Kwan-Leung Chan
John M. Embil
Editors

Endocarditis

Diagnosis and Management

Second Edition

Springer

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Foreword (1st Edition)

Infection remains the number one killer worldwide. Nevertheless, it is the expectation that bacterial infections can be eliminated with antibiotics. Unfortunately, there remain infections due to bacteria that are difficult to detect and difficult to reach, because of minimal blood supply, with even the most potent antibiotics. One of the diseases in this category is infections that initiate on the inner lining of a vital organ, the heart. These infections are referred to as endocarditis since they involve the endocardium, the inner lining of the heart and valves. The initial site of infection is generally in areas exposed to mechanical trauma or prosthetic device. Unfortunately the damage to the heart if not treated can be fatal and often survival requires surgical replacement of one of the valves. Despite the tremendous array of antibiotics and the marked increase in potency of these drugs to eradicate bacterial infection, the efficacy of treating the relatively avascular lining of the heart or its valvular apparatus often eludes the desired effect. This is further complicated by the changing substrate for bacterial endocarditis, namely, artificial valves and devices and the increasing number of individuals who are immunosuppressed because of drug use, human immunodeficiency virus infections, or other debilitating conditions. Endocarditis due to bacteria and other agents remains a continuing threat as well as a challenge in terms of diagnosis, management, and treatment.

Drs. Chan and Embil have brought together the expertise of pathologists, infectious disease experts, cardiologists, pharmacologists, and surgeons to provide a comprehensive approach to the problem of endocarditis. The book is organized to include a chapter on the pertinent pathology followed by population studies. The diagnostic section is extensive, comprehensive, and very clearly written so that both medical and paramedical personnel can appreciate the armamentarium and its application. The management section is broad based to include the treatment of the acute and chronic forms as well as potential sequelae that may occur. Echocardiography has become a major tool in the management of endocarditis and transesophageal echocardiography is now essential in the diagnosis and management of suspected prosthetic valve endocarditis. The role of echocardiography is critically assessed in several chapters dealing with specific clinical situations. The chapters reflect the authors' first-hand experience in dealing with endocarditis. The book in essence brings together the most current and evidence-based approaches as practiced by a group of experts who are intimately involved in the management of this disease.

In a world in which longevity is sought by all and life span has doubled just in the past century, it is expected that bacterial infections will not rob us of this expanding life span. The fact that they can and do in today's world of modern technology and ever-revolving therapies remains a sobering thought. This book is an example of the thoughtful analysis that is required if we are to prevail in our long battle with serious infections such as endocarditis. It is a gem for the student, the teacher, and the practitioner.

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Preface (2nd Edition)

Endocarditis is a serious disease with a high rate of morbidity and mortality. The poor outcome of patients with this condition is due in large part to the delay in making the diagnosis which frequently can be elusive. As a result of its wide spectrum of manifestations, endocarditis can mimic many different conditions ranging from stroke to renal failure. In order to minimize the delay in diagnosis, clinicians need to always be mindful of the possibility that endocarditis may be the cause of the symptoms. There have been ongoing efforts in the development of molecular probes and new imaging techniques to improve our ability to identify the disease early and reliably. New treatment strategies have been studied with the aim to prevent complications and to improve survival. This new addition will provide an update on the current prophylaxis guidelines, the new diagnostic approach in the detection of the disease, the proposed schemas to predict prognosis, and the new treatment strategies to improve the outcome of patients afflicted with this serious condition.

The structure of the previous edition is preserved. The book is divided into three sections with the first section covering the historical perspective and basic principles, the second section dealing with the diagnosis and management approaches, and the last section on specific clinical situations that pose management dilemmas. All the chapters have been updated to include new information from the recent studies. In particular, the approach to the use of antibiotic prophylaxis has been extensively revised to discuss the implications of the current guidelines on clinical practice, and the development of new imaging modalities such as positron emission tomography in the early diagnosis of endocarditis is critically reviewed. Echocardiography particularly transesophageal echocardiography is indispensible in the diagnosis and management of this disease. The recent development of three-dimensional echocardiography has provided unique perspectives of cardiac structures and may be useful in the assessment of perivalvular complications. This additional information can be crucial in optimizing outcome during surgical intervention. The role of three-dimensional echocardiography is illustrated with representative images and has been included in the chapter on echocardiography. The treatment of endocarditis has been updated by the inclusion of the current guidelines together with an appraisal of the recently published randomized trial on the effect of early surgery on embolic events.

This update is timely and should be of interest to all clinicians involved in the care of patients with this serious disease. We believe that this new edition will be a

good resource for internists, infectious disease specialists, cardiologists, and cardiac surgeons alike.

We thank all the contributors for the thoughtful and comprehensive treatment of their topics. Our deepest appreciation goes to our families for their patience and support during the preparation of the book.

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Perspectives on the History of Endocarditis

1

Allan Ronald

Abstract

Bacterial endocarditis was an invariably lethal usually subacute illness until the advent of penicillin. Six decades later it continues to often present enigmatically. However management has improved enormously with more exact etiological and anatomical diagnosis by means of blood culture and cardiac ultrasound, antimicrobial regimens are almost always effective and surgical interventions can usually ensure adequate cardiac function. Now over 90 % of patients are well 1 year after an episode of endocarditis. This is a good news story and a host of clinicians and scientists have made seminal contributions.

Keywords

History of progress with endocarditis • Residual controversies • Major contributors

Key Points

1. Major advances in the diagnosis and treatment of endocarditis over the past 70 years have transformed our ability to care for and cure this illness.
2. Access to surgical expertise has dramatically improved the prognosis of patients with endocarditis.
3. Endocarditis remains an elusive diagnosis because of its many disguises.
4. Early diagnosis and prompt correctly chosen antimicrobial therapy are the most effective way to minimize mortality and morbidity.

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Case Study

Alfred Reinhart was born in 1907 and contracted rheumatic fever at age 10. Rheumatic fever left him with severe aortic insufficiency and for about 10 years he had a diastolic blood pressure of zero. He graduated from Harvard Medical School at age 21. He became ill with *Streptococcus viridans* in 1931. He faced this "incurable" disease with dignity and went on to provide a vivid chronicle of his clinical illness.

The following is his description of extrasystoles [1]:

> The extrasystole has always affected me as if it were a cannon ball, shot point blank at my brain. The sensation is that of a terrific explosion, occurring within the narrow and limited confines of a calcified skull, which refuses to yield to the compressive force. It is like an irresistible force against an immovable object. Most of the time I am helpless before it and simply wait patiently in terror until the ordeal has passed.

Reinhart was convinced he had endocarditis when he noticed petechiae on his wrist [1]:

> At approximately one-quarter to twelve that night, I remember distinctly getting up from my chair and from the table, where my books lay, and taking off my suit coat. No sooner had I removed the left arm of my coat, than there was on the ventral aspect of my left wrist a sight which I never shall forget until I die. There greeted my eyes about fifteen or twenty bright red, slightly raised, hemorrhagic spots about 1 millimeter in diameter which did not fade on pressure and which stood defiant, as if they were challenging the very gods of Olympus. I had never seen such a sight before, I have never seen such a sight since, and I hope I shall never see such a sight again. I took one glance at the pretty little collection of spots and turned to my sister-in-law, who was standing nearby, and calmly said, "I shall be dead within six months".

He died of endocarditis following complications with splenic infarcts, retroperitoneal hemorrhage, embolic stroke, subarachnoid hemorrhage, and pulmonary edema.

This case illustrates some of the protean manifestations of endocarditis, vividly described by an observer with medical knowledge. Despite major advances in the diagnosis and treatment of endocarditis, it remains an elusive diagnosis, and the complications which afflicted Reinhart are still observed today.

Historical Perspective

Historical perspectives are fraught with interpretation and bias. For this author, particular points of interest include recollections and reminiscence from 58 years of medical learning and practice, as an observer to both the science and the management of endocarditis and the personal triumphs and failures in the care of patients with endocarditis. My goal is to provide a historical perspective on what many regard as the most intriguing of infections.

Several authors attribute the initial description to clinicians and pathologists in the seventeenth and eighteenth centuries who described the clinical course and

autopsies in patients who in retrospect almost certainly had bacterial endocarditis. This includes Rivierins in 1646, Lancisi in 1707, Glynn in 1749, Morgagni in 1769, and Baillie in 1797 [2]. Baillie clearly differentiated rheumatic endocarditis from what we now know as bacterial endocarditis [3]. Corvisart in 1806 described the "warty" lesions on heart valves and some of these appear to have been bacterial vegetations [4].

Over the next 75 years, however, rheumatic endocarditis and bacterial endocarditis were not differentiated clinically or pathologically. In 1852 Kirkes was the first to describe emboli arising from heart valves in cerebral, renal, splenic and other arteries [5]. Subsequently Virchow and Backmann each described embolic phenomena and showed that they contained elements which appeared to be bacteria [6, 7]. Specifically, Heiberg described chains of cocci in vegetation [8].

In 1859 Quinquaud used the term "chronic" to describe a patients' course and this allowed subacute bacterial endocarditis to be differentiated from acute [9]. Cayley in 1888 first used the term "infective endocarditis" and this replaced the earlier term "ulcerative endocarditis" [10]. A major advance occurred when Osler in his Gulstonian Lecture in 1885 reported on the clinical course and outcome of 209 cases [11]. As well, he identified the tendency of bacteria to localize on "diseased valves". Osler was also the first to emphasize the importance of bacterial culture [11, 17].

Concomitantly in Paris, Jaccoud also described endocarditis, and subsequently in France the disease is often referred to as "Jaccoud's disease" [12]. The long duration of the illness and its subacute presentation were emphasized by both Osler and Jaccoud [11, 12].

Numerous other individuals have made important contribution. At the end of the nineteenth century, the clinical course of endocarditis and its microbial etiology were described fully [11–15]. Thayer and Blumer recovered gonococci from the blood of a patient with endocarditis in 1895 [13]. Lenhartz introduced material from a vegetative lesion into the urethra of a male patient and produced classical gonococcal urethritis [14]. In 1903, Schottmuller isolated the organism from blood cultures of endocarditis patients which he called *Streptococcus mitiorseu viridans* [15].

The clinical features, including fever and murmur, were well described by Osler in his classic presentations [11, 16, 17]. The appearance of a new murmur and the clinical features of embolic phenomena were identified as being particularly important for the diagnosis.

In 1893 Osler described "red swollen areas on fingertips" now referred to as Osler's nodes and in 1899 Janeway noted the painless lesions on the palms and soles which now bear his name [16, 18].

Horder carried out classical studies linking anti-mortem blood cultures to post-mortem valve cultures and published these in 1905 [19]. Positive blood cultures became the sine qua non for diagnosing endocarditis in the vast majority of patients and this remains as important today as it was in 1905.

A paradigm shift in management occurred in 1945 when Loewe and colleagues treated seven consecutive patients successfully with penicillin [20]. Change occurred rapidly with increasing opportunity to use penicillin and other antibiotics.

By 1947 Seabury reported on the "Penicillin Era" and noted that it completely changed the practice of infectious diseases and cardiology as it pertained to bacterial endocarditis [21].

These advances were transforming medical practice as I commenced medical school in 1957. Although endocarditis was largely cared for, at least in Canada, by cardiologists who had a variable interest in microbes and antibiotics, the experience of caring for and curing this previously uniformly fatal illness was one of the most satisfactory memories of my medical residency at the University of Maryland Hospital. The importance of blood cultures prior to treatment and antimicrobial susceptibility tests was paramount. The broad-spectrum bacteriostatic drugs, such as the tetracyclines and chloramphienicol, were shown to be relatively ineffective. The dose of penicillin was gradually increased, initially from 100,000 units a day, which cured only 41 % of patients, to 600,000 units a day, which was still associated with a substantial mortality [21, 22]. Increasing the dose of penicillin with intravenous and the addition of streptomycin was quickly recognized as the regimen of choice for penicillin-susceptible streptococci [23].

Anderson and Keefer followed 222 patients who were "responsive to antibiotic therapy" [24]. Of those who responded with negative blood cultures, only 21 died within a year – 12 from heart failure, 3 from cerebral emboli, and 2 from renal failure. An additional 22 % died between 1 and 3 years, primarily of heart failure. The risk of a new episode of endocarditis was about 2 %/year.

Huge advances continue to occur in the diagnosis and management of bacterial endocarditis throughout the past 40 years and this history is chronicled within the remaining chapters. The importance of enterococcal, both coagulase-positive and negative staphylococcal, and fastidious gram-negative rod endocarditis have all been recognized, and strategies for early diagnosis and treatment are now routine. The Duke criteria for diagnosis and its continued modification have made the diagnosis more precise [25]. The management of prosthetic valve and intravascular foreign bodies infections have become an ongoing challenge. The appropriate timing for surgical interventions has also become evidence based. In particular, the requirement for surgery to be scheduled earlier with particular pathogens and/or complications has significantly improved outcomes [26, 27].

The role of echocardiography has markedly changed the management of bacterial endocarditis and given us a tool that has enabled the diagnosis to be sensitive and specific. Today it is difficult to envision management of endocarditis without access to this technology. Transesophageal echocardiography has become routine for excluding endocarditis in patients with staphylococcal bacteremia [28].

Recent advances have enabled the serologic and cultural diagnosis of very fastidious microorganisms, including *Coxiella brunet*, *Bartonella sp*, *Streptobacillus moniliformis* and others [29, 30]. Fungal endocarditis remains unusual and often requires surgery to achieve a cure. Infective endocarditis of unknown etiology is now less common due to continued improvements in microbial diagnosis particularly with the advent of nucleic acid technologies.

The ongoing emergence and spread of antimicrobial resistance among bacterial populations, particularly among patients who use intravenous drugs, may require

changes in antimicrobial choices and presumably will lead to treatment failures in a subset where regimens will be less effective [31–34].

The prophylaxis of endocarditis with antimicrobial use during dental and other procedures has decreased dramatically but these changes remain controversial and largely expert consensus-based [35, 36]. A small but significant increase in endocarditis has been observed in the United Kingdom where these prophylactic regimens have been reduced by 85–90 % during the past two decades [35]. Additional population-based studies are required [37].

Infective endocarditis remains a complex illness and continues to fascinate us as clinicians and as scientists investigating the complex biologic processes of host and microbe interactions. Certainly there is more to learn. However, we have reached the point in 2015 where we can usually precisely diagnose the infection, localize it to a site on the endocardium, treat it with an established effective regimen, manage complications including surgical interventions with a low mortality, and expect a favorable outcome in over 90 % of patients. This is remarkable progress over seven decades.

Only the future will identify further landmark events that will be highlighted by individuals recording their memories of this disease. In the meantime, as physicians seeing patients with a wide variety of symptoms, we must continue to remember the lessons learned, always obtain blood cultures before antimicrobial therapy is instituted and remain aware of the many, many presentations of this intriguing illness.

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Pathologic Findings: Valvular Destruction, Perivalvular Abnormalities and Extracardiac Findings

2

John P. Veinot

Abstract

Infective endocarditis (IE) may give rise to numerous extracardiac, cardiac and valvular findings including infected thrombi (vegetations), sequelae of local tissue destruction, and systemic manifestations including vasculitis, emboli and ischemic events. This is an appropriate term as the causal organisms may be bacterial, fungal, rickettsial, or even mycoplasmal. Traditionally a distinction between acute and subacute IE was made depending upon the illness severity and rate of disease progression. This reflected an organism's virulence and the presence of underlying cardiac disease. With anti-microbial treatment these clinical divisions have little significance, and it is preferable to think in terms of active, healing, and healed IE [1, 2]. Endocarditis is now probably best described by its anatomical location and the organism involved.

Keywords

Abscess • Bacteria • Endocarditis • Fistula • Heart • Infection • Pathology

Key Points

1. Infective endocarditis may be definitely diagnosed from surgical or postmortem material. It may be an unexpected finding, and suspicious pathologic specimens should always be evaluated for microbes.
2. It is useful to consider valve thrombus to be infected until proven otherwise. Multiple special histological stains to look for bacteria and fungi are recommended and complimentary.

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3. Grain stain may become negative after antibiotic treatment.
4. Infective endocarditis produces valve destruction usually resulting in valve regurgitation, but rarely stenosis.
5. Very large vegetations are often from culture negative organisms (HACEK) or from fungi.
6. Local perivalvular destructive lesions such as abscesses and fistulas may cause significant complications such as heart failure, and arrhythmias. This is a dynamic process and generally progressive resulting in perivalvular regurgitation, pseudoaneurysm or fistula.
7. Prosthetic valve endocarditis may involve both mechanical and bioprosthetic valves. It may be difficult to treat without surgery.
8. Some of the clinical manifestations related to infective endocarditis are due to systemic sequelae including sepsis, embolization, and immune related complications.

Introduction

Infective endocarditis (IE) may give rise to numerous extracardiac, cardiac and valvular findings including infected thrombi (vegetations), sequelae of local tissue destruction, and systemic manifestations including vasculitis, emboli and ischemic events. This is an appropriate term as the causal organisms may be bacterial, fungal, rickettsial, or even mycoplasmal. Traditionally a distinction between acute and subacute IE was made depending upon the illness severity and rate of disease progression. This reflected an organism's virulence and the presence of underlying cardiac disease. With anti-microbial treatment these clinical divisions have little significance, and it is preferable to think in terms of active, healing, and healed IE [1, 2]. Endocarditis is now probably best described by its anatomical location and the organism involved.

Infective endocarditis may arise in normal hearts with normal valves, or more commonly in patients with abnormal cardiac anatomy [2–4]. The most common pre-existing cardiac valvular lesions are left-sided ones including aortic stenosis (especially the congenitally bicuspid aortic valve), aortic insufficiency, and mitral insufficiency [5–9]. Valves damaged by rheumatic fever continue to be the most common type of predisposing cardiac valvular abnormality in developing countries. However in developed countries degenerative or age related diseases including mitral valve prolapse, degenerative aortic stenosis and mitral annular calcification are becoming a more predominant background for IE [2, 6].

Other important predisposing conditions are congenital heart diseases including ventricular septal defect, patent ductus arteriosus, coarctation, transposition of the great arteries, tricuspid and pulmonary atresia or stenosis, and tetralogy of Fallot [10]. Hypertrophic cardiomyopathy and prosthetic grafts or valves may also predispose to IE [11].

For IE to occur there are usually three features – valvular thrombus, circulating bacteria, and bacterial growth on the valve [12, 13]. Hearts may develop valvular thrombus due to abnormal flow and anatomy. Thrombus may develop due to

regurgitant jet lesions, on contact surfaces or other areas of mechanical trauma. It should be realized that many phenomena of modern medicine including prolonged intubation, immunosuppression, chemotherapy, complex surgical procedures and increased use of anti-microbial agents might contribute to increased susceptibility to develop IE [8]. Other predisposing conditions include immunodeficiency, alcoholism, malnutrition and diabetes [4]. Intravenous drug use (IVDU) may give rise to a repetitive bacteraemia and is an important risk factor for IE.

Catheter and Line Related IE

Intravascular and intracardiac catheters and devices have proliferated, and now include pacemakers, defibrillators, indwelling heart catheters, cardiac assist devices, grafts, and valve or non-valve prostheses. These foreign bodies may be the nidus for infection and may also lead to thrombus formation on neighboring structures or heart valves [14]. Insertions of catheters, pacemakers, and cannulas are routine procedures in modern medical therapy for resuscitation, feeding, hemodynamic monitoring, and therapy of disease [15, 16]. Lines or catheters may contuse, tear, penetrate, perforate, tangle, or thrombose the intracardiac structures. Biofilms of infecting organisms and extracellular matrix may form on the surface of lines or devices and serve as a protective environment for the infective organisms [14, 17].

The most common catheter or line-related lesions involve the right atrium, right ventricle, pulmonary and tricuspid valves [15, 18]. These lesions are rarely significant unless they are infected [15]. The catheter lesions are located on the atrial side of the tricuspid valve or on the ventricular side of the pulmonary valve [18]. The lesions usually follow the line of the catheter and the catheter may be surrounded by thrombus which chronically may organize and fibrose.

Infections in defibrillators and pacemakers may occur anywhere along the lead and are not limited to the tricuspid valve [14]. Pacemakers and defibrillators may have infection involving either the lead or the pouch, and staphylococci are the most common pathogens involved [19]. Fungal infection may also be seen [20]. Septic and bland pulmonary emboli may complicate pacemaker/defibrillator infection. If the device has been in place for some time, lead extraction is usually impossible and open-heart surgery and/or laser extraction may be necessary. Ventricular assist devices are also increasingly used. The percutaneous drive lines are commonly infected and there may be sepsis. Increasingly these defibrillator, pacemaker and assist devices are becoming smaller and solely intracardiac ones are being tested. Whether these will be less or more prone to infection is unknown.

Approach to Infective Endocarditis at Surgery or Autopsy

At surgery or autopsy examination of hearts, valves and vascular prostheses, clinical suspicion that the patient has IE may or may not be present. The presence of a suspicious valvular lesion should prompt a proper workup for IE regardless of the degree of clinical suspicion. Before immersion of the heart or resected valve in fixative, a

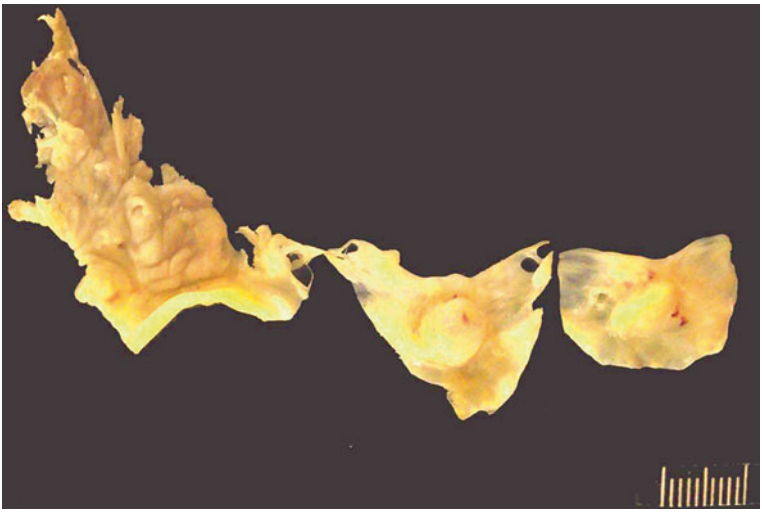

Fig. 2.1 Gross photograph of excised three cusp aortic valve with infective endocarditis. The left cusp has adherent infected thrombus (vegetation). The middle cusp has a small non-ruptured acquired aneurysm (windsock lesion) related to the infection. Ruler = 1 cm

thorough examination should be made to visualize all the valves and perivalvular structures. Sterile instruments should be used if a suspicious lesion is encountered at surgery or autopsy (Fig. 2.1). The proper approach is to assume that all valvular thrombi are infected until proven otherwise. Portions of the actual thrombus should be submitted for culture. Swabs of the lesions are not recommended. Culture results should never be interpreted in isolation. Pre-mortem or pre-operative blood cultures should be consulted. Microscopy of the valve or thrombus to confirm the presence of microorganisms is essential [21]. Molecular analysis is valuable and part of the specimen should be reserved for this if possible [22].

Special stains are useful to detect microorganisms, however treatment with antimicrobial agents has changed the utility of these stains. Gram stain is useful to detect bacteria, but after a few weeks of antimicrobial treatment the organisms may not stain (Figs. 2.2 and 2.3) [2]. Therefore silver stains should always be performed not only to detect fungi but also to detect bacteria that have lost their positive gram staining, yet still can be detected with silver stain of their cell walls (Fig. 2.4). Care must be exercised with silver stain interpretation as this stain also highlights cellular debris and some intracellular organelles. Giemsa stain is useful to detect rickettsial organisms, which may not stain with the other stains. Other histological stains such as stain for acid fast bacilli are useful in some clinical situations.

Correlating the blood culture result with cultures of the tissues and vegetation is essential. Communication with the clinicians may save much frustration if the special stains are negative and the organism is known from prior cultures and/or molecular studies. This is common in patients who have received prior anti-microbial agents [23]. In culture negative IE, the common culprit organisms include Eikenella,

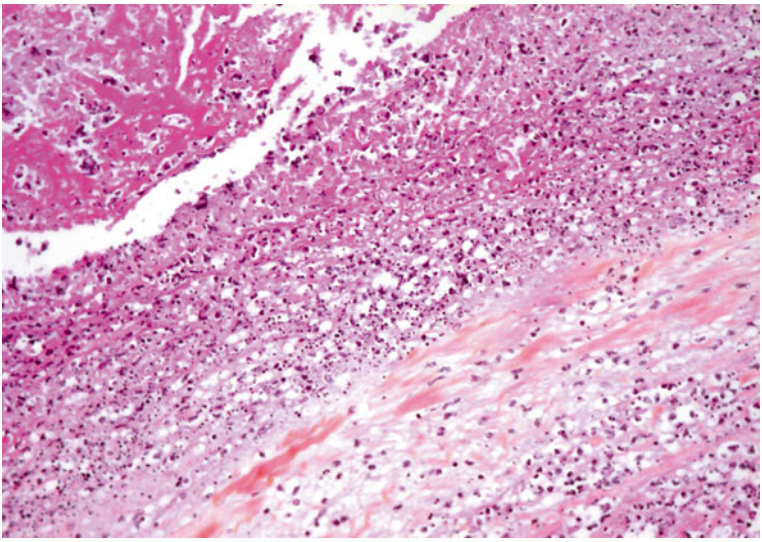

Fig. 2.2 Photomicrograph of valve cusp with infective endocarditis. The valve cusp tissue is heavily infiltrated by acute inflammatory cells and there is inflamed thrombus (left). (Hematoxylin phloxine saffron ×200)

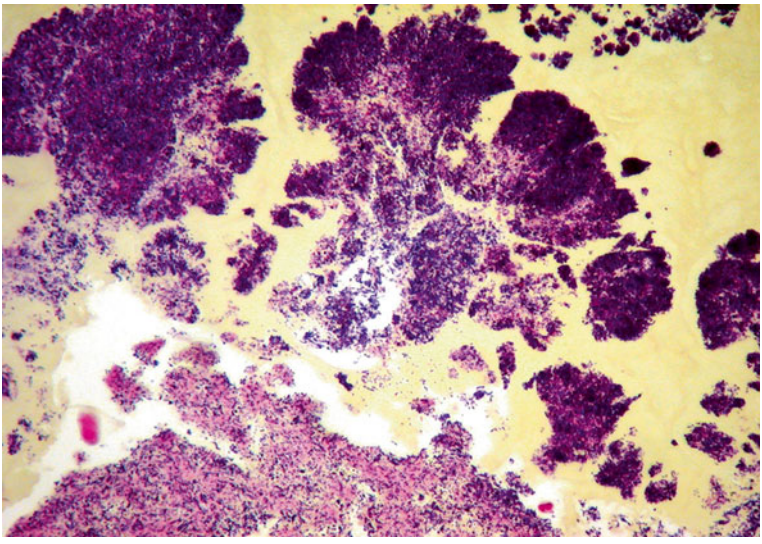

Fig. 2.3 Photomicrograph of valve cusp. This is a gram stain demonstrating large clusters of *blue* staining gram positive cocci bacteria. (Gram stain ×200)

Brucella, Neisseria, fungi, Chlamydia, acid fast bacilli or right-sided endocarditis where the lungs filter out the organisms. HACEK (Hemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella) organisms may be particularly difficult to

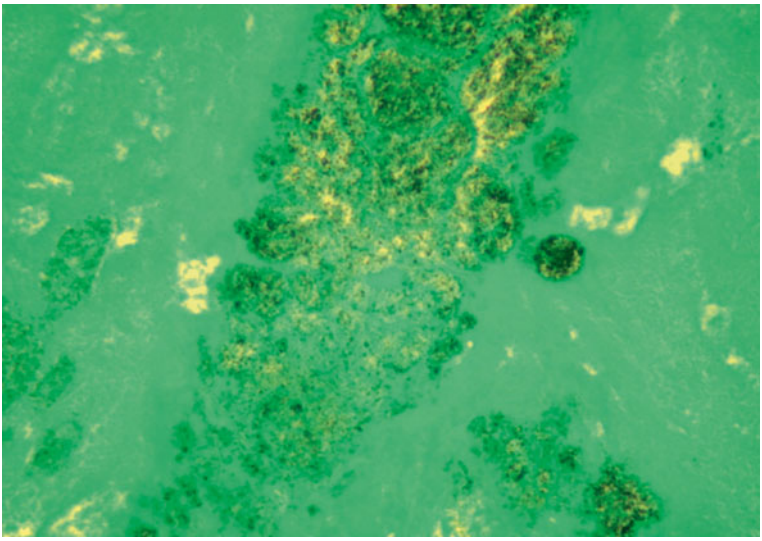

Fig. 2.4 Photomicrograph of valve cusp. This is a *silver* (Grocott) stain demonstrating degenerating clusters of cocci bacteria. This is an excellent stain for fungi, but it is also useful to detect degenerating or dying bacteria after antibiotic treatment. (Grocott ×200)

grow [24–26]. Clinical history and history of treatment and exposures may be very relevant [27]. Electron microscopy, immunofluorescence, polymerase chain reaction (PCR) or other molecular techniques may be valuable in the search for these often culture negative organisms [21, 27–29]. Studies have suggested that PCR may be a better diagnostic tool than culture, especially after anti-microbial therapy, but there remains concern about false positives and background contamination [21, 22, 29, 30].

Pathological diagnosis of healed IE can be difficult, as the findings may be non-specific and organisms frequently cannot be found. The diagnosis can only be made with confidence when the gross and microscopic features are typical, and there are collaborative clinical findings. This is quite common in patients with adequate pre-operative antibiotic treatment.

Active Infective Endocarditis Pathology (Table 2.1)

On gross examination, infected thrombi of variable size, commonly known as "vegetations", are detected along the lines of valve closure or at the low pressure end of jet lesions [2, 12]. They are usually gray, pink or brown and often friable (Figs. 2.1 and 2.5). They may be single or multiple and may affect more than one valve. Common sites are the downstream side of the intracardiac high velocity flow jets, such as the atrial side of the mitral valve or the left atrial endocardium in cases of mitral insufficiency, the ventricular side of the aortic valve, the ventricular septum

Table 2.1 Pathology of valvular sequelae of infective endocarditis

Acute
Vegetations – infected thrombi
Valve ulcers or erosions
Aneurysms
Chord rupture
Annular and ring abscess
Endocardial jet lesions
Flail leaflet or cusp
Chronic
Perforations
Calcified nodules
Valve tissue defects
Valve fibrosis

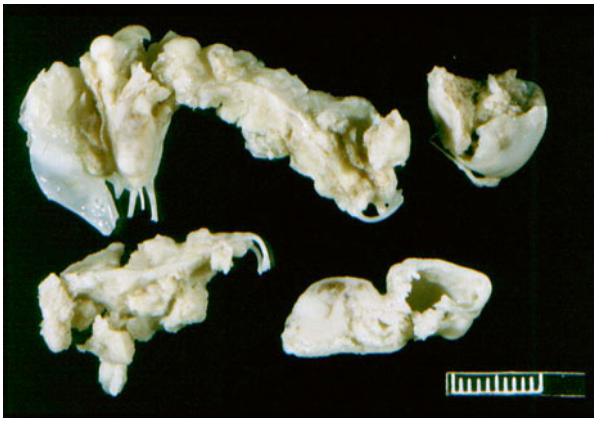

Fig. 2.5 Gross photograph of excised tricuspid valve from a patient with intravenous drug use related bacterial infective endocarditis. Numerous large infected vegetations are present. Ruler = 1 cm

or the anterior mitral leaflet in cases of aortic insufficiency, or on the right ventricular endocardium in ventricular septal defects. Infection may also involve the intima of a blood vessel distal to a coarctation or involve the pulmonary artery side of an infected patent ductus arteriosus (Fig. 2.6). Left-sided valve lesions are more common than right-sided lesions except for cases related to interventional devices, catheters or IVDU [12].

Vegetations may be located anywhere on the valve cusp or leaflet or endocardial surface. In fact this is an important distinguishing feature to note, as valve thrombi associated with non-bacterial thrombotic endocarditis (NBTE) and those related to rheumatic fever do not have this variability in location, and are usually along the lines of valve closure. Libman Sacks lesions in systemic lupus patients and those with lupus anticoagulant (anti-cardiolipin or anti-phospholipid antibodies) may be on both sides of the valve. Thrombi from NBTE, rheumatic fever, Libman Sacks are not associated with valve destruction.

The valve structures may have destructive lesions including perforations, defects, aneurysms, erosions and chordal ruptures (Figs. 2.7 and 2.8). The amount of thrombus

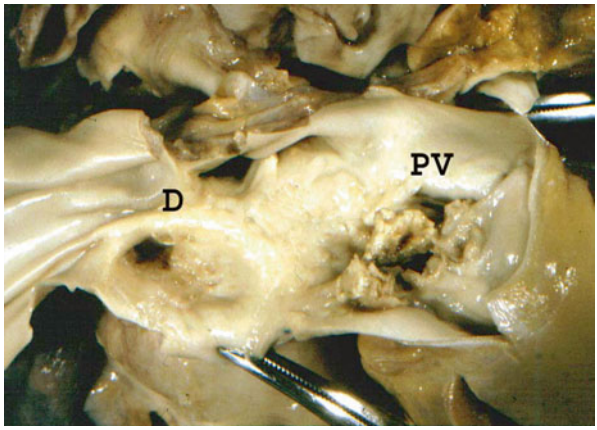

Fig. 2.6 Gross photograph of an opened pulmonary trunk – artery with the opening of a patent ductus arteriosus that had become infected. There is ragged material surrounding the ductus opening (*D*) and the pulmonary valve (*PV*) is also destroyed by the infection

Fig. 2.7 Gross photograph of excised aortic valve with infective endocarditis. There are diffuse ragged cusp defects and the right cusp has a ruptured cusp aneurysm. Ruler = 1 cm

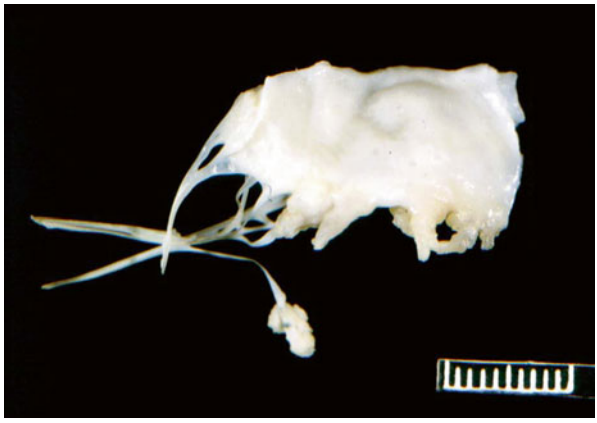

Fig. 2.8 Gross photograph of an excised mitral valve leaflet with infective endocarditis. There is chordal vegetation with chord destruction. Most of the leaflet has no remaining intact chords. Ruler = 1 cm

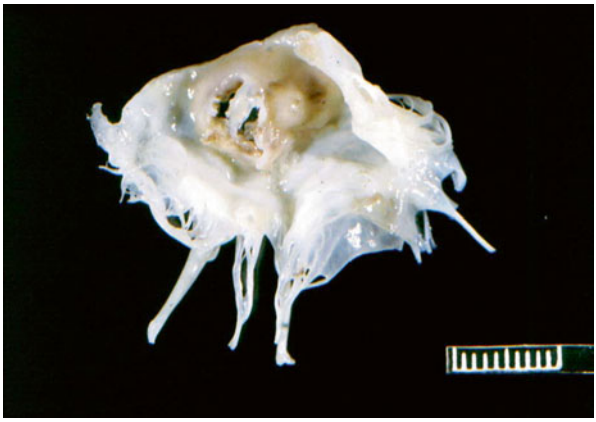

Fig. 2.9 Gross photograph of excised anterior mitral leaflet with infective endocarditis related aneurysm (windsock lesion) formation. These infected aneurysms eventually erode through and form valve perforations. Ruler = 1 cm

and destruction may mask the underlying predisposing valve disease. Thrombi may obstruct the valvular orifice creating stenosis, but valvular insufficiency is a more common complication. Chordal rupture may result in flail leaflets [31]. Leaflet or cusp aneurysms bulge toward the flow surface and may resemble "windsocks", and IE is the most common cause for leaflet aneurysm or diverticulum (Fig. 2.9). If the aneurysm ruptures, the valve may become severely regurgitant due to the resulting cusp or leaflet defect.

On microscopic examination, the appearance of the vegetation depends upon both the virulence and destructiveness of the organism and the duration of the infection. Early in the disease course there are fibrin, neutrophils and clumps of organisms (Fig. 2.2). With therapy the organisms may calcify, and the thrombi organize from the base. Organizing thrombus may show no easily recognizable organisms, and only show acute and chronic inflammation with neovascularization and fibroblastic proliferation. With thrombus organization giant cells may be seen. If giant cells are prominent one should consider doing serology for Coxiella or considering a fungal infection or an autoimmune disease. IE can mimic autoimmune diseases, including many types of vasculitis [9, 32, 33]. Pathological changes in the infected valve tissue depend on the chronicity or duration of the infection, the virulence of the organism and the status of the original valve itself. Electron microscopy, immunofluorescence, polymerase chain reaction or molecular techniques are contributory in the search for organisms [21, 27–29].

Fungal Endocarditis

Fungal endocarditis is usually encountered when there are pre-existing risk factors such as intravenous drug use, prior cardiac surgery, immunosuppression, intravenous hyper-alimentation, antibiotic therapy, long term venous catheters, pacemakers, defibrillators and other intravascular devices [20]. Fungi may infect native or prosthetic valves and also devices. The common organisms are Candida and Aspergillus. Classical clinical manifestations of bacterial IE are often absent. Fungal infected thrombi are usually quite large and friable (Fig. 2.10) [2, 34]. Valve orifice obstruction leading to

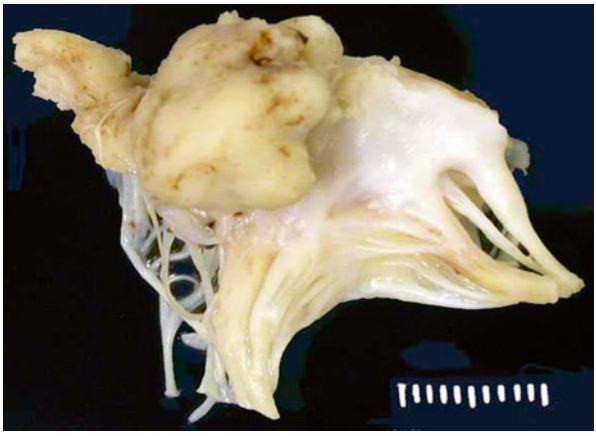

Fig. 2.10 Gross photograph of excised anterior mitral leaflet with large bulky fungal vegetation. This was present on both sides of the leaflet (the back is shown). The infecting organism was Aspergillus. Ruler = 1 cm

clinical valve stenosis may occur if the size of the thrombus is large [17, 20, 35, 36]. Embolic events are not unusual and blood cultures are often negative [36]. The organs receiving the emboli frequently develop abscesses, infarcts or ischemia [20].

Whipple Disease

Patients with Whipple disease have been reported to have symptoms of cardiovascular disease in 58 % of cases. However, at autopsy 79 % have gross evidence of cardiac involvement, and of these 53 % have valvular disease [37, 38]. The mitral valve is the most common valve affected, with the aortic and tricuspid valves also reported to be involved at times. There are periodic acid Schiff reaction (PAS) positive macrophages on light microscopic examination and bacilliform organisms on electron microscopy. Polymerase chain reaction performed on blood may be helpful for diagnosis [28]. The organism is a Gram positive actinomycete, Tropheryma whippelii [38]. The infection may lead to fibrosis and chronic inflammation giving rise to a valve with similar appearance to a post-rheumatic one. The deposits may be nodular and are often not calcified. Similar pathological changes are found in the myocardium, endocardium, and pericardium [39]. History of gastrointestinal disorder should be questioned for, as the diagnosis is usually made by small intestinal biopsy.

Chronic Infective Endocarditis Pathology (Tables 2.1 and 2.2)

With successful medical treatment of infective endocarditis the infected vegetations may organize and the thrombi may form calcific valve nodules. Destructive sequelae of the infection are common (Fig. 2.11). The valve may have defects at the edges or central defects forming irregular perforations. Around the holes or perforation there may be tan nodules of organisms that eventually form fibrocalcific nodules. The

Table 2.2 Pathology of perivalvular sequelae of infective endocarditis

Perivalvular leaks
Prosthesis dehiscence
Annular and root abscess
Pseudoaneurysm
Fistula or sinus formation
Conduction system destruction
Myocardial abscess
Pericarditis
Hemopericardium
Coronary artery compression
Coronary artery erosion, thrombosis or rupture

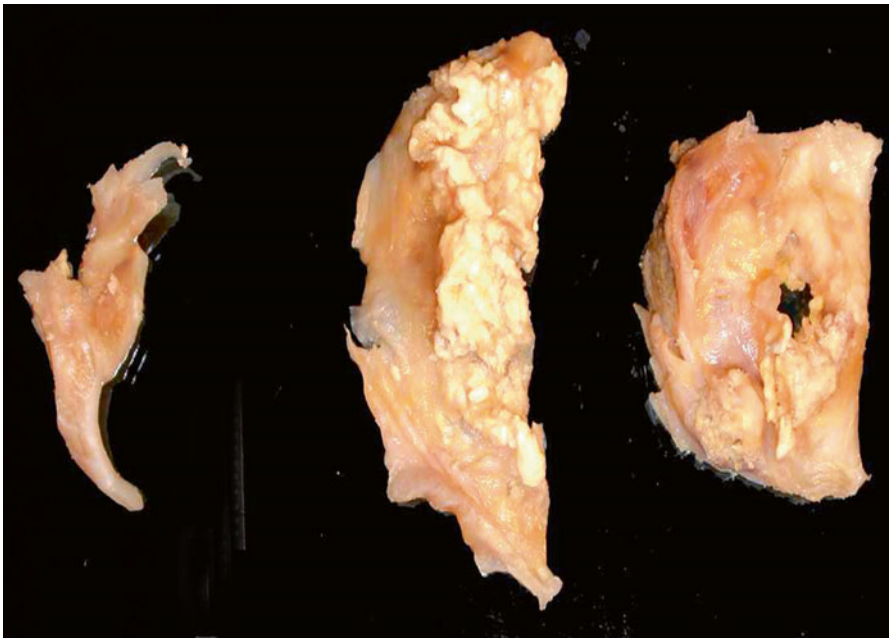

Fig. 2.11 Gross photograph of an excised aortic valve with destructive sequelae of prior infective endocarditis. The right cusp has a defect surrounded by calcified material (old vegetation). Similar material is noted on the other two cusps

destruction of the valve tissue may lead to defects at the closing margins resulting in poor valve coaptation. Distinguishing a post IE perforation from a congenital accessory orifice may be difficult. In atrioventricular valves congenital orifices should have surrounding chordae, while a post-IE perforation would not. Fenestrations, an age related finding, are also confused with perforations. These fenestrations are located laterally on the valve cusps near the commissures and always beyond the line of valve closure.

Chordae may rupture resulting in flail leaflets and valve regurgitation. The ruptured chords may knot and calcify along with the organizing infected thrombi. The valve itself may thicken and the chords may fuse. All these are significant contributors to chronic valve regurgitation.

Ventricular papillary muscles may rupture for multiple reasons due to IE [40]. The infection may extend from an adjacent chord and cause myocardial necrosis and rupture. A coronary arterial embolus may cause a myocardial infarct with papillary muscle rupture, similar to any acute myocardial infarct. Finally an embolus may lead to a myocardial abscess with local tissue destruction resulting in rupture.

Perivalvular Lesions of Infective Endocarditis (Table 2.2)

Extension of the valve infection into surrounding structures predicts a higher mortality, higher risk of significant heart failure and the need for cardiac surgery [28, 41]. In the early stage, perivalvular abscess is largely composed of inflammatory infiltrate, but at later stages necrosis and cavitation usually develop leading to destruction of perivalvular tissue. Perivalvular abscess is not a static complication but is progressive and can evolve into perivalvular leak, fistula and pseudoaneurysm. These perivalvular complications may develop in spite of early valve surgery. Perivalvular leak due to annular abscess may be seen with native valve IE (aortic more than mitral), but are especially common adjacent to infected valve prostheses [7, 42]. Although a perivalvular leak may be technically related to poor tissues, suture unraveling, suture tissue cut through and other technical matters, it is important to keep the possibility of IE in mind with all perivalvular leaks. These leaks may cause clinically significant congestive heart failure and sometimes hemolysis.

Extension of an active valve infection to adjacent cardiac structures is common including infected lesions where adjacent valves come in contact or are contiguous – such as from the aortic valve to the base of anterior mitral leaflet, from the posterior mitral valve leaflet to the left atrial endocardium, and from the aortic valve to the ascending aorta [43]. Jet lesions as a result of valvular insufficiency may cause infected endocardial lesions to form along the path of the regurgitant jet [12, 43].

Infections may also extend from the mitral and aortic valves to the valve annuli (Fig. 2.12) [44]. This complication is considerably more common in the aortic position as compared to the mitral. This may manifest as an aortic root abscess, or the mitral annulus or mitral annular calcification (MAC) may become infected. MAC is a common finding in the hearts of elderly patients [45]. It is considered to be an age-related finding, but it probably represents degenerative changes in the mitral annulus [46]. It is associated with mitral valve disease, especially mitral valve prolapse due to myxomatous/ floppy mitral valve. Uncommonly the calcium extends onto the leaflet producing a mass and the calcium may undergo liquefactive necrosis and grossly mimic IE [47–49]. MAC may ulcerate giving rise to thrombus deposition with potential for embolization and infection. If MAC is infected, there is usually leaflet perforation and myocardial abscess formation (Fig. 2.13) [50]. If the infection spreads into the lateral atrioventricular groove, thrombosis of the

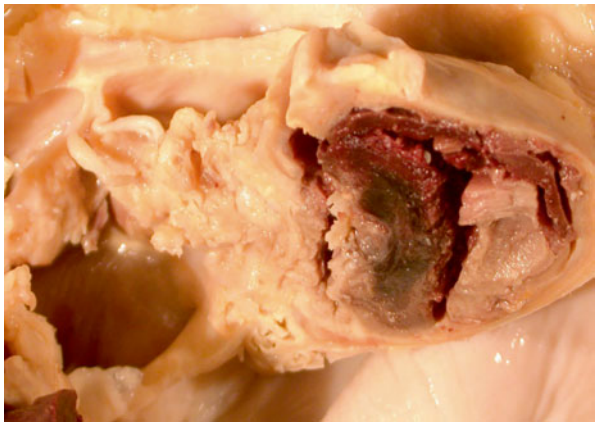

Fig. 2.12 Gross photograph of opened aortic root and aortic valve at autopsy. The aortic valve is destroyed by vegetations (center) and to the right there is a large paravalular aortic root abscess. This root abscess contained infected laminated thrombus material

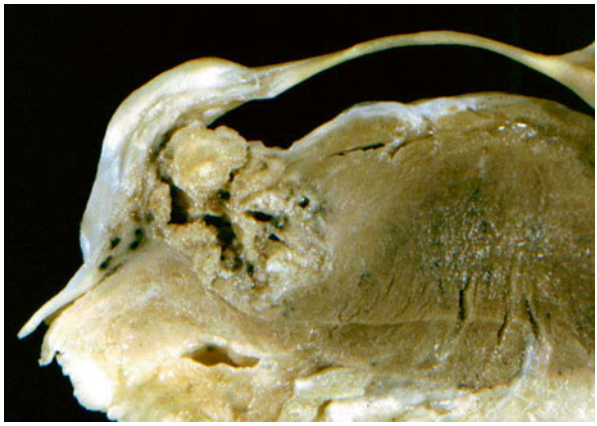

Fig. 2.13 Gross photograph of longitudinal section through the mitral valve, the mitral annulus, and left ventricle. There is mitral annular calcification (MAC) with large abscess formation in the calcific material

circumflex coronary artery may develop because of distortion from the local effects of the infection and development of arteritis. Annular abscesses may also erode into the pericardial surface producing fibrinous or suppurative pericarditis and hemopericardium with tamponade.

Aortic root abscesses may become a significant source of embolic material and they may compress structures around the aortic root. If the proximal coronary arteries are distorted, myocardial ischemic sequelae may result. The formation of annular abscess is not an end event. Rather these structures are progressive with potential formation of perforations or fistulas. Due to the central position of the aortic valve, infection of this valve may form fistulas with practically any chamber (Fig. 2.14) [51]. Each aortic cusp and sinus has its own pattern or propensity for fistula formation and complication (Fig. 2.15). Infection in the left aortic cusp or sinus may spread through the aortic wall and cause pericarditis or tamponade, or a fistula may extend into the left atrium. Infection of the posterior (non-coronary) aortic cusp or sinus may cause a fistula to either the left or right atrium. Infection of the right aortic

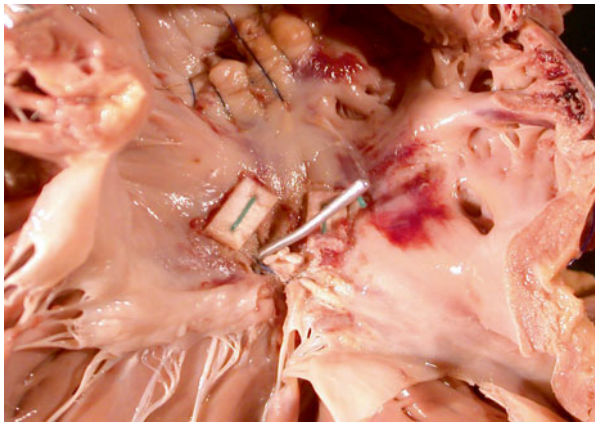

Fig. 2.14 Gross photograph of a heart opened to demonstrate the right atrium and tricuspid valve. Aortic valve fungal endocarditis had caused a fistula to the right atrium. This was closed with pledgets but the disease re-occurred. The metal probe is passed from the aortic region and the fistula is still infected and patent. This is the same patient as Fig. 2.10 (aortic and mitral valve Aspergillus endocarditis)

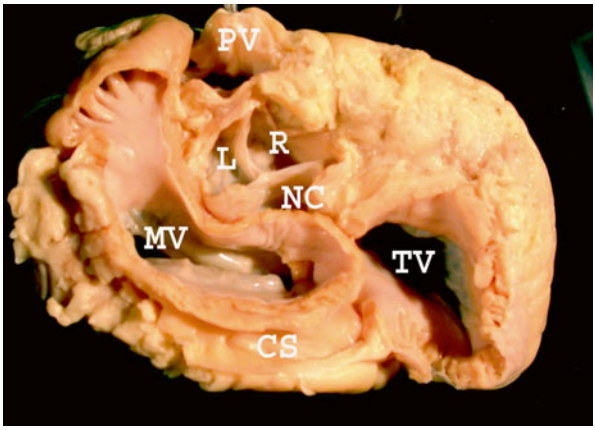

Fig. 2.15 Gross photograph of the base of the heart. The central aortic valve may form fistulas to nearly any chamber. Infections from the right cusp or sinus (*R*) may extend to the epicardium, the right atrium and the right ventricle outflow tract. Infection of the non-coronary cusp or sinus (*NC*) may form fistulas to both the right and left atria. Infections of the left cusp or sinus (*L*) may form fistulas to the epicardium, and the left atrium. Additional abbreviations: *CS* coronary sinus, *MV* mitral valve, *PV* pulmonary valve, *TV* tricuspid valve

cusp or sinus may cause a fistula to the right atrium, and the right ventricle or right ventricular outflow tract. An aorto-right ventricular fistula is possible due to the presence of the atrioventricular component of the interventricular septum. Extension into the myocardium and the conduction system may be found when the infection involves the valve ring or annulus. Fistulas and abscesses are important problems particularly with prosthetic IE, as discussed below.

Involvement of the coronary arteries may be due to distortion from an aortic root abscess or they may become directly infected by local extension through the coronary ostia or by formation of mycotic aneurysms [52]. The latter may occur in normal arteries but also may be superimposed upon an underlying atherosclerotic

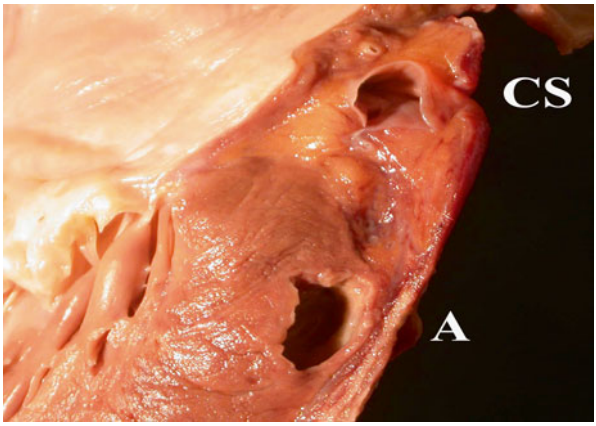

Fig. 2.16 Gross photograph of longitudinal section of the left ventricle wall. The *upper* defect (*CS*) is the normal coronary sinus near the atrioventricular groove. The *lower* large intramyocardial defect (*A*) is an abscess cavity that contained purulent material. The patient had a floppy myxomatous mitral valve that became infected leading to coronary arteritis and myocardial abscesses

plaque. Mycotic aneurysms may thrombose and are a source of infected emboli that may seed the myocardium leading to myocardial abscesses. Myocardial abscesses may also form as a result of local valvular IE extension into the adjacent myocardium (Fig. 2.16). Aortic root abscesses and myocardial abscesses may impinge upon or destroy the conduction system in the areas of the atrioventricular node and His bundle. Clinically this manifests as a progressively worsening degree of heart block and may be an important clinical sign that treatment is failing or disease is progressing.

Extension of infection to the pericardial space may lead to hemopericardium and tamponade or to pericarditis. Fibrinous pericarditis is a common finding with IE, but the pericardium may also become infected leading to suppurative pericarditis.

Infective Endocarditis of Valve Prostheses (Tables 2.1 and 2.2)

Infection of valve prostheses may manifest early after surgery or long after hospital discharge [53–56]. Both bacteria and fungal organisms are important causes of prosthetic IE [35]. Valvular bioprostheses have vegetation, cusp thrombi, destruction, erosion and perforation similar to native valves (Fig. 2.17). With infection of mechanical prostheses, the actual prosthesis usually remains intact and the infection is mainly in the sewing ring and surrounding tissues [42]. The thrombi on a mechanical prosthesis or bioprosthesis may interfere with function, with disc or cusp immobility (Fig. 2.18) [12, 34]. Peripheral emboli are not uncommon [53].

In any prosthesis, sewing ring and perivalvular tissue infection is common and the valve prosthesis may dehisce or become loose when the surrounding tissues develop necrosis [12, 55]. Annular abscess and fistulas are much more common with prostheses, as compared to native valves. It is a disturbing and memorable experience to image a near totally dehisced valve prosthesis by echocardiography and for the surgeon to be able to remove such a valve prosthesis from the patient without much need for dissection. Sutures, pledgets as well as the aortotomy site may become infected.

Fig. 2.17 Gross photograph of an infected Carpentier Edwards bioprosthesis. The ring and cusps have ragged thrombus material that contained bacterial colonies

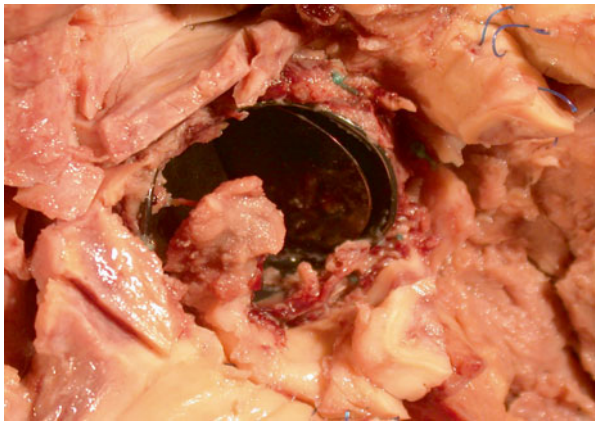

Fig. 2.18 Gross photograph of opened aortic root with a mechanical tilting disc prosthesis placed in the aortic valve position. A large amount of thrombus at the edge of the prosthesis is interfered with the disc movement. This is recurrent Aspergillus infection (same patient as Figs. 2.10 and 2.14). There was recurrent stroke after valve replacement

A large perivalvular leak results in severe perivalvular regurgitation and heart failure, but even a small perivalvular leak can be significant due to the development of severe hemolysis. Destruction of the adjacent tissues may lead to intracardiac fistulas, conduction system destruction and arrhythmias, and coronary artery inflammation and thrombosis [53]. The mortality of prosthetic IE remains high, with or without surgery, and perivalvular complications can develop despite surgery [41]. Fungal infection of a valve prosthesis is a surgical indication due to near total mortality without surgery [17, 36, 54].

Systemic Pathology of Infective Endocarditis (Table 2.3)

Systemic manifestations of IE may be due to generalized sepsis, immune reactions including immune complex disease or related to emboli or ischemia with organ atrophy, ischemia or infarction. Classic peripheral stigmata of IE may not be evident with right sided IE or with infections due to HACEK organisms [28]. Similar to all

Table 2.3 Pathology of systemic sequelae of infective endocarditis

Sepsis
Diffuse alveolar damage
Cholestasis
Systemic emboli
Infarct/atrophy
Abscess
Roth spots
Osler nodes
Janeway lesions
Splenic infarct or rupture
Mycotic aneurysms
Pulmonary emboli
Infarct
Abscess
Empyema
Immune complex phenomena
Vasculitis
Glomerulonephritis

disseminated infections, IE related sepsis may present with fever (or fever of unknown origin), leukocytosis, disseminated intravascular coagulation (DIC), adult respiratory distress syndrome (diffuse alveolar damage), jaundice and other sequelae of hypotension including multiorgan failure.

Renal manifestations include interstitial nephritis and pyelonephritis. There may be immune complex formation between bacterial antigens and antibodies, which deposits in the glomeruli leading to glomerular damage [57]. Focal necrotizing and diffuse proliferative glomerulonephritis may manifest as acute nephritis and renal failure. Type 1 membranoproliferative glomerulonephritis may lead to nephrotic syndrome. Crescentic glomerulonephritis with rapidly progressive glomerulonephritis can also occur. Emboli to the kidney may cause infarction, hematuria, flank pain, and renal abscesses.

Emboli may occur in right and left sided IE [58]. Emboli can occur before therapy, during therapy or even after therapy [28]. Emboli from left sided valve or cardiac lesions may affect any systemic organ leading to visceral infarction, ischemia or organ atrophy. Either bland fibrin platelet material of the vegetation or infected components containing microorganisms may embolize. The propensity for embolization may be related to the size and mobility of the vegetation, as seen on echocardiogram [58, 59].

The effect of the embolic material depends upon the size of the embolus, whether it contains microbes, the size of the occluded blood vessel, the degree of collaterals in the organ and the metabolic demand of the organ. Vascular spasm may also contribute. If there are prominent numbers of organisms in the embolic material, the organ may form an abscess, in addition to an infarct which is referred to as a septic infarct. Coronary arterial emboli may lead to angina, myocardial infarction or

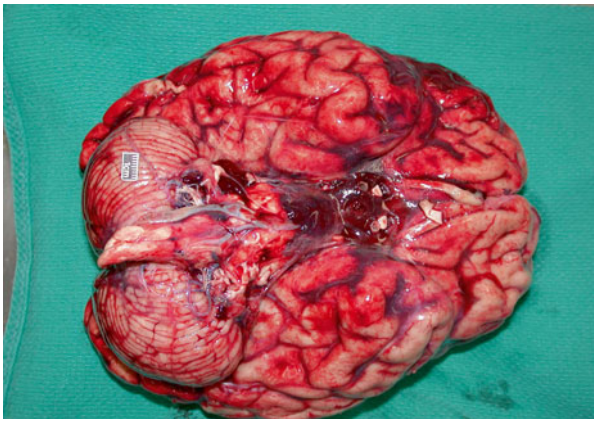

Fig. 2.19 Gross photograph of the base of the brain with adherent blood clot. Subarachnoid hemorrhage occurred due to a ruptured mycotic cerebral artery aneurysm. The mitral valve was infected with bacteria. Ruler = 1 cm

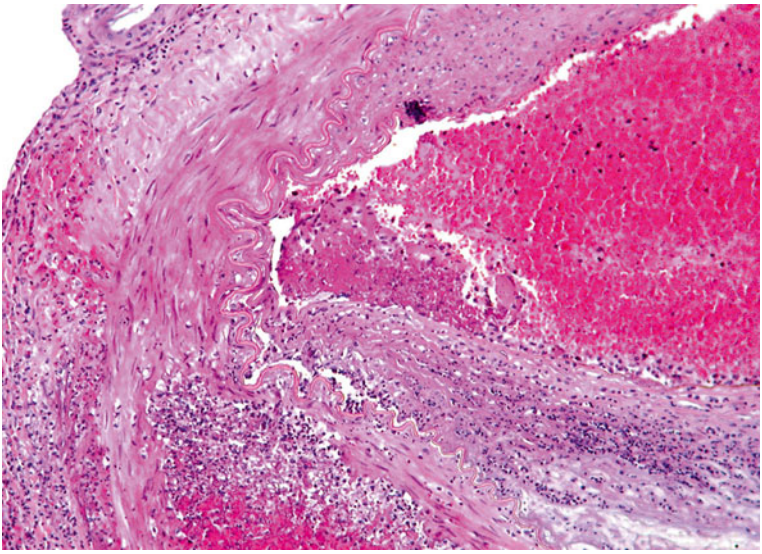

Fig. 2.20 Photomicrograph of the mycotic aneurysm of the cerebral artery from patient with subarachnoid hemorrhage (Fig. 2.19). The artery is acutely inflamed and even has dissection with destruction and splitting of the wall. Thrombus is present in the lumen. Gram stain (not shown) had numerous gram positive cocci. (Hematoxylin phloxine saffron ×100)

sudden death. Embolic myocardial infarcts are usually large, and myocardial abscesses may develop.

The central nervous system is the most common site involved by IE and neurologic deficits maybe due to many different causes [28, 58]. Cerebrovascular embolism may manifest as transient ischemic attacks or stroke. HACEK organisms are associated with more strokes in some studies [26]. Cerebral infarcts may be hemorrhagic and non-hemorrhagic [60]. Mycotic aneurysms of infected cerebral arteries may thrombose or rupture (Figs. 2.19 and 2.20). Other serious neurological complications are cerebral abscesses and meningitis.

Splenic infarcts may cause abdominal, back or flank pain. Splenic infarcts may be bland ischemic infarcts or septic infarcts both of which may lead to abscess formation [28]. Rarely the spleen may rupture leading to intra-peritoneal bleeding. Gut ischemia and infarction may occur if the mesenteric circulation is embolized. Emboli to the limbs may cause acute ischemia or gangrene. When a vascular surgeon performs a thrombectomy or embolectomy in a patient with acute limb ischemia the removed material should be examined for infection with bacterial and fungal stains.

Right-sided endocarditis may lead to infected pulmonary emboli, pulmonary infarction, abscesses and empyema. If large, these pulmonary emboli may cause sudden death. If there is an intracardiac shunt, either pre-existing or developed due to IE, paradoxical embolism is possible with vegetation fragments embolizing into the systemic circulation bypassing the lung.

Osler nodes (tender subcutaneous nodules on the digits), Janeway lesions (red or hemorrhagic non-tender lesion on the palms or soles), and Roth spots (retinal hemorrhages) are due to emboli to small blood vessels. These are now rarely encountered with modern medical care. Petechiae and subungual hemorrhages may be seen on the skin. Small vessel vasculitis may be due to an infected embolus (a mycotic aneurysm) or immune complexes [61].

Mycotic aneurysms may occur in any circulation, but are most common in the central nervous system circulation [28, 62]. Cerebral vessels are commonly involved, followed by visceral arteries and arteries of the extremities. Branch points are usually affected. They may develop in the aortic wall adjacent to the valve or distant to it. These aneurysms weaken the vessel wall and may rupture and hemorrhage even after the infection has been treated (Figs. 2.19 and 2.20). Subclinical rupture may lead to pseudoaneurysm formation. They also may thrombose. Surgical intervention is usually required [28].

Summary

Infective endocarditis continues to be a medically challenging disease despite modern medical advances. In fact modern medical therapy, such as intracardiac catheters and devices, may contribute to the underlying predisposition of some individuals. In many cases careful clinical assessment and blood cultures remains important to determine the infecting organism. The anatomical pathologist, cardiologist, cardiac surgeon, infectious disease consultant, and microbiologist all play an important role in the diagnosis and treatment. Many of the classically described clinical and pathological manifestations are no longer commonly encountered because of timely and effective anti-microbial treatment. In addition to the well-recognized local valvular complications, spread of the infection to perivalvular structures is clinically relevant and confers a poor prognosis despite surgical intervention. Patients with culture negative, fungal and prosthetic IE pose a major clinical challenge in diagnosis and management.

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Changing Populations: The Elderly, Injection Drug Users, Health-Care Associated Endocarditis and Immunocompromised Patients

3

Yoav Keynan and Ethan Rubinstein

Abstract

The epidemiology of infective endocarditis is changing. The combination of increased life-expectancy, the burden of chronic disease, immunosuppression as a result of improving treatment and prognosis of malignancies and transplantation and the increasing device-related and iatrogenic infections have resulted in risk factors for infectious endocarditis. The etiological agents vary according to the underlying predisposing factors with increases in resistant health-care associated infections among the special populations reviewed in this chapter.

Keywords

Endocarditis in injection drug users • Endocarditis among elderly • Immunocompromised patients and health care associated endocarditis • HIV associated endocaridits • Recurrent endocarditis

Key Points

1. Empiric therapy for the management of endocarditis in injection drug users (IVDUs) must target *S. aureus* particularly MRSA and should therefore contain an agent such as vancomycin which is effective against MRSA.

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2. In addition to *S. aureus* and MRSA, Gram negative bacilli such as *P. aeruginosa* and fungi, such as *Candida* spp must be considered when initiating treatment of endocarditis in an IVDU.
3. For IVDUs with right sided endocarditis caused by methicillin susceptible *S. aureus*, a 2 week course of cloxacillin and gentamicin may be sufficient. However, the standard regimen must be used in the following circumstances:
   - Delayed clinical or microbiologic response (>96 h)
   - Right sided endocarditis complicated by the presence of right sided heart failure, large vegetation (>2 cm in diameter), respiratory failure, empyema, the presence of extrapulmonary metastatic foci such as osteomyelitis.
   - Severe immunosuppression (<200 CD for cells/uL)
   - Polymicrobial endocarditis or endocarditis caused by MRSA
   - Therapy with agents other than cloxacillin
4. Surgery must not be delayed until blood cultures become negative, if the patient's condition warrants immediate intervention because of severe valvular destruction.

Over the past 100 years the incidence of infective endocarditis has not changed significantly. This may seem surprising as the detection of bacteremia improved significantly during this time period and the introduction of 2-D echocardiography has been revolutionized the diagnosis of infective endocarditis. Epidemiological studies demonstrate that infective endocarditis accounts for about 1 case per 1,000 hospital admissions (range 0.16–5.4 cases per 1,000 admissions) [1]. The incidence depends on the criteria used to identify cases and on referral and publication bias. When strict criteria were applied to identify all definite, probable, and possible cases of endocarditis in residents of Olmsted County, Minnesota, from 1950 to 1981, the mean annual age- and sex-adjusted incidence rates per 100,000 person-years were 3.8 for total cases and 3.2 for definite and probable cases only. Total rates were 4.3 for 1950 through 1959, 3.3 for 1960 through 1969, and 3.9 for 1970 through 1981 [2]. A follow-up publication from the same region for the years 1970–2000 demonstrated that age- and sex-adjusted incidence of infective endocarditis ranged from 5.0 to 7.0 cases per 100,000 person-years during the study period and did not change significantly over time ($P = 0.42$ for trend). A temporal trend of increase was observed in the proportions of prosthetic valve infective endocarditis cases ($P = 0.09$). Among people with underlying heart disease, there was also an increasing temporal trend in mitral valve prolapse ($P = 0.04$) and a decreasing trend in rheumatic heart disease ($P = 0.08$). However, the absolute numbers were small [3]. A more contemporary series from Olmstead county, Massachusetts illustrated an increasing incidence in Women with a temporal increase in age, especially among women [4]. The same group showed that the American Heart Association published

updated guidelines for IEention in 2007 restricting antibiotic prophylaxis for most at-risk patients undergoing dental and other invasive procedures did not alter the incidence of IE [5].

The stable incidence conceals the fact that the epidemiological, microbiological and clinical features of the disease have changed. Among the prominent changes are increasing age, increasing injection drug users, and immunocompromized patients. These include human immunodeficiency virus (HIV) patients, patients with malignancies receiving chemotherapy, and a growing population of patients receiving particularly aggressive chemotherapy such as bone marrow transplant recipients and patients with solid organ transplants. This chapter is devoted to the changes in the epidemiology and to new insights into the clinical presentation, treatment options and outcomes of these special populations that occurred during the past decade.

The Elderly

Epidemiology

Despite the fact that the incidence of infective endocarditis has not changed, recent studies have shown remarkable changes in the epidemiology and clinical features of the disease. In the 1950s, when rheumatic fever was prevalent, particularly during World War II period, and before the wide use of penicillin, the incidence was highest in patients aged 20–30 years old and only 5 % of patients were over 60 years of age. More recent publications show that the incidence of infective endocarditis has increased in patients older than 50 years, reaching a peak at the ages of 70–74 years of age. Currently, more than 50 % of patients are older than 50 years [6–8]. Murdoch et al. published data from the International Collaboration on Endocarditis (ICE) representing 2,781 adults with definite IE who were admitted to 58 hospitals in 25 countries between 2000 and 2005. The median age of the cohort was 57.9. In this cohort the role of degenerative valvular disease associated with ageing was prominent (mitral (43.3 %) and/or aortic (26.3 %) valve regurgitation) [9].

Fefer et al. [10] collected 108 episodes of infective endocarditis during the years 1990–1999 admitted to a community hospital. The annual admission rate was stable at around 0.4 patients with endocarditis per 1,000 admissions. Sixty episodes (56 %) involved males and 48 (44 %) females, a ratio of 1.3:1. The mean age was 57 (SD 22) years. Thirty three patients (31 %) had prosthetic valve endocarditis and 75 (69 %) patients had native valve endocarditis. Patients with prosthetic valve endocarditis were significantly older than those with native valve endocarditis similar to the findings from the ICE collaboration.

Selton-Suty et al. [11] studied the characteristics of infective endocarditis in the elderly in a university hospital that is both a referral and a primary care centre. They identified 114 consecutive patients treated for infective endocarditis from 1990 to 1993. Of the 114 patients, 25 (22 %) were older than 70 years [mean age 76 (SD 6) years, range 70–91] and 89 were younger than 70 years. In both groups there was a predominance of males in a ratio of 2:1. According to the Duke criteria, the

distribution of diagnostic categories was significantly different in the two groups, with a lower percentage of definite infective endocarditis in the older patients. Infective endocarditis on intracardiac prosthetic devices (valve prostheses or pacemakers) was more common in the older patients compared to the younger ones. The location of infective endocarditis, when vegetations were seen, was similar in the two groups with most cases involving the mitral valve. There were no significant differences between the two groups with respect to clinical signs, auscultatory changes or extracardiac manifestations. Emboli were three times less common in the older patients [2 (8 %) vs 25 (28.1 %), $P<0.04$]. Echocardiographic findings were similar between the two groups. Younger patients were more commonly operated but this may reflect the presence of co-morbidities and frailty resulting in a preferential medical management in older individuals rather than a true difference related to the actual disease process. Similar findings have been confirmed by others, demonstrating the increasing prevalence of infective endocarditis in the elderly [10, 12–14].

There are several possible explanations for the increasing incidence of IE with age: Rheumatic heart disease incidence has declined as did its contribution to underlying valve pathology, from >50 % 40 years ago to less than 5 % in contemporary series [9, 15]. The increase in the prevalence of degenerative valve disease, now accounting for over a third of native valve endocarditis, has contributed to the increase in age. As people live now much longer than before, various minor cardiac lesions can become hemodynamically important creating turbulent flow and allowing for a fibrin-thrombus clot, the basic mechanism of endocarditis to form. In addition, in the elderly, hypertension, atherosclerosis and kidney disease are more common allowing for turbulent flow in diseased vessels to develop. The rates of admission and health-care contact increase with age and the contribution of health-care associated endocarditis is notable among the elderly [9, 16, 17]. Mouth sanitation of the elderly tends to decline with age increasing the risk of local oral infections and bacteremia, thus increasing the risk of developing infectious endocarditis [18]. In addition, prosthetic heart valves are more common in the elderly and the eligible age for cardiac surgery is constantly increasing [19]. Other medical devices such as implantable pacemakers, defibrillators, and stents have become more common increasing the risk of these groups of patients to infectious endocarditis [20, 21]. Finally there are some neoplastic diseases that are more common in the aged that may be associated with infectious endocarditis. Among them ulcerating skin cancers (like basal cell carcinoma, melanoma etc.), polyps and cancers of the colon (associated with *Strep. gallolyticus* endocarditis) [22, 23]. As the world's population is becoming older it is to be expected that in the future more endocarditis will be encountered in the very old. In the year 2030, there will be >1 billion individuals >65 years of age, 19.6 % of the North American population 23.0 % of the European population, 11.5 % of the Latin Americana and Asian population and 4.6 % of the African population will be the elderly and thus this population will become the prime population segment from which endocarditis cases originate [24]. It is thus expected that the trend of ageing endocarditis patient population will continue and even increase in the coming decades.

Bacteriology and Age

Several publications have demonstrated the increased frequency of enterococcus and other streptococci of group D (e.g., *S. bovis*) in causing bacterial endocarditis of the elderly. In the publication of Selton-Suty et al. [11] older patients (≥70 years) with infective endocarditis had a significantly higher percentage of group D streptococci and enterococci compared to the younger patients (<70 years) (47.6 % versus 19.5 %). A publication [25] also demonstrated that among 1,285 patients with left-sided native valve endocarditis, 107 (8.3 %) had enterococcal endocarditis most frequently seen in elderly men, frequently involving the aortic valve, tending to produce heart failure rather than embolic events, and associated with relatively low short-term mortality. Compared to patients with streptococcal endocarditis, those with enterococcal endocarditis were more likely to be nosocomially acquired (15 % vs 1 %; P<0.0001) and have heart failure (46 % vs 35 %; P=0.03). Compared to patients with *S. aureus* endocarditis, patients with enterococcal endocarditis were less likely to embolize (26 % vs 49 %; P<0.0001) and less likely to die (11 % vs 27 %; P=0.001). Multivariable analysis showed that enterococcal endocarditis was associated with lower mortality than other patients with left sided endocarditis (odds ratio [OR] 0.49; 95 % CI 0.24–0.97). A recent report from the ICE collaboration included 4,974 adults with definite IE recorded from 2000 to 2006, 500 patients had enterococcal IE. In the North American subset of the data, enterococcal IE outnumbered other streptococci (oral and intestinal). The patients' mean age was 65 years and 361/500 were male. Nearly a quarter were healthcare related. In this study the 1-year mortality was 28.9 % and increased with age [26].

Di Salvo et al. [27] studied 315 consecutive patients with definite infectious endocarditis. Patients were separated into three groups: group A included 117 patients aged <50 years, group B included 111 patients aged ≥50 and ≤70 years, and group C included 87 patients aged ≥70 years. A presumed gastrointestinal tract port of entry was more commonly detected in group C (19 %) and in group B (16 %) than in the younger patients (5 %), P<0.0001. Similarly, the urinary tract served as port of entry more frequently among the oldest age group (13 %) compared to the other groups (group A- 2 % and group B- 6 %, P<0.005). The most frequent isolated pathogens were compatible with the presumed port of entry: The most common organisms were *Streptococci* found in 45 % of patients. The proportion of *S. bovis* (*Streptococcus gallolyticus*) endocarditis was higher in groups B and C than in group A [25 (22 %), 14 (16 %) and 6 (5 %), respectively, P<0.001]. The proportion of *enterococci* was highest in group C [5 (5 %) in group A, 5 (4 %) in group B, and 8 (9 %) in group C] while *S. aureus* was more frequent in younger patients [34 (29 %) in group A, 19 (17 %) in group B, and 15 (17 %) in group C]. Thus, the bacteriological features of endocarditis in the elderly reflect the common sources of bacteremia relating to the co-morbidities typical of this age group. *S. bovis* probably relates to colonic lesions and enterococci relates to urogenital infections.

The high incidence of *S. bovis* endocarditis in the elderly as well as the difficult clinical course related to this pathogen is also evident when studying the clinical course of these infections compared to other pathogens. Pergola et al. [28] studied

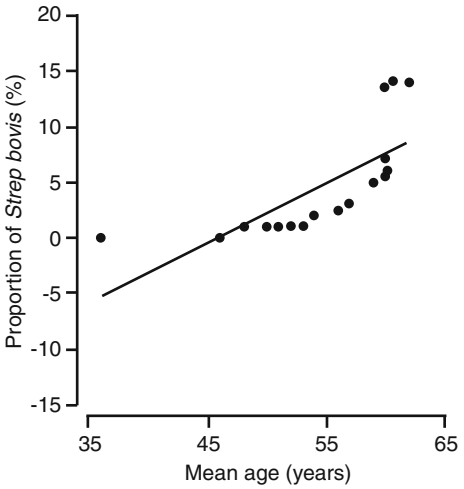

Fig. 3.1 Microbial epidemiology of infective endocarditis. Linear regressions between proportion of *S.bovis* disease and mean age [31]

the clinical, echographic, and prognostic features of *S. bovis* endocarditis compared to endocarditis caused by other streptococci and "other pathogens" in a large sample of patients. Two hundred six patients with a mean age of 57 (SD 15) years with a diagnosis of infective endocarditis formed the study population. *S. bovis* endocarditis was documented in 40 patients, other Streptococci were identified in 54, and "other pathogens" were documented in 112 patients. The mean age was 64 (SD 12) years in the *S. bovis* group, 55 (SD 15) years in the other Streptococci group and 56 (SD 16) years in the "other pathogens" group, $p < 0.05$. Multiple valve involvement, native valves, and large vegetations (>10 mm) were more frequent in patients with *S. bovis*. There was a significantly higher rate of embolism in the *S. bovis* group. Splenic infarcts and multiple embolisms were significantly more frequent in patients with *S. bovis*. Gastrointestinal lesions, anemia, and spondylitis were also observed more frequently with *S. bovis* endocarditis. In a multicenter prospective European study, including 384 consecutive patients with definite IE predictors of embolic events included the size of vegetation, *S. bovis* and *S aureus* as the pathogens, and mortality increased with increasing age on multivariate analysis [29]. A recent Italian multi-center study documented increases in S. gallolyticus among patients over the age of 74 [30]. The relationship between age and prevalence of *S. bovis* endocarditis is depicted in Fig. 3.1 [31].

Clinical Presentation and Echocardiography Findings

In the study by Di Salvo [27] age was not found to be related to the echocardiographic presentation of endocarditis, nor was age related to the incidence and localization of embolic events regardless to the pathogen involved. Elderly patients were surgically managed as frequently as younger patients and their operative risk for mortality and complications was similar to that of younger patients (11 %, 3 %, and

5 % in groups C, B, and A, respectively). Bassetti et al. reported a large Italian prospective study, in which multivariate analysis showed that age was not an independent predictor of in-hospital mortality. Congestive heart failure, chronic heart failure, an altered mental status, and the isolation of S. aureus or CoNS were associated with increased in-hospital mortality [30]. In two reports however, renal failure, complicated endocarditis more frequently in the elderly patients compared to younger patients [32]. Among 44 individuals over the age of 64, the average length of hospital stay was 12 days longer, renal failure and cerebral embolism during an episode of IE were associated with higher rates of death but age was not independently associated with mortality [33]. An additional report documented fewer vegetations and higher prevalence of abscesses resulting in greater gain in the diagnostic yield of transesophageal echocardiography among the aged. Despite the higher rate of abscesses, the proportion that underwent surgery was lower and in-hospital mortality higher [16].

Treatment and Outcome

Age not surprisingly is correlated with higher endocarditis caused mortality. In the study by Selton-Suty et al. [11], mortality was 28 % in the older patients (>70 years) double of that (13.5 %) in the younger patients (<70 years) ($p<0.08$). Multivariate analysis showed that age ($p<0.02$) and the presence of at least one vegetation at echocardiography ($p<0.04$) were independent risk factors for a fatal outcome. Elderly patients with enterococcal endocarditis had similar mortality to younger patients with streptococcal endocarditis [25]. Di Salvo et al. [27] demonstrated that the overall mortality was clearly higher in elderly (17 %) group aged >70 years compared to the younger patients (10 % versus 7 %, respectively, $p=0.02$). Surgical treatment was performed slightly less frequently in the elderly compared than in other groups, although 41 % of elderly patients were operated on. Mortality was relatively high in non-operated elderly patients (21 %), but only 11 % in elderly patients who could be treated with surgical therapy. This difference may reflect a hidden bias were less severe patients were more likely to receive a surgical intervention. For the entire population, including the younger patients, mortality was lower in operated patients than in patients treated with antibiotic alone (6 % vs 15 %, respectively, $P=0.04$). Among the 51 non-operated elderly patients, 7 (14 %) patients had undisputed indication for surgery (severe heart failure, persistent sepsis or multiple emboli). Of them, five were not considered good candidates for surgery because of very poor general condition and two patients declined surgery.

In a logistic regression analysis independent predictors of in-hospital mortality were age ($P=0.003$), prosthetic valve ($P=0.002$), and cerebral embolism ($P=0.006$). Conversely, surgical management was associated with a lower in hospital mortality (regardless of age) ($P=0.03$).

In a report by Netzer et al. [32], 82 younger patients (17–59 years) were compared to 53 elderly patients (65–90 years). There were no significant differences between the two groups regarding comorbidities or clinical presentation except that

renal failure was more common in the elderly. Mortality was significantly higher in the elderly patients [13 (25 %) vs 9 (11 %) respectively, P < 0.04]. A study from the ICE group compared 1,056 patients 65 years or older with IE to younger 1,703 patients. The older age group had lower rate of emboli or valvular perforation but higher prevalence of abscesses. Cardiac surgery was undertaken less frequently than in the younger group (38.9 % vs 53.5 %; P < .001) and a doubling of in-hospital mortality [16]. The reasons for avoidance of surgical interventions were not discussed in that study. In contrast to these publications which demonstrate a higher mortality in elderly patients Gagliardi et al. [33] report similar outcomes in the young and the old. They compared 44 episodes of definite native valve infective endocarditis in patients >64 years with 64 similarly defined episodes in patients >29 years but <64 years old, who were not using intravenous drugs. Clinical presentations, characteristics, and outcome were similar in the two groups. Elderly patients were hospitalized for an average of 12 days longer compared to the younger patients. The occurrence of renal failure and cerebral embolism during an episode of infective endocarditis was associated with higher rates of death (odds ratios, 4.8 and 4.0, respectively). Age however was not a significant contributor to mortality. These results differ from the other authors sited above. It is important to note that in this group of patients the rate of enterococcal endocarditis and *Str. bovis* endocarditis were not significantly higher in the elderly and this peculiarity might explain the lack of difference in outcomes between the two groups of patients.

To conclude, it seems that the elderly may fare worse, during an episode of infective endocarditis, although the extent of excess mortality differs between various studies. Aggressive intervention, including early surgery should not be excluded in the elderly, merely because of the age, as better outcomes especially in the group of patients without severe co morbidities are to be expected.

Injection Drug Users

Infective endocarditis is one of the most common and serious complications of intravenous drug use (IVDU) [34]. The prevalence of drug use has increased in the past 30 years with concomitant increased in incidence of infective endocarditis.

Epidemiology

The incidence of infective endocarditis in IVDU is 2–5 %/year and is responsible for 5–8 % of hospital admissions among IVDU. The overall incidence of infective endocarditis in this population is estimated to be 1–20 cases per 10,000 injection drug users per year [35] and is responsible for 5–10 % of the overall death rate of IVDU [24]. Levine et al. [36] followed all IVDU admitted to the Detroit Medical Center with infectious endocarditis (74 cases) during the early 1980s and compared them with a control group of bacteremic IVDU's who had other infections (106 cases). They found that acute infection accounted for approximately 60 % of

hospital admissions and that infective endocarditis was implicated in 5–15 % of these episodes. The male:female ratio was 5.4:1. Men with infective endocarditis were somewhat older than females (mean age, 32.7 years versus 31.4 years) and had significantly longer histories of addiction (10.2 years versus 7.1 years) than women.

Chambers et al. [37] compared 102 IVDU with endocarditis to IVDU with other causes of fever. Bacterial endocarditis was diagnosed in 23 % of hospitalizations. Logistic regression analysis showed the following variables to be predictive of infective endocarditis in IVDU: cocaine use (OR 138, CI 8–2318), mitral or aortic valve murmur (OR 51, CI 3–779), haematocrit <40 % (OR 25, CI 2–318), proteinuria (OR 14, CI 1–127), and signs of septic emboli, cavity, or effusion on chest x-ray (OR 165, CI 9–3067). Although heroin was the most common drug used it was not independently associated with the development of endocarditis in this study and neither the combination of heroin and cocaine. The mechanism by which cocaine increases the risk of infective endocarditis has not been elucidated. Nevertheless, in other circumstances when heroin was mixed with non-sterile adjunctives the risk of endocarditis with IV heroin use was high. In the last 20 years the rate of HIV in IVDU has been reported to be in the range of 30–70 %, thus the prevalence of the disease in recent series reflects the risk attributed by both conditions. The trend has resulted in an increase in hospital admissions [38]. Changes in drug usage patterns have been associated with the occurrence of endocarditis in areas where the incidence was previously low [39]. An attempt to study the incidence of IE in a Danish urban injection facility using trans-thoracic echocardiography, revealed valvular abnormalities in 20 % of the 206 individuals studied and prior episode of IE was reported in 7 % [40].

