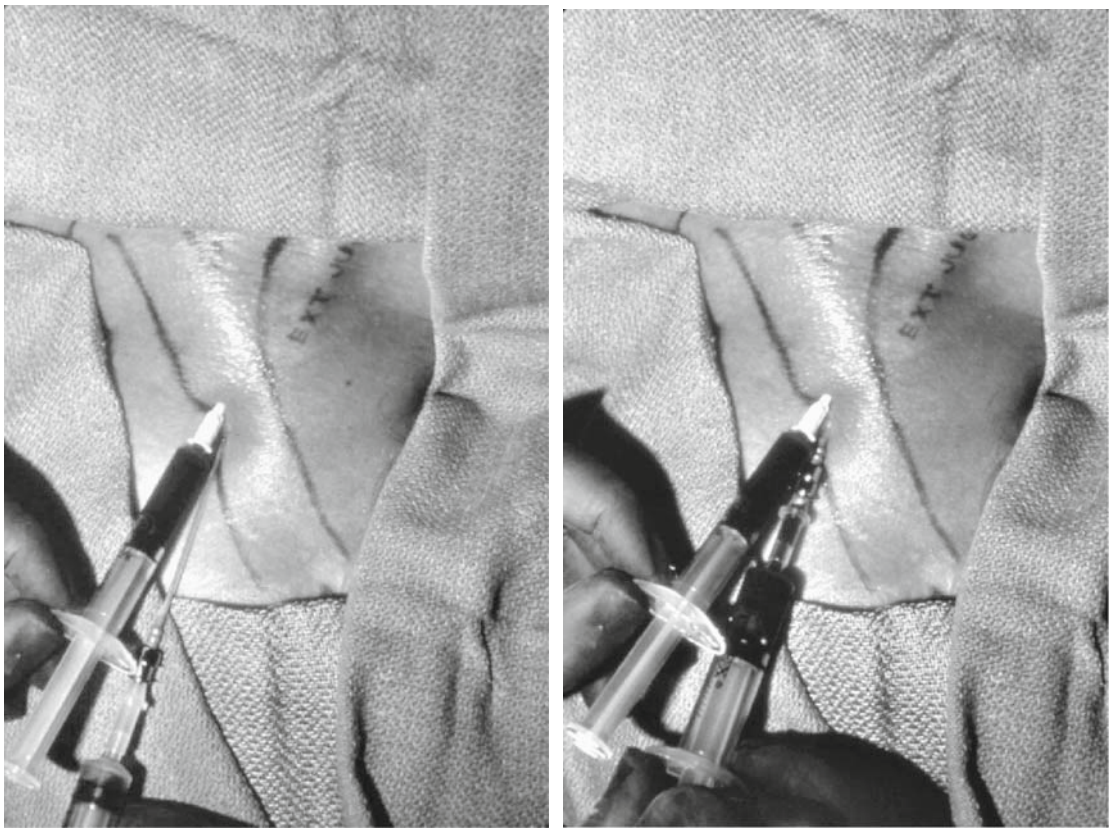
Confirmation of Placement

Optimal location of the IJV is in the superior vena cava proximal to the right atrium. Chest radiography is commonly used to confirm the position of the CVC tip. Clinical controversy regarding the need for postprocedure chest radiography is similar to that described for subclavian vein catheterization. As reported previously, Gladwin et al. [61] found that 14% of IJV catheter tips were malpositioned in a series of 107 consecutive adult patients. Given the risk of unrecognized catheter malposition, which because of small patient size may be greater in children than adults, postprocedure chest radiography is warranted even for patients who are clinically unchanged postprocedure.

Complications and Risks

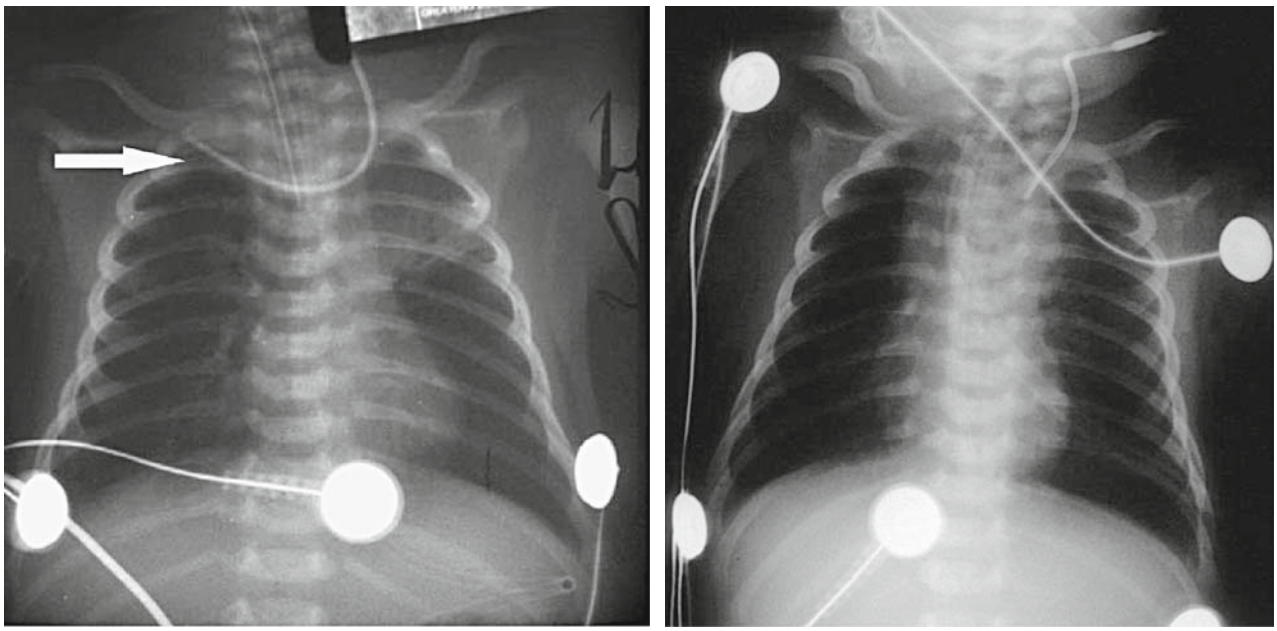
Other than complications related to catheter maintenance (infections and thrombosis), complications related to catheter insertion are uncommon. Arterial puncture is the most common complication and is usually easily resolved with direct pressure to the punctured vessel. Nicolson et al. [75] and Jobes et al. [76] reported an 8% incidence of arterial puncture but minimal sequelae from the arterial puncture because they used the finder needle technique to avoid puncturing the artery with the large-bore needle that is needed to pass the guidewire. Arterial puncture is significantly more common with IJV catheterization than with subclavian vein catheterization, with a reported incidence of 2%–11% in adults [52,72,77]. Pneumothorax and hemothorax are rare complications, with an average incidence of 0% to 0.2% [25,75,78,79].

Catheter tip malposition is a frequent complication of all CVCs, and IJV catheters are no exception. As previously described, dysrhythmias, pericardial tamponade, and mediastinal effusions have been reported when stiff plastic catheters erode through thin vessel walls [58,80,81]. Figure 5.17 depicts several IJV catheter malpositions in children. Figure 5.17B shows a short left IJV catheter with its tip at the IJV–innominate junction. Subsequent chest radiograph reveals a widened mediastinum filled with lipid as a result of vessel erosion by the catheter and extravasation of parenterally administered lipid into the mediastinum (Figure 5.17C). Figures 5.18 and 5.19 depict both correctly positioned and malpositioned



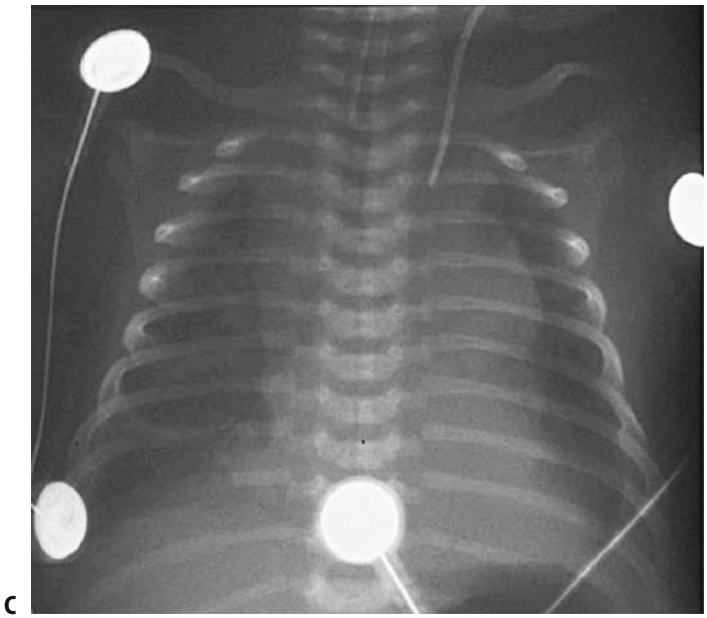
A **B**

Figure 5.16. Finder needle technique for internal jugular vein catheterization, anterior approach. See text for discussion. **(A)** Advancing large bone needle with finder needle in place. **(B)** Successful entry of IJV with large bone needle.



A **B**

Figure 5.17. **(A)** Left internal jugular vein catheter malposition in right subclavian vein. No recognized complications. **(B)** Left internal jugular vein malpositioned in innominate vein. **(C)** Catheter erodes through vessel wall—widened mediastinum with lipid extravasation.



C

Figure 5.17. *Continued*

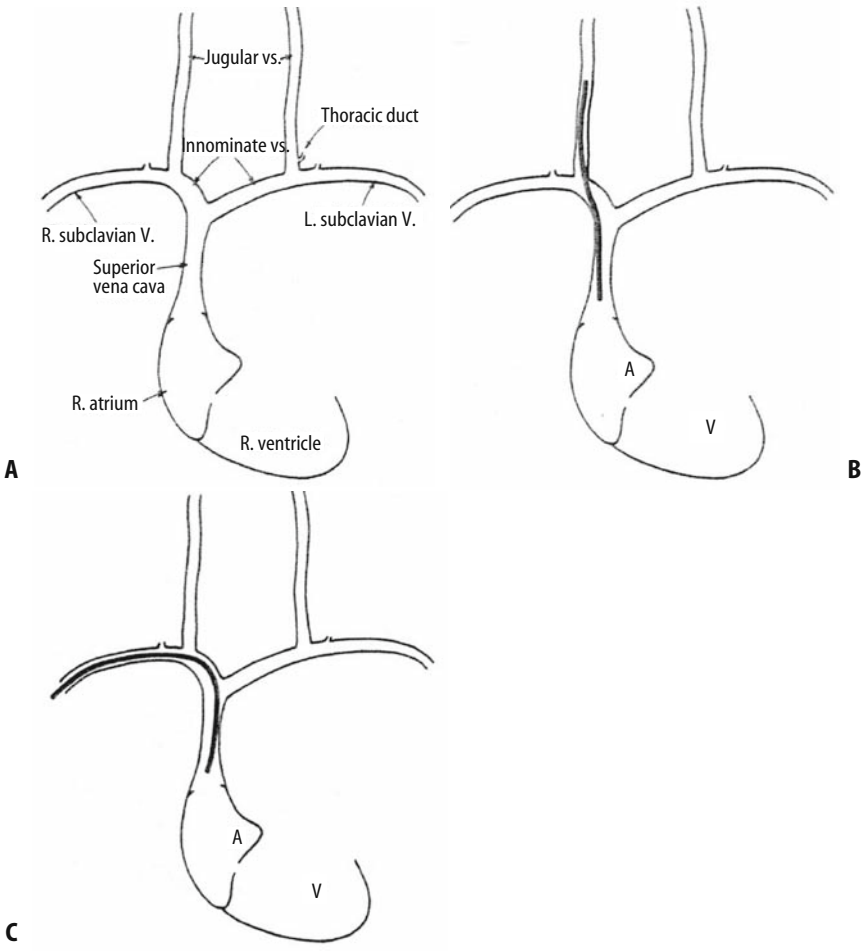


Figure 5.18. Cervicothoracic catheter placement—proper catheter tip positions. A, atrium; V, ventricle. **(A)** Normal vascular anatomy. **(B)** Right internal jugular vein. **(C)** Right subclavian vein. (From Todres D, Cote C. Procedures. In: Cote C, Ryan J, Todres D, Goudsouzian N, eds. A Practice of Anesthesia for Infants and Children, 2nd ed. Philadelphia: WB Saunders; 1993:510–511. Copyright 1993 with permission from Elsevier.)

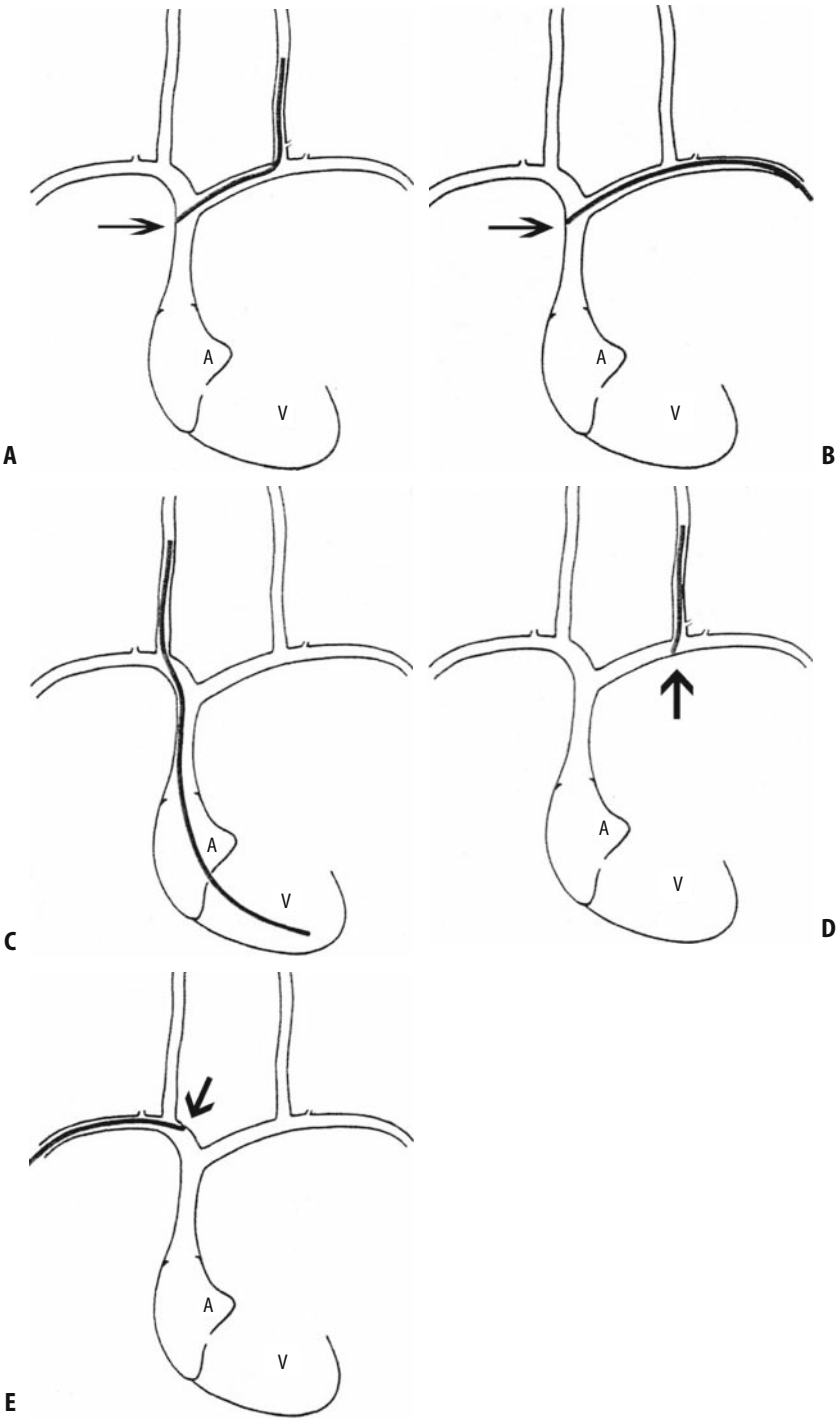


FIGURE 5.19. Cervicothoracic catheter placement—catheter tip malpositions. A, atrium; V, ventricle. **(A,B)** Catheter tips striking lateral wall of superior vena cava—vessel erosion risk. **(C)** Ventricular placement. **(D)** Short left internal jugular vein catheter striking innominate vein wall—vessel erosion risk. **(E)** Short right subclavian catheter striking lateral wall of innominate vein—vessel erosion risk. (From Todres D, Cote C. Procedures. In: Cote C, Ryan J, Todres D, Goudsouzian N, eds. A Practice of Anesthesia for Infants and Children, 2nd ed. Philadelphia: WB Saunders; 1993:510–511. Copyright 1993 with permssion from Elsevier.)

cervicothoracic catheters. Malpositioned catheters are at high risk for vessel erosion.

Axillary Vein Catheterization

Demographic and Historical Data and Indications for Use

The axillary vein is an alternative, and less commonly discussed, access site for central venous catheterization in children. A percutaneous approach to axillary vein catheterization was first described in 1981, and a modified technique was further described in very-low-birth-weight infants [82,83]. These reports demonstrated a high success rate for cannulation with minimal complication rates. The report of Oriot and Defawe [83] included axillary vein catheterization in 226 neonates with only 9 failures. In a few patients, nonpersisting extrasystoles occurred during catheter insertion but disappeared with correct positioning of the catheter. No intrathoracic complications were noted. Metz et al. [84] reported on a cohort of 47 critically ill children (ages 14 days to 9 years) who underwent 52 separate attempts at axillary vein catheterization. Their reported success rate for cannulation was 79%. The most common reasons

the axillary vein was used included (1) poor alternative access sites; (2) need for hyperalimentation; (3) need for central venous pressure monitoring; and (4) preservation of femoral vessels for cardiac catheterization. Martin et al. [85] reported their experience with single-lumen axillary catheters placed in 60 adults in a surgical intensive care unit. Insertion complications were infrequent, and deep venous upper extremity thrombosis occurred in 11% of the patients. They concluded that because the thrombosis rates were similar between axillary vein and cervicothoracic catheters, the axillary vein offered an attractive alternative when other sites were unavailable.

Anatomy

The axillary vein begins at the junction of the basilic and brachial veins running medial, anterior, and caudal to the axillary artery. In the chest at the lateral border of the first rib it becomes the subclavian vein. The artery and vein lie within the axillary fascia, and the brachial plexus runs between the artery and vein (Figure 5.20).

Insertion Technique

Catheter insertion is accomplished with the child placed in the Trendelenburg position, if not contraindicated, and the arm abducted between 100° and 130°. The position of the axillary artery is determined by palpation while retracting the redundant axillary skin with the opposite hand. The vein is punctured parallel and inferior to the artery, as described by Gouin et al. [86]. A 22-gauge short Teflon catheter can be used to cannulate the vein as if inserting a peripheral venous catheter. Alternatively, a thin-walled needle appropriate for the CVC can be used to obtain venous flashback. The needle/syringe should be inserted using negative pressure on the syringe hub. Once venous blood is obtained, the syringe is carefully disconnected from the needle and the guidewire inserted as per standard Seldinger technique. The axillary vein in children is very mobile in the axillary soft tissue, and the greatest challenge to cannulation is fixing the vein in position so that the needle can enter the vessel. Firm traction of the redundant skin can help with this issue.

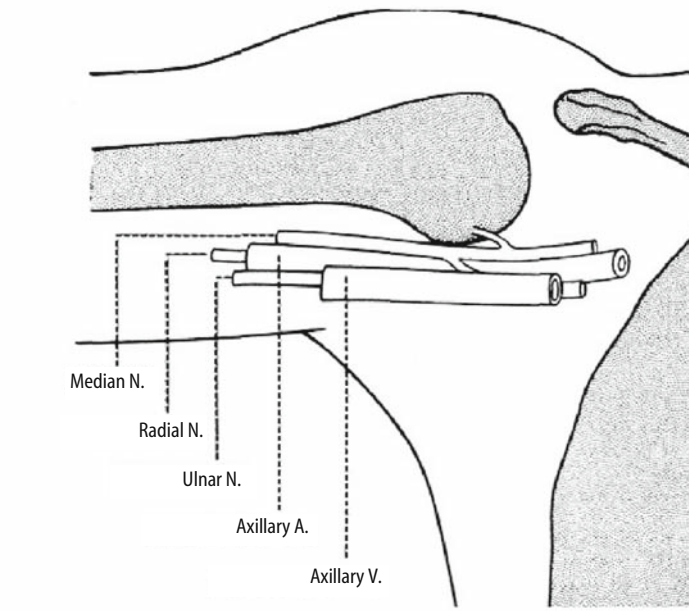


Figure 5.20. Axillary vein anatomy. (From Metz et al. [84]. Copyright 1990 with permission from the American Academy of Pediatrics.)

Complications and Risks

Complications associated with axillary vein insertion include failed cannulation, catheter malposition, arterial puncture, transient paresthesia, pneumothorax, and axillary hematoma [87,88]. The frequency of complications reported by Metz et al. [84] in a pediatric cohort is low, with complications of insertion occurring in 3.8%—one pneumothorax and one hematoma. Four additional complications occurred while the catheter was in place, and these included venous stasis of the arm, venous thrombosis of the subclavian vein proximal to the catheter tip, parenteral nutrition infiltration secondary to catheter dislodgment, and one catheter-related infection. The axillary vein route has a lower rate of successful cannulation and results in higher incidences of catheter malposition and arterial puncture than IJV catheterization, although the IJV route had a greater risk of pneumothorax [88]. Axillary vein catheter insertion success was 84%, which is lower than with IJV catheterization. Martin et al. [88] concluded that this rate of success was acceptable when other sites are less unavailable.

Ultrasound Guidance of Central Vein Catheterization—the New Standard?

Traditionally percutaneous insertions of CVCs have been performed by utilizing anatomic surface landmarks. Recently, bedside Doppler ultrasound has been used to facilitate visualization of veins. This technology has been shown, in some settings, to increase catheter placement success rates, especially for novice operators, and reduce complications. The use of Doppler ultrasound to assist with catheter placement was first reported in 1984 [89]. Gualtieri et al. [51] demonstrated in a prospective, randomized study that subclavian vein catheterization was successful in 23 of 25 (92%) attempts using ultrasound guidance compared with 12 of 27 (44%) using conventional landmark techniques. In a meta-analysis of eight published, randomized trials, Randolph et al. [90] concluded that ultrasound guidance significantly decreases the relative risk of catheter placement failure for cervicothoracic vessel catheterizations, decreases the incidence of catheter insertion complications, and reduces the need for multiple insertion attempts when compared with standard landmark-driven insertion techniques. Additionally, in the hands of less experienced operators, ultrasound guidance improves the success rate of subclavian venous catheterization. In high-risk patients with obesity or coagulopathy, the use of Doppler ultrasound was associated with increased success of cannulation and a decreased frequency of significant complications [91].

The advantages associated with ultrasound-guided CVC placement include detection of anatomic variations and exact vessel location, avoidance of central veins with preexisting thrombosis that may prevent successful CVC placement, and guidance of both guidewire and catheter placement after initial needle insertion The greatest benefit for use of ultrasound guidance may occur for the inexperienced operator and for all operators in high-risk clinical situations. The results from randomized controlled clinical trial

with adults, comparing success rates for catheterization and complication rates, were so compelling in favor of real-time ultrasound-guided placement of percutaneous CVCs that some have called ultrasound guidance the *new standard of care* [36,92].

Complications Associated with Central Venous Catheter Placement

Central venous catheters are associated with numerous complications, some minor and others life-threatening. These complications are primarily related to mechanical complications at the time of catheter insertion or complications that occur during maintenance of the catheter. Catheter-related bloodstream infections and catheter-related thrombosis are major complications that occur during catheter maintenance. They are the subject of excellent recent reviews and are topics of other chapters in this text [93,94] and therefore are only briefly mentioned here. Furthermore, mechanical complications associated with insertion were discussed earlier as they relate to each type of catheterization, and the reader is referred to those sections.

A retrospective review of over 1,400 CVCs placed in children demonstrated that age, sex, type of catheter, primary disease, indication for placement, level of physician training, and operator experience were not associated with increased complication risks [22]. Conversely, in a study by Sznajder et al. [67], the complication rate for inexperienced physicians was double the rate for more experienced physicians when performing CVC insertion.

Pneumothorax

In children, pneumothorax is reported as a complication in 1%–2% of CVC insertions placed by surgical staff surgical and in 4% of patients when performed by nonsurgical staff [10,22,95]. More recent data indicate that a pneumothorax occurred in only 2 of 156 patients (1.2%) who underwent CVC placement by pediatricians skilled in emergency procedures [96].

Arterial Puncture

With the classic Seldinger technique, arterial puncture occurs during CVC insertion in 1.5%–15% [8,9,22,44,96,97]. Merrer et al. [17] demonstrated that catheter insertion during the night was significantly associated with the occurrence of mechanical complications, including arterial puncture.

Catheter Malposition—Femoral Catheters

It is important to determine catheter placement because malposition of CVCs can result in both morbidity and mortality [38,98]. Malposition of femoral catheters in the ascending lumbar vein is an infrequent complication but if left in place can result in tetraplegia. Zenker et al. [38] reviewed contrast radiographs taken immediately after insertion of 44 transfemoral catheters in a neonatal ICU. Malposition of catheters in the left ascending lumbar vein was detected in two newborns. Paravertebral malposition has been previously reported in neonates [99–101]. These reports demonstrate that catheter position was initially misinterpreted or assessed inadequately until the onset of complications. In newborns, the vertebrolumbar and azygous systems represent an extensive, highly variable, intercommunicating network in which alterations in pressure and flow direction may occur. The large capacity of the lumbar veins and the vertebral plexus can compensate for occlusion of the inferior vena cava. Use of catheters misplaced in this posterior system can give rise to retroperitoneal, peritoneal, or spinal epidural fluid extravasation [101,103,104].

Ultrasonography, lateral radiography, or venogram is required when the location of the catheter tip is in question. Catheters in the ascending lumbar vein or vertebral plexus should be removed immediately. Warning signs that may indicate catheter malposition include (1) loss of blood return on aspiration; (2) subtle lateral deviation, or *hump*, of the catheter at the level of L4 or L5 on frontal abdominal radiographs in catheters placed from the left side (see Figure 5.8); (3) a catheter path directly overlying the vertebral column rather than the expected path to the right of midline for a catheter in the inferior vena cava; and (4) resistance to guidewire advancement during insertion [98]. A lateral abdominal radiograph may confirm the posterior position of the catheter; however, we have found that a venogram (injecting dye directly into the catheter; see Figure 5.8) is the best method to confirm proper placement of these catheters.

Catheter Malposition and Postprocedure Chest Radiographs—Cervicothoracic Catheters

As noted previously, Figure 5.19 depicts cervicothoracic catheter malpositions that are potentially hazardous. Three recent reports describing experiences with adult patients conclude that a postprocedure chest radiograph is unnecessary for the asymptomatic patient after IJV catheterization when using fluoroscopy or ultrasound during catheter placement [105–107]. Similar recommendations are made for the subclavian vein approach. A study with adults focusing on the subclavian vein catheterization concluded that postprocedure chest radiograph has minimal benefit and is not necessary unless the patient shows sign of clinical deterioration postprocedure [108]. Others have advocated that a postprocedure chest x-ray may be omitted in cases after line placement when experienced clinicians use good technique and good clinical judgment [63,108].

For pediatric patients, few data-driven recommendations are available; however, Janik et al. [109] report that routine chest x-ray is not indicated after uneventful CVC insertion when monitored with concurrent fluoroscopy. These recommendations were based on a low rate of complications of 1.6%. In addition, all children who had pulmonary complications displayed signs and symptoms suggestive of impaired respiratory function. This recommendation may not be relevant to the pediatric ICU setting, where catheters are rarely placed with fluoroscopic guidance. In the ICU, we recommend chest radiography after all percutaneously placed cervicothoracic CVCs, regardless of postprocedure clinical status.

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6
Shock: An Overview

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Historical Perspective

Shock is one of the most frequently diagnosed, yet poorly understood disorders in the pediatric intensive care unit (PICU). The very definition of what constellation of physical signs and symptoms comprise *shock* remains controversial in part because of the vast array of disorders that cause shock in critically ill and injured children (Table 6.1). Webster's Dictionary defines shock as "any sudden disturbance or agitation of the mind or emotions" [1]. Similarly, shock in medical parlance could be defined as *a sudden disturbance or agitation of the body's normal homeostasis*. Obtaining a more accurate, scientific definition of the clinical state known as *shock* has become increasingly difficult with the recognition of the complexity of the biochemical and molecular perturbations of the shock state.

Although Hippocrates was perhaps the first to describe the constellation of signs and symptoms of shock, the French surgeon Henri Francois Le Dran is widely credited with the first use of the medical term *shock* (literally translated from the French verb *choquer*) in 1737 in his textbook *A Treatise, or Reflections Drawn from Experience with Gun-Shot Wounds* [2]. Le Dran had used the term to describe *a sudden impact or jolt*, and, by happenstance, a mistranslation by the English physician Clare in 1743 introduced the term into the English language to describe the sudden deterioration of a patient's condition following major trauma [3]. The term was further popularized by the English physician Edwin A. Morris, who used it in his 1867 book *A Practical Treatise on Shock After Operations and Injuries* [4]. In 1872, Samuel Gross called shock "the rude unhinging of the machinery of life" [5]. In 1895, John Warren called shock "a momentary pause in the act of death" [6]. In 1940, Blalock defined shock as "a peripheral circulatory failure, resulting from a discrepancy in the size of the vascular bed and the volume of the intravascular fluid" [7]. Finally, the famed physiologist Carl Wiggers [8] offered the following definition in 1942: "Shock is a syndrome resulting from a depression of many functions but in which reduction of the effective circulating blood volume is of basic importance and in which impairment of the circulation steadily progresses until it eventuates into a state of irreversible circulatory failure."

Although all of these descriptions are appropriate, shock is now commonly defined as a clinical state characterized by an inadequate delivery of oxygen and metabolic substrates to meet the metabolic demands of the cells and tissues of the body. We now recognize Gross' *machinery of life* as the mechanisms that ensure adequate oxygen delivery and utilization at the cellular level. Inadequate oxygen delivery results in cellular hypoxia, anaerobic metabolism and resultant lactic acidosis, activation of the host inflammatory response, and eventual vital organ dysfunction.

Shock is a clinical diagnosis and is characterized by hypoperfusion of several organ systems. The initial diagnosis is often based on the clinical presence of decreased urine output, mottled skin, and altered levels of consciousness. Shock may occur with a decreased, normal, or even increased cardiac output as well as a decreased, normal, or increased blood pressure [9,10]. Just as important, shock may occur in the scenario of globally decreased tissue perfusion, as is the case with profound hypotension, or decreased regional tissue perfusion.

Hypovolemic shock, the most common cause of shock in children [9], has been described in the medical literature for over 150 years. For example, a pandemic of cholera claimed more than 23,000 lives in England during 1831 [11]. The accepted treatment at that time was blood-letting, which not surprisingly often failed. A 22-year-old medical graduate of Edinburgh University named William O'Shaughnessy was the first to note that the blood from patients suffering from cholera had "lost a large portion of its water" and later suggested a novel treatment by returning the blood to its "natural specific gravity" by replacing its "deficient saline." O'Shaughnessy sent a letter to the *Lancet* [12] that included the following description of terminal cholera:

> On the floor, before the fireplace . . . lay a girl of slender make and juvenile height; with the face of a superannuated hag. She uttered no moan, gave expression of no pain. . . . The colour of her countenance was that of lead—a silver blue, ghastly tint; her eyes were sunk deep into the sockets, as though they had been driven in an inch behind their natural position; her mouth was squared; her features flattened; her eyelids black; her fingers shrunk, bent, and inky in their hue. All pulse was gone at the wrist,

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Table 6.1. Common causes of shock in children.

Hypovolemic shock
Fluid and electrolyte losses
Vomiting
Diarrhea
Nasogastric tube drainage
Renal losses (via excessive urinary output)
Diuretic administration
Diabetes mellitus
Diabetes insipidus
Adrenal insufficiency
Fever
Heat stroke
Excessive sweating
Water deprivation
Sepsis
Burns
Pancreatitis
Small bowel obstruction
Hemorrhage
Trauma
Fractures
Spleen laceration
Liver laceration
Major vessel injury
Intracranial bleeding (especially neonates)
Gastrointestinal bleeding
Surgery
Cardiogenic shock
Myocarditis
Cardiomyopathy
Myocardial ischemia (e.g., Kawasaki's disease, anomalous origin of the left coronary artery)
Ventricular outflow tract obstruction
Acute dysrhythmias
Post cardiopulmonary bypass
Obstructive shock
Tension pneumothorax
Cardiac tamponade
Pulmonary embolism
Distributive shock
Sepsis
Anaphylaxis
Neurogenic shock

Source: Modified from Thomas and Carcillo [13].

and a tenacious sweat moistened her bosom. In short, Sir, that face and form I never can forget, were I to live to beyond the period of man's natural age.

O'Shaughnessy offers a highly accurate and classic portrayal of the late stages of uncompensated and irreversible shock. However, it was Thomas Latta who followed O'Shaughnessy's advice and first attempted intravenous fluid resuscitation in 1832. Ironically, William O'Shaughnessy received a knighthood for his work on the electric telegraph and not for his work on cholera, and Thomas Latta died a relative unknown less than 1 year after his classic observations.

The modern era of treating pediatric shock did not begin until much later, during the 1960s and 1970s, when intravenous therapy replaced subcutaneous therapy as a means of fluid resuscitation. Deaths associated with diarrheal disease in the United States decreased from 67 per 100,000 infants to 23 per 100,000 infants following the widespread use of metal intravenous catheters, with a further reduction from 23 to 2.6 per 100,000 infants noted by 1985 associated with the use of plastic intravenous catheters [13]. Thomas and Carcillo [13] reviewed data from the Vital Statistics of the United States from 1960 to 1991 and noted an eightfold reduction in the mortality rate from hypovolemic shock from 1/1,000 infants in 1960 to 0.12/1,000 infants in 1991. Significantly, the steepest decrease in mortality occurred during the decade between 1975 and 1985, coinciding with implementation of intravenous fluid therapy using plastic catheters in children. Although numerous factors are responsible for this decline, the development of pediatric critical care medicine as a subspecialty, along with the aggressive use of intravenous fluids, has certainly contributed substantially to this profound reduction in mortality and undoubtedly represents one of modern pediatric medicine's great accomplishments.

Although significant progress has been made in elucidating the molecular and cellular bases of shock, morbidity and mortality from shock remain unacceptably high. For example, Watson and colleagues evaluated a U.S. population sample for all-cause mortality in children in 1995 and noted that the two leading causes of death were trauma and severe sepsis [14]. Orr and colleagues evaluated a 5,000-patient database of children referred from the community setting to five separate pediatric hospitals in 2000 [15]. Shock, defined in this report by the presence of either hypotension or a capillary refill >2 sec was the leading cause of death in these children, regardless of trauma status. Although head trauma was more common among patients who died, shock at the outside community hospital was a major predictor of subsequent death. Of major concern, only 7% of the 5,000 patients were referred for a diagnosis of *shock*, yet more than 40% of these children did, in fact, meet prospectively defined criteria for the diagnosis of shock. Community physicians were more likely to refer these children for respiratory distress when shock was present, even though the presence of shock was a significant risk factor for subsequent mortality. Therefore, despite the dramatic advances in the care of children with shock over the past 50 years, shock remains both common and often underappreciated in children transported to tertiary care pediatric hospitals.

A Brief Overview of Cellular Respiration and the Cellular Basis of Shock

Adenosine triphosphate (ATP) is the energy currency of the cell; therefore, shock is a state of acute energy failure in which there is insufficient ATP production to support systemic cellular function. During stress and periods of increased energy demand, glucose is produced from glycogenolysis and gluconeogenesis. Fat metabolism is the secondary source of energy in this scenario. Long chain fatty acids are oxidized, and carnitine is utilized to shuttle acetyl coenzyme A (acetyl CoA) into mitochondria. Protein catabolism can also contribute acetyl CoA to the Krebs cycle for energy production. Aerobic metabolism provides 20 times more energy than anaerobic metabolism. Glucose is oxidized to pyruvate via glycolysis (also called the *Embden-Meyerhof pathway*), generating only two molecules of ATP in the process. When oxygen supply is adequate, pyruvate enters the mitochondria and is converted to acetyl CoA by the pyruvate dehydrogenase enzyme complex, after which

it is completely oxidized to CO_2 and H_2O via the Krebs cycle (also known as the tricarboxylic acid or citric acid cycle) and oxidative phosphorylation, generating a *net* total of 36–38 moles of ATP for every mole of glucose. Conversely, when oxygen supply is inadequate, pyruvate is reduced by nicotinamide adenine dinucleotide and lactate dehydrogenase to lactate, a relatively inefficient process that generates considerably less ATP.

Cells do not have the means to store oxygen and are therefore dependent on a continuous supply that closely matches the changing metabolic needs that are necessary for normal metabolism and cellular function. If oxygen supply is not aligned with these metabolic requirements, hypoxia will ensue, eventually resulting in cellular injury and/or death. As defined above, shock is a state characterized by an inadequate delivery of oxygen and metabolic substrates to meet the metabolic demands of the cells and tissues of the body. Alterations in cellular function and structure result directly from the consequent derangements in cellular metabolism and energy production. Eventually, these derangements lead to cellular necrosis, with subsequent release of proteolytic enzymes and other toxic products that produce a systemic inflammatory response.

In practical terms, using this operational definition, a state of shock may result from inadequate oxygen delivery, inadequate substrate delivery (*glycopenia*), or mitochondrial dysfunction (*cellular dysoxia*). Oxygen delivery to the cells and tissues is dependent primarily on three factors: (1) hemoglobin concentration (Hb), (2) cardiac output (CO), and (3) the relative proportion of oxyhemoglobin, that is, percent oxygen saturation (SaO_2). Oxygen is transported in the blood combined with hemoglobin, although a relatively small amount is freely dissolved in the plasma fraction of the blood. When fully saturated, each gram of hemoglobin can carry approximately 1.34 mL of oxygen at normal body temperature, such that the oxygen content of arterial blood is determined by

$$CaO_2 \text{ (grams } O_2\text{/mL)} = (Hb \times 1.34 \times SaO_2) + (0.003 \times PaO_2)$$

Oxygen delivery (DO_2) is therefore determined by

$$DO_2 = CO \times CaO_2$$

Generally, more oxygen is delivered to the cells of the body than the cells actually require for normal metabolism. However, a low cardiac output (*stagnant hypoxia*), low hemoglobin concentration (*anemic hypoxia*), or low hemoglobin saturation (*hypoxic hypoxia*) will result in inadequate delivery of oxygen unless a compensatory change occurs in any of the other factors. Adequate glucose delivery depends on the presence of adequate blood glucose concentrations, normal blood flow (or cardiac output), and, for cells with insulin-responsive glucose transporters (e.g., cardiomyocytes), an adequate concentration of insulin. *Glycopenic* shock can therefore be caused by hypoglycemia as well as by extreme insulin resistance. Finally, even when oxygen delivery and glucose delivery is adequate, shock may occur as a result of mitochondrial dysfunction. For example, cyanide poisons the oxidative phosphorylation chain, preventing production of ATP. *Cellular dysoxia* (also known as *cytopathic hypoxia*) may theoretically occur from one or a combination of several mechanisms, including diminished delivery of a key substrate (e.g., pyruvate) to the Krebs cycle, inhibition of a key enzyme involved in either the Krebs cycle or the electron transport chain, or uncoupling of oxidative phosphorylation. One additional mechanism is through activation of the mitochondrial DNA repair enzyme, poly (ADP-ribose) synthetase, or PARS, which is also commonly known as poly (ADP-ribose) polymerase, or PARP, in which more NAD^+ is consumed than ATP is being produced [16–18].

Differences Between Pediatric Shock and Adult Shock

"Children are not small adults" is an oft repeated axiom in the subspecialty of pediatric critical care medicine. Age-specific differences in hemoglobin concentration and composition, heart rate, stroke volume, blood pressure, pulmonary vascular resistance, systemic vascular resistance (SVR), metabolic rate, glycogen stores, and protein mass are the basis for many age-specific differences in the cardiovascular and metabolic responses to shock. For example, newborns have a higher hemoglobin concentration (mostly fetal hemoglobin) but low total blood volumes. They also have the highest total body water composition (Figure 6.1). Newborns have comparatively higher heart rates, lower stroke volumes, near systemic pulmonary artery blood pressures, and higher metabolic rates with high energy needs but the lowest glycogen stores and protein mass for glucose production.

At birth, the normal newborn transitions from fetal to neonatal circulation when inhalation of oxygen reduces pulmonary vascular resistance and allows blood to flow through the lungs rather than bypass the lungs through the patent ductus arteriosus. When pulmonary circulation is firmly established, the ductus arteriosus closes and newborn circulation is ensured. In the presence of shock, acidosis prevents the ductus arteriosus from closing, and elevated pulmonary vascular resistance persists. If untreated, persistent pulmonary hypertension results in right ventricular failure with septal bowing and inadequate cardiac output from the left ventricle. Resuscitation of the newborn with shock therefore requires meticulous attention to maintaining (1) adequate heart rates with chronotropes (newborns predominantly have high

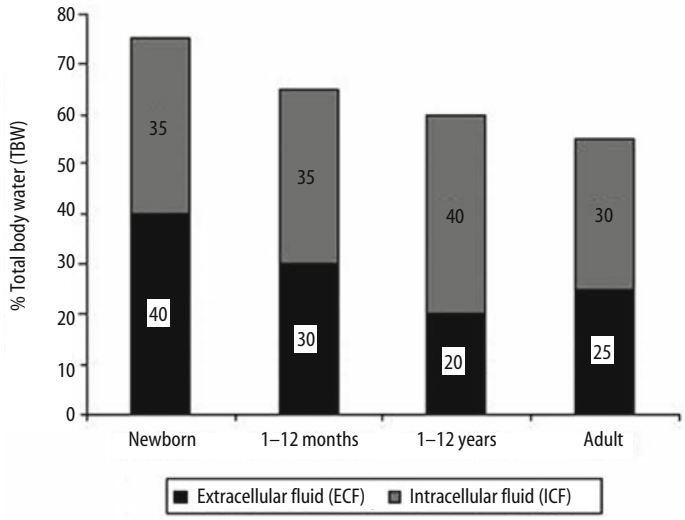

Figure 6.1. Total body water (TBW), which consists of the intracellular fluid (ICF) and extracellular (ECF) fluid compartments, as a percentage of body weight decreases rapidly with age. The ECF compartment consists of the plasma volume (5% TBW) and the interstitial volume (15% TBW). The ECF volume decreases rapidly during the first year of life, while the ICF volume remains relatively constant. Fluid losses usually affect either the interstitial or intracellular compartment.

parasympathetic tone and do not fully develop sympathetic vesicles until the age of 6 months), (2) blood volume (the newborn only has approximately 1 cup of blood [19], and (3) newborn circulation (using pulmonary vasodilators, such as inhaled nitric oxide, and reversing metabolic acidosis). In addition, glucose infusion rates of 8 mg/kg/min or higher are often necessary to prevent hypoglycemia in the presence of low glycogen and protein gluconeogenesis stores. Newborns with refractory shock respond well to extracardiac support life support (ECLS) because mortality is uniformly caused by low cardiac output with high pulmonary and/or SVR.