Bacteriology

In the study of Levine et al. endocarditis was caused by *Staphylococcus aureus* in 60.8 % of the cases, streptococci in 16.2 % of cases, *Pseudomonas aeruginosa* in 13.5 % of cases, mixed bacteria in 8.1 % of cases, and *Corynebacterium JK* in 1.4 % of cases. *S. aureus* endocarditis most frequently involved the tricuspid valve, and streptococci infected left-sided valves significantly more often than other organisms ($P = 0.001$). Biventricular and multiple-valve infections were commonest in patients with pseudomonas endocarditis ($P = 0.05$). In Miro's Spanish series *Staph aureus* was also the most common etiological agent, being usually sensitive to methicillin (MSSA). HIV-positive IVDU had a higher ratio of right-sided infective endocarditis and *Staph aureus* infective endocarditis than HIV-negative IVDUs and the tricuspid valve was the most frequently affected (60–70 %), followed by the mitral and aortic valves (20–30 %) [35].

Clinical Presentation

IVDU and particularly HIV positive IVDU are prone to acquire right sided endocarditis and this has been well documented in older as well as in newer series [35]. Two

thirds of IVDU with infective endocarditis have no clinical evidence of underlying heart disease. Despite the fact that heart murmurs are predictive of infective endocarditis in IVDU, only 35 % of addicts demonstrate heart murmurs on admission [36]. Higher prevalence of left sided endocarditis is reported in IVDU. For example, in a retrospective study of infective endocarditis in IVDU, 67 patients had vegetations documented by two-dimensional echocardiogram. Left-sided involvement was present in 38 (57 %) of these patients, a higher prevalence than reported in older series. Right-sided involvement was limited to only 27 (40 %) cases. This change in epidemiology is important as left sided endocarditis carries higher morbidity and mortality. In this study, valvular involvement was as follows: tricuspid valve alone or in combination with others, 52.2 % of cases, aortic valve alone in 18.5 % of cases, mitral valve alone in 10.8 % of cases, and aortic plus mitral valves in 12.5 % of cases [41] Mitral valve involvement was more common among female IVDU's. Similarly, in the Spanish series the tricuspid valve is the most frequently affected (60–70 %), followed by the mitral and aortic valves (20–30 %) [35]. Involvement of left side of the heart and polymicrobial etiology have been associated with increase in morbidity and mortality [42].

Fever was the most common symptom, present in over three-fourth of patients [43]. Pulmonary symptoms such as pleuritic chest pain (reported in approximately a half of cases), cough, dyspnea and lung infiltrates dominate the clinical picture. Septic pulmonary emboli are reported in 28–47 % and congestive heart failure may accompany at presentation [43, 44].

Treatment and Outcome

As mentioned before, many IVDU with infective endocarditis have right sided endocarditis. This prompted researchers to assess the feasibility of shorter antibiotic courses in this population, as right sided endocarditis has a better prognosis than left sided infection. This approach is particularly attractive as the compliance of IVDU to prolonged hospitalization or home care is low. Chambers [45] published a report confirming the feasibility of treating right sided endocarditis in IVDU with as 2 week course of antibiotics. The shortened course's efficacy was confirmed by a prospective, randomized clinical trial among drug abusers [46]. A short course of a combination of a glycopeptide (vancomycin or teicoplanin) and gentamicin compared with a combination of cloxacillin and gentamicin for treatment of right-side endocarditis caused by *Staphylococcus*. Therapeutic success was significantly more frequent with cloxacillin than with a glycopeptide. No adverse effects were noted among patients in the cloxacillin group. Ribera et al. showed similar results [47]. Thus, a shortened course of penicilliase- resistant penicillin with or without the addition of an aminoglycoside for right sided infective endocarditis in IVDU infected with *S. aureus* sensitive to methicillin seems and acceptable alternative.

Another issue is the best surgical approach for IVDU with endocarditis. To determine the early and late results of surgical treatment for infective endocarditis in IVDU Mathew et al. [48] observed IVDU undergoing surgical treatment for infective

endocarditis. Eighty patients underwent cardiac surgery for the following indications: acute congestive heart failure in 44 (56 %) patients, persistent sepsis in 21 (26 %) patients, and multiple systemic embolization in 15 (19 %) patients. Six patients (7.5 %) died within 30 days of surgery and 13 of 69 patients (17.6 %) died during the follow-up from cardiovascular causes. The probability of survival at 36 months and at 60 months was 0.74 and 0.70, respectively. Seventeen (30 %) of the survivors had at least one major cardiovascular event, six (8.8 %) patients had recurrent endocarditis, ten (14.6 %) patients experienced central nervous system complications and three (4.4 %) patients required repeated valve replacement. Probability of event-free survival at 36 months and 60 months was 0.65 and 0.52, respectively. These authors conclude that since the expected mortality without surgery in patients with infective endocarditis in whom medical treatment fails is almost 100 %, surgical treatment should be advised liberally as it substantially improves the outlook for early and late survival of IVDU with endocarditis. The high cost of surgery and care [49], the likelihood of recurrence pose challenges to surgical management [50].

Recurrent IE

The optimal surgical management of IE in IVDU is complicated by the concerns with recurrence in the prosthetic valve. Although right-sided endocarditis carrier a favorable prognosis, left-sided endocarditis is associated with high mortality and better outcomes are achieved with surgical therapy [35]. The rate of development of PVE among IVDU remains understudied. A retrospective comparison of surgical outcomes between IVDU and non-IVDU was reported by Kaiser et al. [51]. The rate of perioperative complications was similar as was the age adjusted long-term survival. The overall survival at 10 and 15 years was 66 % for IVDU compared to 54 % non-IVDU. The need for reoperation for recurrent infective endocarditis was 17 % of 52 for the IVDU group versus 5 % of 270 for non-IVDU group. Similarly, a study of 358 patients with IE treated with valve replacement, reported that the 16 % of IVDU included in the study accounted for over 55 % of reoperations for recurrent IE. IVDU/HIV were associated with HR of 12.8 for recurrence requiring surgery and the constellation of IVDU/HIV with patch and valve was associated with HR of 34.3 for reoperation [52]. The choice surgical management is influenced by a multitude of factors including perceived risk of recurrence, patient characteristics, need for post-surgical anti-coagulation in poorly compliant individuals. The current optimal management is not evidence based [53].

HIV

HIV-seropositive patients are at risk for infective endocarditis because of three main reasons: intravenous drug abuse, long-term use of central venous catheterization for administration of medications, and as a consequence of immune suppression. Infectious endocarditis is responsible for 5–20 % of hospital admissions and for

5–10 % of total deaths in IVDU patients with HIV infection, but the clinical outcome of the patients depends on the affected valve and the culture germen rather than the HIV serostatus. HIV stage C was found in six cases, and the median (range) CD4 cell count was 22/microL (4–274 cells/microL) [54]. *S. aureus* is the most common pathogen involved .and the infection is more commonly localized to the right side of the heart. It is not clearly defined whether HIV infection is responsible for the worst evolution in these patients and if treatment should be the same as that used in HIV seronegative subjects [55].

Epidemiology

To determine the effect of HIV infection and other factors on infective endocarditis among IVDU Wilson et al. [56] examined the incidence of endocarditis according to HIV status in a cohort of IVDU. Endocarditis incidence (117 cases) was higher among HIV-seropositive than HIV-seronegative IVDU (13.8 vs. 3.3 cases/1,000 person-years). Multivariate analysis of HIV-infected case patients revealed an inverse association between infective endocarditis and CD4 lymphocyte count (OR for 200–499 cells/mm^3, 2.01, OR for <200 cells/mm^3, 3.61) and with alcohol intake (OR for 1–21 drinks/week, 0.43; OR for >21 drinks/week, 0.32). Women had an increased risk of endocarditis (OR, 3.26), as did persons with increasing injection drug use frequency (OR for less than daily use, 3.15; OR for at least daily use, 6.07). See Fig. 3.2. This study confirmed that infective endocarditis is more common among IVDU with advanced HIV immunosuppression even after accounting for injection drug use behaviors. The higher incidence found in woman is surprising as in other populations including IVDU without HIV a higher incidence is found

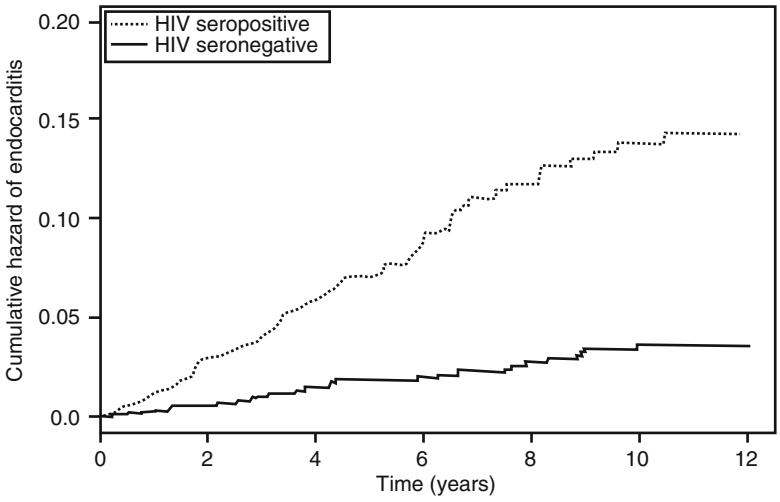

Fig. 3.2 Cumulative hazard of first episode of infective endocarditis over time, by HIV serostatus [56]

consistently in men. A recent Italian study of 189 episodes of IE in 166 patients, documented 19 % prevalence rate of HIV [57]. A study from Baltimore reported decreasing IE incidence from 20.5 per 1,000 person-years between 1990 and 1995 to 6.6 per 1,000 person-years between 1996 and 2002. The majority were male (66 %), African American (90 %), and 85 % were IVDUs [58]. Conversely, infective endocarditis in HIV-infected persons who do not use drugs is rare. In the absence of intravenous drug abuse, HIV-seropositive patients develop left-sided and right-sided infective endocarditis with equal frequencies. In contrast, in the setting of intravenous drug abuse, HIV-seropositive patients develop predominantly right-sided infective endocarditis. The related morbidity and mortality rates in HIV-seropositive patients who do not have an AIDS-defining illness or criteria are similar to rates in HIV-seronegative [59, 60].

Clinical Presentation and Echocardiography Findings

Smith et al. [61] retrospectively reviewed all bacteremic, HIV positive patients with suspected infective endocarditis admitted over a 4 year period that underwent either transesophageal echocardiography (TEE) or transthoracic echocardiography (TTE). Ten (11.5 %) of 87 HIV-positive patients had a clinical diagnosis of infective endocarditis based on the Duke Criteria. The mean age of patients with endocarditis was 37.8 years similar to those without endocarditis 39.9 years (P = NS).

Both patient groups were similar with respect to gender, race, IVDU, renal failure requiring hemodialysis, history of predisposing heart disease, origin of infection, and causative organism. The mean CD4 count (cells/μL) was 200.7 in patients with infective endocarditis and 95.9 in patients without infective endocarditis (P = NS). Of ten HIV-positive patients with infective endocarditis, seven had left-sided heart involvement, two had complications related to infective endocarditis, three required cardiothoracic surgery, and three died.

Abraham et al. [62] retrospectively reviewed the records of patients with suspected infective endocarditis who were referred to the echocardiography laboratory for evaluation and had ≥2 positive blood cultures for the same microorganism.

One hundred seventy-seven cases of bacteremia involving 169 patients were evaluated. Fifty-two patients were HIV positive and 125 were HIV negative. One hundred sixty-eight of the patients (95 %) underwent TEE. HIV-positive patients were on average 12 years younger than HIV negative patients ($P < 0.0001$). HIV-negative patients were more likely to have a cardiac predisposition to endocarditis ($P < 0.003$). There was a higher rate of diabetes in HIV-negative patients ($P < 0.002$), which likely corresponded to their older age. There was also a higher incidence of renal failure requiring hemodialysis in HIV-negative patients ($P < 0.03$), which was likely due to their older age and higher rate of diabetes. More men comprised the HIV-negative group ($P < 0.017$) (for unknown reasons). There was no difference in the rates of active IVDU between the two groups, and the percentage of patients with documented sources of infection that would explain bacteremia, including line infections, was similar.

S. aureus was the causative organism for bacteremia in almost half of all patients in both groups. There was no statistically significant difference in the microorganisms between the HIV-positive and HIV-negative patients, although most involved small numbers of patients. When considering all organisms, the rate of endocarditis in HIV positive patients was lower than in HIV-negative patients (12 % vs 42 %, $P<0.0001$). There was no correlation between the CD4 count and the presence or absence of endocarditis in the HIV-positive group. Multiple logistic regression analysis revealed 5 clinical factors that were predictive of infective endocarditis: HIV status, presence of IVDA, predisposing heart disease, *S. aureus* bacteremia, and bacteremia caused by modified Duke Criteria 1A organisms. In conclusion, bacteremic HIV-infected patients in this study had less infective endocarditis than bacteremic HIV-negative patients.

Robinson et al. [63] reviewed 158 episodes of infective endocarditis among 126 patients HIV infections. They found no difference in maximal temperature, but a lower mean WBC counts was found in HIV infected patients.

Treatment and Outcome

Most series report similar outcomes for HIV infected individuals with IE whether treated medically or surgically. In a retrospective study Mestres et al. [64] described 31 HIV-1-infected patients that underwent cardiac surgery due to infective endocarditis. Hospital mortality was 22.6 %. Nine patients (37.5 %) died between 2 and 171 months (mean 54.5) after surgery. Overall mortality was 50 %. Endocarditis accounts for decreasing proportion of cardiac surgeries in HIV infected individuals and operative mortality in patients with HIV has decreased from 5.6 % to 0.87 % between 2000 and 2010, in a US study [65]. HIV was not an independent predictor of operative mortality and should not dissuade from surgical intervention when required.

Immunocompromised Patients and Health Care Associated Endocarditis

Epidemiology

As medical technology advances, more and more patients have prolonged hospitalizations, are subject to invasive procedures, receive high dose chemotherapy and corticosteroids, spend more time in intensive care setups, and have more central lines, intubations, catheters and other foreign objects inserted. These trends have caused an increase in nosocomial bacteremia and as a result an increase in nosocomial endocarditis.

Cabell et al. [12] studied the demographic and microbiological changes that occurred in patients with infective endocarditis during 1993–1999 and their impact on survival. Among the 329 study patients, rates of hemodialysis dependence, immunosuppression, and *Staphylococcus aureus* infection increased during the study period ($P=0.04$, $P=0.008$, and $P<0.001$, respectively), while rates of infection due to viridans group streptococci decreased ($P=0.007$). Hemodialysis was

independently associated with *S. aureus* infection (odds ratio, 3.1; 95 % confidence interval, 1.6–5.9). Patients with *S. aureus* endocarditis had a higher 1-year mortality rate (43.9 % vs 32.5 %; P=0.04) that persisted after adjustment for other illness severity characteristics (hazard ratio, 1.5; 95 % confidence interval, 1.03–2.3). In a recent international study initiated by the International Collaboration for Endocarditis (ICE), health care-associated infection was the most common form of *S aureus* infective endocarditis. Most patients with health care-associated *S aureus* endocarditis (131 patients, 60.1 %) acquired the infection outside of the hospital. Persistent bacteremia was independently associated with MRSA infective endocarditis (OR 6.2; 95 % CI 2.9–13.2). Patients in the United States were most likely to be hemodialysis dependent, to have diabetes, to have a presumed intravascular device source, to receive vancomycin, to be infected with MRSA, and to have persistent bacteremia [66]. Similar increases in the preeminence of *S aureus* and healthcare related IE are reported from other North American and European studies [67–69].

Mourvillier et al. reviewed 228 consecutive patients admitted to two intensive care units with infective endocarditis between 1993 and 2000. Again, *S. aureus* emerged as the leading pathogen. The overall in-hospital mortality rate was 45 % (102/228). Multivariate analysis revealed the following clinical factors in patients with native valve endocarditis as independently associated with outcome: septic shock (OR 4.81), cerebral emboli (3.00), immunocompromised state (2.88), and cardiac surgery (0.475). Clinical factors in patients with prosthetic valve endocarditis independently associated with outcome were: septic shock (4.07), neurological complications (3.1), and immunocompromised state (3.46) [70]. Nosocomially acquired infective endocarditis carries a worse prognosis compared to infective endocarditis acquired in the community. This is likely the result of several factors: comorbidities such as diabetes, renal failure, heart disease, hypertension and malignancies are common among hospitalized patients; immune suppression as a result of a disease process or its treatment; higher rate of *S. aureus* and enterococcal infective endocarditis (Including MRSA and vancomycin resistant enterococci) [26] associated with increased complications and difficulties in antimicrobial therapy; acquisition of antimicrobial resistant organisms and infection of life sustaining devices [71].

To conclude, in recent years a change in the epidemiology of infective endocarditis has been taking place. The combination of increased life-expectancy, the burden of chronic disease, immunosuppression as a result of improving treatment and prognosis of malignancies and transplantation and the increasing device-related and iatrogenic infections have combined to change the features of patients at risk for infectious endocarditis. The challenges of endocarditis remained unchanged – timely diagnosis, and optimal medical and surgical treatments are still essential for optimal outcome.

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Microbiology of Infective Endocarditis and Microbiologic Diagnosis

4

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Abstract

The microbiology of infective endocarditis (IE) has evolved significantly over the last century. Previously a community-acquired disease affecting predominantly patients with rheumatic heart disease, IE is now being seen in new populations including IV drug users, patients with prosthetic valves, and patients infected through healthcare associated bacteremia. Improved blood culture technologies and non-culture laboratory methods have also resulted in a lower rate of culture-negative cases. Because of differing proportions of particular risk groups, the etiologic agents responsible for causing infective endocarditis vary significantly among continents, countries, regions within countries and even between different years in an individual hospital.

Blood culture remains the single most important investigation in a patient suspected of having infective endocarditis. If appropriately collected prior to antibiotic administration, blood cultures can be expected to yield growth of the causative organism in over 90 % of cases of infective endocarditis. Serologic testing can be useful in determining the cause of IE in true culture-negative cases, which are usually caused by organisms that are difficult to culture including *Coxiella burnetti*, *Bartonella* spp., *Chlamydia* spp. and *Legionella* species. In spite of limitations including the potential presence of PCR inhibitors in clinical samples and the possibility of sample to sample contamination, molecular amplification methods can be useful in establishing the cause of IE. To date, PCR methods have been applied with most success to surgically excised valve tissues.

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Microbiology • Diagnosis • Blood culture • PCR • Serology • Prosthetic valve • Native valve

Key Points
1. The etiologic agents of IE vary between centers due to different risk factor profiles in the patient populations served.
2. Staphylococci and Streptococcus species are the most common etiologic agents of endocarditis, accounting for 80–90 % of cases in most patient populations.
3. The proportion of IE cases caused by Staphylococcus aureus has been increasing due to higher numbers of patients with either health-care-associated IE or a history of intravenous drug use.
4. In addition to appropriately collected blood cultures, microbiologic laboratory techniques useful for determining the causative agents of IE include histology, serologic testing, and molecular diagnostic methods.

Microbiology

Trends

The microbiology of infective endocarditis (IE) has evolved significantly over the last century (see Table 4.1) [1, 2]. Previously a community-acquired disease affecting predominantly patients with rheumatic heart disease, IE is now being seen in new populations including IV drug users, patients with prosthetic valves, and patients infected through healthcare associated bacteremia. Improved blood culture technologies and non-culture laboratory methods have also resulted in a lower rate of culture-negative cases. Because of differing proportions of particular risk groups, the etiologic agents responsible for causing infective endocarditis vary significantly among continents, countries, regions within countries and even between different

Table 4.1 Microorganisms in endocarditis (%)

	Viridans group	Other strep	*S. aureus*	CoNS	Gram-negative	Other	No growth
Prior to 1970	43	12.5	14	4	5.5	3	18
1970s	42.5	16	13	3	5	10	10
1980s	29	19	24	9	4	7.5	7.5
1990s	28	23	28	7	4	5	5
2000s	17	22	31	11	2	7	10

Adapted from: Cabell et al. [1] and Murdoch et al. [2]

years in an individual hospital. The approximate proportions of IE cases caused by different groups of microorganisms as published by Mylonakis and Calderwood are provided in Table 4.2 [3].

This discussion of the etiologic agents of infective endocarditis will begin with native valve endocarditis followed by consideration of special situations including prosthetic valve endocarditis, IE in injection drug users, and culture-negative endocarditis.

Table 4.2 Microbiologic features of native-valve and prosthetic-valve endocarditis

Pathogen	Native-valve endocarditis			
	Neonates	2 months–15 years of age	16–60 year of age	>60 year of age
		(Approximate percentage of cases)		
Streptococcus species	15–20	40–50	45–65	30–45
Staphylococcus aureus	40–50	22–27	30–40	25–30
Coagulase negative staphylococci	8–12	4–7	4–8	3–5
Enterococcus species	<1	3–6	5–8	14–17
Gram negative bacilli	8–12	4–6	4–10	5
Fungi	8–12	1–3	1–3	1–2
Culture-negative and HACEK organisms[a]	2–6	0–15	3–10	5
Diphtheroids	<1	<1	<1	<1
Polymicrobial	3–5	<1	1–2	1–2
Pathogen	Prosthetic-valve endocarditis			
	Early	Intermediate		Late
	(<60 days after procedure)	(60 days–12 months after procedure)		(>12 months after procedure)
	(Approximate percentage of cases)			
Streptococcus species	1	7–10		30–33
Staphylococcus aureus	20–24	10–15		15–20
Coagulase negative staphylococci	30–35	30–35		10–12
Enterococcus species	5–10	10–15		8–12
Gram negative bacilli	10–15	2–4		4–7
Fungi	5–10	10–15		1
Culture-negative and HACEK organisms[a]	3–7	3–7		3–8
Diphtheroids	5–7	2–5		2–3
Polymicrobial	2–4	4–7		3–7

Microbiologic Features of Native-Valve and Prosthetic-Valve Endocarditis (SOURCE Mylonakis et al. [3], by permission of Massachusetts Medical Society)

[a]Patients whose blood cultures were rendered negative by prior antibiotic treatment are excluded. HACEK denotes Haemophilus species (*H. parainfluenzae*, *H. aphrophilus*, *H. paraphrophilus*), *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella kingae*

Community Acquired Native Valve Endocarditis

The organisms that commonly cause native valve endocarditis are members of the normal flora of the skin, oropharynx, and the gastrointestinal and genitourinary systems. The vast majority of native valve endocarditis cases are caused by *Staphylococcus* and *Streptococcus* species. Several recent publications show that *Staphylococcus aureus* seems to have overtaken the viridans group Streptococci as the most common cause of native valve IE [2, 4, 5]. However, a population-based study of IE cases in Olmstead County, Minnesota from 1970 to 2000 revealed no significant trends over time with respect to either the overall incidence of IE or the relative proportion of cases caused by Staphylococci and Streptococci [6]. Likewise, the same researchers conducted a systematic review of all population-based IE surveys prior to 2007 and found no overall temporal trend in *S. aureus* or viridans group streptococcal IE [7]. These apparently contradictory observations likely result from differences in patient risk factors (e.g. low IVDU rates in Olmstead County) and referral patterns (more *S. aureus* IE referred to tertiary care centres).

Staphylococci

Staphylococcus aureus

Two publications from the International Collaboration on Endocarditis (ICE) provide an international perspective on *S. aureus* native valve endocarditis. In one report, the authors used a merged database derived from data collected between 1979 and 1999 at seven sites in five countries. The database included 2,212 cases defined as definite IE based on the Duke criteria; 566 (34 %) of 1,640 native valve IE cases were caused by *S. aureus* [8]. Compared to the patients with native valve IE caused by organisms other than *S. aureus*, these patients were younger (median age 46.0 -vs- 60.0 years) and more likely to have a history of IV drug use (36.9 % -vs- 5.5 %). The valves involved were significantly different between the two groups, with tricuspid involvement much more common in the *S. aureus* cohort (31.3 % -vs- 5.0 %) and aortic valve involvement less common (15.9 % -vs- 31.2 %). Although outcomes varied by center, embolic events (60.6 % -vs- 30.7 %), CNS events (20.6 % -vs- 13.3 %) and in-hospital mortality (19.9 % -vs- 12.2 %) were all higher for the subset infected with *S. aureus*. The mortality rate was particularly high (28.6 %) for patients with *S. aureus* infecting a left sided valve. The other publication from the ICE investigators was based on data collected prospectively at 39 participating centers in 15 countries between 2000 and 2003 [9]. In this cohort, *S. aureus* was again observed to be the most common etiologic agent of definite IE both overall (558/1,779, 31.4 %) and in the native valve IE subset (401/1,247, 32.2 %).

A more recent report used the Agency for Healthcare Nationwide Inpatient Sample to evaluate the etiologic agents of IE between 1999 and 2008. The authors found that of 83,700 discharges, the most commonly identified organism was *S. aureus* (57.5 %). Similar to previous studies, admissions for *S. aureus*-related IE were associated with a higher probability of in-hospital morality compared with streptococcal and/or enterococcal IE (17.5 % vs 8.9 %; P=<0.001) [10].

Medical procedures and (often intravascular) devices that place patients at risk for bacteremia appear to be responsible for at least part of the observed increase in some centers of the proportion of IE cases caused *S. aureus*. Fowler et al. [9] found *S. aureus* IE to be healthcare associated in a substantial proportion of cases. Overall, 218/341 (39.1 %) of *S. aureus* IE was healthcare associated compared to 211/1,221 (17.3 %) of non-*S. aureus* cases. Approximately 60 % of the healthcare associated *S. aureus* IE cases were nosocomial, with the remainder acquired outside of hospital. The patients with healthcare associated *S. aureus* IE had a higher average age, an increased likelihood of mitral valve involvement, and higher in-hospital mortality compared to those with community acquired *S. aureus* IE.

The incidence of MRSA IE has also been noted to be increasing, particularly within the healthcare associated IE subgroup. Excluding community acquired IVDU-associated IE, Fowler et al. reported MRSA as the cause in 100/289 (34.6 %) of native valve *S. aureus* IE in the prospective ICE cohort [9]. The majority (75.9 %) of MRSA IE cases were healthcare associated, with intravascular devices as the presumed source (60.3 %), and diabetes mellitus (34.0 %) and immunosuppressive therapy (17.7 %) observed significantly more commonly than in the non-MRSA *S. aureus* IE group. MRSA infected patients had a lower rate of embolic events, but persistent bacteremia was more common and there was a trend toward higher in-hospital mortality. The proportion of *S. aureus* IE caused by MRSA varied considerably ranging from 43.5 % in US centers to 19.1 % in Australia/New Zealand.

A smaller, more recent study conducted by Hill et al. [11] found that of 72 consecutive cases of definite *S. aureus* IE between June 2000 and December 2006, 22 % were caused by MRSA. Similarly, they found that the majority of cases of MRSA infective endocarditis were nosocomial (75 % compared to 32 % of MSSA). When compared with MSSA, MRSA infective endocarditis was more frequently associated with surgical site infection (38 % vs. 7 %), surgery within the previous 6 months (75 % vs. 21 %), and more commonly involved a prosthetic valve (44 % vs. 30 %). Hill et al. found decreased frequencies of major (6 % vs. 39 %) and minor (0 % vs. 25 %) embolic complications in the MRSA group compared with the MSSA group. They also demonstrated a trend toward increased overall 6-month mortality in the MRSA group (56 % vs. 30 %; $P=0.06$), which was more pronounced in the group with nosocomial MRSA compared with community-acquired MRSA.

Coagulase Negative Staphylococci

In most published case series, coagulase negative staphylococci (CoNS) are reported to cause approximately 5 % of cases of native valve endocarditis [3–5, 12]. A review of 99 native valve IE cases caused by CoNS was recently published based on information obtained from the ICE merged database, which is comprised of IE case data collected between 1979 and 1999 at seven sites in Europe and the US [13]. CoNS strains were determined to be the cause of native valve IE in 6.6 % of 1,504 adult patients in the database (excluding those with a history of injection drug use) who met Duke criteria for definite IE. The species was identified as *S. epidermidis* in 55/65 (85 %) of cases for which specific organism identification was available. Although CoNS are often not considered to be virulent organisms, the rates of heart failure and in-hospital mortality were similar to those observed in patients with

S. aureus native valve IE in the same database. When compared to cases caused by viridans group streptococci, the CoNS patients were older overall, they had a much greater likelihood of healthcare associated acquisition (40 % -vs- 1.3 %), and they had a more complicated clinical course as indicated by higher rates of heart failure, intracardiac abscess, cardiac surgery and mortality.

A more recent study by the same researchers found that healthcare exposure such as long-term hemodialysis, pacemakers and/or implantable defibrillators, history of invasive procedures, and long-term indwelling central catheters all showed an increased risk for CoNS IE compared with viridans group streptococci [14]. Similarly, their study also demonstrated statistically significant increased rates of heart failure, persistent bacteremia and in-hospital death when compared with the group infected with viridans group streptococci. The in-hospital mortality associated with native valve endocarditis caused by CoNS was 25 %, similar to that of patients with native valve endocarditis caused by *S. aureus* (27 %; P=0.44).

Another study by the same researchers compared prosthetic valve endocarditis (PVE) caused by CoNS to cases caused by *S aureus* and viridans group streptococci [15]. Excluding IVDU, researchers found that CoNS accounted for 16 % of the 537 cases of PVE. The rate of intracardiac abscess was significantly higher in patients with CoNS PVE (38 %) than *S aureus* (23 %, p=0.03) or viridans group streptococci (20 %, p=0.09). Over half of the PVE cases caused by CoNS were classified as early or intermediate, suggesting a nosocomial origin relating to the initial surgery or subsequent health care contact. Compared to *S aureus*, the timing of CoNS PVE was less likely to be early (8.7 % vs 23.4 %) and more likely intermediate (47.8 % vs 27.3 %). Furthermore, more patients with CoNS PVE reported symptom durations greater than 1 month compared with patients with *S aureus* PVE (19 % vs 5.7 %, p=<0.01). These findings support the hypothesis that CoNS PVE causes a subacute clinical presentation, contributing to the high rates of heart failure and intracardiac abscess. Overall in-hospital mortality rates trended higher in PVE caused by CoNS (24 %) compared to viridans group streptococci (9.1 %), but did not reach statistical significance (p=0.08).

One particular CoNS species that has been associated with more aggressive disease is *S. lugdunensis*. In a review of 48 published IE cases, Seenivasan and Yu reported that 39 (81 %) involved native valves and 74 % had an acute presentation, with an overall mortality rate of 49 % [16]. Valve destruction was common, with over half of the patients (25/48) proceeding to cardiac surgery; the mortality rate was 65 % among those who did not have surgery.

Streptococci

The viridans group streptococci remain among the most common causes (30–40 % in most series) of community-acquired native valve IE in individuals without a history of IV drug use. The most common species include *S. oralis*/*S. mitis*, *S. sanguis*, *S. mutans*, and *S. salivarius*. These alpha hemolytic organisms are members of the normal flora of the gastrointestinal tract, and they usually cause a subacute presentation of IE. They are the most common causative agents among children and young women with mitral IE. Members of the *S. anginosus* (or *S. milleri*) group most often

grow as pinpoint alpha hemolytic colonies on sheep blood agar. Although often considered to be part of the viridans group, the distinction is important because infections with these organisms are associated with abscess formation, possibly impacting the duration of therapy [17]. The organisms previously designated as nutritionally variant streptococci are now classified as *Abiotrophia defectiva* and *Granulicatella* species. These organisms can be challenging because media supplemented with pyridoxal hydrochloride or L-cysteine are required to support growth, and treatment success requires more aggressive therapy than for viridans streptococci.

Non-enterococcal group D streptococci, the *Streptococcus bovis*/*S. equinus* complex, are an important cause of IE in certain geographical areas. An analysis of the ICE merged database yielded 136 IE cases caused by these organisms, of which 109 (80.1 %) involved native valves [18]. When compared to cases caused by viridans group streptococci, patients were older with more co-morbidities, and multiple valve involvement was more common. When data from two decades of the database were compared, the proportion of streptococcal IE caused by *S. bovis*/*equinus* increased from 10.9 % (1979–1989) to 23.3 % (1990–1999). This proportion was particularly high in France (58 %) compared to other sites in Europe (9.4 %) and the US (16.7 %). A more recent analysis of the ICE prospective cohort study yielded similar results, identifying 165 patients with *S. bovis* IE, representing 6 % of the total cohort and 25 % of all non-enterococcal streptococcal IE [2]. The majority of these cases were native valve endocarditis in non-IVDU (119/165 or 72 %). The rates of *S. bovis* were highest in the European region, representing 10 % of cases and lowest in North America, representing only 2 % of all cases of IE. Previous studies have shown a strong association between *S. bovis* bacteremia and colorectal cancer.

S. pneumoniae was an important agent of IE in the pre-antibiotic era. Its incidence has decreased to 1–3 % now, though a small Scandinavian study showed a fourfold increase from 1981 to 1996 [19]. *S. pyogenes* and Lancefield groups B, C and G streptococci are also rare causes of native valve IE.

Enterococci

The enterococci are the third most common agents of IE overall, causing 5–20 % of cases. In a prospective analysis of over a 5 year period in a center in Spain, IE was found to be present in 17/116 (14.6 %) patients with enterococcal bacteremia [20]. Enterococcal IE was caused by *E. faecalis* in 16/17 cases. Endocarditis was hospital acquired in 6/17 (35.3 %) cases, and 10/17 patients had pre-existing valvular abnormalities. Healthcare associated infection was also noted in an early retrospective review of 38 cases of enterococcal IE published in 1970 by Mandell et al. in which 47 % of infections had developed in elderly men who had undergone GU tract procedures or in younger women following gynecological procedures [21]. In a recent publication based on the ICE merged database (1970–1999), 107 definite left sided native valve IE cases caused by enterococci were compared to cases of other etiologies in the same database [22]. Among the isolates that were fully identified, 92.5 %

were *E. faecalis*, 6.0 % *E. faecium* and 1.5 % *E. durans*; 37.4 % of the strains were not identified to the species level. Patients with enterococcal endocarditis were older (mean age 66.4 -vs- 58.2 years) and more likely to have cancer (21 % -vs- 8 %) when compared to those with non-enterococcal IE. Enterococcal IE was more likely than streptococcal IE to be nosocomially acquired (15 % -vs- 1 %). When compared to *S. aureus* IE, systemic embolization (26 % -vs- 49 %) and in-hospital death (11 % -vs- 27 %) were significantly less common in the enterococcal IE cohort.

A recent publication based on the ICE merged database characterized the current rates of enterococcal IE [23]. Of the 1,616 cases of definite streptococcal or enterococcal IE, 500 cases (30.9 %) were determined to be caused by enterococci. Enterococcal IE was more likely to be healthcare associated than cases caused by oral streptococci (23.4 % vs 4.5 %) and more likely to involve a prosthethic valve (29.1 % vs 16.4 %). As demonstrated previously, patients with enterococcal IE were older (mean age 65.5 vs. 54.6 years), and more likely to have comorbidities such as hemodialysis (8.4 % vs. 1.4 %) and diabetes (22.4 % vs. 11.1 %). Patients with enterococcal IE were more likely to have paravalvular complications in prosthetic valve IE and had overall higher 1-year mortality rates than those with oral streptococci or group D streptococci (28.9 % vs. 14.6 % and 17.8 % respectively, $p = <0.0001$). The majority of the isolates in this study were *Enterococcus faecalis*, accounting for about 90 %. Vancomycin resistant enterococcus (VRE) was isolated in 12 cases; of the 11 strains with identified area of acquisition, 64 % were isolated from nosocomially-acquired IE compared with 13 % of vancomycin-susceptible strains. Notably, VRE accounted for approximately 10 % of all enterococcal IE in North America. Furthermore, the proportion of IE caused by enterococci was higher in North America (50 % of all streptococcal IE) than other regions.

Gram Negative Endocarditis

Overall, Gram-negative agents cause 1–5 % of IE cases. Although *Pseudomonas* spp. and the Enterobacteriaceae are rare causes, the most common Gram-negative agents of native valve IE are members of the HACEK group. The HACEK group includes *Haemophilus spp*. (*H. paraphrophilus*, *H. parainfluenzae*, *H. aphrophilus*, *H. influenzae*), *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* spp. (*K. kingae*, *K. denitrificans*). These organisms are slow growing fastidious Gram-negative bacilli that cause IE with a subacute presentation.

In a recent analysis of the ICE prospective cohort study, HACEK organisms were found to be responsible for approximately 1 % of native valve IE [24]. When compared with non-HACEK IE, patients with HACEK IE were younger (47.4 vs 60.5 years), were less likely to have healthcare associated IE (1 % vs. 24 %, $p = <0.001$), less likely to have diabetes (8 % vs. 18 %, $p = 0.02$), and less likely to have cardiac vegetations on echocardiogram (71 % vs. 83 %, $p = 0.01$). Both in-hospital and 1-year mortality of patients with HACEK IE were significantly less

than that of patients with non-HACEK IE (4 % vs. 18 %, p = 0.001 and 11 % vs. 39 %, p = 0.001, respectively). HACEK IE patients were more likely to have a stroke complication, and were relatively more likely to have a hemorrhagic stroke. *Haemophilus* species were the most common HACEK organism, causing over half of the HACEK IE cases (40/77; 36 *Haemophilus parainfluenzae*, 4 other *Haemophilus* species).

Prosthetic Valve Endocarditis

Overall, prosthetic valve endocarditis (PVE) accounts for 10–30 % of all IE cases. The risk of endocarditis is highest in the first few months following surgery, with cumulative rates of 1.0–1.4 % at 1 year and 3.0–5.7 % at 5 years after valve replacement [25]. Nearly 60 % of cases of PVE occur after the first 60 days, with the median time of diagnosis of 83.5 days from valve implantation [26].

When compared to native valve IE, infection caused by coagulase negative staphylococci (CoNS) is much more common in PVE and IE due to Gram-negative bacilli, fungi and diphtheroids are also more common, while *S. aureus* and enterococci are recovered somewhat less often. A publication based on the ICE merged database found that *S. aureus* has now overtaken CoNS as the leading cause of PVE, responsible for 23.0 % of cases, compared to 16.9 % of infections caused by CoNS [26]. Patients with PVE were more likely to have a healthcare-associated infection compared to those with native valve IE (36.5 vs. 31.0 %, p = 0.01) and were more likely to develop intra-cardiac abscesses (29.7 % vs. 11.7 %, p = <0.001). Healthcare associated PVE was more common in the United States than other regions (trend towards significance) and associated with high rates of *S. aureus* and CoNS. The relative importance of the causative organisms depends on the timing of infection in relation to valve replacement surgery. We accept the definitions of early PVE as infection developing <60 days after surgery, late PVE as >12 months post-replacement and intermediate PVE as those cases occurring between 2 and 12 months.

Early PVE is most often related to intraoperative contamination of the surgical field or post-operative bacteremia. As such, the bacterial flora of the skin and hospital-associated pathogens predominate. Although patients with PVE have higher rates of CoNS infection and lower rates of *S. aureus* infection when compared with native valve IE, *S. aureus* is now the most common cause of early PVE, with MRSA involved in over half of cases [26] CoNS causes about 20 % of early PVE, but is a more significant pathogen in intermediate PVE, likely owing to its comparatively lower pathogenicity and sub-acute presentation [15]. Fungal organisms cause about 10 % of early PVE and Gram-negative bacilli cause approximately 5–10 % of early IE [26].

The distribution of etiologic agents causing late PVE is very similar to that for native valve IE, with the streptococci and *S. aureus* being the most frequently isolated organisms in most reported series. Patients with late PVE tend to have more CoNS and less *S. aureus* when compared to those with native valve IE. The

Gram-negative bacilli and fungi seen in the early period after valve replacement are recovered infrequently in late PVE. The HACEK organisms are isolated in up to 5 % of patients presenting with late onset PVE. In a review of 121 PVE cases over 34 years at a single center in Spain, Rivas et al. found that enterococci and *S. aureus* had overtaken the viridans group streptococci as the leading causes of late PVE when cases occurring between 1987 and 2003 were compared to those from 1970 to 1986 [27]. This change in microbiology was attributed to a higher proportion of hospital-acquired late PVE (22 % vs. 7 %) in recent years.

Intermediate-onset PVE includes a mixture of patients who are presenting relatively late with perioperatively acquired infections and individuals who have developed community-acquired endocarditis. As a result, the pattern of organisms causing PVE developing at this time is essentially an average of the proportions of cases caused by each group of organisms observed in early and late periods.

Intravenous Drug Users (IVDU)

The majority of IE in the IVDU group is caused by *Staphylococcus aureus*, which is responsible for 50–75 % of cases [2, 28, 29]. The streptococci and enterococci are the next most common organisms (7–10 %), with small percentages caused by CoNS, Gram-negatives, and *Candida* species. Polymicrobial IE is relatively common in the IVDU population, occurring in up to 5 % of cases. The use of saliva to "clean" needles or dissolve drugs prior to injection increases the risk of involvement of oral flora, such as *H. parainfluenzae*, *Eikenella corrodens* and *Streptococcus anginosius* group [30].

S. aureus most commonly causes right-sided (tricuspid) endocarditis in the IVDU setting. In the review of definite *S. aureus* native valve IE cases from the ICE merged database (1979–1999) published by Miro et al. 131/149 (88 %) cases in patients with a history of injection drug use involved the tricuspid valve [8]. Of 170 patients with right-sided *S. aureus* IE, 131 (77 %) provided a history of IV drug use. In the same study, MRSA was observed infrequently in the IVDU population: 6/43 (14.0 %) patients with MRSA IE used IV drugs compared to 136/248 (54.8 %) of those with infection caused by susceptible strains. However, increasing rates of MRSA in IVDU have been observed and outbreaks have been documented. One more recent small study of 33 patients with IVDU associated IE in the ICU found that 94 % of patients were infected with *S. aureus*, with 52 % of cases caused by MRSA [31].

Gram-negative IE in drug users can be caused by organisms that are encountered only rarely in non-IVDU patients. *Pseudomona aeruginosa* endocarditis is uncommon and occurs nearly exclusively in IVDU. *Pseudomonas aeruginosa* IE is usually right sided, but can involve left-sided valves, in which case the clinical course is more complicated [32]. A cluster of 36 cases of *Serratia marcescens* IE was seen among heroin users in San Francisco in the 1970s, with high associated mortality [33]. Other Gram-negative bacilli that are occasionally encountered in the setting of IV drug use include *Campylobacter fetus*, *Pasteurella* spp., *Brucella* spp., *Bordetella* spp., *Franciscella tularensis*, *Aeromonas hydrophila* and *Yersinia enterocolitica*..

Blood Culture Negative Endocarditis

Blood culture negative endocarditis (BCNE) rates have historically varied by study population, ranging from 2.5 % to 31 % [34]. These varied rates were observed among studies conducted in Spain (13.7 % [35]), London (12.2 %) and Sweden (20 %) [36]. A review of 26 case series published between 1993 and 2003 showed BCNE rates of about 10 % [4]. More recent data from the ICE database are consistent with these findings, with overall 10 % of patients having negative culture findings [2]. These rates are likely artificially high because of preceding antibiotic therapy. This effect was quantified in a retrospective review of 107 definite IE cases at a center in Spain, in which 14/20 patients with negative blood cultures had received prior antibiotics, leaving 6/107 (5.6 %) with BCNE [37]. Thus, excluding the cases confounded by antibiotic therapy prior to blood cultures, the frequency of "true" culture-negative endocarditis is much less, likely around 5 %. It is estimated that staphylococci or streptococci are implicated in 45–60 % of cases of BCNE when antibiotics precede blood culture by ≥3 days, as evidenced by studies using molecular diagnostic techniques [38]. The remaining 40–55 % of cases are thought to be caused by slow-growing and fastidious organisms such as *Coxiella burnetii*, *Bartonella* spp, *Brucella* spp, *Abiotrophia*, and *Listeria monocytogenes*.

By definition, standard culture methods are inadequate to allow detection of the causative agents of BCNE. The largest study to address the etiology of BCNE, published by Houpikian and Raoult involved 348 patients with suspected BCNE in France [39]. The authors attempted to determine the causative organism using a comprehensive serology panel, shell vial cultures and analysis of valve specimens by multiple methods, including PCR. These investigations showed that 167 cases (48 %) were due to *Coxiella burnetti*, 99 (28 %) due to *Bartonella spp*., 5 (1 %) due to rare fastidious organisms and 73 without an identified cause. Of the 73 undiagnosed cases. Fifty-eight had received antibiotics before the blood cultures leaving only 15 (4.3 %) unexplained cases.

Coxiella burnetti is reported to cause 3–5 % of all endocarditis in France, Israel and Great Britain [40, 41]. Underlying heart disease, immunocompromising conditions and animal contact are the major risk factors. Houpikian and Rault's review of BCNE cases in France included 167 cases of Q fever IE [28]. Of these, 53 patients (35 %) had underlying immunodeficiency and 139 (91 %) had valvular disease, including 27 with prosthetic valves, and 70 % had a history of contact with domestic animals. Reported outcomes of *C. burnetti* IE were previously poor with nearly two-thirds of patients developing congestive heart failure (CHF), but in this study only 38 % developed CHF and mortality was only 3 % (4/150). This improvement likely reflects better and more rapid diagnostics and more timely treatment.

Bartonella spp. are reported to cause 3 % of all endocarditis [40]. In a review of *Bartonella* endocarditis, 75 % of identified cases were caused by *B. quintana* and 25 % due to *B. henselae* [42]. Similar results were found in the study conducted by Casalta et al. in France. *Bartonella* species, diagnosed with serologic testing, caused 1 % of cases of definite IE. Of the eight total cases caused by *Bartonella* species, five (62.5 %) were caused by *B. quintana* and three (37.5 %) by *B. henselae* [41].

Epidemiology is distinct for the two species, with *B. quintana* seen in patients who were homeless or alcoholic with exposure to body lice and *B. henselae* in individuals with a history of exposure to cats [39].

Trophyrema whipplei, the Whipple disease bacterium, is an emerging cause of culture negative endocarditis. In a review of 35 cases published in 2001, the disease was predominant in men, occurred on previously healthy valves in 88 %, with a mortality rate of 57 % (20 of 35 cases) [43]. In a recently published German study in which cardiac valve tissue was cultured and assayed using 16S rRNA PCR followed by sequencing, T. whipplei was the fourth most common organism detected (16 cases, 6.3 %) among 255 of 1,135 assayed valves with evidence of bacterial infection, and the most common among the agents of BCNE [44].

Microbiologic Diagnosis

Blood Cultures

Blood culture remains the single most important investigation in a patient suspected of having infective endocarditis. If appropriately collected prior to antibiotic administration, blood cultures can be expected to yield growth of the causative organism in over 90 % of cases of infective endocarditis. Identification of the organism may allow the treating physician to determine the original source of bacteremia, and facilitates the choice of appropriate therapeutic agent(s) and treatment duration.

The Modified Duke Criteria include blood culture as one of the major diagnostic criteria. In order to fulfill the major microbiologic criterion, blood culture support for the diagnosis of IE is defined as isolation of "typical" microorganisms (viridans streptococci, *Streptococcus bovis*, HACEK group, *S. aureus*, community-acquired Enterococcus spp.) from at least two separate blood cultures, blood cultures persistently positive for "microorganisms consistent with IE", or a single culture positive for *Coxiella burnetti*. Rognon et al. [45] retrospectively applied the Duke Criteria to 179 IE cases over a 10-year period, and found blood culture to be the most important criterion in establishing a diagnosis of definite IE. Over half of 52 pathology-proven IE cases in this series that were classified as "definite IE" using the Duke Criteria before pathology results were available would have been designated as "possible IE" or "rejected" in the absence of blood culture data.

Intravascular infections including IE are characterized by the presence of continuous bacteremia, and in the majority of IE cases most or all of the pre-therapy blood cultures will be positive. Demonstration of continuous bacteremia by definition requires more than one blood culture result, and the yield of blood cultures is dependent on both the number of cultures obtained and the volume of blood cultured. The effects of blood draw volume and timing on culture yield were investigated by Li et al. who analyzed data from all blood cultures drawn on patients in the Veterans Administration Medical Center in Seattle over an 18 month period [46]. For the majority of patients, one blood culture set consisted of 20 ml divided equally between one aerobic and one anaerobic bottle. The investigators found that a second

20 ml blood draw increased blood culture yield by 17–20 %, and that this additional pick-up rate was the same whether the second culture set was drawn immediately after the first, or at any other time within the next 24 h. The addition of a third 20 ml draw within 24 h further increased the blood culture yield by 10 %. Most experts agree that three separate blood culture sets (20–30 ml in two to three bottles) should be sufficient to detect over 95 % of IE associated bacteremias in the absence of preceding antibiotics [47]. In addition to maximizing the diagnostic yield, the practice of obtaining multiple blood cultures can also be useful in determining whether a positive result represents contamination, in which case only one culture would be expected to grow the contaminating organism.

The timing of blood culture draws depends on the overall clinical status of the patient. In the setting of a septic patient with suspected acute IE, therapy should not be delayed to allow blood cultures to be drawn, and two to three separate venipunctures can be performed a few minutes apart while arrangements are made for initiation of empiric antibiotic therapy. This approach is supported by the data reported by Li et al. (see above), who found that the rate of additional positive cultures from a second blood culture set was independent of its timing. Conversely, a clinically stable patient who has been ill for weeks can safely remain off antibiotics for at least 24 h while serial blood cultures are obtained. In patients who have received antibiotic therapy before being worked up for IE, blood culture media containing antibiotic-inactivating resin should be used, and in selected circumstances withdrawal of antibiotics to allow cultures to be drawn would be appropriate.

Newer blood culture media and modern automated blood culture systems represent a significant improvement over older methods. The majority of non-fastidious organisms will trigger a positive signal in blood culture instruments within 72 h. Most clinical laboratories incubate routine blood cultures for 5 days, as most positive cultures appearing after longer incubation represent contaminants. However, some fastidious organisms that cause IE including the HACEK group, *Brucella* species and others may require longer periods of incubation before triggering automated blood culture systems. The majority of fastidious organisms causing IE will grow within 10 days, but others (e.g. *Bartonella* species) can require several weeks to grow and may not trigger blood culture instruments even when they do grow. In the setting of clinically suspected IE, therefore, blood culture specimens require special management within the laboratory. Approaches vary among institutions and include extended incubation of the bottles collected from patients identified as suspect IE cases, terminal subcultures of negative blood culture bottles to solid culture media at the end of the planned incubation period, or a combination of both. Highly specialized culture techniques can be used for isolation of specific rare causes of IE such as *Coxiella burnetti*, *Bartonella* species and *Tropheryma whipplei* when they are suspected; these methods and pertinent biosafety considerations have been reviewed by Houpikian and Raoult [48].

Candida species cause approximately 50 % of proven cases of fungal endocarditis. Although blood cultures are thought to have poor sensitivity for detection of candidemia, more specialized blood culture media have no advantage over standard blood culture bottles for detection of *Candida* species. Special fungal blood culture

media such as Bactec Myco-F-lytic bottles are superior in supporting growth of filamentous fungi such as *Aspergillus* species, and could be considered for use in immunocompromised patients or known IV drug users with suspected IE. The lysis-centrifugation (Isolator) method is superior to other available processes for detection of *Histoplasma capsulatum* from blood samples. Emboli leading to operative intervention are seen relatively commonly in cases of fungal endocarditis given the typically large vegetation size. Because blood cultures are frequently negative in fungal endocarditis, these emboli can provide crucial information about the causative organism, and they should be cultured and stained for fungal organisms when they are encountered and removed.

Methods for Diagnosis in Culture-Negative IE

Serology

Serologic testing can be useful in determining the cause of IE in true culture-negative cases, which are usually caused by organisms that are difficult to culture including *Coxiella burnetti*, *Bartonella* spp., *Chlamydia* spp. and *Legionella* species. The immune response to *C. burnetti* involves development of antibodies against phase 1 and phase 2 antigens. In acute infection, both IgM and IgG antibodies develop against phase 2, with only IgM against phase 1. Endocarditis is a manifestation of chronic Q fever, which is characterized by high anti-phase 1 IgG titers. Positive Q fever serology, defined as a phase 1 IgG titer of >1:800, is listed as one of the major modified Duke criteria. A *Bartonella* antibody titer of 1:1,600 has been reported to have a positive predictive value of 88 % for *Bartonella* IE [48]. However, titers may not be reproducible given lot-to-lot variability of antigen preparations used for testing. Patients with *Bartonella* infection also frequently develop cross-reacting antibodies that result in false positive *Chlamydia* spp. serology. Additional assays to be considered in culture negative IE cases include serologic studies for *Brucella* species and *Legionella* serology or urinary antigen testing.

Molecular Diagnostics

In spite of limitations including the potential presence of PCR inhibitors in clinical samples and the possibility of sample to sample contamination, molecular amplification methods can be useful in establishing the cause of IE. To date, PCR methods have been applied with most success to surgically excised valve tissues.

Because several possible etiologic agents are normally being considered in cases of culture negative IE, the most commonly applied approach involves the use of "universal" PCR primers. These primers are directed against highly conserved sequences that are common to all bacteria, thereby allowing amplification of genetic material from virtually any species of bacteria. The segment to be amplified (most often genes encoding for 16S rRNA) is chosen based on the presence of intervening regions with sequence variability, allowing identification of organisms by sequencing of the PCR product with subsequent comparison of the result to a sequence database. Podglajen et al. (EID 9: 1543–7, 2003) evaluated 16S rDNA PCR/

sequencing of valve tissues resected from 36 patients with clinically definite IE by the modified Duke criteria. PCR identification was possible in 26 of 30 cases with positive blood cultures prior to surgery, and in 5 of 6 culture negative cases (4 *Bartonella* species, 1 *S. gallolyticus*). Another study using 16s PCR identified the microbial etiology in 21 % of patients, half of whom had negative blood cultures [49]. In a recently published German study, 16S rRNA PCR followed by sequencing was used to detect bacterial infection involving valves from 84/878 consecutive unselected patients and from 171/257 patients with suspected or possible IE [44].

When a particular diagnosis is suspected, species-specific PCR assays can also be employed. Protocols have been developed for many of the agents of culture negative IE including *C. burnetti*, *Bartonella* species, *Brucella* species, *Tropheryma whipplei*, *Chlamydia* spp. and *Legionella* species [48].

Histology

In cases of suspected IE for which the causative organism is not known prior to surgical intervention, heart valve material should be submitted for further investigation by histology and culture. Because of preceding antibiotic therapy, bacterial cultures of valve tissue obtained at surgery are positive in only a minority (10–15 %) of cases. Histologic examination of excised valve tissue can be used both to confirm the diagnosis of IE and to determine the probable causative organism. Pathologic findings compatible with IE are considered to be evidence of definite endocarditis within the Duke criteria.

Routine stains including H&E and tissue Gram stains will show infiltrates of inflammatory cells and can allow common causative organisms to be visualized respectively. Special stains including Warthin-Starry (*Bartonella* spp.), Periodic acid-Schiff (*T. whipplei*, fungi), Gimenez (*C. burnetti*, *Legionella* spp.) and Gomori menenamine silver (fungi) stains are needed for detection of less common causes of IE.

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Prophylaxis of Endocarditis

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Abstract

Infective endocarditis is a potentially fatal disease. Even with appropriate treatment, morbidity and mortality can be significant. Prevention of this condition is of paramount importance and antibiotic prophylaxis has become an acceptable means by which to prevent endocarditis from bacteria prone procedures. This chapter provides an overview of the pathogenesis of infective endocarditis and current strategies for prophylaxis.

Keywords

Infective endocarditis • Antibiotic prophylaxis • Bacteremia • Vegetation

Key Points

1. Guidelines exist for antibiotic prophylaxis against infective endocarditis (IE). There is little robust clinical evidence supporting proof that antibiotic prophylaxis decreases the immediate subsequent risk for infective endocarditis. The strength of the evidence rests on animal studies, which may or may not accurately reflect human disease, as well as on expert opinion. Nonetheless, a priori algorithms have been proposed for the health care practitioner, based on patient risk factors for disease as well as the likelihood of bacteremia from a given procedure.

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2. The mechanism(s) by which antibiotics effect prophylaxis remain unclear, but may relate to interfering with bacterial adherence to a fibrinous valvular vegetation and/or clearance of pathogen after such adherence.
3. Current recommendations provide both oral and intravenous regimens, the latter for patients unable to take orally. There is no evidence for superiority of one regimen over the other. The recommendations also provide alternatives for patients with a history of allergy to b-lactams. The suggested regimens may decrease albeit not eliminate the risk of IE.
4. Given that the microbiology and the antimicrobial resistance patterns of the most common pathogens causing infective endocarditis are evolving, guidelines will need to be regularly revised.

Infective endocarditis (IE) is a potentially fatal disease. Even with appropriate antimicrobial treatment, mortality rates range from 10 % to 25 % [1]. As such, prevention of disease is very important. Guidelines have been created to estimate which patients with certain risk factors would most benefit from IE prophylaxis. However, there have been no controlled, clinical trials to demonstrate the protective efficacy of antibiotic regimens in the prophylaxis of IE in humans. Such trials will not likely ever be done for two major reasons: From a study design perspective, the relative rarity of IE developing after a single transient bacteremic episode would require ≥6,000 patients, all with predisposing cardiac disease [2]. Secondly, such a study would also be considered unethical. As such, the guidelines that have been devised have been based on the efficacy of IE prophylaxis in animal models, previous antimicrobial susceptibility testing data of the most likely pathogens, pharmacokinetic studies, and studies on the incidence and prophylaxis of procedure-related bacteremias. Thus, the evidence for these recommendations is at the level of expert opinion, the efficacy is not 100 %, and the changing microbiology of IE may necessitate updated new recommendations.

The fundamental step in the pathogenesis of IE is the development of bacteremia, with subsequent seeding of a previously-damaged endocardial surface. Experimental studies suggest that valvular endothelial damage leads to platelet and fibrin deposition and the formation of a nonbacterial thrombotic vegetation. Circulating bacteria can then adhere to these lesions and multiply within the platelet-fibrin complex, leading to an infected vegetation. Dental treatment has traditionally been considered the major cause of the bacteremia that leads to IE [3], mainly because of historical studies that demonstrated a high frequency of bacteremia after various oral invasive procedures, as well as because of previous studies documenting the viridans group streptococci (VGS, the predominant members of the oral microflora) as the leading cause of IE. The initial recognition of a relationship between viridans streptococcal IE and dental procedures is attributed to Horder in 1909 [2, 3]. In 1923, Lewis and Grant proposed the hypothesis that abnormally structured heart valves may contribute to the development of IE in healthy adults by trapping and retaining organisms from the transient bacteremia [4]. In 1935, Okell

and Elliott, in a series of 138 patients, demonstrated the presence of bacteremia related to tooth extraction; in 64 % of the cases, the isolate was a *Streptococcus* spp [5]. Another study, in 1937 by Burket and Burn [6], confirmed the biological plausibility of the oral cavity as the source of bacteremia when they painted the gingival crevices of 90 patients with *S. marcescens* (which was felt to be non-pathogenic, at the time) before dental extraction. Subsequent to the procedure, 20 % of the blood cultures had recovered the organism. One study demonstrated a "dose-dependent"-like effect, with a significant correlation found between the number of teeth extracted and subsequent positive blood cultures [7]. Thus, it has become well established that bacteremia may occur after dental procedures that compromise mucosal surfaces, especially dental extractions and gingival surgery [8]. This bacteremia, however, is transient, lasting typically no more than 15–30 min [9, 10], as well as low-grade (usually <100 colony forming units/mL of blood) [9]. Transient asymptomatic bacteremia also occurs after a variety of other procedures and manipulations, particularly those associated with trauma to the mucous membranes of the respiratory, esophageal, gastrointestinal (GI), and genitourinary (GU) tracts. If the bacteremia following these procedures is a major cause of IE, in theory, maneuvers that decrease the magnitude and/or the duration of this bacteremia could prevent the development of IE, in patients at risk for the disease.

Prophylaxis of Experimental Endocarditis

The evidence supporting the use of prophylactic antibiotic regimens in humans derives from its proven efficacy in animal models. Experimental IE has been typically produced in rabbits (e.g. New Zealand white rabbit [11]) or rats (e.g. female Wistar rats [12]) via catheter-induced damage to cardiac valves and subsequent intravenous challenge with various amounts of bacterial inocula. These experimental conditions allowed IE to be more effectively and reliably induced than in other models, with a predictable time of onset, thus facilitating analyses. Antibiotics are administered at the same or similar weight-based dose as in humans. The experimental IE is followed with serial blood cultures, with eventual sacrifice of the animal and quantitative culture of the valvular vegetations. Such experiments have helped to elucidate a hierarchy in the infectivity of the pathogens [13]. Adherence of circulating bacteria to the valvular endothelium/thrombotic vegetation is the most critical factor early in the pathogenesis of infective endocarditis [14, 15]. Indeed, *S. aureus*, the VGS, and *Enterococcus* spp., which collectively account for the majority of cases of IE, do so specifically because of virulence factors that permit ligand-receptor interactions between bacterial surface components and constituents of damaged valves. However, the inoculum size (i.e. magnitude of the bacteremia) [13, 16], as well as the duration of the bacteremia after inoculation, are also important determinants of infectivity [13].

Based on such models, antimicrobial prophylactic regimens should be predicted to be efficacious by interfering with one or more of these factors. A previously held belief was that antibiotics prevented IE via elimination of the post-procedure transient bacteremia by killing the microorganisms before, as they entered, or while

they were circulating in the bloodstream, before they seeded the endocardial surface. It seems unlikely, however, that any prophylactic agent could prevent the actual lodgement of circulating bacteria on a suitable nidus: seeding of the vegetation occurs within 30 min of the bacteria entering the circulation [17], while antibiotics usually require hours to exert their antibacterial effect [18]. The notion that prophylaxis is mediated by a bactericidal effect is the result of misinterpretation of negative blood culture results in earlier studies, which resulted from the continued elimination of the bacteria by the antibiotic after transfer of blood (and antimicrobial) to culture media. Indeed, animal [19, 20] and human [21–24] studies with improved culture methods confirm that prophylaxis does not consistently and significantly reduce the incidence of post-procedure bacteremia. Therefore, the operative mechanism by which antibiotic prophylaxis is successful occurs by other means. Prevention of bacterial adherence has been proposed to explain the success of experimental prophylaxis. It was previously demonstrated that inhibitors of cell wall synthesis, such as β-lactams [25] and glycopeptides [20], have the capacity to decrease the adherence of bacteria to platelet-fibrin clots in vitro, possibly by inducing the release of lipoteichoic acid [26]. However, Moreillon and colleagues [27] elegantly demonstrated in the rat model of amoxicillin prophylaxis that inhibition of adherence was not an important mechanism, as the decrease was very marginal and did not prevent infection. Alternatively, successful prophylaxis is mediated by the ability of the administered antibiotic to facilitate elimination of bacteria subsequent to attachment to the vegetation. Studies have demonstrated that such an effect likely occurs by the prolonged inhibition of bacterial growth after inoculation. The determinants of the inhibitory effect include characteristics of the organism (e.g. tolerance), the challenge dose (i.e. the ID_{90}, that is, the minimum inoculum producing IE in 90 % of control animals), and the duration of time the serum concentration of the antibiotic remains above the MIC of the pathogen. Studies have shown that for inocula $>ID_{90}$, the longer the duration of growth inhibition, the greater the likelihood of successful prophylaxis [27–29]. Thus, when VGS or enterococci tolerant to amoxicillin are inoculated into the rat model, single-dose prophylaxis with amoxicillin was efficacious only at the ID_{90} [16, 30, 31]. Against higher inocula, multiple doses of amoxicillin for VGS or amoxicillin and gentamicin for enterococci were necessary for successful prophylaxis [32]. Pharmacokinetic properties inherent to the administered antimicrobial assist in determining the dosage scheme to maximize growth inhibition. For example, single-dose aminopenicillin prophylaxis for *Enterococcus* spp. is not likely effective because blood antibiotic levels are not sustained long enough to completely eliminate the bacteria from the vegetation, whereas single-dose teicoplanin was efficacious [33]. For organisms with demonstrated in vitro susceptibility, amoxicillin has a duration of inhibition of ≥10 h [13]. These features identified from experimental models have thus allowed recommendations for prophylaxis in humans to be devised. What remains unclear, though, is the mechanism by which prolonged serum inhibitory activity eliminates bacteria adherent to vegetation. It had been postulated that growth-inhibited surface organisms would be susceptible to post-antibiotic leukocyte-enhanced opsonophagocytic activity. Animal studies [28], including a neutropenic endocarditis model [16], have

demonstrated that polymorphonuclear leukocytes do not play a role in eliminating bacteria adhered to the vegetation. Therefore, the mechanism by which antibiotic prophylaxis is effective remains undefined.

Although the principle of prophylaxis dictates to administer the antimicrobial agent before commencement of the procedure, experimental studies have demonstrated that prophylaxis may also be effective if given shortly after the procedure. In the rat model, efficacy of prophylaxis could still be maintained if the antibiotic was administered within 2 h of the bacteremia-inducing procedure [16]. Administration of antimicrobials at 4–6 h post-procedure was not effective in preventing IE [16, 34]. As well, although the dogma in the treatment of IE is to use a bactericidal antimicrobial regimen, this philosophy may not necessarily apply to IE prophylaxis, particularly given the lack of evidence that bactericidal properties mediate prophylaxis. In fact, animal studies have confirmed that while bactericidal antimicrobial agents are required for large inocula, bacteriostatic antimicrobial agents are effective for inoculum sizes $\leq ID_{90}$ [35]; hence, the rationale for agents, such as the macrolides (e.g. clarithromycin [36]) and lincosamides (e.g. clindamycin [37]) for penicillin allergic patients.

The applicability of the results from animal studies to humans remains debated. Major issues relate to the size of the inoculum used and the route of challenge. The bacteremia post-procedure in human is estimated to be $<1 \times 10^2$ CFU/mL of blood [9], whereas in experimental models, the inocula used is in the order of 10^6–10^8 CFU/mL [38]. Such large inocula are required to ensure that IE consistently developed in all (90 %) of tested animals, but it may lead to an inaccurate model of disease. Furthermore, most animal models are challenged via the intravenous route to mimic a presumed mucosal micro-trauma-related bacteremia, again potentially introducing sources of error. Lastly, the experimental models used (i.e. rabbits, rats) may not reliably reproduce the pharmacokinetics of the antibiotics in humans, since these small animals clear drugs from their blood more quickly than humans [2].

Patients at-Risk

The American Heart Association (AHA) [39, 40], British Cardiac Society (BCS) [41], and French [42] guidelines stratify cardiac conditions into high- and moderate-risk categories, based on studies that have shown that certain types of structural heart disease are associated with higher risks of developing IE. In 2007 the AHA released revised its guidelines [40] for prophylaxis for infective endocarditis. In these guidelines the number of persons deemed to be at risk of IE is less than previously recognized as the authors identify that:

1. Infective endocarditis is more likely to occur from frequent microbial exposure from random bacteraemias from daily activities than from undergoing dental, GI, or GU procedures
2. Prophylaxis may only actually prevent a small number of persons who undergo dental, GI, or GU procedures

3. There is a high risk of complications of antibiotic therapy, which may exceed the benefit of antimicrobial prophylaxis
4. Maintaining optimal status of the oral cavity may decrease the risk of bacteraemias arising from the oral cavity arising from daily activities, and is likely more important than antimicrobial prophylaxis for IE

Although the exact degree of risk for IE for certain cardiac lesions is difficult to assess, conditions deemed high-risk are inferred from the relative frequencies that particular cardiac lesions occur in a large series of patients with IE. For example, the incidence rates for IE are highest for patients with a previous history of native valve endocarditis (300–740/100,000 patient-years) and for patients with mechanical or bioprosthetic cardiac valves (300–600/100,000 patient-years); these rates are approximately 60–185-fold higher than that of the general population [43]. Presumably, damaged valvular endothelium from a previous IE episode predisposes to subsequent nidus formation for a second episode. In the case of prosthetic valves, IE can occur by seeding of the foreign-body valvular apparatus. Patients with congenital cyanotic cardiac disease (i.e. single ventricle states, transposition of the great vessels, tetralogy of Fallot) also have higher incidence rates of IE, estimated at 100–200/100,000 patient-years; this represents a rate approximately 50-fold higher than that of the general population [43]. The increased incidence of disease in this group is likely related to turbulent, high-velocity flow and stagnant eddies from right-to-left shunts. It should be noted that stratification of cardiac conditions is also determined not only by risk of developing IE, but on the attendant morbidity or mortality should IE develop. Non-cyanotic congential heart disease includes conditions such as bicuspid aortic valve and coarctation of the aorta, as well as atrial septal defect (ASD), ventricular septal defect (VSD), and patent ductus arteriosus (PDA). Surgical repair of the latter three conditions has been reported to be associated with a negligible risk for IE (i.e. no greater risk than the general population). It should be noted, however, that the risk becomes negligible typically 6 months after surgical correction, provided that no other abnormality exists and no residual shunt is found by Doppler echocardiography, during which time endothelialisation of the material is complete [13, 44]. For repairs in which there are residual defects at or near the site of prothetic material, endothelialisation is impaired; thus, these conditions may be associated with increased risk, necessitating consideration of prophylaxis.

Procedures Producing Bacteremia

Dental Procedures

High-risk procedures, in this context, are those procedures associated with a high incidence of bacteremia, with "bacteremia" acting as a surrogate marker for IE risk. There is much controversy, however, about the role of invasive procedures, especially dental procedures, as the causative event leading to IE. The evidence for causality of

odontogenic bacteremia is circumstantial, based on a temporal relation between dental procedures and subsequent manifestation of disease, and the identification of oral microflora (predominantly VGS, occasionally bacteria of the HACEK group) as the major pathogens. However, the mere presence of a temporal relation does not constitute proof of causation, particularly because of the influence of reporting bias: dental procedures are extremely common (e.g. 62.8 % of adults aged 18–64 reported ≥1 dental visit within the last year in 2002 [45]), whereas IE is relatively uncommon (e.g. 3.3 cases/100,000 population/year in the United Kingdom, with similar figures for the United States [46] and France [42]). Furthermore, identification of the same type of bacteria in the mouth and in cardiac vegetations supports the hypothesis that the offending pathogens derive from a mucosally-lined source, but it again may be unfairly blaming dental procedures. There is no doubt that certain odontogenic procedures may occasionally cause transient bacteremias that lead to IE. However, it has been estimated that dental treatment causes no more than 4 % of all cases of IE [47]. A population-based, case-control study by Strom and colleagues comparing 273 hospitalized adults with IE and 273 matched outpatient controls found that the calculated risk for IE was no higher in the first month after the dental treatment than after 2 or 3 months, demonstrating the absence of an association between the two events [48]. Pallasch, using a mathematical model, has estimated that the absolute risk rate for IE from a single dental treatment in the general population to be 1/14,258,714 dental visits [49]. Therefore, although it is convenient to think that gingival instrumentation with bleeding permits oral microflora to access the circulation and establish IE, the evidence that dental manipulation causes IE is weak. How then do the oral bacteria end up on the vegetation? The history of a "recent" dental procedure may, in fact, be a surrogate marker of poor oral hygiene. Patients with poor oral hygiene are at increased risk for bacteremia in the absence of dental procedures, with the size of the inocula likely related to the degree of gingival inflammation [38, 39]. Such transient bacteremia occurs with daily, trivial activities, such as chewing or tooth brushing. Guntheroth [47] devised a mathematical model to determine the cumulative exposure to bacteremia (CEB) resulting from "physiologic" activities (e.g. mastication, brushing teeth), and compared it to that from a "single dental extraction". It was estimated that over a period of 1 hypothetical month, the physiologic CEB was 5 370 min, in contrast to 6 min for surgical CEB. The CEB method was modified by Roberts [38] to include the percentage prevalence of bacteremia related to the dentogingival manipulative procedure (p), the intensity of bacteremia (i, in colony-forming units (CFU)/mL), the length of the bacteremia (t), and the frequency of bacteremia-inducing events estimated for a 1-year period (f). The modified CEB (in CFU min/mL/year) for various activities were as follows: toothbrushing: 6,323; flossing: 3,285; chewing: 3,285; single extraction of a permanent tooth: 0.014. To estimate the relative bacteremic challenge produced by one procedure versus another, the cumulative exposure index (CEI) was calculated, using the single deciduous molar extraction as the standard procedure, as it is widely recognized as causing a "significant bacteremia" [38]. Roberts demonstrated that the CEI for toothbrushing twice a day is 154,219 times greater than that of an extraction. He concludes that dental surgical procedures pose a low risk for IE. Rather, everyday procedures are

Table 5.1 Cardiac conditions for which antibiotic prophylaxis with dental procedures is reasonable

Cardiac conditions for which antibiotic prophylaxis with dental procedures is reasonable[a]
1. Prosthetic heart valves (includes metallic, bioprosthetic, and homograft valves)
2. Previous endocarditis
3. Congenital heart disease (CHD) that include
(a) Unrepaired cyanotic CHD (including palliative shunts and conduits)
(b) Completely repaired CHD with prosthetic material or device (placed surgically or by catheter intervention), during the first 6 months after the procedure
(c) Repaired CHD but with residual defects at or adjacent to the site of a prosthetic device/material
4. Cardiac transplantation recipients who develop cardiac valvular abnormalities

[a]Modified from Table 5.3 reference [40]

much more likely (e.g. 8,000-fold higher risk) to cause transient episodes of low-grade bacteremias, that with time, results in a cumulative risk sufficient to cause IE. The mechanism by which this occurs is proposed to be via small movements of the tooth within the alveola, producing intermittent positive and negative pressures that cause microscopic gingival vascular damage, with subsequent aspiration of organisms into the circulation [38].

Further supporting the refutation of dental procedures as a major cause of IE are studies which raise doubt about the efficacy of pre-dental treatment antibiotic prophylaxis. In a nationwide, case-control study in the Netherlands, van der Meer and colleagues [50] estimated that the protective efficacy of chemoprophylaxis was 49 % for first-ever IE occurring within 30 days of a procedure. The same group, in a prospective, population-based case study, demonstrated that medical and dental procedures cause only a small fraction of IE cases; furthermore, full compliance with prophylaxis might have prevented IE in 47 (17.1 %) of 275 patients with late prosthetic or native valve IE involving a previously known cardiac lesion who underwent a procedure with an indication for prophylaxis. For an incubation period of 30 days, prophylaxis might have prevented IE in 23 (8.4 %) of these 275 patients, or 5.3 % of all patients with endocarditis (i.e. total of 427 cases) [51]. The case-control study by Strom et al. [48] also challenges the usefulness of IE prophylaxis, concluding that even if prophylaxis was 100 % effective, it would reduce the incidence of IE by only 2.0 cases per one million person-years. A case-control study in France by Lacassin and colleagues [52] demonstrated that dental procedures were not associated with an increased risk for IE, and that antibiotic prophylaxis provided a protective efficacy of only 46 %, which was not statistically significant. These studies provide evidence suggesting that from a public health perspective, the routine use of antibiotic prophylaxis will only prevent a limited number of cases and is thus not justified. However, three points need to be emphasized: Firstly, some of the studies [48, 52] still demonstrated an association between procedures in at-risk patients and the subsequent development of IE. Secondly, the studies were population-based, case- or case-control study design, raising the possibility of ecological fallacy in analysis interpretation, where the effect of antibiotic prophylaxis at the population level may be negligible, but may continue to be worthwhile for the individual patient [53]. Indeed, the study by van der Meer [50] admits that the small

Table 5.2 Dental procedures and conditions for which prophylaxis of endocarditis may or may not be required in patients with the conditions listed in Table 5.1

Indications	Procedures and conditions
Dental procedures for which prophylaxis for endocarditis is reasonable in persons with the conditions listed in Table 5.1	All dental procedures for which there will be manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa[a]
Dental procedures and events which do not require prophylaxis for endocarditis	Routine anesthetic injections through noninfected tissue,
	Dental radiographs,
	Placement of removable prosthodontic or orthodontic appliances,
	Adjustment of orthodontic appliances,
	Placement of orthodontic brackets,
	Shedding of primary teeth,
	Bleeding from trauma to the lips or oral mucosa

[a]Modified from Table 5.4 from Ref. [40]

Table 5.3 Recommended prophylaxis regimens for adults for a dental procedure

Route	1st line	2nd line
Oral	Amoxicillin 2 g po 1 h before procedure	Allergic to penicillin: (1) For non-type I (IgE)-mediated allergic reactions: cephalexin or cefadroxil 2 g po 1 h before procedure Or (2) Clindamycin 600 mg po 1 h before procedure Or (3) Clarithromycin or azithromycin 500 mg po 1 h before procedure
Unable to take oral medication	Ampicillin 2 g IM/IV within 30 min before procedure Or Cefazolin or ceftriaxone 1 g IV within 30 min before procedure	Allergic to penicillin (1) For non-type I (IgE)-mediated allergic reactions Cefazolin or ceftriaxone 1 g IV within 30 min before procedure Or (2) Clindamycin 600 mg IV within 30 min before procedure

Cephalosporins (e.g. Cefazolin; Ceftriaxone) should not be used in persons with a history of anaphylaxis, angioedema or urticarial to penicillins

number of cases entered into the trial resulted in a small power that may have failed to detect a significant protective effect, and that there was the possibility that some subgroups may benefit from the use of prophylaxis. Lastly, case-control studies, with all its merits, are not the strongest level of evidence on which current medical decision making is based. These studies do, however, emphasize the importance of carefully identifying at-risk patients that will most benefit from prophylaxis. Furthermore, they underscore the need for more robust studies.

In the absence of a conclusive, prospective, randomized study, expert committees now believe that dental procedures are uncommon causes of IE and have further

questioned the efficacy of antimicrobial prophylaxis to prevent IE in patients who undergo such procedures. Consequently, the BSAC revised their recommendations for peri-dental antimicrobial prophylaxis of IE in 2006 [54] and the AHA did likewise in 2007 [40]. Although anaerobic bacteria are the principal components of the oral microflora and are released into the circulation after dental/oral procedures [21, 55], they rarely cause IE. The predominant organisms of concern are the VGS, which are the targets for prophylaxis. A fundamental component of prophylaxis is good oral hygiene through daily, proper self-care and regular professional care; this aspect is recommended by expert committees [40, 54]. Although antiseptic mouth rinses (e.g. chlorhexidine- or povidone-iodine-based) may reduce the incidence and/or magnitude of bacteremia prior to dental procedures [56], such rinses do not permeate beyond 3 mm into the gingival sulcus and thus do not eradicate bacteria at the entrance into the systemic circulation [57], raising the need by some for more supportive evidence of benefit.

Systemic antibiotic prophylaxis is reasonable for patients with the at-risk conditions listed in Table 5.1, and who will be undergoing any dental procedure that involves the gingival tissues or periapical region of a tooth, as well as those procedures that perforate the oral mucosa (Table 5.2). It should be emphasized, however, that while antibiotic prophylaxis is reasonable in these circumstances, its effectiveness is unknown. Table 5.2 also highlights the procedures and conditions for which prophylaxis is not deemed to be necessary.

In this restricted patient population, antimicrobial prophylaxis should be directed towards viridans group streptococci (VGS). Antimicrobial surveillance data have demonstrated that the VGS may demonstrate a spectrum of antibiotic resistance, a phenomenon observed in isolates from patients with serious underlying illnesses (e.g. febrile neutropenia), as well as less morbid patients. However, the impact of such resistance in VGS on effectiveness of antimicrobial prophylaxis of IE is unknown. Consequently, in the restricted patient population for whom antibiotic prophylaxis is considered reasonable, the options have not changed and are listed in Table 5.3 [3, 13, 39, 40]. In cases where multiple consecutive dental interventions are required, repeated prophylaxis is also required. Because repeated single-dose antibiotic administration may select for resistant organisms which persist in the mouth, multiple procedures are recommended to be carried out in one sitting (if possible) or separated by 9–14 days [39–41].

Other Procedures: Respiratory, Gastrointestinal, Genitourinary

Streptococcal bacteremia can also occur via manipulation of other mucosal surfaces lining the upper respiratory tract (e.g., tonsillectomy [58–60], mastoidectomy [61], septoplasty [62]). As such, the AHA deems it reasonable that patients with at-risk factors (Table 5.1) who undergo an invasive procedure of the respiratory tract (defined as incision or biopsy of the respiratory mucosa, e.g. tonsillectomy, adenoidectomy) receive one of the regimens listed for dental procedures (Table 5.3) [40, 54]. The European Society of Cardiology (ESC) recommendations are in

agreement with these recommendations [40, 54, 63]. The BSAC similarly considers tonsillectomy and adenoidectomy as requiring prophylaxis, and further adds any surgical procedures of the upper respiratory tract and cosmetic piercing of tongue or oral mucosa [54]. Of note, the BSAC considers nasal packing/nasal intubation an at-risk procedure for staphylococcal bacteremia and recommends flucloxacillin at induction or anesthesia or just prior to procedure [54]; this recommendation is not considered in the AHA or ESC recommendations.

The updated recommendations for antibiotic prophylaxis of IE in gastrointestinal (GI) procedures vary. The AHA and ESC recommend against the administration of antibiotics solely to prophylaxis against IE in patients who undergo GI tract procedures, including diagnostic esophago-gastro-duodenoscopy or colonoscopy. Their rationale is, as with dental procedures, there is no published data conclusively demonstrating a link between GI procedures and the development of IE, nor any data that antimicrobial prophylaxis prevents IE in association with these procedures [40].

On the other hand, the BSAC notes that bacteremia may be associated with some GI interventions. The esophageal procedures with the highest associated bacteremia rates are sclerotherapy of esophageal varices and esophageal dilation of a stricture [64, 65]. Earlier studies have demonstrated rates of 31 % for sclerotherapy (61 patients) and 45 % for dilation (59 patients), in which the majority of organisms were VGS [64]. More recent prospective studies support these rates. Zuccaro and colleagues [66] performed blood cultures before and after stricture dilation in 103 patients without valvular heart disease and in a control group of 50 patients undergoing upper endoscopy without dilation. They demonstrated that 21 % (22/103) of patients undergoing dilation had positive blood cultures, with VGS as the predominant isolate. Among 100 procedures in 86 patients undergoing esophageal dilation by Nelson et al. [67], 22 (22 %) were associated with a positive post-dilation blood culture. Although these episodes of bacteremia post-endoscopy are short lived (i.e. typically <30 min), their clinical significance is unclear (as it is with other post-procedure bacteremias). One prospective comparative study randomizing 39 patients to prophylaxis (i.e. cefotaxime, 19 patients) or no antibiotic (20 patients) revealed a significant reduction in post-procedure bacteremic episodes in the group receiving antibiotic (5.3 % vs. 31.6 %, respectively; $p=0.04$) [68]. However, a recent review of the infectious disease complications of GI endoscopy has revealed only two cases of IE after sclerotherapy have been reported, one involving a prosthetic valve (despite prophylactic administration of appropriate antibiotics) and another on a native valve [65]. Nonetheless, current guidelines continue to recommend prophylaxis for these procedures. Endoscopic variceal ligation ("banding") has replaced sclerotherapy as the procedure of choice in the management of varices because of its greater efficacy and fewer associated complications. In a historical cohort study comparing the rates of transient bacteremia between the two procedures, positive blood cultures occurred more frequently in the sclerotherapy group (17.2 %) than in the ligation group (3.3 %, $p<0.03$) [69]. A review of seven studies addressing this issue, including the one mentioned, reports bacteremia rates associated with EVL ranging from 0 % to 25 %, with a mean frequency of 8.8 % [65]. The

attributable risk of IE to endoscopic variceal ligation is unknown, as no cases have currently been reported in the English literature.

Endoscopic retrograde cholangiopancreatography (ERCP) has become a commonly performed procedure. The diagnostic and therapeutic utility of ERCP has been well demonstrated for a variety of disorders, including the management of biliary obstruction, predominantly due to choledocholithiasis or biliary malignancies. The rate of bacteremia after contrast injection or instrumentation of unobstructed pancreatic or bile ducts ranges from 0 % to 15 % (mean frequency of 6.4 %) [65]. Biliary obstruction, however, may lead to infection of the biliary system with a variety of organisms. Although the predominant organisms are Gram-negative bacillary enterics (e.g. *E. coli*, *Klebsiella* spp.) [70, 71], which are common causes of cholangitis/biliary sepsis, they are uncommon causes of IE, although they may cause disease in high-risk patients (e.g. those with prosthetic valves). The major organisms from an infected biliary tree that can cause bacteremia with the potential for IE are *Enterococcus* spp. and VGS [70]. The enterococci are particularly more common among patients with previous biliary endoprosthesis [71]. Instrumentation of an obstructed biliary system has resulted in bacteremia rates as high as 26.5 % (mean 18.0 %) [65], hence the rationale for prophylaxis. Although earlier studies provided some evidence that prophylaxis may reduce the incidence of post-ERCP bacteremia [72, 73], a meta-analysis by Harris and colleagues [74] that reviewed five prospective, randomized placebo-controlled trials failed to show such a benefit among patients who received prophylaxis, arguing against the routine prophylactic use of antibiotics prior to ERCP to reduce bacteremia. This is not to say, however, that antibiotics should not be used in patients with known cholangitis. As well, because the meta-analysis excluded two studies where patients received antibiotics before and after the ERCP, it is possible that continuation of the prophylaxis after the procedure may reduce bacteremia. Therefore, such a regimen continues to be recommended for patients with biliary obstruction and high-risk for IE [39, 41, 42, 75].

Endoscopic ultrasound (EUS) is a relatively new procedure. One of its greatest benefits is the ability to perform fine-needle aspiration (FNA), the two procedures referred to as EUS-FNA. EUS-FNA has been used to aspirate fluid from cystic lesions, pseudocysts, and fluid collections for both diagnostic and therapeutic purposes [76]. The frequency of bacteremia as a complication of EUS and EUS-FNA has been prospectively studied in three separate trials, which included approximately 250 patients [77–79]. These studies did not find a statistically significant increase in the rate of bacteremia when compared with that seen at upper endoscopy. Based on these data, prophylactic antibiotics are not recommended for FNA of solid masses and lymph nodes [76].

Colonoscopy has a surprisingly low rate of bacteremia (2–5 %) [10, 65, 80], most commonly with organisms that are not typically causes of IE. As such, antibiotic prophylaxis is not recommended for this procedure, including when it involves biopsy or polypectomy [81].