Infants and children also have high SVR and vasoactive capacity such that hypotension is a very late sign of shock (Figure 6.2). This is a survival mechanism designed to counterbalance the limited cardiac reserve of the young. Cardiac perfusion occurs to the greatest degree during diastole. Therefore, coronary artery perfusion depends directly on the difference between diastolic blood pressure and left atrial pressure and inversely with heart rate (as an indirect measure of diastolic filling time). Under conditions of hypovolemia, an adult can easily double heart rate from 70 to 140 beats per minute (bpm) to maintain an adequate cardiac output (cardiac reserve); however, the newborn or infant cannot double heart rate from 140 to 280 bpm or 120 to 240 bpm, respectively, because these heart rates will not allow adequate coronary perfusion. Indeed, supraventricular tachycardia with heart rates of 240 bpm or higher frequently lead to inadequate cardiac filling and subsequent poor tissue perfusion. During states of shock, newborns, infants, and children compensate by peripheral vasoconstriction to maintain adequate perfusion to the heart, brain, and kidney, and hypotension is an extremely late and poor prognostic sign. Therefore, shock must be recognized and treated long before hypotension occurs. The hallmark of the care of critically ill children is early recognition and resuscitation before hypotension occurs. Time-sensitive and aggressive fluid resuscitation, inotropic support, systemic and pulmonary vasodilator therapy, and extracardiac mechanical support are more commonly used for children than in adults.

Ceneviva et al. [20] categorized 50 children with fluid-refractory shock according to hemodynamic state (based on hemodynamic data obtained with the pulmonary artery catheter) into one of three possible cardiovascular derangements: (1) hyperdynamic state characterized by a high cardiac output (>5.5 L/min/m^2 body surface area [BSA]) and low SVR (<800 dynes sec/cm^5) (classically referred to as *warm shock*); (2) a hypodynamic state characterized by low cardiac output (<3.3 L/min/m^2 BSA) and low SVR; or (3) a hypodynamic state characterized by low cardiac output and high SVR (>1,200 dynes sec-cm^5) (classically referred to as *cold shock*). In contrast to adults in which the early stages of septic shock are characterized by a high cardiac output and low SVR, most of these children were in a hypodynamic state characterized by low cardiac output and high SVR (cold shock) and required the addition of vasodilators to decrease SVR, increase cardiac index, and improve peripheral perfusion [20]. Children with low cardiac output (as defined by a cardiac index less than 2.0 L/min/m^2 BSA) had the highest risk of mortality.

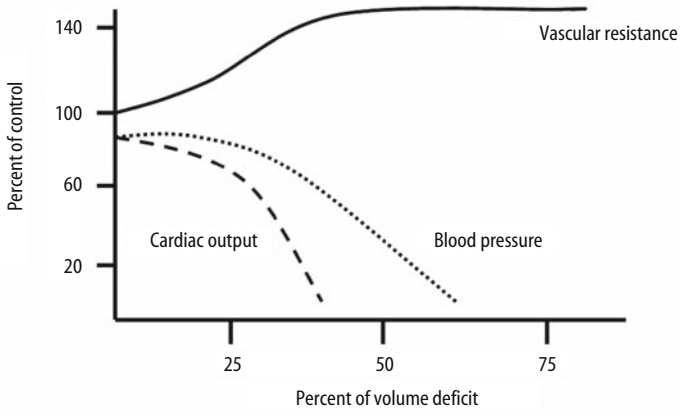

Figure 6.2. The cardiovascular response to hypovolemia. Tachycardia and increased systemic vascular resistance initially maintain adequate cardiac output in the face of dramatic fluid losses (e.g., hemorrhage) during the so-called compensated phase of shock. Further fluid losses lead to a decrease in cardiac output, although blood pressure may be maintained until the late phases of "uncompensated" shock.

These findings have been confirmed in multiple studies [21–26]. For example, Parr and colleagues [23] measured cardiac output using the Fick-dilution indocyanine green dye injection technique in infants younger than 6 months who required cardiac surgery and showed that mortality risk increased in this population when cardiac index was less than 2.0 L/min/m^2 BSA. Notably, a prolonged capillary refill <2 sec was both highly specific and sensitive for a cardiac index >2.0 L/min/m^2 BSA. Inotropic support followed by afterload reduction with sodium nitroprusside and volume loading was effective in improving cardiac output in these children [27]. Children with septic shock appear to require a higher cardiac output than children with isolated cardiogenic shock. For example, Pollack et al. [22] analyzed the hemodynamic data of 42 children with septic shock. The 18 children with septic shock who survived had a significantly higher cardiac index (range, 3.3 to 6.0 L/min/m^2 BSA) than did nonsurvivors. Reynolds et al. [21] reported that pediatric burn victims with fluid-refractory shock had decreased left ventricular stroke work and responded to inotropic support with improvements in cardiac output. Feltes et al. [26] reported echocardiographic findings consistent with decreased left ventricular systolic function and increased afterload in 5 out of 10 children with septic shock.

Congenital cardiac anomalies, endocrine deficiencies, and metabolic disease can also play a more significant role in the pediatric patient. Specific congenital heart disease diagnoses require specific shock resuscitation approaches. Absolute adrenal insufficiency (peak cortisol level <18 mg/dL after adrenocorticotropic hormone stimulation and/or <9 mg/dL increase from prestimulation levels) and thyroid insufficiency are more common in children than adults with refractory shock. Timely hormonal therapy reverses shock in these children. Similar to adults, acquired adrenal insufficiency can also occur from exposure to prior corticosteroids or etomidate [28–40]. Etomidate should therefore be used with caution in children with shock because of its effects on the hypothalamic–pituitary–adrenal axis with some clinicians advocating co-administration of empiric corticosteroid therapy if etomidate is used [41]. Alternatively, ketamine may be considered as an induction agent in children with shock, although it is important to keep in mind that ketamine has a direct myocardial depressant effect and maintains blood pressure stability by augmenting SVR, which may not be well-tolerated by a poorly functioning myocardium. Thus, in the setting of shock, tracheal intubation must be approached thoughtfully and with the anticipation that hemodynamics may further deteriorate, necessitating acute fluid administration and initiation/escalation of inotropic support. Metabolic disease is also more predominant in infancy and childhood and is often exacerbated or brought out by stress, catabolic states, and

shock. Treatment for these children (with the notable exception of those with pyruvate dehydrogenase complex deficiency) should be directed toward reversing the catabolic state by administering glucose ($D_{10}W$) at intravenous fluid maintenance rates with insulin administered for hyperglycemia.

The Pathophysiology of Shock

Normal Hemodynamics

The Frank-Starling Relationship

Cardiac output can be described mathematically as the product of heart rate and stroke volume [CO = HR × SV]. Stroke volume, in turn, is dependent on preload, afterload, and contractility. The eminent German physiologist Otto Frank, while working at the famed Carl Ludwig Physiological Institute in Leipzig, Germany, examined the length–tension relationships in a frog ventricle preparation and noted that the peak ventricular pressure generated during a contraction increases as the end-diastolic volume (EDV) is increased [42]. Ernest Starling, over two decades later, related ventricular filling pressure, or EDV, to cardiac output in a series of highly influential papers published between 1912 and 1914 and in his Linacre Lecture at Cambridge University in 1915. Using a canine heart–lung preparation, Starling noted that cardiac output increased as EDV increased, although he and his collaborators acknowledged that they were not the first to describe this relationship [43]. Starling did, however, suggest that the cardiac muscle fibers contract more vigorously when stretched beforehand, as long as the fibers are not *overstretched*. We now know that this *stretching* of the muscle fibers before contraction results in optimal overlap of the actin and myosin muscle fibers. Importantly, then, as left ventricular EDV (LVEDV) increases to a point corresponding to optimal overlap of the actin and myosin cardiac muscle fibers, stroke volume improves. Increasing LVEDV past this point, however, will result in *overstretch* of these fibers and worsening stroke volume (Figure 6.3).

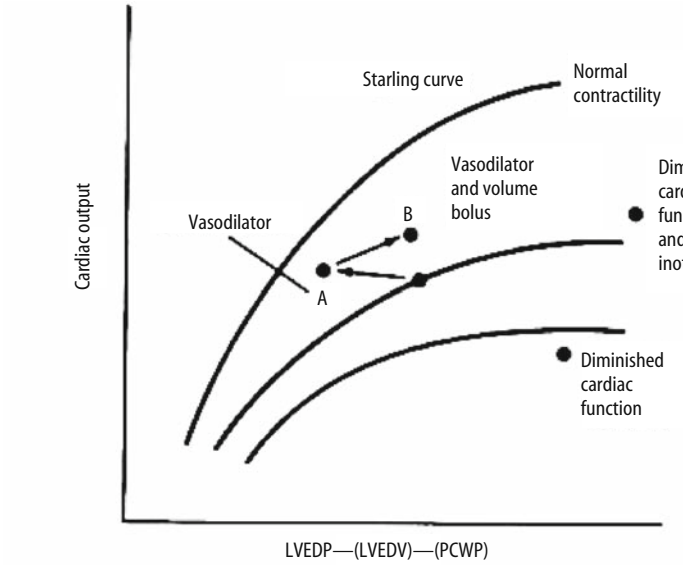

Figure 6.3. Frank-Starling law. Stroke volume moves up along the curve as end diastolic filling increases to a point where the ventricle is overfilled and then stroke volume falls off again. Inadequate preload is defined as the end-diastolic volume below which maximum stroke volume is attained. Congestive heart failure occurs when preload or end-diastolic volume goes above this optimal range. Cardiac dysfunction is represented by downward and rightward displacement of the curve. This curve can be used to demonstrate the therapeutic principles of volume loading, inotropes, and vasodilators. Children who have inadequate stroke volume despite adequate volume loading have reduced contractility. This is represented by a flattened Starling curve. Inotropic therapy improves the Starling curve, moving it upward and to the left. Stroke volume will be greater for any given end-diastolic volume in patients treated with inotropic therapy compared with those left untreated. Patients with severe cardiac dysfunction shock require addition of a vasodilator to improve the Starling curve, moving it further upward and to the left. Concomitant volume loading is often required to move these patients up and along their new and improved Starling curve because vasodilator therapy often reduces preload. LVEDP, left ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic volume; PCWP, pulmonary capillary wedge pressure.

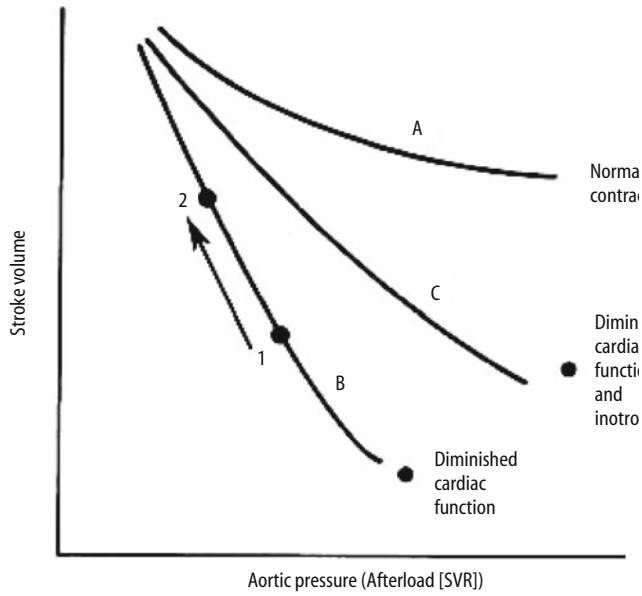

Figure 6.4. Afterload. Afterload is dependent on a combination of factors, including vascular impedance. SVR, systemic vascular resistance.

The relationship between afterload and stroke volume is best viewed in a modified compliance curve. As afterload or aortic diastolic pressure increases, stroke volume decreases. A heart with normal function can tolerate increased aortic diastolic pressures fairly well (Figure 6.4, curve A). However, the heart with decreased contractility does not tolerate increased afterload at all (curve B), although this compromise can be improved by the addition of inotropic support to the failing myocardium (curve C). In addition, this effect of increased afterload explains the salutary effect of vasodilator therapy on stroke volume. Afterload reduction with vasodilator therapy decreases aortic diastolic blood pressure and improves stroke volume particularly in the poorly contracting heart (point 1 to point 2, curve B).

The Peripheral Circulation and Normal Homeostatic Regulation of Arteriolar Tone

The most fundamental function of the cardiovascular system is to provide adequate delivery of oxygen and metabolic nutrients to the various tissues of the host organism. The regulation of tissue oxygen and nutrient delivery is realized at the level of the micro-

circulatory resistance arterioles, appropriately allowing for the differential adaptation of blood flow to regional tissues based on local environmental needs. The microcirculation, therefore, while structurally similar, is not homogeneous in activity, but is adapted with distinct homeostatic strategies for the maintenance of perfusion to each unique tissue bed and organ. As such, organ-specific microcirculations differentially respond to autoregulatory mechanisms, humoral influences, neuronal influences, hypoxia, acid–base status, and locally released endothelial-derived factors.

Autoregulation is the intrinsic ability of an organ, independent of neural and humoral influences, to maintain a constant blood flow despite changes in perfusion pressure. To maintain constancy in organ blood flow, as perfusion pressure is altered there must be a responsive reciprocal change in vascular resistance, mediated by a change in arterial diameter. For example, a decrease in organ blood flow resulting from a decrease in the perfusion pressure triggers a reflex autoregulatory vasodilation and reduction in vascular resistance, reconciling a return of arterial blood flow to steady state (Figure 6.5). Owing to limitations in vasodilation and vasoconstriction of resistance blood vessels, constancy of blood flow as a consequence of autoregulation is limited within a range of perfusion pressures. As the perfusion pressure continues to decrease, however, a point of maximal vasodilation is realized, and any further decrease in perfusion pressure results in an uncompensated decrease in organ blood flow. Similarly, as perfusion pressure increases, a point of maximal vasoconstriction is realized, and any further increase in perfusion pressure results in an uncompensated increase in organ blood flow. Therefore, within the autoregulatory range of perfusion pressure, blood flow is pressure independent, whereas at the extremes of perfusion pressure, blood flow becomes pressure dependent.

Blood flow through a regional vascular bed is directly proportional to the organ perfusion pressure (ΔP), which is calculated as the difference between the arterial inflow pressure (P_a) and the venous outflow pressure (P_v) ($\Delta P = P_a - P_v$). With reasonable approximation, ignoring local extravascular effects, the inflow arterial pressure can be estimated to be the mean arterial pressure (MAP), and the outflow venous pressure can be estimated to be central venous pressure (CVP):

$$\Delta P = MAP - CVP$$

Therefore, for any given ΔP, the blood flow is determined by the resistance to blood flow according to the following equation, analogous to Ohm's Law:

$$Q = (MAP - CVP)/R$$

where Q is arterial blood flow and R is vascular resistance. Under ideal laminar flow conditions, vascular resistance is independent of flow and pressure; therefore, an increase in vascular resistance will decrease blood flow, and a decrease in vascular resistance will increase blood flow for any given ΔP. Control mechanisms in the body generally maintain arterial and venous blood pressures within a narrow range; therefore, changes in organ and tissue blood flow are primarily regulated by changes in vascular resistance. Resistance to blood flow within a vascular network is determined by the size of the vessels, the organization of the vascular network, physical characteristics of the blood, and extravascular forces acting on the vasculature. As demonstrated by the Hagen-Poiseuille equation,

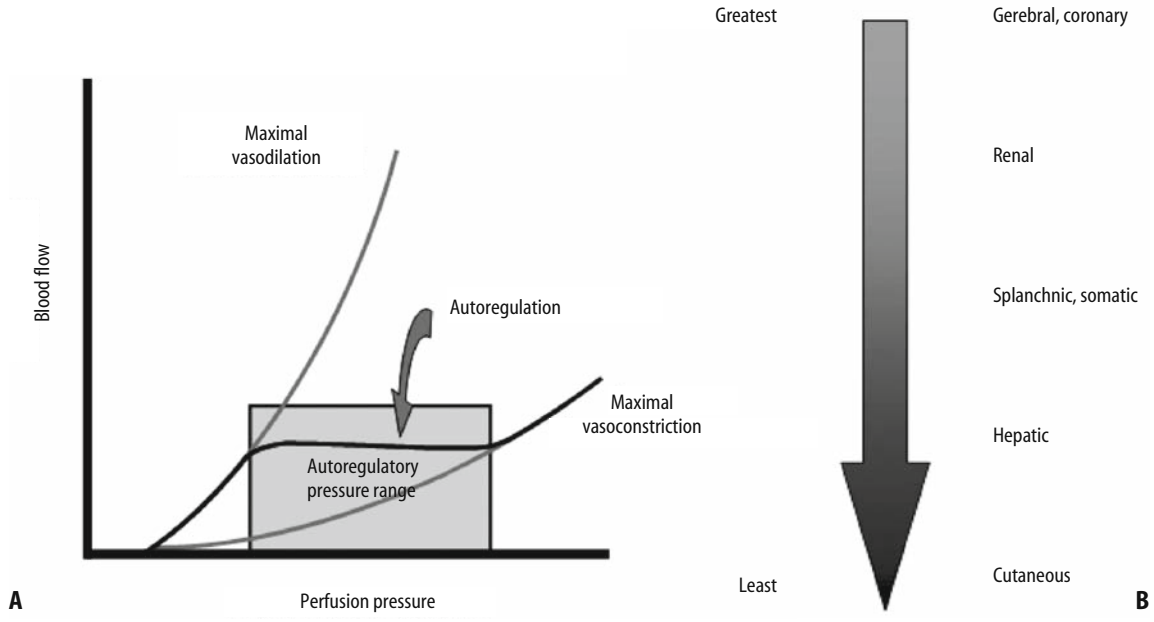

Figure 6.5. Blood flow autoregulation. **(A)** With vascular resistance held constant in the absence of autoregulation, as perfusion pressure is decreased there is a concomitant and proportional decrease in organ blood flow. In the presence of autoregulation, however, decreases in organ perfusion pressure and blood flow elicit a reflex autoregulatory vasodilation and reduction in vascular resistance, reconciling a return of arterial blood flow to steady state. Maintenance of organ blood flow at a constant rate is limited by the ability of the vasculature to vasodilate and vasoconstrict. As organ perfusion pressure decreases there is a compensatory vasodilation to maintain constancy of organ blood flow. As the point of maximal vasodilation is reached, further decreases in organ perfusion pressure result in an uncompensated decrease in organ blood flow. Similarly, as organ perfusion pressure increases, there is a compensatory vasoconstriction to maintain constancy of organ blood flow. As the point of maximal vasoconstriction is reached, further increases in organ perfusion pressure result in an uncompensated increase in organ blood flow. **(B)** The extent to which organ blood flow is influenced by autoregulatory mechanisms differs according to the particular vascular bed: the cerebral, coronary, and renal circulations demonstrate excellent autoregulation, whereas the splanchnic and somatic circulations demonstrate moderate autoregulation, and the cutaneous circulation demonstrates little to no autoregulatory capacity.

$$R = \frac{8\eta l}{\pi r^4}$$

(where η is blood viscosity, l is vessel length, and r is vessel radius), vascular resistance is most effectively controlled by changes in blood vessel diameter (radius to the fourth power), making changes in vessel diameter of primary importance in the regulation of blood flow necessary to meet tissue and organ metabolic demand. However, changes in perfusion pressure, when they occur, will also affect flow. The above relationship also indicates that there is a linear and proportionate relationship between flow and perfusion pressure. This linear relationship, however, is not followed when pathologic conditions lead to turbulent flow, because turbulence decreases the flow at any given perfusion pressure. Furthermore, the pulsatile nature of flow in larger arteries also alters this relationship so that greater pressures are required for a given flow. In other words, pulsatility, like turbulence, increases resistance to flow.

The relationship between flow (i.e., cardiac output), perfusion pressure (i.e., MAP – CVP), and vascular resistance (SVR) is vital to the understanding of the pathophysiologic principles of shock. The perfusion pressure (globally viewed as MAP – CVP) may be more important than blood pressure alone. According to the equation, one can theoretically have a normal MAP but no forward flow (CO), for example, if CVP is equal to MAP. Importantly, when fluid resuscitation is used to improve blood pressure, the increase in MAP must be greater than the increase in CVP. If the increase in MAP is less than the increase in CVP, then the perfusion pressure is actually reduced, and hence cardiac output is reduced. Inotropic agents, and not additional fluid resuscitation, are indicated to improve cardiac output in this scenario.

Understanding this relationship helps guide the management of *blood flow* reflected as cardiac output. Cardiac output can be decreased when perfusion pressure (MAP – CVP) is decreased, but it can also be decreased when the perfusion pressure (MAP – CVP) is normal and vascular resistance is increased. Hence, children with normal blood pressure can have inadequate cardiac output because systemic vascular tone is too high. Cardiac output can be improved in this scenario with the use of inotropes, vasodilators, and volume loading. The cardiovascular pathophysiology of shock can therefore be attributed to reduced cardiac output, to reduced perfusion pressure (MAP – CVP or DBP – CVP), or to both. Reduced cardiac output is caused by either reduced heart rate or reduced stroke volume caused by hypovolemia (inadequate preload), decreased contractility (insufficient inotropy), or excess vascular resistance (increased afterload). Reduced perfusion pressure can be caused by reduced MAP or increased CVP.

The Neuroendocrine Stress Response

The neuroendocrine stress response involves the complex interactions of multiple organ systems that act to maintain homeostasis in response to stress. Also referred to as the *fight or flight response*, the neuroendocrine stress response is dominated by central and sympathetic nervous system activation, which acts to maintain oxygen and nutrient delivery to discrete organ systems under diverse physiologic conditions. The neuroendocrine stress response is, in part, regulated through a series of highly differentiated, closely integrated, cardiovascular reflex arcs, the essential components of which include (1) sensory neurons that detect mechanical, physiochemical, or biochemical changes within distinct tissues; (2) central internuncial neurons that process input from sensory neurons and connect them with autonomic efferent neurons in the brainstem; (3) modulatory neurons that integrate input from the internuncial and/or autonomic neurons from other parts of the central nervous system, particularly the hypothalamus; and (4) sympathetic and parasympathetic efferent preganglionic neurons that synapse with postganglionic neurons directly innervating the organ-specific vasculature. Gann and Lilly further described the stress response as a *neuroendocrine reflex* consisting of an afferent limb, integration at sites within the central nervous system (CNS), and an efferent limb [44].

The Afferent Limb of the Neuroendocrine Reflex Arc

The afferent limb of the neuroendocrine reflex consists of multiple sensory receptors located throughout the cardiovascular system. For example, sensory receptors called *arterial baroreceptors* are found in the walls of the aorta and carotid arteries. The carotid sinus consists of a rich network of baroreceptors that are innervated by the glossopharyngeal nerve and located at the bifurcation of the common carotid artery into the internal and external carotid artery. In addition, major concentrations of baroreceptors are also found in the wall of the aorta near the transverse arch, called the *aortic baroreceptors*, which are supplied by the vagus nerve. These baroreceptors *sense* stretch produced by increased intraluminal pressure and therefore indirectly respond to increases in arterial blood pressure, which leads to increased stretch, resulting in an increased rate of action potential generation of these baroreceptors. Chemoreceptors located throughout the cardiovascular system also respond to changes in pH, PaO_2, or $PaCO_2$. For example, the carotid bodies are specialized chemoreceptors located adjacent to the carotid sinus that relay information via the glossopharyngeal nerve to the nucleus tractus solitarius in the medulla. This vast array of noci- (pain), mechano-, chemo-, and baroreceptors located in the lungs, walls of the atria and ventricles, and central nervous system detect minute changes in intravascular blood volume, pressure, and content and generate signals that are subsequently integrated in the central nervous system.

The Efferent Limb of the Neuroendocrine Reflex Arc

The efferent limb of the neuroendocrine reflex arc consists of the pituitary gland, the brain stem autonomic centers, the adrenal cortex, and the autonomic nervous system. The anterior pituitary gland releases adrenocorticotropic hormone, which in turn stimulates the adrenal cortex to release cortisol. The sympathetic nervous system (which includes the adrenal medulla) releases epinephrine and norepinephrine. Cortisol facilitates the actions of these two catecholamines, which increase cardiac output by increasing heart rate and stroke volume and, as a result, also increase blood pressure. Epinephrine primarily increases heart rate and contractility, whereas norepinephrine primarily increases contractility and systemic vascular tone. To fuel these increased energy needs, glucagon is also released, which increases glucose delivery to the Krebs cycle through activation of glycogenolysis and gluconeogenesis.

Activation of the renin–angiotensin–aldosterone axis further contributes to the neuroendocrine stress response. Decreased renal perfusion results in the release of renin, a proteolytic enzyme that cleaves angiotensinogen, an α_2-globulin produced in the liver, to generate angiotensin I. Biologically inactive angiotensin I is subsequently cleaved to form biologically active angiotensin II via the activity of angiotensin-converting enzyme in the lungs. Angioten-

sin II mediates an increase in systemic blood pressure through two separate and distinct mechanisms, (1) contraction of the vascular smooth muscle resulting in an increase in SVR and (2) sodium and water retention resulting in increased intravascular volume, both through direct effects on the renal tubule and through the stimulation and release of aldosterone. Angiotensin II also stimulates norepinephrine synthesis and release from the sympathetic nervous system and epinephrine release from the adrenal medulla, thereby resulting in secondary vasoconstriction and an increase in systemic blood pressure. Moreover, angiotensin II also stimulates the release of vasopressin (antidiuretic hormone) from the posterior pituitary, resulting in increased reabsorption of free water in the distal collecting tubule (see later). The increase in intravascular volume exerted by the direct renal activity of angiotensin II, and the secondary release of aldosterone and vasopressin, results in an increase in systemic blood pressure. Vasopressin is released by the posterior pituitary gland in response to either a decrease in the effective circulating volume or an increase in serum osmolality. Vasopressin acts directly on both the kidneys and the blood vessels to enhance free water reabsorption (via V_2 receptors) and increase SVR via peripheral vasoconstriction (via V_1 receptors), respectively.

Oxygen Delivery and Oxygen Consumption

Under resting conditions, with normal distribution of cardiac output, oxygen delivery is more than adequate to meet the total oxygen requirements of the tissues needed to maintain aerobic metabolism, referred to as *oxygen consumption* (VO_2). This excess delivery or *oxygen reserve* serves as a buffer such that a modest reduction in oxygen delivery is more than adequately compensated by increased extraction of the delivered oxygen, without any significant reduction in oxygen consumption. During stress or vigorous exercise, oxygen consumption markedly increases, as does oxygen delivery. Therefore, in the majority of circumstances, the metabolic demands of the cells and tissues of the body dictate the level of oxygen delivery. However, very little oxygen is stored in the cells and tissues of the body. Therefore, as oxygen delivery falls with critical illness, oxygen extraction must necessarily increase to meet metabolic demands, and oxygen consumption remains relatively constant (i.e., *delivery independent*; Figure 6.6). However, there is a critical level of oxygen delivery at which the body's compensatory mechanisms are no longer able to keep up with metabolic needs (i.e., the point at which oxygen extraction is maximal). Once oxygen delivery falls below this level, oxygen consumption must also fall and is said to become *delivery dependent* (point A, Figure 6.6).

In years past, a so-called pathologic supply-dependency was believed to exist in association with certain disease processes (e.g., sepsis, acute respiratory distress syndrome). Early experimental models of sepsis [45–47] and clinical data [48] show that the critical oxygen extraction ratio was lower than normal during these critical illnesses, that is, oxygen consumption became delivery dependent at a higher critical DO_2 in critically ill patients (point B, Figure 6.6). This observation implied an intrinsic defect at the cellular level in oxygen extraction. However, most of the clinical data on which this concept of a pathologic supply-dependency is based is suspect because the formulas for DO_2 and VO_2 share common variables:

$$DO_2 = CO \times (Hb \times 1.34 \times SaO_2) + (0.003 \times PaO_2)$$

$$VO_2 = CO \times [Hb \times 1.34 \times (SaO_2 - SvO_2) + 0.003 \times (PaO_2 - PvO_2]$$

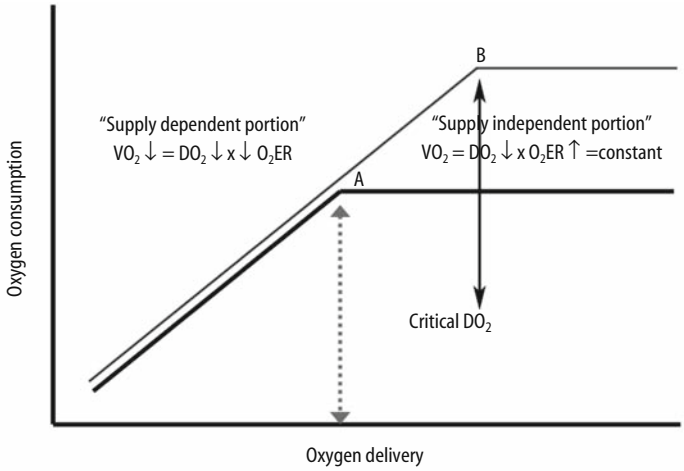

Figure 6.6. The oxygen delivery–oxygen consumption relationship.

Both variables share the measurements of cardiac output and arterial oxygen content. The potential for computation error arises because the measurements of these variables in the calculation of DO_2 and VO_2 result in a mathematical coupling of measurement errors in the shared variables, resulting in false correlation between oxygen delivery and consumption. To avoid potential mathematical coupling, oxygen consumption and delivery should be determined independent of each other. Studies in which VO_2 was directly measured (rather than calculated from the Fick principle) largely have disproved this pathologic supply-dependency hypothesis.

Alterations in Normal Hemodynamics During the Shock State

Following the onset of hemodynamic dysfunction, the homeostatic compensatory mechanisms discussed earlier (and summarized in Table 6.2) are initiated in an attempt to maintain vital organ function. The progression of shock is commonly divided into three phases: compensated, uncompensated, and irreversible shock (Table 6.3) [9,10]. During compensated shock, oxygen delivery to the brain, heart, and kidney is often maintained at the expense of *less vital* organs. Signs and symptoms of the shock state, although often subtle, may be apparent even at this early stage. Notably, hypotension is not a feature during this stage. Rather, increased peripheral vascular tone and increased heart rate maintain a normal cardiac output and a normal blood pressure.

As shock progresses to the *uncompensated stage*, the body's compensatory mechanisms eventually contribute to the further progression of the shock state (e.g., blood is shunted away from the skin, muscles, and gastrointestinal tract in order to maintain perfusion of the brain, heart, and kidneys, leading to ischemia in these vascular beds with subsequent release of toxic substances, further perpetuating the shock state). Cellular function deteriorates further, culminating in end-organ dysfunction.

The *terminal* or *irreversible stage* of shock implies irreversible organ injury, especially of the vital organs (brain, heart, and kidneys). Intervention at this late stage is unsuccessful, and death occurs even if therapeutic intervention restores cardiovascular measurements such as heart rate, blood pressure, cardiac output, and oxygen saturation to normal or even supranormal levels.

Table 6.2. Compensatory responses to the shock state.

Maintain effective blood volume
Decreased venous capacitance (via venoconstriction)
Increased sympathetic tone
Release of epinephrine from the adrenal medulla
Increased angiotensin II (activation of the renin–angiotensin–aldosterone axis)
Increased vasopressin release from the posterior pituitary gland
Decreased renal fluid losses
Decreased glomerular filtration rate
Increased aldosterone release (activation of the renin–angiotensin–aldosterone axis)
Increased vasopressin release from the posterior pituitary gland
Fluid redistribution to the vascular space
Starling effect (fluid redistribution from the interstitial space)
Osmotic effect (fluid redistribution from the intracellular space)
Maximize cardiac performance
Increased heart rate and contractility
Increased sympathetic tone
Release of epinephrine from the adrenal medulla
Preferential perfusion to the vital organs (dive reflex)
Extrinsic regulation of systemic arterial tone
Autoregulation of vital organs (brain, heart, kidneys)
Optimizing conditions for oxygen unloading
Increased concentration of red blood cell 2,3-diphosphoglycerate
Tissue acidosis (bohr effect)
Decreased tissue PO_2

Functional Classification of Shock

Hinshaw and Cox [19] proposed a classification scheme for shock in 1972 that is still useful today. The four major categories of shock include (1) hypovolemic shock (shock as a consequence of inadequate circulating volume), (2) obstructive shock (shock caused by obstruction of blood flow to and from the heart), (3) cardiogenic shock (shock caused by primary pump failure), and (4) distributive shock (shock caused by maldistribution of the circulating volume) (Table 6.4). Although relatively arbitrary, especially when viewed in the context that different features of each category may be present at the same time (e.g., septic shock is often characterized by manifestations of hypovolemic shock, cardiogenic shock, and distributive shock), this classification scheme provides valuable information about the physiologic alterations involved, including changes in preload, contractility, and afterload. Knowledge of these physiologic alterations can then be used to guide appropriate management.

Hypovolemic Shock

Hypovolemic shock is the most common cause of shock in children and claims the lives of millions of children each year worldwide [9,13,49,50]. Diarrheal illnesses leading to dehydration and hypovolemic shock account for as many as 30% of all deaths of infants

Table 6.3. Stages of shock.

Organ system	Compensated shock	Uncompensated shock	Irreversible shock
Central nervous system	Agitation Anxiety ↓ Lethargy Somnolence	Altered mental status Encephalopathy Hypoxic–ischemic injury	Hypoxic–ischemic injury and cell necrosis
Heart	Tachycardia	Tachycardia ↓ Bradycardia	Myocardial ischemia Cell necrosis
Lungs	Tachypnea Increased Work of breathing	Acute respiratory failure	Acute respiratory failure
Kidneys	Oliguria ↑ Urinary osmolality ↑ Urinary sodium $FE_{Na} < 1$	Acute tubular necrosis Acute renal failure	Tubular necrosis
Gastrointestinal tract	Ileus Feeding intolerance Stress gastritis	Pancreatitis Acalculous cholecystitis Gastrointestinal bleeding Gut translocation	Gastrointestinal bleeding Sloughing
Liver	Centrilobular injury Elevated transaminases	Centrilobular necrosis Shock liver	Hepatic failure
Hematologic	Endothelial activation Platelet activation (Procoagulant,hypofibrinolytic)	Disseminated intravascular coagulation	Disseminated intravascular coagulation
Metabolic	Glycogenolysis Gluconeogenesis Lipolysis Proteolysis	Glycogen depletion Hypoglycemia	Hypoglycemia
Immune system	Immunoparalysis	Immunoparalysis	Immunoparalysis

Table 6.4. Classification of shock.

Type of shock	Preload	Afterload	Contractility
Hypovolemic	↓	↑	N
Cardiogenic	↑	↑	↓
Obstructive	↓	↑	N
Distributive	↑, ↓, or N	↓	↑

Note: N, no change.

and young children worldwide. Nearly 8,000 children younger than 5 years of age die every day from dehydration and hypovolemic shock [49–51]. Although diarrheal illnesses are an important cause of hypovolemic shock in children in developing nations, hypovolemic shock is an important problem that affects children in the United States and other developed nations as well. For example, hypovolemic shock accounts for nearly 10% of all hospital admissions and 300 annual deaths of children younger than 5 years of age in the United States alone [49,52].

Traumatic injuries are the leading cause of mortality in children and adolescents. Although closed-head injuries account for the vast majority of these deaths, hemorrhagic shock accounts for a significant number of deaths of children on an annual basis. Blunt trauma is more common in children, which differs from penetrating trauma in that multiple organs are often involved, occult injury is common, and progressive organ damage is frequent due to continued hemorrhage, edema, or ischemia. Blunt trauma associated with motor vehicle accidents is especially common in the pediatric age group. Although penetrating trauma secondary to gunshot or stab wounds is more common in adolescents, these injuries account for a small percentage of all pediatric injuries even in urban trauma centers [53].

The source of blood loss in hemorrhagic shock may be external and readily identifiable. For example, the scalp is highly vascular and lacerations in this area can account for a significant amount of blood loss in children. More commonly, however, the source of blood loss is internal and requires a high index of suspicion. Intraabdominal injuries (e.g., spleen laceration, liver laceration) and long-bone fractures can result in significant blood loss. For example, an occult femur fracture may result in the loss of up to 500–1,000 mL of blood into the soft tissues of the thigh, although isolated femur fractures rarely cause hemorrhagic shock in children [54–56].

Children appear to be at a greater risk for hypovolemic shock than adults because of a number of important age-specific physiological differences. For example, total body water (TBW) as a percentage of body weight decreases rapidly with age (see Figure 6.1). Based on such an analysis, it would seem logical to assume that children, because of their relatively greater percentage of TBW, would be protected against dehydration; unfortunately, this is not the case. Total body water consists of the intracellular (ICF) and extracellular (ECF) fluid compartments. The ECF compartment consists of the plasma volume (5% TBW) and the interstitial volume (15% TBW). The ECF volume decreases rapidly during the first year of life, while the ICF volume remains relatively constant. However, fluid losses usually affect either the interstitial or intracellular compartments. Experimental models utilizing radiolabeled albumin demonstrate that the percentage of body weight lost is directly proportional to the percentage of plasma volume lost (e.g., children who lose 5% of their body weight have lost approximately 5% of their plasma volume) [57]. It is useful to quantify the amount of dehydration based on clinical signs and symptoms or on the percentage of weight loss (Table 6.5). Finally, the total amount of fluid loss required to produce shock is significantly less in children than in adults. For example, 10% dehydration, indicative of moderate dehydration by most accounts, in a 6-month-old child weighing 7 kg (approximately 700 mL fluid loss) is one-tenth the total volume loss required to produce the same degree of dehydration in a 70-kg adult (approximately 7,000 mL fluid loss) [13].

The total blood volume is usually estimated as 7% to 8% of the total body weight, or 70 to 80 mL/kg. Loss of up to 15% of the total blood volume (class I shock as defined by the American College of Surgeons) usually results in minimal signs and symptoms (Table 6.6). Heart rate may increase to maintain adequate cardiac output, although blood pressure is usually maintained in the normal range. Hypotension, in fact, is a relatively late sign of hypovolemic shock. Compensatory mechanisms such as an increased heart rate and peripheral vascular resistance (see Figure 6.2) can maintain a normal blood pressure even in the face of a 30%–40% loss of the total blood volume. Hypotension, therefore, defines a state of *decompensated shock* and is a relatively late and ominous finding in the critically ill or injured child.

Obstructive Shock

Obstructive shock is caused by a mechanical obstruction of blood flow to and/or from the heart. Common causes of obstructive shock include tension pneumothorax, cardiac tamponade, and pulmonary embolism, which are discussed in greater detail in subsequent chapters. Also included in this category are the congenital heart lesions characterized by left ventricular outflow tract obstruction, including critical aortic stenosis, coarctation of the aorta, and

Table 6.5. Clinical signs and symptoms of dehydration in children.

	% Dehydration		
Sign/symptom	Mild (4%–5%)	Moderate (6%–9%)	Severe (≥10%)
General appearance	Thirsty, restless, alert	Thirsty, drowsy, postural hypotension	Drowsy, limp, cold, mottled
Peripheral pulses	Normal rate and strength	Rapid and weak	Rapid, thready, occasionally not palpable
Respirations	Normal	Deep, rapid	Deep, rapid
Anterior fontanelle	Normal, flat	Sunken	Very sunken
Skin turgor	Pinch retracts quickly	Pinch retracts slowly	Pinch retracts very slowly ("tenting")
Capillary refill	Normal (<2 sec)	Prolonged (3–4 sec)	Very prolonged (>4 sec)
Eyes	Normal, tearing	Sunken, dry	Very sunken, dry
Mucous membranes	Moist	Dry	Very dry
Blood pressure	Normal	Normal (low range)	Hypotension

Table 6.6. Classification of hemorrhagic shock in children.

	Class I	Class II	Class III	Class IV
Blood loss(%)	<15%	15%–25%	26%–39%	>40%
Cardiovascular	Normal to ↑ hear rate (HR)	↑ HR	↑↑ HR	↑↑↑ HR
	Normal blood pressure	Normal blood pressure	Hypotension	Profound hypotension
	Normal pulses	Diminished peripheral pulses	Thready peripheral pulses	Absent peripheral pulses
				Thready central pulses
Respiratory	Normal rate	Tachypnea	Moderate tachypnea	Severe tachypnea
Central nervous system	Slightly anxious	Irritable, confused, combative	Diminished response to pain	Coma
Skin	Warm, pink	Cool extremities	Cool extremities	Cold extremities
	Normal cap refill	Mottling	Mottling Pallor	Pallor Cyanosis
		Delayed cap refill	Prolonged cap refill	
Kidneys	Normal urine output	Oliguria	Oliguria	Anuria
		Increased urine specific gravity	Increased blood urea nitrogen level	
Acid–base	Normal pH	Normal pH	Metabolic acidosis	Metabolic acidosis

Source: Modified from the Committee on Trauma of the American College of Surgeons. Advanced Trauma Life Support Course for Physicians, 5th ed. Chicago: American College of Surgeons; 1993.

interrupted aortic arch, which are also discussed in greater detail elsewhere in this textbook.