Genitourinary instrumentation is necessary for the diagnosis and treatment of benign and malignant urological diseases. However, instrumentation and catheterization of the GU tract is also the leading cause of nosocomial urinary tract

infections (UTIs) [82]. Less frequently, bacteremia can result from these interventions, the rates varying with different procedures. Development of bacteremia directly attributable to the GU procedure typically occurs after colonization of the urine. As such, the majority of studies on the use of prophylactic antibiotic regimens prior to GU interventions have assessed the efficacy in preventing UTIs. There have been only a few studies that have assessed the efficacy in preventing bacteremia, reflecting the infrequent occurrence of this complication. When bacteremia occurs, the clinical manifestations range from asymptomatic, to transient fever, to septicemia/urosepsis. IE due to manipulation of the GU tract is extremely uncommon, but has been reported [83–85]. As such, the evidence for IE prophylaxis in GU procedures is scant and is based largely on the efficacy in preventing bacteremia, as well as on expert opinion. Thus, as with GI procedures, recommendations for IE prophylaxis for genitourinary (GU) procedures vary, such that the AHA and ESC recommend against this practice [40].

On the other hand, the Working Party of the British Society for Antimicrobial Chemotherapy (BSAC) recommends IE prophylaxis in GU interventions at risk for significant bacteremia, i.e. cystoscopy; urethral dilatation; transurethral resection; transrectal biopsy [54]. As with lower gastrointestinal procedures, GU procedures will mostly produce bacteremia with Gram-negative organisms (e.g. *E. coli*, *Klebsiella* spp. [86–88]), which are common causes of urosepsis but are uncommon causes of NVE. These organisms may, however, cause IE in high-risk patients (e.g. those with prosthetic valves). Of the organisms arising from the native GU tract, the predominant ones that may cause NVE are *Enterococcus* spp. and the VGS [88]. Although the risk that any particular patient will develop endocarditis is low, the rate of bacteremia following invasive urinary tract instrumentation is high in the presence of bacteriuria. For example, cystoscopy, urethral dilation, and transurethral resection of the prostate (TURP) in the presence of bacteriuria precipitated bacteremia at rates of 25 % [89], 40 % [88], and 52 % [88], respectively. This perioperative bacteremia is usually transient and symptomless; in as much as ~6 % of cases in one study [90], though, it may progress to perioperative septicemia. As such, sterilization of the urinary tract with antimicrobial therapy in patients with bacteriuria should be attempted prior to elective procedures [89, 91]. Such intervention has been shown to reduce the risk of septicemia [92]. Whether it also reduces the risk of IE is unknown. However, in a study of 15 non-catheterized patients with sterile urine, cystoscopy resulted in post-procedure bacteremia in 13 % of patients [93], which can theoretically result in IE in at-risk patients. As well, the incidence of post-procedure bacteremia after transurethral procedures (i.e. TURP, transurethral resection of bladder tumour/TURBT) ranged from 30 % to 45 % in three prospective, comparative studies [94–96], which was reduced by approximately 80–90 % with appropriate antimicrobial prophylaxis [89]. These studies were marked, however, by relatively high rates of bacteriuria in both comparison groups [89], which accounts for the high rates of bacteremia in the absence of prophylaxis. In a meta-analysis of ten randomized controlled trials of antibiotic prophylaxis for TURP in men with sterile urine (i.e. preoperative urine specimen containing $<1\times10^5$ CFU/mL), a significant decrease in the frequency of postoperative

bacteremia was noted with the intervention, albeit with lower baseline rates (4 % vs 1 %, risk difference of –0.02, 95 % confidence interval of -0.04–0.00) [97]. The rate of bacteremia after combined cystoscopy and transrectal biopsy of the prostate was 73 % in one study [93]. Hence, mono-antimicrobial prophylaxis (e.g. aminopenicillins or glycopeptides) is recommended for moderate-risk patients prior to these urological procedures to target the above mentioned Gram-positive organisms. For high-risk patients, combination therapy targeting Gram-positive and Gram-negative flora is recommended.

Antimicrobial Prophylaxis

Because VGS are felt to be the predominant pathogens to potentially cause IE after dental/oral, respiratory, and esophageal procedures, aminopenicillins are the recommended agents for prophylaxis as shown in Table 5.3. In the past, VGS were nearly uniformly susceptible to penicillin and other β-lactams, as well as to lincosamides and macrolides [98]. As such, the current AHA guidelines on IE prophylaxis, which were published in 1997 [39], recommend the use of amoxicillin (ampicillin if the patient is unable to tolerate oral intake). Amoxicillin was recommended over penicillin because it is better absorbed from the GI tract and because it provides higher and more sustained levels [39]. In humans, the elimination half-life of amoxicillin is 50–60 min [99]. Clindamycin or macrolides are alternatives in those unable to tolerate β-lactams. A contemporary review of the antimicrobial susceptibility of VGS demonstrated that amoxicillin at a concentration of ≤0.5 μg/mL inhibited 87 %, 64 %, and 100 % of isolates in the *S. sanguis*, *S. mitis*, and *S. milleri* groups, respectively, as well as two of the three isolates in the *S. salivarius* group [100]. Hence, the use of amoxicillin as a prophylactic regimen was justified. However, several studies have since demonstrated increasing rates of VGS isolates from oropharyngeal specimens [101] and bloodstream infections [98, 102–105] that are not susceptible to penicillin, macrolides, or lincosamides. Furthermore, resistance to these antibiotics can occur with repeated prophylaxis doses for serial procedures distributed closely in time [39, 42]. Therefore, continued monitoring of such resistance patterns is mandatory, and modifications of future guidelines may be necessary. Until such time, amoxicillin remains the recommended prophylaxis regimen for the above-mentioned procedures. When comparing the AHA guidelines from those of Europe (BSC, French), differences in amoxicillin dose is seen. The latter recommend a single 3 g oral dose, which produces serum levels above the MIC of most oral streptococci for a period of 6–14 h [106]. The AHA proposes 2 g, instead of 3 g, because the serum kinetics produced by the two different doses are very similar, although the lower dose is associated with fewer side effects [107]. For patients with a history of penicillin allergy, clindamycin remains appropriate. Alternatives include macrolides, such as clarithromycin or azithromycin, which have demonstrated efficacy in experimental models and have convenient dosing regimens, although they are more expensive. Cephalosporins also have demonstrated efficacy, but should not be used in patients with a history of type 1 (immediate-type/

anaphylaxis) hypersensitivity reaction to β-lactams. For patients unable to take orally, intravenous regimens are recommended and administration of the full dose should be completed within 30 min of the procedure.

For procedures involving the biliary system or the gastrointestinal or genitourinary tracts, the predominant pathogen of concern is *Enterococcus* spp. Previous studies have reported that among cases of enterococcal IE, ~40 % were associated with a recent gastrointestinal or genitourinary procedure (i.e. within 2–6 weeks) [28]. Enterococci however, are notoriously more resistant than VGS, with typically higher MICs to β-lactams [108]. Thus, after administration of amoxicillin, the corresponding serum levels fall below the MIC of enterococci sooner than for VGS, resulting in a decreased period of bacterial growth inhibition. To overcome this issue in high-risk patients, a second dose of the β-lactam is currently recommended 6 h after the first dose to ensure prolongation of adequate serum levels and to enhance protective efficacy. The rationale for the combination of amoxicillin and gentamicin is based on the rat model of *Enterococcus* IE, in which administration of both agents was necessary for successful prophylaxis against inocula $>ID_{90}$ [32]. Alternatively, administration of a single dose of vancomycin (in conjunction with gentamicin) can be used in high-risk patients unable to tolerate β-lactams. The evidence for this recommendation derives from experimental studies in which vancomycin demonstrated prolonged serum half-life, producing serum levels greater than MIC for a longer period of time (compared to ampicillin-based regimens), which resulted in significantly greater area under the curve (AUC) and serum inhibitory activity, and more consistent protective effect [28]. Because of vancomycin's pharmacokinetics, a second dose is not considered necessary. For moderate-risk patients, the second dose of aminopenicillins is optional.

Reasons Against Prophylaxis

Since IE is potentially fatal, prophylaxis seems reasonable. The benefit of giving antibiotic prophylaxis to otherwise healthy people, however, should outweigh its risks. The major complications associated with administration of prophylaxis include allergic reactions, toxic side effects of antimicrobials, adverse interactions with other drugs, and development of resistant organisms.

The most significant adverse event associated with the penicillins is hypersensitivity reactions, which can range from a troublesome rash to life-threatening anaphylaxis. Previous studies that have compared the rates of IE-associated deaths to the rates of deaths from antibiotic-induced anaphylaxis have questioned the benefit of prophylaxis. In a quantitative analysis of published data on prophylaxis in patients with mitral valve prolapse (MVP), Bor and Himmelstein [109] calculate that among ten million patients with MVP undergoing a dental procedure, an estimated 47 non-fatal cases and 2 fatal cases of IE would occur if no prophylaxis were given, compared to 5 cases of IE and 175 deaths due to drug reactions if all patients were given prophylaxis with a penicillin. Similarly, Tzukert and colleagues [110] demonstrated that patients receiving penicillin/amoxicillin propylaxis to prevent IE are five times

more likely to die from anaphylaxis to the drug than from IE, with estimated rates of 1.36 deaths versus 0.26 deaths per million population, respectively. These studies were conducted in the mid-1980s, and national guidelines have since been revised to tailor prophylaxis to at-risk patients. No study has since demonstrated whether the risk-benefit ratio has been modified by the latest recommendations. Nonetheless, the potential for adverse drug-reactions must always be borne in mind. Such a consideration should also include non-allergic toxicities (e.g. aminoglycoside-induced nephrotoxicity), as well as potential drug-drug interactions.

An emerging problem resulting from inappropriate use of antimicrobial agents is the development of *C. difficile*-associated disease (CDAD). *C. difficile* is the most common cause of infectious diarrhea among hospitalized patients. It is well-documented that recent antibiotic use (e.g. within 42 days [111]) predisposes to acquisition of *C. difficile*. Essentially all antibiotics have been associated with risk for CDAD, including those recommended for IE prophylaxis. In a meta-analysis by Bignardi [112], use of ampicillin or amoxicillin was associated with a pooled odds ratio of 3.7 for acquiring disease (95 % CI: 2.6–5.5), while the rates for clindamycin, first-generation cephalosporins, and vancomycin were 9 (6.3–12.9), 2.6 (1.8–3.7), 3.1 (1.8–5.2), respectively. Development of CDAD leads to prolonged hospitalizations [113, 114]. As well, it can be associated with severe disease (i.e. megacolon, perforation, colectomy, shock requiring vasopressor therapy, or death within 30 days after diagnosis) [115]. In certain geographic areas, CDAD is associated with increased mortality rates, with a 1-year cumulative attributable mortality of 17 % [113]. Development of CDAD following antibiotic prophylaxis for dental procedures has been reported [116], as it has after single doses of antibiotics for other procedures [117, 118]. Emergence of CDAD emphasizes the need to weigh the risks versus the benefits of antibiotic prophylaxis.

An additional concern from the large-scale use of IE prophylaxis is the development of antimicrobial resistance. In healthy human volunteers, administration of repeated doses of amoxicillin was followed by emergence of resistant VGS from the oral flora [119]. A case of *S. mitis* IE developing despite seemingly-appropriate prophylaxis has been reported in a patient who received two recent courses of amoxicillin for dental procedures [120]. In the neutropenic cancer patients, exposure to previous β-lactams was associated with an increased risk of bloodstream infection (non-endocarditis) with β-lactam-resistant VGS [121, 122]. Previous exposure to antibiotics has also permitted the emergence of resistant enterococci [123] and *S. aureus* [124, 125]. Consequently, judicious use of antibiotics, in general, is advocated, and administration of antimicrobial prophylaxis should not be done indiscriminately, but tailored to those specifically at-risk for disease.

Emerging Issues

The current recommendations for IE prophylaxis are based on an epidemiology in which VGS were the predominant pathogens. Recent studies have demonstrated that *S. aureus* has become the major cause of IE [126]. An increasing proportion of cases of *S. aureus* bloodstream infection and IE is healthcare-associated [126–128], due to

increasing use of intravascular devices (e.g. central venous catheters, dialysis catheters, prosthetic vascular grafts, pacemakers/defibrillators). These devices can also permit coagulase-negative staphylococci (CoNS, e.g. *S. epidermidis*) to establish endovascular infections. Indeed, the incidence of CoNS IE is also increasing [129]. The existing aminopenicillin-based prophylaxis recommendations are not likely to be effective in preventing *S. aureus* IE, based on in vitro susceptibility testing in which <5 % of clinical isolates are inhibited by penicillin [130–132]. Similarly, they are not expected to be effective against CoNS. There are currently no national guidelines regarding IE prophylaxis for the above-mentioned procedures. The recommendations that exist recommend prophylaxis to minimize the risks of intraoperative contamination and surgical site infection [133]. Typically a first-generation cephalosporin directed primarily against staphylococci is administered in the peri-implantation time period for clean-contaminated procedures, and only for a short duration (e.g. a few doses) [133]. This approach, however, may not be adequate to prevent bacteremia. For devices in which a portion remains external to the patient, and thus provides a persistent portal of entry, the brief administration of the peri-procedure prophylaxis is certainly not sufficient to prevent bacteremic episodes that may occur during the lifespan of the implanted device. In particular, the use of central venous catheters (CVCs) has emerged as a major risk factor for bacteremia and IE [128]. Consequently, healthcare-associated IE (HA-IE), defined as acute IE occurring 48–72 h or more post-admission to hospital and/or IE directly relating to a hospital-based procedure performed during a previous hospital stay within 8 weeks of admission, currently accounts for approximately 7.5–29 % of all cases of IE seen in tertiary hospitals [134]. As such, modification of IE prophylaxis recommendations is required to address this changing epidemiology. One intervention which may be particularly useful for preventing CVC colonization, and therefore may minimize the risk of bacteremia and IE, is the antibiotic lock technique. This technique consists of filling and closing of the catheter lumen with a high-concentration antibiotic solution that acts locally to eradicate catheter-associated bacteremia, but that allows the side effects and toxicity associated with systemic administration of antibiotic to be avoided. Future studies are required before such intervention can be recommended.

Recently there have been conflicting reports with regards to changes in the incidence of endocarditis following the implementation in the 2007 guidelines for endocarditis prophylaxis [40]. From the United Kingdome it has been observed that there has been a rise in the incidence [135] of endocarditis while in the United States a difference has not been observed [136]. This controversy has led to a call for a resolution to the matter suggesting that an international collaboration should be undertaken to do the appropriate clinical trial to answer this important question, about the role of prophylaxis and whether we should resume the same level of prophylaxis as prior to the release of the 2007 guidelines [137].

Conclusion

Guidelines exist to assist clinicians in stratifying their patients' risk of IE in the face of various procedures. Unfortunately, most of the recommendations are not based on robust, scientific evidence, but instead, are consensus expert opinion. In

addition, emergence of antimicrobial resistance and a changing epidemiology of IE will likely necessitate revision of current guidelines, which is not unanticipated, given the dynamic nature of medical knowledge and evolving trends in healthcare.

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Diagnostic Approach to Endocarditis

6

James W. Tam, Nasir Shaikh, Bohdan Bybel, and Davinder S. Jassal

Abstract

Infective endocarditis is a challenging disorder to diagnose. Thorough assessment with history, physical examination, microbiology, blood cultures and the thoughtful application of cardiac imaging, incorporating the concepts of pretest likelihood and clinical utility, will assist in this diagnostic dilemma. Patients with unexplained Staphylococcus aureus bacteremia, prosthetic heart valve or intracardiac electrical devices produce additional challenges. The timing and usefulness of transthoracic echocardiography, transesophageal echocardiography and positron emission tomography will be presented.

Keywords

Infective endocarditis • History • Physical examination • Staph aureus bacteremia • Prosthetic heart valve • Intracardiac electrical devices • Transthoracic echocardiography • Transesophageal echocardiography • Positron emission tomography

Key Points

1. Perform a thorough history, physical examination, routine investigations (including blood cultures), and apply the Duke criteria to establish the diagnosis of IE.

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2. Certain organisms can be very difficult to culture and may give rise to "culture negative" IE. If these organisms are suspected, discussion and consultation with the microbiology laboratory is recommended.
3. When appropriately used, echocardiography (TTE and TEE) is extremely useful in defining both the diagnosis and prognosis of IE.
4. Categorization of patients into strata of clinical probability of disease and into strata of clinical risk for morbidity and mortality may help to determine the most appropriate timing of the echocardiographic examination and the choice of the initial echocardiographic modality.
5. In patients with persistent Staphylococcus aureus bacteremia (SAB) or patients with prosthetic heart valves or intracardiac devices, we recommend a lower threshold for echocardiography and a reduced threshold for the performance of TEE, as well as consideration of PET-CT in equivocal cases.

The diagnosis of infective endocarditis (IE) can be a difficult one to make. Since the late 1970s, attempts have been made to develop diagnostic criteria and algorithms to predict the presence of IE. Making the correct diagnosis is important for a number of reasons including ensuring an adequate duration of antibiotic treatment, determining if there is a need for surgical intervention, and ensuring that another source of infection has not been missed.

In this chapter, we briefly review the history of IE leading to the current diagnostic approach, the existing stratagems for case definitions and the utility of echocardiography in assisting with diagnosis. We also examine specific scenarios whereby the diagnosis of IE may be particularly challenging.

Historical Perspective

Endocarditis, an inflammatory disorder of the endocardium, had been appreciated by the anatomical pathologists for some time. Prior to the bacteriological era, however, the various types of endocarditic lesions could not be categorized as infectious or non-infectious. Austin Flint's chapter on endocarditis likely referred to rheumatic valvular heart disease rather than to IE [1]. However, he utilized the terms "acute", "subacute", and "chronic" in his description and this classification was subsequently adopted as standard nomenclature.

It is instructive to view the understanding of IE through the eyes of a single individual, Sir William Osler, as revealed in successive editions of his textbook, "The Principles and Practice of Medicine." The first edition, in 1892, divided endocarditis into "acute" and "chronic" forms. Acute endocarditis contained "simple" and "malignant" forms [2]. In "simple endocarditis", there were small vegetations with

microorganisms in association with systemic symptoms, fever, and a heart murmur [2]. In "malignant endocarditis", there was an acute IE with "a malignant character" [2]. Symptoms were varied and diverse and might include fever, sweats, weakness, delirium, and emboli. Osler noted that the diagnosis of IE was often "difficult" but was easy when there were "marked embolic symptoms." To the modern reader, his conclusion about the difficulty in diagnosing the disorder continues to be appreciated.

Diagnostic Approach

History and Physical Examination

The diagnosis of IE remained challenging and continued to be dependent upon a constellation of infectious symptoms and signs in association with bacteremia, auscultatory evidence of valvular involvement, and signs of large-vessel and/or small-vessel peripheral arterial embolization. This dependence upon both clinical skills and the bacteriological laboratory were, in the latter part of the twentieth century, supplemented by the addition of echocardiographic visualization of the lesion and of the assessment of its hemodynamic and structural consequences. This formed the mainstay of clinical diagnostic algorithms proposed by Pelletier, von Reyn, and the group from Duke University.

On history taking, careful attention should be paid to predisposing cardiac lesions (prosthetic heart valve, underlying valvular heart disease, and intracardiac shunts). A history of previous coronary artery bypass surgery or coronary stent is not a risk factor for IE. A source for potential bacteremia should also be sought (recent dental surgery, intravenous drug use, and indwelling intravascular catheter).

On physical examination, fever is almost always present. One should look for evidence of hemodynamic compromise (shock or congestive heart failure), new regurgitant murmur, and evidence of septic emboli. Emboli may involve the mucocutaneous surfaces, the skin of the extremities, and/or other major organs such as the brain (producing stroke), the kidneys (producing renal dysfunction), the abdominal viscera (such as the spleen producing infarction and pain), the retina (Roth spots – exudative, hemorrhagic, edematous areas in the retina – see Fig. 6.1), and in the setting of right sided IE, the lungs (producing septic pulmonary infarcts). Cutaneous manifestations such as petechiae (usually on the extremities) are the most common manifestation but are non-specific. Mucous membrane petechiae can be seen on the palate or conjunctivae (often seen with eversion of the eyelids). Janeway lesions (macular, blanching, nonpainful, erythematous lesions on the palms and soles), Osler's nodes (painful, violaceous nodules found in the pulp of fingers and toes) and Roth spots (Fig. 6.1) are more specific for IE, but are not diagnostic [3]. The relative frequency of the various symptoms and signs are provided in Table 6.1 [3].

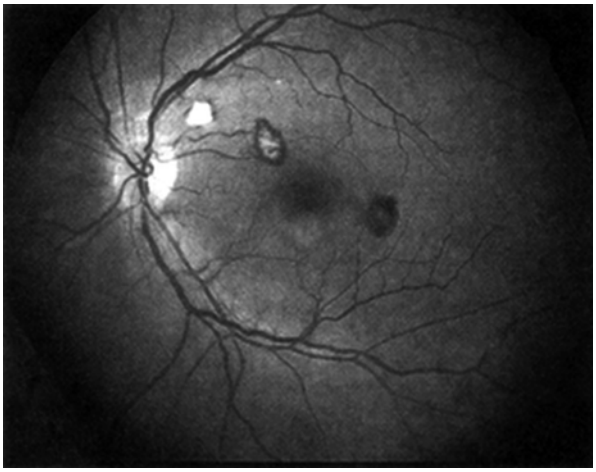

Fig. 6.1 Roth spots in a 40 year-old woman with rheumatic valvular heart disease and Strept. viridans endocarditis. Three lesions, from left-to-right, demonstrate the evolution of a Roth spot. (Circulation 1999;99:1271, with permission)

Table 6.1 Frequency of symptoms and signs in infective endocarditis

Most common – 80–90 % of patients:
Fever (80 %) and heart murmur (90 %)
Fairly common – 30–50 % of patients:
Chills (40 %), weakness (40 %), dyspnea (40 %), embolic phenomenon (>50 %), skin manifestations (20–50 %), splenomegaly (20–60 %), petechiae (20–40 %), clubbing (15–50 %)
Common – 15–25 % of patients:
Sweats (25 %), anorexia (25 %), weight loss (25 %), malaise (25 %), cough (25 %), stroke (20 %), nausea/ vomiting (20 %), headache (20 %), septic complications such as pneumonia/meningitis (20 %), myalgia/arthalgias (15 %), edema/chest pain (15 %), abdominal pain (15 %), splinter hemorrhages (15 %), Osler's nodes (10–25 %), signs of renal failure (10–25 %)
Uncommon – ≤10 % of patients:
Janeway lesions (<10 %), delirium/coma (10–15 %), hemoptysis (10 %), back pain (10 %), changing murmur (5–10 %), new murmur (3–5 %)

Source: Adapted from Mandel et al. [121]

Investigations

General Investigations

Laboratory investigations may reveal anemia, leukocytosis with a left shift, elevated erythrocyte sedimentation rate, and glomerulonephritis (with hematuria or active urinary sediment). Immunologic perturbation may also occur in subacute or chronic cases leading to high titres of rheumatoid factor.

The chest x-ray may show evidence of preexisting valvular disease (valvular calcification or cardiomegaly) or a complication arising from the infection

(congestive heart failure or septic pulmonary emboli). Rarely, suppurative pericardial effusion from periannular abscess formation may produce a globular heart on x-ray.

A careful examination of the electrocardiogram should be made to rule out heart block. This is one of the complications of IE when the infectious process involves the aortic valve annulus and membranous interventricular septum.

Bacteriologic Investigations

Three aerobic blood cultures (with a minimum of 10 mL per bottle), from separate venipuncture sites, should be obtained over at least an hour apart (from first to last sample) with strict aseptic technique and before beginning therapy. Blood cultures inoculated with at least 5 mL of blood had a 92 % detection rate for bacteremia compared to only 67 % for bottles inoculated with less than 5 mL in one study [4]. The estimated yield from blood cultures increased approximately 3 % per mL of blood cultured. Anaerobic cultures may be performed but only rarely will the organism be anaerobic. If a patient has not been treated with antibiotics prior to obtaining the blood cultures, there is minimal benefit beyond three cultures [5]. However, there may be additional diagnostic yield if antibiotics had been administered or if the initial blood cultures were negative.

Not all bacteremias imply the presence of IE. Certain species are more commonly associated with the disease. For example, bacteremias caused by Group A or C streptococci are unlikely to be associated with IE. However, bacteremias caused by Group G streptococci are often associated with IE [6]. Similarly, infection with *Enterococcus faecalis* is associated with IE more often than are other enterococcal species [7]. Most gram negative rods including *Escherichia coli* and *Proteus* are unlikely to cause IE [8]. Organisms such as *Propionibacterium*, *Corynebacterium*, *Bacillus*, and coagulase-negative Staphylococci recovered from blood cultures likely represent skin contamination and are unlikely to cause IE. In such cases, blood cultures should be repeated (using sterile technique) to ensure that the organisms were not contaminants.

Special mention should be made about *Staphylococcus aureus* bacteremia. This will be covered in more detail later in this chapter.

There is a small percentage of patients with a high clinical suspicion for IE who do not have positive blood cultures. The most common reason is partial sterilization due to prior administration of antibiotic therapy. Another possibility for negative cultures is IE due to atypical organisms which are more difficult to isolate in culture such as: *Coxiella burnetii* (Q fever), *Tropheryma whipplei*, *Brucella*, *Mycoplasma*, *Chlamydia*, *Histoplasma*, *Legionella*, *Bartonella*, and the HACEK organisms (*Haemophilus aphrophilus*, *Actinobacillus actinomycetemcomitan*, *Cardiobacterium homini*, *Eikenella corroden*, *and Kingella kingae*). Blood cultures may need to be incubated longer (up to 21 days) for some of these organisms (e.g. HACEK group). Other tests, such as polymerase chain reaction on valve tissue, may need to be performed for *C. burnetii* and *Bartonella*. In other instances, special media may need to be used. Antibody titres for *C. burnetti* can also be helpful. Local microbiology expertise should be sought when an atypical organism is suspected to be the cause of IE.

Echocardiographic Investigations

Prior to the availability of echocardiography, the only way to visualize a vegetation was by surgery or autopsy. The development of echocardiography and the identification of criteria for the diagnosis of IE have significantly advanced our ability to diagnose and treat this disease. Echocardiography has become one of the major diagnostic procedures available today.

The echocardiographic hallmark of IE is an endocardial mass lesion usually referred to as a "vegetation" (as mentioned earlier). This is usually defined as an oscillating mass attached to an endocardial surface, such as a valve or supporting structure, or a structure in the path of regurgitant jets [8]. Additionally, echolucency, suggesting the presence of abscess formation, and Doppler evidence of valvular dysfunction should be sought. Further details on the diagnostic and prognostic information provided by echocardiography are provided in a subsequent chapter of this book.

Both transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) have proven to be extremely useful in the diagnosis of IE. TTE is generally believed to have a lower sensitivity than TEE in diagnosing IE. A negative TTE study (i.e.: no vegetation) does not preclude the diagnosis of IE, but the finding of normal valves (both morphologically and functionally) substantially reduces its probability. In one study, 96 % of patients with normal valves on TTE also had a normal examination by TEE [9]. In addition, TTE has a specificity approaching 100 %, and has therefore very few false positive results [10]. TTE is most suited for visualization of anterior structures including right sided cardiac valves, native aortic valve, and the anterior aspect of prosthetic aortic valves [11].

TEE, although more invasive, is more sensitive and has a better spatial resolution than TTE for the detection of IE (94–100 % sensitivity for TEE versus 44–63 % for TTE) [10, 12]. TEE is especially useful for the detection of smaller vegetations (<5 mm), the diagnosis of prosthetic valve endocarditis, the detection of paravalvular abscess formation (87 % sensitivity for valve abscess with TEE vs. 28 % for TTE) [13], and for the assessment of embolic risk [14]. The negative predictive value of TEE is nearly 100 % for patients with native valves, but patients with prosthetic valves may have a negative TEE and still have IE [15]. In the latter population, clinical assessment is especially important. TEE requires additional personnel and training and has small but finite risk of procedural complication as well as failed esophageal intubation [16].

Roe et al. compared TTE and TEE in 114 cases of suspected IE assessed retrospectively over a 6-year period [17]. Concordant results occurred in 55 % of cases. A change in diagnostic category occurred in 25 % of cases when the results of TEE were added to those of TTE (11 % for patients with native valves and 34 % for those with prosthetic valves). Twenty-two patients were reclassified based upon TEE findings as having definite IE rather than possible. Nineteen of these patients had an intermediate probability of IE, positive blood cultures, and a negative or inconclusive TTE.

More recently, the advent of high-frame-rate imaging particularly with harmonic imaging has led to improvements in transthoracic imaging quality. Two studies have

evaluated the role of modern day TTE in the diagnosis of IE. Reynolds et al. performed a retrospective review of 55 patients with proven native valve IE at a single centre between 1998 and 2001 [18]. The studies were selected and interpreted blindly by an experienced echocardiographer. Despite good or excellent TTE quality, with the addition of second harmonic imaging, the sensitivity of TTE for the detection of native valve vegetation was only 55 %. There were five missed vegetations in cases in which the corresponding TEE images revealed masses greater than 10 mm in size.

At our institution, we examined the prospective role of TTE and TEE in consecutive patients with an intermediate clinical likelihood of native valve IE [19]. We found that TTE was able to make a firm diagnosis in 25 of 36 (70 %) of patients. There was 100 % concordance with TEE in these patients (11 positive, 14 negative). Indeterminate TTE results occurred in the remaining 11 patients (30 %) due to limited image quality or complex underlying native valve disease. TEE results were clearly positive in eight and clearly negative in two cases. The lone remaining case remained equivocal despite TEE. Thus, the value of TEE in patients with suspected native valve IE and intermediate clinical likelihood may be limited to those with recognized suboptimal TTE images or underlying complex valvular abnormality. This is consistent with the findings of Humpl et al. who showed that there was excellent concordance between TTE and TEE in children with suspected IE in whom the potential adverse effects of sedation and esophageal intubation associated with TEE could be avoided [19–22].

Case Definitions and Validation Studies

Case Definitions

A series of diagnostic criteria have been developed by Pelletier and Petersdorf (1977), von Reyn (1981) and the Duke group (1994). The Pelletier and Petersdorf criteria required pathological confirmation of the diagnosis of IE, and thus, were not very useful for prospective clinical diagnosis [23]. The case definitions were improved by von Reyn and colleagues to make them more clinically relevant [21]. In 1994, investigators from Duke University modified the von Reyn criteria to include echocardiographic findings in the diagnosis of IE [8]. In addition, they expanded the category of predisposing heart conditions to include intravenous drug use.

(i) **Pelletier and Petersdorf criteria** (see Table 6.2) – Their classification scheme consisted of three diagnostic categories: definite, probable, and possible. These diagnostic criteria were quite specific but were not very sensitive. Many patients with clinically suspected IE failed to meet diagnostic criteria.

(ii) **von Reyn criteria** (see Table 6.3): The von Reyn system was designed to make the diagnostic criteria more clinically applicable. The classification scheme consisted of four categories: definite, probable, possible, and rejected.

Table 6.2 Diagnostic criteria by Pelletier and Petersdorf

Definite: histologic evidence of endocarditis on autopsy or surgery
Probable:
(a) Uniformly positive blood cultures AND all of:
Underlying valve disease
Evidence of skin or visceral emboli
OR (b) Negative blood cultures AND all of:
Fever >38 °C
New regurgitant murmur
Evidence of skin or visceral emboli
Possible:
(a) Uniformly positive blood cultures AND:
Underlying valve disease OR evidence of skin or visceral emboli
OR (b) Negative blood cultures AND all of:
Fever >38 °C
Underlying valve disease
Evidence of skin or visceral emboli

Source: Adapted from Pelletier and Petersdorf [21]

Pathological confirmation of vegetations, or of an abscess, was still required to define a case as definite. Thus many cases were classified as probable or possible since many patients did not have pathological confirmation (i.e.: by surgery or autopsy) of their disorder. Although the von Reyn criteria lacked prospective validation, the specificity of their classification system was superior to Pelletier and Petersdorf.

(iii) **Duke criteria**: Investigators at Duke University further refined the diagnostic criteria to make the case definitions more clinically applicable to patients suspected of having acute IE. This group has since published modifications in 2000 of their original criteria after the validation studies (see below) were completed [22]. The new criteria include the addition of the presence of Coxiella burnetii as a major criterion, and the elimination of echocardiographic minor criterion. Possible IE has been redefined to include one major plus one minor criterion or three minor criteria (see Table 6.4). In addition, the role for TEE for the diagnosis of IE has been made more explicit to include patients with prosthetic valves and those suspected of having complicated IE (such as a paravalvular abscess) [22].

Validation Studies

After the Duke criteria were published, a number of studies appeared that compared the von Reyn criteria to the Duke criteria for the diagnosis of IE [8, 24, 25]. These

Table 6.3 von Reyn criteria for diagnosis of infective endocarditis

Definite:
(a) Direct histologic evidence of infective endocarditis from surgery or autopsy
OR (b) Bacteriology (Gram stain or culture) of valvular vegetation or peripheral embolus
Probable:
(a) Persistently positive blood cultures plus ONE of the following:
New regurgitant murmur
Predisposing heart disease AND vascular phenomena
OR (b) Negative or intermittently positive blood culture plus ALL of the following:
Fever
New regurgitant murmur
Vascular phenomena (petechiae, splinter hemorrhages, conjunctival hemorrhages, Roth spots, Osler's nodes, Janeway lesions, aseptic meningitis, glomerulonephritis, peripheral emboli, central nervous system emboli, coronary emboli, peripheral emboli)
Possible:
(a) Persistently positive blood culture plus ONE of the following
Predisposing heart disease (definite valvular or congenital disease or cardiac prosthesis excluding permanent pacemakers)
Vascular phenomena
OR (b) Negative or intermittently positive blood culture plus ALL of the following:
Fever
Predisposing heart disease
Vascular phenomena
Rejected:
(a) Endocarditis unlikely, alternative diagnosis generally apparent
(b) Endocarditis likely, empiric antibiotic therapy warranted
(c) Culture negative endocarditis diagnosed clinically but excluded by postmortem

Source: Adapted from von Reyn et al. [22]

studies utilized pathologically-confirmed cases of IE, and retrospectively assessed the ability of the von Reyn and the Duke criteria to categorize the probability of IE. In general, the Duke criteria were more likely to have diagnosed cases as definite (80–100 %) IE and would not have rejected any of the cases of proven endocarditis. On the other hand, the von Reyn criteria defined 50 % of these cases as probable. More importantly, the von Reyn criteria would have rejected 20–50 % of the cases proven pathologically to be IE. The Duke criteria also classified 75 % of confirmed prosthetic valve endocarditis (PVE) cases as definite and rejected no cases of PVE. The von Reyn criteria however, rejected 20 % of these confirmed cases of PVE [26]. Dodds et al. assessed the clinical cases rejected by the Duke criteria and determined the negative predictive value to be at least 92 % [27]. Therefore, at the present time, the modified Duke criteria are the standard diagnostic criteria for patients with suspected IE.

Table 6.4 Modified Duke criteria for diagnosis of infective endocarditis

Major criteria:
(a) Positive blood cultures for infective endocarditis
In the absence of a primary focus, positive cultures from 2 separate blood cultures of one of the following typical organism
Streptococci viridans
Streptococcus bovis
HACEK group (*Haemophilus* species, *Actinobacillus actinomycetes comitants*, *Cardiobacterium hominis*, *Eikenlla* species, *Kingella kingae*)
Community-acquired *Staphylococcus aureus* or entercocci
or Persistently positive blood cultures of a microorganism consistent with IE
or Single blood culture for *Coxiella burnetii* or antiphase I IgG antibody titre >1:800
(b) Evidence of endocardial involvement
New valvular regurgitation
or Positive echocardiogram (oscillating intracardiac mass in the absence of an alternative anatomic explanation OR abscess OR new partial dehiscence of prosthetic valve)
Minor criteria:
(a) Predisposing heart condition OR intravenous drug use
(b) Fever (at least 38.0 °C)
(c) Vascular phenomena (major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, Janeway lesions)
(d) Immunologic phenomena (glomerulonephritis, Osler's nodes, Roth spots, rheumatoid factor)
(e) Microbiologic evidence of positive blood culture not meeting major criterion but excluding single positive culture for coagulase negative *Staphylococci* and organisms that do not cause endocarditis OR serologic evidence of active infection with organism consistent with IE
Definite:
2 major criteria
OR 1 major and 3 minor criteria
OR 5 minor criteria
OR Microorganism demonstrated by culture or histology of a vegetation, embolized vegetation or in an intracardiac abscess
OR Histologic evidence of active endocarditis (vegetation or intracardiac abscess)
Possible:
1 major and 1 minor critieria
OR 3 minor criteria
Rejected:
Firm alternative diagnosis
OR Resolution of manifestations of endocarditis with 4 or less days of antibiotics
OR No pathologic evidence of infective endocarditis at surgery or autopsy after 4 or less days of antibiotics
OR Does not meet criteria for possible infective endocarditis (above)

Source: Adapted from Li et al. [22]

Suggested Approach in Suspected Endocarditis

The meaning and significance of the term "clinically suspected IE" will vary between observers. This may range from a patient with unexplained isolated fever to a patient with the classic findings of fever, new regurgitant murmur, embolic phenomenon, and persistent bacteremia. At our institution, we found significant variation between the assessment of probability of IE between the attending team and the research team [28]. The latter employed a standardized scoring system to determine pre-test likelihood of IE. The determination of probability or likelihood of disease may have a bearing on the selection and timing of echocardiographic evaluation [29]. Various studies have demonstrated no to very minimal utility of echocardiography in patients with low pretest likelihood of the disease [28–30]. In practice, a multispecialty Heart Valve team approach to patient evaluation is essential. This includes evaluation of both the clinical likelihood of IE as well as the clinical risk of an adverse event (see Fig. 6.2) [17, 31]. The team should include specialists in infectious disease, cardiology, and cardiac surgery [32]. This approach would allow for a more complete understanding of the limitations of clinical and noninvasive investigations as well as the need and optimal timing of semi-invasive and invasive strategies and treatment [11].

Patients with evidence of high clinical risk features deserve prompt echocardiographic evaluation that may lead to important and timely medical or surgical intervention (Table 6.5). Although we still recommend baseline TTE in all patients, there should be a lower threshold to proceed to TEE in this high risk group, especially in the setting of persistent *S. aureus* bacteremia or suspected prosthetic valve endocarditis. These special circumstances will be discussed later in this chapter.

Low likelihood patients (no major Duke criteria, one minor criteria such as transient fever, and who meet all of the low risk criteria in Table 6.6) should be observed only [28, 33]. In those patients who are found to have an alternative source of infection, treatment should be directed to that source and echocardiography (TTE and TEE) safely deferred unless there is a clinical change [29, 30].

High likelihood patients based upon the constellation of clinical and bacteriologic criteria (two major Duke criteria or one major and three minor) should be treated as a confirmed case of IE with a prolonged course of antibiotics [28]. Echocardiography (TTE) should be performed promptly to help determine prognostic information that may help with timing of surgery. TEE in this population is especially helpful in the setting of nondiagnostic TTE, prosthetic valves, cardiac implantable electronic devices (CIED), and in the detection of suspected complications (e.g. abscess or fistula formation) [11].

The intermediate likelihood subgroup where the diagnosis of IE is suspected but not confirmed on clinical and bacteriologic grounds, is a population in whom the addition of a positive echo finding would greatly assist in establishing a diagnosis of definite IE. We define intermediate likelihood as one major criterion or three minor criteria prior to echocardiography [28], analogous to the term possible endocarditis in the proposed modified Duke criteria [22]. The American College of Cardiology/American Heart Association guidelines recommend that such patients be evaluated

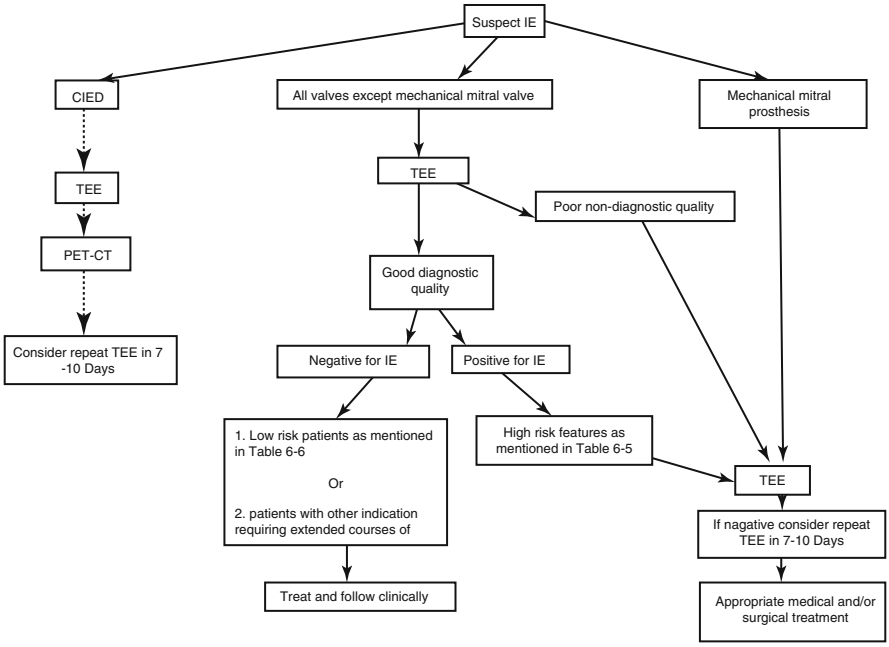

Fig. 6.2 Suggested diagnostic algorithm for a patient with suspected infective endocarditis

Table 6.5 High risk clinical features in patients with suspected endocarditis

Community acquired infection with no primary source identified
Presence of metastatic infectious foci
Presence of hematuria
Underlying native valvular disease or known prosthetic valves
Presence of permanent intracardiac device
Previous endocarditis
Intravenous drug use
Persistent fever or bacteremia after 72 h of adequate antibiotics

Table 6.6 Low risk clinical features in patients with suspected endocarditis

All of the following criteria must be met
Nosocomial source of bacteremia
Sterile blood cultures within 3 days of initial positive blood culture
No permanent intracardiac device
No hemodialysis dependence
No clinical signs of endocarditis or secondary foci of infection

initially with TTE [11]. A diagnostic algorithm is presented in Fig. 6.2. In the intermediate likelihood subgroup, a negative TTE or TEE does not necessarily exclude the diagnosis of IE [18, 31]. A subset of these patients with negative echo findings (TTE, TEE) may still manifest positive findings with time [15]. A repeat TTE/TEE in 7–10 days is often recommended [34].

Cardiac Computed Tomography

Although cardiac computed tomography (CCT) lacks the temporal resolution to adequate visualize valvular vegetations, the high spatial resolution makes it helpful to evaluate complications such as paravalvular abscesses, pseudoaneurysms, and in the setting of right sided endocarditis, septic pulmonary emboli and infarctions. CCT is less affected by acoustic shadowing from prosthetic valves and may have a role in determining mechanical valvular thrombosis [35–37].

Molecular Imaging

The diagnosis of IE may remain equivocal despite use of clinical, microbiological and echocardiographic imaging studies. Nuclear medicine studies, ^{18}F fluoro-deoxyglucose (FDG) positron emission tomography (PET) and radiolabelled white blood cell (WBC) imaging are the most studied and promising [38].

Positron Emission Tomography

Positron emission tomography (PET) measures the metabolic activity of a structure by detecting positron emissions following an injection of radiopharmaceutical ^{18}F-FDG. This modality is now well established in oncology as tumors are usually hypermetabolic [39]. Infectious and inflammatory indications are continually increasing as PET has become more widespread [40]. ^{18}F-FDG is incorporated by activated leukocytes, monocytes, macrophages, and CD4+ T lymphocytes via glucose transporter mechanism and at sites of inflammation or infection is identified by increased tracer uptake. The introduction of hybrid equipment for both conventional nuclear medicine and PET has improved the reliability by allowing precise localization of uptake and is currently the standard of imaging [39]. Near whole body imaging allows for a more complete assessment of the possible cause of infection and for identification of distant complications [38].

Optimization of background myocardial metabolism is considered to be mainly influenced by patient preparation but has been difficult to standardize [41]. Optimal acquisition time is also uncertain. Consideration should be given to the stage of endocarditis and the duration of antimicrobial therapy. There may be limited uptake if only subcentimeter vegetations are present which would be below the threshold of detection [40].

Numerous case reports and small population studies have shown some benefit both in patients with native and prosthetic valves and in those with implanted electronic devices [40]. Saby et al. investigated 72 patients with suspected IE by using abnormal FDG uptake around the prosthetic valve site as a positive finding for IE, and they found a sensitivity of 73 %, specificity 80 %, positive predictive value (PPV) 85 % and negative predictive value (NPV) 67 %, while Kouijzer et al. found sensitivity of 39 %, specificity 93 %, PPV 64 % and NPV 82 % also in 72 patients [42, 43]. Kestler et al. in 47 patients (and 94 controls) found sensitivity of 100 %, specificity 80 %, PPV 90 % and NPV 100 % [44].

As the number of CIED increases, so too has the incidence of related infections. PET/CT can be useful in detection and in treatment decision making. Ploux et al. in ten patients looking at leads only, found a sensitivity of 100 % and specificity of 93 % [45]. Bensimhon et al. in 21 patients showed a sensitivity of 60 % and specificity of 100 % in the detection of pacemaker lead infection [46]. In detecting the presence of infection involving either the pacemaker lead or pacemaker pocket, the sensitivity increased to 80 %, and the specificity increased to 100 %. Sarrazin et al. looked at pacemaker pocket and leads in 66 patients and found a sensitivity of 89 % and specificity of 86 % [47]. Graziosi et al. found in a prospective study with 27 patients, defining abnormal FDG uptake along the lead course as positive, a sensitivity of 63 %, specificity 86 %, PPV 77 % NPV 76 % [48].

Another role for PET is to identify complications arising from IE such as emboli and metastatic infection. VanRiet et al. showed septic emboli in 44 % of 25 patients evaluated [49], and Bonfiglioli et al. showed unexpected septic emboli in 24 % of their study patients [50].

Indications for use of FDG PET/CT include:

- Cases of IE/CIED infection which are difficult to diagnose due to unexpected negative echo or blood culture results
- Cases of fever of unknown origin or bacteremia of unknown origin in patients with CIEDs or with a strong suspicion of IE
- Early detection of embolic events and metastatic infection in known cases of IE or CIED infection.
- Assistance in the decision process as to the need to remove the CIED.
- Monitoring therapy in known infection [40]. The role of PET/CT is included in the suggested algorithm in Fig. 6.2.

Single Photon Emission Computed Tomography (SPECT)

White blood cell (WBC) imaging with SPECT is a common imaging technique for identifying infection. Radiolabelled WBCs accumulate through chemotaxis at sites of infection. Early planar only studies were limited by suboptimal resolution and a difficulty of localization. False negative studies may occur in small sized lesions, and patients who have been on long term antibiotics [39]. Currently with hybrid

imaging the identification and localization of abnormalities are much improved. This allows for better identification of septic vegetations and detection of distant complications. Monitoring of treatment is also possible. Erba et al. found WBC SPECT imaging useful in 51 patients with IE (90 % sensitivity, 94 % NPV, and 100 % specificity and PPV), and the same group showed a sensitivity and NPV of 94 %, specificity and PPV of 100 % in 31 patients with suspected infected CIED using this modality [51].

Special Populations and Endocarditis

There are a number of patient populations that deserve special mention in regards to the diagnosis of IE. These are patients with prosthetic heart valves, patients with *S.aureus* bacteremia, and patients with CIED endocarditis. Diagnostic issues related to these three groups will be covered below.

Prosthetic Valve Endocarditis

More than 60,000 prosthetic heart valves are implanted in the United States annually. Prosthetic valve IE is classified as early (up to 60 days after valve replacement), intermediate (2–12 months), and late (>12 months). IE is a rare complication occurring in 0.5–1 % of cases per year, and its late occurrence is even less common [52]. In patients with prosthetic valves and nosocomial bacteremia, 43 % may have IE [53]. This risk is similar for mechanical and bioprosthetic valves. In mechanical valves, infection is usually located at the sewing ring, in bioprosthetic valves it can also involve the leaflets, while in composite graft it may even affect distal anastomosis or coronary reimplantation site [54].

El-Ahdab et al. evaluated the incidence and outcome of IE in patients with prosthetic valves with *S. aureus* bacteremia [55]. The overall rate of definite IE was 51 %. The incidence was not different between mechanical and bioprosthetic valves, mitral and aortic prostheses, and early (<12 months after prosthetic valve implantation) and late (>12 months after implantation) presentation. There was a higher incidence of definite endocarditis in patients with persistent fever and persistent bacteremia.

In prosthetic valves, the sensitivity of TTE is only 17–36 % and for TEE is 82–96 % [53]. TEE should be the test of choice in suspected prosthetic valve IE, especially in the mitral position, because of its increased sensitivity for the detection of complications (abscesses, paravalvular leaks, dehiscence of the valves) and limitations of TTE in the diagnosis in this setting (reverberations artifact from metallic structures). Conversely, TTE may be preferable to TEE in the visualization of the anterior portion of prosthetic aortic valves.

TEE should be repeated in high risk patients for IE (persistent fever, persistent bacteremia, unknown source of infection), if the initial study is negative [55].

Staphylococcus aureus Bacteremia and Endocarditis

Staphylococcus aureus is the second most common microorganism producing hospital-acquired bacteremia in hospitals in the United States [56], with an annual incidence of Staphylococcus aureus bacteremia (SAB) reported to be 4.3–38.2 per 100,000 person-years in the United States, depending upon the population studied [57, 58]. Endocarditis occurs in approximately 5–30 % of cases of SAB, depending upon the region studied, patient population, criteria and modality use for diagnosis [59–65]. Rasmussen et al. reported only 5 % prevalence of IE in low-risk SAB patients compared with 38 % in SAB patient with high-risk features (Tables 6.6 and 6.7) [60].

S. aureus IE is now a leading cause of endocarditis worldwide, constituting 25–30 % of all cases of IE [66–68]. Methicillin resistant S. aureus (MRSA) accounts for almost 37 % of cases of IE due to S. aureus in the United States and Brazil [66]. The increased number of cases of IE caused by S. aureus is mainly a consequence of intravenous drug abuse occurring in large inner cities, the implementation of cardiac surgery and other invasive cardiac procedures and devices, and the widespread use of intravenous catheters in hospitalized patients [66–71]. The incidence of lead and valvular IE with SAB is higher in patients with prosthetic valve or intracardiac devices, [60, 65, 72, 73] and carries a mortality of 26 % even with appropriate antimicrobial therapy [61]. There is also an increased risk in hemodialysis patients [74–76]. This may be related to the increase use of new grafts material and venous catheters [77, 78].

In 22–48 % of patients, however, an apparent portal of entry is not identified [60, 71, 79–81]. This lack of a source of bacteremia is more common in patients with community-acquired than among patients with hospital-acquired SAB [69, 71, 79–81]. As such, community-acquired SAB, is considered an independent risk factor for IE [60, 64, 69, 71, 80, 81].

Joseph et al. suggested that the risk of IE is low when SAB occurs in the presence of an intravenous catheter without other identifiable sources and without prosthetic valve or intra-cardiac device [65]. Fernandez Guerrero et al. suggested that endocarditis may be an overlooked complication of SAB associated with infected intravenous catheters [80, 82]. This may be due to some cases being undiagnosed because of the subtle clinical presentation, without murmurs or emboli with right sided valvular involvement [82, 83].

Table 6.7 Patient in whom TEE may not be warranted in the setting of *S. aureus* bacteremia and negative good quality TTE

Patients characteristics outlined in Table 6.6
Clearly defined intravenous line related bacteremia with no clinical features of IE, no prosthetic valve nor CIED and no more than mild valvular regurgitation
Neutropenic patients with no clinical features of IE
Patients who are to receive an extended course of antibiotics for other systemic S aureus infection (e.g. osteomyelitis, visceral abscess)
Patients in whom the results of the investigation are unlikely to alter outcome

S. aureus IE is characterized by an acute presentation in which the signs of severe sepsis are predominant while the classic peripheral signs of endocarditis as well as murmur are less common [60, 69, 71, 79, 80]. Patients with S. aureus IE also remain febrile for an average of 9 days. Persistent fever beyond 72 h may be an indication of S aureus IE [55, 80, 81, 84]. The mean duration of breakthrough bacteremia (bacteremia persisting 24 h after the start of appropriate antimicrobial therapy) in patients with S. aureus IE has been estimated to be 3 and 9 days when treated with penicillins and Vancomycin, respectively, and IE should be considered in every patient who has persistent SAB beyond 72 h following antibiotic therapy [55, 64, 80, 81, 84].

Overall, S. aureus IE is quite often clinically indistinguishable from SAB [59, 60, 69, 79, 80]. If undiagnosed and untreated, it can result in serious complications and may be fatal if inadequately treated. The mortality of left-sided S. aureus IE ranges from 20 % to 48 % and is higher than that by other organisms [70, 79–81, 85, 86].

As a result, the presence of IE should be considered in all patients with SAB. The clinical guidelines and recommendations suggest performing echocardiograms in all patients with SAB but this suggestion has not been universally followed [11, 87–90]. In most of the studies the rate of echocardiography has varied from 34 % to 75 %, suggesting there is likely bias in the selection of high risk patients, thus increasing the incidence of positive results in these studies and overestimating the true clinical utility of echocardiography, especially TEE [59–63, 91, 92].

Holland et al. recently performed a systematic review of nine studies including 4,050 patients on the role of TEE in SAB [93]. TEE was associated with higher rates of a diagnosis of IE (14–28 %) compared with TTE (2–15 %). In four studies clinical or TTE findings did not predict subsequent positive TEE findings of IE [59, 62, 94, 95]. Five studies identified clinical or TTE characteristics associated with low risk of IE (NPV from 93 % to 100 %), suggesting TEE is not necessary in this population. These findings are listed in Table 6.7 [60, 63, 65, 92, 93, 96].

Recently, several studies have questioned that perhaps the low risk patients with uncomplicated SAB in whom the vegetations can only be visualized by TEE (and not by TTE) do not carry the same morbidity and mortality as compared to patients with clinically significant IE [61, 69, 93]. As a result, the consequence of missing a diagnosis of IE where TTE is normal and TEE is not performed may not be clinically significant in patients with uncomplicated SAB who are treated with a short course (2 weeks) of appropriate antibiotic therapy. Fowler et al. demonstrated that mortality and embolic rates were higher in patients with definite S. aureus IE whose vegetations were visualized by TTE than in those whose vegetations were visualized only by TEE [71]. They postulated that small vegetations detected only by TEE may represent an earlier stage of S. aureus IE that is more likely to respond to antibiotic therapy and less likely to cause embolic events compared to larger vegetations that are easily identified by TTE. Thus, currently there is no evidence that identification of small valvular vegetations only detectable by TEE improves clinical outcome in low risk patients with uncomplicated SAB.

Venditti et al. reported a low rate of IE (0.5 %) in *neutropenic patients with SAB*, suggesting a low yield of echocardiography, especially when adequate antistaphylococcal therapy is administered promptly [97].

The optimal time to perform echocardiography on SAB patients is currently unknown. At present, neither the American nor European guidelines address specifically the timing of echocardiography in relation to the onset of bacteremia, as this issue has not been studied previously. Endocarditis Working Party of the British Society of Antimicrobrial Chemotherapy in 2012 recommended echocardiography to be performed within the first week of treatment or within the first 24 h if there is other evidence to suggest IE [89]. In most studies, there is a delay of 2–3 days in performing TEE after TTE. Perhaps delaying TEE by several days is enough to permit vegetations to develop in those who supposedly had a negative or indeterminate TTE, thus contributing to the reported superiority of TEE over TTE.

Thus, currently there is not enough evidence to recommend TEE for all cases of SAB (Table 6.7). First, TEE has associated costs and risks [16]. Second, there is not enough evidence demonstrating improved clinical outcomes in patients evaluated with TEE over TTE in these patients. Third, several studies now suggest that it is possible to identify a subset of patients with SAB with a low risk of IE for whom TEE is not essential. Lastly, patients with negative TTE without valvular dysfunction, prosthetic valves or CIED, who are scheduled to receive extended courses of antibiotics for other forms of complicated S aureus infection (for example, osteomyelitis or visceral abscess) may not require TEE at all as management will be likely unaltered. Likewise, even a semi-invasive test such as TEE may not be appropriate in terminally ill or extremely frail patients whose outcome will be unaltered by the results of investigations.

Transesophageal echocardiography should be performed in patients with SAB and nondiagnostic TTE, when the possibility of IE is a serious consideration, when cardiac complications are suspected and when patients have prosthetic valves.

Cardiovascular Device Related Infective Endocarditis

Over the past two decades, the number of individuals worldwide with intra-cardiac prosthesis and indwelling devices including permanent pacemakers (PPM), implantable cardioverter defibrillators (ICD), atrial septal defect (ASD) closure devices, and ventricular assist devices (VAD) has increased significantly. When these patients develop unexplained fever or bacteremia, echocardiography is frequently requested to rule out vegetations involving the device or adjacent structures that may be damaged or abraded by the device, creating a nidus for infection. The following is a summary of the clinical use of both TTE and TEE for the diagnosis of cardiac device related infected endocarditis.

CIED

Cardiac implantable electronic devices, including PPMs and implantable ICDs, have had a significant increase in utilization over the past two decades, owing largely to the broader clinical indications for device implantation and the aging population. In an analysis of CIED implantation in the US alone, implantation rates for PPM and ICD have increased by 20 % and 60 % respectively between 1997 and 2004 [98]. CIED related IE are reported to occur between 0.5 % and 2 % of all cardiac device infections [99–101]. CIED infection is associated with substantial

morbidity and mortality, including the financial costs associated with treatment [99, 102–104]. The mortality rates associated with CIED related IE range from 10 % to 25 %, especially for those with methicillin-resistant S. aureus infection [100, 105–107].

In CIED IE, vegetation formation can occur along the course of the hardware electrode, the tricuspid valve leaflets, or the endocardium of the right sided cardiac chambers [108]. Patients with local signs of CIED infection, with or without fever, with positive or negative blood cultures, must undergo a detailed echocardiographic study to verify the presence or absence of CIED IE. Both TTE and TEE play important roles in monitoring the size and location of the vegetations during antimicrobial therapy both before and after CIED removal.

Several studies have examined the diagnostic and prognostic roles of echocardiography in the diagnosis of IE involving CIED [109–111]. Endocarditis of a PPM or ICD is difficult to diagnose by TTE alone as the leads often produce reverberations and artifacts (particularly when multiple leads are present) that may mask associated vegetations. As a result, when there is a strong suspicion of lead associated infection that is not apparent on TTE, TEE is appropriate. TEE has a higher spatial resolution for the detection of abscesses and allow for an improved study of the hardware leads, vena cava, tricuspid valve apparatus, as well as involvement of the left sided heart structures [112]. In an international registry consisting of ten academic medical centers and a total of 129 patients that prospectively enrolled patients with CIED infections, TTE was able to detect vegetations in only 11 patients. TEE detected vegetations in the majority of patients diagnosed with CIED [113]. Intracardiac echocardiography has recently been used in the detection of vegetations on pacemaker leads [114].

In patients with vegetations involving ICDs, the sensitivity of detection of lead vegetations by TTE ranges from 22 % to 30 % as compared with a sensitivity of 95 % by TEE [115, 116]. The importance of performing a TEE in any CIED patient with unexplained fever or bacteremia, especially in the setting of SAB cannot be overemphasized.

ASD Closure Devices

Percutaneous closure device is an effective, safe, and commonly employed alternative to surgical closure in patients with a patent foramen ovale or ASD who meet appropriate clinical indications for closure [117]. Endocarditis of an ASD closure device is an uncommon occurrence with only a few case reports described in the literature to date, [109–111, 118]. Vegetations described as mobile echodense masses attached to the closure device have been detected by TTE and/or TEE. The relative few reported cases preclude reliable assessment of the sensitivity and specificity of TTE or TEE in this setting.

Ventricular Assist Devices

In symptomatic patients with advanced heart failure, despite optimal medical therapy, mechanical circulatory support with a LVAD has been used successfully as either a bridge to heart transplantation or as destination therapy [119]. In a study of

68 individuals with 2.5 years of follow-up, about one-third of the LVADs may become infected within 3 months of implantation [120]. The associated infection may involve the driveline exist site and pocket, as well as the valves or blood-contacting surfaces of the LVAD.

The role of echocardiography (both TTE and TEE) in the setting of IE of the LVAD is to inspect the potential sites of infection, as pathogens can colonize the inner surfaces of the device and the connecting cannulas. Visualization of vegetation is limited by the reflective internal metal surfaces of the device and the prosthetic tubing. As such, the sensitivity and specificity of TTE and TEE in this setting remains ill defined.

Conclusion

Infective endocarditis can be a difficult diagnosis to make. However, a thorough history, careful physical examination and applying validated diagnostic criteria can improve the diagnostic accuracy. Echocardiography (TTE and TEE) is an extremely useful tool in the diagnosis and prognosis of IE but it needs to be used appropriately. In general, TEE is more sensitive and specific compare to TTE but is also more invasive and associated with a small but definite complication risk. Patient selection for and timing of echocardiography should be based on clinical risk categories (high versus low) and the likelihood of IE (high, intermediate and low). Patients with a high clinical risk should undergo echocardiography on a high priority basis. Patients with definite IE should be empirically treated and an echocardiogram performed not for diagnostic purposes but to guide prognosis and treatment. Patients with a low clinical risk and a low clinical likelihood need not routinely undergo echocardiography, whereas those with low clinical risk and intermediate clinical likelihood should undergo echocardiography to help clarify the diagnosis. We should be particularly vigilant about the diagnosis of IE in patients with persistent SAB and in patients with prosthetic heart valves or intracardiac devices. In these patients, we recommend a low threshold for echocardiography (TTE and TEE). TEE has proven to be very useful and should be performed in the majority of these patients. The development of PET-CT is a promising modality that can be helpful in equivocal cases despite comprehensive echocardiography.

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Role of Transthoracic and Transesophageal Echocardiography in the Management of Endocarditis

7

Christopher Johnson and Kwan-Leung Chan

Abstract

The detection of vegetation or abscess by echocardiography is key to the diagnosis of infective endocarditis. Transesophageal echocardiography (TEE) is superior to transthoracic (TTE) echocardiography in the detection of vegetation or abscess, and should be used in patients at high risk of endocarditis despite a negative TTE. TEE is also preferred in the setting of prosthetic valves and in the detection of perivalvular complications. The usefulness of echocardiography is further enhanced by the development of real-time 3-D imaging capability.

Keywords

Transthoracic echocardiography • Transesophageal echocardiography • Real-time 3-D echocardiography • Abscess • Vegetation • Prosthetic valve • Valvular perforation • Perivalvular complications

Key Points

1. TEE is not necessary in patients with low likelihood of IE and good TTE images.
2. Despite good TTE images, TEE is recommended in the setting of suspected prosthetic valve IE, suspected culture negative IE, and bacteremia with virulent orgranisms such as Staphylococcus aureus.
3. TEE is indicated in the assessment of perivalvular abscess and related complications in both native valve IE and prosthetic valve IE.

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4. Perivalvular abscess is a dynamic process, and TEE can provide useful prognostic information during the follow up including in patients who have undergone cardiac surgery for perivalvular abscess.
5. Real-time 3-D echocardiography is being increasingly used in patients with IE and may yield additional anatomic insight particularly in defining perivalvular complications.

Introduction

Infective endocarditis (IE) has protean manifestations and confirming the diagnosis is frequently difficult leading to a delay in initiating anti-microbial therapy. As vegetation is the hallmark of IE, prompt diagnosis can be facilitated through the use of a reliable, noninvasive test to detect vegetation.

Since its introduction into clinical practice in the 1970s, echocardiography has been intimately involved in the detection of vegetations. Technological advances have dramatically improved the ability of echocardiography to detect vegetation, valvular destruction and perivalvular complications, such that echocardiographic findings are now one of the most important diagnostic criteria for IE [1]. In addition to confirming a diagnosis of IE, echocardiography provides vital prognostic information in complicated endocarditis where surgical intervention may be appropriate. The value of echocardiography in patients with a low likelihood of IE may be questioned, but given the importance of correctly diagnosing IE, echocardiography is clearly indicated in the appropriate clinical setting where endocarditis is likely (Table 7.1) [2].

Table 7.1 Appropriate use criteria for echocardiography in proven or suspected endocarditis

Indication	Appropriateness score (1–9)
A. TTE	
1. Initial evaluation of suspected infectious endocarditis with positive blood cultures or new murmur	Appropriate (9)
2. Re-evaluation of infective endocarditis at high risk for progression or complication or with a change in cardiac status or cardiac exam	Appropriate (9)
B. TEE	
1. As initial or supplemental test to diagnose infective endocarditis with a moderate or high pre-test probability (e.g. staphylococcal bacteremia, fungemia, prosthetic heart valve or intra-cardiac device)	Appropriate (9)
2. Re-evaluation of prior TEE findings for interval change (eg. resolution of vegetation after antibiotics) when change in therapy is anticipated	Appropriate (8)

Adapted from Ref. [2]

Native Valve Endocarditis

Detection of Vegetation

Vegetation is the hallmark of the disease. The ability of ultrasound to produce images of structures inside the heart offers clinicians the opportunity to identify valvular vegetations, which previously required direct inspection at surgery or autopsy. Most vegetations are attached to the upstream side of cardiac valves, along the valve surface facing the lower pressure chamber (e.g. the atrial side of the mitral valve). Unusual locations, such as mural vegetations on myocardium or vegetations attached to the aorta, have been recognized. Left atrial mural vegetations have been found at the site of impingement of a jet of mitral regurgitation due to mitral valve IE. The finding of a mural vegetation on the left atrial wall should prompt a careful search for evidence of mitral valve endocarditis and mitral regurgitation.

Transthoracic Echo The first series describing vegetations detected by echocardiography with pathological correlation was in 1973 using M-mode transthoracic echocardiography (TTE) [3]. M-mode criteria for a valvular vegetation are a non-uniform, shaggy echogenic mass attached to a valve leaflet but not interfering with its motion [2–5]. Compared to autopsy or surgical findings, this definition of vegetation is specific but insensitive [4]. False positive findings include old vegetations from remote endocarditis, thickened leaflets of myxomatous mitral valves, sclerotic aortic valves and mitral valve fluttering related to aortic insufficiency [4]. Some M-mode findings are associated with poor prognosis, including ruptured mitral valve chordae, torn and flail aortic cusps and premature closure of the mitral valve due to severe aortic insufficiency [6]. Historically, such findings were used to identify high risk patients who may need surgical intervention [5].

Two-dimensional echocardiography provides spatial orientation superior to M-mode and has replaced M-mode in the detection of vegetation. The 2D echo definition of a vegetation is an irregularly shaped echolucent mass adherent to valves, endothelial surfaces, or intracardiac prosthetic devices, which usually has a high frequency motion independent of the underlying cardiac structure. Specificity is increased if a vegetation can be imaged throughout the cardiac cycle in multiple views [7, 8, 9]. Healed vegetations would become echodense. Vegetations can be characterized by morphologic features including their size, location, number, shape, mobility, and consistency (Fig. 7.1) [10]. The size of a vegetation that can be detected by TTE depends on the image quality. Early studies with fundamental imaging permitted detection of vegetations greater than 5 mm in maximum dimension [10]. Harmonic imaging permits detection of smaller vegetations in patients with high quality images, but in patients with inadequate acoustic windows, the accuracy of TTE is limited [10, 11]. Compared to transesophageal echocardiography (TEE), TTE underestimates vegetation size by up to 50 %. TTE is not sensitive enough to detect small vegetations, particularly in patients with pre-existing valvular abnormalities (Table 7.2) [12, 13]. The causes of false negative and false

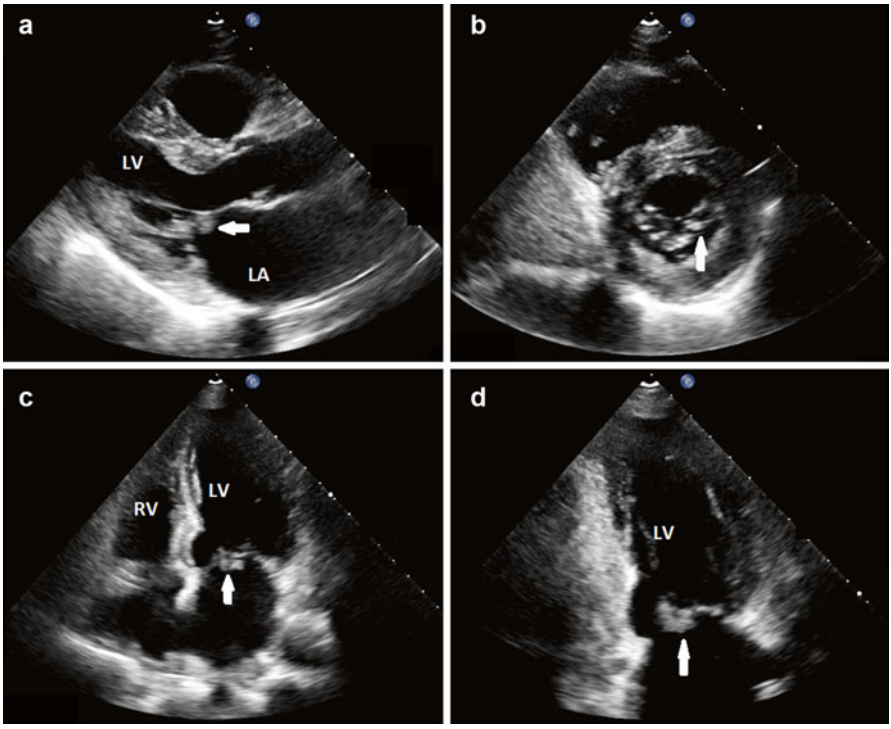

Fig. 7.1 Transthoracic echocardiogram shows a vegetation (*arrow*) on the anterior mitral leaflet in the long-axis (**a**), short-axis (**b**), four-chamber (**c**) and two-chamber (**d**) views. *LA* left atrium, *LV* left ventricle; *RV* right ventricle

Table 7.2 Relationship between vegetation size and sensitivity of transthoracic echocardiography

Vegetation size	Sensitivity %
<5 mm	0–25
5–10 mm	50–69
>10 mm	84–100

From Refs. [12, 13]

positive findings for vegetations are listed in Table 7.3. The overall sensitivity and specificity of TTE for detecting valvular vegetations are 56 % and 91 % respectively (Table 7.3) [12–21].

Transesophageal Echo Transesophageal echo involves the insertion of an ultrasound transducer mounted on a gastroscope into the esophagus and stomach to image the heart. The close proximity of the heart to the esophagus and the lack of intervening structures, such as the chest wall and lungs, ensure higher image quality using TEE compared to TTE. Transesophageal echo has higher sensitivity and

Table 7.3 Transthoracic echocardiography in the diagnosis of valvular vegetation

Reference	Sensitivity %	Specificity %	PPV %	NPV %	Proportion with IE (%)	Proportion with prostheses (%)
Erbel et al. [12]	63	98	92	91	96/176 (55)	ND
Shivley et al. [14]	44	98	88	84	16/24 (24)	3/66 (5)
Birmingham et al. [15]	30	100	100	57	33/63 (52)	2/64 (3)
Shapiro et al. [16]	60	91	86	72	30/64 (47)	0/64 (0)
Lowry et al. [17]	36	83	ND	ND	28/85 (33)	29/85 (34)
Reynolds et al. [13]	55	ND	ND	ND	51/101 (50)	ND
Jassal et al. [18]	84	88	89	82	19/36 (53)	0
Casella et al. [19]	87	85	87	86	33/74 (44)	0
Kini et al. [20]	45	79	56	71	179/486 (37)	49/486 (10)
Barton et al. [21]	58	99	95	89	82/622 (13)	ND
Average	56	91	86	79	567/1731 (33)	83/765 (10)

IE infective endocarditis, *ND* not determined, *NPV* negative predictive value, *PPV* positive predictive value

Table 7.4 Transesophageal echocardiography in the diagnosis of valvular vegetation

Reference	Sensitivity %	Specificity %	PPV %	NPV %	Proportion with SBE (%)	Proportion with prostheses (%)
Erbel et al. [12]	100	98	95	100	96/176 (55)	ND
Shivley et al. [14]	94	100	100	98	16/24 (24)	3/66 (5)
Birmingham et al. [15]	88	97	97	88	33/63 (52)	2/64 (3)
Shapiro et al. [16]	87	91	90	88	30/64 (47)	0/64 (0)
Lowry et al. [17]	93	91	ND	ND	28/85 (33)	29/85 (34)
Average	92	95	96	94	254/513 (50)	34/269 (13)

IE infective endocarditis, *ND* not determined, *NPV* negative predictive value, *PPV* positive predictive value

specificity in the detection of vegetations in patients with suspected endocarditis (Table 7.4) [12, 14–17]. The superior image quality of TEE permits the visualization of small vegetations (2–5 mm) on native heart valves that are commonly missed by TTE (Fig. 7.2) [12, 13]. Despite superior image quality, TEE faces similar limitations as TTE in terms of false-positive and false-negative studies (Table 7.5). Libman-Sacks endocarditis refers to vegetations that occur on the valves of patients with systemic lupus erythematosus (SLE) in the absence of infection [22]. Pathologically, these vegetations are made up of inflammatory cells associated with fibrous tissue and fibrin. On echocardiography, they appear as 2–4 mm protrusions adherent to endocardium, frequently at valve commisures [22]. Echo studies of

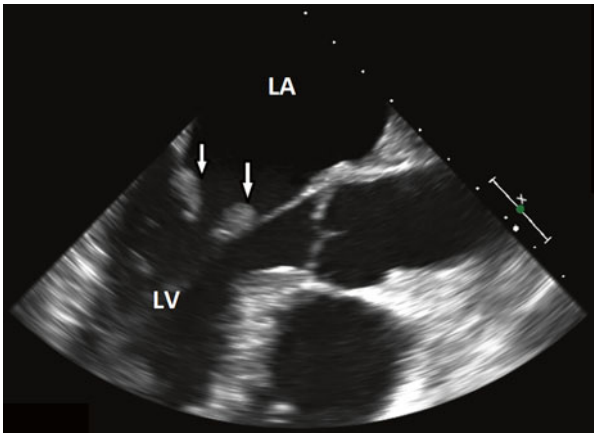

Fig. 7.2 Two mitral valve vegetations (*arrows*) are demonstrated by transesophageal echocardiography when only one vegetation is detected by transthoracic echocardiography. This is in the same patients as in Fig. 7.1. *LA* left atrium, *LV* left ventricle

Table 7.5 Pitfalls in the detection of vegetations by echocardiography

Mimics of vegetation (false positives)
Pre-existing valvular abnormalities
Sequelae of prior valve surgery
Components of prosthetic valves
Normal structures
Thrombi
Tumor
Extrinsic mediastinal masses
Artefacts
Vegetation not detected (false negatives)
Pre-existing valvular abnormalities
Prior endocarditis
Prosthetic material
Suboptimal images
Early disease with small vegetation

patients with SLE have documented these non-infectious vegetations in up to 18 % of patients [23]. They are indistinguishable from vegetations due to IE, therefore the clinical context is essential to avoid misdiagnosis of IE. Antiphospholipid antibody syndrome can be seen as an isolated clinical entity or in association with SLE and also causes Libmans-Sachs vegetations [24]. Nonbacterial thrombotic endocarditis, also called marantic endocarditis, refers to the occurrence of non-infective valvular vegetations in the setting of metastatic cancer, typically adenocarcinomas. The echocardiographic appearance is indistinguishable from infectious vegetations, and awareness of a non-infectious context in the setting of metastatic adenocarcinoma is important to avoid mis-diagnosis [25]. In the setting of pre-existing valvular disease such as severe myxomatous changes of the mitral valve or degenerative changes of

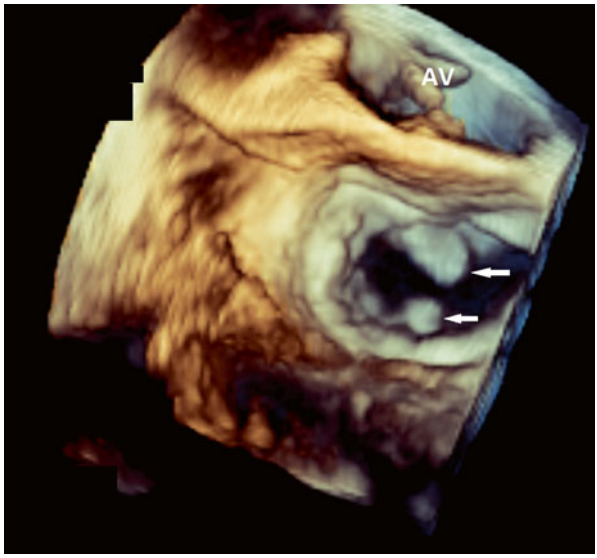

Fig. 7.3 Real-time 3D transesophageal echocardiography from the atrial perspective shows the presence of two vegetations (*arrows*) on the mitral valve. *AV* aortic valve

the aortic valve, detection of vegetation can be difficult, and both false positives and false negatives occur. In addition, during the early stages of endocardial infection, there may not be a sufficiently large vegetation to permit detection with TEE. In such situations, a repeat TEE in 7–14 days can increase the sensitivity for detecting valvular vegetations [11, 26]. The overall sensitivity of TEE for valvular vegetations is 92 % and specificity is 94 % (Table 7.4) [12, 14–17].

Real-time three-dimensional echocardiography has shown good correlation with findings at cardiac surgery in patients with endocarditis, and in some cases real-time three-dimensional echocardiography detects vegetations that are not apparent on 2D TEE [27] (Fig. 7.3). Compared to real-time 3D echocardiography, 2 D TEE underestimates the maximum length of vegetations by 20–25 %, and this may have implications in assessing embolic risk and determining the optimal timing of surgical intervention if indicated [28, 29].

Summary

1. A vegetation is an irregularly shaped, echolucent mass adherent to valves, endothelial surfaces, or intracardiac prostheses, with a high frequency motion or oscillation independent of the associated valve or prosthesis, imaged throughout the cardiac cycle in multiple views.
2. Important causes of false negative TTE images for endocarditis are small vegetations <5 mm, prosthetic valves, and poor image quality.
3. TEE is more sensitive and specific than TTE for detecting vegetations.
4. Echo findings specific for IE should be used in conjunction with clinical findings to avoid misdiagnosis of IE.
5. When the likelihood of IE is high and initial TEE is negative for vegetation, a repeat TEE should be performed in 7–10 days.

Valvular Abnormalities

Perforation of left sided valves is a complication of IE with important implications for clinical management, since a common indication for surgical intervention is heart failure due to valvular regurgitation. The echo definition of perforation is an interruption of leaflet continuity at a site removed from the leaflet coaptation area. Color Doppler imaging shows a high velocity jet traversing the defect through the body of the valve leaflet (Fig. 7.4) [30, 31]. Regurgitant jets from valvular perforations in IE are frequently eccentric. Valvular perforation should never be diagnosed when a regurgitant jet originates from the coaptation area and there is no evidence of interruption of leaflet continuity.

Almost all mitral valve perforations and some aortic valve perforations occur within aneurysms, or diverticuli, arising from the infected valve. An aneurysm or diverticulum of the mitral valve is a saccular outpouching bulging into the left atrium during systole and collapsing during diastole (Fig. 7.5) [31]. Frequently, mitral valve aneurysms and perforations, especially those involving the anterior mitral valve leaflet, are associated with aortic valve vegetations and aortic regurgitation. This likely occurs when the aortic regurgitation jet seeds the mitral valve leaflet. Finding a mitral valve aneurysm and/or perforation in a patient with IE should prompt a careful assessment of the aortic valve for vegetations and aortic regurgitation.

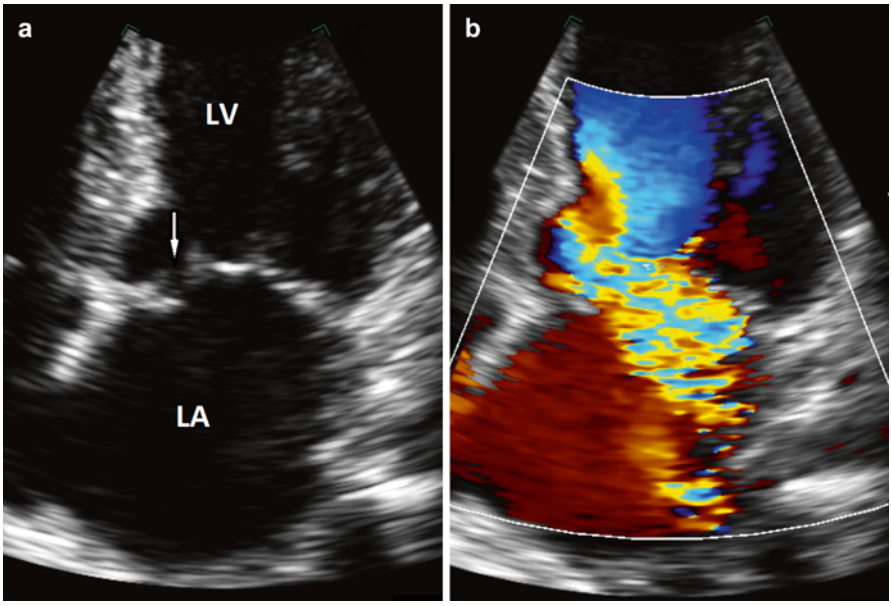

Fig. 7.4 (**a**) A large perforation (*arrow*) is present on the mitral valve. (**b**) Colour flow imaging shows severe mitral regurgitation via the leaflet perforation. *LA* left atrium, *LV* left ventricle

The diagnosis of perforation is a predictor of the need for surgery and early mortality, because patients with perforation frequently have hemodynamically significant valvular regurgitation. Patients with valvular insufficiency due to perforation may be amenable to patch repair which is preferable in these patients [31]. Patients with valvular perforation, but who have no heart failure and respond well to antimicrobial therapy, may not require surgery. Such patients require clinical and imaging follow up to ensure there is no progression of valvular regurgitation and to monitor for evidence that valvular regurgitation is no longer well tolerated.

Endocarditis is the most common cause of mitral valve aneurysm and perforation. There are very few non-endocarditis related causes of mitral valve aneurysm such as osteogenesis imperfecta, Marfan's syndrome, Ehlers-Danlos, and pseudoxanthoma elasticum [32–34].

Transthoracic Echo To directly image leaflet discontinuity by TTE requires high quality images which in most patients cannot be obtained. The sensitivity of TTE for the diagnosis of valvular perforation is low and varies from 11 % to 70 % (Table 7.6) [19, 30, 31, 35] .

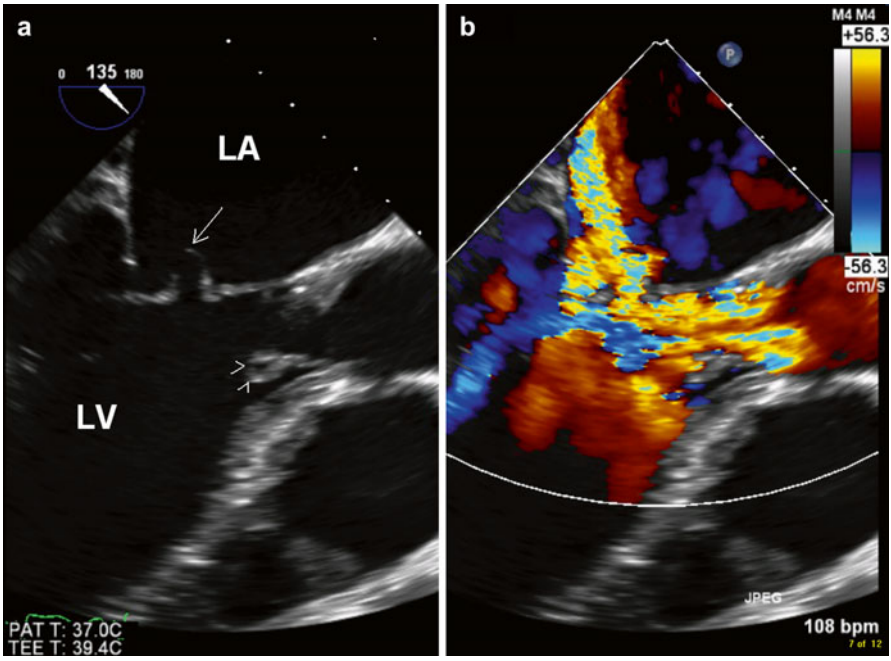

Fig. 7.5 (**a**) Mitral leaflet diverticulum (*arrow*) with perforation is present on the anterior mitral leaflet due to the presence of aortic endocarditis with a large vegetation (*arrow heads*). (**b**) Colour flow imaging shows severe mitral regurgitation via the mitral leaflet perforation. *LA* left atrium, *LV* left ventricle

Table 7.6 Comparison of transthoracic with transesophageal echocardiography in the diagnosis of valvular perforation

Reference	Sample size	Sensitivity of TTE %	Sensitivity of TEE %
Cziner et al. [30]	10	30	90
DeCastro et al. [31]	20	70	100
Vilacosta et al. [35]	13	38	100
Casella et al. [19]	9	11	ND

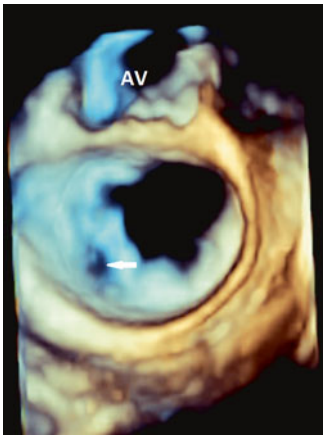

Fig. 7.6 Real-time 3D transesophageal echocardiography from the atrial perspective shows a large perforation (*arrow*) on the lateral scallop (P1) of the posterior mitral leaflet. *AV* aortic valve

Transesophageal Echo TEE is more sensitive for detecting valvular perforation than TTE (Table 7.6) [19, 30, 31, 35]. In addition, most perforations can be directly visualized on 2D imaging rather than relying on imaging the color flow jet traversing the valve leaflet. This direct visualization of a perforated leaflet increases diagnostic certainty (Fig. 7.4). The size of perforations visualized on TEE agrees closely with pathologic examination and range from 2 to 7 mm [31]. Perforations imaged with real-time three-dimensional echocardiography agree closely with surgical findings, and real-time 3D echocardiography detects some perforations missed by 2D imaging, (Fig. 7.6) [27]. The higher sensitivity of TEE for detecting vegetations is important in excluding aortic valvular IE as the cause of mitral valve perforation or aneurysm.