Tension Pneumothorax

A pneumothorax is defined as an accumulation of air in the pleural space. A tension pneumothorax occurs because of the progressive accumulation of air in the pleural space, leading to a shift of the mediastinum to the contralateral hemithorax and subsequent compression (and total collapse) of the contralateral lung and great vessels, compromising both cardiovascular and respiratory function. Whether the air enters the pleural space through a defect in the chest wall, a lacerated or ruptured bronchus, or a ruptured alveolus, a one-way valve effect is created such that air enters during inhalation but cannot exit during exhalation. Accumulation of air continues until the intrathoracic pressure of the affected hemithorax equilibrates with atmospheric pressure. At this point, the accumulation of pressure within the thorax leads to depression of the ipsilateral hemidiaphragm and displacement of the mediastinum (and associated great vessels) toward the contralateral hemithorax. Although the superior vena cava (SVC) is able to move to some extent, the inferior vena cava (IVC) is relatively fixed within the diaphragm and will be compressed. As two-thirds of the venous return in children and adults comes from below the diaphragm [58], compression of the IVC leads to a drastic and profound reduction in venous return to the heart, leading to cardiovascular collapse and signs and symptoms of obstructive shock. Decompression of the pneumothorax via needle thoracentesis or thoracostomy tube placement will improve symptoms and is the treatment of choice.

Pulmonary Embolism

Pulmonary embolism (PE) is uncommonly diagnosed in children and indeed is often only discovered on autopsy [59,60]. In fact, approximately 50% of patients who have fatal PE are not diagnosed until autopsy. However, PE occurs more frequently in children than is commonly assumed [61,62], and, unfortunately, PE is frequently difficult to diagnose and fatal. The clinical presentation often is confusing, perhaps compounded by the fact that very few pediatricians have much experience with this disorder. Results of screening tests, such as oxygen saturation, electrocardiography, and chest radiography, may be normal. Thus, a high index of clinical suspicion is necessary.

A massive PE has a profound impact on gas exchange and hemodynamics. Obstruction to flow through the pulmonary artery results in increased dead space ventilation (i.e., affected lung segments are ventilated but not perfused), which is observed clinically as a substantial decrease in the end-tidal CO_2 ($ETCO_2$) that no longer reflects arterial PCO_2. A widened alveolar-to-arterial gradient, (A-a) PO_2 is present in most children as well. The mechanism for hypoxemia is somewhat controversial, although several mechanisms likely play a role. For example, an intracardiac right-to-left shunt through a patent foramen ovale may occur as right atrial pressure increases and eventually exceeds that of left atrial pressure. In addition, V/Q mismatching is compounded by the accompanying fall in cardiac output that results from massive PE, leading to mixed venous desaturation. Pulmonary embolism increases the right ventricular (RV) afterload, resulting in an increase in the RV end-diastolic volume (RVEDV). The increase in RVEDV adversely affects left ventricular hemodynamics through ventricular interdependence. Specifically, the interventricular septum bows into the left ventricle (LV) and impairs diastolic filling, resulting in decreased LV preload and subsequent hypotension. The diagnosis, pathophysiology, and management of PE are discussed elsewhere in this textbook.

Cardiac Tamponade

The pericardium is relatively noncompliant such that the accumulation of a small amount of fluid (usually less than 200 mL) is sufficient to produce cardiac tamponade. However, chronic accumulation of fluid may accumulate with little to no hemodynamic derangements as the pericardium slowly stretches to accommodate the excess volume. The therapeutic implications of an acute versus chronic pericardial fluid accumulation are also important. For example, removal of even a small volume of pericardial fluid from an acute effusion or hemopericardium will decrease the intrapericardial pressure significantly and relieve symptoms of cardiac tamponade. Conversely, because of the change in the pericardial compliance curves, a large volume of pericardial fluid from a symptomatic, chronic effusion will need to be removed to attain comparable relief of tamponade.

Cardiac tamponade is produced by compression of the heart by accumulation of pericardial fluid beyond a certain threshold. The true *filling pressure* of the heart is represented by the myocardial transmural pressure (i.e., intracardiac pressure minus intrapericardial pressure). Therefore, as intrapericardial pressure rises, the *filling pressure* of the heart decreases and stroke volume falls. The body attempts to compensate for the increase in intrapericardial pressure (and hence transmural pressure) by increasing systemic central venous pressure and pulmonary venous pressure so that the left and right ventricular filling pressures are higher than the intrapericardial pressure. Left and right atrial pressures increase and equilibrate as the intrapericardial pressure rises. Although this equalization of atrial pressures is often touted as a hallmark of cardiac tamponade, it is more commonly observed with inflammation-induced etiologies and should not be relied on as a pathognomonic sign of tamponade in the postoperative cardiac patient [63,64].

Pericardiocentesis is the life-saving procedure of choice for children with cardiac tamponade. Medical stabilization with fluid resuscitation and inotropic support is temporary at best and somewhat controversial as fluid resuscitation may precipitate (i.e., in the case of low-pressure tamponade) or worsen tamponade physiology, especially in children who are either normovolemic or hypervolemic. In the latter scenario, fluid administration will increase intracardiac pressures further, hence increasing intrapericardial pressures and worsening tamponade [65–69]. The pathophysiology, diagnosis, and management of cardiac tamponade are discussed in greater detail later in this textbook.

Cardiogenic Shock

Cardiogenic shock is the term used to describe inadequate oxygen delivery resulting from depressed stroke volume as a result of myocardial failure. Calcium (Ca^{2+}) homeostasis is paramount to this physiologic process as it facilitates both systolic contraction (inotropy) and diastolic relaxation (lusitropy). Following depolarization, Ca^{2+} enters the myocyte via voltage-gated, L-type channels. This increase in intracellular Ca^{2+} triggers further release of Ca^{2+} from the sarcoplasmic reticulum (SR) via ryanodine receptors. Calcium then binds to the myofilament troponin C to cause contraction. Following contraction, Ca^{2+} is removed from the intracellular space back into the SR by a series of Ca^{2+}-regulating proteins, including SR Ca^{2+}-ATPase, sarcoplasmic-endoplasmic reticulum Ca^{2+} (SERCA), and phospholamban. Importantly, phospholamban is subject to functional regulation on the basis of its phosphorylation state modulated by kinases (e.g., protein kinase C, cAMP-protein kinase, Ca^{2+}-calmodulin kinase) and phosphatases (e.g., PP1) [70]. In its phosphorylated form, phospholamban dissociates from SERCA, resulting in increased uptake of intracellular Ca^{2+} into the SR and causing myocyte relaxation as well as having a subsequent positive inotropic effect. This mechanism is also utilized by β_1-adrenergic receptor agonists, which lead to G-protein–coupled receptor activation of adenylate cyclase, resulting in elevation in cAMP levels, activation of protein kinase A, and subsequent phosphorylation of phospholamban—thus having a positive inotropic effect. Also related to this pathway, type III phosphodiesterases hydrolyze cAMP to terminate the activation process. Thus, type III phosphodiesterase inhibitors (e.g., milrinone) prevent the breakdown of cAMP, thereby augmenting both contraction and relaxation, and may have a synergistic effect of prolonging the inotropic effect of β-agonists. In addition, there is mounting evidence that the β_1-adrenergic receptor pathway is dysfunctional in certain settings (e.g., sepsis) [71], so that while the use of β_1-receptor agonists to augment inotropy may be unsuccessful, the use of nonreceptor-based phosphodiesterase inhibition may be a preferred pharmacologic approach [72].

Among the myriad of diseases that are associated with abnormal myocardial function (Table 6.7), a variety of mechanisms may be responsible for contractile dysfunction, including circulating

Table 6.7. Common precipitating causes of cardiogenic shock.

Infectious
Viral myocarditis (coxsackie A and B, adenovirus, other enteroviruses)
Bacterial (fulminant) myocarditis (gram-negative and gram-positive sepsis)
Rickettsial
Protozoal
Metabolic
Storage diseases (glycogen storage disease, mucopolysaccharidoses)
Carnitine deficiency
Acidosis
Hypocalcemia
Inflammatory diseases
Kawasaki's disease
Rheumatic fever
Systemic lupus erythematous
Juvenile rheumatoid arthritis
Hypoxic–ischemic injury
Perinatal asphyxia
Near-drowning
Postcardiopulmonary bypass
Asphyxia/near–sudden infant death syndrome
Myocardial infarction/anomalous left coronary artery
Toxicities
Anthracyclines
Sulfonamides
Calcium channel blockers
B-receptor blockers
Thyrotoxicosis
Cardiac-related causes
Dysrhythmias
Bradycardia
Supraventricular tachycardia
Ventricular tachycardia
Cardiomyopathies
Idiopathic dilated cardiomyopathy
Familial dilated cardiomyopathy
Increased afterload
Aortic stenosis
Coarctation of the aorta
Hypertrophic cardiomyopathy
Coarctation of the aorta
Malignant hypertension/pheochromocytoma
Neuromuscular disorders
Duchenne muscular dystrophy
Spinal muscular atrophy

myocardial depressant factors, myofilament insensitivity to Ca^{2+}, apoptosis and/or necrosis, uncoupling of myocyte mitochondrial energy production, and/or β-receptor downregulation/dysfunction. However, regardless of the underlying pathology, the characteristic mechanical defect in cardiogenic shock is a marked reduction in contractility that shifts the left ventricular end-systolic pressure–volume curve to the right. As a result, at a similar degree of afterload or systolic pressure, the ventricle ejects less stroke volume per beat, resulting in a substantially increased end-systolic volume. To compensate for the diminished stroke volume, the curvilinear diastolic pressure–volume curve also shifts to the right, reflecting a decrease in diastolic compliance or lusitropy so that the increased diastolic filling is ultimately coupled with an increase in LV end-diastolic pressure (LVEDP). Thus, this compensatory mechanism to enhance cardiac output increases LVEDP with a concomitant cost of both increased myocardial oxygen demand and the development of signs of congestive heart failure (e.g., pulmonary edema, hepatomegaly, jugular venous distention, pedal edema) commonly observed in this setting.

Distributive Shock

Distributive shock, as the name implies, results from abnormalities in vasomotor tone that lead to the maldistribution of a normally effective blood volume and flow. Peripheral vasodilation and shunting can lead to a state of *relative hypovolemia*. Distributive shock arises from a variety of disorders and encompasses various states of shock arising from anaphylaxis (*anaphylactic shock*), central nervous system injury (which includes *neurogenic* and *spinal shock*), and *sepsis*. *Anaphylaxis* refers to a systemic, immediate hypersensitivity reaction that is potentially life threatening and characterized by the onset of signs and symptoms within seconds to minutes following exposure to the offending agent (e.g., insect envenomation, medication, food), involvement of multiple organ systems, and involvement of systems distant from the site of exposure. Although the true incidence of anaphylaxis is difficult to define, it is certainly not uncommon, and the most frequent causes of anaphylaxis are foods, hymenoptera stings, and medications.

Anaphylaxis is caused by the release of mediators from mast cells and basophils. Antigen bridging of IgE antibodies bound to FcεRI (high-affinity IgE) receptors on the cell surface leads to the aggregation of the receptors and activation of an enzymatic cascade initiating mediator release. Mast cells and basophils are concentrated near exposed mucosal surfaces, such as the lung and the gastrointestinal tract, and, as such, children with anaphylaxis will typically present with signs and symptoms affecting these organ systems (wheezing, respiratory distress, vomiting, hives, and so forth). Although several mediators are released from the mast cell and basophil, including histamine, platelet activating factor, and the leukotrienes (the so-called slow-reacting substances of anaphylaxis), histamine is the most important mediator of anaphylaxis. Subcutaneous administration of epinephrine is the mainstay of the treatment of anaphylaxis. Additional adjunctive therapies include the administration of systemic corticosteroids and parenteral antihistamines.

Neurogenic shock results from autonomic dysfunction occurring secondary to injury to the spinal cord. Loss of peripheral vascular tone and subsequent increased venous capacitance lead to a relative hypovolemia caused by expansion of the vascular space. Children with neurogenic shock often fail to improve with fluid resuscitation but instead respond to treatment with selective α-adrenergic vasoactive infusions.

Diagnosis of Shock

Shock is primarily a clinical diagnosis. The diagnosis is relatively straightforward in the latter stages of shock as in a child who is lethargic, ashen, gray, tachypneic, cold, and hypotensive (see the description of *the superannuated hag*, earlier). Unfortunately, intervention at this stage (i.e., irreversible shock) is unlikely to be successful. The diagnosis of shock requires a high index of suspicion. Early recognition and timely, aggressive intervention are paramount. Important historical clues in the infant are poor feeding, slow weight gain, sweating with feeds, and fussiness, whereas an older child may complain of sleep difficulties (orthopnea), excessive fatigue, exercise limitations, chronic cough, and palpitations. Family history of congenital heart disease, metabolic disease, and autoimmune disease, along with medication exposure and infectious disease exposure, should be ascertained. The presence of tachycardia, tachypnea, gallop, rales, jugular venous distention, hepatomegaly, and extremity edema are consistent with cardiogenic failure. As discussed above, the body's compensatory mechanisms will maintain adequate function of the vital organs (*compensatory stage* of shock) for a time so that frank hypotension remains both a late and ominous sign.

In its final stages, uncompensated shock can be characterized by the presence of anion gap acidosis. An anion gap >16 mEq/L can be used as a surrogate marker for ATP depletion and energy failure. When oxygen delivery is inadequate, anaerobic metabolism occurs through glycolysis, with pyruvate being converted to lactate and lactic acid, which is responsible for the anion gap. *Glycopenic* shock can be diagnosed when an anion gap exists in the presence of hypoglycemia (inadequate substrate), hyperglycemia (insulin resistance), or euglycemia (inadequate substrate + insulin resistance). When glucose utilization is inadequate, the anion gap is caused by organic acid intermediates produced by catabolism of protein and/or fat to fuel the Krebs cycle.

It cannot be overemphasized that early recognition of shock is critical as time-sensitive, early reversal of clinical signs of shock has been shown to influence outcomes in critically ill patients. In adults, Rivers and colleagues [73] demonstrated the importance of early goal-directed therapies, which maintain not only blood pressure but also oxygen delivery, in improving outcome [73–78]. In this study, adults presenting to the emergency department in shock were randomized early on to receive either therapies directed at achieving normal blood pressure or therapies directed toward achieving not only normal blood pressure but also a superior vena cava (SVC) oxygen saturation ≥70%. In this latter arm, investigators used packed red blood cell transfusion (for patients with a hemoglobin less than 10 g/dL to reverse *anemic shock*) and/or fluids and inotropic support (to reverse *ischemic shock*) if the SVC saturation remained less than 70%. The theory behind this approach is based on the concept of oxygen delivery, as reviewed earlier, in which DO_2 depends on oxygen-carrying capacity (hemoglobin), oxygen content of arterial blood (percent oxyhemoglobin plus dissolved oxygen), and cardiac output. Thus, if the hemoglobin and arterial oxygen saturation are normal, then cardiac output predominantly determines oxygen delivery. As cardiac output decreases and metabolic demands remain the same, the mitochondria extract more oxygen

to maintain a similar amount of energy production; therefore, the oxygen saturation of blood returning to the heart (normally ~75%) decreases.

Rivers et al. [73] observed that patients in the first arm attained a normal blood pressure but had an average SVC oxygen saturation of only 65%. In contrast, those in the second treatment arm received more blood transfusion, fluid resuscitation, and inotrope use to both maintain normal blood pressure and achieve an SVC saturation above 70%. Of note, this early (within 6 hr), goal-directed (SVC saturation >70%) therapy resulted in a nearly 50% reduction in mortality.

In a second analysis of this study, the authors evaluated patients who had shock characterized by tachycardia and decreased SVC O_2 saturation with normal or high blood pressure. Interestingly, these patients had higher mortality rates than those patients presenting with hypotension. When this group of patients with tachycardia, low SVC O_2 saturation, and normotension were evaluated by treatment arms, those who received therapies directed toward a goal SVC O_2 saturation >70% had reduced multiple organ failure and mortality. The authors described this type of shock without hypotension as *cryptic* or *ischemic* shock. *Ischemic* shock without hypotension can be represented by the following equation: Decreased cardiac output = (normal or high mean arterial pressure − central venous pressure) / increased SVR. Their data suggest that reversal of this normotensive *ischemic* shock can reduce organ failure and mortality.

Emergency departments place central lines for measurement of SVC oxygen saturations less frequently in children than in adults, making a corresponding study in children unlikely, although the feasibility of this approach in adults has been confirmed [79–81]. However, in a similar manner, a recent landmark study showed that the predominant factor that reduces mortality and neurologic morbidity in children transported to tertiary care pediatric hospitals is the reversal of shock through early recognition and resuscitation in the referring emergency department [82]. In this study, Han and colleagues examined early goal-directed therapy for neonatal and pediatric shock in community hospital emergency departments, using prolonged capillary refill >2 sec as a surrogate marker of decreased cardiac output rather than decreased SVC O_2 saturation. In all patients with shock, both mortality and neuromorbidity increased with the following progression of clinical signs: tachycardia alone → hypotension with normal capillary refill → prolonged capillary refill without hypotension → and, finally, the combination of prolonged capillary refill with hypotension (which carried the highest mortality risk). Reversal of these clinical signs in the emergency department reduced mortality and neuromorbidity by more than 50%, and each hour that passed without reversal of hypotension or reduction in capillary refill was associated with a twofold increased odds ratio of death. Thus, the ability to both recognize and reverse shock in children may be the most important lessons to be learned in the practice of pediatric critical care medicine.

Management of Shock

Goal-Directed Therapy

Resuscitation to clinical goals remains the first priority in the management of shock. Children should be resuscitated to normal mental status, normal pulse quality proximally and distally, equal central and peripheral temperatures, capillary refill <2 sec, and urine output >1 mL/kg/hr. Because 20% of blood flow goes to both the brain and the kidney, clinical assessment of the function of these two organs can be informative, and a normal mental status and urine output generally suggest adequate cardiac output. Distal pulse quality, temperature, and capillary refill reflect systemic vascular tone and cardiac output. Normal capillary refill and toe temperature ensures a cardiac index greater than 2.0 L/min/m^2. Fluid resuscitation should be monitored using a combination of physical examination findings (palpation of the liver edge, increasing tachypnea, onset of basilar rales on auscultation, and so forth) in addition to monitoring tools (central venous or atrial pressures) as surrogate indicators of when fluid resuscitation has likely been adequate and it is necessary to initiate inotropic therapy. The predictive hemodynamic response to a fluid bolus can often be ascertained by applying gentle but constant pressure over the liver in the right upper quadrant to provide an *auto transfusion* while assessing the immediate hemodynamic response in terms of heart rate and blood pressure changes. The recent studies referenced above add support to the concept that titrating resuscitation to simple clinical parameters is likely to be as effective as utilizing advanced hemodynamic parameters such as SVC O_2 saturation.

Normal heart rate and perfusion pressure for age (MAP − CVP) should be the initial hemodynamic goals. Fluid resuscitation can be monitored by observing the effects on heart rate and MAP − CVP. The heart rate should decrease and MAP − CVP increase when fluid resuscitation is effective. In contrast, the heart rate may increase and MAP − CVP will narrow if too much fluid is given. The *shock index* (heart rate/systolic blood pressure) [78,83–86] can also be used to assess the effectiveness of fluid and inotrope therapy. If the applied therapy (e.g., preload or inotropy) increases the stroke volume, then the heart rate will decrease and systolic blood pressure will increase, resulting in a lower shock index value. However, if stroke volume does not improve with resuscitation, then heart rate will not decrease, systolic blood pressure will not increase, and shock index will not improve.

In the era of early goal-directed therapy, an increasing number of pediatric intensivists consider placement of superior vena cava central venous catheters in order to monitor SVC oxygen saturation, although data supporting this practice in pediatrics does not exist. Nevertheless, targeting a SVC O_2 saturation to >70% is an oft quoted goal. Similar to the approach for adults, the critically ill child in shock should be transfused if the hemoglobin level is suboptimal and if normalized, and then inotropes and vasodilators can be used to improve cardiac output until the SVC saturation is >70%. An additional target sometimes used by clinicians is to maintain a normal arterial to venous oxygen content difference, the so-called $AVDO_2$. The $AVDO_2$ can be calculated as follows:

- (1.39 × Hg) × art. saturation + (PaO_2 × 0.003) = mL O_2/100 mL blood = CaO_2
- (1.39 × Hg) × ven. saturation + (PvO_2 × 0.003) = ml O_2/100 mL blood = CvO_2
- $CaO_2 - CvO_2 = AVDO_2$ (ml O_2 /100 mL blood)

Typical normal values (Hg = 14, PaO_2 90 and SaO_2 = 100%, PvO_2 40 and SvO_2 = 75%) would show an average difference of usually less than 5 ml O_2/100 mL blood, which corresponds to a saturation difference of 25%. When the $AVDO_2$ is greater than 25, suggesting

increased oxygen extraction because of inadequate delivery, cardiac output should be increased with inotrope and vasodilator therapy until the $AVDO_2$ returns to the normal range. The $AVDO_2$ is most accurately determined when the venous saturation is measured in the pulmonary artery. In these circumstances, cardiac output can be measured using either the pulmonary artery catheter and thermodilution or pulse-induced contour cardiac output. In this setting, a typical goal cardiac index is ≥2.5 L/min/m^2 in cardiogenic shock and between 3.5 and 6.0 L/min/m^2 in septic shock. Furthermore, with the aid of either a pulmonary artery catheter (to measure the capillary wedge pressure as an estimate of LVEDP) or a left atrial catheter (as commonly provided by the cardiac surgeon), these surrogates of LVEDP can be trended to that value at which the best cardiac output can be achieved. For example, higher filling pressures may be required to attain the required end diastolic volume to achieve optimal stroke volume in a noncompliant, postoperative myocardium that can be determined during the wean from cardiopulmonary bypass. Thus, advanced monitoring can allow the clinician to optimally achieve these hemodynamic goals in the setting of shock.

Many clinicians use lactate as a serum measure of anaerobic metabolism; however, lactate can be elevated by a number of conditions in the absence of shock. These include metabolic disorders, lymphoproliferative disorders, liver failure, and sepsis. Following lactate levels have been most useful in the setting of preoperative and postoperative cardiogenic shock (although levels can be increased even in the absence of the low flow state). For these patients, mortality risk increases as serum lactate levels rise above 2.0. More helpful may be trending the change in lactate as it has been shown that a change in lactate level of ≥0.75 mmol/L per hour was associated with worse outcomes and was superior to predicting a poor outcome (89% sensitivity, 100% specificity, and a 100% positive predictive value) as compared to single worse values [87]. When used as a hemodynamic goal, a diminishing value over time with an ultimate value <2.0 is generally the target. Others target therapies to the reversal of the anion gap acidosis (goal of <16), which is attributed to anaerobic metabolism in low-flow states and to organic acids in glycopenic states. Even if patients have received bicarbonate it will mask acidosis but it will not mask anion gap. Nonanion gap acidosis caused by the strong ions sodium and chloride is common in patients resuscitated with saline. The acidosis remains even though the anion gap has resolved. The acidosis is caused by strong anion administration (NaCl) but not by energy failure. In the setting of cardiogenic shock, some have used troponin I levels as a therapeutic marker for cardiac injury and dysfunction. Troponin I levels are increased with myocardial injury and become normal with resolution of myocardial injury. Finally, creatinine clearance can be used as a therapeutic marker for renal dysfunction that will improve as renal hemodynamics improve with therapies targeted to support DO_2. Thus, a series of biochemical markers can be trended as surrogates for shock reversal and serve as important correlative data to the clinical examination and hemodynamic parameters that are simultaneously being followed.

Specific Therapy

Fluids

Fluid therapy is the hallmark of shock resuscitation in infants and children. It is used to reverse the hypovolemic state and optimize contractility based on the principle of the Starling curve. Approximately 8% of the total blood volume is contained within the arterial side, 70% in the venous side, and 12% in the capillary beds. The total blood volume in a baby is approximated as 85 mL/kg and decreases slightly (to 65–75 mL/kg) in the infant or child. Rapid resuscitation is often necessary to restore circulating volume. Because of significant vasoconstricting abilities, hypotension is not often observed until 50% of blood volume is lost (see Figure 6.2). Therefore, rapid fluid boluses in increments of 20 mL/kg minimally up to 60 mL/kg may be required to restore intravascular volume. However, if the patient has capillary leak syndrome, as may occur in septic shock, then quite large volumes (up to 200 mL/kg) may be needed in the first hour. Either crystalloids (e.g., 0.9% normal saline or lactated Ringer's) or colloids (e.g., 5% albumin) can be used to restore intravascular volume. Although it appears that less colloid fluids may be needed than crystalloid fluids as they redistribute to the extravascular space more slowly, a recent large, multicenter, randomized, controlled trial demonstrated no differences among outcomes in adults resuscitated with normal saline as compared with 4% albumin [88]. Of note, in a subgroup analysis there was a suggestion that 4% albumin was more effective in patients with sepsis/septic shock compared to crystalloid, although this nearly 5% mortality reduction did not reach statistical significance [88]. Few pediatric-specific data exist, although in a randomized, controlled trial of children with dengue shock syndrome (a disease in which capillary leak is often quite profound), crystalloid and colloids performed equally as well [89]. In light of this, usual practice is to initiate volume resuscitation with crystalloid fluids as a first-line and follow with colloid if needed.

Rapid bolus of volume employing a push technique not only restores intravascular volume but may also *turn off* expression of inflammation and coagulation genes. Numerous studies have shown that rapid and aggressive volume resuscitation within the first hour improves survival not only in animal models but, more importantly, in human shock. Fluid administration should be judicious, however, in neonates and children with cardiogenic failure from cardiomyopathy or congenital heart disease as lower myocardial compliance often results in less volume needed to achieve optimal stroke volume as predicted by Starling curves. Conversely, these children may be pushed off the Starling curve in the setting of overaggressive fluid management. Because of this, titrating in volume boluses as low as 5 to 10 mL/kg is often done while carefully monitoring the trend of CVP, left atrial pressure, pulmonary artery occlusion pressure, MAP, and mixed venous saturation in these patients.

Blood Products

Transfusion with packed red blood cells (PRBC) is absolutely crucial for children with anemia and shock. Mitochondria cannot extract the last 20% of oxygen bound to hemoglobin. Under normal conditions the mitochondria typically extract 25% of oxygen bound to hemoglobin. This is reflected clinically by a mixed venous oxygen saturation of 75% in a healthy patient with an arterial blood oxygen saturation of 100%. In a child with 10 g/dL hemoglobin, only 8 g/dL is available for extraction as 20% cannot be extracted. Thus, 2.5 g/dL is used for oxygen extraction, leaving a surplus of 5.5 g/dL of hemoglobin. In states of hemolysis, anemic shock can develop as surplus hemoglobin is lost (i.e., drops below 5 g/dL). Mortality rates are known to increase as the hemoglobin drops below 6 g/dL in various settings, including hemorrhagic shock. Transfusion of

blood is life saving in these circumstances. Whole blood is available in some parts of the world, while packed red blood cells are available in other parts of the world. The usual hemoglobin concentration of packed red blood cells is 20 g/dL. Because the blood volume of the child ranges from 65 to 85 mL/kg based on age, 10 mL/kg of packed red cells should increase the hemoglobin concentration by approximately 2 g/dL. Blood can be rapidly infused in patients with life-threatening hemolytic anemia; however, furosemide may be needed to prevent fluid overload if hypovolemia is not a concurrent challenge.

Inotropes

Inotropic agents (Table 6.8) are used to increase contractility and, as a result, stroke volume and cardiac output. This effect can best be appreciated by examining the ventricular pressure–volume curve, which is one method by which to define ventricular stroke work (Figure 6.7A). As shown in Figure 6.7B, positive inotropic agents shift the end-systolic pressure–volume relationship (ESPVR) to the left, resulting in a greater stroke work for any given preload and afterload. Most of the inotropic agents are adrenergic receptor agonists and include both endogenously produced catecholamines (e.g., dopamine, epinephrine, and norepinephrine) as well as synthetic analogs (e.g., dobutamine). The exceptions to this pharmacologic mechanism are agents that inhibit type III phosphodiesterase (e.g., inamrinone, milrinone, and enoximone), resulting in elevated cAMP, as well as those agents that increase sensitivity of the myofilament to calcium (e.g., levosimendan).

Adrenergic receptors fall into three categories: α-adrenergic, β-adrenergic, and dopaminergic (DA) receptors. The receptors responsible for inotropic stimulation are the β_1-adrenoreceptors located on the myocardium, whereas the β_2-receptors exist on the vascular and bronchial smooth muscle and mediate vaso- and bronchodilation, respectively. α-Adrenoreceptors include the α_1-subtype located on peripheral vasculature, and stimulation mediates smooth muscle contraction and, thus, vasopressor effects (discussed later). Following their initial descriptions, α_2-receptors were identified on the presynaptic terminals of sympathetic nerves,

Table 6.8. Vasoactive pharmacologic agents commonly used in the management of pediatric shock.

Agent	Dose Range	Comments
Dopamine[1–3]	3–5 μg/kg/min	Renal-dose dopamine (primarily dopaminergic agonist activity); increases renal and mesenteric blood flow, increases natriuresis and urine output
	5–10 μg/kg/min	Inotropic (β_1-agonist) effects predominate; increases cardiac contractility, heart rate, and blood pressure
	10–20 μg/kg/min	Vasopressor (α_1-agonist) effects predominate; increases peripheral vascular resistance and blood pressure
Dobutamine[1,2]	5–10 μg/kg/min	Inotropic effects (β_1-agonist) predominate; increases contractility and reduces afterload
Epinephrine[1,2]	0.03–0.1 μg/kg/min	Inotropic effects (β_1- and β_2-agonist) predominate, increases contractility and heart rate; may reduce afterload to a slight extent via β_2-effects
	0.1–1 μg/kg/min	Vasopressor effects (α_1-agonist) predominate; increases peripheral vascular resistance and blood pressure
Norepinephrine[1,2]	0.1–1 μg/kg/min	Potent vasopressor (α_1- and β_1-agonist); increases heart rate, contractility, and peripheral vascular resistance; absent β_2-effect distinguishes it from epinephrine
Phenylephrine[1,2,4]	0.1–0.5 μg/kg/min	Potent vasopressor with primarily α_1-agonist effects; indicated in tetralogy of Fallot hypercyanotic spells (tet spells)
Vasopressin[1,2,5]	0.0003–0.002 units/kg/min (0.018–0.12 units/kg/hr)	Vasopressor (via V_1) without inotrope activity; may be indicated in refractory shock
Nitroglycerin[1,4,6]	0.5–3 μg/kg/min	Dose-dependent venodilator and vasodilator (cGMP mediated)
Nitroprusside[1,7]	0.5–3 μg/kg/min	Systemic arterial vasodilator (cGMP mediated)
Inamrinone[1,8]	0.75 mg/kg IV bolus over 2–3 min followed by maintenance infusion 5–10 μg/kg/min	Inodilator (type III phosphodiesterase inhibitor); increases cardiac output via increased contractility and afterload reduction
Milrinone[1,9]	50 μg/kg administered over 15 min followed by a continuous infusion of 0.5–0.75 μg/kg/min	Inodilator (type III phosphodiesterase inhibitor); increases cardiac output via increased contractility and afterload reduction
Prostaglandin E_1 (PGE_1)[10]	0.03–0.1 μg/kg/min	Maintains patent ductus arteriosus (cAMP effect)

[1]Correct volume depletion before starting infusion.

[2]Extravasation may produce tissue necrosis (as a general recommendation, should be administered via central venous access). Treatment with subcutaneous administration of phentolamine as follows: *Neonates*, infiltrate area with a small amount (e.g., 1 mL) of solution (made by diluting 2.5–5 mg in 10 mL of preservative-free NS) within 12 hr of extravasation; do not exceed 0.1 mg/kg or 2.5 mg total. *Infants, children, and adults:* infiltrate area with a small amount (e.g., 1 mL) of solution (made by diluting 5–10 mg in 10 mL of NS) within 12 hr of extravasation; do not exceed 0.1–0.2 mg/kg or 5 mg total.

[3]Dopamine has exhibited nonlinear kinetics in children (dose changes may not achieve steady state for approximately 1 hr compared with 20 min in adults).

[4]Exhibits rapid tachyphylaxis (dose may need to be increased with time to achieve same clinical effect).

[5]Dose not well established for children or adults; abrupt discontinuation of infusion may result in hypotension (gradually taper dose to discontinue the infusion); may be associated with profound peripheral vasoconstriction (leading to tissue ischemia).

[6]May cause profound hypotension in volume-depleted patients; nitroglycerin adsorbs to plastics; intravenous solution must be prepared in glass bottles and special administration sets intended for nitroglycerin (nonpolyvinyl chloride) must be used.

[7]Converted to cyanide by erythrocyte and tissue sulfhydryl group interactions; cyanide is converted in the liver by the enzyme rhodanase to thiocyanate (thiocyanate levels should be monitored).

[8]Metabolized in the liver; causes thrombocytopenia (may be dose related); milrinone is now preferred agent

[9]Metabolized in the kidney; relatively long half-life (use with caution in children with hemodynamic instability).

[10]Dose may be decreased once the ductus arteriosus has opened with very little change in therapeutic effects; may cause hypotension, apnea, cutaneous flushing.

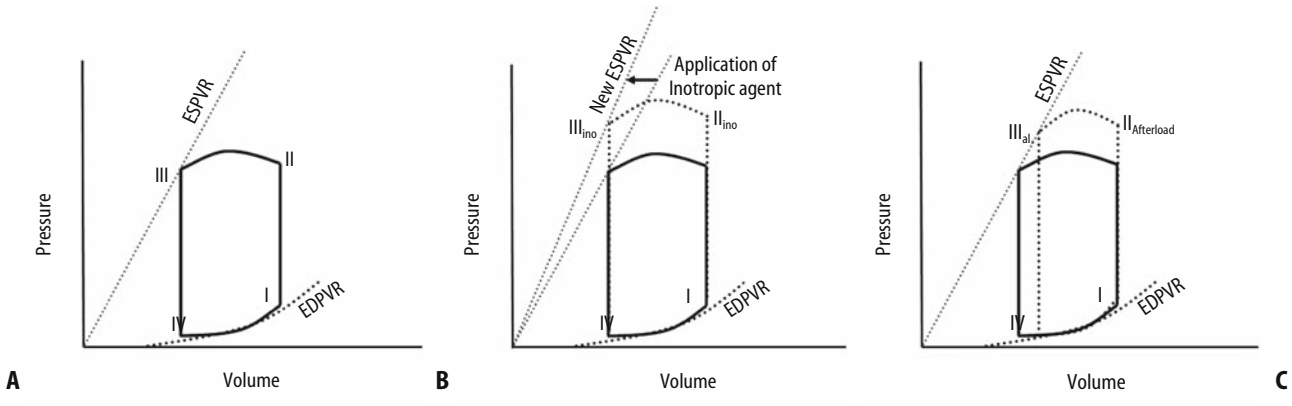

FIGURE 6.7. **(A)** The ventricular pressure–volume curves are defined by the end-diastolic (EDPVR) and end-systolic (ESPVR) pressure–volume relationships. End-diastolic volume increases from Point IV to Point I as the ventricle fills during diastole. As the ventricle contracts, pressure is increased without a change in volume (Point I to II, termed "isovolumetric contraction") until this pressure exceeds that of the aorta (LV) or pulmonary artery (RV) and the semilunar valve is opened and ventricular ejection occurs (Point II to III). After the ventricle empties it undergoes isovolumetric relaxation (Point III to IV). Modifications in preload, afterload, and inotropy affect the ESPVR and, as a result, total stroke work performed by the ventricle. **(B)** Application of an inotropic agent results in a leftward shift of the ESPVR as a result of improved contractility and a higher pressure generated during isovolumetric contraction. Thus, overall stroke work (volume) is augmented. **(C)** Affect of increasing afterload on ventricular stroke work. An acute increase in afterload mediated by the application of a vasopressor agent will increase the ventricular pressure needed to be generated to open the semilunar valve (Point II to Point $II_{afterload}$) to allow for ventricular ejection (to III_{al}). Unless compensatory changes accompany this increased afterload (e.g., increasing preload or contractility), stroke work will actually decrease, although blood pressure may be augmented. This phenomenon explains the risk involved in using vasopressors in the setting of myocardial dysfunction.

and stimulation inhibited norepinephrine release. They have also been identified on postsynaptic smooth muscle where stimulation results in contraction, although the contribution of this mechanism to vasopressor effects of adrenergic agonists is not fully known [90]. From a pharmacokinetic standpoint, nearly all the inotropes used clinically are cleared by first-order kinetics such that changes in infusion rates linearly correlate to plasma concentrations, making them practical to titrate to clinical effect. In addition, the adrenergic receptor agonists are rapidly metabolized by circulating catechol-O-methyltransferase (COMT) followed by deamination (via monoamine oxidase) or sulfoconjugation (by phenolsulfotransferase) such that the effective half-lives of these agents is on the order of minutes. Therefore, these agents are preferably administered via continuous infusion—most commonly via a central venous catheter. Of note, the phosphodiesterase inhibitors are cleared by the kidneys (requiring dosage adjustments in renal failure) and possess a half-life estimated to be 45–60 minutes.

Dopamine

Historically, the mainstay of inotropic therapy in pediatrics has been dopamine, which is the immediate precursor in the catecholamine biosynthetic pathway (Figure 6.8). Because of its unique properties of being able to stimulate dopaminergic (0–3 μg/kg/min), β-adrenergic (3–10 μg/kg/min), and α-adrenergic receptors (>10 μg/kg/min) in a dose-dependent manner, some clinicians refer to this agent as an *inovasopressor*, as both inotropic and vasopressor activities can be observed with escalating dosage. The pharmacologic effect of dopamine is derived from two relatively equipotent properties—direct agonist stimulation of the receptors and indirect release of norepinephrine from the sympathetic vesicles.

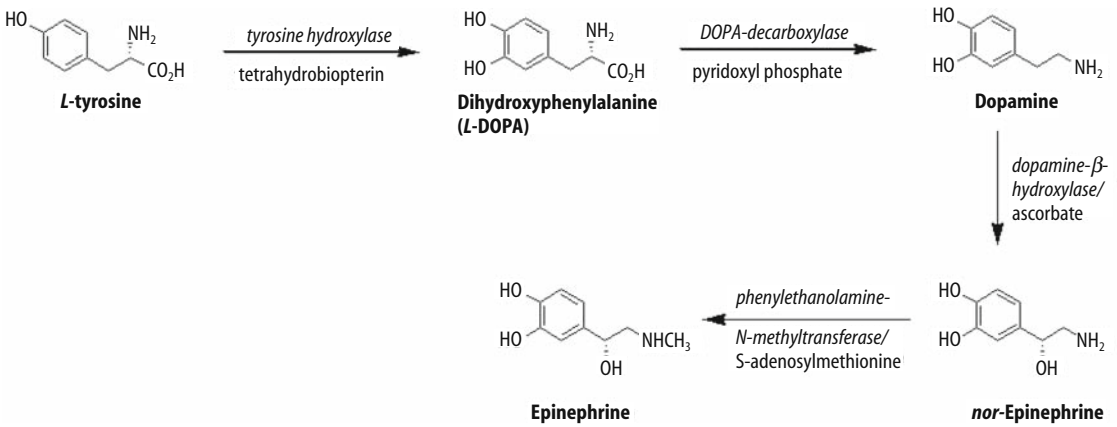

FIGURE 6.8. Catecholamine biosynthesis. (Courtesy of William Joe Wheeler, PhD.)

Because infants younger than 6 months have been considered to not possess their full number of sympathetic vesicles (corroborated by studies of immature animals), it has been suggested that there is a relative age-specific insensitivity to the drug such that increased infusion rates may be necessary [91]. However, these data remain controversial in that Seri et al. [92] have demonstrated clear physiologic responses to normal dopamine infusion rates (3–7 μg/kg/min) in premature infants. Relative *dopamine insensitivity* can also be observed in older children and adults who may have exhausted endogenous catecholamine reserves because of prolonged stress responses before reaching the clinical care setting.

When infused at 3–10 μg/kg/min, dopamine increases cardiac contractility and cardiac output with only modest effects on heart rate and SVR. Because of its general effectiveness and the vast familiarity and experience with this agent, dopamine has remained the first-line inotropic agent for *fluid refractory* shock. Infusion rates can be increased gradually in order to titrate its inotropic effect to the goals outlined earlier. Surveys of common practice suggest that although infusion rates as high as 40 μg/kg/min have been reported, most clinicians stop escalating at 20 μg/kg/min and choose instead to add a second vasoactive agent. Because of the imprecise ability to differentiate infusion rates mediating strictly inotropic effects from vasopressor effects during the transition from β- to α-adrenergic receptor stimulation, some clinicians express concern for the use of dopamine alone in cardiogenic shock. Although relatively few studies have been performed, it has been suggested that, because dopamine alone increases not only mean arterial blood pressure but also pulmonary capillary wedge pressure and myocardial oxygen extraction, clinicians consider adding a vasodilator (e.g., dobutamine) as the combination may be more beneficial than dopamine alone in this setting [93]. Another major effect of dopamine is to selectively increase renal and splanchnic perfusion. However, the ascribed renal protective effect of *renal-dose* dopamine has not been substantiated in recent large clinical trials designed to examine this possible benefit and are more likely to be related to modest improvements in cardiac output associated with even low infusion rates [94]. Dopamine, similar to most inotropic agents, will worsen ventilation/perfusion matching such that intrapulmonary shunt increases and, as a result, PaO_2 may decrease. As an interesting aside, a multicenter, cohort study of critically ill adults with sepsis recently noted that patients who were treated with dopamine had a higher mortality rate than those who were treated with other agents [95]. However, further studies showing increased mortality of patients treated with dopamine will be necessary before the decades of experience with dopamine in critically ill children is abandoned.

Dobutamine

Dobutamine is the inotropic agent synthetically derived from the catecholamine parent structure that possesses mixed β-receptor agonist activities. Thus, dobutamine possesses both chronotropic and inotropic properties mediated through β_1-adrenergic receptor stimulation as well as modest vasodilating effects related to its β_2-adrenergic receptor agonist property. The limitation of vasodilating effects relates to its preparation as a racemic mixture where the (+) isomer has potent effects at the β-receptor and modest α-adrenergic antagonist effects, but conversely the (–) isomer is a selective α_1-adrenergic receptor agonist mediating vasoconstrictor effects [96]. In addition, it has been observed that at infusion rates >10 μg/kg/min, dobutamine can lead to significant afterload reduction and at times hypotension. This is thought to occur because dobutamine at this infusion rate may possess α_2-agonist effects that inhibit release of norepinephrine from the presynaptic terminals to further reduce vascular tone. Similar to dopamine, there may be an age-specific insensitivity to dobutamine in children. Perkin and co-workers demonstrated that children under the age of two years have a reduced response to dobutamine [97]. Despite these complex properties, the primary hemodynamic effects are to increase contractility most often with little change in the heart rate or mean arterial blood pressure despite substantial increases in cardiac output. Because of these properties, dobutamine is most commonly indicated in the clinical setting that necessitates increasing inotropy without augmenting SVR as occurs most commonly with pure cardiogenic shock (e.g., myocarditis). In these cases, dobutamine will increase stroke volume while decreasing central venous pressure and often improves the ratio between myocardial oxygen supply and demand. Another common setting in which dobutamine is considered is following orthotopic heart transplantation. Because myocardial innervation is disrupted in this setting and because dobutamine does not rely on release of norepinephrine stores as dopamine does, it may be a superior agent to dopamine. Conversely, because of dobutamine's effect, this and other inotropes must be used with caution in the setting of hypertrophic cardiomyopathy.