Summary

1. IE is the most common cause of valvular perforations and valvular aneurysms in adult patients.
2. Valvular perforation should be suspected when the origin of the regurgitant jet is remote from the area of leaflet coaptation.
3. Perforations are often seen in the presence of valve aneurysms.
4. TEE is more sensitive and specific for diagnosing valvular perforations by direct visualization of leaflet discontinuity.

Perivalvular Abscess and Related Complications

The natural history of perivalvular abscess has become better understood, largely because of serial echocardiographic studies in patients who undergo surgical intervention as well as patients who are treated medically [36, 37]. Serial echocardiography in such cases has demonstrated that perivalvular abscess is a dynamic process and is the precursor for all other perivalvular complications such as pseudoaneurysm, fistula, and valve dehiscence in the case of prosthetic valve endocarditis. Perivalvular abscess has a predilection for the aortic root, whose central location and proximity to multiple structures can lead to serious complications.

The pathological definition of a perivalvular abscess is a region of necrosis with purulent material that does not communicate with a cardiac chamber or great vessel lumen [38]. On echocardiography, an abscess cavity is a localized abnormal echolucent area within the perivalvular tissue that does not communicate with the circulation (Fig. 7.7) [37]. In addition to identifying the presence of an abscess, echocardiography delineates characteristics of the abscess that are important in planning surgical intervention. These include the maximum thickness of the abscess cavity, the circumferential extent of the abscess, and involvement of surrounding structures. Both long axis and short axis views of the aortic root and ascending aorta are important for determining the extent of an aortic root abscess cavity. X-Plane imaging and real-time 3D echo can delineate the circumferential and longitudinal extent of aortic root abscess.

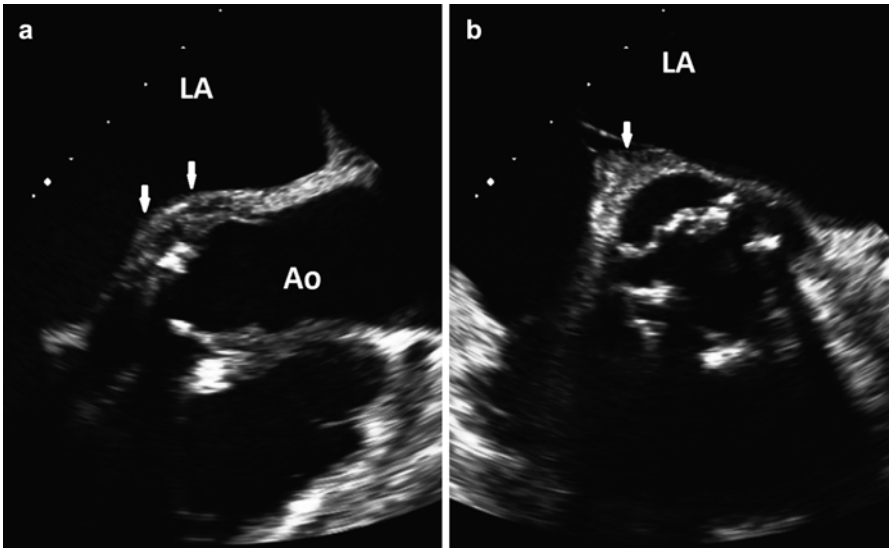

Fig. 7.7 An echolucent mass (*arrows*) consistent with abscess is located at the posterior aortic root and imaged in the long-axis (**a**) and short axis (**b**) views by transesophageal echocardiography. *Ao* aorta, *LA* left atrium

Serial echocardiographic evaluation of abscesses in the setting of IE has demonstrated the development of pseudoaneurysm from abscess cavities (Fig. 7.8) [37]. As necrotic tissue separating the abscess cavity from the adjacent high pressure left ventricular outflow tract or aorta breaks down, a direct communication develops between the left ventricle (LV) or aorta and the abscess cavity [36, 37, 39, 40]. When the LV or aorta communicates with an abscess cavity, the term pseudoaneurysm is used. A pseudoaneurysm appears on echocardiography as an echolucent space or pouch anatomically related to the valve annulus. High pressure flow from the LV or aorta into the pseudoaneurysm creates the appearance of a pulsatile pouch [38].When the pseudoaneurysm originates below the aortic annulus, the connection is between the LV and the pseudoaneurysm cavity and this can be demonstrated with color flow imaging (Fig. 7.8) [41]. Using the color flow jet as a guide may help to directly image the LV to pseudoaneurysm connection on 2D imaging. The maximum dimension of LV to aortic discontinuity on 2D imaging can vary from 1 to 24 mm [41]. Pseudo-aneurysms can originate from the aorta, and using color flow imaging as a guide, the connection from aorta to pseudoaneurysm cavity can be demonstrated on 2D imaging. The only non-infectious cause of aortic pseudoaneurysm is prior aortic valve replacement, particularly when a composite graft has been constructed [42].

The mitral-aortic intervalvular fibrosa (MAIVF) is the fibrous tissue connecting the aortic root near the non-coronary cusp of the aortic valve to the base of the anterior mitral valve leaflet. Pseudoaneursysm of the MAIF may occur by direct

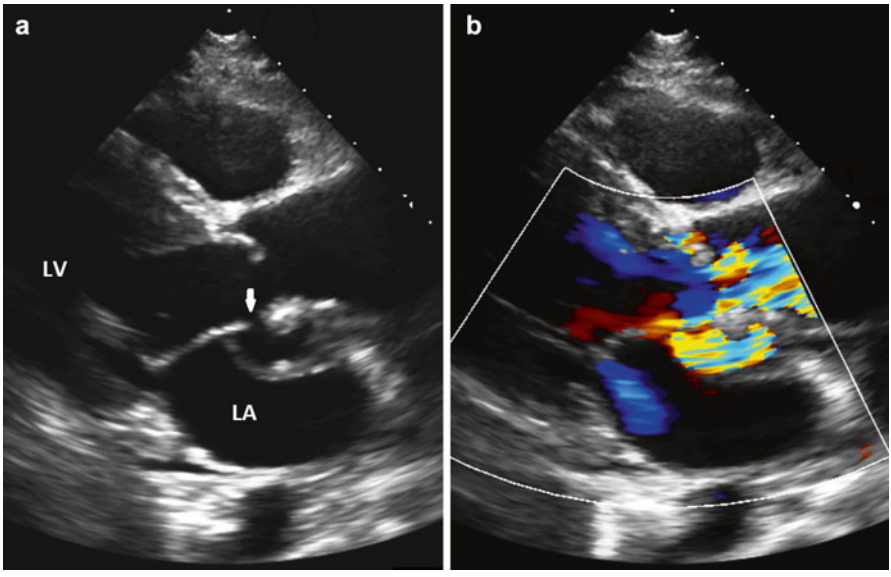

Fig. 7.8 (**a**) A pseudoaneurysm is present at the mitral aortic intervalvular fibrosa and communicates with the left ventricular outflow tract (*arrow*). (**b**) Colour flow imaging shows systolic flow into the pseudoaneurysm. *LA* left atrium, *LV* left ventricle

extension from an aortic root abscess. Fistulas connecting to the left atrium, aorta, or even into the pericardial space are complications of pseudoaneurysms of the MAIVF [43]. The diagnosis is made by visualizing an echolucent cavity at the junction of the base of the aortic root and base of the anterior mitral valve leaflet with systolic expansion and diastolic collapse (Fig. 7.8). Real-time 3-D echo of MAIVF pseudoaneurysm has proven useful in demonstrating the relationship between MAIVF pseudoaneurysm and adjacent cardiac structures [44]. Non-infectious pseudoaneurysm of the MAIF has been reported following aortic valve replacement as a result of surgical trauma [43].

When a perivalvular abscess erodes into two adjacent vascular structures, a fistula develops. The aortic root is related to both great vessels, all four cardiac chambers, and the pericardial space, so that fistulas between any of these structures are possible. In addition, pseudoaneurysm of the MAIVF can fistulize, resulting in a connection between the LV and the left atrium (LA). Hemodynamically, the result of this LV to LA connection can be thought of as "suprannular mitral regurgitation" [45].

Clinical factors predictive of periannular complications are listed in Table 7.7 [38, 46, 47].

The presence of periannular complications of IE has important implications for prognosis. For example, the presence of an abscess may result in recurrent evidence of infection in spite of anti-microbial therapy, which results in a clinical indication for surgery. An abscess complicated by a fistula causing poorly tolerated volume overload may result in heart failure, and thus require surgery on clinical grounds. These examples illustrate how echocardiography defines the underlying periannular pathology that drives clinical indications for surgery in endocarditis complicated by perivalvular abscess. Patients with periannular abscess have a high mortality whether or not they undergo surgery (Tables 7.8 and 7.9) [36–38, 48–50]. In patients referred for surgical intervention, preoperative echo is vital in the planning of surgical intervention and in assessing operative risk. The range of operative procedures in the surgical management of periannular complications of endocarditis is discussed in detail in Chap. 8.

The circumferential extent of abscess and the presence of a fistula have been shown to predict increased operative risk [49]. Hemodynamically significant aortic or mitral regurgitation also increases the operative risk in the setting of abscess [50]. Patients who survive surgery for perianular complications are at continued risk for cardiovascular morbidity. Perivalvular regurgitation is present in the majority of

Table 7.7 Risk factors in the development of perivalvular complications in infective endocarditis

Risk factor	Relative risk	p-value
Prosthetic valve	1.88	<0.01
Aortic position	1.81	<0.01
Coagulase negative staphylocci	1.77	<0.05
Atrioventricular block	2.66	<0.01
Intravenous drug use	2.5	<0.01

Adapted from Refs. [38, 46, 47]

Table 7.8 Short and long term mortality in patients with of perivalvular abscess who received medical treatment only

Reference	Sample size	Early mortality	Late mortality	Late surgery	Mean followup
Byrd et al. [36]	5	0	3	0	3 years
Aguado et al. [48]	10	9	ND	ND	30 days
Choussat et al. [49]	20	ND	8	ND	6 months
Chan [37]	12	0	8	3	4.5 years

TEE transesophageal echocardiography, *TTE* transthoracic echocardiography, *ND* not determined

Table 7.9 Short and long term mortality in patients with perivalvular abscess who were treated surgically

Reference	Sample size	Early mortality	Late mortality	Late surgery	Mean F/U
Byrd et al. [36]	5	2	1	0	26 months
Aguado et al. [48]	30	8	1	4	78 months
Choussat et al. [49]	213	35	87	0	6 months
Chan [37]	31	6	10	8	4.5 years
Cosmi et al. [50]	24	ND	9	0	ND

TEE transesophageal echocardiography, *TTE* transthoracic echocardiography, *ND* not determined

patients who have surgery for periannular complications of IE. Following surgery for aortic valve IE, aortic regurgitation has been reported in 78 % of patients with aortic root abscess versus 26 % in patients without root abscess [51]. Perivalvular leaks causing symptoms or impaired LV function may require repeat valve surgery or device closure [38]. Finally, recurrent or persistent infection can occur post operatively which in some cases requires further surgical intervention. Ongoing clinical and echocardiographic surveillance of patients following medical or surgical therapy for peri-annular complications is important.

Transthoracic Echo Abnormal thickness of the aortic root >10 mm without a cavity can be a sign of perivalvular abscess, and corresponds to surgical findings of an abscess cavity full of purulent material [52]. Abscess cavities can be located at any point on the aortic annulus [40]. TTE may be particularly helpful for aortic root abscesses, especially anterior aortic root abscesses which are relatively close to the chest wall, making them amenable to transthoracic imaging. Short and long axis views of the aortic root and ascending aorta can determine the circumferential and longitudinal extent of the abscess cavity. On color flow imaging of both short and long axis images, an abscess cavity will have no Doppler evidence of communication between the cavity and adjacent great vessels or cardiac chambers. The accuracy of echo in the diagnosis of abscess is summarized in Table 7.10 [38,

Table 7.10 Comparison of transthoracic with transesophageal echocardiography in the diagnosis of perivalvular abscess

References	TTE		TEE		Proportion of abscesses infecting prosthetic valves (%)
	Sensitivity %	Specificity %	Sensitivity %	Specificity %	
Ellis et al. [52]	86	88	ND	ND	17/22 (77)
Daniel et al. [53]	28	ND	87	ND	16/46 (35)
Aguado et al. [48]	80	85	ND	ND	13/36 (36)
Tingleff [40]	ND	ND	100	ND	18/36 (50)
Blumberg [54]	28	90	78	100	12/24 (50)
San Roman [46]	ND	ND	90	100	46/46 (100)
Choussat [49]	36	ND	80	ND	77/233 (33)
Graupner [38]	ND	ND	80	92	36/78 (46)

TEE transesophageal echocardiography, *TTE* transthoracic echocardiography, *ND* not determined

40, 46, 48, 49, 52–54]. While TTE is specific for diagnosing abscess, it has poor sensitivity in detecting an abscess. If abscess is suspected, a negative TTE should not be considered sufficient to rule out this diagnosis, and TEE should be performed. The main reasons for false negative TTE's for abscess are poor image quality and the lack of specificity of echo features on transthoracic imaging. Compared to periaortic abscess, mitral annular abscesses are even more difficult to diagnose by TTE due to the far field nature of the mitral annulus resulting in suboptimal images.

Non-infectious causes of aortic root thickening include inflammatory aortitis, severe atheroma (unusual in the aortic root and ascending aorta), aortic dissection, and recent cardiac surgery (Fig. 7.9) [52]. A thorough knowledge of the normal anatomy and echocardiographic appearance of the atrioventricular groove is required to avoid misdiagnosing the presence of a mitral valve abscess (Table 7.11). The main cause of false positive TEE diagnosis of abscess in the mitral position is degenerative changes of the mitral annulus such as mitral annular calcification, and its more severe form, caseous calcification of the mitral annulus (Fig. 7.10). The typical appearance of caseous calcification of the mitral annulus on echo is a large echodense mass with smooth borders, which on short axis images can have a semilunar shape within the atrioventricular groove [55]. Surgical and pathological inspection reveals the contents to be a paste-like material which microscopically contains calcium and lymphocytes but no infectious organisms [55]. Clinical correlation is essential to avoid misdiagnosis.

Aortic pseudoaneurysm has a propensity to affect the posterior aortic root and can be identified as an echolucent space (Fig. 7.8). Color flow imaging shows flow from the LV or aorta into the pseudoaneurysm. A fistula is a communication with flow between two cardiac chambers or great vessels [38, 46]. A fistula should be suspected when color flow imaging shows turbulent flow originating in one cardiac

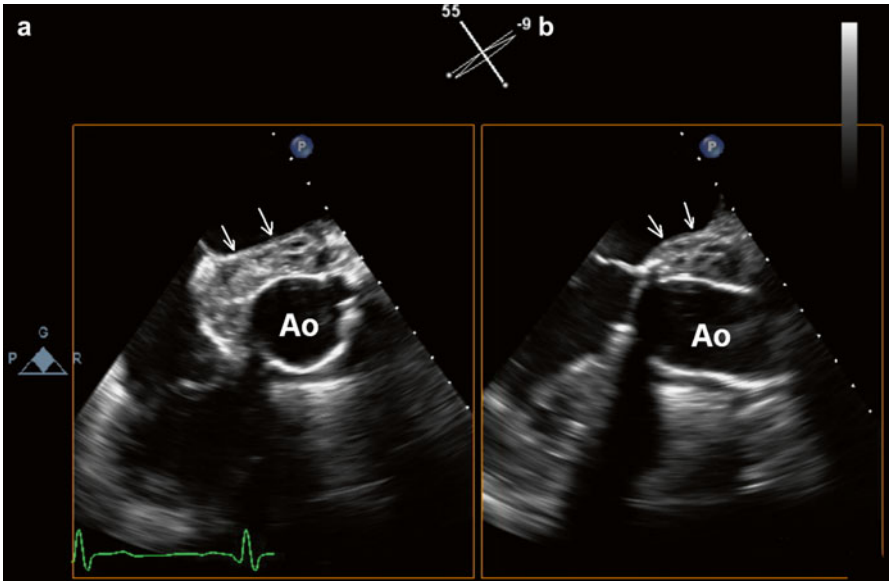

Fig. 7.9 Transesophageal short-axis (**a**) and long-axis (**b**) of the aortic root in a patient who has had recent aortic root replacement showing hematoma (*arrows*) posterior to the aortic graft mimicking abscess. *Ao* aorta

Table 7.11 Normal structures and conditions involving the atrioventricular groove that may mimic mitral annular abscess

Loculated pericardial effusion
Prominent epicardial fat
Descending thoracic aorta
Dilated coronary sinus
Shadowing from mitral annular calcification
Dilated left circumflex coronary artery

chamber or great vessel and terminating in a second great vessel or chamber (Fig. 7.11). Patients suspected to have perivalvular complications should undergo TEE to assess the extent and anatomic relationship of the abnormalities in relation to the adjacent cardiac structures.

Transesophageal Echo TEE is more sensitive and specific for the detection of abscess in both the aortic and mitral positions (Table 7.10) [38, 40, 46, 48, 49, 52–54]. The sensitivity of TEE ranges from 78 % to 90 % with a specificity from 92 % to 100 %. Adhering to the requirement for echolucency to define abscess can result in false negatives, particularly in the early stage of periannular infection [38]. Serial TEE evaluation of periannular infection in patients managed medically has shown that early abscesses appear as abnormal thickening of the aortic root which subsequently cavitates (Figs. 7.7 and 7.12). Therefore, echolucency is a specific sign for

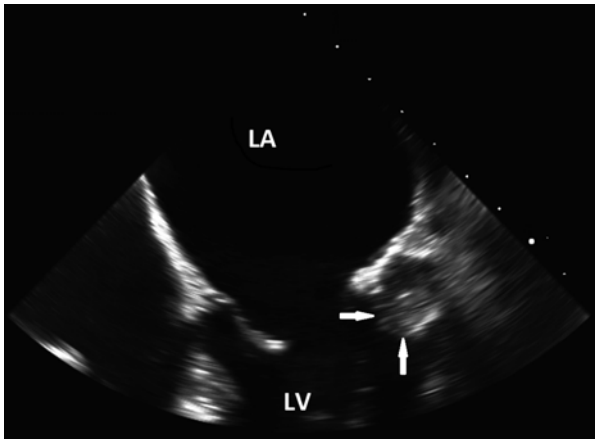

Fig. 7.10 Caseous calcification at the mitral annulus (*arrows*) can mimic mitral annular abscess. *LA* left atrium, *LV* left ventricle

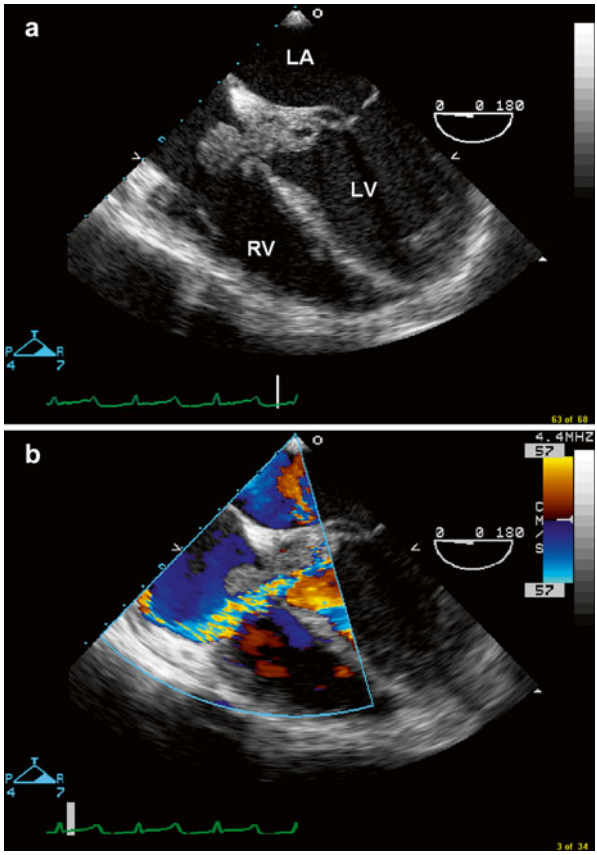

Fig. 7.11 (**a**) Large vegetations involving the mitral and tricuspid valves on transesophageal echocardiography. (**b**) Colour flow imaging shows a fistula connecting the left ventricle with the right atrium. *LA* left atrium, *LV* left ventricle, *RV* right ventricle

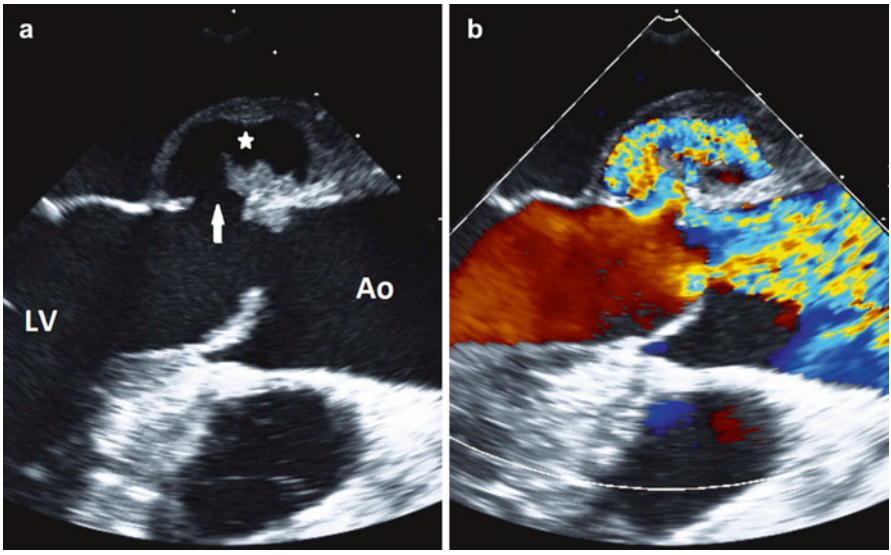

Fig. 7.12 (**a**) A pseudoaneurysm (*star*) is present at the posterior aortic root communicating with the left ventricular outflow tract (*arrow*). (**b**) Colour flow imaging confirms flow into the pseudoaneurysm during systole. This is the same patient as in Fig. 7.8. *Ao* aorta, *LV* left ventricle

abscess but may not be present in the earliest stages of abscess formation. In situations where abscess is suspected but the only finding is abnormal wall thickness, repeat imaging with TEE may document the development of an echolucent cavity, thus increasing sensitivity to detect this complication while avoiding false positives due to non-infectious causes of increased aortic root thickness. En-face views of the mitral and aortic valve using real-time 3D echocardiography demonstrate the location and anatomic relationships of abscess cavities to surrounding structures [27]. In general, 2D imaging is sufficient to detect the presence of an aortic valve abscess. However, detection of mitral valve abscess can be challenging with 2D TEE, and real-time 3D echocardiography may enhance sensitivity to detect abscess complicating native mitral valve endocarditis [27, 44]. Real-time 3D echocardiography can also detect complications of abscess such as pseudoaneurysm or fistula [44].

On TEE, an aneurysm MAIVF demonstrates systolic expansion and diastolic collapse of the interannular zone between the anterior mitral leaflet and the aortic valve (Fig. 7.12) [45]. Color flow imaging allows the identification and localization of perforations and fistulas that may be present within the aneurysm and result in a connection between LV and LA [56, 57]. In some cases, such fistulas can occur without an aneurysm, typically as a complication of aortic valve IE. Fistulas within pseudoaneurysms of the MAIVF are correctly identified by TEE, but rarely demonstrated on TTE [45, 56, 57].

Compared to TTE, TEE is more sensitive and specific for the diagnosis of pseudoaneurysm and fistula. In addition, the circumferential extent, anatomic

relationship and site of communication are better delineated by TEE. As with periannular abscess, TEE offers higher accuracy and more detailed imaging and is therefore recommended in all cases of known or suspected perivalvular complications.

Summary

1. Perivalvular abscess is a dynamic process and is the precursor of perivalvular complications such as pseudoaneurysm and fistula.
2. TTE can diagnose aortic root abscess but rarely diagnose mitral abscess.
3. TEE is more sensitive and specific than TTE in detecting periannular abscess, aneurysms and fistulas.
4. Patients with periannular abscess have high short- and long-term morbidity and mortality despite surgical treatment.

Right Sided Endocarditis

Right sided IE is a particularly common problem in injection drug users. The majority of vegetations in right sided endocarditis are found on the tricuspid valve, usually on the atrial side [57–59](Fig. 7.13). Occasionally, vegetations can encase the entire leaflet or be on the ventricular side of the tricuspid valve. Right sided vegetations tend to be large (10–20 mm or more) regardless of the causative organism. Tricuspid valve regurgitation can be present and can range in severity from mild to severe [57–59]. Compared to left sided endocarditis, right sided endocarditis has a lower mortality rate, 5–7 % in recent series, and patients are less likely to require surgical intervention [60, 61]. Predictors of mortality in right sided endocaridits included vegetation size >2 cm, with autopsy findings confirming massive pulmonary embolus as a cause of death in such cases [60].

Transthoracic Echo Vegetations in right sided IE in injection drug users were initially described on M-mode and 2D echo in 1980 [57]. Most cases of right sided endocarditis are readily diagnosed by TTE, because the vegetations are usually large and the tricuspid valve has an anterior location, making it more amenable to transthoracic imaging compared to left sided valves (Fig. 7.13) [61]. Rarely, right sided vegetations can involve the Eustachian valve. In a large series of endocarditis, Eustachian valve endocarditis represented 3.3 % of all cases of right sided endocarditis [62]. In most cases of Eustachian valve endocarditis, there were also vegetations on the tricuspid valve, and the diagnosis was readily made by TTE. The key to distinguishing vegetation from the normal Eustachian valve was abnormal thickness >5 mm and chaotic, independent motion unrelated to the cardiac cycle [62].

Right sided endocarditis can involve the pulmonic valve. The majority of pulmonic valve endocarditis occurs in patients with prior intervention for congenital heart disease. In the absence of prior cardiac intervention, the usual setting of pulmonic valve endocarditis is either injection drug use or indwelling central lines [63]. The majority of cases are readily diagnosed by TTE, with a sensitivity for detecting

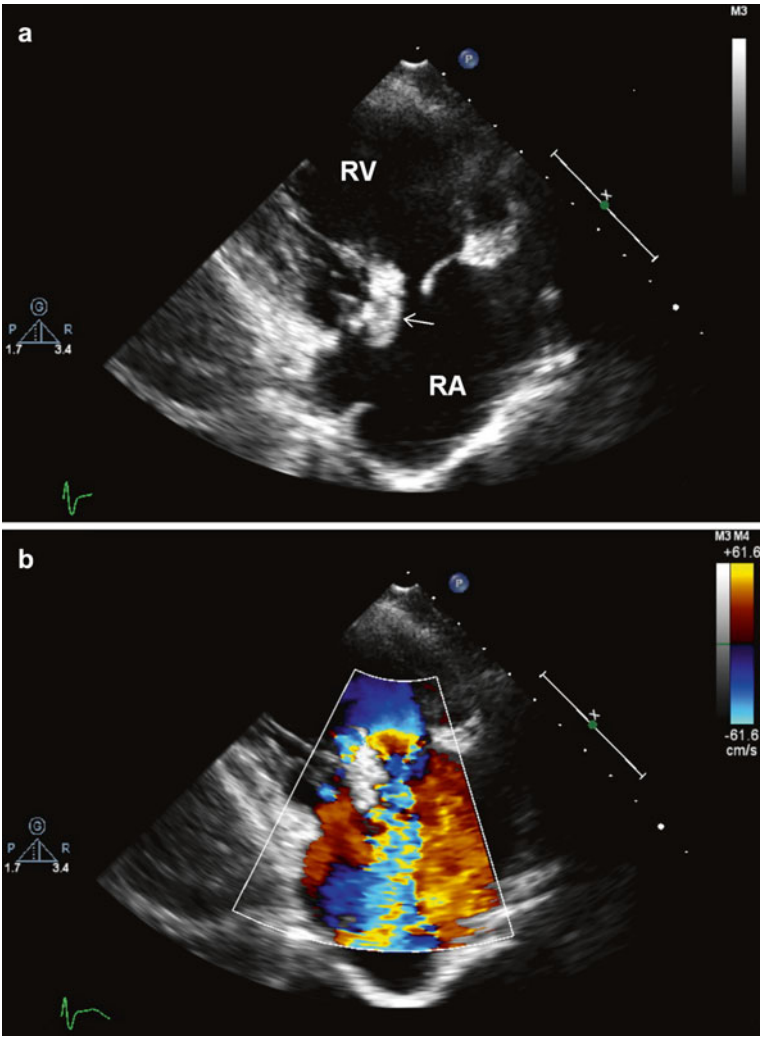

Fig. 7.13 (**a**) A large vegetation (*arrow*) involves the posterior tricuspid leaflet and the anterior leaflet is flail. (**b**) Colour flow imaging confirms severe tricuspid regurgitation. *RA* right atrium, *RV* right ventricle

pulmonic vegetations of 91 % [63]. In addition to the standard parasternal short axis view, a subcostal view can be useful.

Transesophageal Echo Transthoracic echo is usually adequate to diagnose right sided IE and assess the severity of tricuspid valve regurgitation. Although TEE can provide better delineation of the anatomic relationship between vegetation and valve leaflets, the information rarely alters the diagnosis or management [59]. Nevertheless, TEE can be useful in selected patients with suspected right sided IE as defined in Table 7.12 [64].

Table 7.12 Indications for transesophageal echocardiography in injection drug users with suspected right sided endocarditis

Poor transthoracic images
History of prior endocarditis
Pre-existing valve abnormalities
Suspected left-sided endocarditis
Suspected pulmonic valve endocarditis
Patients considered to have possible endocarditis and negative TTE

Adapted from Ref. [64] with permission
TTE transthoracic echocardiogram

Summary

1. Right sided endocarditis is accurately diagnosed using TTE.
2. Vegetations in right sided endocarditis are frequently large (5–20 mm) regardless of causative organism.
3. TEE is reserved for specific situations in suspected right sided IE.

Prosthetic Endocarditis

Detection of Vegetation

Endocarditis can affect bioprosthetic or mechanical heart valves as well as indwelling central lines and pacemaker wires. Vegetations have a predilection for the sewing ring of both bioprosthetic and mechanical valves, although the leaflets of a bioprosthetic valve can be involved. The presence of new perivalvular regurgitation is generally indicative of IE. Echocardiographic evaluation of endocarditis in the setting of prosthetic valves can be more challenging due to reverberations created by prosthetic material.

Transthoracic Echo The sensitivity of TTE for diagnosing endocarditis is lower for prosthetic valves than for native valves (Table 7.13) [65–67]. Therefore TEE should be performed if prosthetic valve endocarditis is suspected even though TTE shows no evidence to support the diagnosis. False positive echocardiographic findings for IE in the setting of prosthetic valves include echogenic masses of non-infectious origin such as sutures, pannus and thrombus. Correlation with clinical and microbiological data is required to avoid misdiagnosis. For bioprostheses, the main cause of false positives is non-infectious degeneration of bioprosthetic valve leaflets [67]. Typically, degenerating bioprosthetic valve cusps have bright and echodense nodules which are easy to distinguish from the soft, shaggy, mobile echodensity typical of a vegetation.

Transesophageal Echo Transesophageal echo is more sensitive and specific for prosthetic valve endocarditis compared to TTE. While TTE detects prosthetic valve endocarditis in about one third of the cases, the sensitivity of TEE for detecting prosthetic valve IE is 77–100 % (Table 7.13, Fig. 7.14) [65–67]. The most common

Table 7.13 Comparison of transthoracic with transesophageal echocardiography in the diagnosis of prosthetic valve endocarditis

References	Sample size	Sensitivity of TTE %	Sensitivity of TEE %
Mugge et al. [65]	22	27	77
Taams et al. [66]	12	25	100
Daniel et al. [67]	33	36	82

TEE transesophageal echocardiography, *TTE* transthoracic echocardiography

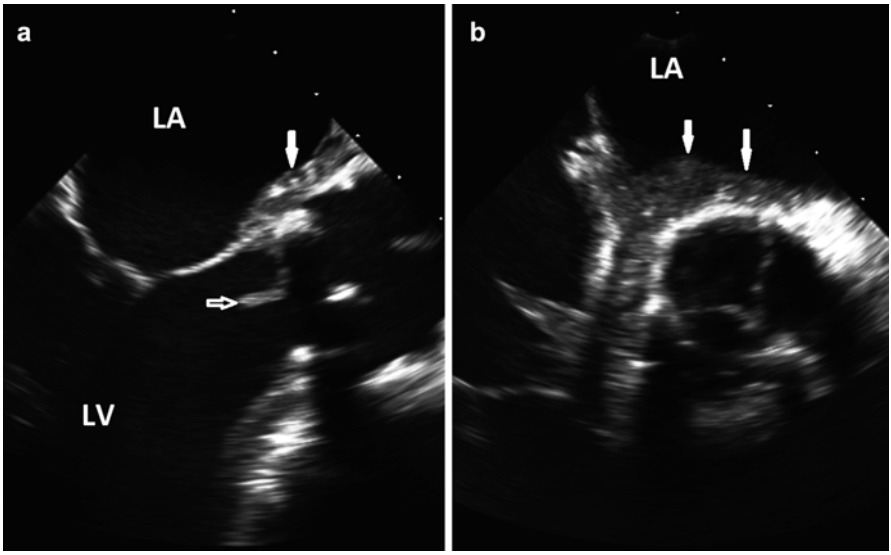

Fig. 7.14 A large posterior aortic root abscess (*arrows*) is imaged in both the long-axis (**a**) and short-axis (**b**) views in a patient with aortic bioprosthetic valve endocarditis. A vegetation (*open arrow*) is present on the bioprosthetic valve. *LA* left atrium, *LV* left ventricle

situation where TEE misses evidence of IE is in patients with aortic prosthetic valves [67]. This problem is magnified in the setting of aortic prosthetic valve infection when there is also a mitral prosthesis, as reverberations from the mitral prosthesis can mask the aortic prosthesis. For bioprostheses, the enhanced image quality of TEE often allows visualization of degenerative leaflets in greater detail than TTE. The bright echogenic appearance of degenerating bioprosthetic valve cusps can usually be distinguished from valvular vegetation. The high image quality of TEE images often reveals bright filaments on the sewing rings, which are generally non-infectious in origin. Prosthetic valve strands are thin, (<1 mm) mobile echodensities of variable length, and pathological examination suggests that these strands are composed of collagen rather than vegetation [68]. Prosthetic valve thrombosis appears indistinguishable from vegetation on TEE. It is important to combine TEE imaging data with clinical and laboratory evidence of infection to distinguish

thrombus from vegetation due to endocarditis [69]. Real-time 3D echocardiography permits accurate identification of vegetations and their relationship to the prosthetic valve sewing ring and leaflets [70, 71]. As in native valve endocarditis, the maximum length of prosthetic valve vegetations is greater when measured with real-time 3D echo versus 2D imaging [71].

The presence of periprosthetic regurgitation, if it is a new finding, raises the possibility of IE. This underscores the importance of obtaining a baseline post-operative echo study in all patients with prosthetic valves. Trace to mild perivalvular regurgitation is not uncommon in patients with prosthetic valves and no IE. The finding of an isolated, tiny perivalvular leak with no other echo findings of endocarditis in the setting of a prosthesis should be interpreted with caution [69]. In bileaflet mechanical valves, normal prosthetic regurgitation is eccentric and should not be confused with a perivalvular leak. Real-time 3D echocardiography can help confirm the location of perivalvular leaks by obtaining an en-face view of the prosthetic valve demonstrating a space between the sewing ring and annulus [71, 72]. In some patients, a full-volume acquisition with color flow imaging can demonstrate perivalvular regurgitation on 3D images [72].

Summary

1. TTE is specific but insensitive for the diagnosis of prosthetic valve endocarditis.
2. TEE is more sensitive and specific for prosthetic valve endocarditis than TTE. Most patients with prosthetic valves and suspected IE should have TEE.
3. Important false positive TEE findings include echodensities of non-infectious origin such as prosthetic valve strands, thrombi, and degenerative changes on bioprosthetic leaflets.

Perivalvular Abscess and Related Complications in Prosthetic Valve Endocarditis

The diagnosis of perivalvular abscess is more difficult in patients with prosthetic IE, because increased perivalvular thickness is a common finding in these patients in the absence of IE. A previous study for comparison is useful in the assessment of these patients, and review of previous intra-operative TEE images at the time of prosthetic valve implant can be helpful in some cases. In cases where an initial study is equivocal, the value of a repeat study in 7–10 days to look for evolutional changes as previously discussed with native valve IE remains very pertinent [26]. Persistent perivalvular abnormalities are common post-operative findings in patients who have had cardiac surgery to treat perivalvular abscess. Up to one third of such patients have peri-valvular leaks post-operatively, and this underscores the importance of comparing with previous studies and repeating the echo if clinical suspicion for perivalvular abscess is high [37].

Transthoracic Echo Perivalvular complications are more difficult to diagnose because the reverberation artifact from the prosthetic valve can mask surrounding structures. This is a particular problem with the posterior aortic root which is obscured in patients with mechanical aortic prostheses. As infection disrupts the sewing ring annulus, part of the ring can dehisce leading to abnormal excessive rocking of a prosthesis. A rocking motion in excess of 15° out of concordance with the supporting structures of the valve has been proposed as a criteria for perivalvular abscess [52]. The degree of rocking is proportional to the circumferential extent of LV-aortic discontinuity. This can vary from as little as one quarter to as much as three quarters of the circumference of the annulus [41]. When examined at autopsy and surgery, valves with excessive rocking have been shown to have dehiscence between 40 % and 95 % of the circumference of the sewing ring. The main false positive sign of abnormal valve rocking relates to mitral and tricuspid prostheses in patients with very large mitral and tricuspid annuli and unusually large atria [52]. In such patients, abnormal valve rocking can be seen without valvular dehiscence.

Transesophageal Echo TEE can overcome many limitations of TTE in assessing the perivalvular region in patients with prosthetic valve IE (Figs. 7.14 and 7.15) [25, 37, 49]. Thus most patients with prosthetic valve IE should have TEE even if the image quality of TTE is adequate. An abscess on the anterior surface of the aortic root in the setting of a prosthetic aortic valve can be difficult to detect by TEE, since the aortic prosthesis can shadow the anterior aortic root which is in the far field of the TEE image plane. In such cases, images from TTE compliment the TEE images, by showing the anterior aspect of the aortic root and ascending aorta. Real-time 3-D echocardiography is very helpful for demonstrating abscess cavities and their relationship to adjacent structures in the setting of complicated prosthetic valve endocarditis. In particular, mitral valve abscess can be challenging to image using 2D TEE. Conversely, real-time 3D TEE allows superb imaging of prosthetic mitral valves and mitral valve annuloplasty rings, and demonstrates dehiscence or abscess cavities in prosthetic mitral valve endocarditis (Fig. 7.16) [71, 72].

Perivalvular regurgitation in the setting of a mitral valve prosthesis is optimally assessed by TEE, which provides detailed information regarding number, size and location of the regurgitation jets. Real-time 3-D echocardiography is particularly useful in evaluating dehiscence of prosthetic mitral valves and mitral annulplasty rings in the setting of endocarditis [72]. An en-face view of the mitral prosthetic valve or annuloplasty ring demonstrates the circumferential extent of the dehiscence (Fig. 7.16) [72]. This information can be useful in the selection of patients for device closure of the perivalvular leak after the infection has been adequately treated. Other perivalvular complications including pseudoaneurysm and fistula are better imaged with TEE. Due to its superior accuracy, TEE should be performed in patients suspected to have perivalvular complications of prosthetic valve endocarditis.

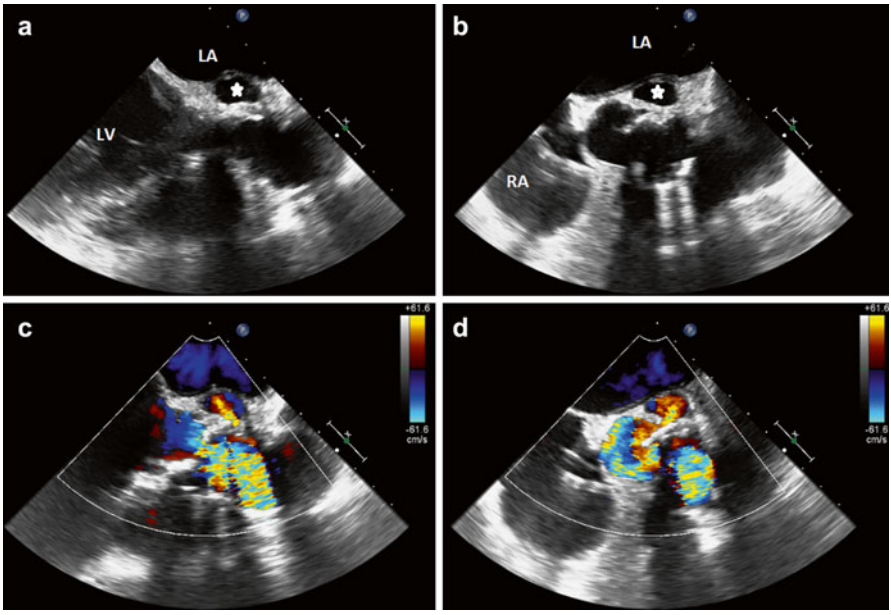

Fig. 7.15 A posterior aortic root pseudoaneurysm (*star*) is imaged as an echolucent cavity in both the long-axis (**a**) and short-axis (**b**) views in a patient with aortic prosthetic valve endocarditis. Colour flow imaging shows expansion and flow into the pseudoaneurysm in both the long-axis (**c**) and short-axis views (**d**) indicating communication with the left ventricular outflow tract. *LA* left atrium, *LV* left ventricle, *RV* right ventricle

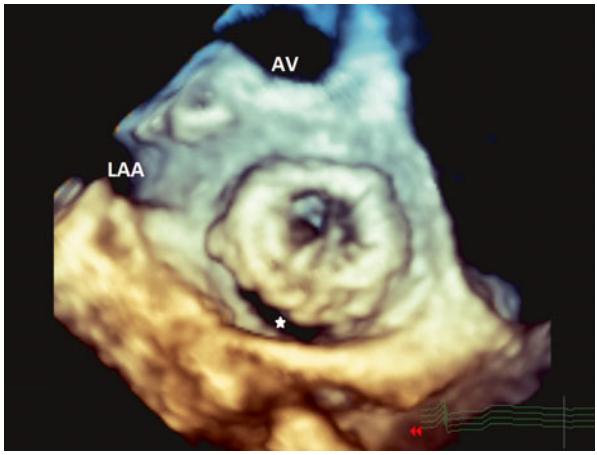

Fig. 7.16 Real-time 3D image of a mechanical mitral valve from the atrial perspective shows a large dehiscence (*star*) at the posterior aspect of the valve. *AV* aortic valve, *LAA* left atrium appendage

Summary

1. Increased aortic wall thickness and excessive prosthetic valve rocking are signs of perivalvular abscess.
2. TEE should be performed in all patients with prosthetic valves and suspected perivalvular complications.
3. TEE may not adequately assess prosthetic valves in the aortic position.
4. Real-time 3D TEE is particularly useful in evaluation of annular complications in prosthetic mitral valve IE.

Endocarditis Associated with Pacemaker Leads and Central Venous Catheters

The past two decades has seen a dramatic increase in the number of implantable cardiac devices, largely due to increased use of implantable cardioverter defibrillators (ICDs) in patients with reduced LV function [73, 74]. Vegetations associated with pacemaker leads can occur either in the atrium or ventricle, ranging in size from less than 5 mm to over 20 mm [75–78]. In addition to vegetations attached to pacemaker leads, vegetations are detected on cardiac valves in up to one third of patients with cardiac device associated endocarditis [78]. While the Duke criteria have a lower sensitivity for diagnosis of cardiac device related endocarditis, positive blood cultures and echo evidence of vegetation remain central to the diagnosis [77]. Echo evidence of vegetation is present in the majority of patients with pacemaker lead IE [75, 77, 78]. Vegetations can appear as oscillating, shaggy masses on one or more pacemaker leads. However, a more atypical appearance, characterized by a sleeve-like echodensity on the lead, may be the only echocardiographic sign of pacemaker associated endocarditis [76]. In contrast to native right sided endocaridits, cardiac device associated vegetations are difficult to detect by TTE, which has a sensitivity as low as 26 % [78]. Reduced sensitivity of TTE for cardiac device associated endocarditis is due to reverberation artifacts from the leads, and the inability of TTE to image the entire intra-vascular course of pacemaker leads. TEE has much higher sensitivity and is essential in suspected endocarditis involving implanted cardiac devices. A recent large, multi-center series of cardiac device related endocarditis reported that TEE could not detect a vegetation, defined as a shaggy oscillating mass, in 37 % of early endocarditis (<6 months from implant) and 18 % of late endocarditis (>6 months from implant) [78]. This relatively low sensitivity of TEE likely reflects the difficulty in imaging the entire length of pacemaker leads, and the fact that lead associated vegetations may have an atypical appearance.

Endocarditis can also arise in the setting of indwelling central venous catheters. This is particularly important in the growing population of patients on hemodialysis and in patients with indwelling catheters for chemotherapy [79, 80]. As is the case for pacemaker lead associated IE, TEE is more sensitive than TTE for the detection of vegetations in the setting of intravascular catheters [76].

Summary

1. TEE is more sensitive than TTE for the diagnosis of pacemaker lead associated IE.
2. Both mobile masses and a sleeve-like echodensity on the intracardiac leads are echo findings of pacemaker associated vegetations.
3. TEE may miss vegetations in some cases of cardiac device associated endocarditis.

Echocardiography and Clinical Decision Making

Detection of valvular vegetation gives echocardiography a central role in establishing the diagnosis of IE [81–84]. Appropriate use criteria by the American College of Cardiology Foundation (Table 7.1) and guidelines published by the European Society of Cardiology (Table 7.14) define clinical situations where it is considered appropriate to perform TTE and TEE in suspected IE [2, 85, 86]. Once the diagnosis of IE is confirmed and antibiotic therapy is established, clinicians are confronted with two critical decisions: is surgery indicated, and if so, when should surgery be performed? Findings on echocardiography, particularly TEE, are essential in determining if surgery is indicated and help judge the appropriate timing of surgical intervention. While surgery in endocarditis is indicated on the basis of clinical complications, echocardiography detects the specific intra-cardiac pathology responsible for clinical manifestations that in turn lead to surgery (Table 7.15) [85]. Not only does echocardiography detect a complication that warrants surgical intervention, it can also help determine the appropriate timing of surgery. Patients whose hemodynamic and infectious status does not warrant emergent or urgent surgery are initially managed medically [87]. One of the most dreaded complications in patients prior to surgery is embolus to the central nervous system, commonly detected by MRI, and clinically evident in 20–40 % of patients with IE [88, 89]. Vegetation size more than 10–15 mm and mitral location are echo findings that predict CNS embolus [89, 90]. Patients with IE are at highest risk for CNS embolus very early after diagnosis, within the first 48 h, with a reduction in risk over 2 weeks, and much lower embolic risk beyond 2 weeks [90]. By detecting large vegetations in patients with surgical indications, clinicians may select some patients for early surgery on the basis of echo findings. Such an approach was tested in the only randomized trial comparing early surgery to usual care in left sided IE, where vegetation size >10 mm and severe valvular dysfunction were echo-based inclusion criteria [91]. Protocol-based, team approaches to IE management have resulted in improved outcomes for patients with IE [92, 93]. Such protocols emphasize the importance of prompt echocardiography, particularly TEE, as a crucial early test to confirm the diagnosis of IE and help inform decisions for early surgery when appropriate [92, 93].

Table 7.14 Recommendations for echocardiography in suspected endocarditis: European Society of Cardiology Guidelines

Recommendation for echocardiography	Class of recommendation	Level of evidence
A. Diagnosis		
1. TTE is recommended as the first-line imaging modality in suspected infectious endocarditis	I	B
TEE is recommended in patients with a high clinical suspicion of infectious endocarditis and a negative TTE	I	B
2. Repeat TTE/TEE within 7–10 days is recommended in the case of an initially negative examination when clinical suspicion of infectious endocarditis remains high	I	B
3. TEE should be considered in the majority of adult patients with suspected infectious endocarditis, even in cases with positive TTE, owing to its better sensitivity and specificity, particularly for the diagnosis of abscesses and measurement of vegetation size	IIa	C
4. TEE is not indicated in patients with a good-quality TTE and low clinical suspicion of infectious endocarditis	III	C
B. Follow-up under medical therapy		
1. Repeat TTE and TEE are recommended as soon as a new complication of infectious endocarditis is suspected (new murmur, embolism, persisting fever, heart failure, abscess, atrioventricular block)	I	B
2. Repeat TTE and TEE should be considered during follow-up of uncomplicated infectious endocarditis, in order to detect new silent complication and monitor vegetation size. The timing and mode (TTE or TEE) of repeat examination depend on the initial findings, type of microorganisms, and initial response to therapy	IIa	B
C. Intra-operative echocardiography		
1. Intra-operative echocardiography is recommended in all cases of infectious endocarditis requiring surgery	I	C
D. Following completion of therapy		
1. TTE is recommended at completion of antibiotic therapy for evaluation of cardiac and valve morphology and function	I	C

Adapted from Ref. [85]

Table 7.15 Echocardiographic findings that warrant surgical intervention in the appropriate clinical context

Recommendation: indication for surgery	Timing	Class of recommendation	Level of evidence
A. Heart failure			
1. Aortic or mitral IE with severe acute regurgitation or valve obstruction causing refractory pulmonary edema or cardiogenic shock	Emergency	I	B
2. Aortic or mitral IE with fistula into a cardiac chamber or pericardium causing refractory pulmonary edema or cardiogenic shock	Emergency	I	B
3. Aortic or mitral IE with severe acute regurgitation or valve obstruction and persisting heart failure or echocardiographic signs of poor hemodynamic tolerance (early mitral closure or pulmonary hypertension)	Urgent	I	B
4. Aortic or mitral IE with severe regurgitation and no heart failure	Elective	IIa	B
B. Uncontrolled infection			
1. Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation)	Urgent	I	B
C. Prevention of embolism			
1. Aortic or mitral IE with large vegetations (>10 mm) following one or more embolic episodes despite appropriate antibiotic therapy	Urgent	I	B
2. Aortic or mitral IE with large vegetations (>10 mm) and other predictors of complicated course (heart failure, persistent infection, abscess)	Urgent	I	C
3. Isolated very large vegetation (>15 mm)	Urgent	IIb	C

Adapted from Ref. [85]

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Surgical Management: Indications, Timing and Surgical Techniques

8

Elsayed Elmistekawy, Vincent Chan, and Thierry Mesana

Abstract

Endocarditis is a lethal disease; almost one third of endocarditis patients will need surgical intervention. Each individual patient with endocarditis needs to be carefully assessed for the infectious process and evaluated for valve dysfunction in order to decide when and how to operate. In this chapter, we focus on timing of surgical intervention and illustrating different surgical options for different valvular pathology. Different techniques of valve repair and choices for valve replacement are discussed. Special situation such as prosthetic valve endocarditis and endocarditis in intravenous drug users are also highlighted. Outcomes for surgical intervention for endocarditis are reviewed as well.

Keywords

Endocarditis • Native valve endocarditis • Prosthetic valve endocarditis • Surgical management • Surgical techniques • Culture negative IE • Perivalvular abscesses • Vegetations • Intravenous drug users

Key Points

1. Surgical consultation early in the course of the disease should be considered in all patients with IE, as about a third of IE patients require surgery during their hospitalization.
2. A thorough pre-operative work-up is crucial and TEE is the gold standard to assess valvular and perivalvular complications.
3. The main indications for surgery are hemodynamic instability, persistent sepsis, and large vegetations with recurrent embolization.
4. Hemodynamic stability must be prioritized over medical control of infection.

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5. Native valve reconstruction is superior to replacement in terms of morbidity and mortality.
6. Prosthetic valve IE, intra-cardiac abscesses, poor ventricular function, staphylococcal IE and culture-negative IE are associated with less favorable postoperative outcomes.
7. Outcome in the first postoperative year predicts the long-term course.
8. In properly selected surgical candidates, good outcome can be expected.
9. The selection of a biological versus a mechanical prosthetic valve should consider patient preference in addition to life expectancy, presence of comorbidities and risks of post-operative renal or neurological complications

Surgery for Infective Endocarditis

Introduction

In spite of recent advances in medical and surgical treatment, infective endocarditis (IE) remain a lethal disease with 1-year and 5-year mortality of 40 % and 70 %, respectively, following surgery [1]. Fortunately, IE is not common. A French survey estimated the incidence of IE at 31 cases per one million adults, and a large European multicenter survey reported only 159 (3.2 %) of 5,001 patients with valvular disease had a history of IE [2, 3]. Thus, surgical treatment of IE constitutes a relatively small portion of all cardiac surgery procedures. Yet, a third of all medically treated patients with IE will ultimately require cardiac surgery [4]. Of 6,153 patients who underwent valve operations at our institution over the last 10 years, 308 (5 %) underwent surgery for IE, of which 84 had prosthetic valve endocarditis.

Surgical procedures for acute IE are technically more demanding than operations for acquired non-infected valvular lesions. The main challenge in acute IE is to address the three coexisting aspects of the disease: (1) the infectious process that requires removal of all infected tissues to prevent recurrence of IE, (2) control of the systemic infection with antibiotics and (3) the altered valvular anatomy and function that should be corrected or restored. This may require extremely complex and high-risk surgical procedures, although operations in sub-acute or chronic IE with no residual infection or perivalvular involvement can be handled similar to conventional valve operations. The decision-making process is key to the final surgical outcome, underlining the critical need for each individual case to be carefully assessed for the infectious process and evaluated for valvular dysfunction in order to decide when and how to operate.

Assessing the Infection

This step is critical in achieving optimal control of an active infection. Failure to fully debride the infected tissue will result in a failed valvular surgery and increase the risk of infection recurrence. First, any predisposing local factors such as

anatomic or functional valve abnormalities, previous cardiac surgery, or factors related to general patient condition (age, renal function, past infections, intravenous drug addiction, immunosuppression, history of cancer, etc.) should be addressed and carefully weighted to determine surgical timing. Next, a possible primary source of infection, either obvious or latent, such as soft tissue abscess or poor dental hygiene, must be identified and eradicated prior to heart surgery. Septic dissemination may also result in non-cardiac infectious localization, including metastatic abscesses (e.g., splenic abscess), mycotic aneurysms and cerebral emboli, which should be addressed. Finally, the causative microorganism should be identified and treated with targeted antimicrobial therapy. Determining the causative microorganism is significant in decision-making, in that it has a direct impact on the course, pathophysiology, and complications of IE, and hence on its management. Staphylococcus aureus IE, for instance, causes more serious valvular damage and is associated with higher embolization and mortality rates [5].

Culture negative IE occurs in 2.5–31 % of all cases of IE and is often challenging to diagnosis and treat [6–10]. Most commonly, culture negative IE occurs as a result of previous treatment with antibiotics. Blood cultures may remain negative for many days after antibiotic discontinuation, and causative organisms are most often oral streptococci [6–10]. Persistent culture negative IE are usually due to fastidious organisms such as nutritionally variant streptococci, fastidious gram-negative organisms of the HACEK group (Haemophilus species, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella species), Brucella species, fungi, and intracellular bacteria [6–10]. Diagnosis in such cases relies on serological testing, cell culture or gene amplification. In culture-negative IE, the most probable organisms should be determined based on epidemiological and demographic characteristics of the individual case. The identified or probable causative organism determines the specific or empiric antibiotic therapy pre- and perioperatively [5–7]. Q-fever IE due to Coxiella burnetii is a leading cause of culture negative IE, is definitely more common in the Mediterranean basin than North America and should be investigated with specific immunological testing [8, 9]. Long-term, eventually lifelong antibiotics therapy is recommended for Q fever endocarditis.

Fungal IE has worse prognosis in particular when present on prosthetic valves, generally does not respond well to medical therapy, and extensive surgery is eventually needed. Thus earlier intervention is usually warranted [10].

Assessing the Valvular Disease

One of the first considerations to risk stratify patients for surgery relates to whether IE involves a native heart valve or a prosthetic valve. The latter is associated with more severe complications, operative technical difficulties, and less favorable results compared to surgery for native valve IE [1]. Surgical results are also better for an initial IE episode than for recurrent IE [1]. All valves and related structures should be assessed to determine the involved valves, extent of disease (e.g., annular involvement), and presence of intracardiac complications (such as abscesses, aneurysm/pseudo-aneurysm, fistula, and aortoventricular/atrioventricular discontinuity). Such complications constitute independent risk factors with adverse impact on operative outcomes and survival.

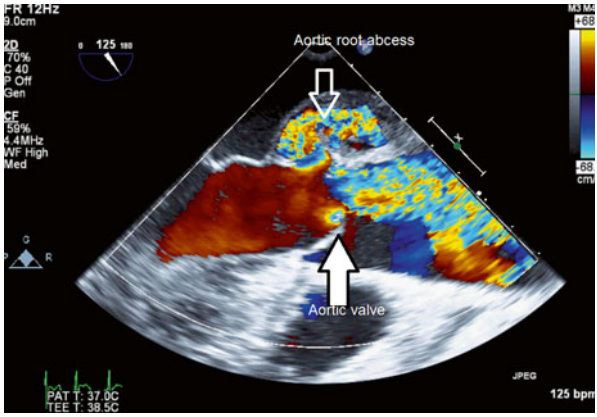

Fig. 8.1 Transesophageal echocardiography demonstrating an aortic root abscess which was evolving into pseudoaneurysm

Transthoracic and transesophageal echocardiography (TEE) has a key role in the diagnosis and management of IE (Fig. 8.1). Echocardiography should be performed once endocarditis is suspected and more importantly repeated as early as necessary to determine surgical timing, prognosis, and nature of follow-up. TEE is the key investigation and absolute gold-standard mandatory for all patients with IE prior to any decision, medical or surgical. In case of conservative medical treatment, serial TEE are necessary to detect early complications which would potentially reorient towards surgery, even in the absence of clinical symptoms. Three-dimensional echocardiography helps delineate complex cardiac morphology such as in the case of a perivalvular abscess, valve dehiscence, cusp or leaflet perforation and fistulas [11]. Computed tomography (CT) and magnetic resonance imaging (MRI) have limited value in assessing cardiac lesions, but may be useful in characterizing embolic events [11].

Making the Surgical Decision: Indications and Timing

The surgical timing in the management of IE is critically important. Although early operation is often the most effective way to treat the patient, in some instances, operating too soon carries a higher risk due to the unstable condition of the patient, excessive cardiac tissue friability resulting in early postoperative periprosthetic leakage, and greater possibility for recurrence due to residual, minimally diseased foci that might go unnoticed during surgery. An undue delay in operation, on the other hand, may result in life-threatening sepsis, multi-organ failure or extensive structural destruction with irreversible damage to cardiac function. Timing of surgery in active IE is therefore as important as determining the type of the operation itself [12–14].

The choice of whether to repair or replace an infective native valve, along with the type of prosthesis whether biological or mechanical is ultimately verified intraoperatively. Surgical techniques can vary along a wide spectrum of complexity,

from the simple stitching repair of a well-defined leaflet perforation to an extensive aortic root replacement, and from an isolated mitral valve replacement to a complex valve and annulus reconstruction. Plans will occasionally require modification or refinement based on the findings in the operating room or due to technical issues encountered intraoperatively.

Oral anticoagulation is associated with adverse outcome in IE, particularly during the initial period of presentation when embolic risk is highest. Ideally, anticoagulants should be avoided, but in selected patients who require anticoagulation for a valve or rhythm indication, unfractionated heparin may be useful [15].

Finally, as the case with any cardiac surgery, patients should be optimized from an end-organ perspective. Hepatic and renal functions are of particular importance, as they have high prognostic value in cardiac surgery and especially for IE patients [16]. In certain cases, delay of cardiac surgery may cause further deterioration in renal and/or hepatic function. This underscores the significance of surgical timing. In patients with a high risk of coronary artery disease, preoperative angiography should be performed to determine the need for concomitant coronary artery bypass grafting.

In view of the fact that cardiac surgery is an integral part of IE management, early consultation with the cardiac surgery team is strongly recommended following the diagnosis of IE. This will allow the surgical team to be fully familiar with the patient, in case surgery is eventually needed. It will also enable medical and surgical teams to discuss the need of and optimal timing for surgery. The American College of Cardiology/American Heart Association Guidelines for the Management of Patients with Valvular Heart Disease also support early surgical consultation in IE cases [14]. The concept of a Heart Team to detect, evaluate, treat and follow longitudinally IE patients is of merit and should be widely adopted.

Overall, there are three major absolute indications for surgical intervention in IE:

1. Hemodynamic compromise: Heart failure is the most frequent and severe complication of IE and necessitates earlier surgical intervention.
2. Persistent and/or uncontrolled infection despite aggressive medical therapy: Uncontrolled infection is most frequently manifested in perivalvular extension in the setting of ‘difficult-to-treat’ organisms. The presence of locally uncontrolled infection also necessitates early surgery.
3. Risk of embolization: The risk of embolism is highest during the first 2 weeks of antibiotic therapy and is related to the size and mobility of the vegetation. Risk of embolization is greater with large (>10 mm) vegetations and particularly high with very mobile and larger (>15 mm) vegetations. The decision to proceed with early surgery in order to prevent embolism is always difficult and specific for the individual patient. Governing factors include size and mobility of the vegetation, previous embolism, type of microorganism and duration of antibiotic therapy [3, 4, 10, 12, 13].

Significant anatomical changes and complications caused by IE, such as aneurysm, fistula and atrioventricular discontinuity, may also be considered as indicators

Table 8.1 Indications for surgery in IE

Absolute indications:
Hemodynamic compromise due to valvular dysfunction
Uncontrolled infection despite appropriate antimicrobial treatment
Fungal endocarditis with vegetations
Embolic event (cerebral or peripheral)
Recurrent embolization
Emboli after adequate antibiotic therapy
Anatomical complications/deformities
Abscess
Fistula
Aneurysm/pseudoaneurysm
Aortoventricular/atrioventricular discontinuity
Prosthetic valve dehiscence and paravalvular leak
Relative indications:
Echocardiographic detection of:
Large vegetations (>10 mm in diameter)
Vegetations increasing in size after 4 weeks of antimicrobial therapy
New conduction blocks

for earlier surgical intervention as they usually indicate imminent hemodynamic compromise. Some authors have advocated other relative indications for surgery (Table 8.1) [3, 10, 17, 18]. Nevertheless, the most common indication for surgery is heart failure followed by persistent sepsis [3, 19, 20].

Surgical outcomes are better in patients with healed IE than in patients with acute IE. However, in the presence of a major indication, or when clinical judgment strongly suggests that surgical indication is imminent, there should be no delay in carrying out the operation, even with active IE. Hemodynamic stability takes priority over infection control when determining the need for surgery.

As already specified, the timing of surgery for IE remains controversial and is often addressed on a case by case basis. The processes employed to determine the timing of surgery have evolved considerably over recent years, owing to advances in medical therapy and diagnostic tools, echocardiography in particular. These advances have also led to a greater frequency of medical managed IE [20]. The routine use of TEE has led to earlier and more accurate identification of valve pathology that may serve as indications for more urgent surgery [11]. Although data on the timing of surgery is limited, some have advocated earlier surgery in patients with large vegetations [3, 18], especially those that are >10 mm in diameter [21], patients with an increase in the size of vegetations after adequate antimicrobial therapy [5], and the presence of vegetations in the setting of a fungal IE since antifungal penetration into vegetations is not adequate for cure [10]. Also, the presence of

annular/perivalvular abscesses often necessitates earlier surgical intervention [22, 23]. Abscesses commonly lead to pseudoaneurysm and/or fistula formation. If echocardiography is not conclusive with regard to abscess presence or extension, the patient should be followed closely with serial echocardiographic studies. Abscesses are found more often in aortic IE, but reported to have a higher incidence of pseudoaneurysm/fistula formation in the mitral position [24]. Septal abscesses associated with aortic IE may cause conduction abnormalities. Indeed, a new conduction block in the setting of IE has a high positive predictive value for the presence of perivalvular abscess [25]. In patients with prosthetic valve IE, risk factors include prosthesis dehiscence and new/dynamic perivalvular leak as documented by serial echocardiography [25]. Increasing perivalvular leak is an ominous sign of circumferential extension of dehiscence and should lead to more aggressive treatment including surgery. A complication of the infectious process that mandates careful evaluation is systemic embolization, a cardinal determinant of mortality and morbidity in IE patients. Embolic events are reported in up to half of IE cases [10]. Of these, up to 71 % are cerebral embolic events [26]. Most embolic events occur within 2 weeks of onset of symptoms or initiating antibiotic therapy [26, 27]. Therefore, the greatest impact of surgical intervention on the incidence of emboli occurs in this early window. An embolic event during the first 2 weeks of antimicrobial therapy or recurrent embolism at any time may also lead to earlier surgery [13].

That said, the presence of a recent cerebral infarct complicates the timing of surgery, because of the risks of systemic heparinization and the potential for cerebral edema due to cardiopulmonary bypass. It is generally agreed that active hemorrhagic cerebral infarcts are an absolute contraindication for surgery [28]. The main controversy on the timing of surgery for non-hemorrhagic infarcts is the concern of hemorrhagic transformation. Some investigators have demonstrated better outcomes when surgery is performed at least 11 days after ischemic and 23 days after hemorrhagic cerebrovascular accidents [29]. Others have reported favorable outcomes even when cardiac surgery is performed within 72 h of a cerebrovascular event as opposed to deferring operation for 8 days [26]. Our practice and current guidelines are to defer the operation as much as possible for 2 weeks after a non-hemorrhagic stroke and 4 weeks after a hemorrhagic stroke [30]. In certain patients, symptomatic embolic cerebrovascular events may be associated with infectious intracranial aneurysms which can rupture [10]. Although uncommon, these aneurysms can sometimes leak slowly, and anticoagulation for cardiopulmonary bypass can predispose these patients to a potentially fatal hemorrhage. Careful imaging studies prior to cardiac surgery should therefore be undertaken if there is any clinical suggestion of a possible infectious intracranial aneurysm. Splenic abscess (or abscess located elsewhere) is another complication of the infectious process in IE that may cause persistent bacteremia/sepsis. It does not usually respond well to antibiotic therapy and should be treated surgically by splenectomy (or surgical drainage and debridement in other locations), or drained percutaneously before valve surgery is performed. In general, every attempt is made to eradicate any identified source of infection before cardiac surgery is performed to prevent recurrence of IE. In their recent study Thuny et al. [31] found that patients who are operated on

within the first week of antimicrobial therapy and most likely to derive substantial mortality reduction are those who are young, with *Staphylococcus aureus* IE, or are complicated by heart failure and large vegetations. However, surgery performed less than a week after diagnosis was associated with a trend to a higher risk of infection recurrence 6-months after surgery (16 % vs. 4 %, P = 0.05).

Both cranial and abdominal computed tomography should be considered in all patients with IE to assess for the presence of any abscess, infarct, hemorrhage, or aneurysm.

Figure 8.2 displays the indications and timing for surgery in different clinical and pathological scenarios.

Operative Management and Techniques

Once the diagnosis is established, proper antibiotic therapy should be initiated with the advice of an infectious disease specialist. Ideally surgery should be performed after blood cultures are clear of an active infection. Antibiotic therapy should be extended to at least 6 weeks postoperatively and are often continued longer. Surgery for prosthetic valve IE is usually more challenging. A detailed review of serial echocardiograms, and other imaging modalities such as CT/MRI or cardiac catheterization is essential to understand the anatomic extent and pathologic process. Careful planning for sternal re-entry approach, establishment of cardiopulmonary bypass, myocardial protection and dealing with patent bypass grafts or aortic root abscess are critical for surgical success.

Exposure and Myocardial Protection

Optimal surgical exposure and myocardial protection are paramount. Full median sternotomy is highly recommended for IE operations. In cases with previous coronary bypass surgery, right thoracotomy may be preferred to access the mitral valve, avoiding possible damage to patent coronary grafts. Access to the mitral valve is excellent through right thoracotomy, although it does not allow easy access to the aortic root, and would complicate the surgery if root surgery is needed. For aortic IE complicated by an aortic root aneurysm or pseudo-aneurysms, particularly in redo operations, cardiopulmonary bypass is preferably established through the femoral vessels prior to sternotomy. Myocardial protection is critical owing to the long duration of operations for complex IE cases, often requiring beyond 2 h of cross-clamp time and myocardial ischemia. Excellent myocardial protection can be achieved via retrograde blood cardioplegia delivered in regular (every 20 min) intervals. This technique avoids the manipulation of direct coronary catheters that can cause migration of infected material into the coronary circulation in patients with infection involving aortic root or in patients with severe aortic insufficiency. Valves are accessed through usual approaches, such as left atriotomy for mitral valve or ascending aortotomy for aortic valve. However, more complex approaches may be required

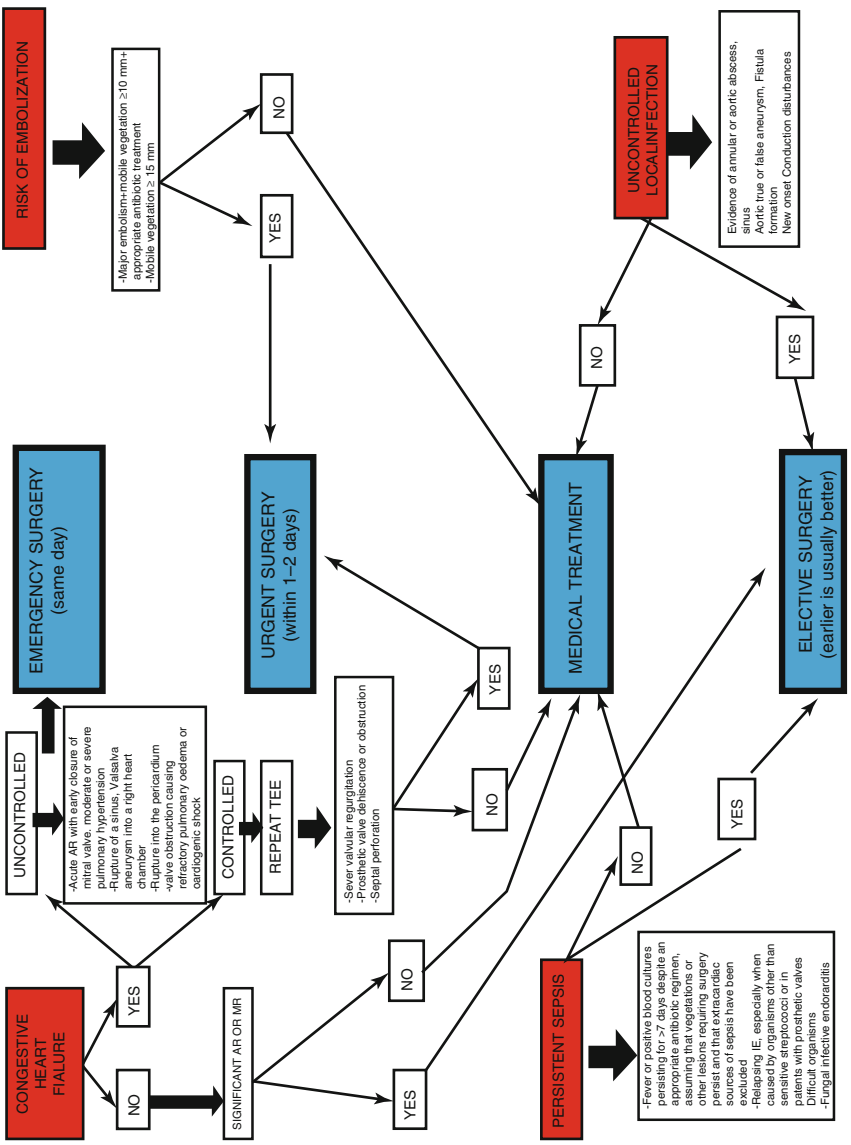

Fig. 8.2 Indication and timing for surgery (Adopted from AHA and ESC guidelines [12, 14]) *AR* aortic Regurgitation, *MR* mitral regurgitation, *IE* infective endocarditis

to evaluate all deformities and achieve optimal debridement of all infected tissues, including the biatrial combined with aortic approach. More extensive cardiac incisions, of course, increase the complexity of the operation, but may be needed for valve debridement and reconstruction.

Repair or Replace

The decision to replace or repair the valve is made after careful anatomical evaluation and optimal valve exposure. Naturally, valve repair is preferred over replacement. Advanced technical skills and sufficient experience in complex repair procedures are crucial to achieve a high success rate of repair procedures. Valve reconstruction is more often feasible in the mitral or tricuspid position than in IE cases involving the aortic valve. This is mainly due to larger amount of leaflet tissue available for reconstruction and more amenable to tissue resection in the case of the mitral and tricuspid valves. The greater prevalence of extensive tissue destruction in aortic IE also reduces the feasibility of aortic valve repair [32]. There are no randomized clinical trials to evaluate the outcomes of valve repair versus replacement in patients with IE. However, retrospective data suggests that native valve preservation may be associated with significantly lower perioperative morbidity and shorter hospital recovery time than replacement [33, 34]. The benefits of valve repair also include eliminating the need for aggressive anticoagulation therapy, thus reducing the immediate risk of bleeding complications as well as the need for lifetime anticoagulation. Notably, there is no significant difference in mortality between patients who receive mechanical or bioprosthetic valve replacement for IE [35]. Therefore, the patient's informed choice is paramount. In cases of aortic valve IE that involve the aortic root, a composite graft or homografts may be required [36]. Although no conclusive data is available comparing homografts and prosthetic valve grafts in terms of durability and risk of recurrent IE, current data from surgical series indicate satisfactory results with the use of homografts [36]. However, the limited availability of homografts precludes the widespread use of this treatment modality.

In a recent study, Savage et al. described the temporal trends in prosthesis use in a large cohort of patients [37]. In a cohort of 11,560 patients, of whom 8,421 (73 %) had native valve endocarditis and 3,139 (27 %) had a prior cardiac operation, they found that biologic valve use increased in frequency (57–67 %) over the course of the study. Conversely, mechanical and homograft valve use decreased (30–24 % and 9–6 %, respectively; both $p<0.001$). Bioprosthesis use also increased in recent years in patients who had a prior cardiac operation from 38 % to 52 %. However, homografts were used more often in reoperations (32 % vs 7 %). In this group, use of a homograft was associated with a higher mortality compared to use of a bioprosthetic valve [37]. In our practice, we favor the use of biological valves to simplify post-operative anticoagulation management which can be challenging in patients who are likely to have a long intensive care course with neurological and renal complications.

Anatomical Assessment

Structural valve and cardiac lesions in IE include lesions that existed prior to the onset of infection and also new lesions caused by the infection itself (Table 8.2). Preexisting lesions may include mitral valve prolapse, valvular stenosis or insufficiency, congenital defects such as a bicuspid aortic valve, or residual lesions from a previous episode of IE. Lesions caused by the current IE include vegetations (most frequent IE lesions), leaflet/cusp perforation, chordal rupture, periannular or intra-ventricular abscesses, aneurysm/ pseudoaneurysm, and fistulae. The type and extent of lesions determine the surgical technique; and hence, the operation can be anywhere along a spectrum of technical difficulty from simple suturing of a leaflet/cusp perforation to complex reconstruction and replacement techniques including homograft implantation. The most common lesions found in IE include:

Vegetations

These are the most common lesions in IE. They are usually found on the ventricular aspect of the aortic valve and on the atrial side in the mitral valve [38, 39]. The size and site of the attachment of the vegetation and the relation to the leaflet/cusp are important. Removal of large or multiple vegetations leaves a large defect in the leaflet that is more

Table 8.2 Structural lesions in infective endocarditis

Lesion	Remarks
Common lesions	
Vegetations	On ventricular aspect of aortic valve, atrial aspect of mitral valve
Leaflet perforation	Usually in the anterior mitral leaflet; anterior mitral leaflet involvement also caused by vegetative aortic IE
Abscesses	Mostly seen in *S. aureus* IE; more common in prosthetic valve IE; in native valves, up to 50 % in aortic valve and 5 % in mitral valve IE
Aneurysm/pseudoaneurysm/fistula	Usually develops from abscess
Uncommon lesions	
Stenosis	More common in mitral and tricuspid valves, prosthetic valve IE and fungal IE
Suppurative pericarditis	Seen in myocardial perforation
Myocardial infarction/ruptured chordae tendinae	Due to coronary emboli or vegetation on subvalvular structures
Preexisting valvular lesions	Especially mitral valve prolapse and degenerative aortic valve changes

difficult to repair and valve replacement might be the proper or only choice in extensive vegetative IE. Due to the smaller surface areas of aortic cusps compared to mitral leaflets, the size of a lesion that could be readily repaired in the mitral leaflet may be too large for aortic cusp repair. This is one main reason why mitral valve repairs are more commonly performed than aortic valve repairs. Vegetations should be removed in one piece to avoid fragmentation, and cardiac manipulation should be minimized to prevent dislodging potential embolic material. The location of vegetation attachment is also important. Repair of lesions in the middle of a leaflet is more feasible compared to vegetations with a base involving two leaflets/cusps and/or the annulus. Discrete lesions in the free margin of the anterior mitral leaflet can be removed with a triangular resection, and for posterior leaflet lesions, a quadrangular resection is usually used (Fig. 8.3). After such marginal resection, one must ensure that the reconstructed leaflet edge has

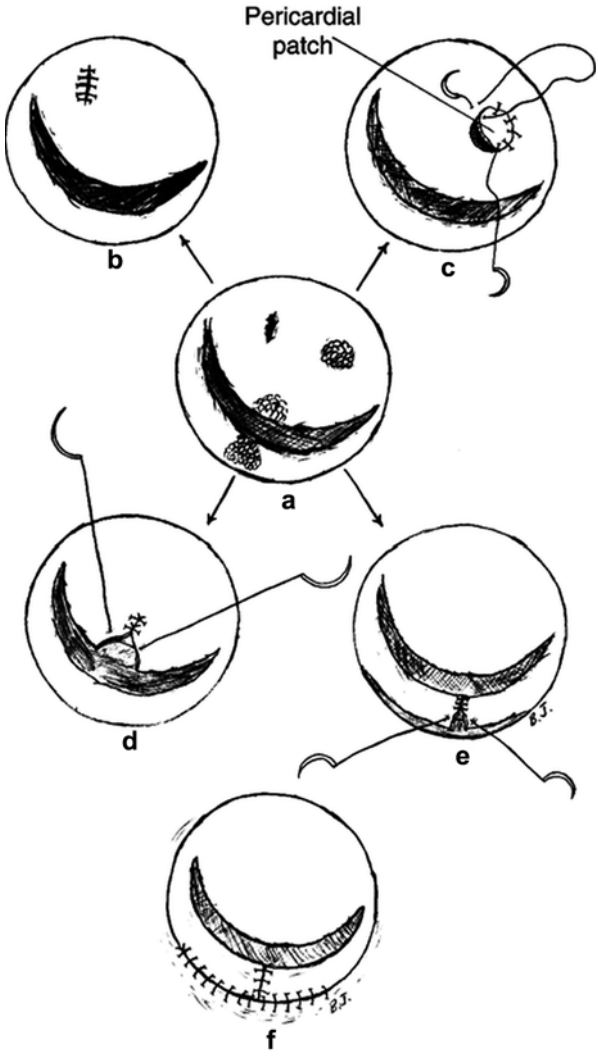

Fig. 8.3 (**a**) Surgical approach to repair the mitral valve in the setting of vegetations or perforations. (**b**) Small perforations with regular margins may be repaired by directly suturing the edges. (**c**) The defect in the anterior mitral leaflet caused by the removal of vegetation can be repaired using a pericardial patch. (**d**) Triangular resection for the removal of a lesion in the free margin of anterior mitral leaflet. (**e**, **f**) Quadrangular resection and sliding plasty for discrete lesions

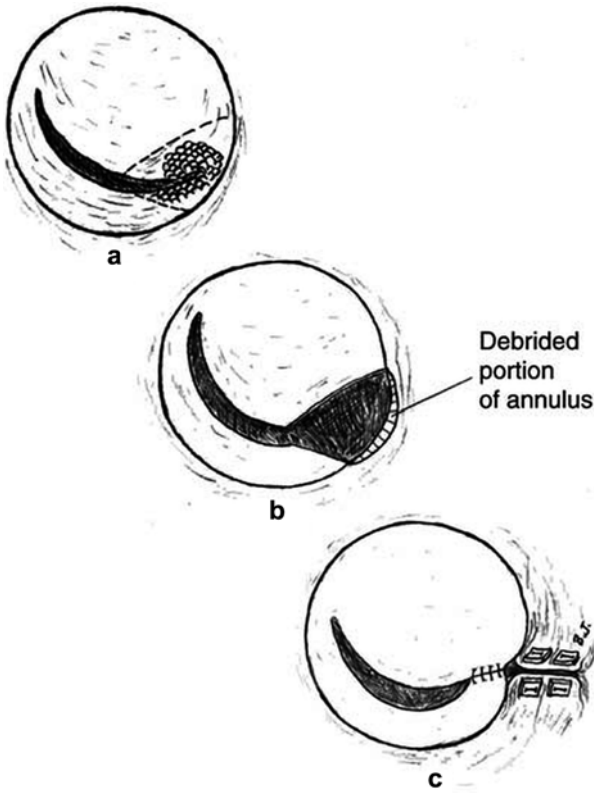

Fig. 8.4 (**a**) Lesions involving both anterior and posterior mitral leaflets at the posteromedial commissure. The *dashed lines* outline where the leaflets will be resected. (**b**) Diseased portions of both anterior and posterior leaflets are resected. The affected annulus is also debrided. (**c**) Reconstruction is performed by directly suturing the edges of the anterior and posterior leaflets and plicating the annulus with pledgetted sutures

enough chordal support in the case of mitral or tricuspid valve and enough coaptation surface with the opposing leaflet. Neochords may be necessary, and in the case of large resection large autologous or bovine pericardial patches should be used. The size of the pericardial patch needs to be much larger than the size of the defect to ensure a proper line of coaptation. Infection involving both mitral leaflets at or near the commissures dictates leaflet resection and debridement of the annulus. In such cases, it may be feasible to perform direct suturing to reconstitute the commissure and to plicate the annulus with pledgetted sutures (Fig. 8.4).

Perforation

Not infrequently, IE leaves behind a perforation in the leaflet/cusp causing valvular insufficiency. Perforations are more common in the anterior leaflet of the mitral valve, and they may be caused by satellite vegetation due to aortic valve IE [38, 39]. Thus, the anterior mitral leaflet should always be carefully examined for the presence of erosions and perforations in patients with aortic IE. Small perforations with smooth, regular margins may be closed by direct suturing of the edges. Prolene is the preferred suture material since it is non-braided, which may allow fewer crevices for micro-organisms to reside. Larger perforations and defects left behind from

partial leaflet resection can be repaired using autologous or bovine pericardial patches (Fig. 8.3b, c). Autologous pericardium is harvested and stripped of fat and connective tissue. Pericardial patches may be used fresh or preserved intraoperatively in a glutaraldehyde-buffered solution and rinsed in saline prior to use [40, 41]. Interrupted sutures are preferred over continuous sutures, and reinforcing pledgets should be used with caution since they represent additional foreign material that may be subject to recurrent infection. We prefer to use multiple single non pledgeted sutures. Debridement of the perforation prior to patch repair is of utmost importance, and the defect after debridement is often bigger than expected initially.

Perivalvular Abscesses

These are the most challenging lesions to correct, since these involve surrounding areas of the infected valve frequently extending to adjacent valves and coronary vessels, as well as ventricular and atrial walls. They must be carefully searched, evaluated, and treated. Extensive debridement of abscesses is the key to immediate and long-term surgical success. Abscesses are predominantly associated with IE caused by *Staphylococcus aureus* and are much more common in aortic IE than in mitral IE (25–50 % in aortic versus 1–5 % in mitral IE) [42]. However, the presence of a mitral annular abscess is more complicated than that of aortic abscesses. In aortic IE, abscesses mostly form at the weakest location of the annulus, near the membranous portion of the interventricular septum, in the vicinity of the atrioventricular node [13–24]. This anatomical predilection of aortic abscesses explains the development of new conduction blocks resulting from periaortic abscess formation. Abscesses below the left coronary cusp, between the posterior wall of the left ventricle and left coronary ostium, are also not uncommon and tend to extend toward the anterior mitral leaflet and the non-coronary cusp section of the annulus. Mitral annular abscesses usually occur in the postero-inferior portion, and this part should be carefully inspected for abscesses when the mitral valve is being resected. A well-defined, small abscess can be drained, debrided, and the remaining defect can be corrected with a pericardial patch. When discontinuity is present between the ventricle and atrium, a modified technique for valve replacement can be used, which consists of interrupted horizontal mattress sutures with pledgets placed on the ventricular side of mitral annulus, carried up through the atrial side of the debrided annulus, and then through the sewing ring of the prosthetic valve. However, the distance between the edge of the ventricle and atrium after debridement and the fragility of the infected tissue poses a failure risk on such a technique either immediately in the operating room or during the postoperative period. To avoid excessive tension on the weakened ventricular or atrial structure, a good alternative is to reconstruct the annulus with pericardium by first attaching the patch to the left ventricle with a running 4-0 or 3-0 prolene suture and then attaching the opposite end of the patch to the atrium. A prosthetic valve will then be placed with pledgetted sutures in the upper portion (atrial side) of the pericardial patch (Fig. 8.5). Thus, the

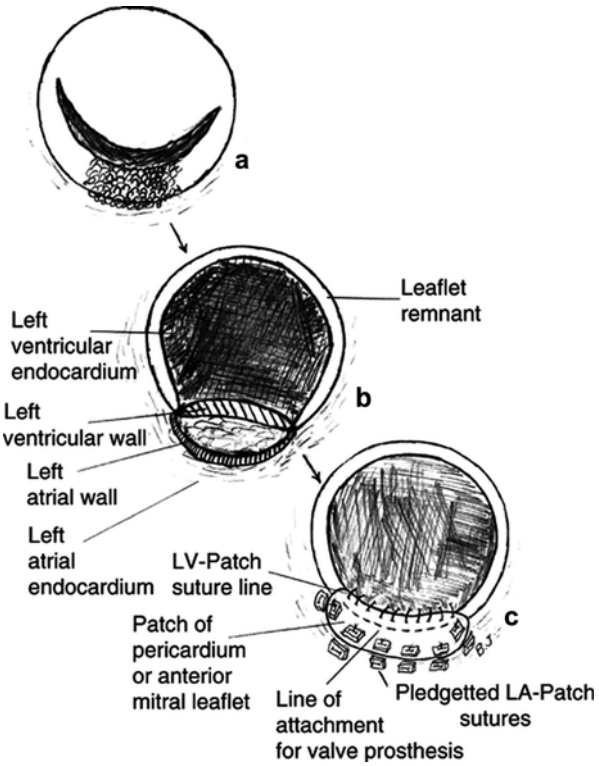

Fig. 8.5 (**a**) Surgical approach to treat abscess involving the mitral annulus. (**b**) The infection is extensively debrided, leaving behind a defect at the atrioventricular junction. The anterior and posterior mitral leaflets are also resected, leaving a narrow rim of leaflet remnant. (**c**) The atrioventricular defect is repaired with a patch tailored from pericardium or, occasionally, when the anterior leaflet is not diseased, from the anterior mitral leaflet. The patch then serves as a part of the anchorage for the prosthetic mitral valve

prosthesis will be more atrially positioned rather than in the ventricular cavity. Biological glue can be used as a good adjunct to such a reconstructive procedure. Glue can be spread posteriorly to the pericardial patch after completion of ventricular suture and before completion of atrial sutures of the patch. The risk of postoperative atrio-ventricular discontinuity is considerably reduced with this procedure. Aortic valve repair is also preferred to replacement, although repair is less feasible with the aortic valve compared to the mitral valve, as previously discussed. Lesions limited to one cusp, sparing the annulus (Fig. 8.6a) can be removed and reconstructed with pericardium. When the annulus is also involved (Fig. 8.6b), annuloplasty accompanies cusp reconstruction. Extensive disease of the noncoronary sinus involving the annulus and the anterior mitral leaflet (Fig. 8.6c) requires a more complicated procedure involving removal of the lesion, reconstruction of the resulting structural defect with a pericardial patch, reconstruction of the noncoronary cusp using a piece of pericardium, and annuloplasty. If the abscess or other structural damage involves the aortic structures extensively, aortic root replacement is the procedure of choice. Root replacement is done in the usual fashion following debridement of the infected tissue. Extra care is taken to place the proximal suture line low (proximally) enough in the left ventricular outflow tract that any discontinuity between the ventricle and proximal aorta is eliminated. Homograft aortic roots are useful in this setting. The anterior mitral leaflet is involved when there is

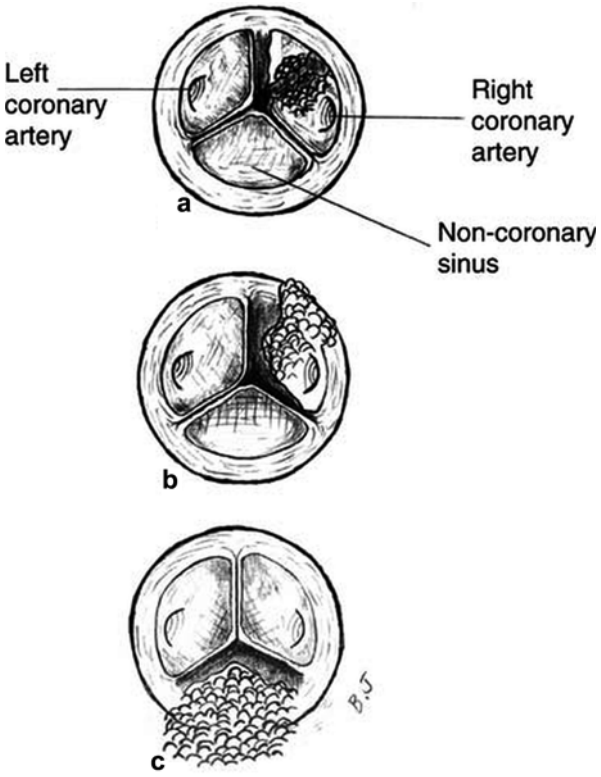

Fig. 8.6 Various locations and extents of infection on the aortic valve. (**a**) Lesion limited to the right coronary cusp, sparing the annulus. The lesion has eroded the cusp, resulting in a tear in the cusp. (**b**) Lesion involving the right coronary cusp and extending to the annulus. (**c**) A diseased noncoronary sinus with extension of the lesion to the annulus and the anterior mitral leaflet

extensive aortic root destruction and extension to the aorto-mitral curtain. Involvement of this critical intersection of aortic and mitral valves requires a complicated surgical approach through both the left atrium and ascending aorta. Homografts which include the anterior mitral leaflets offer the optimal material to repair such defects. This may involve extensive debridement and reconstruction of left atrial roof and atrial septum with a pericardial patch which also serves as the anchor for suturing in place the aortic homograft (Fig. 8.7). Alternatively, the aorto-mitral curtain of the aortic homograft can be used to repair the defect resulting from the debridement (Fig. 8.8).

Surgical Outcomes and Complications

The immediate period after surgery is critical for patients with IE. Many challenging postoperative issues such as bleeding, infection control, rhythm control, fluid management, vasoplegic conditions, organs dysfunction and other postoperative issues require a dedicated team comprised of specialists from cardiac surgery, intensive care, cardiology, infectious disease and other areas such as neurology and nephrology.

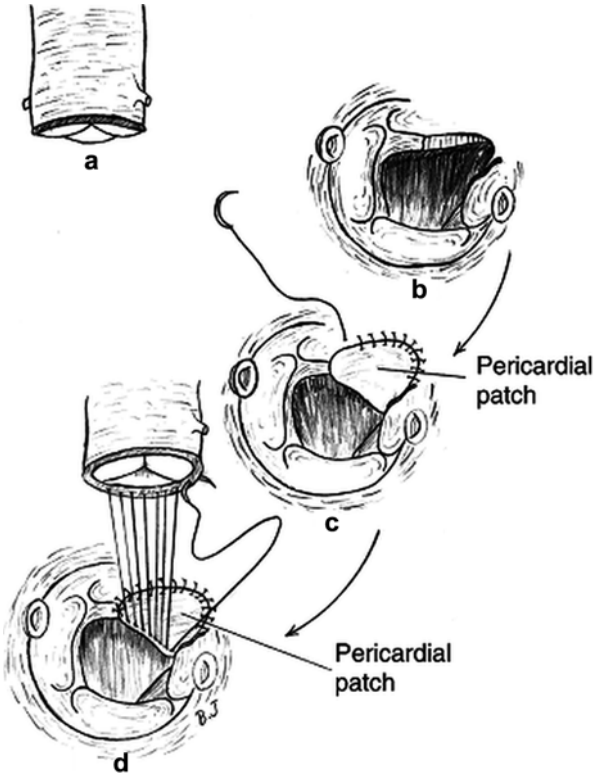

Fig. 8.7 (**a**) An aortic homograft without the aortomitral curtain. (**b**) The defect left from the removal of the aortic root and the diseased aortomitral curtain. (**c**) A pericardial patch is first used to repair the defect at the aortomitral location. (**d**) The aortic homograft is then anchored in place with part of the homograft sutured onto the pericardial patch

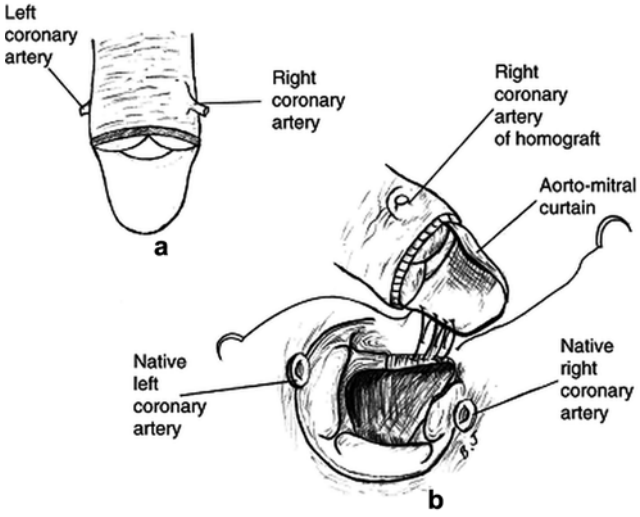

Fig. 8.8 Homografts can be used in the reconstruction of extensively diseased aortic root. (**a**) An aortic homograft with the accompanying aortomitral curtain. (**b**) The aortomitral curtain of the aortic homograft can be used to repair the defect caused by the removal of aortic root lesions extending to the aortomitral location

Table 8.3 Factors adversely affecting surgical outcomes (mortality and morbidity)

Prosthetic valve (versus native valve IE)
Intracardiac abscess
Left-sided (versus right-sided) IE
Aortic (versus mitral) IE
Extensive disease/destruction, multiple valve involvement
Staphylococcal or culture-negative infection
Advanced age
Increasing cardiopulmonary bypass and aortic cross-clamp time
Valve replacement versus repair (affects morbidity only)
Delay in surgery in face of worsening cardiac function
Early prosthetic valve IE (associated with higher rate of late death)
Emergent/urgent surgery due to progressive heart failure
Poor LV function (whether or not due to IE)
Postoperative sepsis (most commonly pneumonia)
Postoperative renal failure
Liver failure

Table 8.4 Hospital (or 30-day) mortality in NVE and PVE

	Mortality		
Study	NVE (%)	PVE (%)	P value
Savage et al[a]. (2014) [37]	9.8	21.1	0.0001
Murashita et al. (2004) [43]	15.5	33.3	0.01
Romano et al. (2004) [56]	6.6	24.2	0.0001
d'Udekem et al. (1997) [19]	4	13	0.062
Wilhelm et al. (2004) [33]	3.2		
Amrani et al. (1995) [57]	8.5		
Akowuah et al. (2003) [58]		24	
Habib et al. (2005) [59]		17 (surgical treatment) 25 (medical treatment)	

Numbers in brackets [ ] indicate reference numbers
[a]Limited to aortic valve IE

Excellent surgical results can be achieved in patients who are young without co-morbidities and in whom the infection has been brought under control, IE is confined to a native valve, and valve damage is amenable to repair or simple replacement. Table 8.3 summarizes factors that negatively affect morbidity and/or mortality after surgical management of IE. Both short- and long-term results are less favorable following surgery for IE involving a prosthetic valve then a native valve (Tables 8.4 and 8.5).

Table 8.5 Survival in NVE and PVE

Survival in NVE						
	Survival (%)					
Study	1-year	5-year	10-year	15-year	20-year	*p* value
Romano et al. (2004) [56][a]	91	82	67.5	48.8		0.0016 vs. PVE)
Wilhelm et al. (2004) [33]	93	81	61			
Amrani et al. (1995) [57]						
Non-complex operations[b]		93.5	93.5			0.042
Complex operations[c]		79.9	76.1			
Moon et al. (2001) [35]			54		44	<0.003 (vs. PVE)
Survival in PVE						
	Survival (%)					
Study	1-year	5-year	10-year	15-year	20-year	*p* value
Romano et al. (2004) [56]	79.7	64.2	33.5	33.5		0.0016 (vs. NVE)
Moon et al. (2001) [35]			41		16	<0.003 (vs. NVE)
Akowuah et al. (2003) [58]			58			
Habib et al. (2005) [59]	62[d]					

[a]Numbers in brackets [ ] indicate reference numbers
[b]Single aortic valve replacement
[c]Aortic valve replacement plus another valve procedure
[d]2–7 year follow-up

The reasons for relatively poor outcomes in patients with prosthetic valve IE relate to higher rates of staphylococcal infection and perivalvular abscess, the presence of less healthy perivalvular tissue, risks of reoperation, and a generally older population compared to patients with native valve IE. Multiple valve disease is associated with more extensive tissue destruction, longer duration of operation, and less favorable results (Table 8.5). The infecting microorganism directly affects mortality and morbidity. Staphylococcal infections, especially those caused by *Staphylococcus aureus*, as well as culture-negative IE are associated with poor outcomes (Tables 8.6 and 8.7) [43]. *Staphylococcus aureus* infections cause more extensive destruction, more frequent abscess formation and greater hemodynamic derangement. Valve repair procedures, especially in the mitral position, are associated with significantly lower postoperative morbidity than valve replacement. However, there is no significant difference between repair and replacement procedures in terms of mortality (Table 8.8). The first postoperative year is of crucial importance, as most of the adverse events occur during this period. Patients who have an event free first postoperative year are likely to have a favorable long-term survival. Table 8.9 summarizes surgical complications. Recurrent IE is a serious postoperative complication and is associated with poor prognosis, especially when it occurs in the replaced prosthetic (versus repaired native) valves. Early recurrent IE is usually due to residual infected tissue, and the

Table 8.6 Effect of infecting microorganism on survival

Study	Infecting microorganism	Early postoperative	*p* value
Mortality (%)			
Mihaljevic et al. (2004) [34]	*Staphylococcus aureus*,	17.8	0.158
	Staphylococcus		
	Epidermidis, or culture-negative		
	Other pathogens	0	
Amrani et al. (1995) [57]	*Staphylococcus aureus*	8.5	
	Other pathogens	0	
d'Udekem et al. (1996) [13]	Staphylococci	22	0.020
	Other pathogens	3	
Habib et al. [59]	All Staphylococci (20 %)	24	
	Staphylococci aureus	20	
	Enterococci	12	0.02

Survival (%)					
Study	Infecting	1-year	5-year	10-year	*p value*
Wilhelm et al. (2004) [33]	*Staphylococcus aureus*	76.5	65	44	0.008
	Other pathogens	98.9	84.9	67	

[a]Numbers in brackets [ ] indicate reference numbers

Table 8.7 Effect of infecting microorganisms on event-free survival

Infecting microorganism	Three-year freedom from events (%)
Staphylococcus aureus	55.6
Culture-negative	47.6
Streptococcus	100

Murashita et al. [43]

recurrence risk can be minimized by complete debridement of the infected tissue and proper surgical technique. Late recurrent IE is more frequent in patients who have abscess at the time of the initial operation [19]. Recurrent IE rates are given in Table 8.10. There is no significant difference in either short- or long-term survival between patients who receive either a mechanical or bioprosthetic valve. A recent study suggests superiority of mechanical valves in the mitral position in terms of mortality for patients 51–70 years of age [44]. However, further studies are required to support this finding. Due to the need for lifetime anticoagulation with mechanical valves, this group has a higher risk of hemorrhage. Reoperation, on the other hand, is more common in bioprosthetic valves due to the propensity for degeneration over time. Bioprostheses have been reported by some to have a higher rate of recurrent

Table 8.8 Valve replacement versus repair

Operative/in-hospital mortality			
Study	Mortality with Repair (%)	Mortality with Replacement (%)	*p* value
Wilhelm et al. (2004) [33][a]	1.7	4	0.67
Mihaljevic et al. (2004) [34]	0	13	0.14

Survival (%)				
Study	1-year	5-year	10-year	*p* value
Wilhelm et al. (2004) [33]				
Valve replacement	96.5	92.5	79	0.1
Valve repair	98	95.4	95.4	
Mihaljevic et al. (2004) [34]				
Valve replacement	78	73	Not significant	
Valve repair	85	85		

Morbidity				
Study	Variable	Valve replacement	Valve repair	*p* value
Wilhelm et al. (2004) [33]	Perioperative morbidity (<30 days after surgery)	62 %	5 %	<0.001
Mihaljevic et al. (2004) [34]	Median of hospital stay	21 days	9.5 days	<0.01

[a]Numbers in brackets [ ] indicate reference numbers

Table 8.9 Postoperative complications

Early complications	Late complications
Failure of repair procedure	Deterioration of repair
Prosthetic dehiscence with/without	Prosthetic dehiscence with/without
significant paravalvular leakage	Significant paravalvular leakage
Sepsis (most commonly pneumonia)	Anticoagulation-related events (in mechanical valves)
Renal failure	
Hemorrhage	Recurrent IE, including prosthetic valve IE
Need for reoperation	Bioprosthesis degeneration
Atrioventricular block and/or arrhythmia (with/without need for permanent pacemaker)	
Recurrent IE, including prosthetic IE	

Table 8.10 Risk of recurrence of infective endocarditis following surgical intervention for endocarditis

Study	Type of IE in the study	Rate of recurrent IE (%)	
		At 5 years	At 10 years
d'Udekem et al. (1997) [19][a]	NVE and PVE	9	21
Mihaljevic et al. (2004) [34]	NVE	5.7[b]	
Akowuah et al. (2003) [58]	PVE	40	

[a]Numbers in brackets [ ] indicate reference numbers
[b]All reinfections occurred within 5 months of surgery

Table 8.11 Comparison of outcomes in mechanical and bioprosthetic valves

Operative mortality: no significant difference
Bleeding: more frequent in mechanical valves (associated with anticoagulation)
Reoperation: higher rate with bioprostheses in younger (<60 years) patients (degeneration)
Recurrent endocarditis: more frequent in bioprostheses
Long-term survival: no significant difference

endocarditis [45–47]. Table 8.11 presents a comparison of mechanical versus bioprosthetic valves.

Other Important Surgical Considerations

Isolated Tricuspid Valve Endocarditis

Isolated tricuspid valve (TV) endocarditis is rare, except in the setting of intravenous drug abuse and in patients with long-term indwelling catheters. Valve surgery is infrequent in isolated TV endocarditis, because of less pronounced impact on hemodynamics compared to the involvement of the aortic or mitral valve. Regurgitation of the TV, however, often accompanies left-sided IE without being necessarily infected. Having both mitral and tricuspid valves infected at the same time is less frequent. In any case, surgical procedures on an infected TV mostly involve excision of vegetation and repair, and not replacement (except if massive destruction of the valve is present), owing to the anatomic and hemodynamic characteristics of the TV and the right heart. The principles and techniques of TV surgery are similar to those for the mitral valve. If TV replacement is required, both biological and mechanical valves can be employed, although bioprosthetic valves may be favored to avoid anticoagulation [47–49]. Recurrence of infection is common in patients who continue to use intravenous drugs.

Intravenous Drug Users

Intravenous drug users predominate in series of young people with IE, and the overall incidence of IE in this group is 1–5 % per year [50]. The TV is infected in up to 70 % of cases of IE in drug users, and the majority has no known preexisting cardiac disease.

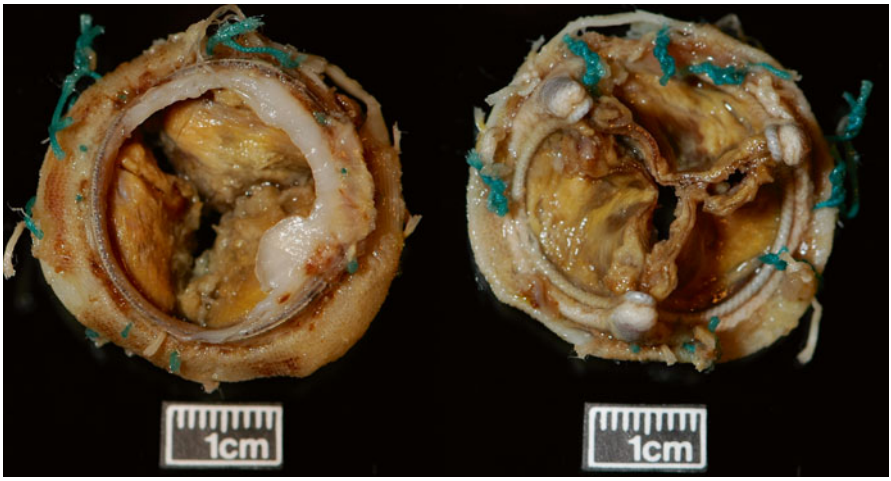

Fig. 8.9 Explanted aortic valve bioprosethesis infected with fungus

Staphylococcus aureus species dominate, although unusual infections including pseudomonas aeruginosa, fungi, Bartonella, Salmonella, and Listeria may be encountered, particularly in patients infected with the human immunodeficiency virus, whose outcome is inversely related to the CD4 count [51]. This group of patients presents particular management difficulties because of their drug-seeking behavior and poor compliance with treatment. They often struggle against prolonged hospitalization, and as a result surgery should be avoided whenever feasible, and either short-course of parenteral antibiotic therapy or oral antibiotic regiment may be considered in view of the difficulties with compliance. Surgery is occasionally required for complications of left-sided disease where indications are the same as for non-drug users. The threshold for intervention and choice of surgical approach may be altered in individual patients in whom recurrence of infection due to continued drug abuse or poor compliance with anticoagulant therapy are real concerns. Use of a homograft may be worthy of consideration in these situations. Infection with the human immunodeficiency virus is not a contraindication to cardiac surgery, but requires a higher degree of vigilance from the health care workers looking after the patient [36, 50, 51].

Prosthetic Valve Endocarditis

Prosthetic valve IE is a serious complication of valve replacement surgery with a reported incidence of 0.5 % per patient-year [52]. Both mechanical and biological valves are prone to IE, while homografts seem to be more resistant to infection. The diagnosis of prosthetic valve IE is usually based on evidence of infection (positive blood cultures) and evidence of vegetation or valvular dysfunction [53].

Early prosthetic valve IE occurs within the first year following surgery and is most often the result of perioperative infection. The most common causative organisms belong to the Staphylococcus species, followed by gram negative and fungal infection (Fig. 8.9). These infections are often severe and frequently associated with

abscess, prosthesis dehiscence, and fistula formation. Although surgery may be technically difficult, it is associated with a lower mortality rate than medical treatment alone. The mortality rate of prosthetic valve IE caused by *Staphylococcus aureus* is about 75 % with medical therapy alone compared to 25 % in patients who undergo surgery [53]. Prosthetic valve IE can result in perivalvar infection and hence dehiscence of an infected prosthesis may occur. In this setting, rapid hemodynamic deterioration is an indication for urgent surgery [54].

Late prosthetic valve IE defined as IE that occurs more than a year after surgery, is usually caused by Streptococci species, followed by Staphylococci species and organisms from the HACEK group. In patients with an uncomplicated infection lacking signs of perivalvular infection or significant vegetation, medical treatment may be sufficient [52].

Culture negative IE is present in more than 10 % of prosthetic valve IE cases. In these cases, clinical judgment and repeated echocardiography should guide diagnosis and management [11]. Fungi are most frequently observed in drug users and immunocompromised patients. Mortality is very high (50 %), and treatment necessitates dual antifungal administration in addition to valve replacement (Fig. 8.9). Most cases are treated with amphotericin B or with azoles. Suppressive treatment with oral azoles is often maintained long term and sometimes for the life of the patient [55].

Summary

Despite advances in the diagnosis and medical management of IE, the need for valve surgery remains high in patients with IE. This is particularly true in patients infected with aggressive microorganisms. The primary consideration for surgical intervention is the hemodynamic derangement resulting from IE. Surgery can be successfully performed to restore hemodynamic stability and to help eradicate infection, even in the setting of active IE. In spite of higher risks of short and long-term complications, surgical results have steadily improved in recent years, particularly in centers of excellence for cardiac valve surgery. Valve repair is preferable to valve replacement, if it is technically feasible. Aortic homografts are ideal in patients with aortic root destruction who require extensive reconstruction of the aortic root and surrounding structures. The management and outcome of patients with IE can be optimized using a multidisciplinary Heart Team approach, with surgical input at the early stage following the diagnosis and continued to be an integral part of management throughout the course of the disease. The early involvement of surgery helps develop a more comprehensive treatment strategy that avoids subsequent delays if and when surgery is required.

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Treatment of Endocarditis

9

Donald C. Vinh and John M. Embil

Abstract

Infective endocarditis, even if adequately treated, can be associated with significant morbidity and mortality. Clinical outcomes are influenced by multiple factors which include valve characteristics, host factors, causative organisms, development of intracardiac, or systemic complications and the therapeutic options.

This chapter will provide an overview of current treatment regimens for infective endocarditis.

Keywords

Infective endocarditis • Treatment of infective endocarditis

Key Points

1. The diagnosis of infective endocarditis (IE) requires early clinical suspicion, based on history and physical examination, and can be supported by appropriate microbiological laboratory investigations (e.g., blood culture, serology) and/or imaging (e.g., echocardiogram).
2. Empiric antimicrobial therapy, based on the most likely pathogens identified from clinical evaluation, may need to be instituted, particularly in patients who are clinically unwell. Once a pathogen has been identified,

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antimicrobial susceptibility testing must be performed, including determination of the minimal inhibitory concentration (MIC) and the presence of in vitro synergy, where applicable.
3. Effective antimicrobial therapy requires the administration of bactericidal agents for an extended period of time.
4. Health care providers should be aware of the possible intracardiac and extracardiac complications of IE.
5. The role of surgical intervention in the management of IE has likely strongly contributed to reduced mortality rates. Indications for surgical intervention exist, with congestive heart failure (from any cause) being the principal need for surgery. When appropriate, early surgical intervention should be performed.

Introduction

Infective endocarditis (IE), if inadequately treated, is fatal. Even with appropriate management, overall mortality rates range from 10 % to 25 % [1–3]. Clinical outcome is influenced by multiple factors, including valve characteristics, host factors, causative organism, development of intracardiac or systemic complications, and management options available.

The therapeutic modality initially used in the treatment of IE is medical. The role of surgery, however, continues to expand; aggressive surgical intervention, particularly in the early stages of developing complications, can be associated with a reduction in mortality. This chapter will focus on the role of medical, and where appropriate surgical, management in native valve endocarditis. Discussion regarding newer antibiotics is provided. Endocarditis involving prosthetic valve/intravascular devices, as well as endocarditis in special patient subpopulations, such as in intravenous drug users and in immunocompromised hosts, are discussed in other chapters.

Principles of Medical Therapy

Infective endocarditis remains a relatively rare disease, with annual incidences ranging from 15 to 60 cases per million [4, 5]. Due to this low rate, good, prospective, randomized controlled trials assessing the benefits of various antibiotic regimens in the treatment of IE have been difficult to perform. Therefore, the principles of antimicrobial selection for IE are based on the understanding of the behaviour of the causative pathogen, proper interpretation of antibiotic susceptibility testing, an understanding of vegetation characteristics, and proper application of antimicrobial pharmacokinetic and pharmacodynamic data. These considerations are complemented by animal

experimental models and by clinical outcomes of published observational studies to form consensus-based guidelines for the optimal management of IE.

Fundamental to the management of IE is early diagnosis and prompt initiation of effective antimicrobial therapy. Therefore, proper laboratory identification of the pathogen to the species level is essential, with subsequent antimicrobial susceptibility testing using standardized protocols to determine the minimal inhibitory concentration (MIC). Testing for synergistic combinations of antibiotics (e.g. high-level aminoglycoside resistance for *Enterococcus* spp.) using standardized protocols should also be done where appropriate.

The MIC of an antimicrobial agent is defined as the lowest concentration which results in maintenance or reduction of inoculum viability; it is the lowest concentration of the drug needed to prevent microbial growth in vitro [6]. The MIC can then be compared to a reference standard database, such as that from the Clinical and Laboratory Standards Institute (CLSI) (formerly the National Committee for Clinical Laboratory Standards (NCCLS)), to interpret whether the pathogen is "susceptible", "intermediate", or "resistant" to the tested antimicrobial. Definitions of these terms are provided Table 9.1. It is important to note that the MIC represents a unique relation between a particular bacterial species and the tested antimicrobial agent. Because different antibiotics are tested at different concentrations, the MIC numbers cannot be directly compared.

The minimum bactericidal concentration (MBC) is the lowest concentration of an antibiotic, expressed in mg/L, that under defined in vitro conditions reduces by ≥99.9 % (3 $\log_{10}$) the number of organisms in a medium containing a defined inoculum of bacteria, within a defined period of time [8]. Although the MBC is an in vitro microbiological method to determine the killing efficacy of antibacterial agents, its routine use in clinical practice is precluded by inaccuracy of measurement, as well as technical limitations (e.g. suboptimal inocula, difficulties with interpretation of a 99.9 % bactericidal endpoint) that produce varying and thus invalid results [9–11]. As such, various working groups for endocarditis, including the British Society for Antimicrobial Chemotherapy (BSAC) and the American Heart Association committee (AHA), do not recommend its routine determination [12, 13]. The value of

Table 9.1 Definitions of terms used in antimicrobial susceptibility testing [7]

Susceptible (S) – implies that infections may be treated appropriately with the dosage of antibiotic recommended for the type of infection and infecting species, unless otherwise indicated
Intermediate (I) – implies that infections may be treated if the antibiotic is able to reach specific tissues where the drug will be concentrated (for example, quinolones in the urine) or when the drug can be used in higher than usual doses without adverse effects. This category also includes a "buffer zone," which should prevent small, uncontrolled technical factors from causing major discrepancies in interpretation
Resistant (R) – isolates are not inhibited by the usually achievable systemic concentrations of the drug in normal dosage and/or fall in the range where specific microbial resistance mechanisms are likely (for example, β-lactamases) and clinical efficacy has not been reliable in treatment studies

the MBC, however, allows for the definition of antimicrobial agents as bactericidal, bacteriostatic, or tolerant.

Bactericidal antibiotics, generally speaking, are those that kill bacteria, whereas bacteriostatic agents are those that prevent the growth of bacteria (i.e. keeps them in the stationary phase of growth). In IE, a bactericidal regimen (either monotherapy or combination therapy) is considered necessary for cure [2, 3, 11, 14]. The actual microbiological definition of "bactericidal" is a ≥99.9 % reduction in viable bacterial density in an 18–24 h period, producing an MBC to MIC ratio ≤4, whereas "bacteriostatic" is defined as a ratio of MBC:MIC >4 [11]. Tolerance occurs among bacterial strains when a bactericidal antibiotic loses its killing efficacy but retains its bacteriostatic activity (i.e. MIC unchanged) and is defined as a ratio of MBC:MIC > 32 [8, 15].

Although conceptualizing antibiotics as being either bactericidal or bacteriostatic may be useful, these categories are not mutually exclusive, but rather represent a continuum of antimicrobial activity. Bactericidal activity is not an invariable property of an antibiotic; it is also influenced by the organism, inoculum burden, as well as growth conditions [10, 11, 16]. For example, cell wall active agents such as β-lactams and glycopeptides are quite effective in vitro in killing *S. aureus*, and would thus be considered "bactericidal". Yet these same agents do not produce the ≥99.9 % in vitro kill of enterococci within the 24 h incubation period, and are therefore "bacteriostatic" for this organism. Inoculum burden critically affects antibiotic activity [17, 18]: within cardiac vegetations, bacteria may reach very high concentrations (10^8–10^{10} organisms per gram of tissue) [11, 17]. Fixed-dose concentrations of antibiotics against standard bacterial inocula in vitro (e.g. 10^5 $\log_{10}$ CFU/g) may not reflect this situation of high bacterial burden in vivo; as such, it may lead to clinical failure. Growth conditions also influence the activity of antibiotics. β-lactams and glycopeptides require bacterial cells to be actively dividing to exert their bactericidal activity. In endocarditis, bacteria within vegetations are in a steady-state growth phase; this slow growth impairs the bactericidal action of cell wall active agents [11, 16]. Therefore, an understanding of bacterial dynamics and pathogen-drug relations is crucial to correct antimicrobial selection.

To further enhance the bactericidal activity of a selected antibiotic regimen requires an understanding of pharmacokinetics and pharmacodynamics, with subsequent optimization of these parameters. Pharmacokinetics (PK) refers to the factors that determine the drug concentrations at the site of infection after a dose of an antimicrobial drug is given; it is affected by the absorption, distribution, and elimination of the drug [19]. For example, the oral formulation of certain antibiotics, in combination with the severity of illness of the host, would lead to slow, erratic, or poor absorption of the drug. This, in turn, would produce variable antibiotic serum levels, which would be disastrous in IE. Hence, the intravenous route is considered the best route of administration because it provides maximal bioavailability [16, 19]. However, with newer antibiotics in which the oral formulation has high (near 100 %) bioavailability, this dogma in the management of IE may change. The concentration of an antibiotic in the serum is also affected by its volume of distribution, its metabolism, and its elimination. With IE, the site of infection is an intravascular vegetation enclosed in a layer of biofilm that renders penetration of antibiotics

difficult. This phenomenon may explain the superiority of some antibiotics over others in the management of IE, depending on their degree of vegetation penetration. It also provides the rationale for using high doses of antibiotics and a prolonged duration of treatment. Another factor that determines efficacy of antibiotic at the site of infection is protein binding. All drugs bind to some extent to serum proteins; however, it is the free (unbound) drug that is active [19]. Antibiotics that are highly protein bound in vivo may actually be clinically ineffective, even though they demonstrate significant in vitro killing activity. Such was the case with cefonicid, a second-generation cephalosporin that was clinically inadequate for the treatment of IE due to *S. aureus* [20]. Lastly, an understanding of how a certain antibiotic is metabolized or excreted, and whether this clearing system is impaired in the host, will allow for optimal dosing while minimizing toxicity.

Pharmacodynamics relates drug exposure (i.e. pharmacokinetics) to the antimicrobial effect of the drug, so as to provide a more rational basis for determining of optimal dosing regimens in terms of the dose and the dosing interval [21, 22]. The two major components of antibiotic activity are its pattern of kill and its post-antibiotic effect (PAE). The pattern of bactericidal activity can be concentration-dependent, in which the rate of kill is directly dependent on the amount of drug (peak serum concentration) relative to the MIC, or time-dependent, in which the bactericidal efficacy is dependent on the amount of time the serum antibiotic concentration exceeds the MIC. For time-dependent antibiotics such as β–lactams and glycopeptides, further increasing antibacterial concentrations above the MIC does not result in proportional increases in killing. The PAE refers to a variety of persistent effects that last after antimicrobial exposure. Examples include the in vitro PAE, which is the extent of growth retardation of bacteria that occurs when drug levels are suddenly eliminated, as well as the post-antibiotic leukocyte effect, in which organisms in the postantibiotic state of growth are more susceptible to the antimicrobial activity of white blood cells [21]. As the vegetations in IE are composed of fibrin, platelets, and bacteria, with few phagocytes [16], the post-antibiotic leukocyte effect would be intuitively negligible in IE. The clinical significance of other PAE in IE remains to be elucidated.

Based on the pattern of bactericidal activity and the PAE, antibiotics can then be divided into three categories [21, 22]: (1) Concentration-dependent killing and moderate to prolonged persistent effects. Examples include aminoglycosides, quinolones, and daptomycin; (2) Time-dependent killing and minimal to no persistent effects, such as β-lactams; and (3) Time-dependent killing and moderate to prolonged persistent effects, including glycopeptides, oxazolidinones, clindamycin, macrolides, and tetracyclines. This framework will determine subsequent modifications of dosing regimens to optimize bactericidal efficacy [21]: For the first group, enhancing peak serum concentration (while avoiding or minimizing toxicity) would be the preferred intervention. For β-lactams, adjusting the interval between infusions or using agents with longer half-lives would be undertaken to increase the duration of exposure. For the third group, enhancing the amount of drug is predicted to be an important determinant of clinical efficacy.

As mentioned previously, in addition to bactericidal and bacteriostatic, antibiotics can also be tolerant (i.e. inhibits bacterial growth but loss of killing activity).

Although the clinical relevance of tolerance in endocarditis is unknown (as MBC is not routinely tested), retrospective microbiological studies have demonstrated this phenomenon among clinical isolates in treatment failures of β–lactams and glycopeptides [23–25]. It may also provide additional rationale for the use of synergistic combination therapy in certain cases of IE.

Selecting the appropriate antibiotic regimen at the start of therapy is but the first step. Re-assessment of antimicrobial performance is continuously required. The only reliable measure of clinical efficacy is ultimate cure without relapse. In the interim, it is important to monitor for evidence of improvement, including defervescence, sterilization of blood cultures, and normalization of inflammatory markers [16, 26, 27]. Failure to demonstrate such features, in the presence of correct clinical and laboratory diagnosis, may reflect pharmacological error (e.g. insufficient dose, dosing interval, or antibiotic serum levels) or the development of IE complications. To ensure pharmacological optimization, consultation with a pharmacist with experience in antimicrobial therapy should be considered. As well, therapeutic drug level monitoring, especially for aminoglycosides and glycopeptides, is recommended [12, 13, 16, 28].

Recognition of syndromes indicating the presence of IE complications is crucial in patient management. These complications can be classified into cardiac and extra-cardiac. The cardiac manifestations include congestive heart failure (CHF), periannular extension of infection (with subsequent abscess or fistula formation, or rupture), valve obstruction, or prosthesis instability. The extra-cardiac manifestations result from embolic phenomena; the major sequelae include neurological compromise (e.g. stroke with or without hemorrhage, mycotic aneurysm) and metastatic infections. The presence of these complications can assist in determining the need and timing for surgical intervention.

In summary, the appropriate treatment of IE requires early diagnosis, as well as prompt effective antimicrobial therapy, and is best managed via a multidisciplinary team approach, involving at least specialists in infectious disease, cardiologists, pharmacists, and cardiac surgeons.

Native Valve Endocarditis (NVE)

The major pathogens causing NVE are the streptococci, enterococci, and staphylococci. Emerging pathogens include fungi. Members of the HACEK group are discussed in the chapter along with pathogens causing culture-negative endocarditis.

Streptococcal NVE

The nomenclature of the streptococci is complex. However, with respect to NVE, it is clinically useful to divide streptococci into the following categories [12, 13, 28, 29]: (1) oral (or viridans) streptococci; (2) *S. bovis* complex; (3) nutritionally-variant streptococci; (4) *S. pneumoniae*; and (5) beta-hemolytic streptococci.

Oral (or Viridans Group) Streptococci

The oral (or viridans group) streptococci are a heterogeneous group of streptococci that constitute a vital part of the normal flora of the human upper respiratory tract, gastrointestinal tract, and female genital tract. Previously, when rheumatic heart disease was prevalent, viridans streptococci were the most common cause of NVE, accounting for as much as 60–80 % of all cases of IE; their incidence over the last 20 years has since decreased [2, 30, 31]. Currently, viridans group streptococci are divided into the following groups [32, 33]: *S. mutans* group, *S. salivarius* group, *S. anginosus* group (previously *S. milleri* group [34]), *S. sanguinis* group, and *S. mitis* group. Although the taxonomy of these organisms will change, what is important for the clinician to understand is the diversity of pathogens that clinically and therapeutically behave as "viridans streptococci" and that there are species-specific variation in antibiotic sensitivities.

Antimicrobial susceptibility testing of the viridans streptococci by CLSI (NCCLS) criteria categorize these pathogens as penicillin-susceptible (MIC $\leq$ 0.12 mg/L), or penicillin non-susceptible, which are further classified as either intermediate (MIC 0.25–2 mg/L) or high resistance (MIC $\geq$ 4 μg/L) [35]. These microbiological laboratory criteria, however, are different than those used by the AHA, BSAC, and the European Society of Cardiology (ESC), The updated guidelines from the AHA define VGS as highly penicillin susceptible if the MIC $\leq$ 0.12 μg/mL. relatively penicillin-resistant if the MIC ranges from >0.12 to $\leq$0.5 μg/mL, or fully resistant if the MIC >0.5 μg/mL [36]. Those from the BSAC are similar, although the MIC distinguishing highly penicillin-susceptible from relatively penicillin-resistant is 0.125 μg/mL (rather than 0.12 μg/mL) [13]. The ESC defines strains fully susceptible to penicillin as those with MIC <0.125 mg/L, those relatively resistant to penicillin as having an MIC 0.125–2 mg/L, and those fully resistant as having an MIC > 0.2 mg/L [37] The rationale for this discrepancy is unclear [38], but establishing lower MIC thresholds to label a viridans streptococci as "intermediate" or "resistance" presumably errs on the side of clinical caution and ensures more aggressive antimicrobial intervention. The clinical criteria are used in the recommendations of antibiotic therapy.

Previously, it was felt that all oral streptococci were fully sensitive to penicillin [39]. Since the 1990s, however, these *Streptococcus* spp. have been displaying increasing resistance to penicillin and other β-lactam antimicrobial agents. In particular, the *S. mitis* group is commonly implicated, especially (although not exclusively) among neutropenic cancer patients, who are exposed to various therapeutic and prophylactic antibiotic regimens [40–45]. Frequently, these penicillin non-susceptible viridans group streptococci also show reduced susceptibility to ceftriaxone, erythromycin and clindamycin [40, 46–48]. Glycopeptide resistance, however, is uncommon [39, 46, 48, 49]. Amongst the viridans group streptococci there are now reports of high-level resistance ($\geq$256 mg/l) to daptomycin, a cyclic lipopeptide antibiotic with bactericidal activity against staphylococci and streptococci [50]. As well, high-level aminoglycoside resistance among the viridans streptococci is uncommon, although if present, it is more commonly reported with streptomycin than with gentamicin [9, 49, 51]. Streptomycin-resistant isolates, however, can still demonstrate in vitro synergistic susceptibility to the combination of penicillin and

gentamicin; conversely, gentamicin-resistant isolates do not always demonstrate high-level streptomycin resistance [51]. As such, testing for resistance to these aminoglycosides for each viridans streptococcal isolate should be performed.

Antimicrobial susceptibility testing dictates not only which antibiotics may be used, but also assists in determining the duration of therapy. Early clinical studies found that when a total dose of 14–16 million units of penicillin was given alone for up to 2 weeks, the relapse rate was 15 %; this rate decreased to <1.5 % with 4 weeks of therapy [52]. Experimental evidence of the combination of penicillin with an aminoglycoside demonstrated more rapid eradication of streptococci from IE vegetations, as assessed by bacterial counts and relapse in animal models after termination of therapy [51]. Clinical studies of the 2-week combination regimen demonstrated a relapse rate of 2 % [53]. However, the patient population in these studies excluded those with shock or metastatic septic foci. Therefore, for IE due to viridans group streptococci that are penicillin- and aminoglycoside-sensitive, a 2-week treatment regimen may be considered, provided that appropriate conditions for short-course therapy are fulfilled. These conditions are outlined in Table 9.2.

The *S. anginosus* (or "*S. milleri*") group has a propensity to form abscesses, as well as to cause hematogenously disseminated infection [54, 55]. More specifically, however, it appears that *S. constellatus* and *S. intermedius* of this group are more commonly associated with abscess formation, whereas *S. anginosus* is more commonly associated with IE [56]. Furthermore, it appears that IE due to the *S. anginosus* group, and *S. anginosus* in particular, may be associated with a higher mortality rate than IE due to other viridans streptococci [56]. As such, the duration of antimicrobial therapy for NVE caused by the *S. anginosus* group may need to be longer than that for NVE caused by other viridans streptococci [36].

The prevalence of penicillin non-susceptible viridans group streptococci has been increasing worldwide, with rates as high as 30–45 % reported [40, 44, 47, 57]. The mechanism of action appears to be alterations in penicillin-binding proteins [58]. The clinical significance is as expected, with increased morbidity and mortality reported among patients infected by these pathogens [41, 59, 60]. The degree of penicillin resistance (i.e. intermediate versus high) affects the antibiotic regimen selected, as well as the duration of therapy. The antibiotic regimens for the treatment of viridans streptococcal IE are provided in Table 9.3.

Table 9.2 Conditions for 2-week combination therapy for penicillin-sensitive and aminoglycoside-sensitive streptococcal endocarditis [9, 12, 29]

1. Penicillin-sensitive oral (or viridans group) streptococcus or *S. bovis* (penicillin MIC ≤0.1 ∝g/mL)
2. Native valve IE
3. No cardiac complications (e.g., intra-cardiac abscess, heart failure, aortic insufficiency, conduction abnormalities)
4. No extra-cardiac complications (e.g., septic embolic foci)
5. No vegetation >5 mm in diameter on echocardiography
6. Clinical response within 7 days: there should be resolution of fever, the patient should feel well, and the appetite should return

Table 9.3 Antibiotic treatment for IE due to Viridans Group Streptococci and *S. bovis* complex

Category	First-line	Duration	Second-line	Duration	Comments
Penicillin-sensitive (MIC ≤0.1 mg/L)	Penicillin G12–18 million units/day IV	4 weeks			Continuous infusion or q4h; BSAC recommends 10–20 million units/day IV (i.e., 2–3 × 10^5 U/kg)
	Ceftriaxone 2 g /day IV	4 weeks			
	Penicillin G (above dose) + gentamicin 3 mg/kg/day IV	2 weeks			See Table 9.2 for indications for 2-week therapy. Gentamicin can be given as once daily dosing; when 3 divided daily dosing is used, aim for peak concentration of 3–4 μg/mL and trough concentration <1 μg/mL
	Ceftriaxone (above dose) + gentamicin 3 mg/kg/day IV	2 weeks			
			Vancomycin 30 mg/kg/day IV q12h	4 weeks	Recommended only for β-lactam intolerance; aim for peak 1-h post infusion and trough 1-h post infusion and trough concentration of 10–15 μg/mL
			Vancomycin (above dose) + gentamicin 3 mg/kg/day IV	2 weeks	Recommended by BSAC, not by AHA
Relatively penicillin-resistant (MIC >0.12 but ≤0.5 μg/mL)	Penicillin G 24 million units/day IV + gentamicin 3 mg/ kg/day IV	2 weeks combined therapy, then 2 weeks β-lactam alone			Continuous infusion or q4h; BSAC recommends up to 30 million units/day IV (i.e,. 3–400,000 U/kg). In situations where the risk of aminoglycoside use is high, 4 weeks of β-lactam alone may be considered; consultation with infectious disease specialist should be considered
	Ceftriaxone 2 g/day IV + gentamicin 3 mg/kg/day IV	2 weeks combined therapy, then 2 weeks β-lactam alone			
			Vancomycin 30 mg/kg/day IV q12h	4 weeks	Recommended only for β-lactam intolerance; aim for peak concentration of 30–45 μg/mL 1-h post infusion and trough concentration of 10–15 μg/mL
Penicillin-resistant (MIC > 0.5 μg/mL) gentamicin 3 mg/kg/day IV			Vancomycin 30 mg/kg/day IV q12 h+	2 weeks combined therapy, then 2 weeks Vancomycin alone	Recommended by BSAC, but not by AHA

See Table 9.4

S. bovis Complex

"*S. bovis*" is the common name used to designate the group D non-enterococcal streptococci, which are common inhabitants of the intestinal flora of humans. The taxonomy of the *S. bovis*/*S. equinus* complex (herein referred to as "*S. bovis* complex") is evolving and currently consists of the following species: *S. bovis*, *S. equinus*, *S. gallolyticus*, *S. infantarius*, *S. pasteurianus*, and *S. lutetiensis* [32, 61]. The significance to the clinician of knowing this nomenclature derives from the association of "*S. bovis*" with certain co-morbidities. Lack of awareness of the species that constitute the complex can lead to underdiagnosis of these serious underlying conditions [62]. Recent epidemiologic data from the International Collaboration on Endocarditis (ICE) has demonstrated that the proportion of IE due to *S. bovis* complex is increasing, accounting for 10.9 % of cases before 1989, with a dramatic rise to 23.3 % of cases after 1989 [63]. Therefore, an understanding of the clinical features of *S. bovis* complex IE is necessary.

The *S. bovis* complex is very similar to the viridans group streptococci in terms of virulence and antimicrobial susceptibility, with the possible exception of increasing clindamycin resistance [64], a bacteriostatic antibiotic not routinely used in the treatment of IE. As such, therapeutic guidelines for these groups of pathogens are identical [2, 12, 13, 16, 28], shown in Table 9.3.

There are, however, subtle but significant differences in the IE due to *S. bovis* complex. These differences can be divided into two categories: IE features, and associated co-morbidities.

With respect to IE features, studies have demonstrated that patients with this disease are typically of older age, male predominance, have higher rates of co-morbid illnesses, with no previously known valve disease [4, 63, 65–67] . Furthermore, this syndrome has a predilection for the mitral valve, although it can commonly involve multiple valves [63, 66, 68, 69]. Recently, *S. bovis* complex IE has also been found to account for a higher proportion of cases among patients with prosthetic valves [63]. The data on whether *S. bovis* complex IE is associated with more frequent embolic and neurologic complications is conflicting [63, 66–69]. The rates, however, of early surgical treatment and of mortality did not differ significantly when comparing *S. bovis* complex IE to viridans streptococcal IE -(63, 67, 69, 70).

The major associated comorbidity of *S. bovis* complex bacteremia is colonic neoplasm, mainly with *S. bovis* biotype I (*S. gallolyticus* subsp. *gallolyticus* as per new nomenclature) [62, 63, 69]. Various studies have demonstrated that 25–80 % of patients with *S.bovis* complex bacteremia harbor a colorectal tumor [71, 72]. The mechanism by which this complex of bacteria is related to neoplasia remains to be elucidated, but bacterial proteins with the potential to induce a chronic infectious or inflammatory process has been proposed [71]. Nonetheless, the association is well described enough that all patients with *S. bovis* complex bacteremia, including IE, need aggressive evaluation of the gastrointestinal tract, especially the colon, when clinically feasible [13, 70, 72, 73]. Other conditions possibly associated with these pathogens include chronic liver disease [69, 74] and various extra-intestinal neoplasms [72, 75].

Nutritionally-Variant Streptococci

The nutritionally-variant streptococci (NVS) were originally identified in 1961 as a novel strain that exhibited satellitism around colonies of other bacteria [76]. These bacteria have fastidious growth characteristics, requiring complex media enriched with vitamin B6 or L-cysteine, as well as pleomorphism and variable Gram-stain reactions [77]. Recent 16S rRNA gene sequencing studies have demonstrated that the NVS are two new genera: *Abiotrophia* (consisting currently of only one species, *A. defectiva*), and *Granulicatella* (composed of *G. adiacens*, *G. balaenopterae*, and *G. elegans*) [78]. Here, they will be collectively referred to as "NVS". These bacteria are members of the normal flora of the oral cavity, as well as the gastrointestinal and genitourinary tracts [79] and account for approximately 5 % of all cases of streptococcal IE [76, 79]. However, because they are fastidious, it is possible that most previous cases were misdiagnosed as culture-negative IE, thus underestimating their prevalence. Routine modern blood cultures can detect the NVS, usually in 2–3 days [76, 80, 81], although the sensitivity of this method is unknown. Subsequent microbiologic identification and antimicrobial susceptibility testing should be performed.

Although the CLSI has established a method for antimicrobial susceptibility testing of the NVS, there is a paucity of well-validated data permitting the CLSI to establish specific interpretive criteria for *Abiotrophia* or *Granulicatella* spp. Thus, currently, interpretive criteria are derived from that for "*Streptococcus* spp. other than *S. pneumoniae*" [77, 82–84].

NVS IE usually occurs as a result of bacteremia in patients with underlying valve injury [76]. Although it is generally characterized by a slow and indolent course, it is usually more severe, and associated with higher morbidity and mortality, than IE due to viridans streptococci or enterococci [76, 85, 86]. In a review of 30 cases of NVS IE, the bacteriological failure rate was 41 %, despite the in vitro bactericidal effects of antibiotics in two-thirds of cases; approximately 27 % of patients required replacement with a prosthetic valve and approximately 20 % of patients developed fatal CHF or major systemic emboli [76, 86]. The slow growth rate of the bacteria and the production of large amounts of exopolysaccharide in vivo may account for the difficulties encountered in treatment [85]. Another contributing factor is antimicrobial susceptibility. When using CLSI (NCCLS) laboratory criteria, almost 50 % of NVS may not be susceptible to penicillin, although there are species-specific variations in sensitivities, with *A. defectiva* being more commonly non-susceptible [76, 77, 82, 87]. Susceptibility testing with aminoglycosides has demonstrated variable sensitivities [88]. Lack of susceptibility has also been demonstrated with other β-lactams (e.g. cefazolin, cefotaxime) [77, 82] as well as macrolides (e.g. azithromycin) [77]. Most strains have, however, remained susceptible to clindamycin, rifampin, quinolones, and vancomycin [82, 87, 88]. As such, IE due to NVS is treated according to the recommendations for treating enterococci (see Table 9.4) [13, 36].

S. pneumoniae

In the pre-antibiotic era, *S. pneumoniae* was responsible for approximately 15 % of all cases of IE [89]. Since the advent of penicillin, pneumococcal IE has become a rare illness, causing 1–3 % of all cases of NVE [89, 90]. Despite the availability of

Table 9.4 Antibiotic treatment for NVE due to penicillin-resistant (MIC >0.5 μg/mL) *Streptococcus* spp. (non-pneumococcus), Nutritionally Variant Streptococci (NVS), and *Enterococcus* spp

Category	First-line	Duration	Second-line	Duration	Comments
Penicillin-resistant (MIC >0.5 μg/mL) *Streptococcus* spp. (viridans group streptococci and *S. bovis* complex)	Ampicillin 2 g IV q4h + gentamicin 3 mg/kg/day IV	4–6 weeks of combined therapy			AHA recommends: 4 weeks if patient is symptomatic ≤3 months; 6 weeks if symptomatic >3 months
	High-dose Penicillin G (e.g. 18–30 million units/day) IV + gentamicin 3 mg/kg/day IV	4–6 weeks of combined therapy			High-dose penicillin G: $3–4\times10^5$ U/kg
			Vancomycin 30 mg/ kg/day IV q12h + gentamicin 3 mg/kg/day IV	6 weeks	
Nutritionally variant streptococci (NVS): *Abiotrophia* spp. *Granulicatella* spp.	Ampicillin 2 g IV q4h + gentamicin 3 mg/kg/day IV	4–6 weeks of combined therapy			AHA recommends: 4 weeks if patient is symptomatic ≤3 months; 6 weeks if symptomatic >3 months
	High-dose penicillin G (e.g., 18–30 million units/day) IV + gentamicin 3 mg/kg/day IV	4–6 weeks of combined therapy			High-dose penicillin G: $3–4\times10^5$ U/kg
			Vancomycin 30 mg/kg/day IV q12h + gentamicin 3 mg/kg/day IV	4–6 weeks of combined therapy	BSAC recommends 6 weeks, because of the high rate of relapse, as well as blood cultures weekly during therapy and after completion of therapy. Vancomycin alone is as effective as penicillin G + gentamicin in an experimental rabbit model, and thus may be considered if the risks of gentamicin toxicity are high

Enterococcus spp.					
Penicillin S Gentamicin S Vancomycin S	Ampicillin 2 g IV q4h + gentamicin 3 mg/kg/day IV	4–6 weeks of combined therapy			
	High-dose penicillin G (e.g., 18–30 million units/day) IV + gentamicin 3 mg/kg/day IV	4–6 weeks of combined therapy			
			Vancomycin 30 mg/kg/day IV q12h + gentamicin 3 mg/kg/day IV	≥4 weeks of combined therapy (BSAC); 6 weeks of combined therapy (AHA)	Indicated only for patients unable to tolerate β-lactams
Penicillin S Gentamicin R Streptomycin S Vancomycin S	Ampicillin 2 g IV q4h + Streptomycin 7.5 mg/kg IV q12 h	4–6 weeks of combined therapy			For streptomycin, aim for peak serum concentration of 20–35 μg/mL and trough <10 μg/mL
	Penicillin G 24 million units/day) IV + Streptomycin 7.5 mg/kg IV q12 h	4–6 weeks of combined therapy			
			Vancomycin 30 mg/kg/day IV q12 h + gentamicin 3 mg/kg/day IV	≥4 weeks of combined therapy (BSAC); 6 weeks of combined therapy (AHA)	Vancomycin indicated only for patients unable to tolerate β-lactams

(continued)

Table 9.4 (continued)

Category	First-line	Duration	Second-line	Duration	Comments
Penicillin S Gentamicin R (MIC > 500 μg/mL) Streptomycin R (MIC >2,000 μg/mL) (i.e., high-level aminoglycoside resistance) Vancomycin S	Ampicillin 2 g IV q4 h	8 weeks (BSAC); ≥6 weeks (AHA)	Vancomycin 30 mg/kg/day IV q12 h	8 weeks (BSAC); ≥6 weeks (AHA)	Surgical intervention may be necessary
	High-dose penicillin G (e.g., 24–30 million units/day) IV				
Penicillin R (β-lactamase +) Gentamicin S Vancomycin S	Ampicillin- sulbactam 2 g IV q4 h + gentamicin 3 mg/kg/day IV	6 weeks			Usually gentamicin resistant, in which case >6 weeks of ampicillin-sulbactam is needed
			Vancomycin 30 mg/kg/day IV q12 h + gentamicin 3 mg/kg/day IV	≥4 weeks of combined combined 6 weeks of combined therapy (AHA)	
Penicillin R (intrinsic resistance) Gentamicin S Vancomycin S	Vancomycin 30 mg/kg/day IV q12 h + Gentamicin 3 mg/kg/day IV	≥4 weeks of combined therapy (BSAC); 6 weeks of combined therapy (AHA)			

Penicillin R Gentamicin R Vancomycin S	Vancomycin 30 mg/kg/day IV q12 h	8 weeks (BSAC) ≥6 weeks (AHA)			Surgical intervention may be necessary for cure
Penicillin variable Gentamicin R Vancomycin R	*E. faecalis* – Ampicillin 2 g IV q4 h + Ceftriaxone 2 g IV q12 h OR Ampicillin 2 g IV q4 h + Imipenem/cilastatin 500 mg IV q6 h	≥8 weeks			Strongly consider consultation with an Infectious Disease specialist. Surgical intervention may be necessary for cure. Prolonged (>2 weeks) therapy with Linezolid may be associated with thrombocytopenia (see text)
	E. faecium— Linezolid 600 mg po/IV q12 h OR Quinupristin/Dalfopristin 7.5 mg/kg IV q8 h	≥8 weeks			

S susceptible, *R* resistant

penicillin, the mortality rate associated with this disease remains high, with case-fatality rates ranging from 28 % to 60 % [89].

Pneumococcal IE is usually preceded by pneumonia and is most commonly seen in alcoholic patients [89, 90]. Underlying valvular heart disease is not a prerequisite for pneumococcal endocarditis [90]. Once IE is established, the course is typically aggressive, with rapid destruction of valvular tissue and subsequent CHF [89, 91]. As well, this disease has a predilection to form large vegetations on the aortic valve, predisposing to embolization that can lead to pneumococcal meningitis [89, 91]. In fact, the triad of pneumococcal pneumonia, complicated by endocarditis and meningitis, is referred to as Osler's triad as well as Austrian syndrome [89, 90, 92].

Patients with pneumococcal IE may be treated medically or with combined medical-surgical therapy. Evidence suggests, though, that persons with this disease be considered for early surgical intervention, as the mortality rate among patients who received medical therapy alone (63–80 %) was much higher compared to the mortality rate of patients who received combination therapy (32 %) [90]. This phenomenon was first noticed prior to the high prevalence of penicillin non-susceptibility among *S. pneumoniae* that is widely appreciated today.

In the early 1990s, *S. pneumoniae* strains that had a high level of resistance to penicillin appeared in the United States [93]. Since then, rates worldwide have generally demonstrated an increase in penicillin non-susceptible strains (PNSP) [94–97]. By the end of the 1990s, approximately 25 % of *S. pneumoniae* stains in the U.S. demonstrated intermediate- (MIC 0.1–1 μg/mL) or high-level (MIC > 2 μg/mL) resistance to penicillin, with similar trends described globally [98–101]. Furthermore, PNSP isolates have also demonstrated increasing resistance to other agents, most notably to macrolides, trimethoprim-sulfamethoxazole (TMP-SMX), clindamycin, tetracyclines, and chloramphenicol [95, 96, 102, 103]. Fortunately, these latter antibiotics are not routinely used in the management of IE. Third-generation parenteral cephalosporins (e.g. cefotaxime, ceftriaxone) and glycopeptides (e.g. vancomycin) currently possess significant activity against these multi-drug resistant pneumococci [100, 104–107]. Thus, these agents remain the recommended mainstay of empiric therapy for *S. pneumoniae* endocarditis as well as definitive therapy for IE due to intermediate- or high-level penicillin resistance [13, 89] (see Table 9.5). If vancomycin monotherapy is selected for the management of pneumococcal IE, it is important that the possibility of meningitis be excluded, as there is concern about the penetration of vancomycin into cerebrospinal fluid in adults [111]. In patients with *S. pneumoniae* IE and meningitis, high-doses of a third-generation cephalosporin should be used [36]. If the isolate is resistant to third-generation cephalosporins (e.g. cefotaxime MIC ≥ 2 μg/mL), then vancomycin and rifampin should be added [36].

Given the aggressive nature of this disease, including the associated risk of meningitis and the high mortality rates with medical therapy alone, the preferable treatment of patients with pneumococcal IE may be a combined medical-surgical approach. This recommendation is largely based on a meta-analysis of 197 cases reported in the English literature of this disease among adult patients in the penicillin era [89]. The mortality rate among 91 patients treated with antibiotics alone was

Table 9.5 Antibiotic treatment for NVE due to *S. pneumoniae* and β-Hemolytic Streptococci

Category	First-line	Duration	Second-line	Duration	Comments
Penicillin-sensitive *S. pneumoniae* (MIC <0.1 μg/mL)	Penicillin G 24 million units/day IV	4 weeks			**Note**: *S. pneumoniae* IE may require combined medical–surgical therapy for cure
	Ampicillin 2 g IV q4 h	4 weeks			
	Third-generation Cephalosporins: ceftriaxone 2 g IV q12 h OR Cefotaxime 2 g IV q4 to 6 h Cefazolin 2 g IV q8 h	4 weeks			Recommended by AHA, but not by BSAC
			Vancomycin 30 mg/kg/day IV q12 h	4 weeks	Vancomycin indicated only for patients unable to tolerate β-lactams
Penicillin-non-susceptible					
S. pneumoniae (*PNSP*):					
Intermediate resistance (MIC 0.1–1 μg/mL) with NO meningitis	Penicillin G 24 million units/day IV	4 weeks			Recommended by AHA, but not by BSAC; data derived from animal model, with concern about its clinical significance [84]
	Third-generation Cephalosporins: ceftriaxone 2 g IV q12 h OR Cefotaxime 2 g IV q4 to 6 h	4 weeks			
			Vancomycin 30 mg/kg/day IV q12 h	4–6 weeks [108]	Vancomycin indicated only for patients unable to tolerate β-lactams or if isolate is resistant to third-generation cephalosporins

(continued)

Table 9.5 (continued)

Category	First-line	Duration	Second-line	Duration	Comments
Intermediate resistance (MIC 0.1–1 μg/mL) WITH meningitis	Third-generation Cephalosporins: ceftriaxone 2 g IV q12 h OR Cefotaxime 2 g IV q4 to 6 h	4 weeks			
			Vancomycin 30 mg/kg/day IV q12 h + Rifampin [109]	4–6 weeks	Vancomycin indicated only for patients unable to tolerate β-lactams or if isolate is resistant to third-generation
High-level (MIC > 2 μg/mL)	Vancomycin 30 mg/kg/day IV q12 h + rifampin [110]	4–6 weeks			Fluoroquinolones as combination therapy may be of use [86]
β-hemolytic streptococci:					Surgical intervention may be necessary for cure
Group A streptococci (*S. pyogenes*)	High-dose penicillin G (e.g., 24 million units/day IV)	4 weeks			
			Cefazolin 2 g IV q8 h	4 weeks	
			Ceftriaxone 2 g IV q12 h	4 weeks	
			Vancomycin 30 mg/kg/day IV q12 h	4 weeks	
Groups B, C, G	High-dose penicillin G (e.g., 24 million units/day IV) + gentamicin 3 mg/kg/day IV	Combination therapy for ≥2 weeks, then penicillin G for 2–4 weeks [107]			
			Vancomycin 30 mg/kg/day IV q12 h + gentamicin 3 mg/kg/day IV	Combination therapy for ≥2 weeks, then vancomycin for 2–4 weeks	

62 %, compared to 32 % among 37 patients managed with a combined modality approach. Similar studies with smaller samples sizes of patients with definite pneumococcal IE support this suggestion [112, 113]. The optimal timing of surgical intervention in this disease remains unknown; perhaps trans-esophageal echocardiography (TEE) may play a role. The optimal duration of antimicrobial therapy, either alone or after surgical intervention, also remains unclear, but 4–6 weeks is recommended [13, 89].

The role of pneumococcal vaccination in providing primary protection against pneumococcal IE is unknown. In one study, *S. pneumoniae* IE developed in two patients who had been previously immunized: one patient developed disease due to a serotype that was represented in the vaccine, whereas the second patient had a history of alcoholism and chronic obstructive pulmonary disease and developed IE due to a strain that was not serotyped [113]. Although no conclusion can be made regarding the efficacy of immunization in primary prevention, it is important to note the possibility of developing pneumococcal disease (endocarditis or otherwise) despite a history of vaccination, as most people develop a humoral response to only ~75 % of the antigens in the vaccine [89]. Recurrence of disease is extremely rare [114] and so the role of immunization for secondary prevention is unknown.

β-Hemolytic Streptococci

IE due to β-hemolytic streptococci (BHS) is extremely uncommon, accounting for ≤5 % of cases [115]. The major pathogens are groups A (*S. pyogenes*), B (*S. agalactiae*), C, and G, with group B being the most common cause of BHS IE [115, 116].

The typical clinical characteristics is one of an acute infection, often occurring on normal heart valves, producing large valvular vegetations, and frequently complicated by embolic phenomena [115, 116]. Most patients have underlying conditions, including diabetes mellitus, malignancy, chronic alcoholism/cirrhosis, varicella, and HIV [116, 117].

Few studies have been published regarding the optimal treatment of this uncommon condition. Because penicillin resistance by the BHS remains uncommon, it remains the cornerstone of therapy, and is recommended as monotherapy in Group A streptococcal IE in patients that do not have allergy to this antibiotic [12, 13]. For the remaining BHS (Lancefield groups B, C and G), for which the penicillin MICs can be higher than for *Streptococcus pyogenes* (group A), there is some evidence regarding the benefit of combined therapy (i.e. penicillin with an aminoglycoside), which is therefore recommended [12, 13]. The antibiotic regimens for the treatment of BHS IE are provided in Table 9.5. The duration of antimicrobial therapy remains ill-defined. Recommendations of 4 weeks for Group A streptococcus and 4–6 weeks for Groups B, C, and G streptococci have been made, in the absence of any complications [53]. Microbiological evidence of sterilization of excised cardiac valves after 4 weeks of a ß-lactam, with or without aminoglycoside for the first 2 weeks, supports this recommendation [118].

A significant proportion (50–60 %) of patients have required adjunctive surgical intervention [115, 116]. The most frequent indication for cardiac surgery was acute

valve insufficiency. The authors of the two largest series to date on BHS IE believe that a more aggressive surgical intervention is associated with diminished mortality rates, although the benefit of surgery could not be clearly demonstrated [115, 116]. Nonetheless, consultation with a cardiac surgeon should be considered early in the course of management.

Enterococcal NVE

Enterococci account for 5–15 % of cases of NVE and is usually due to *E. faecalis* or *E. faecium* [4, 13, 119]. Treatment of enterococcal infections in general, and NVE in particular, is made difficult due to the mechanisms of resistance possessed by these pathogens, which can be divided into three categories: inherent (or intrinsic) resistance, tolerance, and acquired resistance. The inherent mechanisms of resistance are, by definition, species characteristics present in all or most of the strains of that species and are encoded on the chromosome [120]. Tolerance is defined as delayed or decreased bactericidal killing by growth-inhibiting concentrations of bactericidal compounds [121]. As mentioned before, a strain is defined as "tolerant" when the MBC/MIC ratio is ≥32. Acquired resistance occurs either from a mutation in the existing DNA or, more clinically relevant, from acquisition of new DNA.

Enterococci are inherently resistant to certain β-lactams, specifically the semi-synthetic penicillinase-resistant penicillins (e.g. oxacillin, nafcillin) and cephalosporins, as well as to lincosamides (e.g. clindamycin), traditional antimicrobial agents used for Gram-positive cocci [120, 122]. Furthermore, enterococci are intrinsically resistant to trimethoprim-sulfamethoxazole (TMP/SMX) in vivo, aminoglycosides (low level), and aztreonam [120, 123]. The mechanisms responsible for this natural resistance are diverse and have permitted the emergence of the enterococci as major pathogens.

Intrinsic resistance to the aforementioned β-lactams is due to the presence of specific penicillin binding proteins (PBPs) with poor affinity to these antibiotics [120]. Low-affinity PBPs are multifunctional enzymes that can catalyze complete peptidoglycan synthesis under conditions in which all the other normal PBPs are inhibited by β-lactams [124]. In the enterococci, PBP-5 is the predominant low-affinity PBP. It is a normal component of the enterococcal PBP repertoire and is constitutively expressed, thereby allowing bacterial cell survival in the presence of semi-synthetic penicillins and cephems.

Lincosamide antibiotics include lincomycin, naturally produced by actinomycetes, and clindamycin, a semi-synthetic derivative of lincomycin. The enterococci are inherently resistant to clindamycin [120, 123], although there are several mechanisms by which this occurs. For example, *E. faecalis*, the predominant clinical species, is characterized by the LSA phenotype, defined as resistance to not only the Lincosamides, but also to Streptogramins A (dalfopristin, pristinamycin II, virginiamycin M) [125]. This phenotype is mediated by the *lsa* gene, which encodes for a protein that has structural homology to antibiotic efflux pumps of other

Gram-positive organisms [126]. There are two other major mechanisms by which the enterococci have developed lincosamide resistance. One method is by a ribosomal methylase encoded by an *ermAM*-like gene. This enzyme leads to N6 dimethylation of a specific adenine in the 23S rRNA, which confers resistance to lincosamides, but also to macrolides and to streptogramin B antibiotics; this phenotype is designated MLSb [127, 128]. Acquired resistance can also occur via the dissemination of the *linB* gene, which encodes for lincosamide nucleotidyltransferase that leads to inactivation of such antibiotics [127].

TMP/SMX is considered to not be an effective antibiotic for the treatment of enterococcal infections, even though it demonstrates in vitro activity [129]. Treatment failures have been demonstrated in both animal models of endocarditis and in the clinical setting of urinary tract infections [130, 131]. The proposed explanation as to why this combination is not effective is related to the ability of the enterococci to incorporate pre-formed folic acid, which enables them to bypass the inhibition of folate synthesis imposed by TMP/SMX [120].

Low level aminoglycoside resistance (LLAR) is an inherent property of enterococci. High level aminoglycoside resistance (HLAR) is an acquired characteristic and is discussed below. There are two major mechanisms conferring LLAR: First is decreased bacterial cellular uptake, seen in all enterococci [120]. The means by which enterococci are able to limit aminoglycoside uptake relate to the biochemical characteristics of the aminoglycosides, as well as to bacterial metabolism [132]. As aminoglycosides are charged, hydrophilic molecules, they are unable to efficiently cross the lipid-containing cell membrane of enterococci to reach their ribosomal target. Additionally, the anaerobic metabolism of enterococci results in poor active transport of these antibiotics into the cells.

The other method of LLAR is seen only in *E. faecium* and occurs via inactivation of certain aminoglycoside antibiotics (tobramycin, netilmicin, kanamycin, and sismicin) by a chromosomally-encoded enzyme [120]. This additional method explains the differences in MICs of these aminoglycosides seen for *E. faecalis* when compared to *E. faecium*. The typical MIC of tobramycin for *E. faecalis* is in the range of 8–64 mg/L; that of kanamycin is in the range of 250 mg/L [120]. The MICs of tobramycin and kanamycin for *E. faecium*, however, are higher [115]. This resistance pattern is attributed to the production of an aminoglycoside 6′-acetyltransferase (AAC-6′) enzyme [132]. The clinical consequence of this enzyme is that combinations of a cell wall active agent with one of these aminoglycosides (tobramycin or kanamycin) will fail to demonstrate synergism against *E. faecium*. Synergism, or enhanced killing, for the enterococci is defined as a $\geq$2-$\log_{10}$ increase in killing versus the effect of the cell-wall active agent alone when the aminoglycoside is used in a subinhibitory concentration [120]. However, synergy is maintained if the aminoglycoside that is used is either gentamicin or streptomycin.

As a consequence of these inherent mechanisms of resistance, the above-mentioned antibiotics possess no bactericidal nor bacteriostatic activity against the enterococci. In addition, the majority of *Enterococcus* spp. demonstrate "tolerance" to various cell wall active agents, whereby cell growth is inhibited at clinically achievable concentrations, but not cell death. The major antibiotics with such

properties are penicillin, aminopenicillins (amoxicillin, ampicillin), and glycopeptides (teicoplanin, vancomycin). Ampicillin generally has lower MICs than penicillin, and thus may be the preferred agent [123, 133]. Ampicillin MICs for *E. faecalis* generally are 0.5–4.0 μg/mL, whereas for *E. faecium*, the MICs are typically 4–8 μg/mL [123]. The ureidopenicillins (azlocillin, mezlocillin, piperacillin) have approximately the same activity against enterococci as penicillin and ampicillin [133]. This bacteriostatic effect is suboptimal in the management of infective endocarditis, which classically requires a bactericidal regimen. Such an effect can be achieved by the combination of gentamicin or streptomycin to one of these cell wall active agents.

The mechanism of tolerance of enterococci to β-lactams remains unclear, but is clearly distinct from resistance, demonstrated by the fact that each feature can be elicited independently among *E. faecalis* strains exposed in vitro to penicillin [134]. It has been suggested that tolerance may be associated with changes in the autolysis system [135]. β-lactam-induced lysis of bacteria is the consequence of inhibition of biosynthesis of peptidoglycan, as well as to hydrolysis of cell walls by bacterial autolytic enzymes. It has been shown that an increase in autolytic activity among clinical enterococcal isolates correlated with increased penicillin-induced lysis and killing [135]. Conversely, *E. faecalis* strains with reduced or absent autolytic activity were less susceptible to penicillin [136]. However, neither modification of one enterococcal autolysin gene, nor alteration of its expression, resulted in any significant change in MIC or in tolerance to β-lactams [137]. As such, tolerance to β-lactam remains a poorly understood phenomenon.

Because of the limited antimicrobial options, optimal management of ampicillin-susceptible enterococcal NVE should involve the addition of an aminoglycoside (i.e. gentamicin or streptomycin) to a cell wall active agent (i.e. ampicillin or glycopeptides). This combination results in a synergistic bactericidal activity related to the fact that cell-wall active agents markedly increase the penetration of aminoglycosides into the bacterial cell, allowing binding to its ribosomal target [138]. Alternatively, if aminoglycoside therapy is contraindicated (e.g. potential worsening of renal insufficiency), prolonged treatment with a β-lactam, classically ampicillin, while maintaining the serum antibiotic concentration above the MIC of the isolate, may be sufficient (see Table 9.4).

Unfortunately, acquired antimicrobial resistance to aminoglycosides and to cell wall active agents has complicated the management of this disease. High-level aminoglycoside resistance, currently defined by CLSI/NCCLS as an MIC of streptomycin ≥2,000 μg/mL (by agar dilution) or ≥1,000 μg/mL (by broth dilution) or an MIC of gentamicin ≥500 μg/mL, was first described in 1979 [139]. Rates have increased worldwide, with prevalence as high as ~75 % [140], and it is particularly common among strains of *E. faecium* [141] . The mechanism of this resistance is related to the presence of aminoglycoside-modifying enzymes, some of which are located on transferable plasmids [142, 143]. A bifunctional enzyme (2″-phosphotransferase-6′-acetyltransferase) mediates high-level gentamicin resistance, as well as resistance to tobramycin, amikacin, netilmicin, and kanamycin [122, 133]. Streptomycin resistance, however, is mediated by completely different mechanisms. It occurs as a result of ribosomal resistance, in which there is alteration of ribosomal target sites,

or by streptomycin adenyltransferase, which modifies and inactivates aminoglycosides [144]. Because gentamicin and streptomycin resistance may differ among *Enterococcus* spp., aminoglycoside screening should include tests for high-level resistance to both of these aminoglycosides. If one of these antimicrobials demonstrates lack of HLAR, it should be used, if the clinical situation permits. If NVE is due to an *Enterococcus* spp. with HLAR to both aminoglycosides, absence of synergism with a cell-wall active agent can be predicted. As there is no clinical efficacy to using such agent in these situations, and with the inherent risks of aminoglycosides, monotherapy with a cell-wall active agent should be employed.

Acquired ampicillin resistance has compromised the management of enterococcal infections. The two clinically major species each have their own mechanism mediating such resistance. β-lactamase production is exclusively described in *E. faecalis*; this enzyme is felt to have been acquired from *S. aureus* via a transferable plasmid [120, 123]. β-lactamase production occurs at low levels and produces an "inoculum effect", such that at low to moderate inocula (10^3–10^5 CFU/mL), there is only a minor increase in MIC and such penicillinase-producing enterococci usually appear no more resistant than other enterococci [122]. However, at high inocula ($\geq 10^7$ CFU/mL), when sufficient enzymes are produced, such strains are highly resistant to penicillin, aminopenicillins, and ureidopenicillins [122]. As a result of this inoculum effect, β-lactamase mediated penicillin resistance is not detected by routine disk susceptibility testing [120]. In the clinical laboratory, hydrolysis of the chromogenic cephalosporin, nitrocefin, is the definitive test for β-lactamase production [133]. The activity of the penicillinase is inhibited by β-lactamase inhibitors (i.e. clavulanic acid, tazobactam, sulbactam) [122]. Although there have been reports of clinical infection with β-lactamase producing *E. faecalis* [141], it does not appear that this mechanism of resistance is a major virulence factor among enterococci [145, 146].

Non-β-lactamase producing, ampicillin-resistant enterococci is usually *E. faecium*. The mechanisms of this resistance appear to be overproduction of the naturally present PBP5, as well as amino acid substitutions in PBP5 resulting in a further decrease in affinity to β-lactams [122, 123, 145, 146]. Acquisition of this form of β-lactam resistance accounts for the majority of clinically relevant isolates.

In the face of β-lactam resistance, the only therapeutic options, until recently, were the glycopeptides (vancomycin, teicoplanin). These antibiotics function by binding to the terminal D-alanyl-D-alanine present on the pentapeptide side chains of the peptidoglycan precursors, inhibiting peptidoglycan synthesis. In North America, vancomycin is the only glycopeptide currently commercially available and is recommended as the drug of choice for serious enterococcal infection only in cases of significant penicillin allergy or in the treatment of ampicillin-resistant strains. Vancomycin, when combined with gentamicin or streptomycin, does demonstrate synergism against *Enterococcus* spp. in vitro and in vivo [133]. Vancomycin should not, however, be used for ampicillin-susceptible strains, as it usually has higher MICs against enterococci than ampicillin [147]. As well, there is concern that careless overuse of vancomycin contributes to the emergence of vancomycin-resistant pathogens.

Glycopeptide resistance is an emerging problem. First described in the 1980s, vancomycin-resistant enterococci (VRE) have become an important nosocomial pathogen globally. The most common phenotype of resistance, *vanA*, is associated with acquired, inducible, high-level resistance to vancomycin (MIC ≥ 64 μg/mL) and to teicoplanin (MIC ≥ 16 μg/mL) [129]. The *vanA* phenotype is mediated by genetic elements that are carried on a transposon (Tn*1546*) and is transferable to other susceptible enterococci by conjugation [123]. Other acquired glycopeptide-resistant phenotypes have been also been characterized, including *vanB*, as well as *vanD*, *vanE* and *vanG*, which are much less common. The *vanB* phenotype, which is chromosomally mediated, inducible and transferable by conjugation, mediates inducible resistance to vancomycin, but not to teicoplanin [129]. However, the development of teicoplanin resistance occurs rapidly during antibiotic exposure. Bloodstream infection with VRE can be very difficult to treat because there may be concomitant ampicillin resistance, as seen with virtually all *E. faecium* [123]. Vancomycin resistant *E. faecalis*, however, usually remains susceptible to ampicillin. Furthermore, a recent retrospective case-control study demonstrated that patients with bacteremia caused by VRE were more likely to die than were those with vancomycin-susceptible enterococcal bacteremia, with a summary odds ratio for death of 2.52, and a 95 % confidence interval of 1.9–3.4 [148].

In face of glycopeptide resistance, treatment of VRE poses significant challenge. Fortunately, VRE endocarditis remains relatively uncommon, with no local, national, or international incidence rates reported in the English literature. For VRE infections in general, three classes of antibiotics have been approved: the streptogramins, the oxazolidinones, and the cyclic lipopeptides.

Among the approved streptogramin class of antibiotics is quinupristin/dalfopristin (Q/D, Synercid®, Aventis Pharmaceuticals, Inc.). It is a parenteral antibiotic that is structurally related to the macrolides and lincosamides. Its mechanism of action is inhibition of early (peptide chain elongation) and late stages of bacterial protein synthesis [149]. Interestingly, Q/D demonstrates good in vitro activity against *E. faecium*, with MIC_{90} of 1–2 μg/mL, but very poor activity against *E. faecalis*, the predominant enterococcal pathogen, with MIC_{90} of 8–16 μg/mL [149]. The reason for this difference in activity is likely due to decreased 50S bacterial ribosomal binding of Q/D in *E. faecalis* [149]. In in vitro studies, Q/D is bactericidal for VRE [149]. However, in time-kill studies, Q/D demonstrates only bacteriostatic activity; this difference in effect is due to the expression of the MLS_b phenotype (described previously), which encodes for the methylation of the 23S ribosomal binding site [149, 150]. Q/D-resistance has been reported among clinical VRE isolates, ranging from <10 % to 22 % [150]. Furthermore, emergence of Q/D-resistance while on therapy has also been described. Clinical failure with Q/D has been reported with VRE endocarditis [151, 152].

Linezolid (LZL, Zyvox™, Pfizer Inc.) is the only currently available oxazolidinone. It is prepared as a parenteral or as an oral formulation, with the latter having 100 % bioavailability [153]. LZL functions by binding to the 23S ribosomal RNA of the 50S subunit on the bacterial ribosome, thus inhibiting protein

synthesis [153]. By virtue of its unique action, cross-resistance to LZL has not been reported among enterococci that have developed resistance to other antibiotics [154]. LZL has shown consistent bacteriostatic activity against vancomycin-susceptible and vancomycin-resistant *E. faecium* and *E. faecalis*. In murine models [155] and in clinical reports [156, 157], LZL was effective in the treatment of VRE bacteremia. It has also been reported to be effective for VRE endocarditis [158–161], although not consistently [156]. Furthermore, resistance to LZL has developed among VRE in patients receiving the drug for an extended period of time, typically >3 weeks [162–164]. This issue raises some concerns about its use as monotherapy in VRE endocarditis, which typically requires a prolonged course of antimicrobial therapy. Ideally, synergism can be achieved when combined with other antimicrobials. However, using the standard checkerboard assay to determine the fractional inhibitor concentrations (FIC) indices, LZL primarily demonstrated in vitro indifference (i.e. no synergy) against *Enterococcus* spp. when assessed in combination with other antimicrobials [165]. Consequently, the role of LZL in VRE endocarditis remains unestablished.

Daptomycin (Cubicin®, Cubist Pharmaceuticals) is the only currently available cyclic lipopeptide. Its mechanism of action involves the calcium-dependent insertion of the compound into the bacterial cytoplasmic membrane, with subsequent alteration of membrane integrity and transmembrane potential [166] Daptomycin exhibits concentration-dependent bactericidal activity against a broad spectrum of Gram-positive organisms, including drug-resistant strains, such as VRE (and MRSA, see below). One of the initial reports of daptomycin for the treatment of VRE bacteremia showed moderate success in a retrospective analysis of case reports from two centers; the moderate success rate (45 %) was, in retrospect, likely attributable in part to the "low dose" of daptomycin used (4–6 mg/kg IV), the approved dose for skin and soft tissue infections or *S. aureus* bacteremia [167]. Similar results were noted upon analysis of the Cubicin Outcomes Registry and Experience (CORE) 2004 database, which was a retrospective observational chart review of the cases of patients receiving daptomycin for any indication in 45 US institutions [168], as well as other retrospective studies [169] Subsequent analysis of the CORE database, updated to 2007, demonstrated improved outcomes in VRE infections with doses of daptomycin of 8 mg/kg or higher, although the composition of bacteremias/endocarditis due to VRE were not detailed. This post-marketing surveillance data suggesting that higher daptomycin doses may be safe and efficacious was corroborated in multicenter, retrospective observational case series [170]. The rationale for why higher doses of daptomycin may be required for the optimal treatment of such serious infections is based on the observation that daptomycin MICs for *Enterococcus* species are typically higher than those for other Gram-positive organisms (0.5–4 vs 0.25–1 mg/L) [170]. On the other hand, there have been reports of unsatisfactory outcomes of daptomycin monotherapy for serious enterococcal infections [171] suggesting that daptomycin may need to be combined with other antimicrobials for clinical cure, although clinical evidence to support this hypothesis is currently limited.

Staphylococcal NVE

Staphylococcal NVE may be caused by *S. aureus* or by coagulase-negative staphylococci (CoNS, e.g. *S. epidermidis*). It had been previously believed that *S. aureus* caused primarily NVE, while CoNS caused primarily prosthetic-valve endocarditis [36]. Recent, large-scale epidemiologic studies, however, have demonstrated the changing epidemiology of staphylococcal NVE.

S. aureus

S. aureus endocarditis occurs in four clinically distinct populations [172]: intravenous drug users (IVDUs); patients with prosthetic valves; patients with health-care acquired (nosocomial or nosohusial) endocarditis; and non-IVDU patients with community-acquired endocarditis. This chapter will focus on the latter group, as the former groups are discussed in other chapters.