Epinephrine

Epinephrine is the endogenous circulating neurohormone released from the adrenal medulla during stress that possesses β_1-, β_2-, α_1-, and α_2-adrenergic receptor agonist activity. It is a commonly used adjuvant inotrope for patients who fail to respond adequately to dopamine therapy or are too hypotensive to tolerate the vasodilating effects of inodilators such as dobutamine or milrinone. Adults and children who are resistant to either dopamine or dobutamine therapy will frequently respond to epinephrine. At the lower dosage or infusion rates (0.03 toward 0.1–0.3 μg/kg/min, so called *low-dose epinephrine*) its β-adrenergic effects predominate such that it is principally an inotropic agent. Based on this principle, epinephrine has become an increasingly utilized second-line inotropic agent in the setting of low cardiac output states (e.g., postcardiopulmonary bypass). The α_1-adrenergic effect on increasing SVR becomes more prominent as the epinephrine infusion rate approaches and exceeds 0.3 μg/kg/min, in which case it is sometimes described as an *inovasopressor*. Although epinephrine can mediate splanchnic vasoconstriction and theoretically lead to intestinal ischemia, this adverse effect is thought to be less significant in the critical care setting as it is countered by significant augmentation of cardiac output [98]. Patients with heart failure and increased SVR may be harmed by higher dosage epinephrine unless it is concomitantly administered with a vasodilator or inodilator. Noncardiac-related effects of epinephrine include increasing plasma glucose levels, increasing fatty acid levels, and increased renin activity with a concomitant decrease in serum potassium and aldosterone levels.

Phosphodiesterase Inhibitors

The phosphodiesterase (PDE) inhibitors are a class of drugs called *bipyridines* that mediate both inotropy and vasodilation and as a result are often referred to as *inodilators*. These agents mediate their effects by preventing hydrolysis of cAMP (type III PDE inhibi-

tors, e.g., milrinone, amrinone, enoximone, or pentoxifylline) and/or cGMP (type V PDE inhibitors, e.g., sildenafil, dipyrimadole, or pentoxifylline). When type III PDE inhibitors are administered alone, the increase in cAMP improves contractility and also causes vasodilation of pulmonary and systemic arterial vasculature, resulting in decreased ventricular afterload. Unique to this class of agents, PDE inhibitors improve ventricular relaxation (so-called lusitropic property). This effect is mediated by decreased breakdown of cAMP, resulting in activation of protein kinase A, which subsequently phosphorylates the sarcoplasmic reticulum protein phospholamban. This phosphorylation modulates the activation of sarcoplasmic reticulum ATPase (SERCA), resulting in more rapid uptake of cytosolic calcium and thus facilitating more rapid and improved myocyte relaxation [99,100]. As a result of these pharmacologic properties, the main hemodynamic effects of PDE inhibitors are to decrease both systemic and pulmonary vascular resistances, decrease filling pressures, and substantially augment cardiac output, most often with very little change in heart rate. Other effects noted with the use of PDE inhibitors include coronary artery dilation; thus there is little change in myocardial oxygen consumption and putative antiinflammatory effects, which have made it an attractive option in fluid-resuscitated, low cardiac output shock as most commonly occurs in pediatric septic shock [72]. Finally, it is notable that PDE inhibitors mediate their effects independent of β-adrenergic receptor ligation. It has become increasingly appreciated that β-receptor downregulation (e.g., in congestive heart failure), signaling disruption (e.g., in sepsis), and polymorphisms all may affect the manner by which this receptor-based pharmacologic mechanism can be utilized clinically so that PDE inhibitors may provide superior clinical effects in these settings.

The interaction of PDE inhibitors with concomitant inotropes, vasodilators, and even vasopressors can be used to therapeutic advantages in patients with a variety of forms of shock. For example, epinephrine can remain a potent and relatively pure inotrope at higher dosages when combined with a type III PDE inhibitor that will prevent breakdown of cAMP produced by β_1- and β_2-adrenergic stimulation such that increased cAMP inhibits the usual effects of epinephrine-mediated α_1-adrenergic stimulation. In a similar manner, norepinephrine may be a more effective inotrope while maintaining vasopressor effectiveness when administered with a type III PDE inhibitor. The hydrolysis of norepinephrine-mediated β_1-receptor cAMP production is inhibited so that increased cAMP improves both contractility and relaxation. In addition, norepinephrine-mediated α_1- and α_2-adrenergic effects remain unopposed because milrinone possesses no specific β_1-receptor activity and therefore has minimal vasodilatory effect in the face of potent α-adrenergic vasoconstriction. In a related manner, the type V PDE inhibitors (e.g., sildenafil, dipyridamole) may potentiate the pulmonary vasodilator effects of inhaled nitric oxide.

As alluded to above, one major challenge posed by the use of currently licensed PDE inhibitors is their relatively prolonged half-life compared with those of catecholamines and nitrosovasodilators. Although the latter agents are eliminated within minutes, PDE inhibitors are not eliminated for hours. Milrinone is primarily bound to plasma proteins (~75%) and predominantly eliminated by the kidney, whereas inamrinone is predominantly eliminated by the liver; thus, this half-life elimination is even more important in the setting of organ failure. When untoward side effects are encountered (e.g., hypotension), these drugs should be discontinued immediately. Of note, norepinephrine has been reported as being an effective antidote for these toxicities. As mentioned above, norepinephrine, on the basis of its α_1- and β_1- but not β_2-adrenergic activity will increase blood pressure via vasoconstriction (α_1 effect) and cardiac output (β_1 effect) but not exacerbate the vasodilatory effect of the PDE inhibitor.

Other Agents

Of historic note, isoproterenol was an important and commonly used inodilator that possesses both β_1- and β_2-adrenergic activities. It used to be considered an important drug in the treatment of heart block, refractory status asthmaticus, and pulmonary hypertensive crises with right ventricular failure, although its unfavorable safety profile with regard to increasing myocardial oxygen demand resulting in ischemic injury has substantially tempered its use over the past decade. Levosimendan represents a new class of *inodilators* that sensitizes calcium binding in the actin–tropomyosin complex to improve contractility, while simultaneously hyperpolarizing potassium channels to cause vasodilation [101]. To date, levosimendan has received approval for clinical use in 31 countries worldwide, and more patients with heart failure have participated in clinical trials with levosimendan than with any other intravenous inotropic agent; nevertheless, its use in pediatrics has been very limited to date [102,103].

Vasodilators

Vasodilators (see Table 6.8) are used to reduce pulmonary vascular resistance or SVR and improve cardiac output. The *nitrosovasodilators* depend on release of nitrosothiols (nitric oxide donor) to activate soluble guanylate cyclase and release cGMP. Sodium nitroprusside is both a systemic and a pulmonary vasodilator. In the setting of a failing myocardium, careful titration of nitroprusside to achieve lower afterload may improve cardiac output even though changes in blood pressure may not be observed. The usual starting infusion rate is on the order of 0.5–1 μg/kg/min. Nitroglycerin has a somewhat selective dose-dependent effect in that at <1 μg/kg/min it is a coronary artery vasodilator, at 1 μg/kg/min it provides pulmonary vasodilation, and at 3 μg/kg/min it mediates systemic vasodilation. Inhaled nitric oxide is a selective pulmonary vasodilator that can be started at 5 PPM when needed to afterload the RV or decrease pulmonary vascular resistance. Prostaglandins (PG) increase cAMP levels to provide potent systemic and pulmonary vasodilation. Prostacyclin (PGI_2) can be started at 3 ng/kg/min, and an increasing experience with this agent suggests that continuous infusions are necessary to maintain its effect. Numerous PGI_2 analogs continue to be developed (e.g., treprostinil, iloprost, and beraprost sodium); however, their roles in hemodynamic support of the critically ill child remain incompletely defined [104].

α-Adrenergic antagonists also have a role as vasodilators. Phentolamine, which is a competitive antagonist, has been used in combination with epinephrine or norepinephrine to offset the α-adrenergic effects and facilitate the β-adrenergic effects of these agents. Phenoxybenzamine has also been used for afterload reduction in neonates with single ventricle physiology [105,106]. Phenoxybenzamine binds to and inhibits the α-adrenergic receptor through covalent modification, so it possesses a very long half-life elimination making its routine use uncommon in the PICU setting.

Vasopressors

In the setting of distributive shock, low SVR results in significant hypotension and as a result inadequate organ perfusion pressure. Thus, principal pharmacologic agents indicated in anaphylactic, neurogenic, and vasodilatory (warm) septic shock include those mediating vasoconstrictive effects, so-called vasopressors (see Table 6.8). As reviewed earlier, a number of the agents that provide inotropic support at lower infusion rates via β-adrenergic stimulation transition to providing vasopressor activity as a result of α_1-adrenergic agonism at escalating infusion rates. For example, titration upward of dopamine (>10 μg/kg/min) and epinephrine (>0.3 μg/kg/min) infusion rates increase SVR. Without the concomitant increase in inotropy provided by these agents, a simple escalation in afterload will increase blood pressure, but at the expense of less stroke volume and greater ventricular work (see Figure 6.7C). In a similar manner, norepinephrine, which possesses predominantly α_1-adrenergic stimulation, also possesses β-receptor activity so that it can be effective for dopamine-resistant shock on the basis of both inotropic and vasopressor activities. As a result, dopamine and norepinephrine may have their greatest role in the maintenance of adequate perfusion pressure in children with shock.

Different from these *mixed* agonists, phenylephrine is a pure α_1-adrenergic receptor agonist that can be effectively titrated to augment systemic afterload. Because of this property, one of its principal roles in pediatrics historically has been for reversal of *tet spells* (hypercyanotic spells) in children with tetralogy of Fallot. Infants and children with tetralogy of Fallot have a thickened infundibulum that spasms and causes right-to-left blood flow through the ventricular septal defect, which substantially reduces pulmonary blood flow and leads to life-threatening hypoxemia. Therapies used to treat this spell include oxygen and morphine to relax the infundibulum and knee-to-chest positioning to increase afterload and help generate left-to-right flow across the ventricular septal defect. When these maneuvers fail, phenylephrine is implemented to increase systemic arterial vasoconstriction, resulting in to left-to-right shunting and perfusion of the lung. Because phenylephrine has no β-adrenergic effects it does not increase heart rate and hence the heart is better able to fill.

More recently, there has been renewed interest in the use of the hormonal vasopressors angiotensin and vasopressin. Angiotensin interacts with the angiotensin receptor to mediate vasoconstriction through the phospholipase C second messenger system. It has a relatively long half-life compared with the catecholamines. Angiotensin also mediates blood pressure effects through increased aldosterone secretion. It is prudent to determine whether the use of angiotensin reduces cardiac output in children with hypotension because it has no known inotropic effects. Clinical use of vasopressin has been rediscovered as well [107–111]. Unlike angiotensin, vasopressin is administered only in physiologic dosage and is thought to improve blood pressure not only through interaction with the vasopressin receptor and the phospholipase C second messenger system but also by increasing release of adrenocorticotropic hormone and subsequent cortisol release. This vasopressor should also be used with caution because it can reduce cardiac output in children with poor cardiac function. There has not been sufficient experience or clinical studies performed as of yet to fully determine the role of low dosing, hormonal-level dosing, or higher vasoconstrictive dosing of vasopressin in various forms of shock. In current clinical practice, it is most commonly instituted in catecholamine-resistant, refractory, vasodilatory shock, although earlier indications may be identified by on-going studies.

Hydrocortisone

Clinical use of hydrocortisone in shock has also been reexamined in recent years. Centrally and peripherally mediated adrenal insufficiency is increasingly common in the pediatric intensive care setting [112–114]. Many children are being treated for chronic illnesses with corticosteroids with subsequent pituitary–adrenal axis suppression. Many children have central nervous system anomalies and acquired illnesses. Some children have purpura fulminans (Figure 6.9) and Waterhouse-Friedrichsen syndrome [115]. Other investigators have reported reduced cytochrome P450 activity and decreased endogenous production of cortisol and aldosterone in some children. Interestingly, adrenal insufficiency can present with low cardiac output and high SVR or with high cardiac output and low SVR. The diagnosis should be considered for any child with catecholamine-resistant vasodilatory shock. The dose recommended for stress dosing of methylprednisolone is 2 mg/kg followed by the same dose over 24 hours, but practice varies greatly among intensivists. Central or peripheral adrenal insufficiency may be diagnosed in adequately volume-resuscitated infants or

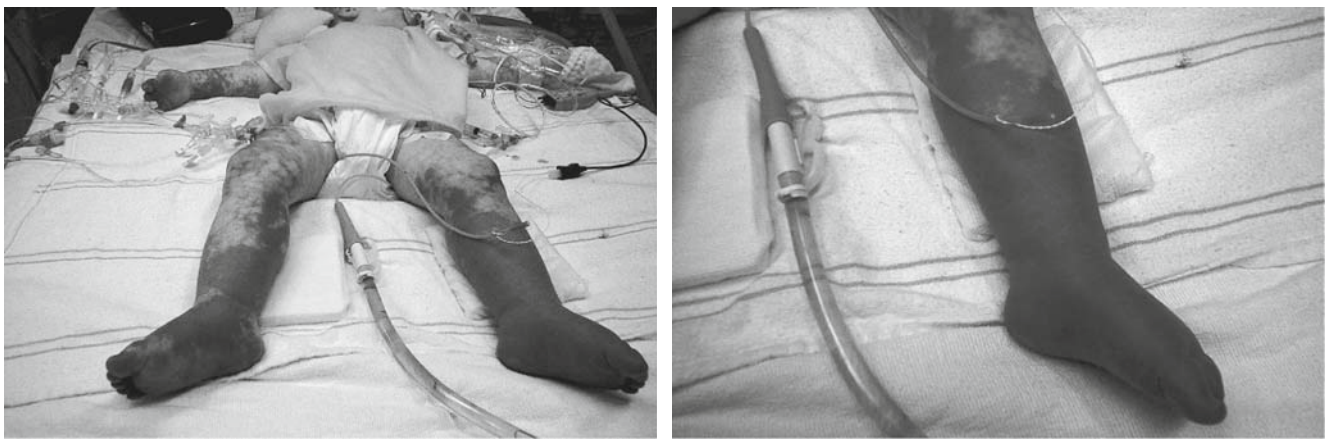

Figure 6.9. (A,B) Purpura fulminans. (Courtesy of Brian R. Jacobs, MD.)

children who require epinephrine or norepinephrine infusions for shock and have a baseline cortisol level <18 mg/dL and/or fail to mount a cortisol response greater than 9 mg/dL above the baseline value in response to adrenocorticotropic hormone stimulation (commonly 250 μg cosyntropin).

When considering the dose of hydrocortisone to be used for patients with shock it is important to understand two concepts. First, hydrocortisone must be multiplied by 6 to be glucocorticoid equivalent to methylprednisolone and by 30 to be glucocorticoid equivalent to dexamethasone dosing. The use of methylprednisolone at 2 mg/kg as a loading dose and then 1 mg/kg every 6 hr is equivalent to 30 mg/kg of hydrocortisone in glucocorticoid equivalent dosing. The use of 0.5 mg/kg of dexamethasone every 6 hr is equivalent to 60 mg/kg/day of hydrocortisone in glucocorticoid equivalent dosing. Neither methylprednisolone nor dexamethasone has any mineralocorticoid effect; however, hydrocortisone has both glucocorticoid and mineralocorticoid effects. For this reason hydrocortisone is generally recommended over methylprednisolone or dexamethasone for adrenal insufficiency. Second, cortisol levels differ during stress and shock so efforts to treat patients with adrenal insufficiency should be directed to achieving these levels. During surgical stress, cortisol levels increase to around 30 μg/dL. However, during acute shock cortisol levels can reach 150–300 μg/dL. Hydrocortisone infusion at 2 mg/kg/day (50 mg/m^2 BSA/day) will achieve serum cortisol levels in the range of 20–30 μg/dL, whereas infusions at 50 mg/kg/day can achieve levels of up to 150 μg/dL. Unfortunately, the majority of clinical data examining the role of corticosteroids in improving outcome in shock are derived from adult studies. It is hoped that a planned multicenter, randomized, controlled trial on the use of corticosteroids in pediatric sepsis and septic shock will ultimately provide pediatric intensivists with insight as to both the correct patient to treat and the correct timing and dosing of corticosteroid therapy.

Glucose and Insulin

The combination of glucose and insulin is an effective inotrope [116] that increases both cAMP and ATP production in the heart. The amount of glucose required to meet glucose delivery requirements is D10W at a maintenance intravenous fluid rate. The amount of insulin required to reverse hyperglycemia can vary from 0 to >1.0 units/kg/hr, with higher concentrations of insulin required in the context of greater insulin resistance. Higher insulin infusion rates can be associated with electrolyte abnormalities. Monitoring of phosphorous, calcium, magnesium, and potassium levels with appropriate replacement is recommended when using this therapy.

The importance of reversing glycopenia was documented by van den Berghe and colleagues in the adult surgical intensive care unit setting [117]. These investigators administered D10W at maintenance rates to meet glucose requirements in all patients. They then randomized patients to strict euglycemic control with insulin to maintain glucose levels between 80 and 120 mg/dL or to usual practice. Patients treated with insulin had a decreased serum glucose/glucose infusion rate ratio (45 vs. 75) compared with those not treated with insulin and remarkably observed a 50% reduction in mortality (3% vs. 7%). All improvements in outcome were attributed to reduction in deaths from septic shock and multiple organ failure. Administration of glucose prevents hypoglycemia, and administration of insulin for hyperglycemia guarantees delivery of the glucose into the organs with insulin-dependent glucose transporters, especially the cardiovascular system. Whether these findings are consistently observed across all critically ill patients remains to be determined, although a recent study of intensive insulin therapy in the medical ICU demonstrated a reduction in morbidity with no significant improvement in mortality [118]. In addition, a confirmatory study in critically ill children showing that strict euglycemic control can improve clinical outcomes in the pediatric population is needed [119–121].

Triiodothyronine

Triiodothyronine is an effective inotropic agent that has long been used to preserve cardiac function in patients who are brain dead and have low T_3 levels [122]. A recent randomized controlled trial in neonates showed that use of triiodothyronine as a postcardiac surgery inotrope improved outcomes [123,124]. Hypothyroidism should be expected in children who require epinephrine or norepinephrine and have trisomy 21, central nervous system illness, or a pan-hypopituitary state [125–127].

Extracorporeal Life Support

In patients who remain in *ischemic* shock (cardiac index <2.0 L/m^2 BSA/min) despite use of the above therapies, extracardiac mechanical support has been associated with up to a 50% survival in children and 80% survival in newborns. These forms of cardiac support include the venoarterial extracorporeal membrane oxygenation (ECMO), the left ventricular assist device, and the aortic balloon counter pulsation device. ECMO is commonly used in smaller children. Venovenous ECMO could be considered but only in the unusual occurrence when shock is caused by ventilator-associated (high intrathoracic pressure) cardiac dysfunction. Venoarterial ECMO is successful when shock is caused by cardiac dysfunction. Criteria for this use includes a CI <2.0 L/m^2 BSA/min or the need for more than 1 μg/kg/min of epinephrine with on-going evidence of inadequate tissue perfusion. Larger children can be managed with the left ventricular assist device or counterpulsating balloon for refractory cardiogenic shock. The left ventricular assist device can be used for prolonged support. These modalities are discussed in greater detail elsewhere in this textbook.

Conclusion

Shock is a common time-sensitive cause of death in critically ill children with excellent outcome when appropriately recognized and treated. Early recognition and implementation of goal-directed therapies attains best outcomes (Figure 6.10). Therapies should be directed to timely reversal of anemia, hypoxia, ischemia, and glycopenia. Fluids and inotropes should be used to reverse hypotension and decrease capillary refill to <2 sec within 1 hr of clinical presentation. Adrenal shock should be recognized and treated with hydrocortisone. Long-term goals after the first hour are maintenance of normal cardiac output, blood pressure, and $SVCO_2$ saturation >70%. Appropriate glucose infusion rates should be delivered and insulin used to reverse hyperglycemia. Fluids, inotropes, vasodilators, vasopressors, hydrocortisone, thyroid, and extracardiac mechanical support devices may be required to accomplish this goal.

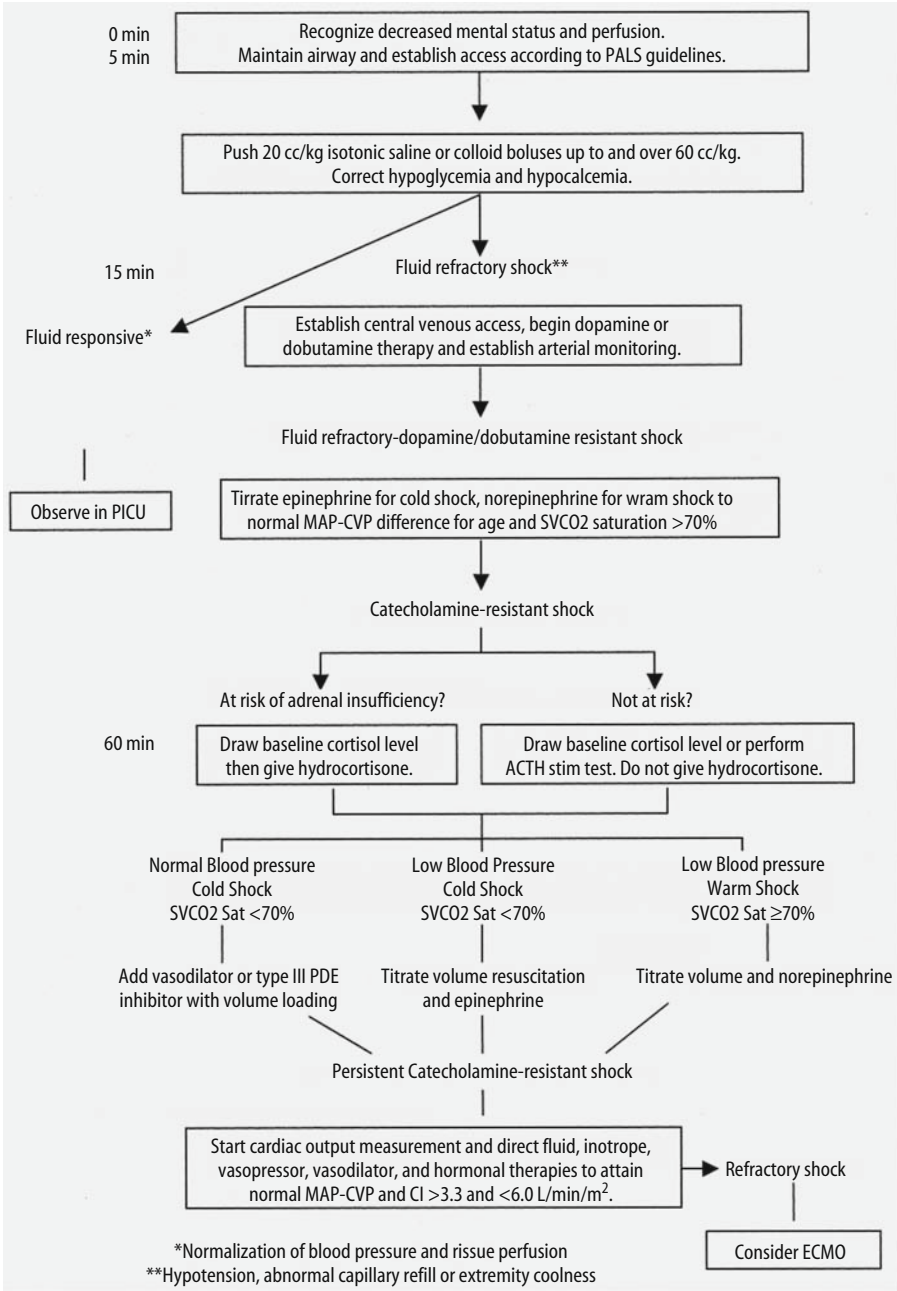

Figure 6.10. Recommendation for stepwise management of hemodynamic support of shock.

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7
Acute Respiratory Failure

Jennifer L. Turi and Ira M. Cheifetz

Introduction

Acute respiratory failure is a major cause of morbidity and mortality in the pediatric intensive care unit (PICU) setting and accounts for approximately 50% of PICU admissions. Although the possible etiologies of respiratory failure are highly variable, multiple causes are included within the top 10 leading causes of death among children [1]. In the infant population, respiratory distress syndrome and sudden infant death account for more than 40% of total mortalities [1]. Developmental differences in children contribute to the prevalence of respiratory failure in this age group. Children have reduced elastic recoil of their alveoli, which can result in increased alveolar collapse in the presence of altered pulmonary compliance. In addition, they have fewer alveoli and less *collateral ventilation* channels (Figure 7.1) that allow ventilation distal to an obstructed airway [2]. The chest wall of an infant is more compliant with more horizontally aligned ribs. This makes it more difficult to generate a greater negative intrathoracic pressure in the presence of poor pulmonary compliance. The relatively weak cartilaginous support of the airways in children compared with adults may lead to dynamic compression (and subsequent airway obstruction) in disease processes associated with high expiratory flow rates and increased airway resistance (e.g., asthma, bronchiolitis) (Figure 7.2). Finally, the airway of a child is significantly narrower than that of an adult, which can contribute greatly to the development of increased airway resistance. The numerous etiologies of respiratory failure in children reflect the multiple levels of involvement of the respiratory system and its integration with other organ systems. Thus, the management of acute respiratory failure in the PICU is a great challenge and requires a thorough understanding of the physiology and potential dysfunction of the various components of the respiratory system.

Definition

Respiratory failure is defined as an inadequate exchange of oxygen (O_2) and carbon dioxide (CO_2) resulting in an inability to meet the body's metabolic needs. Clinical criteria, arbitrarily set at a partial pressure of oxygen (PaO_2) <60 mm Hg and a partial pressure of carbon dioxide ($PaCO_2$) >50 mm Hg, are not rigid parameters but rather serve as a context in which to interpret the clinical scenario. Respiratory failure can be classified both anatomically and physiologically. The anatomic structure of the respiratory system is composed of two main elements—the lungs and the respiratory pump. The lungs include the conducting airways, the alveoli, and the pulmonary circulation. Failure of these elements results in disordered gas exchange and is clinically manifested as hypoxemia. The respiratory pump is composed of the thorax, respiratory muscles, and nervous system. An inability to effectively pump air into and out of the lungs results in hypoventilation and subsequent hypercarbia. Although there are clear consequences of dysfunction of any these components, each also interacts significantly with the others. Therefore, failure of one frequently is followed by failure of the others.

Hypoxemic Respiratory Failure

Adequate gas exchange requires that a sufficient quantity of inspired gas reaches the alveoli, that the inspired gas in the alveoli matches blood distribution in the pulmonary capillaries, and that the alveolar–capillary membrane permits the transfer of gas. Dysfunction at any of these levels, and the hypoxemia that subsequently follows, can result from five potential mechanisms: ventilation/perfusion (V/Q) inequality, shunt, hypoventilation, diffusion impairment, and low fraction of inspired oxygen (FiO_2). Hypoxemia secondary to abnormal gas exchange initially will be accompanied by a normal or low $PaCO_2$ secondary to compensatory hyperventilation. After the compensatory mechanisms fail, hypercapnia may develop. Gas exchange can also be adversely affected by nonpulmonary factors. These include decreased cardiac output, increased O_2 extraction, and/or abnormal hemoglobin, each of which will negatively impact mixed venous saturations and, potentially, limit the lungs' ability to oxygenate the pulmonary blood.

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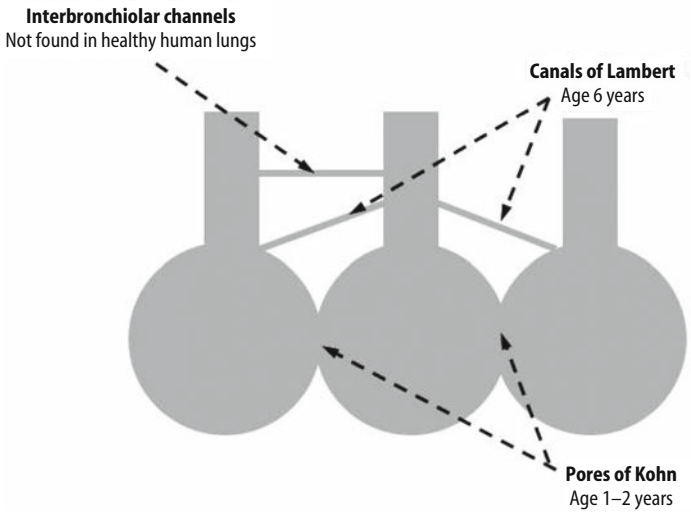

Figure 7.1. Collateral ventilation. The adult lung contains anatomic channels that allow for collateral ventilation distal to an obstructed airway. These channels include (1) interalveolar channels (pores of Kohn), (2) bronchiole–alveolar channels (canals of Lambert), and (3) interbronchiolar channels. The pores of Kohn appear at around 1–2 years of age, and the canals of Lambert appear at around 6 years of age. Notably, interbronchiolar channels develop pathologically and are not found in healthy human lungs in either children or adults. Infants and children are therefore at a greater risk for atelectasis and consequent ventilation–perfusion mismatch due to airway obstruction.

Ventilation/Perfusion Inequality

The most common etiology for hypoxemia in the PICU setting is the unequal matching of alveolar ventilation to capillary perfusion (Figure 7.3). This ratio of ventilation to capillary perfusion determines the concentration of O_2 in the blood. When ventilation and perfusion are unequally distributed, the lung cannot transfer O_2 and CO_2 as effectively. The efficiency of alveolar ventilation will depend on the regional distribution of the inhaled gas as determined by gravitational factors and the compliance and resistance of the circuit. The effect of gravity on the thorax creates an intrapleural pressure gradient that distributes gas to the alveoli heterogeneously. Thus, the greater gravitational pressure at the base of the lung generates less intrapleural pressure and so expands these alveoli less. This creates a seeming paradox in the normal lung, where lower volume alveoli have greater compliance and are more easily inflated than higher volume alveoli because they are situated on the steeper segment of the pressure–volume curve (Figure 7.4) [3]. This results in increased ventilation in the dependent lung regions.

In the lung, both perfusion and ventilation decrease significantly from the base to the apex, although perfusion decreases at a far more rapid rate [3]. Therefore, although the average V/Q ratio is equal throughout the entire lung, there is greater ventilation to perfusion at the apex; while at the base, blood flow is in excess of ventilation (Figure 7.5). This unequal matching of ventilation and perfusion results in the development of an alveolar-arterial PO_2 difference ($A\text{-}aO_2$) with a normal A-a gradient of approximately 5 mm Hg in a young adult.

In the presence of alveolar disease, edema and inflammation worsen compliance and exaggerate the intrapleural pressure gradient. As intrapleural pressure exceeds alveolar pressure, atelectasis or closure of lung units in dependent lung regions will occur during a portion of tidal ventilation. This inverts the normal distribution of ventilation, causing the apex of the lung to receive improved ventilation. Although there are significant changes in the distribution of alveolar ventilation, perfusion is less affected. Perfusion continues to be greatest at the base of the lungs such that poorly ventilated lung units continue to be perfused. Mismatching the distribution of ventilation and perfusion causes well-oxygenated blood from regions of high V/Q to mix with poorly oxygenated blood from regions of low V/Q, resulting in an increased A-a gradient. The elevated A-a gradient cannot be compensated by higher V/Q units because of the sigmoidal shape of the oxygen–hemoglobin dissociation curve. Low V/Q units, which generate a PO_2 on the steeper segment of the curve, will have a more significant effect on hemoglobin saturation than higher V/Q units, which generate a PO_2 on the flatter segment of the curve.

In children younger than 6 years of age, the reduced elastic recoil of the lungs frequently lowers functional residual capacity (FRC) below the closing volume of the alveoli. Therefore, dependent lung regions may close during exhalation, and nondependent regions will be preferentially ventilated [4]. Inhomogeneous ventilation increases as pulmonary compliance worsens and the portions of lung below the closing volume increases. Alveolar ventilation can be further altered by increased airway resistance as seen in croup, bronchiolitis, and asthma.

According to Poiseuille's law, a decrease in the radius of the airway significantly amplifies the increase in airway resistance such that the change in air flow is directly proportional to the airway radius elevated to the fourth power:

$$Q = (\Delta P\ \pi\ r^4)/(8\ \eta\ L)$$

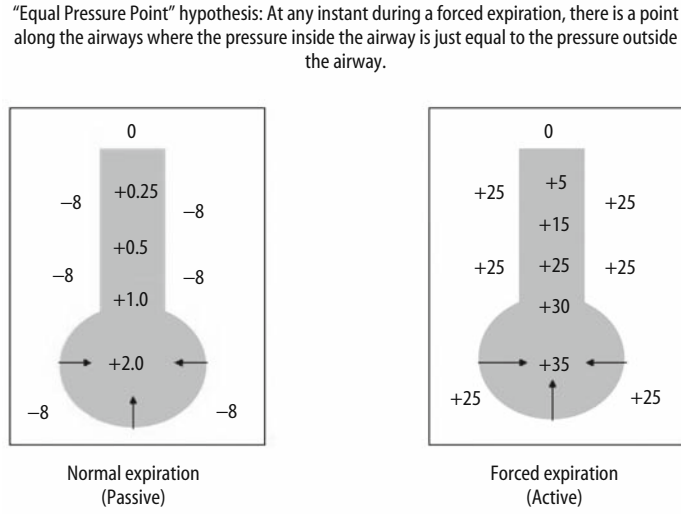

Figure 7.2. Dynamic compression in children. The cartilaginous support of the conducting airways will have spread to its most distal point, the segmental bronchus, by the twelfth week of gestation. After birth, the cartilaginous support of the conducting airways increases throughout the remainder of childhood. The relative weakness of the cartilaginous support in the infant compared with the adult may lead to dynamic compression in situations associated with high expiratory flow rates and increased airway resistance (e.g., bronchiolitis, asthma, or even crying). During a forced expiration, intrapleural pressure becomes more positive with respect to atmospheric pressure. There is a point along the airway that the intrapleural pressure (pressure outside the airway) will be equal to the pressure inside the airway (i.e., transmural pressure gradient is zero). Past this point, the transmural pressure gradient becomes negative, and the airway begins to collapse.

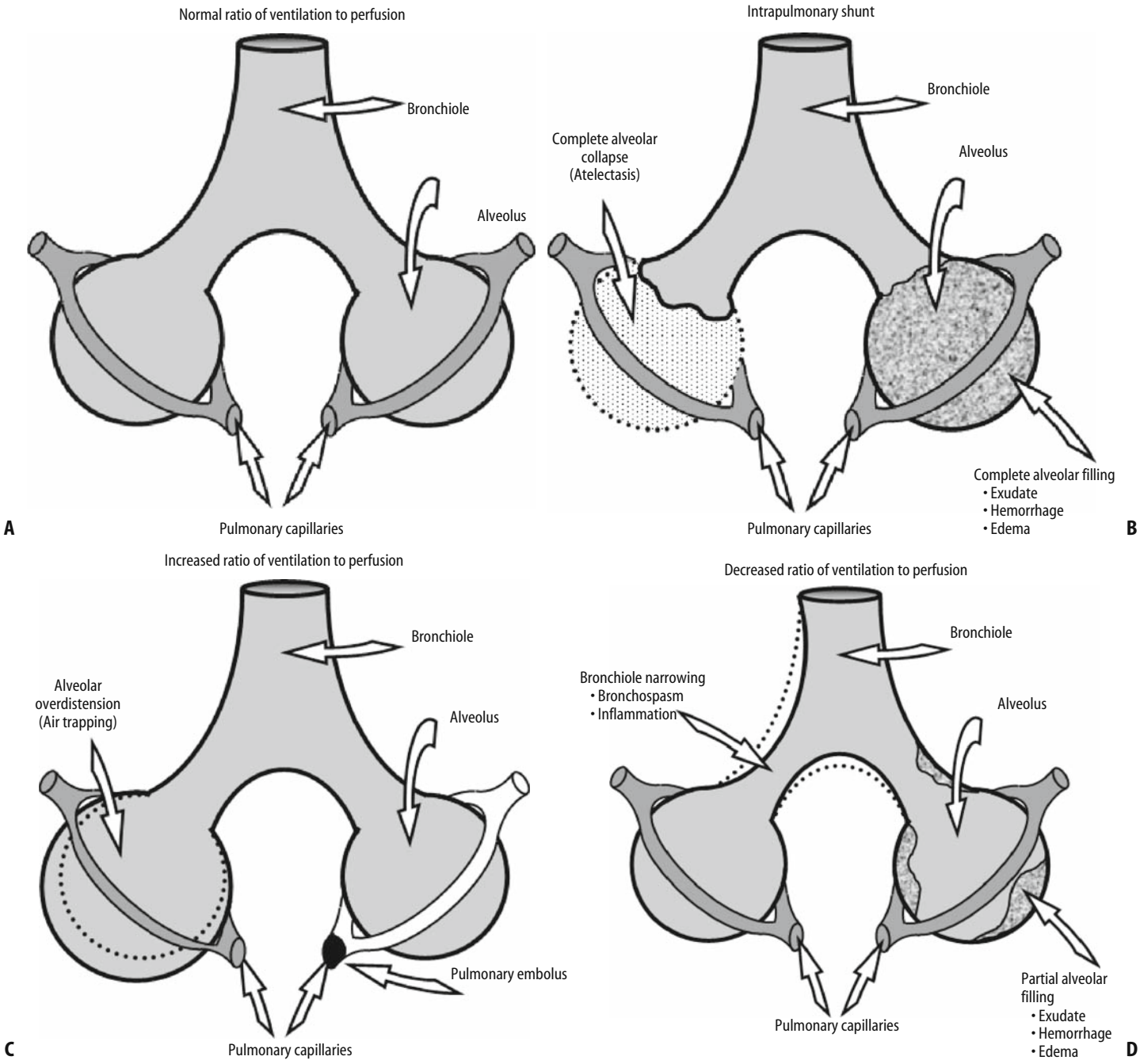

Figure 7.3. Ventilation–perfusion inequality. **(A)** Normal. **(B)** Intrapulmonary shunt. **(C)** Increased ventilation–perfusion ratio. **(D)** Decreased ventilation–perfusion ratio. (Courtesy of Neil W. Kooy, MD.)

where Q is flow, ΔP is the pressure gradient from one end of the airway to the other end, r is the radius of the airway, η is the viscosity of the air, and L is the length of the airway. Therefore, increasing the length of the airway (L), increasing the viscosity of the air (η), or decreasing the radius of the airway (r) will reduce laminar air flow. Changing the airway radius, however, has the greatest effect on flow. Small amounts of edema, therefore, will have a greater effect on the caliber of the pediatric airway compared with the adult airway, resulting in a greater increase in airway resistance (Figure 7.6). Laminar flow is further determined by the Reynolds number (Re):

$$Re = 2\ V\ r\ \rho\ /\ \eta$$

where V is the velocity of the air flow, ρ is the density of the air, r is the radius of the airway, and η is the viscosity of the air. When the Re is less than 2,000, laminar flow is present. Conversely, when the Re number is more than 4,000, turbulent flow is present. Importantly, airway resistance is inversely proportional to the airway radius to the fifth power (r^5) under conditions of turbulent air flow. In the adult, the greatest level of resistance is found in the larger airways because the extensive number of small peripheral airways provides a tremendous surface area. In children younger than 6

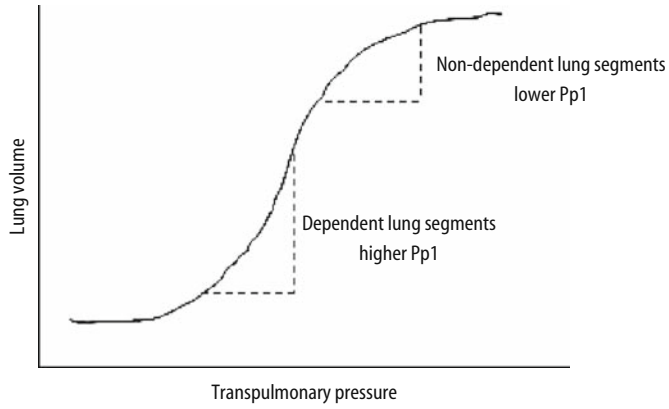

Figure 7.4. Differential ventilation of dependent versus nondependent lung regions. During spontaneous ventilation, a greater proportion of inhaled gas is directed to the dependent regions of the lung. Gravitational forces create a less negative subatmospheric intrapleural pressure (Ppl) at the base compared to the apex of the lung. Alveolar pressure remains the same, so the transmural distending pressure (PA-Ppl) is reduced in the dependent lung segments.

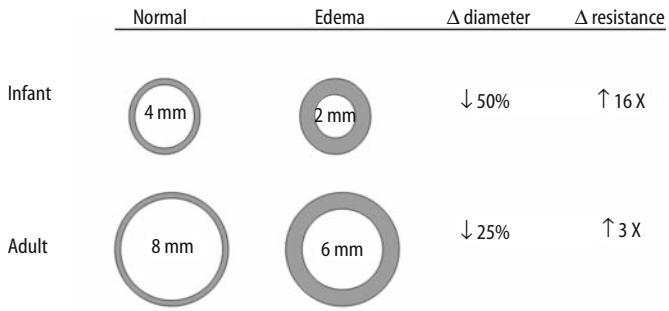

Figure 7.6. Age-dependent effects of a reduction in airway caliber on the airway resistance and air flow. Normal airways are represented on the left (top, infants; bottom, adults), and edematous airways are represented on the right. According to Poiseuille's law, airway resistance is inversely proportional to the radius of the airway to the fourth power when there is laminar flow and to the fifth power when there is turbulent flow. One millimeter of circumferential edema will reduce the diameter of the airway by 2 mm, resulting in a 16-fold increase in airway resistance in the pediatric airway versus a 3-fold increase in the adult (cross-sectional area reduced by 75% in the pediatric airway vs. a 44% decrease in the adult airway). Note that turbulent air flow (such as occurs during crying) in the child would increase the resistance by 32-fold.

years old, where lung growth is not yet complete, the greatest level of resistance occurs at the smaller peripheral airways. Therefore, diseases affecting the smaller airways, such as asthma and bronchiolitis, can significantly increase airway resistance and work of breathing.