Recent studies have demonstrated that *S. aureus* has become the leading cause of endocarditis, accounting for approximately 30 % of cases [172, 173]. Of these, approximately 87 % are NVE [172]. Although a large proportion of cases of *S. aureus* IE are community-acquired [174, 175], there is an increasing prevalence of healthcare-associated disease, owing in part to the growing use of interventional procedures and implantable devices [173]. Community-acquired *S. aureus* NVE may involve right-sided and/or left-sided cardiac structures. Right-sided disease typically has high cure rates with relatively short-course medical therapy alone [36]. In non-IVDUs, *S. aureus* predominantly involves the left-side and is associated with mortality rates ranging from 25 % to 50 % [2, 5]. *S. aureus* NVE is also associated with higher rates of embolization (cerebrovascular and systemic) and persistent bacteremia when compared to NVE due to other pathogens [173, 176].

The management of *S. aureus* infections in general, and NVE in particular, has become increasingly difficult owing to evolving mechanisms of antibiotic resistance. Penicillin was introduced into clinical practice in 1941 and it was demonstrated to be an effective anti-staphylococcal agent. Within 1–2 years of its introduction, however, highly penicillin-resistant isolates of *S. aureus* were found [177]. The mechanism of resistance is due to acquisition of a plasmid-mediated penicillinase. Penicillin resistance propagated rapidly, and currently, >95 % of *S. aureus* strains are resistant to penicillin [178]. However, in the rare instance where an isolate responsible for IE is susceptible to penicillin, it should be used in high-doses (e.g. penicillin G 24 million units/day iv) (Table 9.6).

The emergence of penicillin-resistant *S. aureus* during the 1940s prompted the development of a new class of penicillins that were specifically targeted against these penicillin-resistant strains. The first representative of this class, methicillin, was introduced in 1951. By the mid-1950s, however, methicillin-resistant strains of *S. aureus* (MRSA) were prevalent. This resistance is mediated by the production of an alternate penicillin-binding protein, termed PBP-2a, which is encoded by the *mecA* gene [179]. PBP-2a has low affinity for β-lactams, thus allowing synthesis of the bacterial cell wall despite the presence of normally-lethal β-lactam concentrations [180]. In addition to mediating resistance to methicillin (and other

semi-synthetic penicillinase-resistant penicillin), it also provides resistance to cephalosporins, cephamycins, and carbapenems [168]. The *mecA* gene is encoded on a mobile genetic element, the staphylococcal chromosomal cassette *mec* (SCC*mec*), which also contains insertion sites for plasmids and transposons that facilitate acquisition of resistance to other antibiotics. Consequently, cross-resistance to other classes of antibiotics, such as erythromycin, clindamycin, gentamicin, trimethoprim-sulfamethoxazole (TMP/SMX), and ciprofloxacin may occur [180]. Although MRSA was typically considered a nosocomial pathogen, typing of SCC*mec* has identified community-associated MRSA strains (CA-MRSA) that are distinct from the hospital strains in pathogenicity and antimicrobial susceptibility [181]. Although the majority of MRSA strains causing IE are healthcare-associated [182], IE due to CA-MRSA has also been reported [183]. There is some evidence to suggest that infections with MRSA are associated with increased morbidity and mortality, when compared to infections with methicillin-susceptible S. aureus (MSSA) [184, 185]; this association has also been demonstrated in endocarditis [172, 174, 186]. There is some concern, however, that the increased mortality associated with MRSA infections may be biased by confounding variables, such as length of hospitalization [187] or severity of illness [188]; in other words, the colonization/infection with MRSA represents a surrogate marker of increased length of hospitalization, which, in turn, is a reflection of multiple or severe comorbidities. This latter factor may, in fact, be the principle reason for the higher mortality rates.

The treatment of choice for MRSA, both nosocomial and community-acquired, is the glycopeptide class of antimicrobials. In North America, vancomycin is the glycopeptide commercially available (Table 9.6). Teicoplanin has been used in other parts of the world. At appropriate doses, the efficacy of these glycopeptides in the management of *S. aureus* IE is comparable [189]. However, the efficacy of the glycopeptides is inferior to that of the β-lactams for the management of IE with *S. aureus* isolates that demonstrate in vitro susceptibility to both classes of antimicrobials [188, 190, 191]. This inferiority is reflected in a delayed clearance of bacteremia (i.e. >6 days), higher rates of treatment failure, and higher rates of relapse [192–194]. These effects are due to vancomycin's suboptimal pharmacokinetics (i.e. poor vegetation penetration) and pharmacodynamics (i.e. slower in vitro bactericidal effect [195]) when compared to β-lactams. Thus, in IE with MSSA, β-lactams are the drug of choice.

Increasingly in some parts of the world, strains of *S. aureus* with decreased susceptibility to vancomycin have been recognized. These isolates are inhibited by vancomycin concentrations of 4–8 μg/mL, which is interpreted as "intermediate susceptibility" by CLSI (formerly NCCLS) criteria). Despite this in vitro classification, infections caused by these vancomycin-intermediate *S. aureus* (VISA) strains have not responded well clinically when treated with vancomycin, including cases of endocarditis [196–198]. These strains appear to develop from pre-existing MRSA strains under the selective pressure of prolonged and/or suboptimal administration of vancomycin [199, 200]. In addition to VISA, there has also been increased recognition of heterogeneously vancomycin-intermediate *S. aureus* (h-VISA) strains; these are strains of *S. aureus* containing sub-populations of vancomycin-resistant

daughter cells, typically at a rate of 1 organism per 10^5–10^6 organisms, for which the apparent vancomycin MICs of the parent strain are only 1–4 mg/L (i.e. susceptible) [201]. These sub-populations typically have MICs that are two to eightfold higher than that for the original clinical isolate. The clinical significance of h-VISA isolates remains to be fully elucidated. It has been reported in association with IE [196, 202]. As well, evidence suggests that infections with such strains are associated with clinical evidence of vancomycin treatment failure (defined as persistent fever and bacteremia for >7 days after commencement of vancomycin therapy) with high bacterial load infection [203], although another study found that heteroresistance is not a common cause of persistent or recurrent bacteremia [204]. Therefore, further studies are required to determine the frequency of h-VISA in endocarditis, as well as the significance of heterogeneity in its management.

In addition to VISA and h-VISA, there have been reports of infections with strains of *S. aureus* that demonstrate complete resistance to vancomycin, currently defined as an MIC of vancomycin ≥32 μg/mL [205]. These vancomycin-resistant *S. aureus* (VRSA) strains remain, thankfully, relatively uncommon in the clinical setting. VRSA strains appear to differ from VISA strains with respect to their mechanisms of resistance. VISA strains undergo changes in peptidoglycan synthesis after prolonged vancomycin exposure, resulting in an irregularly-shaped, thickened extracellular matrix on electron microscopy [206]. There is also decreased cross-linking of the peptidoglycan strands, which allows increased exposure of D-Ala-D-Ala residues [207]. These residues bind and sequester vancomycin outside the cell wall, blocking its effect within the cytoplasmic membrane. VRSA strains, on the other hand, develop vancomycin resistance via the acquisition of the *vanA* operon, presumably from surrounding vancomycin-resistant *E. faecalis* [207, 208]. These isolates produce cell wall precursors with D-Ala-D-Lac, instead of D-Ala-D-Ala, that have low affinity for vancomycin, conferring resistance.

Isolated right-sided NVE accounts for only 5–10 % of cases of infective endocarditis [209]. The majority of cases occur in patients with IVDU, but 5–10 % of cases occur in nonusers [210–212]. The major pathogen is *S. aureus* [209, 212, 213]. A previous major cause was rheumatic tricuspid valve disease. With medical progress, it is predominantly occurring as a complication of other cardiac anomalies, as well as from central venous/intracardiac catheterization [209, 214]. Of course, it can also occur as a component of multi-valvular IE [215]. The majority of the clinical literature on the management and prognosis of isolated right-sided *S. aureus* NVE has been extrapolated from the experience in patients with IVDU, which is discussed in Chap. 3.

The symptoms of isolated right-sided *S. aureus* NVE is predominated by non-specific constitutional symptoms, i.e. fever, chills, night sweats, and malaise, which may contribute to a delay in diagnosis. The major reason for seeking medical attention is the development of respiratory symptoms (e.g. dyspnea, pleuritic chest pain, productive cough, hemoptysis), usually the result of septic pulmonary emboli [212]. One study suggests that the triad of recurrent pulmonary events, anemia, and microscopic hematuria (termed "the Tricuspid syndrome") should raise clinical suspicion of tricuspid valve endocarditis [209]. Typically, there is a paucity of cardiac signs and symptoms, although right-sided congestive heart failure may occur.

Table 9.6 Antibiotic treatment for NVE due to *Staphylococcus* spp.

Category	First-line	Duration	Second-line	Duration	Comments
Penicillin S (MIC ≤0.1 μg/mL, and β-lactamase negative)	High-dose penicillin G (e.g., 24 million units/day) IV	4 weeks if uncomplicated IE; 6 weeks if complicated IE (e.g., metastatic septic complications)			Penicillin-sensitive *Staphylococcus* spp. are very uncommon
			Vancomycin 30 mg/kg/day IV q12 h	6 weeks	Vancomycin indicated only for patients unable to tolerate β-lactams
Penicillin R, Methicillin S (MSSA)	Nafcillin or oxacillin 2 g IV q4 h ± gentamicin 3 mg/kg/day IV	β-lactam: 4 weeks if uncomplicated IE; 6 weeks if complicated IE (e.g., metastatic septic complications)			Gentamicin therapy optional, and when used, should be in divided daily doses (see text)
	Cloxacillin 100–150 mg/kg/day (e.g. 2 g IV q4 h) ± gentamicin 3 mg/kg/day IV	Gentamicin: 3–5 days			Recommended duration is for left-sided IE or complicated right-sided IE
					Uncomplicated right-sided IE may be treated for 2 weeks (see text)
	Flucloxacillin 2 g IV q4 to 6 h				Recommended by BSAC (not available in N. America)
			For "penicillin-allergy" history (i.e., NOT type 1/immediate-type hypersensitivity): cefazolin 2 g IV q8 h ± gentamicin 3 mg/kg/day IV	6 weeks	Use cefazolin with caution, as clinical failures associated with isolates producing β-lactamase type A have been reported (see text)

(continued)

Table 9.6 (continued)

Category	First-line	Duration	Second-line	Duration	Comments
			For patients with type 1 (immediate-type) hypersensitivity reactions: Vancomycin 30 mg/kg/day IV q12 h ± gentamicin 3 mg/kg/day IV		Vancomycin has inferior efficacy compared to β-lactams. AHA also recommends considering β-lactam desensitization
Methicillin R (i.e., MRSA, MRSE)	Vancomycin 30 mg/kg/day IV q12 h	6 weeks			AHA recommendation; strongly consider consultation with an infectious disease specialist
	Vancomycin 1 g IV q12 h + 1 of the following: rifampin (300–600 mg po q12 h) OR Gentamicin 1 mg/kg IV q8 h OR Sodium fusidate (500 mg po q8 h)	4–6 weeks			BSAC recommendation
					Vancomycin and gentamicin doses are modified for renal function
					Selection influenced by antimicrobial susceptibility testing
	Vancomycin-resistant staphylococci (i.e., VISA, h-VISA, VRSA, VRSE)				Strongly consider consultation with an infectious disease specialist

S susceptible, *R* resistant

Isolated right-sided *S. aureus* NVE has a low mortality. Relatively-abbreviated courses of medical therapy alone produces cure rates >90 % [216]. In the absence of any intracardiac or extra-pulmonary metastatic disease, right-sided NVE with MSSA may be successfully treated with as little as 2 weeks of a variety of intravenous anti-staphylococcal therapies, typically a penicillinase-resistant penicillin with or without an aminoglycoside (e.g. nafcillin plus tobramycin) [217–219]. An alternative successful regimen has been ciprofloxacin (iv then oral) plus oral rifampin for 4 weeks [220, 221]. It should be remembered, however, that this literature is based on the experience in patients with IVDU, where such regimens produced a relapse rate of ~6 % [195, 222], necessitating prolongation of treatment (e.g. to 4 weeks) for cure. Furthermore, such short-course regimens may not be appropriate in patients with cardiac or extra-cardiac complications, fever lasting ≥7 days, or advanced HIV infection (i.e. CD4 count <200 cells/mm^3) [223].

In right-sided NVE due to MRSA, vancomycin is currently the standard treatment, typically at doses of 30 mg/kg/24 h in divided doses, with monitoring of serum levels [195, 223]. The efficacy of vancomycin treatment for MRSA IE, however, is less than that for β-lactams for MSSA IE, even in the management of right-sided disease [195]. As such, when vancomycin needs to be used, a more prolonged course of intravenous therapy is required. In a retrospective review of 300 cases of *S. aureus* right-sided NVE, chiefly composed of IVDUs, a 28-day course of vancomycin was adequate for most patients, producing a cure rate of ~70–80 % [195]. However, when compared to treatment with β-lactams, the use of vancomycin was associated with delayed clearance of bacteremia and higher rates of complications.

Most of the experience with *S. aureus* right-sided NVE is based on patients with IVDU and suggests that valve replacement is rarely indicated. Surgery should, however, be considered in patients with vegetations >1.0 cm, as these patients are at increased risk for developing new-onset and recurrent emboli [214], right-sided heart failure [224]. Vegetations >2.0 cm are associated with increased risk of death [225]. Persistent fever, clinically-evident right-sided heart failure [213], or increased right ventricular end-diastolic dimension by echocardiography [224] have also defined sub-groups of patients who subsequently required valvular surgery. The occurrence of septic pulmonary emboli, despite antimicrobial therapy, is not considered an indication for surgery if the patient is clinically improving [223, 226, 227]. It should be noted, however, that the experience with surgical intervention in non-IVDU patients with this infection is limited.

In general, tricuspid valve replacement has been avoided in patients with right-sided IE because of the high likelihood of contamination of the prosthetic valve with ongoing IVDU. In patients without drug use, this fear should not preclude such intervention. Alternatively, vegetectomy (i.e. excision of the vegetation only) or tricuspid valvuloplasty can be performed. However, the preferred type of surgery remains to be determined.

Left-sided *S. aureus* NVE is by far more common than right-sided infection. Furthermore, it is a more virulent disease. The overall mortality rate for this infection ranges from 20 % to 65 % [216]. Even when diagnosed correctly and managed with appropriate antimicrobial therapy, the complication rate ranges from 20 % to

50 % [216]. Congestive heart failure is the most common complication, and it portends a poor prognosis. Neurologic manifestations occur in 20–35 % of patients [172, 228]. These typically occur early in the disease, either before or shortly after the administration of antibiotics [229]. Recurrent emboli are infrequent if the infection is adequately controlled with antimicrobial therapy [228, 229]. Neurological complications are accompanied by high mortality rates. Therefore, rapid diagnosis and initiation of antimicrobial therapy may still be the most effective means to prevent neurologic complications.

Antimicrobial therapy, for reasons discussed previously, should include a β-lactam when possible (Table 9.6). For the uncommon situation caused by penicillin-susceptible *S. aureus*, benzyl penicillin at maximal doses is the preferred agent. The treatment of choice for MSSA NVE is a penicillinase-resistant semisynthetic penicillin (e.g. cloxacillin 2 g intravenously every 4 h). Although for other types of *S. aureus* infections, such as cellulitis, first-generation cephalosporins have proven useful as alternatives, the use of such agents (e.g. cefazolin) in the treatment of MSSA NVE is with caution. There have been three previously reported cases of cefazolin failure in patients with such infection. The infecting strain isolated produced β-lactamase type A, which has very high rates of cefazolin hydrolysis. Furthermore, these strains produced high amounts of the enzyme. As such, these isolates demonstrated high MICs to cefazolin. In the context of a cardiac vegetation, where the number of residing organisms can be as high as 10^{10} CFU/g of tissue, Nannini and colleagues propose that an inoculum effect mediated clinical failure [18]. That is, the high quantity of bacteria results in the production of large amounts of enzyme with inherently augmented cefazolin hydrolysis rates, leading to inactivation of the drug and persistence of the infection. As such, the authors caution that cefazolin usage for treatment of MSSA NVE may be associated with clinical failure. It is unclear what the frequency of such isolates is in clinical practice. Therefore, semi-synthetic penicillins (or penicillin itself) should be used whenever possible. In the absence of any complications, 4 weeks of therapy is usually sufficient [13, 36].

The addition of aminoglycosides to β-lactams produces an enhanced bactericidal effect in vitro, as well as in a rabbit experimental model of endocarditis. However, several clinical studies have failed to demonstrate a clinical benefit, as evidence by equivalent efficacy of cure rates when compared to β-lactam monotherapy, when the total length of therapy was 4–6 weeks. There was demonstration, though, that combination therapy did result in significantly faster clearance of bacteremia, but this did not correlate with a more rapid clinical response, as both groups of patients were febrile for approximately the same length of time. There was, however, an increased incidence of nephrotoxicity in the group receiving the aminoglycoside. As such, the use of aminoglycosides (e.g. gentamicin) in the management of MSSA NVE should be limited [230]. The BSAC does not recommend it use in this setting [13], whereas the AHA recommends that if it is used, it be done only for the first 3–5 days of therapy for left-sided disease [36]. Furthermore, the latter group recommends regular administration of gentamicin, such as two- or three-times daily, rather than once-daily therapy, with a total daily dose not to exceed 3 mg/kg in patients with normal renal function.

For MRSA NVE, vancomycin remains the first line recommendation. However, it may be associated with suboptimal outcomes [193, 194]. Optimization of dosage to achieve a 1-h serum peak concentration of 30–45 μg/mL and trough concentration of 10–15 μg/mL have been recommended [36], although higher trough serum vancomycin concentrations of 15–20 mg/L are currently recommended [13, 231]. The BSAC currently recommends the use of a second antibiotic, in addition to vancomycin, with rifampicin (300–600 mg 12 hourly by mouth, modified according to renal function). Their previous recommendations of gentamicin (1 mg/kg body weight eight hourly) or sodium fusidate (500 mg eight-hourly by mouth), have been removed [13]. This suggestion, though, is based on expert opinion. Although rifampin demonstrates potent activity against *S. aureus* in vitro, the in vitro effect when combined with semi-synthetic penicillins, vancomycin, or aminglycosides is highly variable [188]. As well, one study of patients with MRSA IE comparing vancomycin monotherapy to vancomycin plus rifampin showed no statistically significant difference in clinical outcome [194]. Similarly, there is insufficient published evidence to robustly demonstrate a clinical benefit for fusidic acid-based combination therapy [232].

The other major indication to use vancomycin has traditionally been in patients who are unable to tolerate β-lactams. Because of the superior efficacy of this class of antimicrobials, for patients with a questionable history of type 1, immediate-type hypersensitivity reaction to penicillin (e.g. urticaria, angioedema), skin testing should be performed to penicillin [36]. If negative, β-lactams should be instituted. Alternatively, a cephalosporin may be considered [36]; first-generation cephalosporins should be used with caution.

Given the suboptimal efficacy of glycopeptides in the management of MRSA NVE, as well as the emergence of VISA/h-VISA/VRSA, alternative antimicrobial therapy has become increasingly necessary. The newer agents with the potential to address this need are the following: quinupristin/dalfopristin (Q/D), linezolid (LZL), and daptomycin. Trimethoprim-sulfamethoxazole (TMP/SMX) may have activity as well, and thus antimicrobial susceptibility testing should be performed. The clinical experience with these agents in the management of MRSA or VISA/VRSA NVE, however, is limited. Q/D, a streptogramin antibiotic, demonstrates variable in vitro activity against MRSA isolates. Most MRSA strains possess the MLSb phenotype, rendering them cross-resistant to macrolides, lincosamides, and streptogramin B, mediated by methylation of the ribosomal target [233]. Expression of this phenotype may be constitutive or inducible; when it is constitutive, strains are resistant to quinupristin. The combination, Q/D, retains activity, although the bactericidal activity is reduced [233]. Furthermore, although quinupristin demonstrates homogeneous penetration into cardiac vegetations in an experimental endocarditis model, dalfopristin demonstrated a significantly decreased concentration gradient between the periphery and the core of the vegetation, implying poor penetration of the agent that maintains activity of the Q/D combination [234]. There have been few reported clinical cases in the English literature of Q/D in the treatment of MRSA NVE. It has been used successfully in one patient when used alone [235], and in another patient when used in combination with vancomycin and

cardiac surgery [236]. However, when used in a worldwide emergency-use protocol for patients with MRSA infections intolerant of or failing prior therapy, the response rates among the few patients with endocarditis was suboptimal. Only about half of the patients had a clinical response, but among patients that could be bacteriologically evaluated, both were clinical failures, suggesting that Q/D as monotherapy may not be able to consistently sterilize cardiac vegetations [237]. Further data is certainly needed.

The data supporting the use of LZL is conflicting. In a rabbit model of staphylococcal endocarditis, LZL significantly reduced bacterial vegetation densities [238]. The antimicrobial activity of LZL is not affected by inoculum size [17]. As well, there have been several cases described in which LZL was successfully used to treat MRSA or VISA endocarditis (both native and prosthetic) in cases of glycopeptide failure or intolerance [196, 197, 202, 207, 239]. However, this enthusiasm is tempered by experimental data demonstrating suboptimal activity [240], and clinical data demonstrating clinical failure and LZL-non-susceptibility [241–245]. As such, LZL may represent a therapeutic option in the management of MRSA/VISA NVE in certain populations, but emergence of resistance with clinical failure may occur. Additionally, treatment of IE requires long durations of therapy, and LZL has been associated with increased risks of adverse events with prolonged use [246] Daptomycin is the most effective and rapidly bactericidal of the novel anti-MRSA antimicrobial agents; it produces clearance of bacteremia faster than vancomycin and the other agents [247]. In a rat model of MRSA endocarditis, daptomycin produced significant decreases in the residual bacterial counts in cardiac vegetations [248]. Similar results were obtained using simulated endocardial vegetations [249].

Since our original chapter, there has been significant clinical experience with the use of daptomycin in MRSA NVE. While the AHA guidelines from 2005 predate these clinical studies, the BSAC and IDSA recommend daptomycin as a suitable agent for the treatment of MRSA NVE at the standard dose of 6 mg/kg IV (although some expert opinions among the IDSA committee recommend higher doses ranging 8–10 mg/kg) [13, 250].

Owing to the aggressive nature of the disease, with its associated complications, a more aggressive treatment approach has been advocated. Therefore, valve replacement surgery has become an important adjunct in the management of *S. aureus* NVE, allowing for a higher likelihood of successfully eradicating the infection. Indications for cardiac surgical intervention have emerged and are discussed in the section "The Role of Surgery" below. Briefly, these indications include congestive heart failure, persistent bacteremia, hemodynamically-significant valvular dysfunction, perivalvular extension of infection (abscess or fistula), persistent (uncontrolled) infection (e.g. increase in vegetation size after 4 weeks of antimicrobial therapy), and lack of effective antimicrobial therapy available (or alternatively, difficult-to-treat pathogens). Several studies have demonstrated the beneficial role of surgery in these situations, with relatively low operative mortality rates when compared to in-hospital mortality rates with medical therapy alone, and good long-term results [172, 251–254]. Although patient selection bias may contribute to the observed effect, large prospective

randomized studies have not been performed, largely because they represent ethical and methodological challenges.

Coagulase-Negative *staphylococci* (CoNS)

NVE caused by CoNS has become increasingly more common, with most recent estimates of approximately 5–7 % of all cases [255]. However, it is likely that the incidence rate will increase, due to increasing dependence of medical progress on intravascular catheters, indwelling devices, and other invasive procedures.

CoNS are a heterogeneous group of Gram-positive coccal species with a clustered appearance on Gram stain and a negative reaction on tube coagulase test. In practical terms, however, the slide coagulase test is a more rapid surrogate marker of the tube coagulase test, demonstrating very good correlation, albeit with a few exceptions (see below). The CoNS are residents of the normal human skin microflora. CoNS have a propensity to cause foreign body infections because of their propensity to adhere to polymer surfaces and form biofilm [256]. Due to these properties, CoNS account for a significant portion of prosthetic valve endocarditis, discussed in Chap. 11. However, in the native heart, particularly in the presence of pre-existing valvular or congenital heart disease [257–259], the CoNS can cause endocarditis. In general, the clinical course and outcome of the CoNS-NVE is variable, ranging from a subacute, indolent infection with few complications to a fulminant, destructive infection, complicated by valve dysfunction, heart failure, and embolic phenomena. The difference in virulence appears to be species specific, although host factors likely contribute as well. Although *S. epidermidis* is the species most frequently associated with NVE, the clinical characteristics and management of certain other CoNS-NVE are also presented. It is important to note that although CoNS are considered to be low-virulence pathogens, a recent international study demonstrated that patients with CoNS-NVE had rates of congestive heart failure and of mortality similar to, as well as rates of cardiac valvular surgery higher than, patients with NVE due to *S. aureus* [255]. This point emphasizes the virulent nature of these "skin flora" organisms.

S. epidermidis

The large majority of CoNS-NVE is caused by *S. epidermidis*, accounting for rates of 85–91 % of cases [255, 258]. *S. epidermidis* can cause a rapidly progressive and destructive endocarditis, and observational series suggest that successful management requires a combination of surgery and antibiotics [255, 257, 260, 261]

The susceptibility of CoNS to antimicrobial agents is extremely variable. Although community-acquired isolates are frequently susceptible to a wide variety of agents, strains isolated from hospitalized patients are typically resistant to multiple antibiotics [257, 258, 262]. Such multi-resistance makes management of serious infections with CoNS particularly difficult.

The optimal antimicrobial management of *S. epidermidis* NVE is extrapolated from experience with *S. aureus* [13, 36] (Table 9.6). If standardized antimicrobial susceptibility testing demonstrates susceptibility to β-lactams, then these agents are the drugs of choice, as they have been associated with improved survival [184]. Of the

β-lactams, penicillin is rarely an option. An earlier report had suggested that among cases of CoNS-NVE, those that were community-acquired were usually sensitive to penicillin [258]. However, determination of penicillin susceptibility among CoNS has since been refined. Resistance to penicillin among CoNS is mediated by a plasmid-borne, inducible β-lactamase [263]. This resistance phenotype is not detected by routine microdilution techniques and is best identified by pre-exposing the isolate to an appropriate inducing agent, such as oxacillin [262]. Such a technique has demonstrated that only a very low percentage of *S. epidermidis* appear susceptible to penicillin in vitro; of these "penicillin susceptible" isolates, a significant percentage were β-lactamase producers [263]. As such, these isolates were considered resistant. A different study had identified β-lactamase activity in 75 % of *S. epidermidis* isolates [264]. These studies demonstrate that resistance to penicillin via an easily-transferable plasmid carrying an inducible β-lactamase enzyme is highly prevalent.

More problematic, however, is the development of methicillin resistance among CoNS. Although there is geographic variation, methicillin-resistant *S. epidermidis* (MRSE) is very common, particularly among nosocomially-acquired isolates, with prevalence rates as high as 60–70 % [265]. Methicillin resistance is mediated by the inducible *mecA* gene, which encodes an altered penicillin-binding protein (PBP 2a) that has reduced affinity for β-lactams [266]. As such, it confers resistance to all penicillins, including the semi-synthetic penicillinase-resistant penicillins, as well as to cephalosporins and carbapenems [262, 267].

Detection of methicillin resistance is hampered by the fact that MRSE isolates are phenotypically heteroresistant. As such, only a small fraction of organisms ($\sim 10^{-8}$ to 10^{-4} [262, 268]) actually express the resistant phenotype under in vitro testing conditions. Consequently, these isolates may be missed during antimicrobial susceptibility testing. Currently, most clinical laboratories use phenotypic methods to detect MRSE [267]. For all screening methods, oxacillin is preferred, as it is the most sensitive member of the semi-synthetic penicillinase-resistant β-lactams for the detection of resistance [267]. These generally produce reliable and satisfactory results. However, there is the possibility that some resistant strains may not be detected by this method, which could lead to suboptimal therapy. The most accurate method of detecting methicillin resistance is by detection of the *mecA* gene [269]. However, a practical clue on the antibiogram to the presence of MRSE is the presence of resistance to multiple other antibiotics, including erythromycin, clindamycin, tetracycline, chloramphenicol, and gentamicin [262].

S. epidermidis also may possess plasmid-mediated aminoglycoside-modifying enzymes, particularly AAC (6′)/APH (2″) [267, 270]. This latter enzyme has the capacity to inactivate various clinically useful aminoglycosides, including gentamicin, tobramycin, netilmicin, and amikacin. As a result, isolates possessing such enzymes may be resistant to these aminoglycosides. Concomitant methicillin- and aminoglycoside-resistance has been reported in approximately 50 % of isolates surveyed in one study [271].

S. epidermidis may also possess the MLS_b phenotype, encoded by various *erm* genes (predominantly *ermC* [267]), and conferring resistance to macrolides, lincosamides, and streptogramin B.

Rifampin, a bacterial DNA-dependent RNA-polymerase inhibitor, possesses significant anti-staphylococcal activity. Monotherapy with rifampin, however, is strongly discouraged, as it consistently selects for the development of resistant mutants. Resistance to rifampin often develops by mutations in the *rpoB* gene that encodes the β-subunit of DNA-dependant RNA polymerase [272]. Evidence of clinical benefit with the use of rifampin against MRSE has been predominantly in patients with prosthetic valve endocarditis who were being concomitantly treated with glycopeptides and aminoglycosides [273] and is thus indicated in these situations [13, 36]. The use of rifampin (along with teicoplanin) in CoNS-NVE was associated with emergence of rifampin resistance (and teicoplanin resistance) while on therapy in one patient [260]. A contributing factor may have been the simultaneous use of teicoplanin, an alternate glycopeptide, which has been associated with treatment failure when used in the management of staphylococcal endocarditis [13]. Therefore, the use of rifampin for CoNS-NVE remains debatable, with the British guidelines recommending it as a second agent when vancomycin is used for MRSE [13], while the American guidelines do not refer to it as an option [36].

The glycopeptide, vancomycin, remains a cornerstone of therapy for CoNS-related infections. Teicoplanin has also been used, although as mentioned previously, it is not available for use in North America. Furthermore, teicoplanin resistance seems to be particularly common among CoNS [274–276], and has emerged while on therapy in association with clinical failure [260, 277]. As with *S. aureus*, there is concern that the efficacy of vancomycin in CoNS NVE may not be as good as expected. There are two major reasons that contribute to the suboptimal efficacy of vancomycin in the treatment of CoNS NVE. Firstly, as extrapolated from the literature on *S. aureus* IE, the pharmacology of vancomycin may be inadequate, with poor penetration into cardiac vegetations and altered bactericidal activity due to the high bacterial inoculum inherent in such vegetations (i.e. inoculum effect) [17, 278, 279].

The second factor relates to the microbiology of *S. epidermidis*, which possesses the capacity to produce a surrounding biofilm, as well as inherent resistance mechanisms to glycopeptides that can provide a survival advantage. Under in vitro testing conditions (e.g. time-kill studies), both vancomycin and teicoplanin exhibit good bactericidal activity against CoNS [280]. However, such testing is done on planktonic (i.e. free floating) organisms. One of the major virulence factors of *S. epidermidis* is biofilm formation, whereby the bacteria adhere to various surfaces and produce glycocalyx, resulting in colonies of bacteria embedded in a biofilm. *S. epidermidis* bacteria existing in this state demonstrate altered metabolism, with a remarkable ability to tolerate significantly higher levels of antibiotics when compared to their planktonic form [256]. As such, the killing efficacy of achievable peak serum concentration of various antibiotics, including vancomycin, is drastically decreased [279, 281]. Although biofilm formation is a well-known explanation for failure of antibiotics to cure *S. epidermidis* infections associated with prostheses, it likely also contributes to the unsatisfactory results seen in CoNS NVE treated with antimicrobial therapy alone, as evidenced by the high rates of cardiac surgery required [255].

The resistance of *S. epidermidis* to glycopeptides, however, is not mediated solely through biofilm formation. CoNS, including *S. epidermidis*, inherently possess chromosomally-encoded mechanisms of resistance, consisting of overproduction of an abnormally thick cell wall and increased capacity to bind and sequester glycopeptides in the cytoplasm 280, 281. Furthermore, there is altered peptidoglycan cross-linkage, which may further inhibit vancomycin binding to target sites [208, 282]. This glycopeptide resistance is heterogeneously present among populations of CoNS. Complete resistance to glycopeptides at the population phenotype level can be easily selected under laboratory conditions by serial or prolonged exposure of isolates to such antibiotics [283, 284]. It has been hypothesized that extensive use of vancomycin in hospitals may also lead to such selection in vivo, allowing for the emergence of CoNS with increased MICs to vancomycin, with subsequent clinical failure [281, 284]. This feature is alarming, in view of the fact that decreased susceptibility to glycopeptides is correlated with resistance to other antibiotics, including β-lactams, leaving little room for antimicrobial therapy [208, 285].

Due to the emergence of glycopeptide resistance among CoNS, novel classes of antibiotics with alternate mechanisms of action are desirable. Of these, Q/D, LZL, daptomycin, and telavancin are potentially the most promising, based on the following preliminary data. Conclusive clinical efficacy data on these agents, however, is currently limited.

As discussed previously, Q/D (quinupristin/daltopristin) is a combination of two semi-synthetic derivatives of pristinamycin. This combination antimicrobial binds to the 50S bacterial ribosome, resulting in irreversible inhibition of protein synthesis, with subsequent bactericidal effects [149]. Its spectrum of activity is limited to Gram-positive bacteria, however, it has good activity against MRSE. In one study analyzing Q/D activity against 658 isolates of CoNS, >97 % of tested isolated had Q/D MICs of <4 g/L [286]. Of the 186 clinical isolates of *S. epidermidis* specifically, resistance rates to Q/D were <1 % [271]; such rates have been confirmed in other studies [287]. As well, clindamycin susceptibility appears to be predictive of Q/D susceptibility [286], which may allow for clinical laboratories to use clindamcyin as a surrogate antibiotic for Q/D during antimicrobial susceptibility testing. Animal models of endocarditis to determine the efficacy of Q/D have focused on *S. aureus* (see above); based on this data, Q/D displays homogeneous distribution throughout experimental vegetations with effective sterilization [288]. There is at this time, however, a paucity of clinical data. As such, there are no formal recommendations regarding the use of Q/D for the treatment of CoNS NVE with reduced vancomycin susceptibility. However, Q/D therapy was effective in three critically ill (non-endocarditis) patients with MRSE infection unresponsive to vancomycin [289]. Thus, future studies are required for this promising antibiotic. The major limitations in the use of Q/D is incompatibility with several drugs, which is problematic because Q/D is given parenterally, and its numerous drug interactions [290]. Furthermore, there appears to be geographic differences in inherent Q/D resistance among CoNS. For example, 16 % of such isolates were resistant in a study from Taiwan, suggesting that Q/D may not be appropriate empiric therapy in certain regions [291].

Llinezolid (LZL), an oxazolidinone, also possesses activity against MRSE. Among 186 clinical isolates of *S. epidermidis*, the MIC_{50} was 2.0 mg/L, the MIC_{90} was 4 mg/L, and there was 0 % resistance to LZL [286]. As with Q/D, there is a paucity of clinical data on the use of LZL in CoNS NVE, although one case report describes the successful treatment of *S. epidermidis* NVE using an oral LZL regimen. Oral management was likely effective because of the 100 % bioavailability of LZL. The major adverse events associated with the use of LZL include gastrointestinal disturbances, peripheral neuropathies, and hematologic abnormalities [292]. This latter complication, consisting of anemia and/or thrombocytopenia, is particularly problematic with prolonged use (≥2 weeks) of this agent [293]. Prolonged therapy, however, is necessary in the management of endocarditis. As such, it is recommended to monitor for the development of cytopenias with periodic complete blood counts (e.g. weekly [292]). There is some suggestion that supplementation with vitamin B6 may mitigate the cytopenias [294, 295], although further evidence is required.

Daptomycin, a cyclic lipopeptide, also exhibits activity against MRSE. Its mechanism of action involves the calcium-dependent insertion of the compound into the bacterial cytoplasmic membrane, with subsequent alteration of membrane integrity and transmembrane potential [166]. The data on the use of daptomycin for endocarditis, though, is limited. In a rabbit model of endocarditis, a single dose of daptomycin at 10 mg/kg i.v. produced an apparently-effective response, resulting in a mean bacterial burden of 1.8 ± 1.9 $\log_{10}$ CFU per gram of vegetation, compared to 6.9 ± 1.0 $\log_{10}$ CFU per gram of vegetation among rabbits receiving no treatment [296]. However, in another rabbit model using high doses of daptomycin (20 mg/kg or 50 mg/kg) [297], the authors demonstrated a significant antibiotic gradient from the periphery to the core of the fibrin clot, with associated increased survival of staphylococci in the core. For MRSE, differences between bacterial counts in the periphery and in the core of the same clots were approximately 2–3 $\log_{10}$ CFU/g. However, in an in vitro simulated endocardial vegetation pharmacodynamic model [249], >70 % penetration was achieved by daptomycin, associated with large bacterial density reductions (>4 $\log_{10}$ CFU/g). Currently, there is a paucity of clinical experience with daptomycin in MRSE NVE, owing to the single-center infrequency of the disease relative to MRSA. However, the International Collaboration on Endocarditis has demonstrated that daptomycin could be used successfully treatment of MRSE NVE, although their sample sizes (daptomycin vs. standard of care therapy) were small and included native valve and prosthetic valve IE cases [298]- Nonetheless, based on this limited experience and extrapolation for the MRSA literature, daptomycin is increasingly recognized as a treatment option for MRSE NVE.

Telavancin, a novel lipoglycopeptide, demonstrates bactericidal activity against staphylococci and exhibits substantial antimicrobial activity against staphylococcal biofilms, producing a decrease in the number of bacteria eluted from in vitro biofilms [299]. Currently, there are no reports of the use of telavancin in the treatment of CoNS NVE.

Based on the most recent data from the International Collaboration of Endocarditis (ICE), CoNS NVE (85 % of which were due to *S. epidermidis*) was frequently

complicated by heart failure (49/99 patients, 49 %) and intracardiac abscess (15/99, 15 %). For these reasons, patients with *S. epidermidis* NVE more frequently required cardiac surgery when compared to *S. aureus* NVE (54 % vs. 35 %, respectively, $p<0.001$) [255]. Furthermore, the rates of mortality with CoNS NVE were similar to those of *S. aureus* NVE (19 % vs. 25 %, respectively, $p=0.21$), dispelling the belief that CoNS NVE is a benign disease. Given the high rates of cardiac complications associated with *S. epidermidis* NVE, early cardiac surgery consultation is suggested.

S. lugdunensis

S. lugdunensis NVE requires special mention because of its reputed aggressive nature. *S. lugdunensis* was first described by Freney et al. in 1988 [300], deriving its species name from Lyon (Latin adjective of Lugudunum), the French city where it was first isolated [284]. As with other CoNS, it is commonly found on the skin [301]. *S. lugdunensis*, however, is particularly common in the perineal area, which was felt to be the source of NVE in 10 of 21 cases where a portal of entry was known [302].

The identification of *S. lugdunensis* in the microbiology laboratory can be made difficult because some strains may test positive on the slide coagulase test (see above) [303]. As such, such isolates may be misidentified as *S. aureus*. This misidentification can be overcome by performing the tube coagulase test, which is negative for *S. lugdunensis*. Other features suggestive of *S. lugdunensis* include the production of ornithine decarboxylase and pyrrolidonyl arylamidase [300]. The correct identification of *S. lugdunensis* is critical because of the severe disease associated with it, which may be anticipated or pre-empted with early speciation.

S. lugdunensis NVE is uncommon, with a recent review of the English literature identifying 48 reported cases [302]. Of these, a fulminant course with symptoms <3 weeks in duration was reported in 74 % of cases. Cardiac complications were particularly common: intracardiac abscess formation (23 %), perforation and destruction of a valve (21 %), and large vegetations (11 %). Systemic emboli with metastatic foci of infection occurred in 32 % of cases.

S. lugdunensis is generally susceptible in vitro to β-lactams [302, 304]. In a study of 59 clinically significant isolates of *S. lugdunensis*, 76 % were β-lactamase negative, and all strains were susceptible to oxacillin, cephalothin, gentamicin, rifampin, and vancomycin [305]. Therapy should be guided by susceptibility data, and in most instances, a beta-lactam plus rifampin or gentamicin is adequate therapy [306]. Because the MICs of penicillin are usually ≥2 dilutions lower than that of oxacillin, penicillin intravenously may be the drug of choice once antimicrobial susceptibility testing confirms it as an option [302, 307].

Unfortunately, because of the destructive nature of this pathogen, surgical intervention is almost always necessary, despite "adequate antimicrobial coverage". In particular, *S. lugdunensis* NVE is characterized by a shorter, more aggressive clinical history, perivalvular abscess formation, and a high mortality rate. In a review by Vandenesch et al. in 1993 [308], the mortality rate from this disease was 70 %, and only 35 % of the cases underwent surgery. After 1993, with early cardiac surgery

occurring in 64 % of cases, the mortality rate was 18 % [302]. Although the numbers are small, it is felt that the decrease in mortality is attributed directly to early surgical intervention.

Other Coagulase-Negative *staphylococci*

Case series have also reported CoNS NVE due to *S. warneri* [309–311], *S. capitis* [312], and *S. saprophyticus* [313, 314].

S. warneri, a skin commensal but representing only 1 % of the skin staphylococci in normal individuals [309], is associated with an acute and aggressive presentation of NVE. It appears to have a predilection for valve destruction or abscess formation [310, 311]. As such, optimal management from cases reported suggests that a combined medical and surgical approach is warranted. Similarly, *S. saprophyticus*, a typical pathogen for community-acquired urinary tract infections, can also have a virulent presentation [313].

S. capitis, a member of the normal flora of the human scalp, face, neck, and ears [315], is reportedly associated with a more benign course, in which a 4 week course of antimicrobial therapy is usually sufficient, provided that the patient has a sustained clinical response [312].

Gram-Negative Bacilli

Non-fastidious Gram-negative bacilli are rare causes of bacterial endocarditis, accounting for 5–10 % of cases [316, 317]. Within this category, the major categories of the pathogens of NVE are the Enterobacteriaceae and the Non-fermentative Gram-negative bacilli.

The family Enterobacteriaceae is defined as facultatively anaerobic Gram-negative bacilli, characterized by a negative oxidase reaction and the ability to metabolize nitrites to nitrates. The major pathogens within this family with the ability to cause NVE are the following: *E. coli*, *Klebsiella* spp., and *Salmonella* spp., although reports of cases due to other Gram-negative enteric pathogens have been described.

E. coli NVE is rare, with only 39 cases (both definite and probable) identified in a review of case series from the English literature [318]. The major risk factors identified were diabetes mellitus and previous heart disease. The most likely source of for *E. coli* NVE was urinary tract infection. Based on the reported cases, the most common site of infection was the mitral valve [318, 319]. Valvular vegetations were typically large, and intra-cardiac complications such as perforation and abscess were reported. Arterial embolization was also common [319]. Various antibiotic regimens were used, based on antimicrobial susceptibility testing, and included third-generation cephalosporis and fluoroquinolones, as well as combination therapy with aminopenicillins, and aminoglycosides. Surgery appears to play an important role, as evidenced by trends in mortality rates: Prior to 1960, the mortality rate was 100 %, whereas after 1960, the mortality rate was 57 % ($p < 0.05$ by χ^2-test). Correspondingly, none of the patients prior to 1960 underwent surgery, whereas

52 % of patients had undergone surgical intervention after 1960. This fact would suggest the need for a low threshold for surgical consultation in cases of *E. coli* NVE that does not respond promptly to antimicrobial therapy.

Klebsiella spp. are very rare causes of NVE, accounting for approximately 1.5 % of reported cases in a comprehensive review of this condition by Anderson and Janoff [317]. Among the 23 cases of *Klebsiella* endocarditis in which the affected valve was specified, the majority (17/23 cases, 74 %) involved the aortic valve, followed by the mitral valve. The most common source was the urinary tract. Of the cases in which antibiotic usage was reported, aminoglycosides and cephalosporins were most commonly administered (86 % and 67 % of cases, respectively). However, a wide variety of antimicrobial agents were administered, including combination therapy. The selection of antibiotics used was influenced by the time period in which these sporadic episodes occurred; as such, it is not possible to conclude superiority of one antibiotic regimen over others. Of the 31 patients with *Klebsiella* NVE, 10 were cured, 10 died, and no outcome was reported for 11 subjects. Of the 10 who were cured, medical therapy alone was effective in 5 cases, whereas surgery was a component of management in 4. In the remaining 1 survivor, the use of surgery was not specified. Of the 10 patients who died, 4 received only medical therapy, whereas surgery was used in 2 cases; in the remaining 4 cases, the use of surgery was not specified. The mortality, however, appeared to decrease over time. The mortality rate for *Klebsiella* NVE was 73 % in cases reported prior to 1980, but only 22 % in those published after 1980. Furthermore, the mortality rate tended to be lower for patients who underwent valve replacement during the course of their infection, when compared to those who did not. In conclusion, based on this literature review, bactericidal antimicrobial agents with the greatest in vitro activity against *Klebsiella* spp. should be used, and strong consideration should be given to combination synergistic therapy (e.g. third-generation cephalosporins and aminoglycosides). The optimal duration of therapy is unknown, but a minimum of 6 weeks seems prudent. However, because many patients fail to respond to medical treatment alone, early consultation with a cardiac surgeon is appropriate.

Salmonella spp. are well-recognized causes of endovascular infections such as endocarditis, but can also cause infectious endarteritis (also referred to as infectious aortitis and mycotic aneurysms), and vascular graft infections [76, 320]. The exact incidence of the different species as causative agents for NVE is difficult to estimate, largely because of the unresolved nomenclature of the *Salmonella* genus [321]. Nonetheless, frequently observed species include *Salmonella enterica* serovar *enteritidis*, *S. enterica* serovar *choleraesuis*, and *S. enterica* serovar *typhi* [76, 322]. In approximately 30 % of cases, diarrhea preceded the onset of endocarditis from 3 weeks to 5 months, or occurred concomitantly with the symptoms of endocarditis [320]. *Salmonella* spp. have a predilection for previously diseased cardiac valves. As such, the tricuspid valve is frequently involved in *Salmonella* endocarditis among intravenous drug users (IVDUs) [76, 323]. In cases of *Salmonella* NVE among non-IVDUs, the mitral valve was involved in 36.6 %, followed by the aortic valve in 16.6 % [320], likely related to known risk factors, such as rheumatic heart disease and mitral valve prolapse [76]. Another major risk factor is advanced

HIV/AIDS, likely related to the increased risk for non-typhi *Salmonella* spp. bacteremia in this population [76]. *Salmonella* endocarditis is characterized by a destructive process, characterized by valve perforation, valve ring abscess, atrio-ventricular wall perforation, and/or valvular cusp rupture [320]. Other frequent complications include atrial thrombus formation / mural endocarditis, myocarditis, and pericarditis [324]. As a result of this destructive capacity, previously reported mortality rates are ~70 % [325].

The optimal antibiotic treatment for *Salmonella* spp. endocarditis is unknown, largely because of the paucity of clinical data and the general limitations associated with an animal model of this disease. The issue of antimicrobial selection has been further complicated by the emergence of resistance to various antibiotics, including those used for treatment of NVE, such as ampicillin. Ampicillin resistance is mediated by TEM-type beta-lactamase-encoding plasmids [326]. Because of the emergence of ampicillin-resistant *Salmonella* spp. and the dogma that bactericidal antibiotics are obligatory in the management of endocarditis to achieve cure, third-generation cephalosporins and fluoroquinolones have become the treatment of choice for *Salmonella* spp. NVE [320].

Using a rabbit model of endocarditis caused by *S. enteritidis* (*S. enterica* subsp. *enteritidis*), the efficacies of different antibiotic regimens in sterilization of valvular vegetations has been estimated [327]. The efficacies varied with the *S. enteritidis* isolate used. For ampicillin-susceptible *S. enteritidis*, both ampicillin and cefotaxime produced the greatest reduction in the number of organisms isolated from the vegetations at the completion of therapy (ampicillin: 2.20 ± 1.1 $\log_{10}$ CFU/g of vegetation; cefotaxime: 1.36 ± 0.7; control: 8.32 ± 1.2); there was no significant difference in effect between these 2 agents. Ofloxacin also decreased the number of organisms recovered from the vegetations (3.17 ± 1.5), but appeared to be less active than cefotaxime. For vegetations seeded with ampicillin-resistant isolates, cefotaxime and ofloxacin were both equally effective (3.59 ± 1.6 and 3.99 ± 1.08, respectively). Interestingly, the efficacy of cefotaxime was reduced against ampicillin-resistant isolates (3.59 ± 1.6) compared to ampicillin-susceptible isolates (1.36 ± 0.7). The maintained bactericidal effect of cefotaxime and other broad-spectrum cephalosporins against ampicillin-resistant isolates is thought to be related to the stability of the antimicrobial agents to the plasmid-mediated β-lactamase [328]. Based on this animal model, the following antimicrobial regimens may be used for *Salmonella spp.* endocarditis: For ampicillin-susceptible isolates, ampicillin should be used. Cefotaxime may also be used, and should be used for ampicillin-resistant isolates. For patients unable to tolerate cephalosporins, fluoroquinolones may be an alternative, if the isolate is susceptible. For life-threatening infections, empiric combination therapy with a third-generation cephalosporin and a fluoroquinolone has been recommended until susceptibility results are available [329]. There is some clinical evidence to support the use of these antibiotics [322, 324, 330–332]. There is no clinical data that suggests that combination therapy (i.e. third-generation cephalosporin plus a fluoroquinolone) is more effective than monotherapy.

Resistance to the extended-spectrum cephalosporins and fluoroquinolones, however, is emerging, mostly as a result of agricultural use of antibiotics [333]. The

exact resistance rate, however, varies with different serovars and different antibiotics [334]. Resistance to fluoroquinolones is predominantly due to mutations in the DNA gyrase genes and can be predicted by resistance to nalidixic acid by disk diffusion method during antimicrobial susceptibility testing [334, 335]. Resistance to extended-spectrum cephalosporins is due to the production of β-lactamases, both extended-spectrum β-lactamases (ESBLs, particularly the CTX-M types) and AmpC β-lactamases (particularly the CMY-2 type) [334]. The increasing MICs of the salmonellae to these antibiotics are occurring in isolates with established resistance to chloramphenicol, ampicillin, and trimethoprim-sulfamethoazole. Consequently, the antimicrobial armementarium for the treatment of multi-resistant *Salmonella spp.* endocarditis is frighteningly limited. Alternative agents that may demonstrate in vitro activity include imipenem, azithromycin, and aztreonam [329, 335]. However, their roles in the management of *Salmonella* spp. endocarditis are unproven. Some antimicrobial agents may demonstrate good in vitro activity (e.g. first- and second-generation cephalosporins [329], aminoglycosides [320, 327]), but are not clinically effective.

Based on the above rabbit model, however, medical management alone of *Salmonella* spp. endocarditis is not likely to be effective. After 3 days of antimicrobial therapy with agents demonstrating in vitro bactericidal activity, the cardiac vegetations remained infected and complete sterilization was never achieved [327]. Clinical experience also supports the essential role of surgery in reducing the mortality of *Salmonella* endocarditis [320, 325, 329]. The most common indications for surgery have been cardiac failure, relapsing bacteremia, and myocardial abscesses [320, 322]. In the patients who survived, valve replacement was necessary. Thus, physicians should have a low threshold for surgical intervention. If surgical intervention is successful, antimicrobial therapy should be continued for a minimum of 6 weeks; many consultants would subsequently follow with several months of suppressive therapy, even for patients who are well [329, 335].

A special form of endovascular infection associated with *Salmonella* spp. is the mural (non-valvular) endocarditis, including infection of ventricular post-infarction aneurysms. This manifestation is related to the organism's unique ability to adhere to the damaged endothelium of the heart and arterial walls. Patients with this type of infection have extensive disease from the endocardium to the pericardium, with pseudo-aneurysm formation, abscess formation, fibrosis, and hemorrhage [320]. If involvement of the pericardium (i.e. *Salmonella* spp. pericarditis) develops, it may be complicated by tamponade [320, 325]. Diagnosis of mural endocarditis can be confirmed by cross-sectional echocardiography, revealing ventricular aneurysm, thrombus, and/or pericardial effusion with thickening [320]. Left-ventricular angiography by follow-through from a pulmonary artery injection, to minimize the risk of thrombus dislodgment, can also be performed [320]. Antibiotic therapy should be initiated, but alone, does not eradicate the infection. If there is tamponade, pericardiocentesis or pericardiectomy is required [325]. Resection of ventricular aneurysm must also be performed [320].

Salmonella spp. also have the capacity to establish non-cardiac, endovascular infection (i.e. mycotic aneurysm, or endarteritis or infectious aortitis). The most

commonly isolated serotypes are *Typhimurium*, *Enteritidis*, and *Choleraesuis* (in decreasing order) [335]. Most of the patients with mycotic aneurysm due to *Salmonella* spp. have pre-existing atherosclerotic disease at the site of subsequently infected aneurysm [320, 329, 335]. One study demonstrated that the attack rate among adults >50 years of age with *Salmonella spp*. bacteremia was 25 % [336]. The most common site of infection is the abdominal aorta, particularly the infrarenal portion [337]. The most common presentation included fever, abdominal pain, and/or back pain [337]. The diagnostic modality of choice is computed tomography (CT) of the abdomen with contrast, because of its ability to detect changes in the arterial wall and the periaortic tissue [337].

The management of *Salmonella spp.* endarteritis has changed significantly. In previous times, the disease was uniformly fatal [335]. Early surgical intervention, however, has greatly increased survival. In a review of 148 cases from 1948 to 1999, patients who underwent combined medical/surgical therapy had a 62 % survival rate [338]. The survival rate was further increased to 77 % among 30 patients who specifically underwent excision of the infected vessel with extra-anatomical bypass via construction of an axillo-bifemoral graft [338]. However, anatomic in situ grafting may be acceptable if the infected area is limited and debridement is complete [339]. It may be the only option for supra-renal or thoraco-abdominal mycotic aneurysms. In addition to surgical management, a prolonged course (≥6 weeks) of parenteral antibiotics is recommended [329, 335], with the agent selected based on antimicrobial susceptibility testing of cultures obtained intraoperatively.

Pseudomonas spp

Pseudomonas aeruginosa NVE is a rare disease which usually affects right-sided heart valves in IVDUs [36, 340] and is further discussed in Chap. 3. Left-sided *P. aeruginosa* NVE in non-IVDUs has also been described [341]. The major risk factors identified were underlying valvular heart disease, hemodialysis, cardiac catheterization/surgery, gastrointestinal and genitourinary tract procedures. Left-sided disease is characterized by an aggressive infection poorly responsive to antimicrobial therapy and is associated with mortality rates higher than isolated right-sided involvement [36]. Treatment failure may be attributed to the lack of correlation between in vitro and in vivo susceptibilities (e.g. as a result of biofilm formation), extremely large numbers of organisms present in infected vegetations, the phenotypic heterogeneity of the pathogen, and the frequent development of resistance on therapy [342–344]. In the absence of randomized controlled studies, but on the basis of clinical experience, the suggested management of left-sided *P. aeruginosa* endocarditis consists of immediate valve replacement, accompanied by a 6 week course of high-dose, combined (β-lactam plus aminoglycoside) antimicrobial therapy [345]. The AHA recommends high-dose tobramycin (8 mg/kg/day iv in once-daily doses), with maintenance of peak and trough concentrations of 15–20 μg/mL and ≤2 μg/mL, respectively, in combination with either an extended-spectrum penicillin (e.g. ticarcillin, piperacillin) or ceftazidime or cefepime in full doses [36].

Carbapenems, however, have rapid bactericidal action against *P. aeruginosa* [344], with low intrinsic resistance rates [346]. Thus, they may be potentially considered in place of an extended-spectrum penicillin, in combination with an aminoglycoside. It should be mentioned, however, that the use of combination anti-pseudomonal therapy remains controversial. In the setting of suspected infection by *P aeruginosa*, the use of more than one drug empirically is desirable to assure susceptibility to at least one antimicrobial agent. However, once susceptibility testing results are available, it is unclear if combination therapy remains necessary, provided that pharmacokinetic parameters are optimized. Although there is no adequately-powered, direct study of the effect of combination therapy on *P. aeruginosa* endocarditis, a recent meta-analysis favored the use of combination therapy for *P. aeruginosa* bacteremia, with an approximately 50 % mortality reduction [347]. The authors caution, however, that the studies in the systematic review varied considerably in the types of antimicrobial used and there was considerable clinical heterogeneity.

Native Valve Endocarditis Due to Anaerobic Bacteria

NVE due to anaerobic bacteria is rare, with studies performed in the 1970s reporting them as the etiologic agent in 2–5 % of cases [348]. Most cases of anaerobic NVE are caused by Gram-negative bacilli (predominantly *Bacteroides fragilis* group, other *Bacteroides* spp., and *Fusobacterium* spp.). Anaerobic Gram-positive rods (predominantly *Propionibacterium* spp.) have also been reported.

Among the 53 cases of endocarditis due to anaerobic Gram-negative bacilli (GNB) reviewed in the English literature [338], the majority (20/53, 38 %) are due to *B. fragilis* group. This group of bacteria includes *B fragilis* (sensu stricto), which is the most common isolate, and other species, such as *B. distasonis*, *B. ovatus*, *B. thetaiotaomicron*, and *B. vulgatus* [339]. These bacteria are part of the normal GI flora. As such, the most common sources for *B. fragilis* group NVE were the gastrointestinal and the genital tracts [348, 349]. NVE with this group of bacteria is frequently complicated by systemic embolization, occurring in 60–70 % of cases [348]. In case studies published prior to 1974, *B. fragilis* group endocarditis was associated with a high mortality rate (14/17 cases, 81 %) [348]. This dismal prognosis was most likely due to the lack of an effective antimicrobial agent with anaerobic coverage at that time. Of note, members of the *B. fragilis* group are resistant to penicillins, mostly through the production of beta-lactamase [350]. With the introduction of metronidazole in the 1970s, there has been a significant reduction in death rates among patients infected with *Bacteroides* spp. in general [348]. This decline is related to the high prevalence (>99 %) of clinical isolates that are susceptible to metronidazole [350]. Other agents that retain this level of efficacy against clinical isolates include chloramphenicol and the carbapenems; β-lactam/β-lactamase inhibitor combinations also demonstrate activity against the majority (95–99 %) of isolates [350]. The development of antibiotics with effective anti-*Bacteroides* activity has facilitated the medical management of this rare endocarditis.

Fusobacterium spp., also members of the *Bacteroidaceae* family, represent a rare cause of endocarditis. The two major clinical species of this genus are *F. necrophorum*, the etiologic agent of Lemierre's syndrome (septic internal jugular vein thrombosis) and *F. nucleatum*. Both organisms have been reported to cause NVE [351]. As with *B. fragilis* group NVE, arterial embolization was the most common complication [351]. In the pre-antibiotic era, the mortality rate from *Fusobacterium* bacteremia was approximately 80 %; the rates of *Fusobacterium* NVE per se are unknown [351]. With the advent of antibiotics, the mortality rate has significantly diminished, owing to the general susceptibility of most *Fusobacterium* spp. to penicillin [348]. All reported cases of *Fusobacterium* endocarditis have had a favorable clinical course with antimicrobial therapy alone [348, 351].

Propionibacterium acnes is an anaerobic, non-spore-forming, Gram-positive bacterium that demonstrates slow growth in vitro. It is part of the normal flora of the skin and mucous membranes [352]. Although frequently considered a contaminant, *P. acnes* has the capacity to cause serious infections. *P. acnes* has caused endocarditis involving prosthetic valves as well as native valves [353]. The capacity of this "benign" organism to do so relates to its ability to adhere to tissues with structural abnormality (e.g. rheumatic cardiac valves) or to foreign material (e.g. prosthetic valves) [352]. *P. acnes* endocarditis can be complicated by abscess formation, congestive heart failure, and arterial embolization [353]. The mortality rate for *P. acnes* NVE is unknown, but the mortality rate for prosthetic valve endocarditis is 21–46 % [354]. Successful treatment of the few cases of NVE have used a combined modality approach [352, 353]. *P. acnes* is usually susceptible to penicillin, ampicillin, vancomycin, and gentamicin [352, 353, 355].

Fungal Endocarditis

Fungi are uncommon but emerging causes of infective endocarditis, most recently accounting for 1–10 % of organisms isolated, including ~10 % of cases of prosthetic valve endocarditis [356].

Simplistically, fungi are classified as yeasts or moulds. Yeasts are facultatively anaerobic, unicellular, non-filamentous fungi that are typically spherical or oval in shape. The most common yeasts involved in fungal endocarditis (FE) are the *Candida* spp. [356, 357], although FE with the other opportunistic yeasts (e.g. *Cryptococcus* spp. [358–360], *Saccharomyces* spp.[361], *Trichosporon* spp. [362–365], and *Rhodotorula* spp. [366, 367]) have been sporadically reported. Moulds are aerobic, filamentous fungi. The predominant moulds involved in FE are the *Aspergillus* spp. [357]. Dimorphic fungi are those organisms that exist as moulds (mycelial form) when incubated at room temperature under laboratory conditions and yeast phase, yeast-like cells or spherule form when grown in human tissue or incubated at 37 °C on synthetic laboratory media. *Histoplasma capsulatum* is the most commonly reported dimorphic fungus involved in FE [357, 368].

The development of antifungal therapies with diverse mechanisms of action is increasing. Currently, there are five classes of antimycotic agents that may be used for invasive fungal infections. These are the polyenes, the azoles, the allylamines, the fluoropyrimidines, and the echinocandins. To establish the spectrum of activity

of these agents requires standardization of an antifungal susceptibility testing procedure. Such a procedure requires two components: a standardized method for in vitro testing, as well as criteria for the interpretation of such results that correlates with clinical outcome. Standardized methodologies for yeast [369, 370] and for molds [371] have been adopted, and interpretive breakpoints for susceptibility testing of *Candida* spp. to azoles and echinocandins have been established [372]. This is an emerging field in diagnostic microbiology.

The main antifungal polyenes are natamycin, nystatin, and amphotericin B. Of these, ampthotericin B (AmB) remains the drug of choice for the treatment of most invasive fungal infections [373, 374]. AmB acts by hydrophobically binding to the ergosterol component of fungal membranes, creating aqueous pores consisting of an annulus of 8 AmB molecules [375]. These channels render the fungal cytoplasmic membrane permeable and allow the leakage of vital molecules from the cells, leading to cell death. As such, AmB is predicted in vitro to exert a fungicidal activity, although this effect varies with the fungal species targeted. Unfortunately, cross-reactivity to cholesterol in the mammalian cell membrane accounts for its toxic effects that often limits the dose of medication administered or requires premature termination of treatment.

Based on clinical experience and current interpretive criteria, the antimycotic spectrum of activity of AmB is extensive. It includes most commonly clinically encountered yeasts (e.g. *Candida* spp., *Saccharomyces* spp., *Trichosporon* spp.), molds (e.g. *Aspergillus* spp.) and dimorphic fungi (e.g. *Histoplasma capsulatum*, *Coccidioides* spp., *Blastomyces dermatitidis*) [374]. It should be remembered, however, that AmB does not reliably cover all fungal pathogens. Resistance to AmB may either be inherent or acquired. *C. lusitaniae*, for example, has been reported to be inherently resistant to AmB [373, 376], although a review by Ellis [374] suggests that the data, in fact, may be contradictory and that most strains appear susceptible by contemporary in vitro criteria. Furthermore, it is important to remember that despite appearing susceptible in vitro, invasive fungal infections may be frequently associated with clinical failure, possibly due to associated patient co-morbidities. Although acquired resistance to AmB has been sporadically reported, it does not appear to be a significant factor in the management of patients [374].

The major issues related to use of AmB are infusion-related adverse events and nephrotoxicity [377]. Of these, the most serious is the latter. In a study of patients with suspected or proven aspergillosis (non-endocarditis) [378], AmB was administered for a mean of 20 days and a median of 15 days to 239 patients; 53 % developed nephrotoxicity (defined as doubling of baseline creatinine). Of these, about 15 % required renal dialysis. To circumvent the problems of renal toxicity, various lipid formulations of AmB have been created: AmBisome (Astellas Pharma US, Inc), a unilamellar liposomal preparation; Abelcet (Enzon, Inc), a ribbon-form lipid complex; and Amphocil or Amphotec (Intermune, Inc., Burlingame, Calif.), a discoidal complex of cholesteryl sulfate and AMB. These different formulations all contain AmB, but they differ with respect to reticuloendothelial clearance, volume of distribution, peak serum concentration (Cmax), and area under curve (AUC) [377, 379]. Although these are major differences from a pharmacological perspective, the

clinical significance of this difference is unclear. However, these formulations do represent significant improvement in terms of renal-sparing properties relative to the conventional preparation of AmB (i.e. AmB deoxycholate) [380–382]. In terms of efficacy, numerous trials demonstrated that the lipid formulations were consistently at least as effective as conventional AmB [379, 381, 383]. This equivalence (and potential superiority) may be related to the higher dosages permitted with these preparations. Certain preparations may also have more advantageous distribution to sites of infection. For example, administration of AmBisome in a rabbit pharmacokinetic model demonstrated sixfold more AmB in brain tissue than administration with other agents [384]. The clinical significance remains to be established, but in the presence of endocarditis with embolic disease to the central nervous system, such property may favor its selection. Conventional AmB has poor penetration into cardiac vegetations [385, 386]. The penetration of the various lipid-based formulations for AmB into cardiac vegetations has not been published.

Nystatin is an established antifungal agent, but is restricted to topical use as it is ineffective orally and severely toxic when administered intravenously [387]. Because it has demonstrated broad in vitro antifungal activity against clinically relevant fungi, including those resistant to fluconazole and amphotericin B products, there has been renewed interest in its use via an altered preparation. Liposomal nystatin is one such formulation, and there is some evidence to suggest that it may be effective as salvage therapy for patients with invasive aspergillosis refractory to or intolerant of AmB [388]. Its role in the management of endocarditis remains speculative.

The azoles are divided into the older imidazoles, such as miconazole and ketoconazole, and the triazoles, which currently include fluconazole, itraconazole, voriconazole, posaconazole, and ravuconazole. These agents function by inhibiting the lanosterol 14α-demthylase enzyme, leading to decreased synthesis of ergosterol the main sterol in the fungal cell membrane [375]. The depletion of ergosterol alters membrane fluidity, thereby reducing the activity of membrane-associated enzymes and leading to increased permeability and inhibition of cell growth and replication [389]. Consequently, azoles are predicted in vitro to exert a fungistatic effect, although this varies with the azole and with the fungal species targeted. A major distinction between the imidazoles and the triazoles is the preferential affinity of the latter for fungal, as opposed to human, cytochrome P-450 enzymes, which subsequently accounts for its improved toxicity profile [390].

The spectrum of activity of the azoles expands with newer generations. The imidazoles are not used in the treatment of systemic fungal infections because of poor pharmacokinetics, unpredictable drug interactions, and/or adverse events profile [391]. Fluconazole is a highly water-soluble triazole, developed in both oral and parenteral preparations. The oral formulation has very good absorption, with ~90 % bioavailability [392]. The spectrum of activity of fluconazole relative to fungal causes of endocarditis includes the majority of *Candida* spp., *Cryptococcus neoformans*, *Trichosporon* spp., and the dimorphic fungi [391, 393]. Of note, fluconazole does not possess activity against all yeasts (e.g. *C. glabrata*, *C. krusei*) [394] and has no clinically meaningful activity against filamentous fungi (e.g. *Aspergillus*

spp., *Fusarium* spp., *Scedosporium* spp., and the Mucormycetes, such as *Mucor* spp.) [391, 395]. In a rabbit model of endocarditis, the ability of fluconazole to penetrate into cardiac vegetations appeared superior to that of AmB [396]. The distribution of fluconazole is excellent, including CSF penetration, with achieved CSF levels of approximately 80 % of corresponding serum levels [397]. As such, it may be the drug of choice for endocarditis caused by susceptible yeasts complicated by septic emboli to the central nervous system. Fluconazole is safe, even at doses up to 1600 mg daily [398]. In contrast to imidazoles, fluconazole has significantly less interaction with human cytochrome enzymes, and thus does not interfere with the synthesis of mammalian sterol-based hormones [391].

Itraconazole is a highly lipid soluble triazole with a broader spectrum of activity. In addition to *Candida* spp., *Cryptococcus neoformans*, and endemic dimorphic fungi, itraconazole also has activity against *Candida* non-albicans spp. and *Aspergillus* spp. [391, 395]. As with fluconazole, itraconazole possesses no reliable activity against other filamentous fungi. The major limitation of itraconazole is its formulations. Initially introduced as a capsular form, which demonstrated erratic absorption, the preparation was modified to a novel, cyclodextrin-based oral solution, which demonstrated a bioavailability 60 % greater than that of capsules [399]. Recently, an intravenous formulation has been developed. Clinical studies have demonstrated efficacy in prophylaxis against yeast and mold infections in patients at high-risk for disease (i.e. allogeneic stem cell transplant recipients) [400, 401]. The literature on the use of itraconazole in fungal endocarditis is limited. The major shortcomings of itraconazole are its lower rates of tolerability and increased potential for drug interactions, when compared with fluconazole [399].

Voriconazole, a second-generation triazole derivative of fluconazole, has a very wide-spectrum of activity, including *Candida* spp. (albicans and non-albicans), *Cryptococcus neoformans*, *Aspergillus* spp., endemic dimorphic fungi, as well as other yeasts (e.g. *Trichosporon* spp.) and emerging molds (e.g. *Fusarium* spp., *Scedosporium* spp.) [402]. Voriconazole, however, has no significant clinical activity against the Mucormycetes [391, 402]. In addition to demonstrating in vitro activity against these fungi, the magnitude of the activity is significantly higher; for example, voriconazole is several-fold more active than the predecessor triazoles against *Candida* spp. [391]. Furthermore, voriconazole has both an oral and parenteral formulation, with excellent bioavailability (98.99 %, slightly decreased with concomitant food intake) [403]. As with fluconazole, voriconazole has good penetration into the CSF and brain parenchyma, and it has been used in the treatment of CNS aspergillosis (with improved, albeit unsatisfactory, survival rates) [402, 404, 405]. The major adverse events associated with voriconzole include: dose-related transient visual disturbances (up to 10 % of patients); hepatic toxicity; neurological side effects (e.g. hallucinations, abnormal dreams, neuropathy, paresthesia); nausea/vomiting; interactions with certain medications; and QT interval prolongation [402, 406]

The major adverse events associated with voriconzole include the more-common, dose-related transient visual disturbances (up to 10 % of patients), as well as the uncommon potential for hepatic dysfunction [402]. Unfortunately, cross-resistance

to voriconazole, among isolates resistant to fluconazole and itraconazole, can occur [391]. Such a factor must be borne in mind when selecting empiric antifungal therapy.

Posaconazole is an analogue of itraconazole, and has potent activity against *Candida* spp. *Aspergillus* spp., as well as dematiaceous molds and Mucormycetes [391]. Ravuconazole, another derivative of fluconazole, also has in vitro activity against a variety of yeasts and molds. The allylamine antifungals inhibit squalene epoxidase, an enzyme involved in the synthesis of lanosterol, the precursor of ergosterol [407]. Among this class of agents, terbinafine is the most effective to date. Up to this point, terbinafine has been used principally in the management of dermatophytic infections. However, in vitro, terbinafine is highly active against a broad spectrum of pathogenic fungi, including *Candida* spp. (albicans and non-albicans), and filamentous fungi [407, 408]. Among three patients with bronchopulmonary aspergillosis not responsive to the usual antimycotic therapies, systemic terbinafine resulted in eradication of *A. fumigatus* [409]. There is some evidence, however, that the anti-*Aspergillus* activity of terbinafine is greater for the non-fumigatus species [410]. Results from in vitro testing in combination with polyenes and azoles against *Candida* spp. and *Aspergillus* spp., suggests that the therapeutic potential of terbinafine may extend well beyond its current use and that further investigations are warranted [411, 412].

The only fluoropyrimidine antimetabolite antifungal currently available is 5-fluorocytosine (5-FC, flucytosine), which exists in both oral and intravenous formulations [395]. 5-FC exerts its effect by being preferentially taken up within fungal cells, where it is converted to 5-fluorouracil (5-FU) [395, 407]. 5-FU has two fates: It is converted to 5-fluorouridine triphosphate (5-FUTP), which is subsequently incorporated into fungal RNA, leading to inhibition of protein synthesis. 5-FU is also converted to fluorodeoxyuridine monophosphate (5-F-dUMP), which inhibits thymidylate synthetase and interferes with DNA synthesis. Monotherapy with 5-FC is strongly discouraged because resistance occurs rapidly [398, 407]. Combination therapy with amphotericin B and flucytosine is considered to be the treatment of choice for cryptococcal infections [413]. One case report describes the use of this combination in the management of a child with repaired congenital heart disease who developed *C. albicans* endocarditis [414]. The authors suggest that this antifungal combination should be considered an option, although their patient also underwent surgical intervention, and so the clinical benefit of the combination therapy per se is unclear. 5-FC/azole combination therapy has also been proposed, as it appeared more efficacious in an animal model of invasive candidal disease, when compared to azole monotherapy, with significant decrease in tissue fungal burden and prolonged survival [415]. Case reports in humans have also reported on the efficacy of such combinations [416, 417]. Currently, there is no clinical data on the efficacy of this combination for fungal endocarditis.

The echinocandins are a novel class of semi-synthetic lipopeptides that inhibit the synthesis of β-(1,3)-D glucan, a polysaccharide in the cell wall of many pathogenic fungi that is responsible for the cell wall's strength and shape [395]. Consequently, these agents render the fungal cell wall osmotically unstable.

Caspofungin (Merck &Co., Inc.), the prototypical echinocandin, has broad-spectrum activity against *Candida* and *Aspergillus* spp. and is approved by the Food and Drug Administration (FDA) in the United States for treatment of aspergillosis in patients refractory to or intolerant of other therapies [418]. Caspofungin also has demonstrated potent in vitro and in vivo activity against *Candida* spp. and has approved indications for treatment of candidemia, intra-abdominal abscesses, peritonitis, pleural space infections, and esophageal candidiasis [418]. Cases in which Caspofungin has been successfully used as lone therapy for candidal native-valve endocarditis (i.e., without valvular replacement) have been reported [419–421], as well as with Micafungin [422]. The echinocandins, however, have poor CNS penetration in animal models [423, 424], and there is concern that it may be inadequate as therapy for fungal endocarditis that is complicated by unrecognized embolic foci of infection [425].

Candida spp.

Candida spp. is the most common cause of FE and is responsible for 33–44 % of all cases [357]. Approximately 50 % of FE cases are caused by *C. albicans* [357]. *Candida* endocarditis occurs in the setting of particular risk factors, including structural cardiac valvular abnormalities, use of broad-spectrum antibiotics, central lines, parenteral nutrition, and surgery [357, 426]. A previous review had reported intravenous drug abuse as a major risk factor for FE [427]. The epidemiology of risk factors, however, has since changed: In a review spanning 1995–2000, only 4 % of patients were reported as drug abusers [407]. Since then, data from the International Collaboration on Endocarditis and similar registries have demonstrated a further shift in epidemiology, with most candidal IE occurring in the context of prosthetic devices [356, 428, 429]. With the increasing use of the above risk factors as a reflection of medical progress, it is probable that the incidence of candidal FE will increase.

The management of candidal FE remains poorly defined. An inherent difficulty in establishing treatment guidelines is the low incidence of this disease, thus precluding any appropriately powered, randomized, controlled clinical trials.

Prior to the advent of newer antifungal therapies, AmB was the only agent available. As such, the dogma in management of FE was to remove the infected tissue, replace the valve, and provide 6–8 weeks of AmB therapy [430]. The importance of surgical intervention in the management of *Candida* endocarditis is exemplified by the differences in mortality rate without (~90 % [414]) and with (~45 % [427]) surgery. Surgical intervention should be performed as soon as possible, with removal of the valve and surrounding infected tissue. Current guidelines in North America recommend combined medical and surgical therapy, with medical therapy defined as AmB with or without flucytosine at maximal tolerated doses for a total duration of therapy of ≥6 weeks after surgery [394]. This recommendation is based on a non-statistically significant trend toward better outcome among patients who underwent surgery. It is also supported by a report that 160 days of AmB therapy did not sterilize a cardiac valve [431], emphasizing the need for surgical removal. This initial step of combined medical/surgical therapy, termed the “induction phase”, is the first

of a 2-phase management plan. The purpose is to provide rapid control of infection. After a clinical response to the initial "induction phase", "prophylactic therapy" should be instituted. While the recommendation for combined medical-surgical therapy of Candidal NVE has been the standard approach, data from the International Collaboration on Endocarditis may suggest that in individual cases, medical therapy alone *could* be as successful as combined therapy [428]. The authors did note the potential for bias in their study, in that the group who underwent surgery may have had increased morbidity or complications at presentation, accounting for the lack of survival benefit observed. Further, most of these patients had prosthetic material, which may preclude extrapolation to those with native valve involvement. Thus, clinical judgment is required to assess the relative risks for each patient."

The development of the azoles may now provide an alternative to AmB in the treatment of this condition. It has been shown that fluconazole is as effective as AmB for the treatment of candidemia (without endocarditis) [432]. Furthermore, in non-neutropenic, non-endocarditis patients, fluconazole in combination with AmB (0.7 mg/kg per day given only for the first 5–6 days) trended toward improved success and more-rapid clearance of candidemia (excluding *C. krusei*) from the bloodstream, although it was not statistically significant [433]. It has also been used during the "prophylactic" stage (see below). Animal models, however, have suggested that fluconazole may be an effective agent for primary therapy of *Candida* endocarditis, as it demonstrates superior ability to penetrate cardiac vegetations than AmB [396]. The clinical data regarding the use of fluconazole for treatment of *Candida* NVE, however, is limited to a few successfully-managed cases in the English literature [433–436]. Future studies are required.

Candida endocarditis has a propensity for relapse after valve replacement, and therefore requires careful follow-up for ≥1 year. This recommendation is based on small series of patients, in which typical follow-ups have ranged 6–12 months. However, relapse has been described in patients several years after treatment was discontinued [386, 437]. Thus, it has been suggested that "cure" be defined as the absence of infection for ≥2 years after withdrawal of antifungal treatment [434]. Therefore, "prophylactic therapy" is used after a clinical response to the "induction phase", to minimize the risk of relapse and to attempt a cure. The duration of this phase is poorly defined, but given the potential disastrous complication of recurrence, life-long suppressive therapy has been suggested [438]. In patients that are not deemed appropriate surgical candidates for valve replacement, or that refuse surgery, prophylactic therapy is used with the goal being life-long suppression [394, 426].

An alternative antimycotic is the echinocandin, caspofungin. The advantage of this agent is that it is fungicidal in vitro and in vivo against most isolates of *Candida* spp., including *C. krusei* and *C. glabrata* [394]. These two yeasts may demonstrate intrinsic (*C. krusei*) or acquired (*C. glabrata*) resistance to fluconazole, and they may also be less susceptible to AmB [394]. Furthermore, it has a benign toxicity profile and requires no modification of dose in patients with renal insufficiency. Case reports have described its successful use in the treatment of *Candida* endocarditis, both native [419, 439] and prosthetic [420] valves (see Chap. 11) However, it

may not be the agent of choice if cerebral septic emboli complicate the endocarditis, as it penetrates poorly across the CNS and may permit the development of candidal brain abscesses [425]. Further studies on its efficacy are required.

Aspergillus spp.

Aspergillus spp. are ubiquitous, filamentous fungi with hyaline, septated, branched hyphae. These molds have the capacity to cause several diseases in both healthy and immunocompromised hosts. *Aspergillus* spp. are the second most common fungal organism, after *Candida* spp., causing endocarditis in patients with previous valvular surgery [357]; this condition is discussed in the chapter on prosthetic valve endocarditis. *Aspergillus* spp., albeit much less commonly, can also cause endocarditis in patients without prior cardiac surgery. The two major manifestations of cardiac aspergillosis in the native heart are *Aspergillus* NVE and *Aspergillus* mural (non-valvular) endocarditis.

Aspergillus NVE is much less common than endocarditis involving prosthetic valves, with a review by Gumbo et al. [440] identifying 61 cases in the English literature. As with other forms of invasive aspergillosis, immunocompromised status (defined as presence of hematologic malignancy undergoing chemotherapy, administration of large or prolonged doses of corticosteroids, solid-organ transplant recipient receiving anti-lymphocyte therapy) was a major risk factor for *Aspergillus* NVE [440]. Advanced HIV, with marked CD4 T lymphocytopenia, also appears to be a risk factor [441].

The major clinical manifestations of *Aspergillus* NVE were fever (reported in 74 % of cases), systemic embolization (69 %), and a new regurgitant heart murmur (41 %) [427, 440]. Embolic phenomena frequently involved the central nervous system (brain, eyes), skin, and the aorta/large vessels [440, 442]. Involvement of the brain can manifest with focal or general neurologic deficits. Ocular involvement manifests as endophthalmitis with sudden visual loss; this complication has been reported in 13 % of cases [440]. As a corollary, it has been suggested that any patient with *Aspergillus* endophthalmitis should be evaluated for endocarditis, which has been associated in up to 40 % of cases [443]. Skin involvement typically presents as subdermal nodules [440] or necrotic lesions [444]; either can serve as a substrate for biopsy that may allow for earlier presumptive diagnosis [440, 442]. Vascular involvement can manifest as occlusive embolism, typically of large vessels (e.g. ilica, femoral, subclavian arteries) [440]. Alternatively, *Aspergillus* spp., as a result of their angioinvasive properties, can rapidly seed vascular walls and create focal areas of weakness that lead to aneurysmal disease. These aneurysms can occur in multiple vascular beds (e.g. ascending aorta, circle of Willis, peripheral) and can subsequently rupture [442]. Embolic disease to the kidney has been reported in 40 % of cases [440]. Local complications can also develop, including pancarditis and cardiac rupture [445].

The major species reported as causing *Aspergillus spp.* NVE include *A. fumigatus*, *A. flavus*, *A terreus*, and *A niger* [440, 442]. As with other forms of invasive aspergillosis, *A. fumigatus* was the most common cause of *Aspergillus spp.* NVE. This frequency may relate to the fact that *A. fumigatus* has smaller conidia

(2- to 3-μm), which allow for more efficient inhalation and bypass of the physical barriers of the respiratory system [441], from which they subsequently gain access to the bloodstream.

Aspergillus spp. NVE most commonly affects the mitral valve and typically produces large vegetations, with the average size being approximately 40 mm [440]. Despite these large persistent endovascular vegetations, blood cultures are usually negative due to the facts that fungemia is intermittent and that *Aspergillus* spp. almost never grow in conventional blood cultures media [440, 442]. The sensitivity of blood culture for isolating *Aspergillus* spp. is 10–30 % at most [430]. However, these large vegetations can usually be visualized by echocardiography, with transesophageal echocardiography (TEE) demonstrating higher sensitivity than transthoracic modality. Culture of embolic material, usually a cutaneous lesion, is a reliable means of establishing a rapid, presumptive diagnosis. Serologic diagnosis, by detecting host antibody response to the mold, has not proven an effective means of early diagnosis of infection with *Aspergillus* spp. [446]. One major reason is the fact that humoral immunity appears to play a minor role in providing host protection during invasive aspergillosis, although patients who recover from invasive aspergillosis develop detectable antibodies to *Aspergillus* spp. [447]. As well, the sensitivity and specificity of tests for detection of antibodies to *Aspergillus* spp. are low [447, 448].

Promising tests for earlier and more reliable detection of invasive aspergillosis, in general, include antigen detection tests and nucleic acid amplification. Galactomannan (GM) is a polysaccharide cell-wall component that is released by growing hyphae. The most recent test for detection of GM is an enzyme immunosorbent assay (EIA), which has been shown in multiple studies to be a useful diagnostic tool for IA in neutropenic patients with cancer. However, the reported sensitivity and specificity have been variable (57–100 %, and 66–100 %, respectively) [449]. β-D-glucan is a cell wall component of yeast and filamentous fungi. It has been found to be detectable in the blood in various invasive fungal infections, including those caused by *Candida* spp., *Aspergillus* spp., as well as *Fusarium* spp., *Trichosporon* spp., and *Saccharomyces* spp. [450]. The roles of these fungal antigen detection tests in early diagnosis of fungal endocarditis remain to be determined. In a limited study of native- and prosthetic-valve *Aspergillus* endocarditis, the GM and the β-D-glucan were positive in samples prior to the cardiac surgery that provided the confirmatory diagnosis, suggesting that these markers may assist in the diagnosis of *Aspergillus* spp. IE [451]. Interestingly, the GM declined with therapy, whereas the β-D-glucan did not, suggesting that GM may also be useful to guide therapy. Further studies are need. Of the nucleic acid-based tests, the use of polymerase chain reaction (PCR) for early but robust confirmation of *Aspergillus spp.* endocarditis is promising.

The optimum management in patients with *Aspergillus spp.* NVE remains undefined. Most authors recommend a combination of medical and surgical therapy [440]. For medical treatment, in addition to managing the general complications of endocarditis, administration of antifungal therapy is crucial. AmB has traditionally been the mainstay of treatment for *Aspergillus* spp. infection. However, the optimal

dosage, total dose, and length of therapy have not been established. As mentioned previously, the nephrotoxic effect is the most common reason to limit dose or terminate therapy [377]. AmB also penetrates poorly into cardiac vegetations [385]. Nonetheless, based on retrospective data of few patients who survived *Aspergillus* endocarditis, the recommended total dosage of AmB is 2.5–3.0 g (or 50 mg/kg) [452]. It is important to remember that despite these high doses with a seemingly effective antifungal agent, clinical success is not guaranteed. The liposomal AmB, with its renal-sparing properties, has been used successfully to treat cases of Aspergillus spp. endocarditis [453, 454]; in a few cases, surgery was not required [455, 456].

Because of the adverse events associated with AmB, other agents with activity against *A. fumigatus*. have been used. 5-FC alone had no effect on survival in an experimental rabbit model of *A. fumigatus* endocarditis, but when used in combination with AmB (deoxycholate), valve sterilization was achieved in 30 % of tested animals [457]. The combination has also proved effective in lowering mortality in neutropenic patients with pulmonary aspergillosis who did not receive a bone marrow transplant [458]. There is a paucity of data on this combination in Aspergillus endocarditis. Nonetheless, the adverse events profile of 5-FC necessitates regular monitoring of blood levels of the drug, as well as complete blood cell count and hepatic enzyme profile, to avoid the risk of toxicity.

Itraconazole, an azole with activity against *Aspergillus* spp., appears more efficacious than monotherapy with AmB in animal models [457]. However, its pharmacology (i.e. variable intestinal absorption, unpredictable drug interactions) has limited its use in primary treatment of *Aspergillus* endocarditis. It has been used successfully, however, as antifungal prophylaxis against recurrence once primary treatment was completed [454, 456].

Voriconazole, a broad-spectrum triazole antifungal, is an appropriate agent for therapy for invasive aspergillosis [459]. Superior outcomes were obtained for hematological patients with aspergillosis who were treated with voriconazole, compared with conventional amphotericin B, in a large randomized trial [460]. It is now licensed for treatment of documented aspergillosis and other less common mold infections [459]. Given the superiority of voriconazole over AmB in the above trial, voriconazole could be considered the drug of choice for *Aspergillus* endocarditis, although no study currently exists to support this suggestion. One case report describes the successful use of oral voriconazole (in conjunction with aggressive surgical debridement) to treat *Aspergillus spp.* prosthetic valve endocarditis with multiple embolic complications [461].

Caspofungin is an echinocandin with activity against *Aspergillus* spp. At this time, there have been no reports on the use of Caspofungin monotherapy for the management of *Aspergillus spp.* endocarditis.

The optimal duration of antifungal therapy in the acute management of *Aspergillus spp.* NVE remains undefined, although one study suggests that AmB deoxycholate at 1 mg/kg/day (or lipid-based equivalent) for ≥6 weeks is required [440]. This suggestion is based on the fact that embolic episodes with lesions that contain live *Aspergillus spp*. occurred in patients despite having received up to

6 weeks of AmB at 1 mg/kg/day. Furthermore, the mortality was high, despite a mean cumulative dose of 27 mg/kg of AmB. In certain cases, combination of AmB with 5-FC should be considered. The optimal duration of azoles in the management of acute disease is undefined, although this point may be moot as these are the agents most likely to be used for suppressive therapy (see below).

Surgery is an important adjunct to medical treatment and is recommended in all cases [357, 440, 446, 458]. Evidence supporting this suggestion derives from the dismal mortality rates among all patients with *Aspergillus spp.* endocarditis treated with medical therapy alone (100 %) versus the survival rates for those who undergo a combined medical/surgical approach (<20 %) [461]. However, one study found that surgical intervention with valve replacement did not improve mortality rates, when compared with rates for patients who underwent antifungal therapy alone [426]. This discordance may be related to the antifungal therapies available that constitute medical therapy. Radical debridement of necrotic tissue with valve replacement using biomaterials (bioprosthesis or homografts) with or without aortic root replacement is the recommended procedure [442]. Lavage of the endocardium with an AmB solution is not efficacious and is no longer considered standard technique [442].

Despite the use of medical and surgical interventions, recurrence rate can be as high as 40 % [442]. This high rate of relapse indicates the need for long-term antifungal maintenance therapy (sometimes referred to as "prophylaxis"), after treatment of the acute episode. Azoles have been used for this purpose, particularly itraconazole. Although voriconazole is not licenced for prophylaxis, a guinea pig model suggests that it is highly efficacious in the prevention and treatment of Aspergillus endocarditis and may be superior to itraconazole [462]. A minimum of 2 years of maintenance therapy is recommended using itraconazole, although given the potential disastrous complication of recurrence, life-long therapy may be advocated for some patients [463].

Aspergillus spp. mural endocarditis (ME) is a distinct clinical syndrome that differs from valvular endocarditis. Defined as growth or vegetations along the lining of the walls of the cardiac chambers with or without antecedent valvular lesions, it most commonly develops in patients with high levels of immunosuppression, particularly recipients of solid organ transplants [440, 445]. ME is highly characteristic of *Aspergillus* spp. and it has been demonstrated in one-third of patients with *Aspergillus spp.* endocarditis [445]. ME typically results from de novo seeding of an abnormal area of endocardium, or as a contiguous extension of infection from underlying myocardial abscess [463]. On autopsy, it appears as white-yellow-grey excrescences typically several millimeters in diameter [445]. This diagnosis is difficult to confirm, even by echocardiography, although TEE is likely more sensitive [440, 445, 464]. The major complication associated with *Aspergillus spp.* ME is embolic phenomena, typically producing micro-emboli leading to metastatic septic foci, rather than large occlusive emboli [445, 463]. Fistulous tracts and cardiac rupture may also occur. The optimal management of this condition is poorly defined, but likely a combined medical and surgical approach, as for *Aspergillus* NVE, may be appropriate [440, 465].

Endemic mycoses

The major endemic mycoses include histoplasmosis, coccidioidomycosis, blastomycosis, paracoccidioidomycosis, sporotrichosis, penicilliosis, chromoblastomycosis, lobomycosis, and mycetoma. These dimorphic fungi are found globally but each has a specific geographic niche. Most systemic infections with these pathogens occur after inhalation of conidia, while subcutaneous mycoses are caused by the inoculation with vegetable matter or soil. Of these organisms, *Histoplasma* spp. and *Coccidioides* spp. are the most common endemic mycoses associated with endocarditis.

The dimorphic fungus *Histoplasma capsulatum* causes histoplasmosis, which has a worldwide distribution but is especially more prevalent in certain parts of North and Central America. In the United States, it is endemic in the Ohio and Mississippi river valleys [466]. In Canada, endemic regions include Quebec, Nova Scotia, and eastern Ontario [467–469]. Bird and bat droppings enhance the growth of the organism in soil by accelerating sporulation [470]; these environmental factors also contribute to its geographic distribution. Infection occurs by means of inhalation of airborne mycelia, with conversion to yeast forms in the lung and subsequent hematogenous dissemination. Immunocompetent individuals with primary infection caused by low-level exposure are usually asymptomatic or experience minor respiratory illness, even though they have foci of microorganisms widely distributed throughout their bodies [470]. Symptomatic lesions at these sites of hematogenous spread define disseminated histoplasmosis. This latter condition is particularly more common among people with impaired cellular immunity, such as those with AIDS and those at the extremes of age [470].

In a systematic review of the English literature from 1965 to 1995, Ellis and colleagues identified 270 cases of FE, of which 15 (5.5 %) were due to *H. capsulatum* [357], thus making it the fourth most common cause of FE of that time period. Unfortunately, certainty of the diagnosis remains unclear since the authors were not able to report on how such a diagnosis was made in each case. The general diagnostic modalities identified in the meta-analysis included blood culture, culture of cardiac vegetation, and histopathologic examination of the cardiac valve. Of these, the latter two are accepted methods for definitive diagnosis of histoplasmosis, with culture of tissue specimens typically requiring 4–6 weeks for growth [470]. Blood cultures may be helpful, depending on the methodology used. The Isolator lysis-centrifugation method is considered the optimal method because it has consistently proven to be more effective for overall recovery and earlier detection of *H. capsulatum* from blood specimens, when compared to broth systems, including commercially-available radiometric ones [470, 471]. Adjunctive tests which may be generally helpful for diagnosis of the various *Histoplasma*-related syndromes include the following [470]: (1) Serologic tests, of which the complement fixation test using both yeast and mycelial antigens, as well as the immunodiffusion assay which identifies the H and M precipitin bands, are the standard tests to detect antibodies to *H. capsulatum*; (2) Fungal stains, such as silver stain of tissue sections (e.g. bone marrow) or Wright's stain of peripheral blood smears; and (3) Polysaccharide antigen detection in sterile body

fluids, such as the blood, urine, CSF, or bronchoalveolar lavage fluid. The high frequency of *H. capsulatum* FE from 1965 to 1995 was not subsequently seen in a retrospective systematic review of FE from 1995 to 2000 performed by Pierrotti and Baddour, in which a similar methodology identified only 2/150 (1.3 %) of cases [426].

A literature review, however, focusing specifically on the diagnosis of *Histoplasma* endocarditis identified a total of 43 cases in the English literature since 1943 [368]. In 42 of 43 cases in that series, the diagnosis was secured via histopathology and/or culture of valve material, along with adjunctive tests. Infection occurred on both native valves (36/43, 84 %) and on prosthetic valves (7/43, 16 %) and predominantly involved left-sided cardiac structures. More than 70 % of cases occurred in the setting of disseminated histoplasmosis. Although the respiratory route is the portal of entry for *H. capsulatum*, the authors' series demonstrated that active pulmonary histoplasmosis was generally not present at the time of endocarditis diagnosis.

The treatment of *Histoplasma* endocarditis remains poorly defined. Although traditional dogma for the management of FE dictates a combined medical-surgical approach, studies addressing this issue for *Histoplasma* endocarditis are inconclusive. In the meta-analysis by Ellis et al. [357], the survival rate was 63 % (5/8) for patients treated with antifungal agents alone, compared to 35 % (8/23) for patients treated with antifungal agents and surgery. Similarly, Bhatti et al. [368] demonstrated that of 10 patients who underwent combined modality treatment, 8 survived, which was comparable to the 8/11 patients who survived with medical therapy alone. However, Kanawaty and colleagues recommended combined modality treatment, based on 71 % survival rate (5/7 patients) for those receiving medical-surgical therapy compared to 44 % survival rate (4/9 patients) among those who received medical therapy alone [472]. A recent multi-center study noted that 2/14 patients who underwent combined medical-surgical therapy died, while 1/3 patients who underwent medical therapy alone died [473]. That study also demonstrated the utility of the *Histoplasma* spp. antigen test (from urine or serum) in the diagnosis of IENone of the results demonstrated statistical significance.

Of the antimycotic agents used in the management of *Histoplasma spp.* endocarditis, amphotericin B is the most commonly reported. The mean cumulative dose reported was 3.4 g (range: 1.3–7 g) [368]. The use of azoles is limited to case reports as adjunctive therapy to amphotericin B and is restricted to ketoconazole and itraconazole [368]. The role of newer generation imidazoles (e.g. voriconazole) or echinocandins (e.g. caspofungin) in the treatment of *H. capsulatum* FE, or in the prophylaxis of individuals at high-risk for reinfection, is unknown.

Coccidiomycosis is a fungal infection caused by *Coccidioides* species endemic to deserts of the southwestern United States, as well as to Central and South America. The *Cocccidioides* genus currently consists of two species: *C. immitis* and *C. posadasii*; the two species are morphologically identical but genetically and epidemiologically distinct [474]. *C. immitis* is geographically limited to California's San Joaquin valley region, whereas *C. posadasii* is found in the desert southwest of the United States, Mexico, and South America. The two species appear to co-exist

in the desert southwest and Mexico [474]. Clinical microbiology laboratories do not currently routinely distinguish these two species.

Endocarditis due to *C. immitis*/*posadasii* has been reported in six patients [475]. In all cases, no valvular destruction was identified, but all cases manifested with impaired valvular function and evidence of disseminated disease. Serologic tests using the complement fixation method revealed a wide range of titers (1:2 to 1:2048). Histopathologic examination of the involved cardiac valves demonstrated spherules, the predominant form of Coccidioides spp. in human tissue. In addition to valve involvement, *C. immitis*/*posadasii* has been reported to cause myocardial abscesses [475].

The optimal treatment of coccidioidal endocarditis is unknown. Of the six patients identified in the English literature, only two survived. Their treatment consisted of surgical excision and amphotericin B (one with deoxycholate, one with liposomal complex) for an unspecified period of time, followed by suppressive azole therapy (one with itraconazole, one with fluconazole, censored follow-up).

Non-valvular Cardiovascular Infections

Although non-valvular cardiovascular infections are much less common than valvular endocarditis, they nonetheless have the potential to be fatal. Certain cardiovascular infections, such as infected pacemakers and implantable defibrillators, as well as prosthetic graft infections, are discussed in other chapters. This chapter will focus on myocardial abscesses, mural endocarditis, and mycotic aneurysms. Table 9.6 summarises the antimicrobial treatment strategies for non-valvular endocarditis caused by *Staphylococcus spp*.

Myocardial abscesses are rare but can develop by several mechanisms. The classification system by Chakrabarti [476] is summarized in Table 9.7, and divides myocardial abscesses into the following categories: (A) Endocarditis-related; (B) Septicemia-related; or (C) Miscellaneous (see Table 9.7). The most commonly identified cause of myocardial abscess (MA) is endocarditis-related, resulting from contiguous extension of valvular or mural endocarditis [476]. Hematogenous seeding during bacteremia or fungemia is also relatively common [476]. In this latter case, several areas of myocardium are often involved [477], and abscesses in multiple organs, typically the brain, lungs, and kidneys, also occur [476]. Miscellaneous causes of myocardial abscesses include trauma and penetrating injuries, iatrogenic (e.g. catheterization, angioplasty), and anatomic abnormalities (e.g. aneurysm infection, infection of infarcted myocardium, infection of myxoma) [476]. *S. aureus* is the most frequently reported bacterial isolate in patients with MAs; other causes include streptococci, *C. perfringens*, *Bacteroides* spp., *E. coli*, *Candida* spp., and *Aspergillus* spp. [476, 477]. Fungal MAs are more common in immunocompromised patients. Paravalvular MAs are usually recognized in the context of endocarditis that is failing to improve or clinically deteriorating. Non-paravalvular MAs are usually subtle, with most previous cases diagnosed at autopsy. The major complication of MAs is rupture. In MAs that develop in an area of recent myocardial

infarction, the risk of rupture is increased sevenfold [478]. Rupture can result in tamponade, hemopericardium, and/or purulent pericarditis. Other complications include fistulae, cardiac arrhythmias, or septic shock. Although conduction disturbances detected by serial electrocardiograms in a patient with suspected or proven endocarditis is highly suggestive of a paravalvular MA, the diagnostic modality of choice for all MAs is TEE [476]. The management of non-paravalvular MAs is poorly defined. No comparative studies have been reported in the English literature that compare differences in outcome between patients treated with medical therapy alone versus those treated with combined (medical/surgical) therapy. The management of peri-annular MA is more clearly defined. Identification of an abscess as an extension of valvular endocarditis is an indication for surgery [1, 479], in conjunction with adequate antimicrobial coverage. Furthermore, early surgery is advocated, with the goal of achieving more rapid control of the infective process, to improve the chances of survival and to prevent the development of further perivalvular destruction [480]. Surgical intervention usually requires drainage of abscess, debridement of necrotic tissue, closure of any fistulous tracts that have developed, as well as valve replacement (for paravalvular MAs) [1, 36]. There is some limited evidence that in select patients, paravalvular MAs may be treated successfully with medical therapy alone [36]. Recommended criteria for this form of management include those who have small (<1 cm) abscess as well as those who do not have evidence of abscess-related complications (e.g. heart block, progression of abscess during therapy, valvular dehiscence, or valvular insufficiency) [36]. In these patients, the potential for complications does however continue to exist, and so it is recommended that such patients be monitored closely with serial TEEs (i.e. at 2, 4, and 8 weeks after completion of antimicrobial therapy) [36]. The duration of antimicrobial therapy after surgical intervention remains poorly defined. One review suggests the following approach [481]: Patients undergoing surgical intervention for NVE should be treated for a minimum of 4–6 weeks with appropriate intravenous antibiotics; the full duration of antibiotic therapy after valve replacement or repair is based on the intraoperative culture results. If the intraoperative cultures were negative and the patient preoperatively had already received a complete course of medical therapy, treatment with intravenous antibiotics for seven more days is sufficient. If the intraoperative cultures are negative but the patient had not received a full course of preoperative therapy, antibiotics are continued for a total of 4–6 weeks (including both the preoperative and postoperative period). If the intraoperative cultures were positive, the antibiotics should be continued for an additional four to six postoperative weeks. This latter recommendation is a conservative estimate, although a retrospective single-center review of 358 patients concluded that it was unnecessary to continue treatment for patients with negative valve culture results for an arbitrary 4–6-week period after surgery [482]. The authors concluded that 2 weeks of treatment appears to be sufficient to prevent relapse, and, for those operated on near the end of the standard period of treatment, simply completing the planned course should suffice [482].

Mural endocarditis typically results from seeding of an abnormal area of endocardium during bacteremia or fungia; alternatively, it may develop as an extension

Table 9.7 Classification of myocardial abscess*

1.	Endocarditis-related	1. Contiguous from
		(a) Valvular IE (perivalvular abscess)
		(b) Mural IE
		2. Hematogenous seeding of myocardium
2.	Septicemia-related	Hematogenous seeding of myocardium, usually in association with abscesses elsewhere
3.	Miscellaneous	1. Trauma and penetrating injuries
		2. Iatrogenic (e.g., catheterization, angioplasty)
		3. Anatomic abnormalities (e.g., aneurysm infection, infection of infarcted myocardium, infection of myxoma)

*Adapted from reference [476]

of infection from underlying myocardial abscesses [477]. The organisms associated with mural endocarditis include *Staphylococcus* spp., viridans streptococci, *Enterococcus* spp., *Salmonella* spp., *Klebsiella* spp., *Bacteroides fragilis* group, *Candida* spp., and *Aspergillus* spp. [477]. Mural endocarditis most commonly presents with non-specific constitutional symptoms, i.e. fever and chills. The diagnosis of mural endocarditis may be difficult. Blood cultures may be positive, although the data reflecting the sensitivity of this procedure on diagnosis is unknown. Echocardiography is likely the most useful diagnostic modality, with TEE probably superior to TTE [464, 483–486]. Nonetheless, echocardiography may be negative in some cases. The complication most frequently associated with mural endocarditis is peripheral embolization, although cardiac rupture and the development of fistulae have been reported [477]. Although no studies exist to guide optimal therapy of this condition, it is likely that a combined approach is necessary, with early surgical intervention warranted to prevent the development of complications [477, 483].

A mycotic vascular aneurysm is a localized dilation of the blood vessel wall that is infected. Infection of a vascular wall can occur as a complication of bacteremia by one of two mechanisms: Firstly, bacteria circulating in the intraluminal space can seed an atherosclerotic lesions, with subsequent local invasion, and formation of a true aneurysm. Alternatively, circulating bacteria can invade the vasa vasorum (the blood vessels ramifying on the outside of a major artery), leading to necrosis of the tunica intima, with subsequent pseudoaneurysm formation. Arterial bifurcation points are the most common sites of mycotic aneurysm formation [36], due to turbulence of blood flow that creates a temporary ebb, which permits circulating bacteria to adhere to the vascular wall. Mycotic aneurysms can be anatomically divided into two categories: Intracranial mycotic aneurysms (IMAs), which is the most frequent mycotic aneurismal complication of endocarditis [36], and extracranial mycotic aneurysms (EMAs), which include mycotic aneurysms of the aorta, of the visceral arteries, and the arteries of the extremities.

IMAs are an infrequent but potentially fatal complication of endocarditis. The overall mortality rate is approximately 60 %, although this rate is dependent on the status of the aneurysm: for unruptured IMAs, the mortality rate is 30 %,

whereas the rate increases to ~80 % once rupture has occurred [36, 487]. IMAs occur more frequently in the anterior circulation, especially the distal middle cerebral artery and its branches, and may be multiple [487, 488]. The clinical presentation of patients with IMAs is non-specific, with the majority being asymptomatic until rupture occurs. The most common manifestations include fever and chills, headache, lethargy/altered level of consciousness; focal neurologic deficits (e.g. aphasia, hemiparesis) can also occur [36, 487]. The variable presentation is likely a reflection of the location and progression of the aneurysm, and whether there is any mass effect.

The diagnosis of an IMA should be suspected in a patient with known endocarditis who develops neurological signs and symptoms, at which point rupture with either subarachnoid hemorrhage, intraventricular hemorrhage, or direct intracerebral destruction of the brain has probably occurred. Of note, the development of IMAs can be quite rapid. In an animal model, it has been demonstrated that the time interval from septic embolism to aneurismal dilatation can be as short as 24 h [487]. The propensity of IMAs to bleed is the principal reason why anticoagulation should be avoided, if possible, in the management of patients with NVE. The differential diagnosis of new neurological deficit in such a patient should also include embolic infarction and, less commonly, bacterial meningitis. Cerebrovascular imaging is thus required. Computed tomodensitometry (CT) of the cerebrovascular system, without contrast, is useful as an initial diagnostic modality, with sensitivity of 90–95 % for detecting an intracerebral hemorrhage (ICH) [36]; it may also be able to identify the location of the IMA. In the absence of an ICH, angiography should be performed (either magnetic resonance angiography (MRA) or CT angiography (CTA)) to detect IMAs. Both of these modalities have excellent sensitivities and specifities (90–95 % each) [36]. Both techniques may be false-negative, however, for aneurysms <5 mm in diameter, in which case, conventional cerebral angiography may be used [36]. Examination of the cerebrospinal fluid (CSF) does not aid in diagnosing the presence of an IMA or in consistently identifying the etiologic pathogen [487].

The diagnosis of IMAs in a patient without known endocarditis may be more difficult. Clues suggestive of an infectious etiology when an incranial aneurysm is identified include a fusiform appearance or an atypical location [489]. In these situations, an IMA should be suspected and investigations for endocarditis should be pursued.

The management of IMAs primarily involves a prolonged course of appropriate antibiotics that achieve therapeutic levels in the central nervous system. The surgical management of IMAs remains controversial: its presence is not an unequivocal indication for surgical intervention. Resolution of IMAs with antimicrobial therapy alone is well documented. On the other hand, rupture of an IMA is associated with significant morbidity and unacceptable mortality. Unfortunately, no clinical data exist that have reliably identified patients at risk for rupture, in whom prophylactic surgery would be of greatest benefit. As such, the role of surgery in the management of IMAs must be individualized, based on the patient and aneurysm characteristics. One algorithm suggested, based on the authors' experiences at the Mayo Clinic, is as follows [487]: Patients with unruptured IMAs should be observed during

antibiotic therapy, with a serial angiograms (MRA or CTA) at 4–6 weeks. If the IMA enlarges, surgical resection should be considered. If the IMA regresses, surgery can be deferred. If the IMA persists after an adequate course of antimicrobial therapy, surgical intervention could be considered if the residual aneurysm is large, if the patient wishes it, and if the patient's general condition permits. Of note, new IMAs can form after the initial ones have regressed, underscoring the need for regular follow-up of these patients until all of the aneurysms have regressed, or until ≥2 serial angiograms have demonstrated stability in size.

For IMAs that are peripherally located that have ruptured, surgical resection should be performed, provided that the patient's condition can allow for surgical anesthesia. For IMAs that are proximately located, a more conservative approach may be considered, because clipping of these aneurysms in the acute stage may be difficult. In these situations, a trial of antibiotic therapy can be pursued. This will allow fibrosis of the vascular wall, which may make subsequent clipping feasible. If the patient has multiple aneurysms, then the ruptured one should be resected, along with other accessible peripheral aneurysms. The remaining ones are treated with antimicrobial therapy, with serial angiographic imaging; if there is evidence of enlargement, resection should be considered.

The role of endovascular occlusion of IMAs has been described in case series, although the limited power and follow-up of the patients prevents any robust conclusion about the efficacy of this modality [487].

Extracranial mycotic aneurysms (EMAs) can involve the aorta, the visceral arteries, or the arteries of the extremities. Infected aneurysm or pseudo-aneurysm of the aorta is a rate but life-threatening condition. The overall hospital mortality ranges from 5 % to 40 %, although the anatomic location of the EMA, the infecting pathogen, and accompanying comorbidities are important factors affecting prognosis. In a single-center retrospective study of 17 patients over 20 years, the operative mortality for supra-renal EMAs was 43 %, while that for infra-renal EMAs was 10 % [490].

The most common organisms involved in EMAs are *S. aureus* and *Salmonella* spp. [339, 491, 492]. The latter is discussed in the section on *Salmonella spp.* NVE. Other common pathogens include *Streptococcus* spp. (*S. pneumoniae* [493], viridans streptococci [494], β-hemolytic streptococci [495], Gram-negative rods (e.g. *E. coli* [496]), and anaerobes (e.g. *B. fragilis* group, *Peptostreptococcus* spp., and *P. acnes*) [492].

The standard management of EMAs involves a combined approach. Medical therapy (i.e. adequate antimicrobial coverage of long-term duration) is required, but in itself is not sufficient because of the difficulty of antibiotics to penetrate into aneurysms [497]. Therefore, debridement/resection of the infected aorta and the surrounding infected tissue, followed by revascularization (either in situ or extra-anatomic grafting) is also required [498]. Traditionally, aortic ligation with extra-anatomic bypass was the standard treatment for mycotic aortic aneurysms [498]. However, extra-anatomic bypass may not be practical or feasible if visceral arterial involvement is present; for example, in mycotic aneurysms of the suprarenal aorta, no remote or extraanatomic routes may be available to maintain perfusion to the

viscera. As well, in the presence of bacteremia, even a remote graft may be at risk for hematogenous seeding. Furthermore, long-term patency may be compromised. An alternative procedure is in situ reconstruction of the infected aorta with a prosthetic graft. Placement of a foreign body into an infected surgical field seems counter-intuitive, as it has potential for developing early- and late-graft infection. Indeed, such a complication has been previously reported, necessitating a high rate of reoperation [499–501]. However, reports of the safety, durability, and efficacy of in situ reconstruction in the presence of a mycotic aortic aneurysm have also been described [502, 503]. To further decrease the risk of in situ graft infection, various modifications (e.g. omental wrapping [501], antimicrobial-coated graft [504, 505], cryopreserved allograft [506, 507]) have been used. Although there are no guidelines regarding the proper indication for in situ reconstruction, the presence of gross purulent infection at the aortic site is likely a contra-indication to this procedure.

The optimal duration of antibiotic treatment for aortic EMAs is not well defined. Recommendations have varied from ≥4 to 6 weeks to life-long therapy [498], the latter being especially recommended in the presence of an in situ prosthetic graft.

Endovascular repair is an emerging field in vascular surgery. Although most experience is in the repair of sterile aneurysms, cases of successful treatment of infected aneurysms have been reported [503, 508]. In the absence of more robust evidence, it has been suggested that this modality may be currently best suited as a temporalizing measure to rapidly stop the bleeding of a ruptured aortic EMA, followed by definitive surgery [498].

The Role of Surgery

Despite medical progress in the diagnosis and antimicrobial therapy of IE, more than half of patients with IE suffer a serious complication, and the mortality rate is unacceptably high: ~20 % during the initial hospitalization and ~40 % at 1 year [509]. The major causes of death are structural complications and hemodynamic instability. As such, cardiac surgery, principally valve replacement, has become an important adjunct to medical therapy. Cardiac surgery is currently used in 25–50 % of cases, and several studies suggest that combined medical and surgical therapy can reduce both early- and late-mortality in patients with a complicated course.

Several indications for surgery in patients with IE have been proposed by Olaisson and Peterson [1], as well as the AHA, with varying strengths of evidence. The former are provided in Table 9.8. Consensus indications for surgery during IE include the following: acute anatomical cardiac destruction; congestive heart failure (CHF); hemodynamically-significant valvular dysfunction; perivalvular extension of infection (abscess or fistula); persistent (uncontrolled) infection; and lack of effective antimicrobial therapy available (or alternatively, difficult-to-treat pathogens). Surgery is also indicated for the majority of cases of prosthetic valve endocarditis (discussed in Chap. 11) and for the management of mycotic aneurysms (see above). There is a lack of consensus on the indications of surgery in the management of embolic complications.

CHF, regardless of the pathogenesis, is the strongest predictor of mortality in patients with IE. As such, it is the strongest indication for surgery [1]. Among patients with NVE who develop moderate-to-severe (New York Heart Association III or IV) CHF and are treated with medical therapy alone, the mortality rate is 56–86 %; among patients treated with combination medical and surgical therapy, the mortality rate is 11–35 % [1]. Therefore, CHF is a bad prognostic factor. Furthermore, patients with IE who undergo cardiac surgery have higher perioperative mortality rates if they do so in CHF (15–35 %), when compared to patients without CHF (5–10 %) [479]. As such, early cardiac surgery, ideally at the onset of CHF and before the onset of physiologic compromise, should be performed. Of note, the beneficial effect of surgery persists even in the presence of co-morbidities; as such, the development of other complications (e.g. acute renal failure) is not a contraindication to proceed to surgery [511].

Anatomical destruction, such as acute valvular destruction with insufficiency, rupture of the chordae tendinae or papillary muscles, will usually manifest as CHF, necessitating cardiac surgical intervention. Other sequelae of acute destruction include rupture into the pericardium and septal perforation; these may manifest with acute hemodynamic compromise. In these situations, emergent surgery is indicated.

Physiologically-significant valve dysfunction can manifest as insufficiency, producing a syndrome of CHF, or with valvular obstruction. The latter may occur, for example, as a result of large vegetations or thrombi superimposed on a stenosed native or on a prosthetic valve. Such obstruction can compromise cardiac output; hence the need for urgent surgery.

Perivalvular extension of infection can develop as paravalvular myocardial abscess or as an intracardiac fistula. The former has been previously discussed. Intra-cardiac fistulous tracts usually develop from either aortic root abscesses or pseudoaneurysms that rupture into adjacent chambers. These fistulae may be single or multiple and generally extend from the aorta to the right atrium, right ventricle, or the left atrium [480]. As well, aortic insufficiency from IE may produce a septic regurgitant jet that strikes subaortic structures, creating secondary sites of infection. Abscesses form at such sites in the left ventricular outflow tract, especially in the mitral-aortic intervalvular fibrosa or junctional tissue between the anterior mitral leaflet and the aortic valve. This leads to pseudoaneurysm formation and rupture into the left atrium, creating a left ventricular-left atrial shunt [512]. The diagnostic modality for detection of these fistulous tracts is TEE [512].

Persistent bacteremia has been defined as bacteremia with an organism identical to the initial isolate, despite ≥7 days of antimicrobial therapy to which the isolate was susceptible [1, 513, 514]. However, positive blood cultures after 1–4 days of antibiotic therapy have been predictive of complicated bacteremias [515–517]. In the absence of an extracardiac source (e.g. metastatic septic foci), persistent bacteremia indicates a failure of antimicrobial therapy and the most likely source would be intracardiac. As such, diagnostic imaging (e.g. TEE) should be pursued. Persistent fever is not synonymous with persistent bacteremia. In acute uncomplicated infective endocarditis, defervescence occurs within 1 week of effective antimicrobial therapy in 75 % of patients and by 2 weeks in 90 % of patients [518]. The presence of fever during

Table 9.8 Indications for cardiac surgery in infective endocarditis

Indications for surgery	Timing[1] • Emergency: same day • Urgent: within 1–2 days • Elective surgery: after at least 1 or 2 weeks of antibiotic treatment.	Class of evidence[a]	Level of evidence[b]
Heart failure			
Aortic/mitral IE with severe AR or valve obstruction causing refractory pulmonary edema or cardiogenic shock	Emergency	I	B
Aortic/mitral IE with fistula into a cardiac chamber causing refractory pulmonary edema or cardiogenic shock	Emergency	I	B
Aortic/mitral IE with fistula/rupture into pericardium causing refractory pulmonary edema or cardiogenic shock	Emergency	I	B
Aortic/mitral IE with severe AR or valve obstruction and persisting heart failure or echocardiographic sings of poor hemodynamic tolerance (early mitral closure or pulmonary hypertension)	Urgent	I	B
Aortic/mitral IE with severe AR but no heart failure	Elective	IIa	B
Right heart failure secondary to severe tricuspid regurgitation with poor response to diuretic therapy	Urgent/elective	IIa	C
Uncontrolled infection			
Locally uncontrolled infection (e.g. abscess; false aneurysm; enlarging vegetation)	Urgent	I	B
Persisting fever and positive blood cultures for >7–10 days after commencing appropriate antimicrobial therapy and not related to an extra-cardiac cause	Urgent	I	B
Infection caused by fungi or multi-resistant organisms	Urgent/elective	I	B
Prevention of embolism			
Aortic/mitral IE with large vegetation (>10 mm) resulting in one or more embolic episodes despite appropriate antibiotic therapy	Urgent	I	B
Aortic/mitral IE with large vegetation (>10 mm) and other predictors of complicated course (e.g. heart failure, persistent infection, abscess)	Urgent	I	C

(continued)

Table 9.8 (continued)

Indications for surgery	Timing[1] • Emergency: same day • Urgent: within 1–2 days • Elective surgery: after at least 1 or 2 weeks of antibiotic treatment.	Class of evidence[a]	Level of evidence[b]
Isolated very large vegetation (>15 mm)	Urgent	IIb	C
Persistent tricuspid valve vegetations >20 mm after recurrent pulmonary emboli	Urgent/elective	IIa	C

Adapted from references [37, 510]

[a]Class of evidence: class I: evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective; class II: conflicting evidence and/or divergence of opinion about the usefulness/efficacy of the given treatment or procedure; class IIa: weight of evidence/opinion is in favour of usefulness/efficacy; class IIb: usefulness/efficacy is less well established by evidence/opinion; class III: evidence of general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful

[b]Level of evidence: level of evidence A: data derived from multiple randomised clinical trials or meta-analyses; level of evidence B: data derived from a single randomised clinical trial or large non-randomised studies; level of evidence C: consensus of opinion of the experts or small studies, retrospective studies, registries

[1]Timing: Emergency: same day; Urgent: within 1–2 days; Elective surgery: after at least 1 or 2 weeks of antibiotic treatment

therapy should be categorized as "persistent" if there has been no defervescence after 1–7 days, or as "recurrent" if there was an initial period of decreased temperature [26, 517]. Persistent fever after the first week of hospitalization suggests a septic embolic focus (e.g. visceral abscess) or an intracardiac complication, either of which may or may not be the result of inadequate antibiotic therapy [517]. Recurrence of fever suggests a focal septic complication, noninfectious embolic phenomenon (e.g. visceral infarct), a drug-hypersensitivity reaction (drug fever), or, least commonly, the emergence of a resistant strain [517]. In a single-center, prospective study of 193 patients with IE, 57 % of patients had "persistent" or "recurrent" fever. Of the patients with "persistent" fever, 56 % were due to cardiac complications. "Recurrent' fever was most often caused by hypersensitivity reactions to β-lactams [26].

The presence of difficult-to-treat pathogens is an indication for surgical intervention [1]. Frequently cited examples include *Pseudomonas aeruginosa*, fungi (e.g. *Candida* spp., *Aspergillus* spp.), *Coxiella burnetti*, and *Brucella* spp., organisms for which antimicrobial therapy exists, but when used alone, unlikely to lead to eradication. It is becoming clear, however, that even for pathogens with "adequate" antimicrobial agents available, surgical intervention combined with medical therapy may be the superior treatment of choice. Examples of such situations include NVE with *S. aureus*, certain coagulase-negative staphylococci, and β-hemolytic streptococci (see previous sections). This decision is particularly true in the presence of any of the above complications.

The role of surgery in preventing CNS complications remains ill-defined. Neurological complications occur in 20–40 % of patients with IE [36, 519], and can manifest as brain infarction, mycotic aneurysms with/without intracerebral hemorrhage, bacterial meningitis, or toxic encephalopathy. The purpose of surgery would be to prevent septic embolic phenomena. Emboli, however, can occur before diagnosis, during therapy, or after treatment is completed. Identification of predictive factors to estimate an individual patient's risk of embolization has been difficult. Previous attempts to use echocardiography to identify high-risk vegetation characteristics, and thus to identify a sub-group of patients who may benefit from prophylactic surgery, have produced conflicting results. More recent studies have demonstrated that the large majority of embolic complications occur before the diagnosis and institution of antimicrobial therapy [228, 229]. Even with antibiotic treatment, the risk of embolization remains elevated for the first 2 weeks [520]: in one study [176], 65 % of embolisms occurred during this period. The risk decreases to 15 % after 1 week of treatment, and then to 1 % after 4 weeks of treatment [479]. Thus, the preventative effect of surgery would be maximal in the first few days of treatment. However, this potential benefit is tempered by the fact that early cardiac surgery would expose a number of patients, who would not have otherwise developed this complication, to the risks inherent with surgery. As well, these patients would be exposed to the risks associated with prosthetic valves (i.e. lifelong anticoagulation for metallic prosthetic valves, re-do surgery for bioprosthetic devices, risk of prosthetic valve endocarditis). As such, the traditional indication for valvular surgery for IE to avoid embolization has been the development of ≥2 major embolic events, although this recommendation is arbitrary [36]. Objective risk factors that may aid in decision-making include the size of the vegetation at baseline, the progression of the vegetation size on therapy, and the infecting microorganism.

Vegetation size intuitively should correlate with risk of embolization. Larger, pedunculated vegetations are potentially more friable at the surface or the neck; when such pieces are disrupted, it results in emboli. Although early data correlating vegetation size to risk of embolization were inconsistent, several subsequent large studies [110, 176, 521, 522] and a meta-analysis [176] have shown that vegetation size (specifically >10 mm) is a strong predictor of thrombo-embolic events. There is some concern, though, that this "threshold" size not be dogmatic in determining the need for surgery. Vegetation size alone does not precisely identify all high-risk patients: not all patients with large vegetations invariably develop embolic complications, and conversely, some patients with relatively small vegetations do. Therefore, other factors clearly must be contributing to the likelihood of embolization. In addition to vegetation size, valvular location has been reported to be important in some studies [176]. As well, the infecting microorganism may play a role, but the data is not adequately powered [176, 520]. In addition to vegetation size, vegetation echogenicity theoretically may contribute to predicting a patient's risk for embolizaton. Low density vegetations are fresh, and thus friable, and would have a greater capacity to embolize than a high-density vegetation, which is more typical of a chronic and healed vegetative mass [176]. Several studies [176, 523], however, demonstrated that there was no relationship between vegetation echogenicity and the risk of embolization.

Change in vegetation size is a useful sign. One study suggests that a decrease in vegetation size on antimicrobial therapy is indictive of a rapid healing process [524]. In practical terms, however, most vegetations remain constant in size, despite appropriate antimicrobial therapy; this occurred in ~84 % of vegetations in one study [176]. Failure of the vegetation to regress, however, was not associated with a worse prognosis. Growth of vegetation on antimicrobial therapy is ominous. Several studies [176, 524] have demonstrated that this feature is associated with poor control of the infection and a higher incidence of embolization.

In conclusion, future studies are required to better delineate the risk factors that most accurately predict embolization and whether prophylactic cardiac surgery in such patients is beneficial.

For the patient with IE who has already developed neurological deficit(s), cardiac surgery may still be indicated if the risk of recurrent embolism is high or if there are concomitant complications. Management thus is determined by the nature of the neurologic lesion, as well as the nature of these other complications. Although the most common CNS complication is embolic disease without hemorrhage [525], a CT scan of the head should be the first step to determine the presence of intracranial hemorrhage [36, 519, 525].

In the absence of any hemorrhage, only small studies exist to guide management. Maruyama and colleagues report the development of severe neurologic deterioration in 29 % (4/14 patients) who underwent valve replacement within 5 days of an acute, non-hemorrhagic, cardiogenic embolism [526]. Matsushita et al. also reported fatal neurologic deterioration in two patients who underwent emergency cardiac surgery within 5 days of their stroke [527]. They also noted better outcomes among patients with ischemic events if they were medically treated for 11 days prior to surgery and for 23 days prior to surgery if they had hemorrhagic strokes. Other groups have demonstrated similar results [519, 525]. Thus, it has been recommended that, when possible, cardiac operation be delayed 2–4 weeks for patients who have non-hemorrhagic, cardiogenic emboli [36, 519, 525, 528].

If hemorrhage is identified on CT, the most likely cause is ruptured mycotic aneurysm. As such, angiogram (e.g. MRA, CTA, or conventional) should be performed. Neurosurgical consultation should be obtained to assist in management. Cardiogenic embolism with hemorrhage is associated with an increased risk for perioperative stroke in cardiac surgery [529]. Therefore, surgical management of the aneurysm (e.g. clipping) may be necessary. In patients who undergo aneurysm clipping, subsequent valve replacement should be delayed for 2–3 weeks, if the patient is stable [525]. Cardiac operations should be performed only when there is stabilization of the neurologic status clinically, and CT imaging demonstrates resolution of cerebral edema with no ongoing bleeding. If surgical intervention for the aneurysm is not deemed necessary, and the patient is stable, an interval of 4 weeks between the neurologic event and cardiac surgery is recommended [519, 525].

For patients with intracerebral hemorrhage and progressive cardiac failure, the prognosis is extremely poor. In this situation, the benefit from cardiac surgery may outweigh the risk of cerebral deterioration associated with the surgery.

Splenic involvement in IE can be divided into two complications: splenic infarct and splenic abscess. These two conditions are not mutually exclusive, but represent a pathophysiological spectrum. Splenic infarct in IE occurs as a result of arterial compromise, due to embolization of portions of sterile fibrinous vegetations embolizing into the terminal arteries of the spleen. Splenic abscess is a suppurative collection which can develop in patients with IE either as a result of septic emboli or infection of prior infarct. The incidence of splenic complications of IE is unclear, largely because septic infarcts typically have no symptoms or localized findings, and thus may go unrecognized, whereas the incidence rates for splenic abscesses have been based on retrospective studies, and is thus influenced by recall bias. With these limitations, the incidence rate of splenic complications in IE has been estimated at 35–40 % [36, 530]. Clinically recognized splenic abscess occurred in 2–5 % of IE cases [530, 531]. Among cases of splenic abscess from all causes, 10–20 % are due to endocarditis [532]. One study has demonstrated that the risk of splenic embolization in IE is equivalent for aortic and for mitral vegetations [533].

Splenic infarcts are most often asymptomatic [533], although in patients at high risk for venous thromboembolism, such as IE, the most common presenting symptom is left upper quadrant abdominal pain [534]. The diagnosis can be easily obtained by abdominal ultrasonography (U/S) or CT. CT demonstrates superior sensitivity when compared to U/S (~96 % vs 75–90 %, respectively) [532]. On CT, splenic infarcts typically appear as multiple, peripheral-based, wedge-shaped hypodense lesions without significant contrast enhancement [533, 535]. They may vary in size, but they rarely involve the entire organ. CT also has the capacity to identify lesions as small as several millimeters [532]. The clinical significance of splenic infarcts is that these lesions are at risk for intra-abdominal hemorrhage during valvular surgery for the IE, as a result of anticoagulation during cardiopulmonary bypass [533]. Furthermore, splenic infarcts may predispose to splenic rupture. Other complications include pseudocyst formation, as well as superinfection with subsequent development of splenic abscess [536]. In the absence of any complications, an isolated splenic infarction can be managed safely with medical treatment [533, 536].

Splenic abscesses, on the other hand, are usually symptomatic, with evidence of sepsis being most prominent [533]. The classic triad consists of fever, leukocytosis, and left upper quadrant abdominal pain [532, 537]. Fever is by far the most common symptom, occurring in >90 % of cases [532, 537]. Thus, patients with endocarditis, abdominal complaints, signs of sepsis (e.g. recurrent or persistent fever), or recurrent or persistent bacteremia should be evaluated for any potential foci for relapse, particularly the spleen. CT is very useful for identification of a splenic abscess, which typically appears as a solitary, round-to-irregular shape, centrally-located, hypodense lesion that is contrast enhancing [533]. Air within the cavity is pathognomonic of abscess [533]. There is, however, considerable overlap between the CT patterns of splenic infarcts and abscesses. In addition to the morbidity to the patient, the major clinical significance for a splenic abscess is that it may serve as a source of subsequent bacteremia and seeding of a prosthetic valve inserted for management of IE. The other major complications of splenic abscesses include rupture into the

peritoneal cavity, which is the most common, as well as rupture into contiguous spaces, producing visceral abscesses, peritonitis, or empyema [537].

The management of a splenic abscess requires a combined medical and surgical approach. Splenic abscesses respond poorly to antibiotic therapy alone. Although antibiotics are effective in clearing the bacteremia of IE, they do not penetrate well into splenic abscesses; consequently, organisms in the abscess are not eradicated and can still be cultured. Previous studies have demonstrated 100 % mortality rates for patients undergoing medical therapy alone. Robinson and colleagues [531] identified 27 patients who developed splenic abscesses among 564 patients with IE between 1970 and 1990. Of these, there were 13 deaths: 10/13 (77 %) of the patients who did not undergo splenectomy died, compared to 3/17 (18 %) of the patients who underwent splenectomy. A literature review by Johnson et al. [538] demonstrated that the survival rate for 17 patients with splenic abscess who did not undergo splenectomy was 0 %, compared to 95 % who did. In situations in which antimicrobial therapy alone appears successful initially, recurrence of abscess formation is common. Based on this evidence, the recommended definitive management of splenic abscesses in patients with IE has been splenectomy [36, 531, 537, 539–541], of which the goal is to eradicate the extra-cardiac focus of infection as a prerequisite to successful management of IE. If possible, the AHA 2005 guidelines [36] recommend that splenectomy be performed prior to valve replacement surgery, to minimize the risk of contaminating the valve prosthesis as a result of bacteremia from manipulation of the abscess. This recommendation, although conceptually logical, is not based on evidence in the literature. However, in one series of ten patients with IE in whom splenectomy was performed for splenic abscesses, the splenectomies were staged and performed at a mean time interval of 11.2 days *after* valve replacement (range: 3–24 days) [533]. Although follow-up data is not completely provided, three-tenths (30 %) of the patients who underwent splenectomy died: one in the post-operative period from bleeding, and two at unspecified times from "cardiac causes". Another study suggests that splenectomy can be performed before or after valvular surgery, depending on the patient's clinical status [531]. Laparoscopic splenectomy for splenic abscess, although potentially more difficult technically, appears to be a safe and effective alternative to open surgery [539, 540].

More recently, radiographically-guided percutaneous aspiration or catheter drainage has become popular. The advantage is that it spares the spleen, and thus avoids the risks of the hyposplenic state (e.g. overwhelming post-splenectomy sepsis). Success rates with this procedure have ranged from 75 % to 100 %, although several catheterizations may be needed to achieve cure [532]. Furthermore, this procedure has been associated with high rates of failed attempts, which subsequently have required rescue splenectomies [537]. However, the need for a rescue splenectomy does not appear to be significantly associated with increased mortality rates [532, 536]. It has been recommended that percutaneous aspiration or catheter drainage be contra-indicated in a select sub-group of patients, namely those with multi-loculated abscesses, septations, tenaciously thick abscess contents, or abscess rupture/bleeding [532, 537].

In conclusion, the role for surgery in the management of IE or its complications is expanding. Although the risks for surgical intervention in patients with complicating features such as those discussed in this chapter are real, there is ample evidence that combined modality treatment is beneficial in specific instances.

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Blood Culture Negative Endocarditis

10

Yoav Keynan, Stephanie Smith, and Thomas J. Marrie

Abstract

Blood culture negative endocarditis is defined as definite or probable endocarditis in which three or more aerobic and anaerobic blood cultures collected over 48 h remain negative despite prolonged (greater than 1 week) incubation. Culture negative endocarditis constitutes a significant percentage of all cases of endocarditis in an institution and is a particularly challenging condition for the clinician treating such a patient. An organized approach to diagnosis and treatment is necessary. The most common cause of culture negative endocarditis is prior antibiotic therapy but an increasing number of organisms that cannot be grown in blood cultures given current techniques account for a varying percentage of cases depending on geographic location and laboratory technology. Nucleic acid amplification techniques, immunohistochemistry and transmission electron microscopy on vegetations all have a role in making a diagnosis. In hospital mortality is similar to that of culture positive endocarditis.

Keywords

Culture negative • Endocarditis • Q fever • Bartonella • Tropheryma whipplei • Fungi • Polymerase chain reaction

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Key Points

1. Blood culture negative endocarditis is defined as definite or probable endocarditis in which three or more aerobic and anaerobic blood cultures collected over 48 h remain negative despite prolonged (greater than 1 week) incubation
2. Incidence of culture negative endocarditis ranges from 2.5 % to 31 % of reported cases of endocarditis.
3. Prior antibiotic therapy is the most common cause of culture negative endocarditis.
4. Agents that cannot be cultured from the blood using current techniques constitute a large portion of the causes of culture negative endocarditis.
5. Rarely culture negative endocarditis is due to sterile vegetations, so called marantic endocarditis as a result of malignancy or conditions associated with high titres of antiphospholipid antibodies.
6. Mortality from culture negative endocarditis is similar to that from culture positive endocarditis.
7. Serology, histology, immunohistochemistry, nucleic acid amplification techniques and transmission electron microscopy all have a role in diagnosis of culture negative endocarditis in selected cases.

Introduction

Infective endocarditis (IE) with negative blood cultures presents a challenge to managing physicians. Having arrived at the diagnosis of endocarditis several challenges remain: choosing the diagnostic work-up to determine the etiology, choice of antibiotics and duration of treatment. Given these difficult diagnostic and management issues, it is not surprising that blood culture negative endocarditis (BCNE) is associated with higher morbidity and mortality compared with blood culture positive endocarditis. In a study by Murashita et al. [1], BCNE was found to be an independent predictor of decreased survival and increased events after surgery. Another study by Zamorano et al. [2] showed that patients with true BCNE had a significantly higher mortality and need for surgical repair than those with negative blood cultures due to previous antibiotic use (100 % composite end-point versus 64 %).

The goals of this chapter are to provide up-to-date knowledge on blood culture negative endocarditis, the role of molecular methods in establishing the etiological diagnosis, and to suggest strategies for diagnosis and management of this problem.

Definition and Incidence

Blood culture negative endocarditis is defined as definite or probable endocarditis in which three or more aerobic and anaerobic blood cultures collected over 48 h remain negative despite prolonged (greater than 1 week) incubation [3]. Definite or probable endocarditis is defined according to Duke criteria [4].

The incidence of BCNE ranges from 2.5 % to 31 % of endocarditis in various series [5]. A more recent study by Werner et al. [6] found that of 116 episodes of endocarditis, 20 % were culture negative. Forty-five percent of these episodes were preceded by antibiotic use. In another series of 221 cases of IE, 51 (23.1 %) had negative blood cultures. The most common reason for culture-negativity was antibiotic therapy prior to the blood draw, accounting for 47 % [7]. Studies using comprehensive diagnostic methods including serology, microscopy and PCR report an incidence of 5 % [8]. This discrepancy in the incidence of BCNE can be explained by varied use of culture techniques, molecular diagnostic and serologic tests. The improved identification aided by molecular tests have also allowed for identification of a variety of organisms not previously detected by blood culture [9].

Etiology of BCNE

A list of causes of BCNE can be seen in Table 10.1.

There are a large number of bacteria that occasionally cause endocarditis anywhere in the world. These uncommon causes of endocarditis include *Mycobacterium spp*, *Mycoplasma spp*, *Campylobacter fetus*, *Pasturella spp*, *Bordatella spp, Francisella tularensis, Aeromonas hydrophilia*, *Yersinia enterocolitica*, *Streptobacillus moniliformis, Neisseria gonorrhea*, *Listeria monocytogenes*, *Lactobacillus spp*, *Nocardia spp*, *Erysipelothrix rhusiopathiae*, *Clostridium spp*, non-toxigenic *Corynebacterium diptheria* [14]. For example, *Corynebacterium diptheria* accounted for >10 % of IE cases in a pediatric series from New-Zealand [15]. Although these are uncommon causes, not all of these would be classified as BCNE according to strict criteria as many of them can be cultured using routine blood culturing methods.

The HACEK organisms, which are uncommon causes of endocarditis, have traditionally been classified as BCNE although with newer culturing techniques, these may be detected using routine blood culture methods with subculturing on enriched media and application of MALDI-TOF [16].

A number of recent studies have looked at the etiology of BCNE when strict definitions are applied. Houpikian and Raoult [17] studied 348 cases of culture negative endocarditis in Marseille, France from 1983 to 2001. Forty-eight percent

Table 10.1 Mortality in BCNE case series

Study	Mortality culture positive	Number of BCNE	Mortality BCNE
Zamorano et al. (2001) [10]	12.6 %	20	15 %
Werner et al. (2003) [6]	NA	116	7 %*
Krcmery et al. (2007) [11]	15 %	76	13 %
Siddiqui et al. (2009) [12]	20.5 %	83	25.6 %
Ferrera et al. (2012) [13]	30.8 %	80	26.3 %
Siciliano et al. (2014) [7]	33.40 %	51	31.40 %

*Lowest mortality rate reported in BCNE series

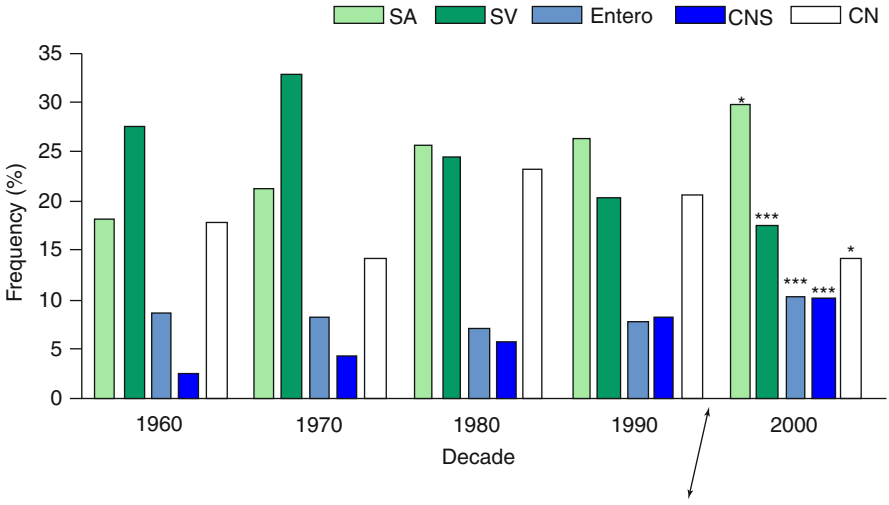

Fig. 10.1 Proportion of cases attributed to culture negative endocarditis over five decades (Modified from Slipczuk et al. *SA Staphylococcus aureus*, *SV Strep viridans, Entero Enteroccocus, CNS coagulase negative staphylococci, CN culture negative*)

of the cases were due to *Coxiella burnetii*. A further 20 % were due to *Bartonella* species and 5 % due to *T whippelii, Abiotrophia spp., Mycoplasma hominis,* and *Legionella pneumophila*. Of the 73 cases with no etiology, 58 occurred in patients who had been receiving antibiotics prior to blood cultures, 6 had right-sided endocarditis and 4 had a permenant pacemaker. In five patients no explanation for the culture negative endocarditis could be found. Fournier et al. [18] published a study in 2010 of 819 suspect cases of BCNE. Using a comprehensive testing strategy including serologic studies, histologic examination and broad range PCR testing of valvular speciments, they were able to identify a cause in 495 cases. The majority of cases (315) were caused by zoonotic infections including *Coxiella burnetii* and *Bartonella spp*. Eighteen cases were caused by fastidious organisms including 12 cases of *T whippelii*. There were 19 cases of non-infective endocarditis. Two hundred and sixty four cases had no etiology found. A contemporary German study of 1,135 cardiac valves comprehensively analyzed for bacterial infection using culture, PCR amplification of the bacterial 16S rRNA gene, and subsequent sequencing bacterial endocarditis was diagnosed in 255 (22.4 %) patients. Using specific PCR, fluorescence in situ hybridization, immunohistochemistry, histological examination, and culture *T. whippelii* was the fourth most frequent pathogen, found in 16 (6.3 %) cases [19]. The fact that *T. whippelii* outnumbered *Bartonella*, *Coxiella burnetii*, and other common culprits of BCNE suggests the possibilities of geographic variation and methodological differences account for some observed differences in etiology. Figure 10.1 (Slipczuk et al.) summarizes the proportion of BCNE in series over five decades [20].

Clinical Approach to the Patient with BCNE

In the case of BCNE, the patient's history can provide valuable clues to the possible etiology and can therefore direct further investigations. A history of previous antibiotic therapy should be elicited as this is the most common cause of BCNE. It has been shown that even a short course of antibiotic treatment can cause long lasting suppression of bacterial activity [21].

A variety of animal exposures may predispose to certain microbiologic etiologies. Contact with goats [22], sheep and cows should suggest infection with *C burnetii*. However, the interval between exposure and the late clinical manifestation of IE makes the exposure link difficult to ascertain at times. The human body louse has been implicated in transmitting *Bartonella quintana* and *Bartonella henselae,* the former should be suspected in the context of homelessness [23] while the latter should be suspected in cat owners. Travel to the Middle-East and ingesting unpasturized milk should suggest infection with *Brucella spp.* Legionella should be considered in a patient with a history of recent hospitalization. Immunosuppression or prolonged antibiotic therapy should suggest endocarditis due to fungi.

Physical examination may be helpful in establishing a diagnosis of endocarditis but is unlikely to aid in uncovering the etiology. In a study carried out at St. Thomas' Hospital from 1975 to 2000, 63 patients with BCNE were identified [24]. In this study 17 % of patients were afebrile; 20 % had cerebral emboli; 19 % had splinter hemorrhages; 17 % hematuria; 15 % splenomegaly; 13 % rash; 10 % clubbing; 8 % pulmonary emboli; 4 % peripheral emboli; 4 % subconjunctival hemorrhage and 4 % Osler's nodes. A study from Slovakia reported significantly lower risk of embolization in BCNE compared to culture positive IE [11].

Approach to Treatment

When a diagnosis of possible infective endocarditis is made, diagnostic studies to determine the etiologic agent, especially in the case of BCNE, may take days to weeks. A prospective epidemiologic study by Werner et al. [6] looked at total symptom duration until hospitalization and until treatment in 111 cases of BCNE. They found symptom duration until hospitalization time of 23 days and a symptom to treatment time of 27 days. A recent study of 221 episodes of IE documented symptoms duration of >30 days in more than half of the individuals with BCNE [7]. Delays in initiation of treatment did not result in increased morbidity and mortality in most studies [2, 7, 10, 11, 13], with one exception [25]. When choosing empiric treatment, a history of previous antibiotic use, recent exposures (animals, IVDU, travel, dental procedures) underlying medical conditions (prosthetic versus native heart valves) as well as knowledge of prevalence rates of causative organisms can help to guide therapeutic choices. When the patient is acutely ill and while awaiting results of various diagnostic studies, empiric treatment should be initiated. Rational empiric treatment should include an antibiotic that is active against the bacterial cell wall (cloxacillin 12 g/day or vancomycin 1 g every 12 h) and an aminoglycoside (e.g. gentamicin 1 mg/kg every 8 h) [26]. If a patient has had significant exposure to

farm animals, treatment with ciprofloxacin 750 mg every 12 h in combination with rifampin 600 mg once daily or doxycycline can be initiated to cover for *Bartonella* or *Coxiella* infection. A combination of a cell wall active agent (vancomycin or cloxacillin) plus an aminogylocside and rifampin should be used in culture negative prosthetic valve endocarditis [13]. If the patient continues to deteriorate despite initiation of empiric therapy, treatment for HACEK, *Abiotrophia* and *Bartonella* can be initiated with ceftriaxone and gentamicin [26]. Outcomes of therapy vary with most series indicated comparable mortality to culture positive endocarditis [1, 2, 10–13] and one study reporting lower mortality rate (7 %) [25]. These results should be interpreted with caution, as the inclusion of individuals in whom prior antimicrobials were administered may bias the results. Table 10.1. Selected studies comparing the mortality of BCNE.

Diagnostic Methods

The profile of general laboratory results does not help to differentiate BCNE from culture positive cases although the levels of C-reactive protein were significantly lower (median 58 mg/L vs. median 106 mg/L in patients with culture-negative endocarditis compared with culture-positive endocarditis patients [7].

Culture

Culture of three sets of blood drawn within a 24–48 h period is usually sufficient to make a diagnosis of culture positive endocarditis and alternatively indicate a possibility of BCNE [27]. Because of the almost linear relationship between the yield of bacteria from the blood and the volume of blood drawn, 10–20 ml of blood is optimal for each culture [28]. If the patient has received antibiotics, blood should be processed in the presence of an antimicrobial agent removal device such as cationic or polymeric adsorbent resins with sodium polyanetholsulfonate. These are now included in many commercially available blood culturing systems.

Laboratory isolation of fastidious organisms from the blood has improved. The key to successful isolation is to ensure the laboratory is aware the patient is suspected of having endocarditis. Most organisms of the HACEK group can be isolated on enriched or chocolate agar with the exception of *Aggregatibacter actinomycetemcomitans* which may take up to 6 weeks of incubation [29]. *Abiotrophia spp*. are now readily isolated due to the addition of B6 in commercial blood culture media [30, 31].

Specific media are required for some pathogens. *Legionella spp*. requires buffered charcoal yeast extract for optimal growth. Most *Mycobacteria spp* can be isolated in standard blood culture systems but the use of Middlebrook 7H13 broth should be considered especially for *Mycobacterium tuberculosis* [17]. Intracellular bacteria such as *Coxiella burnetii* and *Bartonella spp*. require cultivation in cell cultures [32, 33].

The shell vial technique has been successfully used for isolation of *Tropheryma whippelii* and *Chlamydophila psittaci* [34, 35].

The use of matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI TOF MS) is increasing in the microbiology laboratory. This technology is revolutionizing the processing of specimens in the laboratory, resulting in rapid identification of the infecting organisms. Although the use of MALDI TOF on blood cultures has not been studied in the context of suspected IE, the utility of the technology has been documented. Several, difficult to identify BCNE causing organisms were identified rapidly and accurately using MALDI TOF [36–38], suggesting that the routine use in the microbiology laboratory may fill some of the diagnostic gaps.

Histology

Histologic analysis of excised valves can aid in making a diagnosis of infective endocarditis. Histologic parameters are components of the Duke criteria [39]. The absence of inflammation makes the diagnosis of IE very unlikely.

A number of different stains can be used to help identify various organisms implicated in IE as well as confirm the presence of inflammation. Hematoxylin and eosin staining can identify a pattern of inflammation consistent with IE. Tissue gram stains allow differentiation between gram positive and negative organisms as well as giving skilled technicians information about morphology. This may allow for a preliminary identification [40]. The periodic acid-Schiff (PAS) stain is especially valuable for detection of *Tropheryma whippelii* [41], demonstrating the presence of foamy histiocytes with infiltrates of neutrophils, lymphocytes and mononuclear cells [42]. The PAS stain can also be used to detect the presence of fungi.

Giemsa stain, traditionally used for detection of parasites can detect a variety of bacteria including *Bartonella* species. The presence of inflammation is also highlighted since Giemsa stains white blood cells [43].

The acradine orange stain is a non-specific fluorscent stain, which can detect any living organism including bacteria, *Mycobacteria spp.*, and a variety of fungi. In Bartonella endocarditis, the valves tend to be fibrotic and calcified, less vascularized, with less extensive formation of vegetations [44]. Warthin-Starry silver impregnation technique is a very sensitive method for detection of *Bartonella* species [45].

A variety of specific stains can also be used based on clinical indications. If the patient has risk factors for a mycobacterial infection, valves should be stained with Ziehl-Nielsen staining for acid-fast bacteria. The Gimenez stain allows detection of *C burnetii* and *Legionella* species [40]. The Kinyoun stain can also detect mycobacterial species. It also stains large macrophages containing dark red granules seen in Chlamydia endocarditis.

For detection of fungi, the Gomori-Grocott's silver stain provides the best contrast [40, 46].

Immunohistologic Methods

Specific antibodies have been developed to detect a variety of pathogens in tissue. Immunoperoxidase stains, enzyme-linked immunosorbent (ELISA) assays and direct immunofluorescence have all been used to detect causative agents of BCNE. *Coxiella burnetii* and *Bartonella sp.* have been detected using these techniques [14, 44, 47, 48]. Direct immunofluorescence can be performed on paraffin-embedded tissue [49].

Electron Microscopy

Although EM is able to resolve morphologic details that cannot be seen with light microscopy, its usefulness is limited [50]. It is both expensive and time consuming and therefore is reserved for only very difficult cases of BCNE where other methods have failed. In the case of BCNE that led to the isolation of *Tropheryma whippelii,* the etiologic agent of Whipple's disease, the microorganism was first visualized by transmission electron microscopy of the infected valve (Fig. 10.2). Figure 10.3 shows TEM of a vegetation from a patient with endocarditis treated with antibiotics – notice the damaged bacteria. Figure 10.4 shows a scanning electron micrograph of a patient with *Candida parapsilosis* endocarditis showing the many large oval fungal cells.

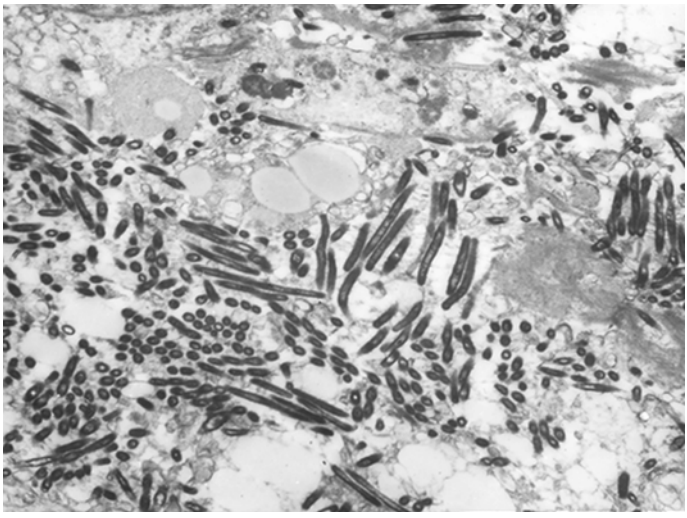

Fig. 10.2 Transmission electron micrograph from a patient with BCNE due to *Tropheryma whippelii.* Note the many long rod like bacteria. The round cells are rod that have been cut transversely

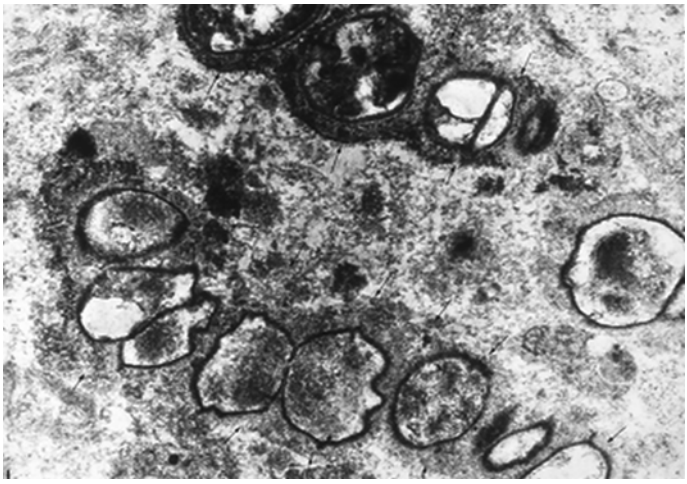

Fig. 10.3 TEM showing damaged bacterial cells from a patient with BCNE. In this instance the negative blood cultures were due to prior antibiotic treatment

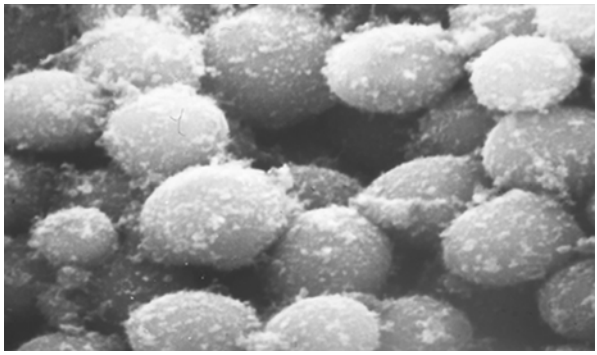

Fig. 10.4 Scanning electron micrograph showing fungal cells in a patient with *Candida parapsilosis* endocarditis

Serology

Serologic testing for *C burnetii, Bartonella spp, Mycoplasma pneumoniae, Legionella spp, Chlamydia spp,* and *Brucella spp* is included as diagnostic criteria for IE according to both the Duke and modified Duke criteria [4, 51].

C. burnetii and *Bartonella spp* are the most common agents of BCNE. Serologic tools are available to identify these two species and they should be used routinely as part of diagnostic work-up for every patient with BCNE. On the other hand, positive serologic tests for *Mycoplasma, Legionella, Chlamydia* and *Brucella* should be interpreted with caution due to low positive predictive value and frequent cross-reactions [17, 27, 52].

A large study reported 740 patients with infective endocarditis, 549 of which were classified as definite endocarditis using the Duke criteria. The authors applied a comprehensive evaluation and were able to identify the etiological agent in 476 of the cases. Serological analysis by immunofluorescence, provided approximately three fourths of diagnoses and PCR was the second most identified the etiology in additional 109 patients for whom serological results were negative [18].

Molecular Techniques

Sequence analysis of bacterial 16S rRNA genes using polymerase chain reaction (PCR) has been used directly on clinical specimens to establish an etiological diagnosis in BCNE. This molecular technique has been shown to be more sensitive than conventional blood culturing techniques for the detection of bacteria [9, 53]. The infecting pathogen was identified in 2.4 % of clinical specimens where standard bacterial culture had failed. Its main advantages are that it is culture independent and that most bacteria can be detected in a single reaction. Cases of BCNE due to previous antibiotic therapy represent an excellent indication for application of PCR [54].

In one study of 51 patients (52 valves) with suspected endocarditis and 16 patients with no endocarditis this approach had a sensitivity of 41.2 %, a specificity of 100 %, a positive predictive value of 100 % and a negative predictive value of 34.8 %. This was compared with 7.8 %, 93.7 %, 80 % and 24 % for culture and 11.8 %, 100 %, 100 %, and 26.2 % for Gram stain [55]. A recent study from 8 UK and Irish centers, included 151 patients with IE. Use of 16S rDNA PCR yielded a etiological diagnosis in 43/69 BCNE. The sensitivity, specificity, positive predictive value and negative predictive value of the 16S rDNA PCR assay were: 67 %, 91 %, 96 % and 46 %, respectively [45]. Similarly, a study comparing the utility of valvular tissue culture to PCR for 74 patients with IE documented a sensitivity of valve culture 26 % and specificity 62 % while those of PCR were 72 % and 100 %, respectively [56]. The improved performance of the PCR was emphasized in individuals who received >5 days of antimicrobial therapy prior to surgery.

This technique is limited by the number and quality of DNA sequences available in GenBank and the EMBL databases. As some of the reference sequences are too short or contain too many undertermined nucleotides, confident assignment of clinically derived sequences cannot be made. Microbial DNA contamination can also occur. Therefore caution must be exercised in the interpretation of PCR based sequence analyses when the organism has not been observed in stained valve tissue [57].

The improved ability to detect the infecting organism in excised cardiac tissue compared to routine culture has been reproduced in a myriad of studies [54, 58–62]. The current guidelines reflect these observations and recommend that samples of excised heart valve from cases of culture-negative IE be referred for broad-range bacterial PCR and sequencing [63].

As our databases improve, molecular techniques will be used increasingly in the assessment of patients with BCNE [64, 65]. The routine application of 16S rDNA pyrosequencing and other genomics-based approaches directly to blood cultures is hampered by low microbial burden in comparison to host DNA at present [66].

Selected Infectious Agents of BCNE

Coxiella burnetii

Coxiella burnetii is an obligate intracellular bacterium and the causative agent of Q fever. Q fever is a zoonosis that can cause acute and chronic disease. It demonstrates phase variation (phase I to phase II) which can be helpful in diagnosis of chronic infection as in general in chronic Q fever the antibody titre to phase I antigen exceeds that to phase II.

Epidemiology: Q fever is prevalent in all countries where it has been studied. It accounts for 3–5 % of infective endocarditis worldwide (except New Zealand) [26]. A recent study from France reported the etiologic diagnosis of 348 cases of definite culture negative endocarditis according to Duke criteria [17]. In this study, *Coxiella burnetii* accounted for 48 % (167) of all cases. Over 400 cases of Q fever endocarditis have been reported in the literature to date [14, 67]. Over half of all cases have been reported from one laboratory in France [68].

Endocarditis is the most common manifestation of the chronic form of Q fever accounting for 78–80 % of all cases and 8–11 % of all cases of Q fever, acute or chronic. More cases have been reported from Great Britain, France and Israel [33] than from North America.

Farm animals such as sheep, goats and cattle are the primary reservoir of disease although cats and dogs have also been affected. When infected, all of these animals shed desiccation resistant *C. burnetii* in urine, feces, milk, and birth products [14]. Because *C burnetii* is very resistant to physical agents, it is able to survive in the environment for long periods and can be spread over long distances by wind [69]. It is thought that humans become infected by inhalation of dust contaminated by fluids from infected livestock [68]. Persons may also become infected by ingesting unpasturized milk or milk products. In a study by Houpikian and Raoult [17] risk factors for Q fever endocarditis included male sex, age older than 60 years, valvular heart disease, rural life, exposure to animals, and consuming raw milk. The largest outbreak of Q fever occured in the Netherlands between 2007 and 2010 [70]. Subsequent to this outbreak 284 cases of chronic Q fever were identified, of which over a half (53.7 %) had proven, 64 (22.5 %) probable, and 69 (24.3 %) possible chronic Q fever. Among proven and probable chronic Q fever patients, vascular infections accounted for more than a half (56.7 %) and it was more prevalent than endocarditis (34.9 %). An acute Q fever episode was recalled by 27.0 % of the patients [71].

Signs and Symptoms

The diagnosis of Q fever endocarditis is often delayed due to lack of echocardiographic findings and negative blood cultures. The most common symptoms include low grade or intermittent fever, fatigue and weight loss. Fever and congestive heart failure are the most common signs of Q fever endocarditis and are seen in 68 % of patients [14]. Splenomegaly and hepatomegaly may be prominent and may lead to the clinician to investigate for causes of liver disease or hematologic malignancy causing further diagnostic delays. Clubbing of the digits was found in one third of patients which is higher than for other causes of endocarditis [72]. Other possible signs include immune complex deposition related renal impairment and purpuric skin rash [73]. As with other causes of endocarditis, Q fever endocarditis can present with embolic manifestations such as stroke.

Laboratory findings of Q fever endocarditis include circulating immune complexes, positive rheumatoid factor, anemia, thrombocytopenia, microscopic hematuria and marked hyperglobulinemia [72]. Serum transaminases especially aspartate aminotransferase and alkaline phosphatase may also be elevated.

Diagnosis

Transthoracic echocardiography only picks up 12 % of vegetations in patients with Q fever endocarditis [72] although transesophogeal echo has improved sensitivity. On pathologic examination of the valves of patients with Q fever endocarditis, vegetations have a nodular appearance with a smooth surface or the valves may actually appear normal. Histologic examination reveals changes of both acute and chronic inflammation. Immunohistochemical staining reveals *C burnetii* only in macrophages at sites of inflammation and valvular injury and only in the vegetations [74].

Coxiella burnetii should be considered as a possible etiologic diagnosis in anyone with BCNE. Diagnosis can easily be made using serologic testing, detecting antibodies to phase I and phase II antigens. Q fever endocarditis is characterized by high titres to both phase I and phase II antigens of *C burnetii*. An IgG titre of $\geq$1:800 is very sensitive and has high positive predictive value [75]. However one should never make a diagnosis of Q fever endocarditis based only on serology. Coxiella burnetti can also be isolated from blood or from valves. It can be cultured using a shell vial technique but needs to be done in a level three laboratory. Detection of *C burnetii* DNA by PCR can also be done on blood or heart valves [76]. Positron emission tomography is useful in diagnosing Q fever endocarditis and intravascular infection [77].

Prognosis and Treatment

Untreated Q fever endocarditis has a high mortality rate and the poor outcomes reported in older literature were most likely due to diagnostic delays. The morality in more contemporary series is 5–13 % [78, 79]. The mortality was almost double in individuals with vascular infection (18 % vs 9.3 %) [71]. The standard treatment for Q fever endocarditis has been a tetracycline in combination with a quinolone for 3–4 years. Despite this prolonged course, relapses and positive valve cultures still occurred. This is related to the fact that in vitro, these antibiotics are only bacteriostatic. The addition of hydroxychloroquine to doxycycline was studied by Raoult

et al. [79, 80]. The combination of doxycycline and hydroxychloroquine compared with doxycycline and ofloxacin shortened the duration of therapy but had no effect on mortality, valve surgery or tolerance. Therefore a combination of doxycycline and hydroxychloroquine should be used for a minimum of 18 months. Surveillance of antibody titres to phase I antigens should be measured every 2 months and treatment can be stopped when IgG phase I antibodies decrease below a titre of 800 [14]. Surgery should be reserved for those with hemodynamic instability.

Patients with acute Q fever who have valvular heart disease should be treated pre-emptively with doxycycline and hydroxychloroquine for 12 months. This prevents subsequent Q fever endocarditis [81].

Bartonella spp

Bartonella spp are small facultative intracellular gram negative bacteria. They cause a variety of clinical syndromes. *B henselae* is the causative agent of cat scratch disease, meningoencephalitis; bacillary angiomatosis and hepatic peliosis in HIV-infected patients [82]. *B. qunitana* causes trench fever, lymphadenopthy and bacillary angiomatosis. Endocarditis has been reported with *B henselae, B qunitana, B elizabethae* and *B vinsonii* [14] and more recently *B. koehlerae* [83] and *B.alsatica* [84]. *B henselae* and *B quintana* account for approximately 3 % of all cases of infective endocarditis [26] whereas *B elizabethae* and *B vinsonii* are exceedingly rare as causes of endocarditis.

Epidemiology

Bartonella spp have a worldwide distribution but the majority of cases have been reported in North America and Western Europe. *B henselae* is transmitted to humans by a cat scratch or bite or the bite of an infected flea, the cat being the resevoir. *B quintana* is carried by the human body louse and humans are the most likely reservoir. Risk factors associated with *B henselae* include underlying valve injury and contact with cats. The risk factors associated with *B quintana* are homelessness and alcoholism (conditions associated with body lice) [85]. Prothetic valve infection with *Bartonella spp* has been rarely reported. The mean age of patients with *Bartonella* endocarditis is 48 years which is much lower than for other causative agents of infective endocarditis. *Bartonella* endocarditis affects predominantly men.

Signs and Symptoms

Bartonella spp generally cause a subacute insidious form of endocarditis often leading to delay in diagnosis. At presentation, most patients have fever and they often present with signs and symptoms of heart failure [85]. Aortic valves are preferentially affected. Patients often present with manifestations of embolic phenomenon most likely as a result of delayed diagnosis and the large size of vegetations.

Due to the large size, echocardiography [TTE or TEE] can identify vegetations in 100 % of patients with *B henselae* and 95 % of patients with *B qunitana* endocarditis [85].

Examination of excised valves shows destruction and inflammation of valvular tissue with no well-formed granulomas and fibrosis [44, 86]. Giemsa and Warthin-Starry stains are best at showing granular organisms in the vegetation or valvular tissue. Gram staining and PAS are not helpful [86].

The etiologic diagnosis can also be documented using serology. Serologic testing can be done using enzyme immunoassays or IFA assays. An IgG titre over 1:800 is considered positive. These tests can often not differentiate between *Bartonella spp*. There is also low-level cross reactivity with *C burnetii* and significant cross-reactivity with *C pneumoniae* [52]. Inoculation of blood or valvular tissue in tissue culture or on blood agar can be used. More recently PCR detection has been used. It is rapid and can distinguish between *Bartonella* species [32].

Treatment and Prognosis

Bartonella spp are susceptible to beta-lactam agents, aminoglycosides, macrolides, tetracyclines and rifampin in-vitro. A standard antibiotic regimen has not been definitely established but retrospective data support a combination of gentamicin for 2 weeks and doxycycline for 6 weeks as the treatment of choice, and improved survival was associated with aminoglycoside therapy [23, 87]. The addition of ceftriaxone did not improve outcomes [88]. A large proportion of patients require valvular surgery due to the destructive nature of both *B henselae* and *B quintana*. In one series, valve replacement was performed in over 90 % of cases of *Bartonella* endocarditis [87].

Brucella

Brucella spp are small, facultative gram negative intracellular bacteria. The reservoir is domesticated animals such as cattle, goats and sheep. *B melitensis* occurs in goats and sheep and it is this strain which causes most cases of human brucellosis.

Epidemiology

Brucella spp are found worldwide. Infection in humans is caused by ingestion of unpasturized milk or milk products contaminated with the bacteria or by close contact with infected livestock or their bodily fluids. Brucellosis can present as an acute, subacute or chronic disease. Endocarditis is a rare complication of brucellosis occurring in 0.6 % of those with *Brucella* infection and accounting for 1–4 % of all cases of infective endocarditis [89, 90]. Risk factors include valvular heart disease and appropriate exposure [91].

Signs and Symptoms

Brucella endocarditis generally presents as a subacute illness with progression over 1–3 months. Symptoms and signs are generally non-specific but include fever, myalgias, fatigue and hepatosplenomegaly. In patients with prosthetic valves, relapse of bacteremia after appropriate treatment for acute Brucellosis should be a clue.

Brucella endocarditis predominantly affects the aortic valves and is generally destructive to the valve resulting in ulcerative lesions and ring abscesses. Myocardial abscesses have been found in 43 % of patients in a post mortem study [92].

Diagnosis depends on isolation of *Brucella spp* from blood or cardiac tissue. Although cultures of *Brucella* require longer incubation periods, 80 % of cases have positive blood cultures. Automated blood culture instruments generally yield positive cultures in 4–10 days but it is still suggested that cultures be held for 21 days [93]. Serology is a safer and effective method of diagnosing *Brucella* infection. At least two serological tests have to be combined to avoid false negative results. Serum agglutination is used first for screening and complement fixation will confirm its results [93]. A titre of 1:160 is considered positive for active infection. Serologic cross-reactivity occurs between *Brucella, Yersenia* and *Francisella spp* [94].

Treatment and Prognosis

Surgical treatment in combination with medical therapy is necessary in the majority of patients with *Brucella* endocarditis, prognosis is adversely affected by the presence of heart failure and pericardial effusion [95]. In the presence of prosthetic valve or congestive heart failure, consideration should be given to combined surgical and medical intervention [96]. In a series by Reguera et al. [91], 72 % of 11 patients required valve replacement with 91 % survival. Standard therapy should include a combination of doxycycline and rifampin or streptomycin for a minimum of 3 months. A recent study compared four antimicrobial regimens: ceftriaxone combined with oral antibiotics; aminoglycosides combined with oral antibiotics; oral antibiotic combinations; and aminoglycoside plus ceftriaxone combined with an oral antibiotic. The study was not powered to detect differences between the four combinations but there was trend toward lower mortality in the two groups receiving aminoglycoside as part of the regimen [95, 97]. If valve replacement is undertaken, antimicrobial therapy should continue for 6–8 weeks postoperatively [89]. Antibody titres can be used to monitor response to treatment.

Fungi

Fungal endocarditis has become an important cause BCNE due to increasing numbers of immunocompromised patients and those with prosthetic valves. Fungal pathogens account for 1–6 % of all cases of infective endocarditis [98]. The most common fungi to cause endocarditis are *Candida spp* which account for 48–50 % of all cases [99]. Of these, half are non-Candida spp. *Non-C albicans* are more common in health care associated endocarditis whereas *C albicans* is more common in those with injection drug use as a risk factor [99]. *Aspergillus spp* accounts for a further 24 % and *Histoplasma spp*. cause 6 % of infections. The yield of blood cultures is approximately 80 % for *Candida spp* and lower for *Aspergillus spp* [100]. The remainder of reported infections are caused by a variety of yeasts and moulds including *Trichosporon, Cryptococcus, Pseudallescheria boydii, Trychophyton* and *Scopulariopsis brevicaulis* [99].

Epidemiology

Yeasts and moulds are ubiquitous in the environment but generally do not cause clinical disease unless under exceptional circumstances. The risk factors for the development of fungal endocarditis are similar to those for any invasive fungal infection. These are well outlined in a review by Pierrotti et al. [66] that looked at 143 cases of fungal endocarditis over a 5 year period. These include underlying cardiac abnormalities, prosthetic valves, presence of central venous catheter, and use of broad-spectrum antibiotics. Immunosuppression and total parenteral nutrition have also been identified as strong risk factors for the development of fungal endocarditis. The occurrence of fungemia and IE is increasing in the context of nosocomial bloodstream infection and IE in the intensive care unit setting [101, 102].

Signs and Symptoms

The most common features of fungal endocarditis do not allow distinction from other forms of endocarditis. In a review of 270 cases, Ellis et al. [99] found that 45 % of patients had major embolization causing ischemia at the time of diagnosis. This is much higher than for other causes of endocarditis.

Echocardiography is able to identify vegetations in approximately 80 % of cases of fungal endocarditis giving a sensitivity of 77 % [99]. Echocardiography identified vegetations more often in those with native valves compared with those with prosthetic valves [98].

Routine blood culturing systems detect fungal pathogens in 46–54 % of cases of fungal endocarditis. Positive blood cultures were seen more frequently in yeast related IE than in mould-related IE [98].

Histologic examination of excised valves provided the most sensitive means of pathogenic identification in cases of fungal endocarditis. Ellis et al. reported a sensitivity of 95 %.

Treatment and Prognosis

Treatment for fungal endocarditis should generally include both medical and surgical therapy. Amphotericin B is the drug for which the greatest amount of experience has accumulated and should be the drug of choice for *Candida* endocarditis until susceptibility testing can be completed. Other options include the addition of flucytosine to amphotericin B, or fluconazole. Voriconazole, posaconazole, caspofungin, and intravenous itraconazole have been shown to be effective in the animal model of fungal endocarditis [103]. In-vitro therapeutic concentrations of caspofungin display activity against *C. albicans* biofilms, which have been shown to be otherwise resistant to treatment with fluconazole and amphotericin B and in animal model of intravascular infection [104, 105]. For endocarditis caused by *Aspergillus spp*. voriconazole has been used successfully in conjunction to surgery and has become the drug of choice [106–110]. Generally, patients require greater than 6 months of therapy and may need life-long suppressive therapy in cases where operative management cannot be undertaken. Even with optimal surgical and medical management, the prognosis for those with fungal endocarditis has been poor compared with endocarditis caused by other pathogens. In the two largest series of patients reported in

the literature, the mortality rates were 77 % and 56 % respectively [98, 99]. Patients with mould endicarditis had a higher mortality rate than those with yeast endocarditis.

Abiotrophia and *Granulicatella spp*

Abiotrophia spp and *Granulicatella spp*, formerly known as nutritionally variant streptococci due to the requirement of pyridoxal and additional nutrients to the culture media, were reclassified separate genus based on analysis of 16S rRNA sequences [111–113].