Despite the smaller lung size in children, pulmonary arterial pressure is very similar to that of adults. This allows the pressure in the pulmonary capillaries to remain greater than alveolar pressure more consistently resulting in more continuous perfusion of the entire lung. Subsequently, in the child with normal lungs, there is less V/Q inequality.

Hypoxemia caused solely by V/Q inequality will correct by breathing 100% oxygen ($FiO_2 = 1.0$), because alveolar nitrogen is *washed out*, and the PAO_2 in all ventilated alveoli is equalized, as determined by the alveolar gas equation below:

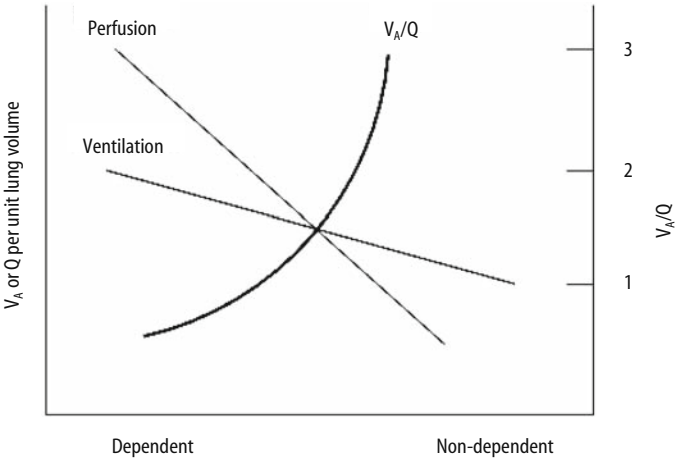

Figure 7.5. Differential distribution of ventilation (V_A), perfusion (Q), and ventilation–perfusion ratio in the lung. The dependent lung regions preferentially receive better ventilation and perfusion than the nondependent lung regions. However, the perfusion gradient is much steeper than the ventilation gradient such that the ventilation–perfusion ratio is higher in the nondependent (apex) I regions than the dependent (base) regions. (Adapted from West JB. Ventilation/Blood Flow and Gas Exchange, 3rd ed. Oxford: Blackwell; 1977:33–52.)

$$PAO_2 = FiO_2\ (P_B - P_{H_2O}) - PaCO_2$$

Although this equation can be used to quantitate the degree of hypoxemia attributable to V/Q inequality versus shunt, reabsorption atelectasis of partially obstructed low V/Q units can convert these areas to true shunt and introduce some inaccuracy into the measurement.

In a spontaneously breathing patient, a normal $PaCO_2$ can frequently be maintained at the expense of increased ventilation. The elevated CO_2 from lower V/Q units will stimulate increased alveolar ventilation so that the $PaCO_2$ does not rise. Because the CO_2 dissociation curve is more linear than the sigmoidal shape of the O_2 dissociation curve, $PaCO_2$ can be maintained more effectively. If alveolar ventilation cannot increase secondary to muscle weakness, lung disease, or increased sedation, then V/Q inequality will also result in an elevated $PaCO_2$.

The development of an A-a gradient can be lessened by effective hypoxic pulmonary vasoconstriction (HPV) in which pulmonary vessels constrict in response to the presence of regional alveolar hypoxia. Hypoxic pulmonary vasoconstriction is strongest and can create the greatest diversion of blood flow when the hypoxic region of lung is small [5]. Hypoxic pulmonary vasoconstriction is stimulated by a low PAO_2 [6] with its site of action primarily at the small pulmonary arteries and veins [7]. Low mixed venous saturations can significantly limit the effectiveness of regional HPV. The decrease in the PAO_2 caused by the lower SvO_2 may decrease perfusion to well-ventilated lung regions and result in inappropriate shunting of blood to more poorly ventilated segments, resulting in the development of an increased A-a gradient [8]. The effectiveness of HPV can be generally restored by augmenting cardiac output and subsequently increasing the mixed venous saturation.

Shunting

Shunting results from deoxygenated blood entering the arterial system without first passing through ventilated regions of lung. Two types of shunt exist: (1) anatomic or fixed shunts and (2) intrapulmonary or true shunts. Anatomic shunts occur when systemic venous blood enters the left ventricle without having entered the

pulmonary circulation. In a normal, healthy child, about 2%–5% of the total cardiac output represents a "normal" anatomic shunt (venous blood from the bronchial veins, thebesian veins, anterior cardiac veins, and pleural veins directly enters the left-sided circulation). Anatomic shunts also include intracardiac shunts associated with congenital heart lesions. Conversely, intrapulmonary shunting (true shunts) can occur via either extraalveolar arteriovenous connections or, more typically, capillaries perfusing alveoli that receive no ventilation. The degree of desaturation will be determined by the relative proportion of shunted versus unshunted blood. This shunted blood, or venous admixture, can be calculated as the amount of blood that would need to mix with arterial blood to account for the A-a gradient. Measurement of this shunt fraction can be made while a patient is breathing 100% oxygen. Although this will not define the anatomic pathway of the shunt, it can be used as a useful marker to follow the efficacy of gas exchange.

$$Q_S/Q_T = (c_c - c_a)/(c_c - c_v)$$

where Q_S is shunt flow, Q_T is total pulmonary blood flow, and c_c, c_a, and c_v represent the end capillaries, arteries, and mixed venous O_2 content, respectively. The O_2 content can be calculated from an estimate of dissolved O_2 and hemoglobin saturation, whereas arterial and mixed venous PO_2 are measured directly. End capillary PO_2 is assumed to be equal to alveolar PO_2 calculated by the alveolar gas equation. Normally, there is less than 5% shunt representing the admixture from the bronchial veins that supply the lungs. Supplemental O_2 will have minimal effect on the degree of hypoxemia, because the red blood cells passing through the lungs at an FiO_2 of 0.21 are already near maximally saturated (approximately 97%), and the supplemental O_2 never reaches the blood that bypasses nonventilated regions of the lung.

Hypoventilation

Decreased alveolar ventilation results in inadequate delivery of O_2 to the alveoli. Unlike other mechanisms of hypoxemia, hypoventilation is associated with elevated levels of $PACO_2$. Hypoventilation decreases the O_2 delivered to the alveoli given the indirect relationship of PAO_2 to $PACO_2$ via the alveolar gas equation (although, by the alveolar gas equation, clinically significant hypoxemia, i.e., PaO_2 <60 mm Hg, does not occur under normal conditions, breathing ambient air at sea level until a $PACO_2$ >72 mm Hg is attained). There is, however, no change in the A-a gradient. Hypoxemia caused by hypoventilation can be easily corrected with supplemental O_2.

Diffusion Impairment

Alterations in diffusion capacity impair the equalization of PO_2 between the alveolar gas and capillary blood gas. This can occur secondary to a thickening of the blood–gas barrier, increased O_2 extraction caused by abnormally saturated venous blood, or decreased alveolar capillary volume cause by lung injury or destruction. In practice, however, it is difficult to determine the degree to which hypoxemia is caused by diffusion impairment rather than by V/Q inequality as the two often occur together. The rate of diffusion as determined by Fick's law is dependent on the thickness and area of the alveolar membrane and the difference in partial pressure of gas between the alveolus and the blood:

$$\text{Fick's law of diffusion: } V_{gas} = \frac{A \times D \times (P1 - P2)}{T}$$

where V_{gas} is the volume of air diffusing through the alveolar–capillary membrane per time, A is the surface area available for diffusion, D is the diffusion coefficient, T is the thickness of the alveolar–capillary membrane (or diffusion distance), and (P1 − P2) is the partial pressure difference between the alveolus and the blood. Therefore, hypoxemia will ensue in disease processes where the alveolar membrane is thickened or the area is reduced (i.e., severe lung fibrosis), where transit time through the alveolar capillaries is increased (i.e., hyperdynamic circulation), or where the PAO_2 is decreased because of low V/Q matching or low FiO_2 (high altitude). Although limitation to diffusion is rarely thought to be the primary cause of hypoxemia, even in the case of pulmonary edema or fibrosis, it can significantly worsen hypoxemia caused by V/Q mismatch or shunt. Because CO_2 diffuses approximately 20 times more readily than O_2, diffusion abnormalities are not associated with hypercarbia. Supplemental O_2 will increase the gradient between the alveolus and the capillary blood and, therefore, improve hypoxemia secondary to impairments in diffusion.

Low Fraction of Inspired Oxygen/High Altitude

Decreased oxygenation can result from low barometric pressure or low FiO_2. Although this rarely leads to respiratory failure, its effects can be extremely exacerbated in the presence of lung disease and V/Q mismatch. Hypoxemia associated with low FiO_2 or high altitude is readily corrected with supplemental O_2.

Hypercapnic Respiratory Failure

Failure of the respiratory pump is characterized by disturbances in ventilation with subsequent CO_2 retention. In the steady state, CO_2 production is balanced by CO_2 elimination such that $PaCO_2$ is directly proportional to the quantity of CO_2 produced and inversely proportional to alveolar ventilation (Figure 7.7).

$$PaCO_2 = \frac{VCO_2 \cdot K}{V_A}$$

While minute ventilation (V_E) is the product of tidal volume (V_t) and respiratory frequency, alveolar ventilation (V_A) is determined by the difference between total minute ventilation and the

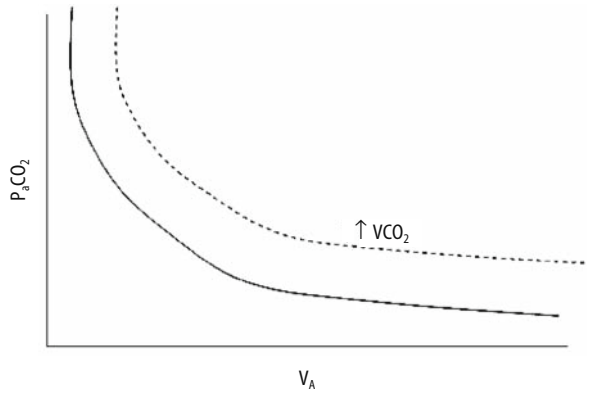

Figure 7.7. Relationship of $PaCO_2$ to alveolar ventilation (V_A). As V_A increases, $PaCO_2$ decreases. As CO_2 production (VCO_2) increases, this relationship is shifted upward and to the right.

degree of both anatomic and physiologic dead space ventilation (V_D):

$$V_E = V_t \cdot \text{frequency}$$

$$V_A = V_E - V_D$$

Therefore, CO_2 balance can be altered if minute ventilation is decreased or dead space ventilation is increased.

Alveolar minute ventilation can be altered by changes in tidal volume or respiratory frequency. Adequate respiration requires signals from the central nervous system to be transferred via the spinal cord, peripheral nerves, and neuromuscular junction to the respiratory muscles. The action of these muscles on the chest wall generates a more negative intrathoracic pleural pressure to allow inspiration. Expiration then follows using the energy stored during the preceding inspiratory phase as elastic recoil. Ventilation can become ineffective in the presence of an inadequate ventilatory drive, altered chest wall structure or muscle function, or compromised pulmonary mechanics.

Hypercarbia related to an inadequate control of the ventilatory drive can result from dysfunction centrally, at the level of the brain stem, or more peripherally at the spinal or peripheral nerve pathways. Failure of the central drive of respiration is most commonly caused by an overdose of sedative, narcotic, or hypnotic drugs. Less commonly, hypoventilation may result from brain stem injuries at the level of the middle to lower brain stem or from abnormal autonomic regulation of breathing at the level of the central nervous system with little or no response to hypercapnia [2]. The inability to effectively respond to CO_2 can be acquired congenitally, as seen in central hypoventilation syndrome, or as a result of posterior fossa tumors, encephalitis, severe asphyxia, or inborn errors of metabolism, such as pyruvate dehydrogenase deficiency. Alternatively, other brain injuries or lesions, some intoxications, and hepatic encephalopathy can lead to increased respiratory drive (i.e., hyperventilation) and, therefore, eventual ventilatory failure because of coexistent respiratory or neuromuscular disease [9].

Effective ventilation requires that the inspiratory muscles be able to generate sufficient force to overcome the resistive and elastic loads imposed by the airways and lung parenchyma, respectively. The primary muscle of inspiration, the diaphragm, is typically involved in hypercarbia associated with disordered respiratory muscle function. Normally, contraction of the diaphragm draws air into the lungs both by its piston-like caudal displacement and by its elevation of the lower ribs as the muscle contracts against the relatively noncompressible abdomen. Furthermore, it can increase the transverse diameter of the thorax because of the coupling of the upper and lower ribs [10]. The diaphragm has a significant level of reserve, with only approximately 10%–15% of its motor units being active during rest [11]. This allows the diaphragm to respond to increased levels of work for prolonged periods of time.

During increased inspiratory effort, the sternocleidomastoid, scalene, and intercostal muscles are recruited to augment inspiration by orienting the ribs in a more horizontal direction, thus increasing the transverse diameter of the thorax. Both the diaphragm and accessory inspiratory muscles are less effective in children younger than 2 years of age because of their more compliant chest walls and the more horizontal position of the ribs at rest [10]. Although abdominal muscles are typically considered expiratory muscles, they also serve to augment inspiration by decreasing end-expiratory lung volume below FRC to assist inspiration by the outward elastic recoil of the chest wall during the subsequent inspiration [9]. In addition, expiratory muscles may serve to elevate the diaphragm to achieve a more optimal muscle fiber length for maximal contraction [10].

Excessive work of breathing can fatigue the respiratory muscles, resulting in an inability to generate the increased pleural pressure required to maintain an adequate alveolar ventilation in the face of increased requirements [12]. Muscle fatigue occurs when the energy supply is no longer adequate to meet demand, whether because of increased demand, increased resistive forces (i.e., large airway obstruction, asthma), increased elastic loads (i.e., edema), or decreased energy supply. Blood flow to the diaphragm and other inspiratory muscles is determined by cardiac output, perfusion pressure, oxygen-carrying capacity of the blood, and the ability of the muscles to increase perfusion in response to increased demand. Decreased blood flow to these muscles will decrease substrate delivery. With increased activity, the diaphragm requires approximately 10 to 20 times greater oxygen delivery to meet its metabolic demands [13,14]. Factors that impair oxygen delivery to the muscles, such as hypoxemia, anemia, or decreased cardiac output, can increase the onset of fatigue [15]. Ventilatory muscle function can likewise be affected by metabolic disturbances. Decreased levels of potassium, phosphorus, magnesium, or calcium can result in decreased muscle strength [9]. Similarly, malnutrition can markedly reduced the strength and endurance of respiratory muscles [16]. Likewise, a number of drugs that are capable of altering metabolism can impair muscle function. These include adrenocorticosteroids that promote atrophy and aminoglycosides and calcium channel blockers that can interfere with neuromuscular transmission [17].

Muscle weakness, or the fixed inability to generate adequate inspiratory force, is determined by the adequacy of neuronal drive, innervation, neuromuscular transmission, and fiber-type distribution as well as length–tension and force–velocity relationships [9]. A weak muscle has a fixed reduction in the force that it is capable of generating and, therefore, will require more energy to perform a given amount of work [18]. Respiratory muscles are susceptible to weakening by disseminating neuromuscular disorders, spinal cord injuries, muscular dystrophies, Guillain-Barré, and myasthenia gravis. Ventilatory pump failure does not typically occur until respiratory muscle strength is below 50% of its predicted value. Beyond that level, the severity of CO_2 retention is proportionate to the degree of weakness [19]. This threshold can be further decreased in the presence of associated conditions. Factors that decrease the ability of a muscle to generate maximal force, whether because of atrophy, immaturity, or disease, predispose the muscle to developing fatigue.

Muscle function can be further compromised by alterations in chest wall geometry as is seen with hyperinflation. This increase in FRC above the normally predicted value can occur in diseases characterized by airway obstruction, such as asthma and cystic fibrosis, and result in loss of elastic recoil of the chest wall that impedes optimal muscle function. The optimal muscle fiber length for inspiratory muscles corresponds to FRC; volumes greater than FRC will decrease this length. At shorter muscle fiber lengths, the muscle will generate less force [12]. Thus, adequate alveolar ventilation will require more energy. Furthermore, hyperinflation flattens the diaphragm and decreases its ability to efficiently generate pressure. Subsequently, its ability to facilitate thoracic expansion is decreased [20]. Hyperinflation likewise alters the spatial arrangement of the diaphragmatic muscle fibers such that contraction of the fibers now arranged in series and perpendicular to the chest wall will result in paradoxical inward movement of the thorax [18].

Increased respiratory work load, caused by increased airway resistance or by worsening compliance of the respiratory system, can greatly contribute to ventilatory failure either alone or in conjunction with other factors. In the absence of a disorder of the central drive for respiration, ventilatory failure can be seen as an imbalance between respiratory work load and ventilatory strength and endurance. Although the presence of depressed respiratory drive, flail chest, or neuromuscular disease may precipitate hypercarbia, more frequently, they exacerbate hypercarbia in the presence of poor pulmonary compliance or increased airway resistance. Furthermore, pure alterations in alveolar ventilation will result in hypoxemia as well as hypercarbia because of the effect of an elevated PCO_2 level on the alveolar gas equation. Hypoxemia may be further exacerbated by a prolonged decrease in minute ventilation, which increases airway closure and atelectasis and, consequently, increases V/Q inequality or shunting.

In addition to alterations in alveolar ventilation, CO_2 elimination can be greatly affected by altered dead space ventilation. Dead space ventilation is characterized by the amount of ventilation that does not participate in gas exchange. Physiologic dead space is composed of anatomic dead space, a fixed volume representing the gas volume in the conducting airways, and alveolar dead space, representing the volume of gas that reaches the alveoli but does not participate in gas exchange secondary to inadequate perfusion. The volume of alveolar dead space can be estimated by comparing the arterial PCO_2 with the end tidal PCO_2. To calculate physiologic dead space [2]:

$$V_D = (P_aCO_2 - P_ECO_2) \cdot V_E / P_aCO_2$$

$$V_D/V_t = (P_aCO_2 - P_ECO_2) / P_aCO_2$$

In infants and adults, the normal V_D/V_t ratio is <0.3. An increase in this ratio, signifying an increase in dead space ventilation, will necessitate an increase in V_E to avoid the development of hypoxemia and hypercarbia.

Evaluation of Respiratory Failure

The development of respiratory failure is often preceded by a period of increased work of breathing to compensate for worsening gas exchange. Although the clinical signs of impending respiratory failure can be fairly nonspecific, recognizing these signs can provide an opportunity to anticipate and intervene before true respiratory failure develops. Tachypnea is typically the first manifestation of respiratory distress, particularly in infants, and is an attempt to minimize the work load of the muscles. Although tachypnea is a sensitive sign of failure of gas exchange and the ventilatory pump, it is not specific and can signify the presence of a number of other conditions. However, when combined with other signs of increased work of breathing or abnormal breathing patterns, it can signify impending respiratory failure. These signs include the presence of nasal flaring and the use of accessory muscles, especially the sternocleidomastoids. The presence of paradoxical abdominal movements can also indicate weakness or fatigue of the diaphragm. A prolonged expiratory phase and prominent use of abdominal muscles can indicate severe expiratory flow limitations as seen with asthma or airway obstruction. Expiratory grunting, caused by premature closure of the glottis during active exhalation, is an attempt to maintain or increase functional residual capacity and lessen atelectasis. Finally, cyanosis, while a major sign of hypoxemia, can be a late finding. The development of cyanosis requires at least 5 g/dL of deoxygenated hemoglobin. Therefore, a greater degree of desaturation is required for the development of cyanosis in an anemic patient. Although clinical judgment is of primary importance in assessing the patient for impending respiratory failure, arterial blood gas measurements can also provide significant information in the diagnosis of respiratory failure and in monitoring the response to therapy.

Oxygenation

The most sensitive measure of the failure of gas exchange is the A-a gradient. This difference between the PAO_2 and the PaO_2 can help interpret the decrease in arterial oxygen tension. The PAO_2 is calculated using the alveolar gas equation:

$$PAO_2 = FiO_2 \cdot (P_B - P_{H2O}) - \frac{PaCO_2}{R}$$

The A-a gradient is then calculated by subtracting the measured PaO_2 from the calculated PAO_2. The normal A-a gradient in the supine position will increase with age [21] and can be calculated by

$$\text{A-a} = 2.5 + [0.21 \cdot \text{age (years)}]$$

The presence of a decreased PaO_2 with an increased A-a gradient suggests the presence of V/Q mismatch, right-to-left shunt, or diffusion abnormality. Conversely, a decreased PaO_2 with a normal A-a gradient suggests hypoventilation as the etiology for the hypoxemia.

Carbon Dioxide Retention

The normal $PaCO_2$ is between 37 and 42 mm Hg. This is directly proportional to the amount of CO_2 produced and inversely proportional to that eliminated. To appropriately manage ventilatory failure, it is necessary to determine whether the CO_2 retention is acute or chronic. This can be evaluated using the Henderson-Hasselbach equation:

$$[H+] = 24 \times (PaCO_2/HCO_3^-) \quad \text{or}$$

$$pH = 6.1 + \log[HCO_3^-/(0.03 \times PaCO_2)]$$

Conversely, more readily applicable estimates can be used in which pH will change by 0.08 for every 10 mm Hg acute change in PCO_2 from 40 but will only change by 0.03 for every 10 mm Hg chronic change in PCO_2 from 40. The presence of chronic respiratory failure with superimposed acute decompensation will present with an intermediate change in pH. A more severe change in pH suggests a metabolic component. Conversely, patients can compensate for metabolic acidosis by decreasing their $PaCO_2$. This change should result in a decreased $PaCO_2$ to 100 times the last two digits of the pH such that a pH of 7.29 results in a $PaCO_2$ of 29 torr. The presence of a higher $PaCO_2$ suggests the presence of a mixed metabolic and respiratory acidosis [9].

Treatment of Respiratory Failure

Resuscitation of the patient with impending respiratory failure should initially include the administration of supplemental oxygen and the evaluation of airway patency. The airway should be cleared of secretions or mechanical obstruction and the head maintained in a neutral sniffing position. The use of an artificial oral or nasal

airway can also be helpful to maintain patency of the airway. If, despite these interventions, the patient manifests severe hypoxemia, increasing hypercarbia with the development of acidosis, or develops the need for airway protection, mechanical ventilation is indicated. The need for mechanical ventilation must also be based on the clinical scenario, the rate of clinical deterioration, and the patient's response to therapy. The decision should be weighed keeping in mind the risks and benefits of tracheal intubation and mechanical ventilation. Similarly, the presence of preexisting respiratory disease may result in an inability to compensate and in the need for earlier tracheal intubation.

Mechanical ventilation provides a means of supporting the respiratory system rather than a therapeutic modality. As such, the primary goal of mechanical ventilation is to ensure adequate oxygen delivery by adequately maintaining alveolar ventilation, maximizing V/Q matching, and decreasing patient work of breathing. An additional important objective is to avoid the development of ventilator-induced lung injury. Ventilator-induced lung injury can be caused by several mechanisms, including oxygen toxicity, lung overdistention, and *shear* injury to the alveoli caused by repeatedly opening collapsed lung regions—each of which serves to further exacerbate inflammation. The attempt to achieve these two goals of treatment have led to the development of strategies of lung protective ventilation to achieve adequate levels of oxygenation using a FiO_2 less than 0.60 and *low* peak inspiratory pressures and *small* tidal volumes.

The profound hypoxemia seen in acute respiratory distress syndrome (ARDS) and other disorders manifested by V/Q mismatch and intrapulmonary shunting can be alleviated by re-recruiting and stabilizing nonventilated alveoli. Positive end-expiratory pressure (PEEP) can stabilize alveoli and decrease both V/Q mismatch and shunt, as well as prevent alveolar shear injury. However, high levels of PEEP may overdistend recruited alveoli and interfere with cardiac output. This overdistention can result in significant volutrauma, which can further injure alveoli and exacerbate capillary leak.

The recognition that excessive distending pressure can cause significant ventilator-induced injury, or volutrauma, has led to a decrease in set tidal volumes from the previously accepted use of tidal volumes of 10–15 mL/kg. Acute lung injury is typically an inhomogenous process. The use of these larger tidal volumes results in overdistention and, therefore, greater injury to the regions of lung with better compliance. Use of tidal volumes of 6 mL/kg result in significantly less overdistention and subsequent volutrauma [22]. The low tidal volume study published by the ARDS Network in 2000 demonstrated a significant reduction in mortality in adults with ARDS ventilated with lower tidal volumes when plateau pressures were limited at 30 cmH_2O or less [22].

The pressure–volume curve can be used to more effectively guide the application of PEEP and peak inspiratory pressure (PIP). The addition of PEEP can be used to improve compliance of the respiratory system above the lower inflection point on the pressure–volume curve (Figure 7.8). It should be noted that the lower inflection point on a dynamic pressure—volume loop will overestimate the required PEEP because of the confounding variable of inspiratory flow. Peak inspiratory pressure can then be set to maintain inspiratory pressure below the upper inflection point. Beyond the upper inflection point, compliance again worsens as there is minimal improvement in tidal volume for the increased pressure. The attempt to maintain tidal volumes of approximately 6 mL/kg and PIPs less than 32 cmH_2O can precipitate the development of

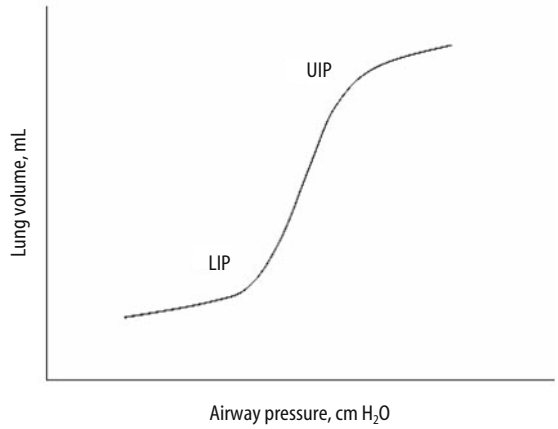

Figure 7.8. Lung pressure–volume curve in a child with acute respiratory failure. LIP, lower inflection point; UIP, upper inflection point.

hypercarbia and respiratory acidosis. This state of *permissive hypercapnia*, with the $PaCO_2$ well in excess of 60–80 torr and pH 7.20–7.30 has been well tolerated by most patients, particularly if the rise in CO_2 occurs slowly to allow some degree of renal compensation [23].

In summary, mechanical ventilation for respiratory failure should optimize alveolar ventilation, maximize V/Q matching, and decrease patient work of breathing while reducing the risk of developing ventilator-induced lung injury. This can typically be achieved by maintaining the FiO_2 less than 0.60, using an optimal level of PEEP to recruit and stabilize alveoli without causing overdistention or hemodynamic compromise, and setting low tidal volumes while maintaining the PIP less than 32 cmH_2O. Inability to achieve these parameters using conventional mechanical ventilation suggests the need for more nonconventional modalities of support, such as high-frequency oscillatory ventilation, high-frequency jet ventilation, or extracorporeal membrane oxygenation.

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8
Pediatric Transport Medicine

Derek S. Wheeler and W. Bradley Poss

A certain Samaritan . . . went to him and bound up his wounds, pouring oil and wine, and set him on his own beast, and brought him to an inn, and took care of him.

Luke 10:33–34.

Pediatric Transport Medicine: A Brief History

The transport of seriously ill or injured patients to the hospital (scene or prehospital transport), between hospitals (interhospital transport), and in the hospital (intrahospital transport) represents an important component of the provision of pediatric critical care. The history of transport medicine can be traced to biblical times, although formally organized systems of transport of critically ill patients were not developed until much later. The development of transport systems has often mirrored the development of military transport systems. For example, wounded soldiers were often carried from the battlefield by chariots during ancient Greece and Rome. During the Battle of Blenheim in 1704, the Duke of Marlborough demanded that his wounded soldiers be transported safely to the rear of the battlefield *by all available wagons from the surrounding countryside* [1]. During the Napoleonic wars, horse-drawn carriages and balloons were used to evacuate battlefield casualties [1–3].

Baron Dominique-Jean Larrey, Napoleon's chief surgeon, is credited with developing the first organized, formal military transport system [4]. He designed a system of field triage and transport, many of the concepts of which are still in use today. Railroad cars were used to transport injured soldiers during the American Civil War (1861–1865) [5], and the first organized systems of emergency care and transport of battlefield casualties in the United States were developed at that time [4]. The concept of air medical transport, first introduced during the Napoleonic wars, was later refined during the Franco-Prussian War (1871), when 160 casualties were transported from the siege of Paris in hot-air balloons [3,6]. In 1913, Samuel Cody, a pilot in the U.S. Army, first suggested and demonstrated an airplane that was designed specifically for transport of sick or injured patients [7]. However, it was not until World War I nearly 4 years later that airplanes were first used by the Serbian army to transport wounded soldiers and later during the war by the French and U.S. armies [8,9]. Airplanes were widely used for transporting wounded soldiers during World War II [3,9,10]. The first U.S. strategic aeromedical evacuation was performed in 1943, when five injured soldiers were flown in a B-54 transport plane from Karachi, India, to Walter Reed Army Hospital in Washington, DC [11]. The patients were accompanied by Lieutenant Elsie S. Ott, an Army nurse, who was so tired at the end of the 7 days that it took that she forgot her own name [5,11]. Largely through Lt. Ott's efforts and subsequent recommendations, the feasibility and practicality of long-range transport of critically injured patients were demonstrated. Dramatic improvements in prehospital care and transport systems design were further made during the Korean and Vietnam Wars, which provided the framework for the evolution of the civilian trauma systems used today [1,6,10,12–15].

The civilian hospital-based model of critical care transport was first used in Europe during the polio epidemic of the 1950s. Anesthesiologists accompanied polio patients requiring mechanical ventilatory support to regional centers [5]. However, it was not until the late 1960s and early 1970s that the specialties of trauma surgery and neonatology began to apply the advances made in military transport medicine to the transport of their respective patient populations [16–18]. Usher [19] demonstrated the value of regionalization of neonatal intensive care in 1970, documenting a twofold improvement in the mortality rate of critically ill newborns cared for in regional centers as opposed to community hospitals. The concept of regionalized neonatal intensive care was further promoted by repeated studies showing improved outcome of critically ill infants transferred to regional centers [17,19–24]. As trauma and neonatology transport programs evolved, they were frequently called on to transport critically ill infants and children. Pediatric critical care transport programs were later developed as logical extensions of these transport programs, and pediatric transport medicine is now recognized as its own unique subspecialty within pediatric critical care medicine.

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Regionalization and Rationale for Intrahospital Transport

Advances in the science and technology of critical care medicine have resulted in dramatic improvements in outcomes for critically ill or injured children. It is clear that children are different from adults and require more specialized care [25–27]. It is unreasonable, however, to expect every hospital to be able to provide comprehensive care for the wide range of complex medical and surgical problems that afflict the critically ill or injured child. The need for categorization and regionalization of pediatric critical care services is driven by several factors. First and foremost, while approximately 15% of the 3 million children hospitalized in the United States each year are cared for in free-standing children's hospitals or specialized inpatient pediatric wards at tertiary care centers, the vast majority are admitted to small, community hospitals that may be quite varied in their capability to care for sick children [28–30]. These hospitals may be perfectly capable of caring for the *routine* diseases of childhood, yet at the same time be poorly trained and ill-equipped to deal with the complexities inherent to the care of critically ill or injured children. Furthermore, even *routine* diseases of childhood may at times deteriorate and necessitate a higher level of care than the available resources. In these instances, interhospital transport to a pediatric critical care center is required.

Hospitalization in a location remote from home can represent a tremendous financial, logistic, and emotional burden to families of critically ill and injured children. For these reasons, many hospital-based community physicians and trauma surgeons are tempted to admit children to local adult medical and surgical intensive care units rather than transport them to a pediatric intensive care unit (PICU) in another city or state. Several studies, however, have documented significantly improved outcomes when critically ill and injured children receive care in the PICU versus the adult intensive care unit [25,27,31–37]. The presence of a pediatric intensivist supervising and coordinating care, in particular, is associated with improved outcomes [33–35]. Again, in these instances, interhospital transport to a pediatric critical care center is necessary to ensure the best possible outcome.

Aside from the aforementioned issues, the subspecialization of pediatrics has further highlighted the need for interhospital transport of critically ill and injured children. Children suffering from rare or complex medical disorders frequently require transport to quaternary referral centers that specialize in these diseases. For example, not all tertiary care centers offer solid organ or bone marrow transplantation; children requiring these services would therefore need to be transported safely to centers that do offer these services. As an interesting aside, several studies of both children and adults have suggested that outcomes for certain surgical procedures are linked with case volume. For example, studies show that hospitals with a high volume of cases in AIDS treatment and surgery for pancreatic cancer, esophageal cancer, abdominal aortic aneurysms, and congenital heart disease have better outcomes compared with low-volume hospitals [reviewed in 38]. A study in the state of California estimated that more than 600 deaths per year could be prevented by selective referral to centers with a high volume of cases of the aforementioned disorders [39]. Children and adults cared for in centers with a high volume of liver [40, 41] and kidney transplantation [41] also have better outcomes than low-volume centers. In these studies, centers performing more than 20 liver transplants have better outcomes than centers performing less than 20 liver transplants per year [40]. Finally, a theoretical analysis in the state of California suggested that selective referral to high-volume congenital heart disease centers would prevent nearly 50 deaths per year. In this study, selective referral to high-volume centers increased the distance of interhospital transport by a mean of 12.7 miles [42].

Guidelines for the categorization and regionalization of pediatric critical care services have been previously published [37,43–48], although it is evident that changes need to be made. For example, in 1997, the Division of Hazard and Injury Data Systems, U.S. Consumer Product Safety Commission, surveyed the National Electronic Injury Surveillance System (NEISS) and noted some disturbing trends. Although 96% of the estimated 5,929 U.S. hospitals with emergency departments using the NEISS provided inpatient pediatric care, only 4% had both a PICU and a pediatric trauma service. Only 33% of those hospitals lacking pediatric critical care and trauma services had existing written transfer agreements with a facility able to provide such care [49]. Interhospital transport represents an important component of the overall system of emergency medical services for children (see Chapter 3). The system necessarily includes categorization of different hospitals according to their ability to provide emergency care for children. Predetermined, written transfer agreements among community-based emergency departments, community hospitals, specialized pediatric emergency departments, and tertiary care pediatric centers must exist to in order to ensure that critically ill or injured children are rapidly transported to facilities that can provide the optimal level of care [29,37,43–45,50]. Children deserve quality care when they are critically ill or injured. Categorization of hospitals to define the level of care provided, as well as regionalization of services to ensure access to that care, will provide the best possible outcome when an emergency occurs.

Regionalization of pediatric intensive care has only intensified the need for specialized pediatric critical care transport teams with the capability to transport the critically ill or injured child from smaller community hospitals to tertiary care centers and children's hospitals [51]. Although there is a large body of literature on critical care transport of adults and neonates, the interest in research on critical care transport of the pediatric patient is relatively new, and the available literature, therefore, is limited. In November 1986, the American Academy of Pediatrics (AAP) published guidelines for the transportation of pediatric patients, primarily to address the need for a more formalized organization of pediatric transport programs across the country [52]. These guidelines were revised further by a consensus conference made up of experts from the disciplines of pediatric emergency medicine, pediatric critical care medicine, neonatology, and trauma surgery in 1991 [50,53]. These guidelines address a number of issues related to the organization and administration of a pediatric transport program and have been instrumental in developing and formalizing standards of care for pediatric transport medicine.

Most critically ill and injured children will receive their initial hospital care in the emergency department of a small community hospital, and many of these patients will ultimately require transfer to a tertiary pediatric care center (i.e., interhospital transport). Several options for interhospital transport exist, including transport by the same transport team that brought the child from the scene to the emergency department (i.e., the prehospital transport team), transport by the prehospital team supplemented by a physician or other provider with specialized skills (emergency nurse, paramedic, respiratory therapist, etc.), and transport by a

dedicated pediatric critical care transport team. Despite the longer waiting period required for the team to mobilize and travel from the tertiary care center, transport by a trained, dedicated, specialized pediatric critical care transport team is usually the safest and preferred option [16,54–64]. Regardless of the mode selected, transport should never diminish the level of care provided to the child, and the level of care provided during the transport should, at a minimum, be equal to that of the referring hospital. More importantly, with the advent of the concept of the "mobile intensive care unit," the care provided during transport should be equal to that of the tertiary care center itself.

The Transport Team

Organization of the Transport Team

The key to a successful transport program is a well-organized transport team [16,50,52,53,58,65–67]. Ideally, the different administrative roles and responsibilities for the various components of the transport team are shared among several individuals, including the medical director, transport coordinator, and communications center. Dispatchers, team members, pilots, drivers, and administrative support personnel obviously play important roles as well.

The Medical Director

The medical director of the transport system should be a physician with critical care expertise, ideally with subspecialty training in the care of critically ill neonates (e.g., systems primarily involved with the transport of critically ill neonatal patients), infants, and children (e.g., systems primarily involved with the transport of critically ill pediatric patients) [66]. The medical director should have a background in pediatric transport medicine. Currently, however, there are no accredited transport medicine training programs or specific requirements for subspecialty training in pediatric transport medicine, although fellowship training programs in both neonatology and pediatric critical care medicine generally offer substantial training in this area. The medical director is ultimately responsible for the performance of the transport team, and, as such, administrative time dedicated solely to the needs of the transport team should be provided by the hospital administration. Specific administrative responsibilities include but are not limited to (1) team development and supervision (including selection of team personnel and periodic review); (2) training and education; (3) establishment of standards, protocols, and guidelines; (4) ensuring compliance with local and national standards; (5) dealing with legal and accreditation issues; (6) service as liaison to the hospital administration; (7) service as liaison to the community; (8) generation of transport agreements with referring institutions; (9) development of a strategic plan and mission statement; (10) quality assurance and quality improvement; (11) selection of equipment and medications; (12) financial planning and revenue generation; (13) supervision of transport database management; (14) research coordination, supervision of data collection, and research publication; and (15) development and supervision of outreach programs [66].

Transport Coordinator

The transport coordinator works closely with the medical director, serving as a liaison between the medical director and transport team personnel. This individual should have an intimate knowledge of the day-to-day operations of the transport team and, as such, often serves as an active member of the transport team. The transport coordinator reviews every transport, assessing the appropriateness of any care that was provided, reviewing response times, and confronting and troubleshooting any problems with transport equipment, team personnel, or referring hospital personnel. The transport coordinator conducts monthly (or more frequent as needed) meetings with the entire transport team, schedules team personnel for transport duty, and acts as a liaison between the transport team and the hospital administration. Finally, the transport coordinator usually deals directly with the nonmedical aspects of the transport team, including ordering supplies and equipment, overseeing billing and accounting, handling insurance issues, and administering vendor contracts.

Communications Center

The communications center is a vital link between the transport team and the outside world, serving as the central contact between the referring hospital and the transport team. In many transport systems, the communications center receives the initial call for referral, obtains vital statistics (name of the patient, age, diagnosis, referring physician's name and telephone number, etc.), mobilizes the appropriate transport team (based on standard protocols), directs the call to the receiving physician or online medical control, and updates the transport log. The communications center also assists with the logistics of the transport, including checking local weather conditions, determining the location and distance to the referring hospital, checking road conditions and potential construction delays, and contacting the appropriate vendor (for either ground, helicopter, or fixed-wing transport).

Most systems are set up in such a manner that the communications center is centrally located (often in the emergency department) and receives all calls from both prehospital emergency medical services (EMS) units and referring hospitals. Once the initial referral is received, the communications center is responsible for establishing the lines of communication between the referring physician and the duty transport physician (called direct or online medical control). Providing a mechanism for the referring physician to communicate directly with the transport physician will improve the care of the child before arrival at the medical center and will allow the PICU to be better prepared for the patient's arrival by having necessary resources readily available. The physician with direct medical control must have the authority to accept a critically ill or injured child for transfer and provides advice for the further resuscitation and stabilization of the child before the transport team's arrival. If a physician is not a member of the transport team, the receiving physician in the PICU should act as direct medical control and communicate directly with both the referring physician and the transport team during transit.

Composition of the Transport Team

Pediatric critical care transport teams will encounter a broad array of medical and surgical problems, with diseases affecting the neurologic (including closed-head injury) and respiratory systems representing the most common reasons critically ill children require interhospital transport [13,68,69]. Because neonatal transport teams encounter a narrower spectrum of illnesses, they historically

have been successfully staffed by nonphysician providers (usually an advanced practice nurse or specially trained neonatal nurse accompanied by a neonatal respiratory therapist) [69]. On the other hand, pediatric critical care transport teams are just now beginning to utilize nonphysician-accompanied transport teams. Currently there are five different models of transport team composition: (1) nurse-nurse, (2) nurse-respiratory therapist, (3) nurse-respiratory therapist-physician, (4) nurse-physician, and (5) nurse-paramedic. Although the team composition in many programs remains the same regardless of patient acuity, other programs utilize some method of triage to determine team composition. In most programs, the transport team is composed of a PICU nurse who has received additional, specialized training in transport medicine and a pediatric respiratory therapist. Many transport programs also utilize pediatric residents at either the second- or third-year level of training [12,70–74]. Hospitals with pediatric critical care or neonatology fellowship programs often utilize these fellows on critical care transport teams, again depending on patient acuity.

The need for a physician as a third member of the team is a matter of some debate [50,52,55,69,74–81]. McCloskey et al. [76] found that physician-led interventions were not required in 91% of 191 transports that were reviewed retrospectively. In 66% of these transports, no medications were administered that required the presence of a physician. Strauss and Rooney [80] reviewed the 1-year experience of the pediatric transport service at the University of Wisconsin to determine the number of interventions performed by transport physicians during transport. Thirty percent of the patients (43% of trauma patients and 22% of medical patients) required no interventions at all, 18% of medical patients and 10% of trauma patients required tracheal intubation, and 9% of medical patients and no trauma patients required central venous catheter placement for vascular access. The findings of all of these studies are in direct contrast to a previous retrospective report that found that the presence of a critical care physician significantly decreased the frequency of secondary insults during transport [82].

Kronick et al. [83] suggested that the training background of the referring physician greatly influences the need for transport interventions. Transport patients from nonpediatrician referrals were significantly more likely to require procedural intervention than those patients referred by pediatricians. Similarly, patients were more likely to require procedural intervention if the referring physician's training was not recent.

Smith and Hackel [84] suggested that the transport team composition should be based on the particular skills that may be required during a transport. Ideally, data collected at the first telephone contact with the referring hospital would reliably predict the need for a physician-accompanied transport. However, numerous studies have demonstrated the difficulty of predicting the need for the presence of a physician during interhospital transport. For example, pretransport Pediatric Risk of Mortality (PRISM) scores underestimate the requirements for intensive care, as well as the need for major interventions during interhospital transport [85–87]. Other studies have shown that subjective judgment, even when coupled with objective information such as the pretransport PRISM score and vital signs, does not predict the need for physician presence during transport [79,80]. A recent study by Orr et al. [88] provides some hope that an effective triage tool is realistic. In this cohort study, the investigators noted that pretransport systolic blood pressure, respiratory rate, oxygen requirement, and altered mental status accurately predicted subsequent in-hospital mortality. The frequency of unplanned events and need for performance of major interventions during interhospital transport also increased as the risk of mortality (based on these four measures) increased.

Neither the PRISM score [89] nor the Pediatric Index of Mortality (PIM) score [90] is easily applicable to the neonatal population, and many of the scores currently designed for specific use in this population utilize data acquired *after* the transport team has arrived at the referring hospital [91,92]. Broughton et al. [93] designed and retrospectively analyzed the Mortality Index for Neonatal Transportation (MINT) score, which utilizes data collected at the first telephone contact with the referring hospital. These investigators found that the MINT score could accurately and reliably predict the severity of illness and risk of mortality in the neonatal population.

It should be emphasized that none of the triage scores or subjective criteria discussed in the preceding paragraphs were designed to specifically predict whether or not a physician should be included on the transport team. One obvious answer to this debate would be to include a physician on every transport, regardless of patient acuity. However, financial constraints render this an unattractive and unrealistic option. As a possible solution, many transport programs in the past have utilized pediatric residents at either the second- or third-year level of training or critical care fellows in this capacity [12,70–74]. However, work-hour restrictions instituted in July 2003 have limited residents and fellows to a maximum of 80 work-hours per week, which has put an effective end to this practice. Ultimately, the composition of a transport team will be dictated by individual transport requirements as predicted, albeit rather poorly, by pretransport information, as well as by local practices and protocols. The rapid advances in telecommunications technology, specifically in the field of telemedicine, are likely to result in better allocation of resources in the future, allowing for more accurate, rapid patient assessment and triage for interhospital transport [94].

Training

Transport team members (e.g., physicians, nurses, respiratory therapists, and emergency medical technicians [EMTs]) should be well versed in all relevant aspects of neonatal and pediatric critical care and transport medicine. Currently, there is no standard curriculum or published guidelines regarding team training, although it is recommended that team members be trained according to a formal program approved by the medical director [12,14,53,58,66,71,95,96]. Transport nurses should have a minimum of 5 years of clinical experience, with at least 3 of the 5 years focused on clinical care in the NICU, PICU, or emergency department setting [66]. Similar recommendations for EMTs and respiratory therapists are not currently available [66]. Although certification and training with courses such as Pediatric Advanced Life Support (PALS), Advanced Pediatric Life Support (APLS), and the Neonatal Resuscitation Program are recommended, they are by no means a substitute for experience and periodic training and education.

Equipment

Regardless of what type of transport team is utilized, it should be well equipped and prepared to deal with any emergency that may take place (Table 8.1). All medications, supplies, and equipment necessary for resuscitation and stabilization of critically ill or injured children should be carried by the transport team, as the

Table 8.1. Equipment and medications for transport of the critically ill or injured child.

Airway		
Oral airways	Succinylcholine	
Nasal airways	Vecuronium (or other intermediate- or long-acting muscle relaxant)	
Laryngoscopes (assorted blades, spare light bulbs)	Morphine	
Magill forceps	Midazolam	
Stylets	Ketamine	
Endotracheal tubes (all sizes)	Fentanyl	
Yankauer suction catheters	Atropine	
Suction catheters	Glycopyrrolate	
Tracheostomy tubes (all sizes)	Lidocaine	
Respiratory		
Nebulizer for aerosols	Albuterol	
Oxygen tank and oxygen blender	Racemic epinephrine	
Oxygen hood	Methylprednisolone	
Resuscitation bag-valve-mask with pressure manometer	Diphenhydramine	
Masks (neonatal, infant, child, and adult sizes)		
Transport ventilator		
Cardiac/resuscitation		
Defibrillator (with infant and adult paddles)	Epinephrine	Sodium bicarbonate
Infusion pumps	Dopamine	Naloxone
Intravenous catheters and accessories	Dobutamine	Calcium chloride
Central venous catheterization procedure tray	Prostaglandin E_1	Bretylium
Peripheral arterial line procedure tray	Furosemide	Amiodarone
Thoracostomy tube procedure tray	Digoxin	0.9% Normal saline
Cervical collars	Nitroprusside	Lactated Ringer's
Backboard	Adenosine	5% albumin
Intraosseous catheters	Nifedipine	D5W, D10W, D25W
	Hydralazine	Inamrinone
	Diazoxide	
Monitoring/miscellaneous		
Cardiorespiratory monitor	Phenobarbital	*Refrigerated medications
Temperature probes	Fosphenytoin	Lorazepam
Pulse oximeter	Diazepam	Succinylcholine
Blood pressure cuffs (neonatal, infant, child, and adult sizes)	Lorazepam	Prostaglandin E_1
Arterial blood pressure transducers	Thiopental	Pancuronium
Central venous pressure transducers	Dexamethasone	
End tidal CO_2 monitor	Insulin	*Controlled substances
Spare batteries	Ceftriaxone	Diazepam
Electrodes	Ampicillin	Midazolam
Stethoscope	Gentamicin	Phenobarbital
Portable blood gas analyzer	Cefotaxime	Thiopental
Urinary catheters	Heparin	Fentanyl
Dressings, splints, bandages	Activated charcoal	Ketamine
Tape	Hydrocortisone	Morphine
	Vitamin K	
	Acetaminophen	
	Mannitol	

Note: Medications that may be required only in specific clinical situations and are otherwise used infrequently should be added on a case-by-case basis.

referring hospital may not have the necessary equipment or medications readily available. As a general recommendation, the supply of medications, intravenous fluids, and oxygen should be sufficient to last twice as long as the expected duration of the transport [58]. Similarly, battery pack life for monitors and transport equipment should also be sufficient to last twice as long as the expected duration of the transport. The need for special medications that require refrigeration, such as prostaglandin E_1, should be ascertained before departure. Transport equipment and supplies should be checked and restocked as necessary following each transport, and proper in-servicing of all team members in the care and use of all transport equipment should be part of the orientation to the team and the regular training program.

Protocols

Development and review of protocols designed for specific situations (e.g., cardiac arrest during transport, basic monitoring, use of controlled substances) should be established and approved by the transport medical director. Each transport team member should be held responsible for learning and complying with these protocols.

Table 8.2. Modes of transport.

Ground	Helicopter	Fixed wing
Advantages	Advantages	Advantages
Availability	Rapid transit time	Rapid transit time over extremely long distances
Convenience (only two transfers of patients required: hospital to ambulance and ambulance to hospital)	Ability to reach inaccessible or remote areas	Able to fly above or around inclement weather
Ideal environment for "mobile ICU"		Cabin size larger than helicopter's
Relative cost		Cabin pressurization
Disadvantages	Disadvantages	Disadvantages
Not ideal for long distance transports	Adequate, unobstructed landing space required (field, helo pad, etc.)	Airport required
Limitations of road and traffic conditions	Limitations of weather conditions (more prone to weather restrictions than is ground transport)	Multiple transfers required (at least four transfers required: hospital to ambulance, ambulance to aircraft, aircraft to ambulance, ambulance to hospital)
	Multiple transfers may be required	Long distance from airport to either referring or referral hospital
	Limited range because of fuel capacity (compared with both ground and fixed wing)	Noise and vibration interfere with monitoring the patient
	Limited cabin space	Environmental stresses of altitude
	Lack of cabin pressurization	High maintenance costs
	Noise and vibration interfere with monitoring of the patient	Expensive
	High maintenance costs	
	Expensive	
	Safety(?)	

Mode of Transport

The choice of mode of transport is determined by several factors, including (1) severity of illness or injury, (2) distance to the referring hospital, (3) weather and traffic conditions, (4) safety, (5) resource availability, and (6) cost. The advantages and disadvantages of each mode of transport (ground, helicopter, and fixed wing) are listed in Table 8.2. Regardless, all transport vehicles should provide sufficient space, power sources, safety equipment, and climate control [50,52,58,67]. Available power sources should be compatible with all transport equipment, and sufficient oxygen and compressed air should be available [50,52,58,67]. Importantly, equipment compatibility should be determined well in advance (i.e., agreements with carriers should be set up long before any transport is performed).

Medicolegal Issues

Transport agreements between institutions should ideally be formalized and approved before performing any transport. The specific responsibilities of the referring institution and the receiving institution should be specifically delineated in these agreements. These agreements assume even greater importance when transport occurs beyond state boundaries. Finally, transport programs should seek accreditation through the Commission on Accreditation of Ambulance Services and the Commission on Accreditation of Medical Transport Systems [66]. Medicolegal issues specifically pertaining to interhospital transport have been reviewed previously, and the interested reader is directed to these reviews for additional information [16,50,52,53,58, 65–67,97–105].

Stabilization of the Critically Ill or Injured Child for Transport

Most authorities recognize that the postresuscitation phase, particularly the time surrounding interhospital transport, represents a dangerous phase in the overall care of the critically ill child. Following resuscitation and stabilization, there is a risk of clinical deterioration either from a recurrence or progression of the original problem or from complications associated with the resuscitation itself. The risks of interhospital transport during this period of potential physiologic instability must be balanced against the benefit of caring for a child in the specialized, sophisticated PICU environment. Children cared for in PICUs have better outcomes than children cared for in adult intensive care units [25,27,31–37]. Accepting some risk to transport a critically ill child in need of pediatric intensive care would therefore seem justifiable. However, what is the risk involved with an interhospital transport? An absolute risk value is difficult to quantify, as several factors play into the equation. An early report suggested both a low morbidity and a low mortality rate for patients who were cared for in a PICU following interhospital transport [106]. Conversely, prospective studies by Kanter et al. showed excessive mortality and morbidity following the interhospital transport of critically ill pediatric patients [85,87]. The problem most evident with both of these studies is that specialized pediatric transport teams were not used. Rather, the referring hospitals were responsible for initiating and performing the transport. The question is whether the morbidity and mortality would have improved with the use of a specialized pediatric critical care transport team. A follow-up study showed improved outcomes with the use of specialized pediatric transport teams [56]. Although the incidence of physiologic deterioration

between the two groups was similar in this study, the incidence of ICU-related mishaps (unplanned extubation, equipment failure, loss of vascular access, etc.) was 2% in those transports performed by the pediatric teams compared with 22% in the transports performed by nonspecialized teams.

Management of the Airway

Airway compromise and respiratory problems are among the most common indications for transporting a critically ill child to a tertiary care center. Failure to properly maintain a stable airway will place a patient with an already tenuous status at further and unnecessary risk. Studies have shown that some form of airway intervention is required in approximately 50% of all pediatric interhospital transports [107,108]. There is no consensus opinion on whether the possible need for airway management during an interhospital transport necessitates the presence of a physician on the team. On the contrary, the results of several studies would suggest that nurses and/or respiratory therapists may be trained to successfully perform tracheal intubation [109–113]. Suffice it to say that all members of the transport team should be well-versed in the various techniques of basic airway management, including the various modes of oxygen delivery, airway positioning and the jaw-thrust technique, the use of airway adjuncts such as the oral and nasopharyngeal airway, tracheostomy care, and the application of positive pressure ventilation with the bag-mask. At least one member of the transport team should be proficient in tracheal intubation.

In general, for children undergoing interhospital transport, a conservative approach to airway management is recommended (Table 8.3). When in doubt—*intubate*. It is much easier to tracheally intubate a patient at the referring hospital than in the back of a speeding ambulance or in the rear of a noisy helicopter in flight. Auscultation, end-tidal carbon dioxide measurement, and chest radiography should confirm proper placement of the tracheal tube. A chest radiograph absolutely must be obtained before the transport team's departure, with the additional goals of verifying placement of central lines, if present, and ruling out pneumothoraces. Further airway management includes placement of a nasogastric tube for gastric decompression as well as frequent suctioning of the tracheal tube. The combination of a small tracheal tube, dry gases, and airway secretions increases the risk of tube plugging and occlusion. The instillation of 3 to 5 cc of normal saline followed by suctioning of the airway should therefore be performed on a frequent basis during transport.

Accidental extubation is a relatively frequent and potentially life-threatening complication of tracheal intubation, with a reported incidence of 3% to 13% [114–117]. Because of the potentially catastrophic consequences of an accidental extubation during the transport of a critically ill infant or child, properly securing the tracheal tube in place before leaving the referring hospital, as well as the judicious use of pharmacologic restraints, assumes paramount importance. The proper use of sedatives and muscle relaxants has been shown to decrease the incidence of accidental extubation [108,115,117]. Furthermore, nurse–paramedic transport teams can safely administer muscle relaxants and sedatives under medical control provided by a physician [118,119]. Finally, some transport medicine experts recommend changing an oral tracheal tube to a nasotracheal tube, except in the presence of a basilar skull fracture. Although there is evidence that nasotracheal tubes are secured more firmly, result in fewer accidental extubations [120], and are often better tolerated [121] than oral tracheal tubes, many transport teams rely on orotracheal fixation techniques with excellent results.

Table 8.3. Indications for endotracheal intubation before interhospital transport.

Impending respiratory failure
Upper airway obstruction
Loss of protective airway reflexes
Increased intracranial pressure and need for controlled ventilation
Apnea
Cardiac arrest

Respiratory Care and Ventilatory Support

Respiratory failure accounts for nearly half of all PICU admissions [122] and represents one of the most common reasons children require interhospital transport. Beyer et al. [75] noted that respiratory illness accounted for 75%, 54%, and 28% of all transports in children under 1 month of age (including neonates), 1 month to 1 year of age, and older than 1 year of age, respectively. Diseases of the upper airways (e.g., foreign body aspiration, croup, epiglottitis) and lower airways (e.g., bronchiolitis, asthma, pneumonia) account for the majority of respiratory disorders requiring interhospital transport [75,85,123]. However, children may also require ventilatory assistance for diseases that may not have a primary respiratory cause. For example, children who are unable to protect their airway or maintain adequate control of ventilation secondary to head injury, meningitis, or other neurologic diseases will require tracheal intubation and ventilatory assistance. Respiratory care and ventilatory support, therefore, represent vital aspects of the care of the critically ill or injured child requiring interhospital transport.

Most critically ill children can be adequately ventilated during transport using manual resuscitation bags. The major advantage inherent to manual positive pressure ventilation is that the caregiver can "feel" changes in the patient's lung compliance and intervene accordingly. However, manual ventilation may be less advantageous than mechanical ventilation in that one member of the transport team is completely occupied and unavailable for providing further assistance to the remaining members of the transport team. More importantly, variation of the rate and tidal volume provided, a situation compounded by caregiver fatigue, will lead to minute-to-minute changes in effective minute ventilation and possible respiratory compromise. Studies have demonstrated a high incidence of unintentional hyperventilation resulting in clinically significant changes in arterial partial pressure of carbon dioxide (PCO_2) that are associated with the use of manual ventilation during transport [124–127]. Ideally, then, a transport ventilator should be used rather than manual bagging. If manual bagging is necessary or unavoidable, however, an appropriately sized bag with a pressure-limited pop-off valve and inline manometer should be selected.

Although transport ventilators allow for more consistent ventilation than manual ventilation, their use adds a degree of complexity to the interhospital transport that requires a basic understanding of the principles of assisted ventilation. Close monitoring of critically ill children requiring ventilatory assistance is necessary in order to facilitate adequate oxygenation and ventilation, minimize complications, and ensure patient safety. However, clinical observation and auscultation of breath sounds may be quite difficult in the loud, moving environment of an ambulance, helicopter, or fixed-wing aircraft [128,129]. Portable monitors should display

a continuous electrocardiogram, heart rate, respiratory rate, and blood pressure (either invasively via an indwelling arterial catheter or noninvasively via cuff). Temperature should be monitored frequently to avoid hypothermia. Oxygen saturation monitoring via continuous pulse oximetry represents one of the most important advances in critical care medicine in the past few decades and should be considered the standard of care during interhospital transport. In addition to showing real-time changes in oxygen saturation, pulse oximetry also provides a measurement of heart rate obtained independently from the electrocardiogram and can be used as a crude measure of the adequacy of peripheral perfusion.

Although this technology continues to be refined, the excessive motion artifact resulting from movement of the ambulance or aircraft may limit its utility during transport. End tidal carbon dioxide monitoring (capnography) provides a continuous measurement of the adequacy of alveolar ventilation, proper placement of the tracheal tube [130–132], and the amount of dead space ventilation and, hence, pulmonary perfusion. A more detailed discussion of capnography may be found elsewhere in this textbook. Finally, the use of portable arterial blood gas (ABG) analyzers is invaluable to the ventilatory management of critically ill patients, especially on lengthy transports [133]. In addition to ABG results, these monitors often provide measures of hemoglobin and serum electrolytes.

An important consideration to the provision of respiratory care and ventilatory assistance during transport that should not be overlooked is maintaining an adequate supply of oxygen [15,68]. The amount of time that a tank will supply oxygen can be determined using the following formula:

$$\text{Minutes of oxygen flow} = \frac{\text{Cylinder pressure} \times \text{Cylinder factor}}{\text{Flow of oxygen (in liters per minute)}}$$

where the cylinder factor of a size D, E, and H tank is 0.16, 0.28, and 3.14, respectively. Additional considerations include the adequate humidification and warming of all respiratory gases. The presence of a tracheal tube reduces the surface area of the respiratory passages available for warming and humidification of inhaled air by 25% [134]. Inadequate warming of the inhaled gases causes significant heat loss that may lead to hypothermia, especially in neonates and infants. Inadequate humidification causes increased insensible water losses and airway obstruction from dry, inspissated secretions. Finally, adequate sedation and neuromuscular blockade will prevent patient–ventilator dysynchrony and will facilitate ventilation and oxygenation during interhospital transport.

Vascular Access and Hemodynamic Support

All children with suspected ductal-dependent congenital heart lesions (e.g., hypoplastic left heart syndrome, interrupted aortic arch, tricuspid atresia with pulmonary atresia or severe stenosis) should be given a prostaglandin E_1 infusion (0.03–0.05 μg/kg/min). Apnea is a significant complication of prostaglandin E_1, and infants should therefore be tracheally intubated and placed on mechanical ventilation before transport.

Critical Care at Altitude

Changes in altitude can have a significant impact on the cardiorespiratory and hemodynamic status of the patient. In addition, changes in altitude can also adversely affect transport team members. Most fixed-wing aircraft have the ability to adjust cabin pressures and thereby reduce to some extent the effects of altitude. For example, if cabin pressurization is set to 5,000 feet, the barometric pressure within the cabin is equivalent to the atmospheric pressure at 5,000 feet above sea level, regardless of the actual altitude of the aircraft. However, cabin pressures are rarely set to the atmospheric pressure at sea level. Therefore, a basic understanding of the physiology of altitude is essential for each and every member of the transport team.

To fully appreciate the effects of altitude on cardiorespiratory physiology, a basic understanding of the laws of physics pertaining to the behavior of gases is required. The British chemist John Dalton stated in 1801 that the total pressure exerted by a gaseous mixture is equal to the sum of the pressures that would be exerted by the gases if they alone were present and occupied the total volume (this is now commonly referred to as Dalton's law). In other words, the pressure of a gas, such as air, is equal to the sum of the partial pressures of the individual gases in that mixture:

$$P_{air} = PN_2 + PO_2 + \text{etc.}$$

Therefore, the partial pressure of oxygen (PO_2) at any given altitude, given that oxygen comprises 21% of the atmosphere, may be calculated as follows:

$$P_{air}\ (\text{sea level}) = 760\,\text{mm Hg} \rightarrow$$
$$PO_2 = 760\,\text{mm Hg} \times 0.21 = 160\,\text{mm Hg}$$

Alveolar PO_2 (PAO_2) may then be calculated using the alveolar gas equation:

$$PAO_2 = FiO_2\,(P_{air} - P_{H2O}) - PACO_2$$

Assuming that there is no significant intrapulmonary shunt, PAO_2 will closely approximate the arterial PO_2 (PaO_2)—they should, in fact, differ by approximately 5–10 mm Hg given the normal physiologic shunt. Note that if the aircraft cabin is pressurized to an altitude of 5,000 feet (almost equal to the altitude in Denver, CO), the FiO_2 of air remains 0.21. Atmospheric pressure is much lower, however, such that the oxygen content of inspired air (and, as a result, the partial pressure of oxygen in the alveoli) is significantly reduced (Table 8.4). Therefore, as altitude increases, the subsequent decrease in atmospheric pressure will result in alveolar hypoxemia and an increase in pulmonary vascular resistance because of hypoxic pulmonary vasoconstriction unless supplemental oxygen is administered or the FiO_2 on the ventilator is adjusted to compensate for these changes.

The effects of changes in pressure on the volume of a gas were independently described by the Irish natural philosopher Robert Boyle in 1662 and by the French physicist Edme Mariotte in 1676

Table 8.4. Effects of altitude on oxygenation.

Altitude	P_B	PIO_2	$PACO_2$	PAO_2	PaO_2
Sea level 0 ft	760	150	40	110	105
Cleveland, OH 450 ft	747	147	40	107	102
Denver, CO 5,280 ft	640	125	34	91	86
Pike's Peak, CO 14,114 ft	450	85	30	55	52
Mt. Everest 29,028 ft	253	43	7.5	35	30

Note: The alveolar gas equation states that $PAO_2 = FiO_2(P_B - P_{H20}) - PACO_2$, where $PIO_2 = FiO_2(P_B - P_{H20})$; $FiO_2 = 0.21$ (remains constant despite change in elevation); and $P_{H20} = 47$ mm Hg. $PACO_2$ decreases with altitude because of hypoxic stimulation of the arterial chemoreceptors and subsequent increase in alveolar ventilation.

and are now commonly known as Mariotte Boyle's law, or simply Boyle's law. Boyle's law states that the product of the volume and pressure of an ideal gas is constant, given constant temperature. In other words, as the pressure of a gas increases, at fixed temperature, the volume decreases. Conversely, decreasing the pressure of the gas increases the volume. Accordingly, the volume of gas, that is, air, within any enclosed space (e.g., inner ear, paranasal sinuses, bowel, tracheal tube cuff, pneumothorax) will increase with altitude as the pressure decreases. These changes must be appreciated and anticipated before ascent of the aircraft (e.g., decreasing the volume of air in the tracheal tube cuff, placing a nasogastric tube to low continuous suction in children with bowel obstruction, increasing suction to evacuate a pneumothorax).

Finally, the potential adverse effects of altitude on the transport team members should be recognized. For example, altitude will potentiate the effects of certain medications, sleep deprivation, fatigue, and hypoglycemia. Changes in altitude may produce vertigo. Insensible water losses are also increased at altitude, so transport team members should keep well hydrated before, during, and after the flight.

Intrahospital Transport

Although the need for an efficient, organized system of pediatric emergency care has been the focus of intense study in recent years, the intrahospital transport of the critically ill or injured child remains a relatively new and neglected area of investigation. Children admitted to the PICU via the emergency department, operating room, and inpatient ward will require safe and rapid intrahospital transport. In addition, critically ill or injured children often require transport to other areas of the hospital from the PICU for diagnostic tests such as computerized tomography, magnetic resonance imaging, and nuclear medicine studies. Finally, children in the PICU may require transport to and from the operating room for surgical procedures.

Adult studies have shown that serious adverse events occur during the transport of critically ill patients to and from the ICU environment. For example, Indeck et al. [135] reported a 68% incidence of physiologic derangements during the period of time patients were outside the ICU. Smith et al. [136] reported a 34% incidence of equipment-related mishaps during intrahospital transport. In the only comprehensive pediatric study of intrahospital transport available [137], significant changes in at least one physiologic variable (heart rate, respirations, blood pressure, oxygen saturation, arterial PCO_2, or temperature) were reported in 71.7% of 180 intrahospital transports. Although there were no cardiac arrests or deaths reported in this study, at least one major therapeutic intervention was required in 13.9% of the transports performed.

Studies have shown that adverse events in tracheally intubated patients who are transported within the hospital are related predominantly to altered ventilation [125,137,138]. A study by Tobias and colleagues [127] reported a high incidence of unintentional hyperventilation associated with the use of manual ventilation, with end tidal CO_2 tension less than 25 mm Hg in 62% of intrahospital transports. In a more recent study, there was a statistically and clinically significant change in the end tidal CO_2 tension of patients transported from the operating room to the PICU using manual ventilation compared with ventilation with a portable transport ventilator [124]. Future studies are required to determine the optimal method of providing ventilatory support to children during transport to and from the PICU.

Extrapolation from the adult literature, as well as from the few pediatric studies that are available, would suggest that critically ill children transported within the hospital are at risk for a wide array of adverse events and mechanical mishaps. The utility of the diagnostic test or therapeutic intervention requiring removal from the PICU environment must therefore be weighed against the anticipated risk of clinical deterioration. The available literature suggests that approximately two-thirds of all intrahospital transports are performed for diagnostic studies that do not result in changes in management [126,135]. The severity of illness and anticipated duration of the transport should determine the personnel and equipment required; however, the transport of a critically ill child within the hospital from one location to another should never diminish the level of care provided. Again, the concept of the "mobile intensive care unit" should be adhered to, that is, the care provided during the transport should be equal to that of the PICU itself. In this regard, Link et al. [138] showed that the use of a dedicated transport team for the transport of critically ill patients within the hospital minimizes the risk of adverse events.

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9
Withdrawal of Life Support

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Introduction

Most childhood deaths in developed countries occur in inpatient hospital settings, primarily intensive care units [1–3]. Many of the treatment modalities available for supporting patients with life-threatening illness are technologically complex and invasive. For many patients the use of such modalities can lead to full or partial recovery, whereas for others such modalities may increase suffering and prolong an inevitable death. Intensive care support is often instituted on admission with the goal of cure only to become apparent that it is causing unnecessary or futile pain and suffering. Physicians and families are commonly faced with the arduous task of deciding whether life-sustaining therapies are helpful or harmful to the child. Such decision making is always intellectually difficult and emotionally draining for both physicians and families. Nevertheless, studies have shown that approximately 50% of children who die in modern intensive care units do so after a decision has been made to limit or withdraw support [4–9].

Making the Decision to Forgo Life Support

Decisions to forgo life support for critically ill patients should be guided by ethical and legal principles and by professional guidelines [10–17]. The term *forgo* refers to withholding or withdrawing treatment, both of which are deemed by most to be morally and legally equivalent [12]. Physicians caring for critically ill adults rely on the *ethical principle of respect for persons* [10]. This principle respects the autonomy of adults to make decisions for themselves regarding what is done to their own bodies and includes the right to refuse life-sustaining therapies. In the case of incapacitated adults, physicians invoke the *ethical principle of substituted judgment*. This principle posits that incapacitated adults are likely to have had prior expressed wishes concerning their end-of-life care and that individuals close to them know what these wishes are. It is the responsibility of the surrogate decision-maker to make the choice that the incapacitated patient would have wanted. Advance directives serve to preserve an individual's autonomy should he or she become incapacitated at some time in the future.

Most children, however, have not reached the developmental or cognitive level necessary to make decisions regarding the use of life support. Pediatricians rely on the *ethical principle of beneficence* when making such decisions for children [10,11]. Beneficence obligates physicians to base decisions regarding the use of specific treatment modalities on the benefits they are likely to provide to the child. The accompanying *ethical principle of nonmaleficence* requires physicians to avoid or minimize potential harm to the child as a result of treatment. These principles have resulted in the *best interest standard* that requires physicians and families to pursue treatments that take into account the overall welfare of the child. Some older children and adolescents are capable of expressing their wishes. Current guidelines emphasize that physicians and parents should give great weight to the expressed views of children when employing the best interest standard [12–14].

Conflicts between physicians and parents regarding what is in the child's best interest are common. Parents are the natural surrogate decision-makers for children [10,18,19]. However, parents may have other interests, such as the loss of the parental role, the need to avoid emotional distress, and concern regarding the effect of the child's death on family integrity, that can potentially confound their decisions. Physicians must make their own independent assessment of what is in the child's best interest, share this assessment with the family, and make recommendations on how to proceed. Physician–family communication is a crucial element of decision making for children. In the intensive care environment, many physicians and services frequently contribute to the child's care. Parents must know the identity of the attending physician ultimately responsible for their child's care. The physician must be available and willing to meet with the parents on a regular basis to impart information, explore parents' concerns, render opinions, and answer questions.

Adequate information is essential to good decision making [12–16]. Parents should be presented with medical facts as well as their meaning and significance to the child and family. Likewise, treatment options should be discussed along with the physician's recommendations. It is not enough to present options; the physician should also provide advice as to what he or she believes is the best option for the child under the given circumstances [12]. General pediatricians and subspecialists who have long-standing relationships with the child and family can be extremely helpful in

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discussions with families regarding the withholding or withdrawal of life support from a critically ill child. Physicians from different specialties and backgrounds may, however, have different views. Physicians should discuss their views and reach consensus among themselves before making recommendations to parents. Disagreements among physicians, real or perceived, regarding the forgoing of life support places undue stress on parents and leads to mistrust [9]. Once a recommendation is presented to forgo life support, parents may need time to consider it and discuss it with their family members. Parents may disagree with the physicians' advice; however, an honest and compassionate recommendation regarding whether or not life support should be used can emphasize to parents the shared nature of the decision making and help to relieve any doubt or guilt the parents may feel.

Physicians are not obligated to provide treatments that in their judgment will not benefit the patient [20]. However, physicians should make a concerted effort to reach agreement with parents to forgo life support before such a decision is carried out. Hospitals should have mechanisms to address unresolved conflicts among physicians, patients, and families. For example, one role of institutional ethics committees is to provide a forum for open discussion of medical, moral, and legal issues involving decisions to forgo life support in a particular case [21]. However, ethics committees do not have the authority to force a decision one way or the other. Studies suggest that ethics committee consultations are useful in resolving conflicts regarding end-of-life decisions and reduce the use of nonbeneficial treatments in intensive care units [22,23]. When physician–parent consensus cannot be reached, it may be possible to transfer the child's care to another physician or institution that is willing to comply with the parents' wishes, if such is available [12].

Providing Care During Withdrawal of Life Support

In the intensive care setting, a decision to withhold life support usually refers to establishing a *do not resuscitate* order, whereas a decision to withdraw life support refers to discontinuing one or more treatment modalities (i.e., mechanical ventilation) with the expectation that death will occur as a result. Such decisions must be accompanied by a careful evaluation of the child's palliative care needs [24,25]. The focus of palliative care is relief of the child's symptoms rather than cure of the underlying disease. Experts agree that certain elements of palliative care are appropriate for most critically ill children and should be applied regardless of whether or not their illness is likely to be terminal [24,25]. A child's palliative care needs are almost certain to change, however, once a decision to withdraw life support has been made. It is important to recognize that such patients continue to require considerable care in relation to their physical, emotional, social, and spiritual needs.

Compassionate withdrawal of life support requires clinicians to assess each monitoring device or treatment modality applied to the patient with respect to the patient and family's goals [26]. For example, the goals for a dying child may include alleviation of pain, an opportunity to be held, and avoidance of a prolonged death. Blood tests, radiographs, and vital sign monitoring may be more burdensome to the child than beneficial and therefore best discontinued. Two methods for withdrawing mechanical ventilator support from critically ill patients have been described, *terminal extubation* and *terminal weaning* [26–28]. Terminal extubation involves removal of the endotracheal tube from a ventilator-dependent patient. Proponents of terminal extubation argue that it is direct and minimizes patient discomfort by shortening the dying process. Terminal weaning involves a rapid decrease (i.e., occurring over a few hours or less) in FiO_2 and ventilator rate and pressures to minimal settings, followed by extubation. Proponents of terminal weaning argue that it minimizes dyspnea and aspiration. Either method is acceptable depending on the patient's comfort level [27,29]. In the case of brain death, extubation should be performed rather than weaning because the patient is already dead and patient comfort is no longer a concern.

Opiates and benzodiazepines are routinely used for treating pain, anxiety, and dyspnea in dying children [15,29]. Meperidine is not recommended because its active metabolite normeperidine produces central nervous system excitation that can manifest as anxiety, tremors, and seizures [15]. Clinicians should apply the concept of anticipatory dosing when administering sedatives and analgesics. For example, terminal extubation is likely to produce an abrupt change in the patient's ability to ventilate. Because dyspnea can be anticipated, sedatives and analgesics should be administered before extubation in order to prevent symptoms of air hunger. Many critically ill children have been receiving opiates and benzodiazepines before a decision is made to forgo life support and may have developed some degree of tolerance. Dosages of such agents should be rapidly titrated to achieve adequate symptom control. Physicians recognize that increasing dosages of sedatives and analgesics may, in addition to controlling pain and suffering, hasten death. This so-called *double effect* is morally and ethically acceptable and minimizes discomfort at the end of life [30,31]. Increasing dosages of sedatives and analgesics may be administered to dying patients as long as the intent is to treat pain and suffering and not to cause the patient's death. It has been suggested that intent be documented in the medical record [15]. For example, when medications are prescribed on an "as needed" basis, the order should explicitly state what the medication is to be given for (i.e., pain).

The practice of *terminal sedation*, the use of high-dose barbiturates and even propofol to sedate the patient to the point of unconsciousness at time of death, has been defended by some [15]. However, we do not advocate this approach because the distinction between alleviating suffering and euthanasia becomes obscure. Neuromuscular blocking agents have no role in treating patients' pain or suffering because they have no analgesic or sedating properties. Neuromuscular blockade masks patients' symptoms, thereby preventing their adequate assessment and treatment. Neuromuscular blocking agents should be discontinued and their effect worn off before life support is withdrawn. In rare situations when neuromuscular blocking agents have been used for a long duration, clearance of the drug may be delayed and pharmacologic reversal incomplete. Physicians will have to weigh the degree of suffering caused by withdrawing life support from a patient without full neuromuscular function versus continuing treatment that has become unduly burdensome. Major professional organizations such as the American Medical Association and the American Academy of Pediatrics do not support the practice of physician-assisted suicide or euthanasia [24,32].

Other factors such as noise, lighting, privacy, and the emotional attitudes of staff can influence patients' and families' levels of comfort at the time of death. Staff must be cognizant of how their words and body language can be perceived by families as kind and empathetic or as uncaring and detached [9]. Staff must

demonstrate a caring presence without interfering with family privacy and togetherness. For patients in whom death appears imminent on withdrawal of life support, care is usually best given in the intensive care unit in order to provide continuity. Patients who are likely to survive for more than a few days are best taken care of on a general ward where a more intimate and less stressful environment can be created. In this context, inpatient hospice can offer the most comfortable and dignified end-of-life care. Some parents may request that they take their child home to die. With appropriate home care resources and support, death at home seems to be the most compassionate and respectful option [33].

One of the most important needs of parents is maintaining a relationship with their child at the time of the death [34]. Parents should be given the option of being with their child when life support is withdrawn and during the death. Parents may want to hold their dying infant or toddler or lie in bed with a child who is older. Most parents prefer unrestricted visiting but may need help from staff in directing and supporting other family members. Staff can help parents create memories of their child's last days that bring comfort in the future. For example, mementos such as a lock of hair, handprint, picture, blanket, or favorite toy or article of clothing serve as symbols of the child's life and are especially meaningful to parents. Parents should be allowed the opportunity for religious rituals and family customs at the time of death. These practices help to maintain the parent–child relationship and build lasting memories.

Providing Care After the Death

Parents and families should be allowed to stay with their child's body as long as they wish after the child's death. Sensitivity and discernment are required to determine the most appropriate time to discuss the options of organ donation and autopsy with parents. Federal regulations require that institutions receiving Medicaid or Medicare have a trained, designated person approach families of deceased patients for organ donation [35]. The designated person is most often a representative of the local organ procurement agency. The representative will usually come to the hospital to discuss organ donation with the family and make the request. Research has shown that decoupling the death telling from the request for organs, participation of an organ procurement worker in the request, and making the request in a quiet, private place enhances families' consent rate for organ donation [36]. Many parents find comfort in the altruistic act of donating their child's organs. Even in situations when the organ procurement agency decides that the child is not an eligible donor, the child's lack of eligibility should be explained to the parents who may otherwise wonder in the future why they were not asked to donate [9].

Physicians also need to explain and request permission for autopsy from parents. Depending on the location and circumstances of the death, autopsy may not be an option but rather required by law. In some jurisdictions when the law requires an autopsy, the parent may be allowed to identify the child's body at the hospital, thereby avoiding a distressing trip to the county morgue. If organ donation is possible and the law requires an autopsy, the medical examiner's office should be contacted in order to request the parents' permission for organ donation and coordinate plans.

Follow up of parents and families after the child's death is an important part of end-of-life care. Sympathy cards, letters, and telephone calls from staff are deeply appreciated by most parents. Formal memorial services and bereavement support for families are powerful means of helping families adjust to their loss. Meeting with the child's physician at some point after the death is helpful in bringing some sense of closure. Physicians can use these meetings to discuss autopsy findings, answer questions, provide referrals, inquire into family members' feelings, and provide anticipatory guidance regarding preventive health practices during bereavement, such as adequate rest, diet, open communication, steady routines, and avoidance of major decision or life-style changes [37]. Most parents perceive these activities as a willingness on the part of the hospital and staff to provide ongoing emotional and informational support.

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10
Brain Death

Sam D. Shemie

History of the Brain Death Concept

The concept of brain death was influenced by two major advances in health care in the 1960s: the development of intensive care units with artificial airways and mechanical ventilators that treated irreversible apnea, thus interrupting the natural evolution from brain failure to cardiocirculatory death; and addressing ethical concerns associated with organ donation arising from the then-new discipline of transplantation surgery. Before the introduction of mechanical ventilators in the mid 20th century and the evolution of resuscitative measures, a nonbrain or circulation formulation was used to determine death.

Historical records indicate that Rabbi Moses Maimonides was the first to suggest that the brain was of primary importance in sustaining life when he noted that decapitated individuals would invariably die. The clinical appearance of brain death was first described in a seminal work by the French in 1959 and termed *coma dépassé* [1], meaning *a state beyond coma*, which described 23 cases in which loss of consciousness, brain stem reflexes, and spontaneous respiration was associated with absent encephalographic activity. In 1968, the Ad Hoc Committee of the Harvard Medical School, lead by neurologists Schwab and Adams, undertook to define irreversible coma and brain death [2]. They established a new, neurologically based definition of death, defined as "unresponsiveness and lack of receptivity, the absence of movement and breathing, the absence of brain-stem reflexes and coma whose cause had been identified." Also recommended was an isoelectric encephalogram with repetition of all tests after a period of at least 24 hours.

In the 1970s, Mohandas and Chou emphasized the importance of irreversible loss of brain stem function in brain death [3], the importance of which was then the focus of a published statement by the Conference of Medical Royal Colleges and Their Faculties in the United Kingdom in 1976 [4]. Subsequently championed by Pallis and Harley, the brain stem formulation of brain death was formally adopted in the United Kingdom in 1995 [5]. In the United States, the Uniform Determination of Death Act [6] codifies the whole-brain formulation in stating "an individual who has sustained irreversible cessation of all functions of the entire brain, including the brainstem, is dead." This formulation is the one most commonly applied worldwide and forms the foundation for legal codification in many Western nations.

Brain death examination is a prerequisite to organ donation, and its concept has been internationally accepted as a medical and legal definition of death in the majority of countries with advanced health care systems. Despite the widespread acceptance of the criteria, there are limitations in the levels of evidence to support many of the procedures and substantial variability of clinical practice internationally and within nations. This chapter focuses on the medical aspects of the diagnosis to guide pediatric intensive care unit (PICU) practitioners in the field.

The Neurologic Determination of Death: Concept, Terminology, and Clinical Relevance

Whole-Brain Versus Brain Stem Death

Brain death is defined as the irreversible loss of the capacity for consciousness combined with the irreversible loss of all brain stem functions, including the capacity to breathe. It is important to understand that the clinical evaluation documents the complete loss of brain stem function, but it does not distinguish between brain stem death, as may be seen in massive brain stem infarction, or whole-brain death that involves the cerebrum and brain stem. The whole-brain formulation accepted in the United States is characterized by irreversible loss of function of both the cerebral hemispheres and the brain stem. An intact brain stem is integral to the preservation of most regulatory and homeostatic mechanisms, while the reticular formation, thalamus, and cerebral hemispheres all play roles in the preservation of consciousness. Global disruption of these structures forms the basis for whole-brain death.

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Clinical evaluation of these structures in the context of brain stem death is essentially identical to that used for the evaluation of whole-brain death. The brain stem formulation accepted in the United Kingdom requires irreversible cessation of brain stem functioning and is based on the fact that the reticular formation forms the basis of consciousness and that the brain stem nuclei preserve regulatory and homeostatic mechanisms. Destruction of the brain stem and reticular formation should result in unconsciousness [7]. United States experts have argued against using the brain stem formulation because of the possibility of a *super locked-in syndrome* in which awareness might be retained in the absence of all other signs of brain stem activity [7].

Brain Death Versus Brain Arrest

Brain death is a term and a concept that remains a source of misunderstanding for many practitioners, casual observers, and the public. There is ongoing animated discourse in bioethical, religious, socioanthropological, and philosophical circles [8]. International variabilities in criteria or definition may fuel this debate and lay doubt to the credibility of the diagnosis. It may be difficult to comprehend "death" in an individual whose vital functions—heart beat, warmth of circulation, and tidal movement of the lungs–are maintained by life support technology. Persistence of some neuroregulatory function may be observed with variable preservation of anterior pituitary function [9], and theoretical argument occurs as to the possibility of functioning nests of neurons [10]. Although brain death may be discussed, perceived, or argued as death of the brain, from an ICU-based physiologic perspective, it is better understood as irreversible brain arrest. It is the maximum clinical expression of irreversible neurologic failure.

The event of a cardiac arrest, if irreversible, leads to death that is subsequently determined by cardiocirculatory criteria based on the absence of heart beat and circulation. Once brain arrest occurs and is irreversible, death is subsequently determined by neurologic criteria. This neurologic determination of death is the process and procedure to determine death. It should never be confused with other forms of severe brain injury, such as persistent vegetative state, cortical death, or anencephaly. Brain injury in these conditions may be catastrophic and irreversible, but it is not complete, because clinical signs of residual brain stem function persist.

The concept of brain death has been criticized as a social construct created for utilitarian purposes to permit transplantation [11]. Scientific advances have made this historical argument increasingly illegitimate. Traditional cardiopulmonary definitions of death (asystole, circulatory arrest, and apnea) are no longer sufficient in the face of advancing technology that may support and/or replace complete and irreversible loss of heart and/or lung function. Every solid organ can be supported by ICU-based technology or replaced by transplantation except the brain. If the heart is completely and irreversibly arrested, death has not occurred if the circulation is being supported by a machine such as extracorporeal membrane oxygenation or other forms of artificial heart technology, as long as neurologic function is salvageable. Cardiorespiratory function can be sustained in any form or severity of brain failure. Although it was once considered that brain death invariably leads to hemodynamic stability and cardiac arrest [12], it is now clear that aggressive cardiorespiratory support, hormonal therapy, and nursing care can maintain somatic functions indefinitely [13]. These continued advances in technology and transplantation have made brain-based determination of death more relevant and valid today than in its origin.

Demographics and Etiology

The most common etiologies of brain injury leading to brain death in children are traumatic brain injury, hypoxic–ischemic encephalopathy after cardiac arrest, and cerebrovascular accidents. The demographics have changed over time for adults, for whom cerebrovascular accidents now exceed traumatic brain injury as the primary cause leading to brain death [14]. Acute neurosurgical lesions account for the majority of cases and include traumatic brain injury, intracranial hemorrhage related to vascular malformations or tumors, and acute hydrocephalus. Other causes in children include infection (meningitis, encephalitis), metabolic encephalopathies (hepatic failure, diabetic ketoacidosis, inborn errors of metabolism, hyponatremia) and vasculitis [15].

The true incidence of brain death is not known, as there is currently no mechanism for mandatory reporting. This is problematic, as countries report their organ donor rates as *per million population*, which does not account for the wide variation of motor vehicle and cerebrovascular fatality rates between countries and within geographic regions of each country. Indirect estimates suggest the incidence of brain death is progressively decreasing [16]. Successful public health policy is reducing the incidence of traumatic brain injury, early field interventions and advances in neuroprotective therapy decrease mortality, and earlier neuroprognostication leads to recommendations to withdraw to life-sustaining therapy prior to brain death occurring. Table 10.1 lists the demographics of brain death in children from a large single center experience [15]. Of all deaths in the PICU, 16%–38% are brain death (Figure 10.1), depending on the geographic location and type of unit, disease severity, end-of-life practices, and application of the diagnostic criteria.

Table 10.1. Demographics of pediatric brain death in the Hospital for Sick Children, Toronto, from January 1990 to December 1997.

Etiology	N = 199 (%)
Acute neurosurgical lesions*	91 (46%)
Hypoxic–ischemic encephalopathy†	66 (33%)
Infection‡	24 (12%)
Miscellaneous§	18 (9%)
Age	Mean 5.80 ± 5.2 years
	Median 4.15 years

*Includes head trauma from motor vehicle accident, intracranial bleed from arteriovenous malformations, nonaccidental injury, intracranial tumor in isolation, and acute hydrocephalus.

†Includes postcardiac arrest or respiratory arrest patients, near–sudden infant death syndrome, near-drowning, asphyxia, and hypovolemic shock.

‡Includes meningitis, encephalitis, and generalized sepsis.

§Includes metabolic encephalopathy from liver disease, diabetic ketoacidosis, inborn errors of metabolism, hyponatremia, and vasculitis.

Source: Adapted from Tsai et al. [15].

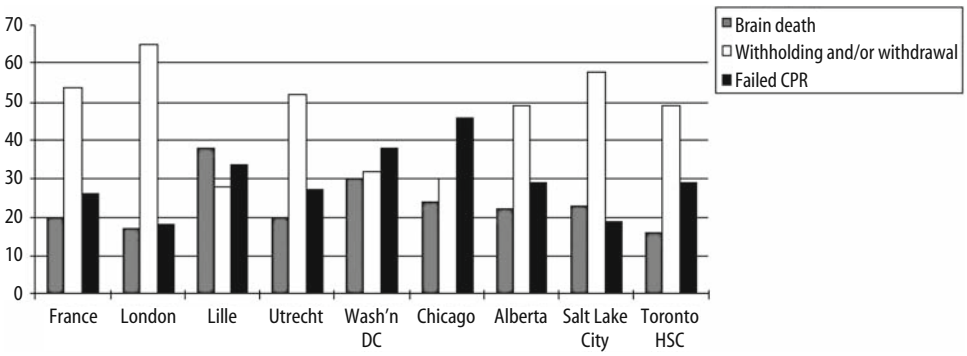


Figure 10.1. Comparison of reported rates of modes of death of children admitted to a pediatric intensive care unit. (Adapted from Martinot et al. [57]. Reprinted with permission.)

Pathophysiology

Regardless of the primary etiology of brain injury, tissue edema or mass effect leads to the final common pathway characterized by increasing intracranial pressure, which progressively impairs cerebral blood flow. As pressure rises inside the rigid intracranial vault, it may do so heterogeneously throughout the brain or selectively within compartments. Pressure-related ischemia ensues, leading to further neuronal/glial injury and edema. This contributes to a continued rise in intracranial pressure until intracerebral pressure exceeds arterial inflow pressure and cerebral circulatory arrest occurs. In response to rising intracranial pressure, the brain herniates through paths of least resistance (Figure 10.2), most commonly seen as downward descent of the brain stem and cerebellum through the foramen magnum (Figure 10.3). The duration of time from injury to brain death may vary, depending on mechanism and severity of initial injury and the response to neuroprotective therapies. Acute and massive rises in intracranial pressure as seen with explosive brain death [17] or with sudden intracranial hemorrhage, may present immediately with herniation. Slower rises in intracranial pressure in response to acute injury and gradual cerebral edema (e.g., hypoxia–ischemia) make take many days.

Minimum Clinical Criteria

Brain Stem Reflexes

Brain death is fundamentally a detailed clinical examination that documents the complete and irreversible loss of consciousness and absence of brain stem function, including the capacity to breathe. The following criteria used in the clinical assessment for brain death determination are remarkably similar throughout the world [18].

1. Established etiology capable of causing brain death in the absence of reversible conditions capable of mimicking brain death
2. Deep unresponsive coma
3. Absent brain stem reflexes as defined by absent gag and cough reflexes and the bilateral absence of
   a. Motor responses, excluding spinal reflexes
   b. Corneal responses
   c. Pupillary responses to light with pupils at mid size or greater
   d. Vestibulo-ocular responses
4. Absent respiratory effort based on the apnea test
5. Absent confounding factors

An absolute prerequisite is the absence of clinical neurologic function with a known, proximate cause that is irreversible. There must be definite clinical and/or neuroimaging evidence of an acute central nervous system (CNS) event that is consistent with the irreversible loss of neurologic function. Coma of unclear mechanism or etiology precludes the diagnosis. Deep unresponsive coma implies an absence of centrally mediated response to pain. Any motor response in the cranial nerve distribution, CNS-mediated motor response to pain in any distribution, seizures, or decorticate and/or decerebrate responses is not compatible with the diagnosis.

Spinal reflexes, or motor responses confined to spinal distribution, may persist. A proportion of patients may continue to display some reflex spinal activity, which can confuse the bedside staff or

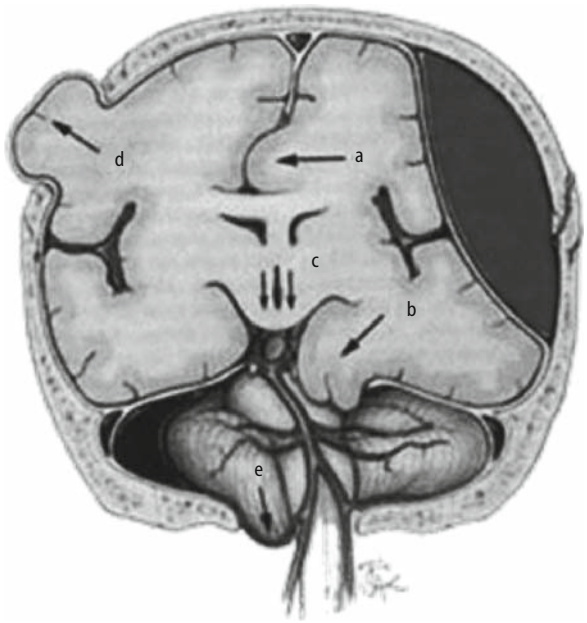


Figure 10.2. Sites of potential herniation in response to intracranial pressure: a, subfalcial; b, uncal; c, downward (central, transtentorial); d, external herniation through a defect in the cranial vault (e.g., craniectomy); e, tonsillar. (From www.uth.tmc.edu/. . ./skull_brain/skull.html. Copyright 2000, 2001, John H. Harris, Jr, MD, and Thea T. Troetscher, RN. Reprinted with permission.)

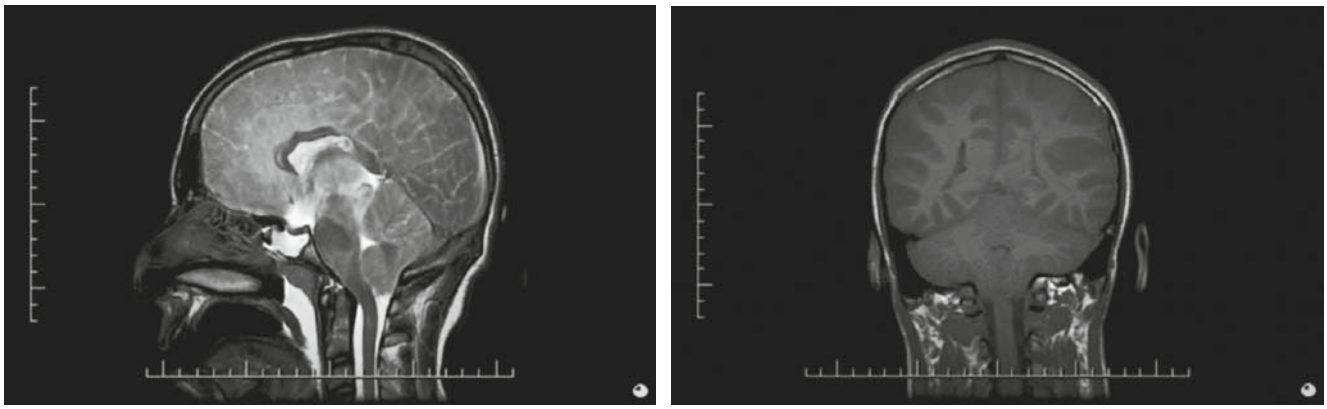


Figure 10.3. Sagittal T2 **(A)** and coronal T1 **(B)** magnetic resonance imaging series after brain death, demonstrating downward herniation of brain stem and cerebellum through the foramen magnum.

the inexperienced clinician and be disturbing to family members. They should be anticipated, and explanations should be provided to families. Observed spinal reflex activity may range from subtle twitches to the more complex *Lazarus sign* and may be seen in 13%–39% of cases [19,20]. Persistence of these reflexes is compatible with brain death. If disagreement arises as to their interpretation, an ancillary test should be performed.

The oculocephalic, or so-called dolls eyes, reflex is a less potent stimulus to the vestibular system, contraindicated when cervical spine injury is suspected and is generally not required. However, Ashwal recommends that the reflex be evaluated and documented in neonates and infants in whom the vestibulo-ocular reflex may be more difficult to determine [21]. In newborns, the suck reflex may be included [22].

Apnea Testing

Determination of persistent apnea is required as a fundamental part of the clinical criteria and is based on the absence of any sign of respiratory effort (mediated by the medullary respiratory center) in response to acute hypercarbic stimulation. In less technically advanced nations apnea determined by ventilator disconnection may be sufficient [18]. However, most Western guidelines require documentation of apneic threshold as determined by arterial blood gas analysis. In the United Kingdom a threshold $PaCO_2 \geq 50$ mm Hg is required [5], but American [23] and Canadian [22] guidelines recommend an apneic threshold $PaCO_2 \geq 60$ mm Hg and an increase of 20 mm Hg above baseline. Some guidelines also require documentation of an acidemic pH < 7.28 [22].

Optimal performance of the apnea test requires a period of preoxygenation followed by 100% oxygen delivered to the trachea (e.g., insufflation via endotracheal catheter inserted into the distal trachea) upon disconnection from mechanical ventilation. To correctly interpret an apnea test, the certifying physician must continuously observe the patient for respiratory effort throughout the performance of the test. The rate of rise of $PaCO_2$ during the apnea test is nonlinear, depends on body temperature (metabolic rate) and basal $PaCO_2$ [24], and often requires 10–20 min off the ventilator. There are risks of hypoxemia, hemodynamic instability, arrhythmia or cardiac arrest during the apnea test [25]. This may be anticipated with coexisting respiratory dysfunction, myocardial injury, or hemodynamic instability and reduced by preoxygenation. In those with high risk of apnea test complications, the time off the ventilator can be minimized by reducing the ventilator rate before the test, maintaining continuous positive airway pressure during the testing [26] or administering exogenous CO_2 [27].

The recommended apneic thresholds are based on substantial and long-term clinical experience, but are somewhat empirical. Higher hypercarbic breathing thresholds beyond those recommended has been reported in an isolated pediatric case report [28]. Caution must be exercised in considering the validity of the apnea test if in the physician's judgment there is a history suggestive of chronic respiratory insufficiency and responsiveness to only supranormal levels of carbon dioxide or if the patient is dependent on hypoxic drive. Inability to perform or complete the apnea test mandates ancillary testing.

Confounding Factors

The following confounding factors preclude the clinical diagnosis:

1. Unresuscitated shock or hypotension
2. Hypothermia
3. Severe metabolic disorders capable of causing a potentially reversible coma
4. Peripheral nerve, muscle dysfunction, or neuromuscular blockade potentially accounting for unresponsiveness (e.g., Guillain-Barré syndrome)
5. Clinically significant drug intoxications (e.g., alcohol, barbiturates, sedatives, hypnotics); therapeutic levels and/or therapeutic dosing of anticonvulsants, sedatives. and analgesics do not preclude the diagnosis
6. The acute post resuscitation phase after cardiac arrest

It is well recognized that hypothermia (core temperature <32.2°C) induces hyporeflexia and that at temperatures <28°C areflexia may ensue [29]. Despite this fact, level of consciousness and core temperature may be poorly correlated [30], and the effects of brain injury on temperature effects are unclear. Many guidelines include specific core temperature thresholds for clinical determination of brain death, but recommended thresholds are wide, ranging from 32.2°C to 36.5°C.

Severe metabolic abnormalities, including glucose, electrolytes, liver, or renal dysfunction and inborn errors of metabolism, may play a role in the patient's clinical presentation. It is important to distinguish metabolic abnormalities that play a role in the presentation (e.g., acute hyponatremia and resultant cerebral edema) from those that may arise during the ICU treatment phase but do not necessarily contribute to brain arrest (e.g., hypernatremia from diabetes insipidus). If the primary etiology does not fully explain the clinical picture, and if in the treating physician's judgment the metabolic abnormality may play a role, it should be corrected, or an ancillary test should be performed.

Brain death determination in the presence of recognized therapeutic or self-administered drug intoxication requires attentiveness to the pharmacokinetic profile of the identified agent [30]. When the identity of the administered agent is unknown, drug screening should be considered and time should be allotted for metabolism and elimination of the drug. Alternatively, ancillary testing to confirm cerebral circulatory arrest is recommended.

It is important to distinguish barbiturate intoxication as the primary etiology of coma, where cerebral blood flow persists, versus high-dose barbiturates used for the treatment of refractory intracranial hypertension. The electroencephalogram is of no use to distinguish these situations. Existing evidence suggests that for patients who fulfill minimum clinical criteria under the circumstances of high-dose barbiturate therapy utilized for refractory intracranial hypertension to achieve deep coma or electrocerebral silence, death can be confirmed by the demonstration of absent intracerebral blood flow [31].

Neurologic assessments may be unreliable in the acute postresuscitation phase after cardiorespiratory arrest [32]. In cases of acute hypoxic–ischemic brain injury, clinical evaluation should be delayed for 24 hr subsequent to the cardiorespiratory arrest, or an ancillary test should be performed.

Physician Expertise

The levels of expertise and specialties of declaring physicians vary by country and region, most often including intensivist, neurologist, and/or neurosurgeon [18]. Some guidelines recommend attending staff level to augment the rigor of the determination [22], but this is not uniform throughout the world. Regardless of specialty, the physician should be experienced in the ICU-based management of severe brain injury and neurologic evaluation. Critical care physicians, neuroscience specialists, anesthesiologists, trauma surgeons, and emergency medicine physicians are frequently involved in the care of critically brain-injured patients. Appropriate training supplemented by substantial clinical experience may be more important than the specialization of the attending physician. Most guidelines explicitly exclude those physicians involved in organ transplantation from brain death determination processes.

Subsequent Clinical Examinations and Time Intervals

The presumed purpose of a second examination is to ensure independent confirmation and/or confirm reversibility over time. Most clinical guidelines require two clinical examinations within a predetermined time interval depending on the etiology of brain injury, ranging from 2 to 24 hours. Most commonly, it is recommended that a 24-hr observation period between examinations be observed in hypoxic–ischemic brain injury. Guidelines, however, tend to be less specific regarding appropriate interval times in all other clinical circumstances.

Interval waiting times have progressively diminished since the earliest guidelines of the Ad Hoc Committee of the Harvard Medical School. Some guidelines such as those developed by the Australia and New Zealand Intensive Care Society [33] mandate that two different physicians determine brain death when organ transplantation is being considered; most do not. More commonly a single physician may perform both clinical examinations. Recent Canadian guidelines [22] mandate two physician examinations in accordance with existing legislation but have eliminated the requirement for any predefined time interval between examinations for all age groups outside of the newborn period, regardless of the mechanism of brain injury.

Legal Time of Death

The following scenario may be commonly experienced: an individual has the first brain death determination on Monday, the second on Tuesday, and proceeds to surgical procurement of organs on Wednesday. The ICU staffs, medical records, insurance executors, and, most important, the family, are not sure which day the patient died. The medical literature and daily practice is often unclear on the issue of timing of legal death in the case of brain-dead patients, because two examinations for brain death are required in most jurisdictions. Following the first determination of brain death, Pallis and Harley state that the patient becomes a "ventilated cadaver" [5]. It is acknowledged that, in experienced hands, the second examination for brain death is invariably consistent with the first and that an apnea test need not be repeated during the second evaluation [30]. In some jurisdictions, two examinations are mandated for postmortem donation, but only one for the diagnosis of death without donation [22]. Although regional legal statutes should be clarified, it is most reasonable to conclude that the declaration of death should be legally established at the time of the first brain death examination [22].

Ancillary Testing

Brain death is fundamentally a clinical examination, and, when all the minimum clinical criteria have been met, there is no need to consider ancillary diagnostic testing (excluding age adjustments) [22,23]. However, the indications for ancillary testing vary by jurisdiction and age, and a number of international guidelines still mandate ancillary diagnostic testing to establish brain death [18]. In general, the following indications should apply:

1. Inability to complete any part of the minimum clinical criteria (e.g., spinal cord injury or respiratory instability that precludes apnea testing, ocular trauma precluding eye examination)
2. Confounding conditions that cannot be resolved
3. Uncertainty or disagreement among certifying physicians
4. Helping families understand brain death

In jurisdictions such as the United Kingdom that accept brain stem death, the use of ancillary testing is limited, provided that a well-established etiology for brain stem death is identified and that conditions known to mimic absent brain stem function are excluded. There are currently no techniques available to directly evaluate flow or function of the brain stem in isolation.

Electroencephalography

The electroencephalogram (EEG) is readily available in most tertiary medical centers worldwide, has a long historical experience in practice, and is the most common ancillary test recommended. It was a component of the first guidelines for brain death [2] and remains strongly recommended in the United States [34]. It can be performed at the bedside but has significant limitations. The EEG detects cortical electrical activity but is unable to detect deep cerebral or brain stem function, and thus it may be isoelectric in the presence of viable neurons in the brain stem and elsewhere. Some patients may remain indefinitely in a vegetative state with a flat EEG but are clearly not brain dead [35,36]. The high sensitivity requirement for recording may result in detection of electric interference from many of the devices that are commonplace in the ICU setting. The EEG is also significantly affected by hypothermia, drug administration, and metabolic disturbances. These factors, resulting in false positives or false negatives, diminish its clinical utility. Although it is still required in many jurisdictions, the relevance of the EEG for brain death is under question, and a number of recent guidelines recommend testing of intracerebral blood flow as the ancillary test of choice [22,37].

Tests of Intracerebral Blood Flow

Tests that show absent blood flow to the brain are generally accepted as establishing whole-brain death with certainty, as it is accepted that the brain without a blood supply for an extended period of time is completely and irreversibly arrested. They provide evidence of global brain death, that is, both the cerebral hemispheres and posterior fossa structures can be assessed. Because these tests have been used to define brain death, there are no reliable studies to assess their validity before clinical brain death has occurred. The tests are not confounded by drugs, metabolic disorders, or hypothermia. Blood pressure stability should be ensured as damaged brain may have lost autoregulation and blood flow will vary with changes in perfusion pressure. Rarely, perfusion tests give false-negative results in which some perfusion of arterial or venous intracranial structures is found in the presence of clinically and pathologically confirmed brain death [38]. This occurs principally in those conditions in which intracranial pressure is lowered through some decompressive mechanism (e.g., decompressive craniectomies, skull fractures, ventricular shunts, or infants with pliable skulls). Although a number techniques are in evolution, the two generally recommended diagnostic tests capable of identifying complete cerebral circulatory arrest are cerebral angiography and Tc-99m hexamethylpropylene-amine oxime (Tc-HMPAO) radionuclide angiography.

Four-Vessel Cerebral Angiography

Visualizing both the anterior and posterior cerebral circulations is the traditional gold standard among ancillary tests for brain death [39]. Cerebral circulatory arrest occurs when intracranial pressure exceeds arterial inflow pressure. External carotid circulation should be evident, and filling of the superior sinus may be present. The absence of any intracranial filling of internal carotid or vertebral arteries should be demonstrated. Angiography requires technical expertise and is performed in the radiology department, necessitating transport. Arterial puncture and catheter-related complications have been described. Radiocontrast can produce idiosyncratic reactions and renal dysfunction.

Nuclear Medicine Imaging Techniques

Radionuclide angiography for brain death confirmation has been widely accepted for a number of years and is easy to perform [40]. Newer radiopharmaceuticals, such as Tc-99m hexamethylpropylene-amine oxime (Tc-99m HMPAO) and ethyl cysteinate dimer (ECD), have been studied extensively in the past decade with enhanced detection of intracerebral, posterior fossa, and brain stem blood flow. They are lipid soluble, crossing the blood–brain barrier, and penetrate into the brain parenchyma in proportion to regional blood flow. They are detected with single photon emission computed tomography (SPECT) and provide information on both arterial cerebral blood flow and uptake of tracer within perfused brain tissue. Their ability to show the presence or absence of brain perfusion rather than just intracranial circulation makes them close to the ideal test [41]. The lack of signal from the intracranial compartment and the normal uptake in other parts of the head produce the *empty light bulb* (Figures 10.4 and 10.5) and *hot nose* signs [42]. Traditional gamma cameras used for this technique are immobile, necessitating patient transfer for study, but newer technologies are portable, allowing for studies to be performed at the bedside where available.

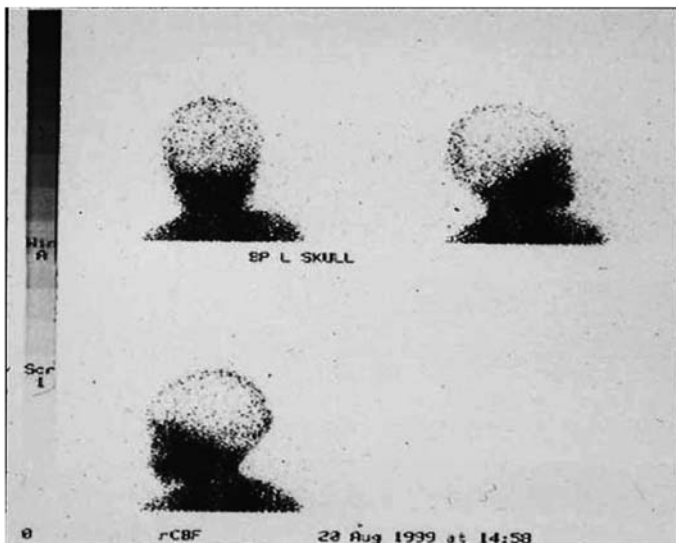


Figure 10.4. Nuclear medicine–based cerebral blood flow scan (^{99m}Tc-labeled hexamethylpropylene-aminoxime) demonstrating the absence of intracerebral blood flow in a child after brain death. Intact scalp and facial blood flow support the image of the "empty light bulb."

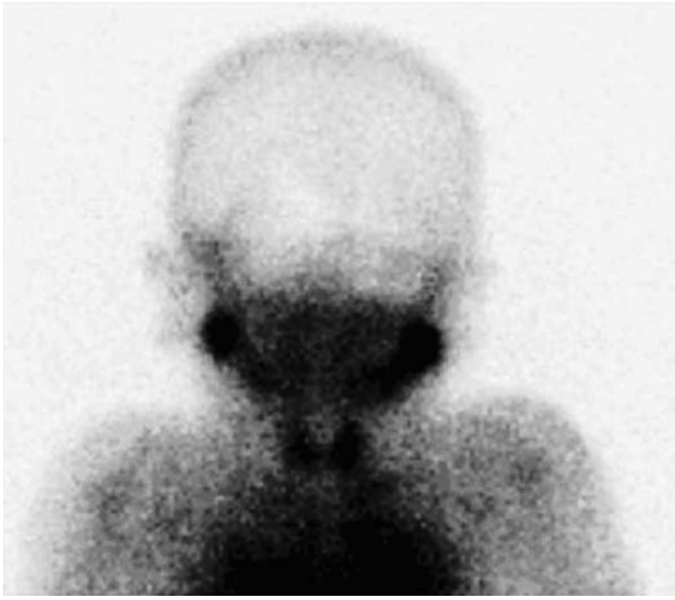


Figure 10.5. Cerebral blood flow scintigraphy study of a 7-year-old girl who was resuscitated after a submersion injury, showing no flow of ^{99m}Tc-labeled hexamethylpropyleneaminoxime to the brain. (Courtesy of Karen Tong, MD, Department of Neuroradiology, Loma Linda University School of Medicine.)

Transcranial Doppler Ultrasonography

Using a pulse Doppler instrument, the intracranial arteries are insonated bilaterally, including the vertebral or basilar arteries. Brain-dead patients display either absent or reversed diastolic flow or small systolic spikes [43]. The noninvasiveness and portability of this technique are advantageous, but the technology requires substantial clinical expertise for proper application and is not widely available.

Magnetic Resonance Angiography with Magnetic Resonance Imaging

Loss of intracranial perfusion with magnetic resonance angiography is the most definitive aspect of magnetic resonance imaging perfusion. In addition, there is loss of intracranial flow, transtentorial and tonsillar herniation, variable gray–white differentiation, and relative contrast enhancement of the nose and scalp, similar to that found with nuclear medicine tests. Widespread experience in its use for this indication is limited. Computed tomographic angiography is a recent addition to computed tomographic technology, which follows the intravenously injected contrast into the arterial circulation. The test provides adequate resolution for purposes of assessing whether intracranial perfusion is present or not. Similar to magnetic resonance angiography, widespread experience in its use for this indication is limited but holds future promise.

Other Tests of Interest

At this time, there are no other convincing contenders for ancillary testing. Somatosensory evoked potentials and brain stem auditory evoked responses have been studied in brain death but are limited in suitability [44,45]. Each test activates a discrete sensory pathway and thus examines specific and anatomically limited tracts through the brain stem. They do not test the functional integrity of other CNS structures and are not sufficient stand-alone tests for brain death. The atropine test, whereby the expected rise in heart rate is absent, allows too limited an assessment of medullary function to be very useful [46]. Its anticholinergic action is meant to abolish any residual vagal tone mediated by the dorsal motor vagal nucleus in the medulla.

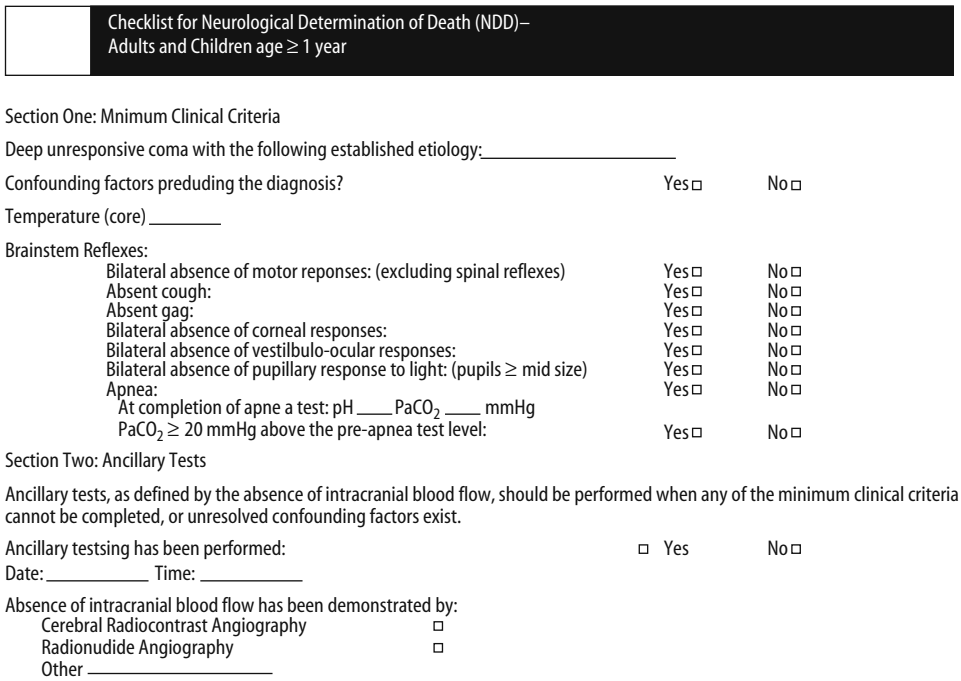
Age-Related Adjustments

It is widely accepted that adult criteria may be applied to children, although the age limits are inconsistent among guidelines. There is little or no scientific basis for published age-related adjustments and disagreement on whether clinical examination alone is sufficient for children below 1 year. The interval times between examinations and requirements for ancillary testing in the newborn and infant period are inconsistent. Ashwal [21] provides recommendations based on the patient's age that are similar to the recommendations of the American Academy of Pediatrics Task Force on Brain Death in Children [47]: (1) for term newborns (greater than 38 weeks' gestation) and young infants aged 7 days to 2 months, the clinical examination and a radionuclide brain flow study should be done; (2) for those 2 months to 1 year, two examinations and EEGs separated by at least 24 hr was suggested, and a repeat examination and EEG would not be necessary if a concomitant radionuclide angiographic study failed to visualize cerebral arteries; and (3) for those over 1 year of age, an observation period of at least 12 hr is recommended.

Farrell and Levin [48] indicate that a clinical history, physical examination, and apnea test are sufficient in diagnosing pediatric brain death, and adult guidelines may be used for infants >7 days of age. Similarly, recent Canadian guidelines emphasize that brain death in term newborns, infants, and children remains a clinical diagnosis, and ancillary testing by cerebral blood flow imaging should be reserved for cases where the minimum clinical criteria cannot be completed or confounding factors exist [22].

Variabilities and Practice Controversies

Numerous investigators have described consistency in concept, but significant variability in diagnostic criteria in Canadian [49], American [50], international [18], and pediatric studies [51,52]. Although the brain stem criteria are quite uniform, inconsistencies are evident in observation time, apnea testing, examination intervals, provisions for anoxic brain death, pediatric age-adjusted criteria, confirmatory laboratory testing, required expertise of physicians, and legal standards. Although various publications are used as reference documents [2,23,53], hospitals or regions may make individual adjustments to existing guidelines, thus exaggerating the inconsistencies among different hospitals in the same country [49,50]. In addition, there are concerns about incomplete brain death documentation in medical charts [54] that may reflect a problem of documentation or, more concerning, a lapse in performing the full clinical examination. These inconsistencies risk damaging the credibility of the determination, and there is a strong need for standardization of brain death criteria within countries and internationally. Checklist-based documentation should be ensured, an example of which is shown in Figure 10.6 [22].



Checklist for Neurological Determination of Death (NDD)–
Adults and Children age ≥ 1 year

Section One: Mnimum Clinical Criteria

Deep unresponsive coma with the following established etiology:_____

Confounding factors preduding the diagnosis? Yes □ No □

Temperature (core) _____

Brainstem Reflexes:

Bilateral absence of motor reponses: (excluding spinal reflexes)	Yes □	No □
Absent cough:	Yes □	No □
Absent gag:	Yes □	No □
Bilateral absence of corneal responses:	Yes □	No □
Bilateral absence of vestilbulo-ocular responses:	Yes □	No □
Bilateral absence of pupillary response to light: (pupils ≥ mid size)	Yes □	No □
Apnea:	Yes □	No □
At completion of apne a test: pH ____ $PaCO_2$ ____ mmHg		
$PaCO_2$ ≥ 20 mmHg above the pre-apnea test level:	Yes □	No □

Section Two: Ancillary Tests

Ancillary tests, as defined by the absence of intracranial blood flow, should be performed when any of the minimum clinical criteria cannot be completed, or unresolved confounding factors exist.

Ancillary testsing has been performed: □ Yes No □

Date: _____ Time: _____

Absence of intracranial blood flow has been demonstrated by:

Cerebral Radiocontrast Angiography	□
Radionudide Angiography	□
Other _____	

Figure 10.6. Sample brain death checklist.

End-of-Life Care and the Obligations of the Pediatric Intensive Care Unit

For patients who die as a result of severe brain injury, standard end-of-life care should include offering the option of organ and tissue donation for eligible patients. Routine provision of the opportunity to donate has become law in a number of jurisdictions, reflecting strong societal support for organ donation. Although the benefits of organ donation have been traditionally linked to the needs of transplant recipients, it is increasingly apparent that families desire the opportunity as a fundamental part of, rather than distinct from, end-of-life care. Families of children who die in PICU may offer organs despite being ineligible, and, in follow up, of those who were not asked to donate, 37% wanted the opportunity to be presented [55].

All patients who are suspected of being brain dead should have an assessment to document this fact, to diagnose death, and to establish donor eligibility. Once established, the person or group best trained and most experienced should conduct the consent discussions, based on local organizational or institutional practice. Fundamental deficits in these processes have been identified in adults [56] and children [15]. Brain death is the exclusive domain of ICU practice. Correspondingly, the ICU, in collaboration with regional organ donation/procurement services, should be responsible for ensuring that this occurs.

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11
The Pathophysiology of Brain Death and Care of the Potential Organ Donor

Sam D. Shemie

Introduction

Successful medical management of the organ donor is critical to actualizing the individual or family's intent to donate and maximizing the benefit of that intent. This interval of care in the pediatric intensive care unit (PICU) begins with brain death and consent to donation and culminates with surgical organ procurement. It generally ranges from 12 to 48 hr or longer and is related to the time required for repeated brain death declarations, consent discussions with the family, procurement logistics of donor/organ evaluation, and donor/recipient matching.

During this phase, risks for hemodynamic instability and compromise of end-organ function are high, and there is significant opportunity for enhancing donor multiorgan function and improving organ utilization. The brain-dead organ donor is a distinct and challenging pathophysiologic condition resulting in multifactorial shock. The current level of evidence supporting practices in donor management is limited by the inherent lack of prospective trial data and is based largely on adult human and animal studies. However, PICU care should be tailored by principles similar to the management of any patient with multifactorial shock. It is important to treat the donor as one would treat the transplant recipient. This can be accomplished by understanding the physiology of brain death coupled with aggressive and attentive PICU management.

Organ Utilization

Figure 11.1 shows the Canadian experience of organ utilization across all age groups, comparable to international rates [1]. Utilization rates vary from region to region and from transplant center to transplant center. Rates for heart and lung utilization have the greatest capacity for quantitative improvement. For the purposes of most international reports, a *donor* is one who has provided at least one organ that has been transplanted. Pediatric investigators have reported rates of 3.6 organs per donor (of 7 possible organs), but 22% of consented pediatric donors failed to provide *any* transplantable organs primarily because of hemodynamic instability during the phase of PICU donor care [2]. The goal of PICU-based donor management is to improve the utilization of organs from consented donors to transplant recipients. The potential benefits of aggressive medical management of the organ donor may include increased number of donors providing transplantable organs, increased number of organs transplanted per donor, and improved graft function, graft survival, and patient survival.

Physiology of Brain Death

The deterioration of cardiovascular function associated with intracranial hypertension will vary with rapidity of rise of intracranial pressure (ICP) [3], time after herniation, and presence of coexisting forms of myocardial injury (e.g., traumatic myocardial contusion, ischemia after cardiac arrest, shock, or hypoxemia). In the face of markedly elevated ICP, mean arterial pressure (MAP) rises in an effort to maintain cerebral perfusion pressure. As ICP rises further, cerebral herniation into the brain stem ensues, and brain stem ischemia is initiated in an orderly, rostrocaudal fashion (see Chapter 10, Figures 10.2 and 10.3). Initial apnea, bradycardia, hypotension, and drop in cardiac output are mediated by vagal (parasympathetic) activation resulting from midbrain ischemia. Brain stem ischemia then progresses toward the pons, where sympathetic stimulation is superimposed on the initial vagal response, resulting in bradycardia and hypertension (Cushing's reflex or triad). During this period, the electrocardiogram may be characterized by sinus bradycardia, junctional escape beats, and even complete heart block [4]. Further extension into the medulla oblongata occurs, at which point the vagal cardiomotor nucleus becomes ischemic, preventing tonic vagal stimuli. This results in unopposed sympathetic stimulation, which may last for minutes to hours and manifests as arterial hypertension with elevated cardiac output with the potential for tachyarrhythmias [4]. This period of unopposed sympathetic stimulation is often termed *autonomic storm*, during which

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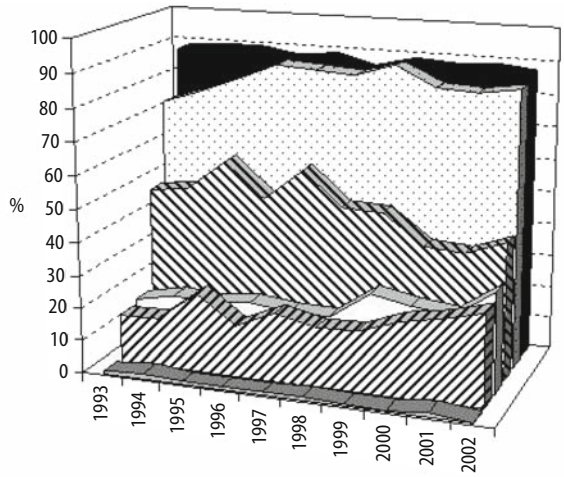

	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
Intestine/Multivisceral	0.7	1.5	0.7	0.7	0.7	1.0	0.5	0.4	1.7	0.2
Lungs	14.3	15.0	24.2	15.5	20.7	17.8	18.2	22.7	25.0	28.3
Pancreas	16.1	18.6	17.9	19.3	17.7	17.8	26.2	23.6	22.4	30.6
Heart	47.9	49.6	59.2	48.7	58.3	47.8	47.4	38.6	37.6	42.2
Liver	73.6	77.4	82.3	87.4	86.5	85.8	89.5	83.7	83.1	85.0
Kidneys	88.4	89.3	89.4	87.2	88.7	85.5	88.6	87.5	88.7	87.0

Figure 11.1. Organ-specific utilization rates for deceased donors, Canada, 1993–2002. (From Badovinac et al. [1].)

time cardiotoxicity occurs and severe vasoconstriction may compromise end-organ perfusion [5].

Neurogenic Myocardial Dysfunction

The sympathetic storm is responsible for potentially reversible myocardial injury, best studied in subarachnoid hemorrhage [6] and termed *neurogenically stunned myocardium* [7]. Endogenous catecholamine-related increases in peripheral vascular resistance may result in a sudden increase in myocardial work and oxygen consumption leading to myocardial ischemia or infarction and subsequent elevation of cardiac troponins I and T [8]. Patients dying of acute intracranial events show scattered foci of transmural myocardial injury that are not seen in patients dying of noncerebral causes [9]. Myocardial necrosis after subarachnoid hemorrhage is a neurally mediated process that is dependent on the severity of neurologic injury [10]. Brain-dead cardiac donors with elevations in cardiac troponin I are found to have diffuse subendocardial myocytolysis and coagulative necrosis and a high incidence of graft failure after transplantation [11]. The magnitude of the rise of epinephrine after brain death and the extent of myocardial damage also depends on the rate of rise in ICP in a canine model [3,12]. Dogs experiencing a sudden rise in ICP demonstrated a higher epinephrine surge and poorly functioning donor hearts. Surgical sympathectomy [13] or pharmacologic sympathetic blockade in humans [14] and animals [15,16] effectively prevents the ICP-related catecholamine cardiotoxicity and the electrophysiologic, biochemical, and pathologic changes characteristic of neurogenic injury in the heart. Although the ICP-related sympathetic storm is characterized by myocardial injury and high systemic vascular resistance, it is soon followed by period of sympathetic depletion and a low systemic vascular resistance state. Brain-dead patients become functionally decapitated, and the sympathetic system is anatomically interrupted, similar to high spinal cord injuries.

Neurogenic Pulmonary Edema

Neurogenic pulmonary edema is an unopposed sympathetic stimulation that mediate the myocardial injury and is likely responsible for the neurogenic pulmonary edema often seen in the management of patients with acute elevations of ICP (Figure 11.2). Practi-

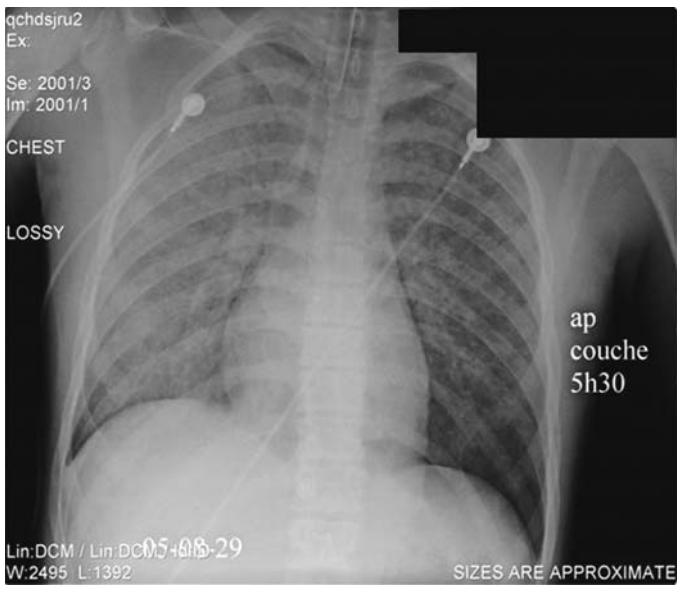

Figure 11.2. Chest x-ray showing neurogenic pulmonary edema in an adolescent with acute intracranial hypertension.

tioners should be aware of this fulminant presentation of sudden onset respiratory failure with large-volume, frothy tracheal secretions. In primate models of acute intracranial hypertension, acute heart failure ensues with reversal of flow in the pulmonary circulation caused by massive rises in left atrial pressure [13]. Rupture of pulmonary capillaries can occur from this retrograde blast of vascular hydrostatic pressure [17]. This hydrostatic pulmonary edema is responsive to high positive end-expiratory pressure and is generally reversible with time [18].

Cardiovascular Performance and Monitoring

The etiology of perfusion failure in brain-dead patients is complex and time dependent. It may be characterized by low preload caused by vascular volume depletion, myocardial dysfunction, and variable systemic vascular resistance states, ranging from extreme vasoconstriction from ICP-related sympathetic drive to vasodilation from sympathetic arrest. Resuscitation of the cardiopulmonary system benefits the function of all end-organs in the brain-dead donor. The varieties of changes in volume status, cardiac inotropy, and peripheral vascular resistance that occur after brain death are similar to those in any critically ill patient with shock of diverse etiology. Intensivists should titrate cardiovascular therapy to clinical, biochemical, and hemodynamic endpoints that ensure restoration of intravascular volume status without hypervolemia and appropriate support of the myocardium and vascular system to ensure optimal cardiac output for organ perfusion. Evaluation of cardiocirculatory status is a global assessment of multiple variables. Traditional and vigilant hemodynamic assessments should be provided, based on physical findings, vital signs, central venous pressure, urinary output, central or mixed venous oximetry, and serial lactate measurements. Escalation of support should be accompanied by escalation of hemodynamic monitoring.

Echocardiographic parameters have also been demonstrated to be beneficial in predicting successful cardiac transplant outcomes [19,20]. Echocardiographic systolic myocardial dysfunction is present in 42% of adult brain deaths and associated with ventricular arrhythmias [19]. Diffuse wall motion abnormalities are a risk factor for 30-day heart transplant mortality [21]. Single echocardiographic evaluations may have limitations in detecting the reversible myocardial dysfunction often seen after brain injury [7]. The utility of serial echocardiograms to evaluate improvement in myocardial dysfunction in the brain-dead donor and to better predict cardiac allograft survival has been reported in adults [22] and is evolving into routine practice.

Right-sided pressures may underestimate left-sided pressures after brain death and may increase risk for elevated left-sided filling pressures and pulmonary edema [23]. Expert consensus supports pulmonary arterial catheterization (PAC) and cardiac output monitoring in adults, particularly if the donors are hemodynamically unstable or initial ejection fraction is less than 40%–45% [24,25]. Pulmonary arterial catheterization and goal-directed hemodynamic therapy of initially unacceptable donors, in conjunction with hormonal therapy, may improve the rate of organ procurement without compromising transplant outcomes [26]. The Transplantation Committee of the American College of Cardiology has recommended titrating volume infusions and dopamine to thermodilution indices [27]. Justifications for PAC are not limited to the precise titration of hemodynamic support but are also required for the evaluation of suitability for heart and lung transplantation. As the use of PAC in PICU care is limited, serial echocardiography at 6- to 12-hr intervals has been recommended [25].

Hemodynamic Targets and Support

Following the sympathetic storm, a reduction in sympathetic flow results in a normotensive or hypotensive phase. This stage is characterized by impaired cardiac inotropy and chronotropy, impaired vascular tone, and a reduced cardiac output. Clinical deterioration (progressive hypotension, oligoanuria ± cardiac arrest) during the interval from brain death to procurement is common without aggressive intervention [28]. Cardiovascular support should be based on rational physiology and should be preceded by volume resuscitation to normovolemia.

Preload

Significant volume depletion is anticipated in brain-injured patients after brain death because of fluid restriction, diuretics, hyperosmolar therapy, third space losses, hemorrhage, and/or diabetes insipidus. In addition, a low systemic vascular resistance state may result in relative hypovolemia. In a Canadian study of 77 pediatric organ donors [29], 53% suffered sustained hypotension and 35% deteriorated to cardiac arrest. This was more common in patients treated with inotropic agents in the presence of a low central venous pressure (CVP) and in those without antidiuretic hormone replacement, emphasizing the importance of adequate restoration of intravascular volume.

The optimal volume status of the brain-dead patient is controversial and transplant-organ specific. Disparity exists between lung and kidney interests (dry lungs vs. wet kidneys). In a study of crystalloid fluid management in 26 brain-dead donors, a significant increase in the alveolar-arterial oxygen gradient was seen in those who achieved a CVP of 8–10 compared with those whose CVP was maintained at 4–6 mm Hg [23]. Some authors advocate maintaining a CVP of 10–12 mm Hg to volume replete those patients from whom only abdominal organs are to be procured, a CVP < 8 mm Hg for potential lung donors, and a CVP of 8–10 mm Hg if both thoracic and abdominal organs are to be harvested [30]. This approach is impractical. Effectively, euvolemia is the reasonable goal, and the assessment of volume status should be based on experienced clinical evaluation.

Systemic Vascular Resistance and Vasoconstrictor Agents

The functional sympathectomy associated with brain death results in low systemic vascular resistance that often requires the use of vasoconstricting agents. The concern over the use of α-agonists such as norepinephrine or phenylephrine has arisen because of the fear of inducing central and peripheral vasoconstriction and subsequent ischemia in vascular beds supplying potentially transplantable organs. However, in studies of other causes of shock states with low systemic vascular resistance (septic patients), norepinephrine, as compared with dopamine, was demonstrated to increase mean perfusion pressures without adverse effects to renal and splanchnic blood flow [31,32].

Vasopressin and Catecholamine Sparing in Brain Death

Arginine vasopressin (AVP) is a unique agent because it can be used for a variety of applications (e.g., hemodynamic vasopressor

support, diabetes insipidus therapy, and hormonal therapy). However, practitioners should be cautioned regarding the multiple and confusing dosing units used throughout the literature. Brain death and hypotension are often associated with vasopressin deficiency [33]. Low-dose arginine AVP infusions have been shown to improve hemodynamic stability and spare catecholamine use [33,34]. Prolonged hemodynamic stability can be maintained after brain death with low-dose AVP (1–2 U/hr), permitting a significant decrease in epinephrine and extended preservation of renal function [35]. In a rigorous randomized study of volume-resuscitated brain-dead organ donors supported with dopamine, 0.30 mU/kg/min infusion of AVP significantly increased MAP and systemic vascular resistance and spared dopamine use compared with further fluid loading [36]. Pediatric donors given AVP (41 ± 69 mU/kg/hr) respond by increasing MAP and weaning α-agonists (norepinephrine, epinephrine, phenylephrine) without significant differences in the quality of kidneys, livers, and hearts recovered [37]. Similar catecholamine-sparing effects of AVP have been demonstrated in septic shock patients with low systemic vascular resistance [38,39].

Optimal dosing of AVP in relation to its effects on organ procurement and graft survival are unclear. Concern has been expressed regarding risks of splanchnic ischemia in vasodilatory shock [40,41]. Although it is suggested that doses of AVP exceeding 0.04 U/min (approximately 40 mU/kg/hr) may be associated with excessive vasoconstriction in sepsis [38], brain-dead donors respond to AVP infusions of 0.04 to 0.1 U/min (40 to 100 mU/kg/hr) [33] without histologic evidence of cardiac damage [42]. Available literature suggests that the use of AVP at doses up to 0.04 U/min in adults (2.4 U/hr, 40 mU/kg/hr) and 0.0003–0.0007 U/kg/min (0.3–0.7 mU/kg/min) in children can be recommended to support the MAP and spare catecholamines [25].

Contractility

The preferred choice of contractility agents in PICU practice varies according to individual medical center. Traditionally, dopamine or dobutamine has been used as the initial inotrope of choice for the brain-dead patient. However, no randomized trials exist comparing the hemodynamic effects of dopamine to other inotropes or vasopressors and their influence on graft survival. β-Agonist therapy should be used with caution in potential heart donors, given concerns about myocardial adenosine triphosphate (ATP) depletion and desensitization of β-receptors. If the heart is being considered for donation, dopamine or its equivalent should not be escalated beyond 10 μg/kg/min [25].

Metabolic and Endocrine Management

Glycemia and Nutrition

Hyperglycemia is common in brain-dead donors [28]. It may be secondary to insulin resistance, as pancreatic function appears to be preserved [43] and aggravated by corticosteroid therapy and dextrose-based fluid replacements used for diabetes insipidus. Insulin is variably and inconsistently considered as part of hormonal resuscitation cocktails. The hypothesis that tight glycemic control in the brain-dead donor improves graft survival has not been tested but has been recommended by expert consensus [24,25]. Hyperglycemia has been shown to be an independent risk factor for poor outcome after severe brain injury in children [44] and adults [45]. Dextrose infusions and nutrition are generally withheld in the acute PICU management after brain injury [46], a practice supported by animal models [47]. Malnutrition or depletion of cellular glycogen stores may be common during the phase of care leading to brain death [48].

The influence of donor nutrition on graft survival has been studied in several animal studies but not formally in humans. In a rabbit and porcine model, improved liver transplant survival was shown from donors receiving enteral nutrition versus fasting donors [49]. A significant improvement in hepatic sinusoidal lining cell viability has been demonstrated in rats with liver grafts from donors receiving enteral feeding and intraperitoneal glucose before liver procurement. Glycogen appears to protect the hepatic graft upon rewarming in rats [50]. The importance of nutritional support in the human multiorgan donor, however, is not clear. Studies of donor-specific predictors of graft function following liver transplantation suggested a length of stay in the ICU of longer than 3 days as a risk factor [51]. A contributing factor to this association may be the effect of starvation on the liver with depletion of glycogen stores. In a controlled prospective randomized study of 32 patients it was shown that an intraportal infusion of insulin (1 IU/kg/hr) and glucose could reglycogenate the liver, increase glycogen utilization during cold and rewarming periods, and improve transaminase levels [52]. However, the only human series of liver transplants that included donor nutritional status failed to identify an independent effect of donor nutrition on postoperative liver graft function [53]. As a general approach, intravenous dextrose infusions should be given routinely, and routine enteral or parenteral feeding should be initiated or continued as tolerated.

Diabetes Insipidus and Hypernatremia

Dysfunction of the posterior pituitary in brain-dead donors is common; anterior pituitary function is often preserved [54]. Histologic observations of the pituitary gland demonstrate various degrees of edema, hemorrhage, and tissue necrosis, depending on the mechanism and site of traumatic or ischemic brain injury [55]. This is likely to be a result of compromised blood supply to the cell bodies arising in the deep supraventricular and paraventricular nuclei of the hypothalamus, whose neurons supply the posterior pituitary and regulate AVP secretion. Anterior pituitary function is often preserved, implying that some blood supply via the hypophyseal arteries, which arise extradurally, is reaching the median eminence of the hypothalamus [54]. Undetectable levels of antidiuretic hormone (ADH) have been noted in 75% of brain dead donors, and diabetes insipidus is present in up to 87% [29,30,54,55]. Diabetes insipidus may commonly appear before the diagnosis of brain death [55] and is associated with hemodynamic instability and the compromise of transplantable organ function [28,29]. A reasonable urine output target range is 0.5–3 mL/kg/hr after brain death. Diabetes insipidus can be defined as a urine output >4 mL/kg/hr associated with rising serum Na ≥145 mmol/L and serum osmolarity ≥300 mOsm and decreasing urine osmolarity ≤200 mOsm [25].

Desmopressin and Diabetes Insipidus

Analog 1-desamino-8-D-arginine vasopressin, or desmopressin (DDAVP), is commonly used for the treatment of diabetes insipidus in brain death without adverse effect on early or late graft function after renal transplantation [56]. It is highly selective for the vasopressin V_2 receptor subtype found in the renal collecting duct and thus has a relatively pure antidiuretic effect with no significant vasopressor activity [57]. Desmopressin has multiple potential

routes of administration (intravenous [IV], intramuscular, subcutaneous, intranasal, endotracheal) and corresponding variability of dose recommendations. In brain death, it is preferable to rely on the IV route with a recommended dosing range of 0.5–10 μg IV every 6–8 hr [58]. Given its lack of vasopressor action, it can be safely titrated to the effect of ablating polyuria.

Arginine Vasopressin and Diabetes Insipidus

Many authors have advocated the use of AVP for the treatment of diabetes insipidus in organ donors [24,25,27,58–60]. In pediatric case series, doses of AVP between 0.25 and 2.7 mU/kg/hr have been used to successfully treat hypothalamic diabetes insipidus [61–64]. Doses between 0.5 and 15 U/hr of AVP have been advocated for adults, with concerns about high doses causing coronary, renal, and splanchnic vasoconstriction and potentially jeopardizing cardiac, renal, pancreatic, and hepatic function [58]. The safety and efficacy of a combination of DDAVP (for its antidiuretic effect) with AVP as a vasopressor on cardiovascular and laboratory endpoints has been described [36]. The upper limit of AVP recommended by the Transplantation Committee of the American College of Cardiology is 0.8–1.0 U/hr (13–17 mU/kg/hr) to treat diabetes insipidus [27].

Sodium Homeostasis

Hypernatremia is frequently encountered, resulting from the preceding hyperosmolar therapy for initial brain injury or poorly controlled diabetes insipidus. Donor hypernatremia >155 mmol/L at procurement has been shown to be independently associated with hepatic dysfunction or graft loss after transplantation [53,65–67]. A prospective study has demonstrated the benefit of correcting donor sodium (Na) ≤155 mmol/L with equivalent graft success compared with donors who were never hypernatremic [65]. The mechanism of hepatic injury related to hypernatremia is unclear but may be related to the accumulation of idiogenic osmoles resulting in intracellular swelling after transplantation into the normonatremic recipient. Ideal serum Na target range is ≥130 and ≤ 150 mmol/L.

Thyroid Hormone

Thyroid hormone increases cardiac output by improving contractility and chronotropy and decreasing systemic vascular resistance [68]. The use of thyroid hormone therapy in brain-dead donors is largely based on experimental animal models and human case series. Investigators describe variable levels of thyroid hormones after brain death and varying and conflicting effects of thyroid hormone administration. Thyroid-stimulating hormone (TSH) T_4 and T_3 levels were below normal in a majority of 22 brain-dead donors [69]. Other studies have shown that these patients are suffering from *sick euthyroid syndrome* rather than TSH deficiency and do not require thyroid supplementation [54]. In the baboon model, T_3 levels become depleted after brain death and the resulting transition to anaerobic metabolism is reversed with T_3 replacement [70]. In a comparative study in brain-dead patients, T_3, cortisol, and insulin promoted aerobic metabolism, reduced the need for inotropic support, and improved the rate of cardiac graft procurement [71,72]. Other investigators were unable to demonstrate any improvement in echocardiographic function or organ retrieval rates with a similar hormone regimen [73]. Serum free T_3 concentrations in organ donors may not correlate with hemodynamic stability [55]. Infusion of T_4 does not reduce vasopressor requirements in pediatric donors [74], but this may be related to impaired peripheral conversion to T_3.

Combined Hormonal Therapy: Thyroid Hormone, Vasopressin, and Methylprednisolone

Despite conflicting literature regarding use of thyroid hormone, there is strong evidence supporting combined hormonal therapy for organ donors, defined as thyroid hormone, vasopressin, and methylprednisolone (insulin is inconsistently included in this strategy). The United Network for Organ Sharing (UNOS) database shows a 46% reduced odds of post-transplantation death within 30 days and a 48% reduced odds of early cardiac graft dysfunction with the use of combined hormonal therapy in a large retrospective cohort [75]. Benefit was also found for those donors receiving corticosteroids alone or in combination with T_3/T_4. More recent analysis of UNOS data suggests a substantial benefit from hormone therapy with minimal risk. A multivariate logistic regression analysis of 18,726 brain-dead donors showed significant increases in kidney, liver, and heart utilization from donors receiving three-drug hormonal therapy. Significant improvements in 1-year kidney graft survival and heart transplant patient survival were also demonstrated [76]. Although there are numerous theoretical advantages of parenteral T_3 over T_4 (stability for IV infusion, does not require peripheral tissue conversion), it is extremely expensive compared with IV T_4 and may not be commercially available in many countries. In those UNOS patients receiving hormone therapy, T_4 was used in 93% and T_3 in 6.9% of cases, with insufficient numbers to discriminate any benefit of T_3 over T_4 (Rosendale and Kauffman, personal communication). Currently, expert consensus strongly recommends the use of combined hormonal therapy for any donor with hemodynamic instability or reduced ejection fraction on echocardiography [24,25].

Brain Death as an Inflammatory State

Brain death is associated with the upregulation and induction of the inflammatory response in all somatic organs [77], triggering a cascade of mediators that may affect graft function. Transient focal cerebral ischemia upregulates the transcriptional levels of tumor necrosis factor-α and interleukin-6 [78]. Rapid rises of ICP cause immune activation in peripheral organs, resulting in enhanced immunogenicity [12]. In animal models, brain death has a detrimental role on hepatic dysfunction related to immune activation and independent of hemodynamic instability [79] and magnified by longer ischemic times [80]. In comparison to living related kidney donors, kidneys from brain dead donors have significantly higher levels of proinflammatory mediators on biopsy (endothelial E-selectin and proximal tubular expression of HLA-DR antigens, intracellular adhesion molecule-1, and vascular cell adhesion molecule-1) [81]. Delayed renal graft function and acute rejection in the recipient is correlated with higher indices of free radical–mediated injury in the donor [82]. Evidence that neurogenic pulmonary edema may be alleviated with glucocorticoids also suggests that an inflammatory component exists in this process [83,84]. Recent animal work suggests that this inflammation is triggered by the acute hemodynamic effects of ICP-related neurogenic myocardial dysfunction, resulting in hydrostatic pressure–based neurogenic pulmonary edema and rupture of the alveolar-capillary membrane [17].

Brain death is an important risk factor in and of itself that influences graft outcomes, mediated by postischemic reperfusion injury and other nonantigen-dependent inflammatory pathways [85]. The inflammation and fibrosis occurring in donor orgins may potentiate graft immunogenicity [86]. A resultant increase in host allore-

sponsiveness may develop and contribute to reduced graft survival [87]. These findings may be used to introduce specific cytoprotective interventions in the brain-dead donor to reduce the immunogenicity or the proinflammatory status of the graft and better maintain or increase organ viability.

Corticosteroids and Lung Protection

Several publications have advocated the use of high-dose methylprednisolone in an effort to diminish inflammation thought to be present in donor lungs [60,75]. The evidence for this is largely based on a single retrospective analysis of 118 consecutive lung donors administered a nonuniform protocol of methylprednisolone (mean 14.5 mg/kg) compared with 38 donors not receiving methylprednisolone and demonstrating a significant improvement in donor oxygenation and lung procurement rate [88]. A recent analysis of the California Donor Network database demonstrated an independent effect of methylprednisolone on the successful procurement of lungs from the donor [89]. The UNOS database showed that heart graft survival benefit was also found in those donors receiving corticosteroids alone [75]. Although the optimal dose and time effect (if any) of corticosteroids in brain-dead donors are uncertain, guidelines recommend methylprednisolone 15 mg/kg every 24 hr [25].

Transfusion Thresholds

There are no rigorous studies that assess the role of red blood cell transfusions for short-term organ preservation during organ donor maintenance. Consensus conferences recommend maintaining a hemoglobin level ≥100 g/L or a hematocrit >30% [58,60]. Large platelet transfusion requirements during liver transplant surgery are independently associated with more severe hepatic dysfunction after transplantation, but this is likely more indicative of a more technically complicated procedure and sicker recipient [90]. There is no literature identified to guide platelet or plasma factor replacement in the donor. Invasive procedures associated with bleeding risk may require correction of thrombocytopenia and coagulation status. Blood drawing for donor serology and tissue typing should occur before transfusions to minimize the risk of false results related to hemodilution. In regions where blood is routinely leukocyte depleted and the risk of transmission of cytomegalovirus (CMV) is negligible, it may not be necessary to give CMV-negative blood to CMV-negative donors [25].

Invasive Bacterial Infections

Isolated cases of transmission of solid-organ infection from donor to recipient may have significant consequences, including graft infection, sepsis, and poor initial graft function [91–95]. However, although approximately 5% of all donors will be bacteremic at the time of procurement, the routine use of prophylactic broad spectrum antibiotics (vancomycin and ceftazidime/cefotaxime) in the recipient has prevented transmission of bacterial infection in all organ recipients from a total of 124 bacteremic donors [96,97]. No differences in acute mortality or graft survival were found. Other authors have described the successful transplantation of organs from donors declared brain dead from meningitis caused by *Neisseria meningitides, Streptococcus pneumoniae*, and *Escherichia coli* without transmission to the recipient [98]. The finding of positive cultures does not preclude donation but may delay procurement until 24–48 hours of treatment has been established. Prophylactic antibiotic therapy for the organ donor is generally not recommended. Initial baseline blood, urine, and endotracheal cultures should be obtained for all donors and repeated daily. Positive blood cultures or presumed infections are not contraindications to organ donation. Antibiotic therapy should be initiated in cases of proven or presumed infection. Duration of therapy depends on the virulence of the organism and should be determined in consultation with the transplant team and infectious disease services.

Organ-Specific Considerations

Heart

Potential heart donors should undergo routine screening by electrocardiogram (ECG) and two-dimensional echocardiography. Serologic markers such as donor troponins I and T have been linked to early cardiac graft failure [99,100] and should also be measured. The majority of studies linking donor variables to heart transplant outcomes are in adults and related to known risk factors such as coronary artery disease, left ventricular hypertrophy, older age, diabetes mellitus, and chronic hypertension [21,60,101]. Although these variables may be indications for coronary angiography in the adult donor, they generally are not relevant to the pediatric population. Extrapolation from adult studies would suggest that myocardial dysfunction in the pediatric donor, as manifest by greater inotropic support [21,102], reduced ejection fraction and/or wall motion abnormalities by echocardiography [21,60], is an important factor. Reduced function should not preclude consideration for transplantation based on a single evaluation. Ejection fractions less than 40%–45% do not necessarily translate into high transplant risk, as they may be related to inadequate cardiovascular resuscitation (volume, inotropic support) or neurogenic myocardial dysfunction that is reversible with time. Adult data have shown significant improvements in echocardiographic function with time and conventional support [22], with up to 78% of potential donors demonstrating clinically significant improvements [103].

Pulmonary artery catheterization data have been linked to favorable transplant outcomes [26]. Reduced ejection fraction or hemodynamic instability has been recommended as an indication for PAC in adults to allow for both precision of hemodynamic support and evaluation of suitability for heart and lung transplantation [24]. In children, initial echocardiography for heart donor evaluation should be performed only after hemodynamic resuscitation, and repeated echocardiography should be considered after ≥6 hr [25].

Lungs

Pulse oximetry, serial arterial blood gas monitoring, endotracheal tube suctioning, chest x-ray, bronchoscopy, and bronchoalveolar lavage are considered standard in the lung-specific care of donors. Mechanical ventilation should be tailored to the following general targets: Fraction of inspired oxygen (FiO_2) titrated to keep oxygen saturation ≥95%; partial pressure of arterial oxygen (PaO_2), ≥80 mm Hg; pH 7.35–7.45; $PaCO_2$, 35–45 mm Hg; positive end-

expiratory pressure (PEEP), 5 cm H_2O. The "ideal" lung donor has been defined as follows [104]:

- Age <55 years
- ABO compatibility
- Clear chest radiograph
- PaO_2 > 300 on FiO_2 = 1.0; PEEP, 5 cm H_2O
- Tobacco history <20 pack-years
- No chest trauma
- No evidence of aspiration or sepsis
- No prior cardiopulmonary surgery
- Sputum Gram stain: no organisms
- No purulent secretions at bronchoscopy

Bronchoscopy, Bronchopulmonary Infections, and Antimicrobial Therapy

The consensus of expert opinion supports the use of bronchoscopy for the purposes of examining the tracheobronchial tree for abnormalities and collecting microbiologic specimens [24,59,105]. Pathologic studies of lungs rejected for donation have indicated that bronchopneumonia, diffuse alveolar damage, and diffuse lung consolidation are the three most common reasons for being deemed unsuitable [106]. Between 76% and 97% of bronchoalveolar lavages (BAL) will grow at least one organism [107,108]. The most commonly identified organisms included *Staphylococcus aureus* and *Enterobacter*, and, in 43% of transplants, similar organisms were isolated from recipient bronchoscopy. Pulmonary infection in the graft recipient results in significantly lower survival compared with recipients who do not develop early graft infection [109]. Recipients with donor BAL cultures positive for either Gram-positive or Gram-negative bacteria had longer mean mechanical ventilation times and inferior 6-month to 4-year survival rates than those with negative bacterial BAL cultures [110]. The etiology of donor death is not associated with lung transplant mortality [111] but may influence the type of organisms found on BAL and subsequent graft infection risk. Trauma donors (vs. intracerebral hemorrhage) may be at higher risk for aspiration and for intubation under less sterile field conditions and were generally ventilated longer [112].

Donor Lung Injury, Oxygenation, and Ventilator Strategies

Many potential donors have various etiologies of donor-related lung injury and dysfunction that may include neurogenic pulmonary edema, aspiration, atelectasis, pulmonary contusion, bronchopulmonary infection, alveolar-capillary inflammation, and diffuse alveolar damage. Primary pulmonary allograft failure has pathologic features of acute lung injury (ALI), occurs in 12%–50% of transplanted patients [111,113,114], and is often associated with inadequate lung preservation, ischemia–reperfusion injury, and cellular rejection [115]. Traditional oxygenation criteria used as a threshold in the acceptance of donor lungs include a donor PaO_2 >300 mm Hg on FiO_2 of 100% and PEEP of 5 cm H_2O (P/F ratio >300) [105,116]. However, recent and evolving efforts have improved the current criteria for donor selection. Physiologic, microbiologic, and histologic evaluations of rejected lungs from the California transplant registry show 41% of rejected lungs were judged suitable for transplantation based on pulmonary edema, intact alveolar fluid clearance, and histology [117]. In a case series of 15 brain-dead adults, lung grafts that did not meet the usual criteria for transplantation were found to have higher dynamic and static elastance measurements than donor lungs that met standard transplantation criteria [118]. The outcomes of 49 marginal donors (i.e., failing to meet one or more of the ideal criteria) showed no significant difference in duration of post-transplant mechanical ventilation or P/F ratio compared with ideal donors [116]. Investigators have also challenged donor PaO_2 criteria by arguing that physiologic donor factors influence peripheral arterial PaO_2 independent of isolated individual lung function [106]. Despite poor global oxygenation, parenchymal abnormalities isolated to one lung may not preclude procurement of the contralateral lung [119].

Similar to the management of lung injury in general, alveolar recruitment and pressure-limited ventilation strategies should be used for potential donors. Excessive fluid administration deteriorates alveolar-arterial oxygenation gradients in potential donors [23] and may be indications for diuresis. Prolonged ventilation in the supine position results in loss of alveolar expansion and microatelectasis. In an experimental rat model, donor lungs develop microatelectasis despite PEEP and a relatively short ventilatory period before organ procurement [120]. Prevention of alveolar collapse enhances postmortem preservation of pulmonary grafts in a rabbit model [121]. Recruitment maneuvers in the form of high sustained PEEP for short durations may be a useful adjunct to prevent alveolar stress and collapse [122]. Lung donors failing traditional oxygenation criteria (P/F <300) respond to aggressive bronchial toilet using bronchoscopy, physiotherapy, increasing tidal volume, and increasing PEEP with improvements in P/F ratios <300. Lungs were subsequently transplanted without differences in ICU length of stay or 30-day mortality compared with recipients of ideal donors [123]. Recent guidelines suggest that there should be no predefined lower limit for the P/F ratio that precludes consideration for transplantation. Timing of evaluation, temporal changes, response to alveolar recruitment, and recipient status should be considered [25]. In cases of unilateral lung injury, pulmonary venous partial pressure of oxygen during intraoperative assessment is required to reliably evaluate contralateral lung function.

Liver

Potential liver donors should be assessed by the following: aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin (direct and indirect where available), INR (or prothrombin time [PT]) (repeated every 6 hr), serum electrolytes, creatinine, urea, hepatitis B surface antigen (HBsAG), hepatitis B antibody (HBcAb), and hepatitis C virus antibody (HCV Ab). There is no indication for routine liver imaging. The most robust predictors of early graft dysfunction or failure include older donor age in adult transplantation (>45 years), [51,124], very young age in pediatric transplantation [51], reduced liver sizes, moderate to severe steatosis on liver biopsy, prolonged cold ischemia time (>12–18 hr) [67,125,126], and donor hypernatremia (Na >155 mmol/L). Donor hypernatremia is independently associated with death or retransplantation at 30 days [67], but this risk reverses with the correction of hypernatremia [65].

Although liver allograft dysfunction has been reported to be associated with prolonged ICU stay [51,127], this was supported by univariate analysis but did not hold true by multivariate analysis [127]. In a cohort of 323 orthotopic liver transplants, longer donor hospitalization was not found to be associated with primary liver graft dysfunction [125]. Large platelet transfusion requirements during surgery are independently associated with more severe hepatic dysfunction after transplantation [53], although this may

be indicative of a more technically complicated procedure, sicker recipient, or poorer quality graft with subsequently greater sequestration of platelets within the donor liver. The sinusoidal lining cells (SLCs) of the liver are particularly vulnerable to the effects of preservation–reperfusion injury, the extent of which depends on the duration of cold ischemia rather than reperfusion. Cold preservation causes the SLCs to become edematous and detach into the sinusoidal lumen [128]. Although some authors recommend routine donor liver biopsy studies for all liver donors in an effort to decrease the rate of early graft dysfunction or failure [129,130], the use of a biopsy in the decision making of liver suitability has generally been restricted to evaluating the amount of steatosis or the presence of active hepatitis C in the appropriate risk groups.

Kidney

A normal creatinine clearance (>80 mL/min/1.73 m^2), as estimated by the formula of Schwartz et al. [131], defines the optimal function threshold for transplantation. However, an abnormal serum creatinine or calculated creatinine clearance in a donor does not necessarily preclude use of the kidneys. Urinalysis is essential to rule out kidney abnormalities, and serum creatinine and serum urea (blood urea nitrogen) measurements should be taken every 6 hr.

Delayed graft function predicts the development of adverse events such as decreased graft survival, decreased recipient survival, and increased allograft nephropathy [132]. Donor risk factors predicting kidney allograft dysfunction include hemodynamics, age, and cold ischemic time. Donor hemodynamic instability is correlated with post-transplant acute tubular necrosis in adults [28,133,134] and children [29]. Reduced graft survival or acute tubular necrosis may occur in organs retrieved from donors receiving high-dose dopamine (>10 μg/kg/min), but these effects may be limited to donors who are hypotensive at the time of organ retrieval [134]. Hemodynamic resuscitation may improve outcome, as donor use of dopamine and/or noradrenaline is independently associated with a lower risk of acute rejection [135] and a lower rate of delayed graft function [136]. It is suggested that the time taken to optimize donor cardiovascular status may reduce renal ischemic injury [137].

In an analysis of the Collaborative Transplant Study database of kidney transplants, cold ischemic preservation time >12 hr resulted in progressively worsening recipient graft survival, particularly once the cold ischemia time (CIT) was ≥48 hr [138]. Other analyses have suggested that CIT is predictive of poorer graft survival [139] or function [133] if it is >24 hours. Preservation incorporating pulsatile perfusion, rather than cold storage, may reduce the incidence of delayed graft function [140]. Currently its use is largely restricted to higher risk settings of older donor age or nonheart-beating donation.

Donor age ≥40 or ≤10 years is independently associated with risk for graft failure [139,141]. Older kidneys have a higher incidence of renovascular or parenchymal injury [141]. Adult donor characteristics that are independently associated with graft failure risk include creatinine >133 μmol/L, history of hypertension independent of duration, and cerebrovascular accident (CVA) as the cause of donor death [139]. Although traumatic (vs. cerebrovascular) etiology of brain death is associated with improved renal graft survival, this association may be confounded by the lack of adjustment for the presence of atherosclerotic disease in older donors with CVAs [142]. Traumatic brain injury is associated with an increased risk of acute rejection [135]. If contrast angiography is performed (e.g., cerebral, coronary), N-acetylcysteine with hydration should be administered both before and after the angiographic procedure in order reduce the risk of contrast nephropathy [143] in potential donors, particularly in those with reduced renal function.

Optimal Time of Organ Procurement

In general, after brain death has been declared and consent to organ donation has been granted, all efforts are made to complete logistics and initiate procurement as quickly as possible. Expediting the interval from brain death to surgical procurement may allow grieving families to leave the hospital sooner and reduce PICU length of stay. This approach may also have been influenced by the misperception that brain-dead patients are irretrievably instable [28].

As a concept fundamental to PICU multiorgan support, resuscitation of the cardiopulmonary system benefits all end-organs. Neurogenic myocardial injury related to primary brain injury is largely reversible with time and treatment [10, 22,103]. Australian investigators advocate a delay in organ procurement until marginal donor lungs have been optimized with aggressive bronchial toilet using bronchoscopy, physiotherapy, increasing tidal volume, and increasing PEEP [89,123]. In a large cohort study of 1,106 renal transplant recipients, longer duration of brain death (time from declaration of brain death to onset of cold ischemia) improved initial graft function and graft survival, suggesting that the time taken to optimize donor cardiovascular status may reduce ischemic injury [137]. Despite early reports to the contrary [51], liver allograft dysfunction is not associated with prolonged ICU stay by multivariate analysis [125,127]. A period of time may be needed to determine the trend of elevated AST or ALT, as generally accepted upper limits may be exceeded if the levels are falling rapidly (e.g., following a hypotensive episode with resuscitation).

Temporal changes in multiorgan function after brain death demand flexibility in identifying the optimal time of procurement. Recent consensus guidelines stress the importance of taking the necessary time in the ICU to optimize multiorgan function for the purposes of improving organ utilization and transplant outcomes [25]. Reversible organ dysfunction can be improved with resuscitation and reevaluation and may include the following:

- Myocardial/cardiovascular dysfunction
- Oxygenation impairment related to potentially reversible lung injury
- Invasive bacterial infections
- Hypernatremia
- The need to evaluate temporal trends in AST and ALT
- The need to evaluate temporal trends in creatinine
- Any other potentially treatable situation.

This treatment period may be extended 24–48 hr and should be accompanied by frequent reevaluation to demonstrate improvement in organ function toward defined targets. Extending the interval of donor care in the ICU to optimize transplant outcomes should be factored into donation consent discussions and should be consistent with the wishes of the family or surrogate decision maker.

Decisions Regarding Transplantability

End-of-life care in the PICU includes all efforts to actualize the opportunity and expressed intent to donate organs. Given that the management of brain death and the organ donor is the exclusive domain of PICU practice, it is incumbent on critical care practitioners to assume leadership in this regard, in collaboration with organ procurement agencies and transplant programs. Table 11.1

Table 11.1. Standing orders for organ donor management.

It is important to take the time necessary in the PICU to optimize multiorgan function for the purposes of improving transplant outcomes. Resuscitation and reevaluation can improve reversible organ dysfunction (myocardial/cardiovascular dysfunction, oxygenation impairment related to potentially reversible lung injury, invasive bacterial infections, hypernatremia, or any other potentially treatable situation) and can allow for the evaluation of temporal trends in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or creatinine. This extended period can range from 12 to 24 hr and should be accompanied by frequent reevaluation to demonstrate improvement in organ function toward defined targets. Once optimized, donors should have surgical procurement procedures arranged emergently. There are no predefined demographic factors or organ dysfunction thresholds that preclude the consent for donation and offering of organs for transplantation. Note that dosing recommendations apply to children ≤60 kg, beyond which adult dosing should apply.

Standard monitoring
- Urine catheter to straight drainage, strict intake and output
- Nasogastric tube to straight drainage
- Vital signs q1h
- Pulse oximetry, three-lead electrocardiogram (EKG)
- Central venous pressure (CVP) monitoring
- Arterial line pressure monitoring.

Laboratory investigations
- Arterial blood gas (ABG), electrolytes, and glucose q4h and as needed
- Complete blood count (CBC) q8h
- Blood urea nitrogen (BUN), creatinine q6h
- Urine analysis
- AST, ALT, bilirubin (total and direct), international normalized ratio (INR) (or prothrombin time [PT]), partial thromboplastin time (PTT) q6h

Hemodynamic monitoring and therapy
- General targets: age-related norms for pulse and blood pressure (BP)
- Fluid resuscitation to maintain normovolemia, CVP 6–10 mm Hg
- Age-related treatment thresholds for arterial hypertension:
  - Newborn to 3 mo >90/60
  - >3 mo to 1 yr >110/70
  - >1 yr to 12 yr >130/80
  - >12 yr to 18 yr >140/90
- Wean inotropes and vasopressors, and, if necessary,
- Start nitroprusside 0.5–5.0 μg/kg/min, or esmolol 100–500 μg/kg bolus followed by 100–300 μg/kg/min
- Serum lactate q2–4h
- Central venous oximetry q2–4h; titrate therapy to central MVO_2 ≥60%

Agents for hemodynamic support
- Dopamine ≤10 μg/kg/min
- Vasopressin 0.0003–0.0007 U/kg/min (0.3–0.7 mU/kg/min) to a maximum dose of 2.4 U/hr
- Norepinephrine, epinephrine, phenylephrine (caution with doses >0.2 μg/kg/min)

Glycemia and nutrition
- Routine intravenous (IV) dextrose infusions
- Initiate or continue enteral feeding as tolerated
- Continue parenteral nutrition if already initiated
- Initiate and titrate insulin infusion to maintain serum glucose 4–8 mmol/L

Fluid and electrolytes
- Targets:
  - Urine output 0.5–3 ml/kg/hr
  - Serum sodium (Na) 130–150 mmol/L
  - Normal ranges for potassium, calcium, magnesium, phosphate

Diabetes insipidus
- Defined as:
  - Urine output >4 ml/kg/hr, associated with
    - Rising serum Na ≥145 mmol/L and/or
    - Rising serum osmolarity ≥300 mOsm and/or
    - Decreasing urine osmolarity ≤200 mOsm
- Diabetes insipidus therapy
  - Titrate therapy to urine output ≤3 mL/kg/hr
    - IV vasopressin infusion 0.0003–0.0007 U/kg/min (0.3–0.7 mU/kg/min) to a maximum dose of 2.4 U/hour, and/or
    - Intermittent 1-desamino-D-arginine vasopressin (DDAVP) 0.25 to 10 μg IV q6h

Combined hormonal therapy
- Defined as:
  - Tetra-iodothyronine (T_4) 20 μg IV bolus followed by 10 μg/hr IV infusion (or 50–100 μg IV bolus followed by 25–50 μg IV bolus q12h)
  - Vasopressin 0.0003–0.0007 U/kg/min (0.3–0.7 mU/kg/min) to a maximum dose of 2.4 U/hour.
  - Methylprednisolone 15 mg/kg (≤1 g) IV q24h
- Indications:
  - Two-dimensional (2D) echocardiographic ejection fraction ≤40% or
  - Hemodynamic instability (includes shock unresponsive to restoration of normovolemia and requiring vasoactive support [dopamine >10 μg/min or any other vasopressor agent])
  - Consideration should be given to its use in all donors

Hematology
- Hemoglobin (Hg) optimal ≥90–100 g/L for unstable donors, lowest acceptable ≥70 g/L
- Platelets, INR, PTT no predefined targets, transfuse in cases of clinically relevant bleeding
- No special transfusion requirements

Microbiology (baseline, q24h, and as needed)
- Daily blood cultures
- Daily urine cultures
- Daily endotracheal tube (ETT) cultures
- Antibiotics for presumed or proven infection

Heart specific
- 12-lead EKG
- Troponin I or T, q12h
- 2D echocardiography
  - Should be performed only after fluid and hemodynamic resuscitation
  - If 2D echo ejection fraction ≤40%, then repeat echocardiography at q6–12h intervals

Lung specific
- Chest x-ray q24h and as needed
- Bronchoscopy and bronchial wash Gram stain and culture
- Routine ETT suctioning, rotation to lateral position q2h
- Mechanical ventilation targets:
  - Tidal volume (Vt) 8–10 ml/kg, positive end-expiratory pressure (PEEP) 5 cm H_2O, peak inspiratory pressure (PIP) ≤30 cm H_2O
  - pH 7.35–7.45, partial pressure of arterial carbon dioxide ($PaCO_2$) 35–45 mm Hg, partial pressure of arterial oxygen (PaO_2) ≥80 mm Hg, oxygen (O_2) saturation ≥95%
- Recruitment maneuvers for oxygenation impairment may include
  - Periodic increases in PEEP up to 15 cm H_2O
  - Sustained inflations (PIP at 30 cm $H_2O \times 30$–60 sec)
  - Diuresis to normovolemia

Note: These orders apply to children ages newborn to 18 years and are intended for care provided within the PICU [25].

provides an example of standing orders for pediatric donors to help guide practice [25]. It is important for PICU staff to know that individual programs may have different function thresholds for accepting organs, depending on program experience and urgency of recipient need. Although the nonutilization of organs is most commonly related to organ dysfunction, it is also related to donor characteristics and/or flaws in the processes of transplant evaluation and decision making. A four-center Canadian review of heart and lung utilization identified deficits in the consent to individual organs, the offering of organs, and the utilization of offered organs unrelated to organ dysfunction [144]. Consent should be requested for all organs regardless of baseline function, and all organs should be offered. Ideally, final decisions about transplantability should rest with the individual transplant programs represented by the organ-specific transplant doctors. Management of marginal organs should include resuscitation and reevaluation to allow for potential organ rescue and utilization. Transplant programs should be accountable to the donor family and PICU donation efforts for the nonutilization of organs to ensure that all useable organs are used. This evolving collaboration to establish best donor management practices in the PICU must be linked to ensuring optimal organ utilization, which in turn must be linked to transplant graft and patient outcomes.

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