Epidemiology

A adjacens and *A defectiva* account for approximately 2 % of all cases of infective endocarditis with more than 100 cases being reported in the literature [30]. Three species of *Granulicatella* have been described: *G. adiacens, G. elegans and G. balaenopterae* and *G. adiacens* is most frequently associated with IE, at equal or greater frequency compared to *Abiotrophia* [114]. Risk factors include underlying heart disease which is found in approximately 90 % of patients with *Abiotrophia* endocarditis. They are part of the normal oral, genitourinary and intestinal floras.

Signs and Symptoms

IE caused by *Abiotrophia* often presents as a slow indolent course. Embolization occurs in approximately one third of patients [14] and neurological manifestations have been frequently reported [115]. Classic peripheral manifestations of endocarditis including clubbing, petechiae and Osler nodes are not usually present. Mitral and aortic valves are affected with equal frequency.

Diagnosis

Abiotrophia spp require cysteine for growth. Now that cysteine is routinely added to culture media, both *A adjacens* and *A defectiva* can be detected in routine blood cultures within 2–3 days. Subcultures require addition of pyridoxal hydrochloride or L-cysteine for growth. Alternatively, *Staphylococcus aureus* can be used to induce satellite growth. Gram staining and morphology are variable. Commercially available identification systems such as Rapid ID 32 Strept can differentiate *Abiotrohia* from viridans streptococci. The use of VITEK 2 and MALDI TOF MS have improved the ability to identify the organism [36, 116].

Vegetations are seen in 64 % of all cases of *Abiotrophia* endocarditis and can therefore be helpful in making a diagnosis. Histological identification of Abiotrophia species in excised valves is difficult as bacteria are morphologically altered within the vegetation [30].

Prognosis and Treatment

Despite improvements in culture techniques, infective endocarditis due to *Abiotrophia and Granulicatella spp* continues to have a higher mortality when

compared to other forms of viridans streptococci. Approximately one fourth of patients require valve replacement and one third fail initial antimicrobial therapy. This is most likely due to the high beta-lactam resistance rates among *Abiotrophia* and *Granulicatella* strains [117]. Treatment outcomes have improved with the addition of gentamicin to penicillin and the guidelines recommend a regimen similar to Enterococcal endocarditis [63, 118, 119].

Mycobacterium spp

Mycobacteria are acid fast bacteria that rarely cause endocarditis. Isolated case reports of *Mycobacterium tuberculosis* endocarditis have been reported [120]. Generally these cases are in the context of disseminated or miliary TB and diagnosis of endocarditis was made incidentally at autopsy [121]. Most cases involved patients with valvular heart disease. Non tuberculous mycobacterial endocarditis has been reported with the rapid-grower group of *Mycobacterim chelonae, Mycobacterium fortuitum* and *Mycobacterium avium-intracellulare* most frequently implicated [14]. The majority of involve prosthetic valves with only six cases of native valve non-tuberculous mycobacteria endocarditis being reported in the literature [122, 123]. It is felt that these infections are due to nosocomial introduction at the time of surgery.

Diagnosis may be made by isolation of mycobacteria from blood culture although the diagnosis may be made more quickly by histologic examination of excised valves. Acid fast bacilli can be detected using Ziehl-Neelsen staining [124].

Combination therapy is necessary as for any mycobacterial infection but duration of therapy has not been well studied due to the paucity of cases. The utility of antimicrobial susceptibility is hampered by the lack of correlation with clinical outcomes. Combined surgical and medical therapy may be required, but mortality remains high [125].

Mycoplasma spp

Mycoplasma endocarditis is extremely rare with *Mycoplasma hominis* being most frequently reported in the literature [126, 127]. The increase in number of reported cases can be attributed to the advent of PCR based diagnosis of cardiac tissue submitted during surgery [128, 129]. The antimicrobial management involves administration of tetracyclines (intrinsic resistance to penicillins and erythromycin among *M. hominis*) [130, 131].

Legionella spp

Legionella spp are small gram negative intracellular bacteria that are associated with nosocomial pneumonia. Cases of *Legionella* endocarditis have been reported in the literature. The first case was reported in 1984 in a patient with bioprosthetic

valve [132]. The second report was a series of seven patients all with prosthetic valves at Stanford University Hospital Center [133]. Legionella prosthetic valve endocariditis as accounted for the vast majority of patients [134–136]. One case of endocarditis in a patient with aortic root replacement is reported [137]. *Legionella pneumophila*, *Legionella micdadei*, *L. dumoffii* and more recently *L. longbeachae* [138] have all been implicated.

Epidemiology

Legionella spp are normally found in water. There have been a number of nosocomial outbreaks of legionellosis related to contaminated water systems including hot water tanks and air-conditioning systems.

Signs and Symptoms

Patients often have non-specific symptoms such as low-grade fever, malaise and weight loss. Anemia and thrombocytopenia were frequently observed. There has been only one report of an embolic complication [136].

Vegetations are rarely reported on echocardiography and direct visualization of excised valves revealed only small vegetations in six of eight surgically treated patients.

Diagnosis

Legionella spp can be cultured using routine blood culture systems but amount of growth is often inadequate. It is therefore advisable to subculture blood to buffered charcoal yeast extract (BCYE) agar periodically if one is suspecting *Legionella* as the cause of endocarditis. The use of 16s r RNA sequencing to identify *Legionella spp* has resulted in identification of potential new species causing IE [139].

Prognosis and Treatment

Valve replacement in combination with antimicrobial therapy has been used in the majority of cases. Erythromycin in combination with rifampin, ciprofloxacin and doxycycline, have all been used to treat *Legionella* endocarditis. The European guidelines recommend Erythromycin with rifampin [119]. Levofloxacin possess better in-vitro activity and in several studies resulted in improved outcomes (time to defervescence, duration of admission and mortality) when compared to macrolides for legionnaire's disease [140–142]. Due to rarity of *Legionella* IE, the outcomes have not been compared to macrolides, and few case reports document successful treatment with levofloxacin [136]. Duration of therapy was at least 5 months and no relapses or deaths have been reported.

Whipple's Disease Bacterium: *Tropheryma whippelii* Endocarditis

Whipple's disease is a rare bacterial infection that causes a chronic systemic illness characterized by arthralgias, weight loss, diarrhea, abdominal pain and generalized lymphadenopathy. It occurs primarily in men over the age of 40 years. Whipple's

disease bacterium, also known as *Tropheryma whippelii*, was first isolated in 2000 [34]. The frequency of *Tropheryma whippelii* was thought to be rare [143] but emerging evidence with the application of sequencing based diagnosis of surgically removed tissue suggest that its incidence was underestimated. A recent German study, analyzed valve tissue from 1,135 patients by applying conventional culture techniques, PCR amplification of the bacterial 16S rRNA gene, and subsequent sequencing. *T. whippelii*-positive heart valves were confirmed by specific PCR, fluorescence in situ hybridization, immunohistochemistry, histological examination, and culture for *T. whippelii*. Among 255 proven IE cases *T. whippelii* was the fourth most frequent pathogen, accounting for 6.3 % of cases, and was significantly more common than *Bartonella quintana, Coxiella burnetii*, and members of the HACEK group [19]. There are no consistent signs and symptoms that may lead one to consider *T whippelii* as a cause of endocarditis. Although many patients have signs and symptoms of Whipple's disease. Richardson et al. and Herrmann [144, 145] reported cases of isolated *T whippelii* endocarditis. In the report by Geissdorfer et al. only one case of TWIE formally fulfilled the Duke criteria for the diagnosis of IE prior to valve excision, and 87 % of patients had valvular heart disease prior to the diagnosis of IE [19].

Diagnosis is made by histologic examination of tissue. PAS staining reveals PAS positive macrophages and the presence of *T whippelii*. PCR identification can also be used from either a valve or a duodenal biopsy specimen. The organism can be grown in tissue culture using the shell vial technique but the time for the organism to grow is prolonged – 2–6 months.

Treatment of *T whippelii* endocarditis has not been standardized. Most patients with Whipple's disease are treated with cotrimoxazole, ceftraixone or doxycycline for a minimum of 6 weeks and more frequently for 6 months to a year [143]. The prognosis of *T whippelii* endocarditis is as yet unknown.

Culture-Negative Endocarditis Due to Right Sided Endocarditis

It has traditionally been believed that right-sided endocarditis is more likely to be culture-negative due to bacteria being filtered by the lungs. There is very little evidence in the literature to support this claim. In our clinical practice, the majority of right-sided endocarditis is identified through routine blood culture and or transesophageal echocardiography. Risk factors for right-sided endocarditis include intravenous drug use and valvular heart disease.

Non-infectious Causes of Endocarditis

Non-infectious causes of endocarditis are classified as nonbacterial thrombotic endocarditis (NBTE). A review of 171 cases of NBTE found that 59 % of cases were in patients with underlying malignancy, carcinoma of the ovaries, billiary system, pancreas, lung and stomach were most commonly reported [146]. The

vegetations were located predominantly on the mitral and aortic valves. The majority of patients in this series had no underlying valvular heart disease. There was a high rate of systemic emboli (41 % of patients). This study suggests that the main risk factor for the development of NBTE is an underlying hypercoagulable state whether congenital or acquired. A myriad of rheumatic diseases with or without anti-phospholipid syndrome have been associated with cardiac vegetation. In a French study of 759 patients with BCNE, a causative microorganism was identified in 62.7 %, and a noninfective etiology implicated in 2.5 %. After exclusion of infectious etiologies by the use of cultures, serology, broad-range PCR of blood and valvular tissue additional etiologies were investigated. The diagnosis of neoplasic or autoimmune disease was established based on histology and the presence of antinuclear antibodies in 19 (2.5 %). The authors systematically evaluated for presence of antinuclear antibodies in cases with no identified etiology in addition to obtaining additional information from physicians. These cases were classified as Marantic (7 cases) and autoimmune (12 cases) based on laboratory and clinical criteria [18]. In this series as well as others Behcet's disease was associated with BCNE [147, 148].

Non bacterial thrombotic endocarditis was first described by Libman and Sacks in 1924 and is not uncommonly referred to as Libman Sacks endocarditis [149]. The pathogenesis of NBTE in antiphospholipid syndrome is fascinating. Valvular vegetations in this setting are a consequence of the hypercoagulable state and endothelial damage by elevated levels of cytokines and complement activation [150]. Beta 2 glycoprotein I is the major target against which antibodies are directed in the antiphospholipid syndrome. These antibodies activate endothelial cells and monocytes with resultant expression of cellular adhesion molecules, upregulation of tissue factor production and platelet activation thereby promoting clot formation [150].

Illustrative Case

Case History: Culture Negative Endocarditis

This 76 year old female was admitted to hospital on June 3, 1991 with an 8 day history of fever, chills, anorexia, nausea, vomiting, and weakness, along with hip and knee pain. Four days prior to admission she saw her family doctor and was treated with ciprofloxacin.

Because of progression of her illness to the point where she was unable to look after herself (she lived alone) she came to the hospital. At this time she gave a history of hospitalization for pancreatitis 6 months earlier. She underwent upper gatrointestinal endoscopy while hospitalized and in retrospect feels that she has been febrile ever since.

She was in mild distress and her temperature was 37.8° orally. There was a III/VI pansystolic murmur at the apex with radiation to the axilla. Bilateral knee effusions were present. The white blood cell count was 9.6×10^9/L; serum creatinine 85 mM/L. Blood cultures were drawn and treatment was begun with cloxacillin for what was assumed to be cellulitis.

One day later she complained of shortness of breath and crackles were noted at both bases. A chest radiograph was compatible with mild congestive heart failure. The blood cultures were reported as negative the next day and a consultation was sought with Infectious Diseases. The consultant ordered a transesophageal echocardiogram which showed three plus mitral regurgitation and a large vegetation on the posterior leaflet of this valve. Therapy was begun with vancomycin. On day 7 a respiratory arrest occurred and after resuscitation she was transferred to the intensive care unit. On day 12 her mitral valve was replaced. A paravalvular abscess was present. The valve had myxoid features and a vegetation was evident (Fig. 10.5). A Gram stain showed scant intracellular gram positive cocci (Fig. 10.6). Despite prolonged incubation the cultures of the valve remained negative. She had a complicated post-operative course but eventually she made a full recovery.

Comment

This is a classic case of culture negative endocarditis due to prior treatment with antibiotics. The endocarditis was due to a gram positive coccus. Molecular methods (as discussed in this chapter) could have been used to identify the micro-organism. Given the combination of fever and a regurgitant murmur, endocarditis should have been suspected at the time of admission. At least three blood cultures should have been done but whether these would have let to an etiological diagnosis is speculative. The clinicians could have waited a couple of days before starting antibiotics and performed additional sets of blood cultures.

Fig. 10.5 Photograph of mitral valve from the patient with culture negative endocarditis. The red areas represent residual vegetation

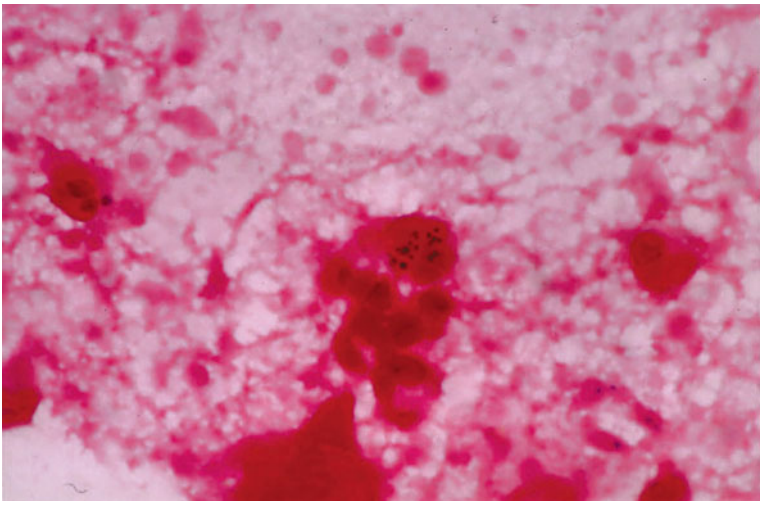

Fig. 10.6 Gram stain of material from the paravalvular abscess. Note the Gram-positive material within the white blood cells. Magnification x 1000

Conclusions

Blood culture negative endocarditis remains a formidable clinical challenge. Molecular diagnostic methods combined with serological studies have greatly improved the diagnostic yield, and the dawn of proteomics and genomics era in the microbiology laboratory is likely to improve our understanding of the epidemiology of BCNE.

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Prosthetic Valve Endocarditis and Cardiovascular Device Related Infections

11

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Abstract

Infections are known complications of prosthetic valves (PV) and cardiovascular devices (CD). PV and CD placement is increasing secondary to an extension of the indications for their use as well as an aging population. Thus there is an expanding population at risk for infection. Cardiac devices susceptible to infection include cardiovascular implantable electronic devices, coronary artery stents, pulmonary conduits, ventricular assist devices (VADs), total artificial hearts (TAHs) and intra-aortic balloon pumps. Rates of infections vary between devices with the highest rates occurring for VADs and TAHs.

Given the serious nature of PV and CD-related infections, establishing a prompt diagnosis and identifying the infectious etiology are important. In addition to pathogen-directed antimicrobials, surgical management may be required. Early consultation with a multidisciplinary team including infectious disease specialists, cardiologists, and cardiac surgeons is important to best determine optimal and patient tailored treatment.

Keywords

Endocarditis • Prosthetic valve • Cardiovascular device • Cardiovascular Implantable Electronic Device (CIED) • Ventricular Assist Device (VAD)

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Key Points

1. Infections related to prosthetic valves and cardiovascular devices carry high morbidity and mortality.
2. Several sets of blood cultures should be taken for suspected prosthetic valve or cardiovascular device related infections, preferably prior to antibiotics if patients are hemodynamically stable.
3. Microbiology of prosthetic valve and cardiovascular device infections varies depending upon the device and time from surgery with staphylococci predominating.
4. Transesophageal echocardiogram (TEE) is preferred over transthoracic echocardiogram for establishing the diagnosis of endocarditis in patients with prosthetic valves or cardiovascular device related infections.
5. Treatment of prosthetic valve and cardiovascular device related infections involves medical and often surgical approaches.
6. A multidisciplinary approach to management should be encouraged.

Introduction

Infections related to prosthetic heart valves (PVs) and cardiovascular devices (CDs) carry significant morbidity and mortality. As a result of an aging population as well as expansion of indications for their use, the rate of PV and CD placement has increased in recent years. A clear understanding of infectious complications of PVs and CDs is critically important to ensure proper diagnosis and management and optimize outcomes.

Cardiac prosthetic material includes PVs (mechanical and bioprosthetic), pulmonary conduits, permanent pacemakers (PPMs), implantable cardioverter defibrillators (ICDs), cardiac resynchronization therapy (CRT), ventricular assist devices (VADs), total artificial hearts (TAHs), cardiac stents, and intra-aortic balloon counterpulsation (Table 11.1).

Infections of PVs and CDs involve interplay of the foreign material/device, the microorganism and the host [1]. Foreign material in PVs and CDs can include tissue (homograft and xenograft), metal and polymers. The type of material, the shape of the device and the surface of the device can all influence development of infection with irregular, hydrophobic and synthetic surfaces more prone to bacterial adherence compared to smooth, hydrophilic biosynthetic surfaces [1].

Microorganisms causing PV or CD infection can bind to prosthetic material, bind at the site of attachment of prosthetic material to endothelium or bind to endothelium itself. Damage to endothelium exposes matrix proteins, which allow platelets and fibrin to deposit. Microorganisms preferentially localize and adhere to these damaged areas. PVs and CDs may also become coated with host proteins such as fibrinogen or fibronectin. Microorganisms, predominantly staphylococci, can produce proteins called microbial-surface proteins recognizing adhesive matrix molecules (MSCRAMMS), which can bind to host proteins coating prosthetic material.

Table 11.1 Types of cardiac devices and valves with potential for infection

Prosthetic heart valves
Mechanical
Bioprosthetic
Transcatheter aortic heart valve related
Pulmonary conduits
Cardiovascular implantable electronic device
Permanent pacemaker
Implantable cardioverter defibrillator
Cardiac resynchronization therapy
Ventricular assist devices
Total artificial hearts
Intra-aortic balloon pumps
Coronary stents

Staphylococcus aureus MSCRAMMS are important for adherence and colonization in animal models of infective endocarditis (IE) and VAD related infections [2, 3]. Once bound to endothelium or foreign material, microorganisms can produce extracellular polysaccharides known as biofilm, which acts to significantly inhibit antimicrobial penetration and action as well as limit host defenses [4]. Organisms known for notable biofilm production include coagulase negative staphylococci (CoNS), *S.aureus*, viridins group streptococci (VGS), enterococci, *Pseudomonas aeurginosa* and *Candida* species (spp.) [4].

Patient characteristics including age, sex, severity of underlying cardiac illness and co-morbidities can influence infection rates and outcomes and are important considerations when deciding on management of PV and CD infections.

Treatment of PV and CD infections involves intravenous antimicrobials and often surgical management. Although uncomplicated PV IE may be cured medically, depending on the pathogen, infections involving CDs often require device removal given high failure rates without surgical intervention and device removal.

Prosthetic Valve Endocarditis

Amongst patients with IE 20–24 % involve patients with a PV [5–8]. More than 90,000 PV are now placed annually in the United States [9]. The incidence of prosthetic valve infective endocarditis (PVIE) is 0.1–2.3 % per patient year [10] with the highest risk of PVIE being in the first post-operative year. A recent large study with patients aged 65–80 with aortic PVs showed that bioprosthetic valves had a higher risk for IE compared to mechanical valves with a mean follow-up of 12.6 years (Hazard ratio 1.6; 95 % CI: 1.31–1.94) [11].

Amongst patients with IE the presence of a PV itself is a risk factor for the development of IE. Farinas et al. found that patients with a preoperative New York Heart Association (NYHA) class III status, alcohol consumption, previous endocarditis, fever in the ICU and post-operative gastrointestinal (GI) bleeding were all risk factors for PVIE [12].

In early PVIE (within 60 days of surgery) infecting organisms are acquired in the perioperative period and are often nosocomial or non-nosocomial healthcare associated. Organisms causing PVIE more than a year after the initial operation are generally community acquired related to episodes of transient bacteremia. Data from the international collaboration on endocarditis, however, has shown that health care associated PVIE (including infections acquired nosocomial or non-nosocomial healthcare associated) is a significant contributor even in patients with late onset infections [7]. Amongst patients with healthcare associated PVIE, 62 % occurred after 2 months and 30 % occurred more than 1 year after valve surgery [7].

Microbiology of PVIE varies depending on the time elapsed since surgery. Some studies classify PVIE infections into early (occurring less than 2 months post valve replacement surgery), intermediate (between 2 months and 1 year) and late infections (occurring more than a year after surgery). Microbiology of intermediate infections is traditionally described as a mixture of early PVIE and late PVIE. Many studies do not use the intermediate classification and instead classify infections into early or late infections. The definition of a late PV infection varies in the literature with some studies using >2 months and others using >1 year. One of the largest studies on microbiology of PVIE using data from the International Collaboration on Endocarditis, however, defined late PVIE as being >2 months after valve replacement [7]. Of PV infections, 10–15 % occur less than 2 months from surgery [7, 13]. *S.aureus* and CoNS are responsible for most of the infections in the early period. Between 2 months and 1-year post surgery *S. aureus* and CoNS still remain the predominant pathogens (~50–60 % of isolates) [14, 15]. Methicillin-resistant *Staphylococcus aureus* (MRSA) infections tend to occur in early and intermediate PVIE compared to late [14]. Beyond 1 year community acquired organisms start to emerge as pathogens including Streptococcal infections (including viridians group streptococci as well as others) and enterococcal PVIE [16]. HACEK organisms (*Hemophilus species*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*) contribution to both early and late PVIE vary with more recent studies [8, 14–16] showing very little contribution compared to older studies [10]. There is a paucity of data from developing countries examining the microbiology of PVIE. A recent study from Turkey showed a significant contribution of gram-negative organisms and fungal infections in early PVIE [16]. In late PVIE in this study *Brucella* was a significant pathogen causing 22 % of infections [16]. Fungal infections of prosthetic valves are rare with *Candida albicans* being the most common [17].

Cultures are negative in 10–20 % of cases of definitive PVIE [5, 7, 8]. Although uncommon in North America, *Coxiella burnetti* (Q fever) endocarditis was the most commonly identified pathogen in a study of 348 cases of culture negative IE with specimens sent to the French National Reference Center for Rickettsial Diseases. Of the 167 patients with *C.burnetti* IE 42 % had a prosthetic valve [18] (Table 11.2).

Patients with PVIE tend to be older than patients with native valve infective endocarditis (NVIE) with a mean age of 65 in a study of 556 patients with PVIE [7]. Similar to NVIE there is a male predominance. Fever is present in 40–80 % of patients, congestive heart failure (CHF) present at presentation in 20–65 %, a new

Table 11.2 Microbiology of PVIs

Early infections (<2 months post surgery)	Late infections ≥2 months post surgery
S.aureus	*S.aureus*
CoNS	CoNS
Enterococcus	VGS
Culture negative	Enterococcus
Other pathogens[a]: fungi, non-HACEK gram negative bacilli, anaerobes, polymicrobial, streptococci including VGS	Other Streptococci[b]
	Culture Negative
	Other pathogens[a]
	Fungal, HACEK, non-HACEK gram negative bacilli, anaerobes, polymicrobial

S. aureus: *Staphylococcus aureus*, *CoNS* Coagulase negative Staphylococci, *VGS* Viridins Group streptococci, *HACEK* Hemophilus species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*

[a]<10 % of organisms isolated

[b]Includes *Streptococcus bovis*, *Streptoccoccus group B*, *C* and *G*

or changing murmur in 65 %, and cerebral vascular accident (CVA) present in 5–18 % [7, 19, 20].

Although originally intended for NVIE, diagnosis of PVIE is largely based on the modified Duke's criteria [21]. All patients suspected of PVIE should ideally have several sets of blood cultures obtained, prior to antimicrobials, if the clinical stability of the patient allows a brief delay. Cultures are positive in the majority of patients but may be negative in patients with previous antibiotic exposure or those with fastidious organisms. In patients who are culture negative, particularly those who did not have antimicrobials prior to cultures, a more extensive search for a pathogen should be done guided by local epidemiology and patient risk factors. Testing for *Brucella*, *Bartonella*, *Coxiella burnetti*, *Legionella pneumophilia*, *Chlamydia pneumoniae*, *Mycoplasma hominis and Tropheryma whipplei* may be considered and usually require serology and/or PCR [18].

Patients being investigated for PVIE should have a transesophageal echocardiogram (TEE). Although transthoracic echocardiogram (TTE) is often suggested as an initial investigation [22], it lacks the necessary sensitivity to be useful in investigating patients with suspected PVIE. Sensitivity of TTE in detecting vegetations in PVIE was 15 % in one study whilst sensitivity of TEE was 80 %[23]. Compared to NVIE where TEE sensitivity is >90 %, TEE in patients with PVIE is less sensitive [23]. TEE is also useful for evaluating complications of IE such as perivalvular abscess. Daniel et al. showed that TEE was significantly better at detecting abscesses with a sensitivity of 87 % compared to TTE, which had a sensitivity of only 23 % ($P = 0.001$) [24].

Imaging to look for emboli can be useful to identify patients who may require surgical intervention, identify potential complications (i.e. mycotic anyersum) and also establish diagnosis in cases where IE is not definitive. Central nervous system (CNS) emboli, are common in IE and up to 50 % of cerebrovascular complications in patients with IE are silent [25].

Table 11.3 Surgical criteria for PVI [29, 30]

Vegetation	Vegetation >1 mm (especially anterior mitral leaflet), increase in vegetation size on adequate antimicrobial therapy
Valve	Aortic or mitral valve insufficiency with CHF, Valvular dehiscence or rupture
Extension	Abscess, fistula, or heart block
Microorganism	Fungal infections including *Candida spp.*, multidrug resistant gram-negative Bacilli or enterococci, *Pseudomonas aeruginosa*, Brucella
Others:	Persistent blood cultures after 1 week of antimicrobial therapy, recurrent embolic events, relapse after completion of medical therapy, CHF unresponsive to medical therapy

Treatment for PVIE requires antimicrobial therapy with or without surgical intervention. All patients should have consultation with an infectious diseases specialist as well as a cardiovascular surgical consultation particularly if they meet any criteria for surgical intervention (Table 11.3) [26]. Chirillo et al. found that mandatory and immediate involvement from a multidisciplinary team consisting of surgeons and infectious disease specialists improved in hospital and 3-year mortality in patients with PVIE compared to patients in a historical era [5].

Patients should be carefully selected for surgical intervention depending on various factors including the integrity of the valve, extension of the infection, vegetation characteristics and organism isolated (Table 11.3) in addition to comorbidities and surgical risk assessment. A recent study in patients with PVIE receiving early surgery for valve replacement (within 60 days) found no mortality benefit at 1 year [27]. Similarly, another study using the same cohort data but specifically looking at mortality in patients with *S.aureus* PVIE also found no mortality benefit of early surgery at 1 year follow up [28]. Patients who survived beyond 7 days after early valve replacement surgery, however, did have a mortality benefit at 1 year compared to patients who did not have surgery (risk ratio, 0.53 (95 % CI, 0.30–0.97), P = 0.04) [28]. Timing of surgical intervention depends upon the patient's clinical status and the indication for surgery. The decision of surgical timing should be made by a multidisciplinary team including Cardiologists, Cardiothoracic surgeons and Infectious Diseases specialists [29]. Patients with PVIE and cardiovascular implantable electronic devices (CIEDs) should have these devices removed [29].

Empiric antimicrobial therapy should be guided by the Infectious Diseases Society of America (IDSA) guidelines [30] and local epidemiology but would typically include vancomycin 15 mg/kg IV every 12 h, gentamicin 1 mg/kg IV every 8 h and rifampin 300 mg po TID until results of blood cultures and susceptibilities are available. Table 11.4 shows the different treatment regimens for PVIE based upon organism isolated [30]. For MRSA PVIE or CoNS resistant to methicillin vancomycin should be used as well as rifampin and gentamicin. If vancomycin cannot be used due to allergy or other serious intolerance daptomycin 8 mg/kg IV daily can be used [32].

Enterococcal PVIE should be treated with 6 weeks of therapy of a cell wall active agent and aminoglycoside as beta lactam antibiotics and vancomycin alone are not bactericidal against enterococal infections. Therefore aminoglycoside synergy for

Table 11.4 Treatment regiments for PVIE based upon IDSA guidelines [30]

Infection	Primary regiments	Duration
VGS and *S.bovis* with penicillin MIC ≤0.12 μg/ml	Penicillin 24MU ÷ Q4-6 h IV	6 weeks
	Or	
	Ceftriaxone 2 g IV daily	6 weeks
VGS and *S.bovis* with penicillin MIC >0.12 μg/ml	Penicillin 24MU ÷ Q4–6 h IV	6 weeks
	Or	
	Ceftriaxone 2 g IV daily	6 weeks
	Plus	
	Gentamicin 1 mg/kg IV TID	6 weeks
Abiotrophia defectiva, *Granulicatella* or *Gemella* species	Treat similar to enterococcal IE (see below)	6 weeks
MSSA	Cefazolin 2 g IV Q 8 h	6 weeks
Or	**Or**	
Methicillin S CoNS	Cloxacillin 2 g IV Q 4h	6 weeks
	Plus	
	Rifampin 300 mg po TID	6 weeks
	Plus	
	Gentamicin 1 mg/kg IV TID	2 weeks
MRSA	Vancomycin 15 mg/kg IV BID	6 weeks
Or	**Plus**	
Methicillin R CoNS	Rifampin 300 mg po TID	6 weeks
	Plus	
	Gentamicin 1 mg/kg IV TID	2 weeks
Enterococcus	Ampicillin 2 g IV Q 4 h	6 weeks
Ampicillin sensitive [31]	**Plus**	
	Gentamicin 1 mg/kg IV TID	6 weeks
	Or	
	Ampicillin 2 g IV Q 4 h	6 weeks
	Plus	
	Ceftriaxone 2 g IV Q 12 h	6 weeks
Enterococcus	Vancomycin 15 mg/kg IV BID	6 weeks
Ampicillin resistant	**Plus**	6 weeks
	Gentamicin 1 mg/kg IV TID	
HACEK	Ceftriaxone 2 g IV daily	6 weeks
Hemophilus, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella*	**Or**	
	Ampicillin 2 g IV Q 4 h[a]	6 weeks
	Or	
	Ciprofloxacin 500 mg po BID	6 weeks
Early culture negative endocarditis	Vancomycin 15 mg/kg IV BID	6 weeks
(Infections ≤1 year after surgery)	**Plus**	
	Cefepime 2 g IV TID	6 weeks
	Plus	
	Rifampin 300 mg IV/PO TID	6 weeks
	Plus	
	Gentamicin 1 mg/kg IV TID	2 weeks

(continued)

Table 11.4 (continued)

Infection	Primary regiments	Duration
Late culture negative endocarditis	Ampicillin-sulbactam 3 g IV Q 6 h	6 weeks
(Infections >1 year after surgery)[b]	**Plus**	
	Rifampin 300 mg IV/PO TID	6 weeks
	Plus	
	Gentamicin 1 mg/kg IV TID	6 weeks
Gram negatives	Culture results to guide therapy	6 weeks
(Enterobacteriaceae, Pseudomonas)	Pseudomonas infections should receive combination therapy	

Mean Inhibitory Concentration (*MIC*), *Viridians group streptococci* (*VGS*), *Streptococcus bovis* (*S. bovis*), methicillin susceptible *staphylococcus aureus* (*MSSA*), methicillin resistant staphylococcus aureus (*MRSA*), coagulase negative staphylococci (*CoNS*)
[a]For Penicillin allergic patients with type 1 allergy Vancomycin 15 mg/kg BID can be used instead
[b]Alternative combination: Vancomycin+ Gentamicin+ Rifampin+ Ciprofloxacin for 6 weeks

the whole duration of therapy (6 weeks) is needed. A recent small study showed that a shorter duration of aminoglycoside therapy (2 weeks) was effective in patients with *E.faecalis* IE [33]. This study involved mostly patients with NVIE with 36 % of patients with PVIE. Although more studies are needed to fully evaluate the efficacy of this approach, short course aminoglycoside therapy could be considered for patients with enterococal PVIE in whom long-term aminoglycosides are highly undesirable or relatively contraindicated. High-level resistance to gentamicin in enterococci can occur due to aminoglycoside modifying enzymes [34]. These enzymes covalently alter the aminoglycoside and inhibit binding to the ribosome. Isolates with high-level resistance to gentamicin may still be susceptible to streptomycin, which can be used for synergy in such cases. Recently updated IDSA guidelines indicate that ceftriaxone in combination with ampicillin may be considered in patients with *E.faecalis* PVIE when aminoglycosides are contraindicated or with high-level resistance to gentamicin [31]. A non-randomized multicenter cohort study of patients with *E.faecalis* IE demonstrated similar mortality rates between patients treated with ceftriaxone and ampicillin compared to those treated with ampicillin and gentamicin; 35 % of the patients in the study had PVIE [35]. Fewer patients in the ceftriaxone and ampicillin group had treatment interruption due to adverse events. A study of 500 patients with enterococcal IE (both prosthetic and native valve) showed that >90 % of enterococci isolates were *E.faecalis* [36]. *E.faecalis* is usually ampicillin susceptible as opposed to *E.faecium*, which is usually ampicillin resistant. Vancomycin resistant enterococcus (VRE) PVIE is rare and optimal treatment is unknown. Linezolid, daptomycin, tigecycline and gentamicin have all been used either as single agents or in combination therapy for VRE IE [37].

Staphylococcal PVIE (*S.aureus* and CoNS) is treated similarly to NVIE with the exception of the addition of rifampin for 6 weeks duration as well as the use of gentamicin for 2 weeks duration.

Early-onset culture negative PVIE should be treated with vancomycin, rifampin, and cefepime for 6 weeks duration with addition of gentamicin for the first 2 weeks

[30]. Late-onset PVIE is managed with the same regimens as for native valve IE with the addition of rifampin.

PVIE from *Candida* spp. needs surgical assessment for valve replacement. Treatment typically requires therapy with liposomal amphotericin B (3–5 mg/kg) +/− flucytosine or an echinocandin +/− amphotericin B [38]. Step-down to fluconazole can be done if the isolate is susceptible and once blood cultures have cleared. Monotherapy with fluconazole or an echinocandin has been used successfully in several cases [39, 40]. Patients without valve replacement should have lifelong suppressive fluconazole while those with valve replacement should have antifungal therapy continue for a minimum of 6 weeks post replacement [38] (Tables 11.3 and 11.4)

Gram negative PVIE typically requires 6 weeks of therapy with an intravenous agent(s) tailored to the organism depending upon culture results. Combination therapy for pseudomonal PVIE is suggested [30].

In hospital mortality for PVIE is 20–25 %[5, 7, 13] and is higher than that for NVIE [7]. Chirillo et al. found that age over 70 years, *S.aureus* infection, CHF, multi-organ failure and intra-cardiac abscess were all independent predictors of mortality at 3 years [5]. Similarly, the International Collaboration on Endocarditis PVIE data showed that risk factors for in hospital mortality included age over 75 years, *S. aureus* infection, health care association, persistent bacteremia, CHF, stroke, and abscess [7].

Guidelines for antibiotic prophylaxis for IE were revised in 2007 [26]. Prophylaxis prior to dental procedures that manipulate gingival tissue, periapical region of teeth or perforation of the oral mucosa was recommended to high-risk patients only. High risk patients for IE includes all patients with PVs, those with previous IE, cardiac transplant recipients with valuopathy, congenital heart disease (CHD) with unrepaired cyanotic disease, CHD completely repaired with prosthetic material or device until 6 months post procedure, or CHD with repairs which would impair endothelialization [41]. Preferred prophylaxis is with amoxicillin 2 g orally as 1 dose 30–60 min prior to the procedure. Penicillin allergic patients can take 1 dose of clindamycin 600 mg orally. Alternative agents include cephalexin 2 g or azithromycin 500 mg.

High-risk patients who undergo bronchoscopy with incision or biopsy of the mucosa should also receive prophylaxis prior to the procedure. A single dose of cefazolin 2 g IV or ceftriaxone 1 g IV can be given prior to the procedure. For patient undergoing a gastrointestinal (GI), or genitourinary (GU) procedure antibiotic prophylaxis is not recommended even for high-risk patients. Patients with an established GI or GU infection, however, should have prophylaxis given with enterococci coverage (i.e. ampicillin or vancomycin). Patients with established urinary tract infection or colonization with enterococcus should have antimicrobial therapy to treat this prior to having a cystoscopy.

Transcatheter Aortic Valve Replacement

The advent of Transcatheter Aortic Valve Implantation (TAVI) has allowed otherwise high risk surgical candidates to have correction of severe aortic stenosis. Since 2002 over 50,000 TAVI procedures have been done worldwide [42]. Of the two

Health Canada approved TAVI systems, SAPIEN valves (Edwards Lifesciences, Irvine, CA) use bovine material and CoreValve ReValving system (Medtronic, Minneapolis, MN) uses porcine material.

Fever following TAVI is common occurring in ~20 % of patients [43] which may cloud the diagnosis of an infection. A recent case series identified 29 patients in the literature reported to have IE related to TAVI [44]. Twenty eight percent of cases were from *E.faecalis* and ~15 % from CoNS. Most patients were treated medically, and 6 month mortality was 39.6 % [44]. Falcone et al. prospectively followed 51 patients with TAVI and 102 patients with traditional surgical aortic valve replacement (AVR) [45]. Patient's receiving surgical AVR were younger and less likely to have severe CHF, but they had a higher incidence of early, intermediate and late post-operative infections [45]. Bacteremia was statistically higher in the surgical AVR group 19 % compared to 8 % in the TAVI group [45]. None of the patients in the study had IE.

Pulmonary Conduits

Right ventricle to pulmonary artery conduits are used for surgical repair of a wide range of congenital heart diseases including pulmonary atresia or stenosis, tetralogy of Fallot, transposition of the great vessels, and truncus arteriosis. Conduits can be make of a variety of materials including Gore-Tex® but most commonly are bioprosthesis, either cryopreserved homografts or xenografts [46]. Van Dijck et al. retrospectively examined 738 patients with right ventricular outflow tract (RVOT) conduits [47]. Incidence of IE in patients with homografts was 0.8 %/year while patients who received Medtronic Melody® Transcatheter pulmonic valve replacement (TPVR) had a incidence of IE of 3 %/year [47]. The Medtronic Melody TPV is made of bovine jugular vein with a trileaflet valve and delivered by catheter with fluoroscopic guidance.

Medtronic Melody® TPVR was given FDA approval in 2010 for patients with ROVT conduits with regurgitation or stenosis needing repair. A recent study examining incidence of infective endocarditis in 311 patients from 3 clinical trials with TPVR found an annual event rate of a first IE episode of 2.4 % per patient year [48]. Patients with IE confined to their pulmonic valve had an event rate of 0.88 % per patient year [48]. Ninety five percent of the organisms from the 21 patients with IE were staphylococci or streptococci [48]. High RVOT gradient pre and post-implant were both found to be risk factors for IE [48]. Two of the six patients with TPVR related IE were treated medically and survived. Four of the patients with TPVR related IE had their devices replaced with only two of the patients surviving.

Cardiac Implantable Electronic Device Infections

Infections related to CIEDs have increased likely related to an aging population and the expansion of indications for their use. CIED devices include PPMs, ICDs and CRTs. Voigt et al. showed a 210 % increase in CIED related infections from 1993

to 2008 using files from the United States Nationwide Inpatient Sample [49]. Incidence of CIED infections is 1.6/1,000–4.8/1,000 device years [50–52]. Some studies have suggested an increased rate of infection for ICDs compared to PPM [50] but other studies have not supported this [53]. CIED related infections are broadly categorized into [54, 55]:

1. Those involving the pocket:
   (a) Uncomplicated Pocket Infections
   (b) Complicated Pocket Infections (Lead or endovascular involvement or positive blood cultures)
2. Those causing endovascular infection without signs of pocket infection
   (a) Lead Infection
   (b) IE of native or prosthetic valves

Infections that involve the pocket can either stay localized or have potential to become blood borne and involve the lead, heart valves or both. Infections with endovascular involvement could have originated in the pocket, seeded from a transient bacteremia, or seeded from infection at a distant site. Infections involve the pocket in ~59–69 % of cases [56, 57] with 17–21 % having a pocket infection and bacteremia [56, 57]. Sohil et al. reported device related IE in 23 % of CIED infections [56]. Most CIED infections occur in the first year after implantation but ~1/3 can present after a year [53]. Risk factors for infection in a Danish study of 46, 299 patients with PPMs included male sex, younger age, absence of prophylactic antibiotics, and multiple PPM operations [50]. Lekkerkerker et al. identified device revisions and renal failure as risk factors for CIED infections in a study involving PPMs, ICDs, and CRTs [53].

Microbiology of CIED infections is predominated (~80 %) by S*taphylococci* with a slightly higher CoNS contribution compared to *S.aureus* [56, 57]. After S*taphylococci*, gram-negative bacilli contribute to about 10 % of pathogens [56]. Other pathogens such as anaerobes, fungi and mycobacteria collectively contribute to less than 10 % of infections. In one study, 44 % of *S.aureus* isolates involved in CIED infections were MRSA [57]. Microbiology of generator or lead erosion involves skin microorganisms including CoNS, *S.aureus*, *Propionibacterium spp.*, and *Corynebacterium spp.* [56].

Diagnosis of a CIED infection can be challenging. Signs of pocket infection include tenderness, erythema, swelling, wound dehiscence, or pus. Pocket erosion may be evident with visible leads or generator. Systemic signs of infection, including fever and malaise, are present in less than half of patients with CIED infections [57] but patients with documented IE are febrile in 80 % of cases [58]. TEE should be done in all patients with positive blood cultures. Bacteremia with *S. aureus* in one large study of PPM infections was associated with definitive or possible IE in 54 % of patients compared with 12 % for patients with gram-negative bacteremia [50]. At least three sets of blood cultures should be done in the evaluation of a patient for a CIED infection. Tarek et al. reported that blood cultures were positive in 94 % of patients with documented CIED endovascular infections but only positive in 21 %

of patients in pocket infections without endovascular involvement [57]. If there is skin breakdown, drainage or sinuses at the site of the pocket these should be swabbed for bacterial culture and sensitivity. If bacterial cultures are negative fungal cultures and mycobacterial cultures should be done.

CIED infections are treated by device removal and antimicrobials [54]. If infection limited to the pocket (including device erosion) device removal is still recommended as the entire device is presumed to be infected with relapse rates of approximately 50 % with device retention. Ten to 14 days of antimicrobials are suggested in addition to the removal for treatment of pocket infections. Empiric coverage with vancomycin, or daptomycin is recommended for patients presenting only with infection of the pocket with the agent tailored depending on culture results [55]. Patients with positive blood cultures should have a TEE to evaluate the heart valves as well as the leads for evidence of vegetations. If TEE is negative for IE, 10–14 days of IV antimicrobials targeted to the organism are suggested for non-*S. aureus* infections and 2–4 weeks for *S.aureus*-related infections [54]. Those with valve infections should be treated similarly to patients with PVIE (Table 11.3). Patients with lead vegetations without valve infection should receive between 2 and 6 weeks of IV antibiotic therapy depending upon the presence of complications such as venous thrombi as well as the organism [54]. New devices can be placed 14 days after negative blood cultures for patients with infective endocarditis, while 72 h of therapy prior to new device placement is appropriate for those with lead vegetations only, and those with infections isolated to the pocket [54]. CIED removal can generally be done percutaneously with open surgical removal rarely needed. Lead extraction may be difficult more than 1 year after device placement due to the presence of adhesions [59]. Laser lead extraction increases the success of removal in such patients depending on local expertise.

A recent study of 502 patients with lead extraction for an ICD infection found a 1 year mortality of 20 % but mortality was significantly lower in patients who only had a pocket infection [60]. Patient with pocket infections with bacteremia had a higher mortality than those with pocket infections alone, but a lower mortality than patients with endovascular infection.

VAD Infections

Ventricular assist devices (VADs) differ form other cardiac devices in that they maintain a percutaneous connection via a driveline. This percutaneous connection thus can act as a portal of entry to infection. Previously used mainly to provide hemodynamic support as a bridge to transplant, VADs are increasingly used as destination therapy in patients who are not transplant candidates [61]. VADs are also used in some patients as a bridge to hemodynamic recovery following acute cardiac insults such as viral cardiomyopathy. Continuous flow VADs are now the standard of care [62] and represent >95 % of VADs placed since 2010 in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database [61]. One-year survival for patients with VADs is 80 %, with decreased survival for

patients with biventricular VADs (BiVADs) [61]. Infection occurs in 22–50 % of continuous flow VADs [63–66]. A recent study of over 101 VAD infections found an incidence rate of 32.8/100 person years of VAD support [63].

Recent consensus guidelines have characterized infections in patients with VADs into three main classifications [67].

1. VAD specific infections
   (a) Pocket infections
   (b) Drive line infections (deep or superficial)
   (c) Pump or cannula infections
2. VAD related infections
   (a) IE
   (b) Mediastinitis
      i. VAD related or Non-VAD related
   (c) Blood stream infections
      i. CVC Present: VAD related or CVC related
      ii. CVC Absent: VAD related or VAD non-related
3. Non-VAD infections

CVC: Central Venous Catheter

In VAD specific infections organisms are thought to enter from the percutaneous driveline site causing either superficial or deep infections or can migrate further and involve the pocket and/or the pump. Further extension of infection itself or a bacteremia can cause a VAD related infection involving structures such as the heart valves or the mediastinum. Most VAD infections (50–80 %) involve the driveline [63, 65]. Forty six to 50 % of infections will have an associated bacteremia [63–65] of which roughly half are VAD associated and 5–16 % will have IE [64]. Trauma to the driveline site is a risk factor for driveline infections. Risks for VAD infections in general include renal failure [65], the presence of depression [65], the use of total parental nutrition [64] and duration of VAD therapy. Diabetes was found to be a risk factor for developing a blood stream infection in patients with VAD infection [66].

Diagnosis and classification of the VAD infection is critical to appropriate management. Several sets of blood cultures should be drawn in all patients with a suspected VAD infection as well as collection of cultures from the driveline site if signs of infection are present, such as erythema and/or increased drainage or purulence. Infections of the pocket may be clinically apparent with erythema, tenderness and warmth over the site but occasionally can be silent. Additional imaging with ultrasound or CT scan may be needed to look for pocket and/or pump infection or mediastinitis. Echocardiography should be done to look for concurrent IE and may also show features such as outflow tract dehiscence or vegetations that may be signs of pump and/or cannula infection [67]. Patients with endovascular infection are more likely to have fever, an increased blood cell (WBC) count and meet criteria for Systemic Inflammatory Response Syndrome (SIRS) compared to patients with local driveline infections [63]. Although usually not feasible for technical reasons and the ongoing need for cardiovascular support, if the VAD is removed, cultures for

bacterial and fungal pathogens should be taken intra-operatively from the pocket as well as from the internal and external sites of the inflow and outflow cannulae [67].

VAD infections usually occur within the first few months of placement with a median time of 2–4 months [63, 65]. Microbiology is predominated by *Staphylococci* (40–47 %) and gram-negative bacilli (24–32 %) [63–65]. Fungal pathogens, most often *Candida* spp., account for 8–14 % of VAD infections [63, 64] and carry a higher mortality compared to bacterial infections [64].

Treatment of VAD infections is complex and related to the classification of infection. For infections that are confined to the driveline 2–4 weeks of antimicrobial therapy +/− surgical debridement depending upon the depth and extent of infection has been suggested [63]. For infections that involve the pocket, however, chronic suppressive therapy in addition to the initial 2–4 week course of antimicrobials and surgical debridement may be necessary [63]. Those with IE should have a minimum of 6 weeks IV therapy and then chronic suppressive therapy. Infections involving the pump and cannula should receive 4–6 weeks of IV antimicrobial therapy combined with surgical debridement followed by chronic suppressive therapy [63]. Unlike PVIE, the large surface area of the VAD makes eradication of organisms after 6 weeks unlikely. VAD replacement should be considered if infection is failing medical management and if technically feasible.

Patients with VAD infections have increased mortality with the 1-year hazard ratio of mortality in one recent study of 5.6 (95 % CI, 2.4–12.8; $P < 0.0001$) [63] and the 1-year survival in another study of 43 % [63]. Analysis of patients with VAD infections who survive to transplant however has shown that overall post-transplant mortality is not altered [66]. Therefore, VAD infections should not be a contraindication to transplant.

Standard antimicrobial surgical prophylaxis should be used in patients undergoing VAD infections and tailored to local microbiology. Some institutions use ongoing antibiotic prophylaxis beyond the standard post-op period. Stulak et al. showed in a retrospective cohort with two institutions utilizing different prophylactic strategies that ongoing antibiotic prophylaxis did not decrease drive line infections [68]. A recent study of fungal VAD infections also showed that fluconazole prophylaxis did not decrease fungal VAD infections in their study [64]. A combined approach of improved surgical techniques in driveline placement, inpatient education and ongoing outpatient management of the driveline can decrease driveline infections [69]. Transcutaneous energy transfer and free-range resonant electrical energy systems are being developed for use with VADs [70]. These would allow, similar to the AbioCor TAH, for the VAD to be self-contained without an external driveline and could potentially decrease infections.

Total Artificial Heart Infections

SynCardia systems CardioWest total artificial heart (TAH) was granted FDA approval in 2004 as a bridge to transplant and remains the only TAH granted such approval in the USA [71]. In 2014 the FDA approved the Freedom® portable driver

allowing patients to be discharged from hospital with an implantable TAH. AbioCor, the first self-contained TAH was given FDA approval in 2006 for humanitarian use. In a clinical trial of 14 patients with end stage heart disease, 11 of the patients developed infections (event rate 0.52 per subject/month) and 4 patients died from sepsis or multi-organ failure [72].

TAHs represent a very small proportion of artificial assist devices. According to the INTERMACs database between 2008 and 2013 TAHs represented less than 3 % of devices. Similar to VAD patients, infections occur frequently in this population and contribute to mortality. A study of 47 patients with TAHs implanted for a minimum of 1 year from 1987 to 2011 showed that 53 % of patients develop infections requiring IV antibiotics [73]. Interestingly patients with a lower body surface area had an increased risk of death [73]. Another study of 90 patients with SynCardia TAH showed that 14 % of patients developed mediastinitis [74].

Coronary Artery Stent Infections

Infections of coronary artery stents are rare events but carry high mortality. Percutaneous coronary intervention (PCI) may introduce vessel trauma and inflammation, which can be potentiated by the indwelling stent. Microorganisms introduced at the time of PCI or from a subsequent bacteremia can then seed the inflamed vessel and stent. Drug eluting stents (DES) have immunomodulation and anti-proliferative effects and may act as local immunosuppressants. However, a recent review of 29 cases of infected coronary artery stent infections showed a similar percentage of infections in patients with bare metal stents (48.5 %) and DES (55.2 %) [75].

Microbiology of coronary stent infections typically involves gram-positive organisms. Bosman et al. found that skin organisms were responsible for all cases of infections in their review of 29 patients [75]. Fever was the most common presenting sign in this study present in 93 % of patients, 51 % had chest pain and leukocytosis was present in 44 % [75]. The majority of patients with coronary artery stent infections present within a few days up until the first month after implantation [75, 76].

Diagnosis of a stent infection may be difficult and can be associated with pseudoaneurysm or mycotic anyersum [77, 78]. Complications include vessel or myocardial rupture, myocardial infarction, pericarditis, and purulent pericarditis [78]. Bosman et al. identified that the presence of a pseudoaneurysm in 78 % of patients with coronary stent infections [75]. Arterial weakening with anyersum formation is a known complication of both drug eluting stents (DES) and bare-metal stent implantation [79]. ECG changes may be present if myocardial ischemia is present or in the case of an anyersum [80]. Diagnosis of stent infection with coronary angiography has been successful in many cases [80]. PET-CT scans have been used with success in a small number of patients. Both WBC scans and TEE have high rates of false negatives limiting their utility [75, 78]. TEE may be useful to evaluate for a concurrent IE.

Treatment of stent related infections should ideally involve removal of the infected material accompanied by systemic antimicrobials targeted to the organism. Mortality of stent related infections is high with an infection related mortality of 48 % in the Bosman et al. review [75].

Intra-Aortic Balloon Pump Infections

Intra-aortic balloon pumps (IABP) provide circulatory support for a wide range of conditions including cardiac catheterization, cardiogenic shock, weaning from bypass and unstable angina [81]. IABP infections are rare events and can be difficult to diagnose. The Benchmark Counterpulsation Registry which contains information on >20,000 patients with IABP lists many complications of IABP insertion including limb ischemia, severe bleeding and balloon failure/leak but does not list infection as a complication. A small prospective study of patients with IABP found that 15 % of patients had a bacteremia following insertion with up to 50 % of patients meeting SIRS criteria [82]. Pawar et al. examined 2,558 patients with IABP and found 14 had bacteremia and 7 had a surgical site infection. *P. aeruginosa* was the most common organisms in bacteremic patients and *S. aureus* was more common in patients with surgical site infections [83]. Aksnes et al. in a small study of patients with IABP showed that sepsis was associated with a longer duration of IABP placement and with patients who had received a prosthetic valve [84].

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Pediatric Infective Endocarditis and Congenital Heart Disease

12

Sarah Forgie

Abstract

Pediatric infective endocarditis (PIE) is an infection of the endocardial surface of a child's heart. Children with abnormal hearts from congenital heart disease are at higher risk for PIE. This chapter describes the epidemiology, etiology, diagnosis, treatment and prevention of PIE – focusing on children with congenital heart defects. In the future, the incidence of PIE will likely continue to increase and the etiologic agents will likely become more difficult to treat as antimicrobial resistance increases. Research is needed in the areas of primary prevention of PIE, improved diagnostic methods for PIE and effective therapies for PIE caused by multidrug resistant pathogens. In the interim, health care providers need to be cognizant of PIE in children with CHD because early diagnosis and therapy can decrease morbidity and mortality.

Keywords

Pediatric • Infective endocarditis • Congenital heart disease

Key Points

1. Children with abnormal hearts from congenital heart disease are at higher risk for PIE. Those at highest risk include: children with prosthetic cardiac valves (or cardiac valves that have been repaired with prosthetic material), a past history of PIE, unrepaired cyanotic congenital heart disease, congenital heart defects that have been completely repaired with prosthetic material within 6 months of surgery, repaired congenital heart lesions with residual defects at or near prosthetic material, or children with cardiac transplants who develop valvulopathy.

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2. The frequency of PIE continues to increase, because of increased successful cardiac surgeries for extremely complicated cardiac defects; premature neonates surviving at earlier gestational ages; and the increased use of intravascular devices.
3. The etiology of PIE is slightly different from adults, with *Staphylococcus aureus*, viridans group streptococci and coagulase negative staphylococci being common causes, but other pathogens such as group B streptococci, *Streptococcus pneumoniae* and *Haemophilus influenzae* also causing PIE. Candida spp. cause PIE more frequently in premature infants. When compared to adults, the HACEK organisms and enterococci rarely cause PIE.
4. The diagnosis of PIE can be difficult, and a multifaceted approach using clinical findings, laboratory evidence and echocardiographic findings is required. Clinical findings in children may be very subtle and in infants may be indistinguishable from sepsis or heart failure and classical immunological signs such as Janeway lesions and Roth spots are rarely seen in children; the amount of blood that can be drawn from children varies with their weight and this may affect the yield of positive blood cultures; and the sensitivity and specificity of echocardiograms varies depending on the age and characteristics of the child.
5. Treatment of PIE requires prolonged, intravenous, bactericidal antimicrobials and the antimicrobial must target the etiologic agent.
6. The conjugate pneumococcal vaccine plays a role in preventing pneumococcal PIE, and the use of antimicrobial prophylaxis must take into account the degree to which the child's underlying heart defect creates a risk of PIE, the risk of bacteremia with the procedure and the potential adverse effects and cost of the prophylactic agent to be used.

Introduction

Pediatric infective endocarditis (PIE) is an infection of the endocardial surface of a child's heart with bacteria, rickettsia, chlamydiae, mycoplasmas or fungi [1]. Any part of the endocardium, where turbulent blood flow occurs can become a nidus for infective endocarditis [2] (Table 12.1).

Children with abnormal hearts from congenital heart disease (CHD) are at higher risk for PIE. It is difficult to determine the incidence of CHD among live born infants because many cardiac lesions are not diagnosed in the neonatal period. A conservative estimate of the number of American children with CHD detected in the first year of life is 8 cases per 1,000 live births [3]. Risk factors for the development of CHD are diverse, and may include: maternal diabetes, exposure to rubella or teratogenic drugs such as indomethacin, cocaine or alcohol during pregnancy and certain genetic syndromes. There are 18 distinct congenital cardiovascular defects with

Table 12.1 Areas of a child's heart that may serve as a nidus for PIE

Heart valves	Normal native valves
	Abnormal native valves
	Prosthetic valves
Septal defects	Septal defect pre-operatively
	Repaired septum post-operatively
Artriovenous shunts	Native shunt
	Artificial conduits
Arterioarterial shunts	Patent ductus arteriosus
Endocardium	Especially at sites of "jets" or turbulent flow

multiple anatomic variations, and these defects can be divided into two broad categories – cyanotic and acyanotic CHD. In the latter group, the largest proportion are ventricular septal defects, while atrial septal defects, atrioventricular canals, pulmonary valve stenosis, patent ductus arteriosus (PDA), aortic valve stenosis and coarctation of the aorta are some of the other types of acyanotic CHD. Amongst the cyanotic heart lesions, tetralogy of Fallot and transposition of the great arteries are the most common [3].

The American Heart Association has further defined the risk of PIE in children with CHD (whether repaired or unrepaired). Those at highest risk include children with prosthetic cardiac valves (or cardiac valves that have been repaired with prosthetic material), a past history of PIE, unrepaired cyanotic congenital heart disease, congenital heart defects that have been completely repaired with prosthetic material within 6 months of surgery, repaired congenital heart lesions with residual defects at or near prosthetic material, or children with cardiac transplants who develop valvulopathy [4].

Epidemiology

The epidemiology of PIE continues to change. Well into the twentieth century, one third to one half of PIE was a direct result of underlying rheumatic heart disease with seeding of damaged heart valves by alpha-hemolytic streptococci. As effective antibiotic therapies for streptococcal pharyngitis emerged, the incidence of rheumatic heart disease decreased [5]. Despite this decrease in rheumatic heart disease, the frequency of PIE has been continuing to increase. There are several reasons for these epidemiological changes, but the most plausible involves the huge advances in many areas of medicine including: increased successful cardiac surgeries for extremely complicated cardiac defects; premature neonates surviving at earlier gestational ages; and the increased use of intravascular devices [6–9].

Over half of PIE cases are related to surgery for congenital heart disease. The ***type of surgery*** is an important determinant in the risk for PIE. Overall, the highest annualized risk for PIE is in children that have had repair or palliation of cyanotic congenital heart disease (especially repair of pulmonary valve stenosis or pulmonary valve atresia or aortic valve replacement). In contrast, those that had repair of

atrial septal defect secundum or mild pulmonic stenosis are at low risk for PIE. In addition to the type of surgery, the ***time from surgery*** also alters the risk for PIE. Generally, the incidence of PIE immediately after most surgical procedures is low, but increases over time. However, there are exceptions. First of all, when prosthetic valves or conduits are used, the risk for PIE is high even in the first 2 weeks after surgery [6, 10]. Secondly, for certain surgeries such as a patent ductus arteriosus (PDA) repair, ventricular septal defect (VSD) repair or atrial septal defect (ASD) repair, the risk of PIE is negligible 6 months after surgery [11, 12].

Premature neonates are another group at risk for PIE. These premature infants often have PDA lesions, which put them at risk for PIE. Additionally, as the gestational age decreases, more invasive procedures are required for survival. Transient bacteremias from skin trauma and mucous membrane trauma, coupled with the use of high lipid total parenteral nutrition, an immature immune system and frequent use of central venous catheters put these children at high risk for bacteremia. The central venous catheters not only breech the skin, they also induce trauma to the right side of the heart (both endocardium and valves) and often induce clot formation and intracardiac thrombi [13, 14]. Use of these catheters in the neonatal population and congenital heart disease (including PDA) are the top risk factors for PIE [2].

In 10 % of children, there is no identifiable underlying risk factor [15]. These children develop bacteremia and seed normal heart valves. Intravenous drug abuse and degenerative heart disease – common risk factors for endocarditis in adults, rarely play a role in PIE.

Etiology

The etiology of PIE is slightly different than IE in adults. Overall, causative agents isolated from blood cultures include the gram positive cocci – viridans streptococci (32–43 % of isolates), *Staphylococcus aureus* (27–33 % of isolates), coagulase negative staphylococci (2–12 % of isolates), and *Streptococcus pneumoniae* (3–7 % of isolates). Later data from 2000 to 2003 that reviewed over 1,500 pediatric admissions with endocarditis showed a slightly different epidemiology with *S. aureus* causing 57 % of cases and viridans group strep causing 20 %. Other causes included: coagulase negative staphylococci (14 %); Group A Streptococci (3 %); Group B Streptococci (2 %); *Escherichia coli* (2 %); *Streptococcus pneumoniae* (1 %); and *Haemophilus influenzae* (1 %) [9]. Unlike adults, enterococci and bacteria from the HACEK group (*Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, and *Kingella*) are isolated less frequently [9, 16, 17]. However, organisms from the HACEK group (especially *H. parainfluenzae*) are the most common cause of gram negative PIE [18]. (Although gram *negative* enteric organisms such as *Escherichia coli* and *Pseudomonas aeruginosa* frequently cause bacteremia in infants and older immunocompromised children, these organisms rarely cause PIE). Fungi such as *Candida albicans* and other *Candida* species are seen more commonly in premature neonates, who require central venous catheters. Five to 15 % of neonates with candidemia will develop PIE [19].

In children with prosthetic material (including indwelling lines, patches, conduits or artificial heart valves) PIE is usually caused by *S. aureus* or coagulase negative staphylococci. Both of these organisms may be implanted at the time of surgery, and if infection occurs, it can be seen within weeks to months after surgery. The timing of infection varies between these organisms. *S. aureus* is often seen within 2 months of surgery, while coagulase negative staphylococci can be seen up to 1 year after surgery [9]. Although rare, *Staphylococcus lugdenensis* deserves special mention. This coagulase negative organism may be misidentified as *S. aureus* with slide coagulase testing, because it produces a clumping factor. In contrast with other coagulase negative staphylococci, it is associated with more aggressive infections involving native valves, similar to *S. aureus*. In adults, the case fatality of *S. lugdenensis* endocarditis is 50 % versus 40 % for *S. aureus* [20, 21]. This organism is often sensitive to beta lactams including cloxacillin, but despite the use of appropriate antibiotics, 80 % of cases require surgery [22].

In children with native valve endocarditis, the most common isolates are viridans streptococci and *S. aureus* [9]. *Abiotrophia* species, *Granulicatella* species, *Gemella* species and enterococci are seen less commonly. PIE in children more than 2 months after cardiac surgery can also be caused by viridans streptococci, *Abiotrophia* species and/or enterococci [3, 7].

In premature neonates, coagulase negative staphylococci, *S. aureus*, and *Candida* species are the most common etiologic agents. Rarely, *Streptococcus agalactiae* (Group B streptococci), *Klebsiella pneumoniae* and Enterobacter spp. are isolated as causes of PIE in this population [9, 10, 23, 24].

In 5–7 % of children with PIE, the blood cultures are negative [16]. The most common reasons for negative blood cultures include: previous antibiotic therapy; inadequate blood culture technique or PIE caused by an organism with special in vitro growth requirements. Fastidious organisms associated with culture negative endocarditis may include: *Legionella pneumophilia*, *Bartonella henselae* and *quintana*, *Brucella melitensis* and *abortus*, *Coxiella burnetii*, *Pasteurella* sp., *Chlamydia* species, and filamentous fungi [25–28].

Diagnosis

Sometimes, the diagnosis of PIE can be easy to make – an older adolescent with bacteremia, a new heart murmur and peripheral stigmata, fits classic descriptions of infective endocarditis. However, in most cases of PIE, the presentation and subsequent diagnosis is not as straight forward. A multifaceted diagnostic approach that uses clinical findings, laboratory evidence and echocardiographic findings is required that is sensitive enough to detect PIE, but specific enough to reject cases that are not PIE. In adult medicine, the Duke Criteria offer a combination of subjective and objective findings to diagnose endocarditis [29]. The Duke criteria are superior to several other criteria for the diagnosis of PIE [30]. There have been some changes made to the original Duke Criteria, and the Modified Duke Criteria are even more sensitive than the previous criteria in diagnosing PIE (Tables 12.2, 12.3, and 12.4) [31].

Table 12.2 Use of the modified Duke Criteria to classify a child with suspected endocarditis as a definite case, a possible case or a rejected case of PIE

Definite infective endocarditis according to the Modified Duke Criteria:
Pathological criteria
Microorganisms demonstrated by culture or histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or
Pathological lesions; vegetation or intracardiac abscess confirmed by histological examination showing active endocarditis
Clinical criteria:
2 major criteria; or
1 major criterion and 3 minor criteria; or
5 minor criteria
Possible infective endocarditis according to the Modified Duke Criteria:
1 major criterion and 1 minor criterion; or
3 minor criteria
Rejected infective endocarditis according to the Modified Duke Criteria:
Firm alternative diagnosis explaining evidence of infective endocarditis; or
Resolution of infective endocarditis syndrome with antibiotic therapy for <4 days; or
No pathological evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for <4 days; or
Does not meet criteria for possible infective endocarditis as above

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Table 12.3 Terms used in the Modified Duke Criteria to make a diagnosis of PIE

The major criteria
1. Positive blood cultures
(a) With certain organisms known to be associated with endocarditis; or
(b) Sustained bacteremia as shown by persistently positive blood cultures; or
(c) Single positive blood culture or positive serology for *Coxiella burnetii*
2. Evidence of endocardial involvement
(a) With a positive echocardiogram
The minor criteria
1. Predisposition to PIE; or
2. Fever; or
3. Vascular phenomena; or
4. Immunologic phenomena; or
5. Microbiological evidence

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Table 12.4 Determining when to use TTE or TEE in children with suspected PIE

TTE – Use as a first line test for supportive evidence of PIE in children who satisfy the Modified Duke Criteria for PIE
TEE – As an adjunct to TTE, consider TEE use in:
1. Children with a poor thoracic window from:
Obesity; *or*
Excess muscularity; *or*
Implanted prostheses in a surgically repaired heart; *or*
Pulmonary hyperinflation
2. Children who are at risk for aortic root abscess:
With S.aureus bacteremia and/or
Changing aortic root dimensions on TTE

Defining the Terms Used in the Modified Duke Criteria for Diagnosis of Pie

In order to make a diagnosis of PIE with the Duke Criteria, certain findings must be satisfied. Major criteria provide evidence of a sustained bacteremia with certain organisms and concomitant endocardial involvement.

The Major Criteria

Evidence of Bacteremia with Certain Organisms

Two separate positive blood cultures with: *Viridans Streptococci*, *Streptococcus bovis*, *HACEK group*, *Staphylococcus aureus or community acquired enterococci in the absence of a primary focus* [31]

The typical organisms that cause endocarditis in children include: viridans Streptococci, *S. aureus*, coagulase negative staphylococci, and *S. pneumoniae*. Rarely, enterococci and organisms from the HACEK group may be isolated. To maintain high specificity, certain organisms are given more weight than others. Bacteremia with viridans Streptococci, organisms from the HACEK group and *S. aureus*, are given primary diagnostic weight, because these organisms are almost always associated with PIE [32, 33]. However, other organisms, such as enterococci, may be associated with bacteremia in the absence of PIE. The Duke Criteria only gave diagnostic weight to this organism if it was community acquired and there was no primary focus [34]. For organisms such as *S. pneumoniae* and coagulase negative staphylococci, in order to satisfy a major criterion, evidence of sustained bacteremia must be seen.

Evidence of Sustained Bacteremia

Number of Positive Blood Cultures

At least two positive cultures drawn at least 12 h apart, or all of three or a majority of ≥ four separate positive blood cultures (*with the first and last sample drawn at least 1 h apart*) [31].

In order to show sustained bacteremia, according to the Modified Duke Criteria, a certain number of blood cultures must be positive over a period of time. Two or three cultures are more than adequate to detect episodes of bacteremia and fungemia caused by common pathogens. The dogma of using more than three cultures dates back to conventional non-automated blood culture methods [35]. However, with continuous blood culture monitoring systems that are used in most microbiology labs, virtually all clinically important bloodstream infections can be detected with two blood cultures [36]. *It is rarely necessary to collect more than two cultures in a 24 h period unless the patient has been on antibiotics or the initial cultures are negative* [37]. So why do the Duke Criteria recommend more than two cultures? In adults, two blood cultures will detect 90 % of bacteremias and 3 blood cultures will detect over 99 % [38]. Additionally the patterns of positivity vary depending on the type of bacteremia. In other words, two blood cultures are sufficient to detect bacteremia, but more are required to substantiate the diagnosis of continuous bacteremia and endocarditis. A single positive blood culture is difficult to interpret. However, several positive blood cultures are more easily interpreted. For example, with infective endocarditis (continuous bacteremia), if the first blood culture is positive, the probability that subsequent cultures will be positive is between 95 % and 100 %. With a true bacteremia, but no endocarditis, if the first blood culture is positive, the probability of subsequent cultures being positive is lower (between 75 % and 80 %). If only one blood culture is positive and the subsequent ones negative, it is more likely that the first isolate was a contaminant [36].

Timing of Blood Cultures

There does not seem to be a significant difference in detection of bacteremia if the cultures are obtained simultaneously or over intervals in a 24 h period, but to determine if the bacteremia is continuous, drawing the cultures over a period of time is useful [39]. If the child is not acutely ill, withholding antibiotics and repeating cultures is justified, otherwise it is prudent to draw two sets of blood cultures from different sites simultaneously and then give empiric antibiotics.

Volume of Blood Drawn for the Blood Culture

The volume of blood inoculated into the blood culture vials is very important in children. Unlike adults, where a standard volume of blood is inoculated into several sets of tubes, no such standard exists for children. At times, minute amounts of blood are used to inoculate the pediatric blood culture bottle. Reasons for this include: difficult venous access, fear of withdrawing too much blood or the belief that children have much higher levels of bacteremia (so less blood is needed to reveal a positive blood culture) [40–44]. However, using small volumes of blood may miss bacteremias,

because over 60 % of infants and children with sepsis have low level of bacteremias (<10 colony forming units (CFU) per milliliter of blood) [45]. These low level bacteremias can only be detected when larger amounts of blood are cultured (up to 4.5 % of a child's total blood volume). Therefore, the volume of blood drawn for culture should be based on the child's total blood volume which can be determined by the child's age and weight [46–48]. For example, a child who weighs more than 30 kg who has 60 ml (or two sets of adult blood cultures drawn) and an infant who weighs less than 1 kg who has 2 ml of blood drawn will both lose 3 % of their total blood volume. Some centers have created simple policies where children over a certain weight (such as 30 kg) will have adult blood cultures drawn (10 ml each in an aerobic and anaerobic blood culture vial), while smaller children have a minimum of 1 ml, (but preferentially 3 ml) of blood inoculated into a pediatric blood culture vial [49].

Evidence of a *Coxiella burnetii* Infection

Single positive blood culture for Coxiella burnetii or anti-phase 1 IgG antibody titer >1:800 [31]

Unlike adults, most children have few symptoms when infected with *C. burnetii* [50]. Self limited febrile illnesses and pneumonia have been reported, and rarely, chronic infections manifest as osteomyelitis or endocarditis [26, 51–54]. A high index of suspicion in children that have been in contact with farm animals and/or pets is required to make the diagnosis of Q fever.

Evidence of Endocardial Involvement

Echocardiogram positive for PIE with: *an oscillating intracardiac mass on valve or supporting structures*, *in the path of regurgitant jets*, *or on implanted material in the absence of an alternative anatomic explanation*; *or abscess*; *or new partial dehiscence of a prosthetic valve*; *new valvular regurgitation* (*worsening or changing of preexisting murmur not sufficient*) [31].

Since the late 1970s, echocardiography, has been a useful adjunctive test for the diagnosis of infective endocarditis [55]. It can show the site of infection, and determine the extent of valvular damage. Cardiac function can also be determined and used as a comparison later in the course of the infection [56]. In adults, transthoracic echocardiography (TTE) has a sensitivity of 70 % in detecting vegetations. When used in patients with high risk for infective endocarditis, transesophageal echocardiography (TEE) is a far more sensitive and specific test [57, 58].

Unfortunately, there is little data for children and the optimal use of these technologies. Two published studies showed a sensitivity of 46 % and 67 % for TTE using the Duke Criteria [59, 60]. Using the modified Duke Criteria, in children who weighed less than 60 kg, TTE had a 97 % sensitivity. However, in children who weighed more than 60 kg, the sensitivity dropped to 70 % [61]. One study examined the additional benefit of TEE in children who satisfied the Duke Criteria for PIE. Using TEE as the gold standard, TTE had a sensitivity of 86 % for all events, and 93 % sensitivity for detecting vegetations. The authors concluded that TTE has a high degree of sensitivity for supplying supportive evidence of endocarditis and that TEE had little additional benefit. However, there are times when a TTE may be

falsely negative: if the vegetations are very small (that is below the detectable limit for TTE at 2 mm) or if the vegetations have already embolized [33]. Additionally, TTE may not be effective in children with a poor thoracic window, like the obese or very muscular adolescent, in children with repaired complex heart defects (whose artificial grafts conduits and valves may interfere with TTE), or in children with pulmonary hyperinflation [62]. In those cases, TEE should be used as an adjunct to TTE [6, 63]. TEE should also be considered in children with a suspicion of aortic root abscess (*S. aureus* bacteremia, and/or changing aortic root dimensions on TTE) since abscesses in this area are difficult to assess with TTE [64–67].

The Minor Criteria

Predisposition to PIE

Children who have had cardiac surgery – especially those with underlying cyanotic congenital heart lesions are at high risk for PIE [6, 7]. Within that group, the risk of PIE is highest in children who have had repair of pulmonary atresia or stenosis, and children who have had replacement of their aortic valve. Children with other implanted foreign material (such as vascular conduits) are also at high risk for PIE if hemodynamic problems and turbulent flow persist postoperatively [68]. Neonates with CHD (including PDA) and/or indwelling intravascular devices are also at high risk for PIE [16]. Finally, previous PIE is also a risk factor for recurrent PIE [4].

Fever

A temperature over 38 °C is another minor criterion. Since many children present to their physicians with a fever, distinguishing between a viral infection and PIE can be difficult. It is important to maintain a high index of suspicion for PIE in children with CHD and draw blood cultures under the following circumstances: if a child presents with more than 48 h of low grade fevers and flu-like symptoms (such as, decreased intake, fatigue, weakness, arthralgias, myalgias, rigors and/or diaphoresis) or if a child presents acutely with high fevers but a source cannot be found on history or physical examination [69].

Vascular Phenomena

Signs and symptoms of vascular phenomena are more common in adults. *Arterial emboli* in large vessels, *septic pulmonary infarcts*, *mycotic aneurysms*, *intracranial hemorrhages*, *conjunctival hemorrhages* and *Janeway lesions* (flat non tender lesions on the palms and soles) are listed as minor clinical criteria in this category [70]. If conjunctival hemorrhages are seen they are often accompanied by other petechiae on the hands, feet, and trunk and in the mouth.

Immunologic Phenomena

In children with PIE, *glomerulonephritis* is more common than *Osler's nodes* (painful erythematous nodules in the pulp space of the fingers) or *Roth's spots* (retinal hemorrhages). All three of these findings along with a *positive rheumatoid factor* are considered minor criteria in this category.

Microbiological Evidence

If an organism is isolated, but does not meet the major criteria (too few positive cultures or inadequate time delay between cultures), it can still be included as a minor criterion. (An exception is a single positive culture for coagulase negative staphylococci or organisms that usually do not cause PIE). If blood cultures are negative, but there is serological evidence of active infection with an organism consistent with PIE, this can also fit into this category.

Signs and Symptoms of PIE

The signs symptoms of PIE vary with the underlying pathology. Generally, there are four underlying phenomena associated with PIE that can cause various signs and symptoms. These may include: *bacteremia*, *valvulitis*, *immune response* and/or *septic emboli*.

Children with bacteremia may present subacutely with flu-like symptoms such as: decreased food or fluid intake, fatigue, weakness, arthralgias, myalgias, rigors and/or diaphoresis. If these symptoms persist, it is important to rule out PIE. Children with bacteremia and CHD can also present acutely with high fevers, and if a source cannot be found on history or physical examination, other serious illnesses such as PIE must be ruled out.

Neonates and premature infants with bacteremia and PIE may present with symptoms that are indistinguishable from sepsis or heart failure. Symptoms may include apneas, temperature instability, increased work of breathing, feeding difficulties and/or blood pressure instability.

Babies with valvulitis and heart failure may present with failure to thrive and tiring during feeds, a new or changing murmur, tachycardia, tachypnea, an enlarged heart and/or an enlarged liver.

The most common symptoms from the *immune phenomena associated with PIE* are hematuria from glomerulonephritis. Certain findings, such as Roth's spots, Janeway lesions and Osler's nodes, which are common in adults, are rarely seen in children with PIE.

Septic emboli in children with PIE have various presentations. Fever and increased work of breathing may be one presentation of pneumonic emboli. Neonates often present with extra-cardiac foci of infection such as osteomyelitis or pneumonia. Children with surgical repair of cyanotic heart disease may present with

declining oxygen saturations as an indication of graft infection and shunt obstruction. Infants or children with catheter-related right sided PIE may present with pulmonary signs related to septic emboli in the lungs.

Ancillary Tests

A complete blood count is useful in a child with fever, and can be helpful in diagnosing serious illnesses such as PIE. Hemoglobin is often low, and the anemia may be caused by hemolysis or anemia of chronic disease. Leukocytosis may or may not be present. Elevated acute phase reactants (ESR, CRP) are present in a large proportion of patients. A urinalysis may show hematuria from immune complex glomerulonephritis, and this may be accompanied by red cell casts, proteinuria, and renal failure.

Other diagnostic tests such as polymerase chain reaction (PCR) may be useful in certain instances. This test offers high specificity and positive predictive value in patients with definite IE versus rejected IE. It can be used for surgically resected material in cases of possible IE, on blood for cases of suspected IE if cultures are sterile, or in cases where the organism grows in blood culture but only minor criteria are met [17, 71, 72].

Treatment

Overall, the approach to treatment of PIE is very similar to that of adults. In patients who are not acutely ill and whose blood cultures are negative, antibiotics may be withheld for greater than 48 h while additional blood cultures are obtained [57]. When therapy is started, certain principles apply. Bactericidal, intravenous antimicrobials must be used for prolonged periods.

Bactericidal antimicrobials should be used to treat endocarditis to reduce the risk of relapse or failure to control the infection [73]. Bactericidal drugs may be used alone but certain drug combinations such as a beta lactam plus an aminoglycoside act synergistically to sterilize vegetations caused by susceptible bacteria such as enterococci faster than either drug alone. When combination therapy is used, the drugs should be administered at the same time, or following each other in order to maximize the synergistic killing effect on the pathogen.

Parenteral drugs are recommended over oral drugs because of higher bioavailability and sustained concentrations in the bloodstream. Smaller children and neonates have smaller muscle mass, and the intramuscular route for prolonged therapy of endocarditis is not recommended.

Prolonged therapy is required for several reasons. First of all, the infection is in an area of impaired host defense – the bacteria are encased in a mesh of fibrin, and can multiply in this area protected from the immune system. Secondly, when bacteria reach high population densities within the vegetation, they start to reproduce more slowly. This slowed metabolic rate is a distinct disadvantage for certain

antibiotics which require active cell wall synthesis for maximal activity [74]. Finally, short term therapy is often associated with relapse.

Treatment of PIE Caused by Viridans Streptococci in the Absence of Prosthetic Material [57]

If the organisms are penicillin susceptible (penicillin minimum inhibitory concentration or MIC <0.12 μg/ml), there are several options for therapy which offer high cure rates: A 4 week course with monotherapy, or shorter therapeutic courses with combination therapy. Shorter courses should not be used in children with prolonged symptoms (more than 3 months), abnormal renal function and/or extra-cardiac foci of infection or abscesses.

There are several choices for antimicrobial monotherapy. Four weeks of *penicillin G* (200,000 units/kg/day in four to six divided doses) or *ampicillin* (300,000 mg/kg/day in four to six div doses) are especially advantageous in children with renal or otic problems because aminoglycosides are avoided [75]. An alternative monotherapeutic agent is parenteral *ceftriaxone* (100 mg/kg once daily) which offers the advantage of once daily dosing. Although its efficacy has not been proven in children, extrapolation from adult data and other pediatric infections indicate that it is likely effective [76].

In uncomplicated PIE, combination antimicrobial therapy can be used for shorter treatment durations. Antimicrobial combinations that have been successful over 2 week treatment periods include beta lactams (*penicillin G*, *ampicillin or ceftriaxone*) plus *gentamicin*. Adult studies offer the option of once daily dosing of gentamicin (3 mg/kg) when treating endocarditis caused by viridans streptococci [77]. There is some data about the use of once daily dosing of gentamicin in pediatric patients with gram negative infections associated with urinary tract infections, febrile neutropenia, and cystic fibrosis. Doses in these studies ranged from 4 to 7.5 mg/kg/day [78]. There is little data about once daily dosing of gentamicin with PIE, but decreased toxicity, lower cost and ease of administration make it an attractive option. Therefore, the suggested gentamicin synergy doses for treatment of PIE caused by viridans streptococci is 3 mg/kg/day in one or three divided doses. Renal function should be monitored as well as gentamicin serum levels (aiming for a trough concentration of less than 1 μg/ml).

If the viridans streptococci are relatively penicillin resistant (penicillin MIC >0.12 μg/ml and ≤0.5 μg/ml), combination therapy is more effective. *Penicillin G* (at a higher dose of 300,000 u/kg/day in four to six div doses) or parenteral *ceftriaxone* (100 mg/kg/day) should be used for a minimum of 4 weeks, and during the first 2 weeks of therapy, *gentamicin* (3 mg/kg/day in one or three divided doses) should be added.

Certain gram positive organisms are very difficult to treat when they cause PIE. They are either streptococci that are highly resistant to penicillin (MIC >0.5 μg/ml) or certain organisms such as Abiotrophia species, Granulicatella species, or Gemella species. For these organisms, combination therapy with

penicillin G (300,000 mg/kg/day in four to six divided doses) or *ampicillin* (300,000 mg/kg/day in four to six divided doses) or *ceftriaxone* (100 mg/kg once daily) plus *gentamicin* (3 mg/kg/day in one or three divided doses) for the entire course of 4–6 weeks is recommended.

For children who are unable to tolerate beta lactams, *vancomycin* (40 mg/kg/day in two to four divided doses) can be used in their place for the treatment of PIE. Higher doses of vancomycin may be required to obtain trough concentrations of 15–20 μg/ml [79].

Treatment of PIE Caused by Viridans Streptococci with Prosthetic Material in Place [57]

If the strains are susceptible to penicillin, (MIC ≤0.12 μg/ml) treat with *penicillin G* (200,000 units/kg/day in four to six divided doses) or parenteral *ceftriaxone* (100 mg/kg/day) for 6 weeks and if the isolate does not exhibit high level resistance to aminoglycosides, add *gentamicin* (3 mg/kg/day in one or three divided doses) for the first 2 weeks. The use of synergistic gentamicin is based on data from enterococcal endocarditis [80]. If the organism is relatively penicillin resistant (MIC >0.12 μg/ml and ≤0.5 μg/ml), use combination therapy with a beta lactam and aminoglycoside for 6 weeks minimum, monitoring for renal toxicity and gentamicin serum levels throughout the course of therapy. If the child has intolerance to beta lactams, vancomycin may be used as a substitute.

Treatment of PIE Caused by Staphylococci (*S. aureus*, Coagulase Negative Staphylococci) [57]

Methicillin susceptible *S. aureus* PIE in the absence of prosthetic material can be treated with *cloxacillin* (200 mg/kg/day in four to six divided doses) or *cefazolin* (100 mg/kg/day in three to four divided doses) for a minimum of 6 weeks. *Gentamicin* (3 mg/kg/day in three divided doses) may be added for the first 3–5 days because it may accelerate the killing of the organisms [81]. However, adult data has shown that aminoglycoside use in synergistic doses resulted in a higher incidence of renal dysfunction [82].

Most coagulase negative staphylococci are resistant to methicillin and penicillin (with the exception of *Staphylococcus lugdenensis*, which is rarely resistant to beta lactams and may be treated for 6 weeks with cloxacillin) and the rates of methicillin resistant *S. aureus* (MRSA) are increasing. If the staphylococci are resistant to methicillin, then *vancomycin* (40 mg/kg/day in two to four divided doses to target a trough concentration of 15–20 μg/ml) should be used for 6 weeks, and *gentamicin* may be added for the first 3–5 days [83]. An adult randomized control trial showed that daptomycin was non inferior to vancomycin or anti staphylococcal penicillins for right sided endocarditis caused by *S. aureus*, and an observational study showed that daptomycin was effective in adults with left sided endocarditis [84, 85].

Daptomycin is now recommended as an alternative to vancomycin in adults with endocarditis caused by MRSA [85]. There are several newer agents, ceftaroline, ceftobiprole, tedizolid, telavancin, dalbavancin and oritavancin that are showing promise in the treatment of pneumonia or skin and soft tissue infections caused by MRSA in adults, but more studies are needed to establish their use in PIE [86].

PIE caused by staphylococci in the presence of prosthetic material is often caused by coagulase negative staphylococci. Treatment consists of a minimum of 6 weeks of *vancomycin* (40 mg/kg/day in two to four divided doses to target a trough concentration of 15–20 μg/ml) and oral or intravenous *rifampin* (20 mg/kg/day in three divided doses) plus *gentamicin* (3 mg/kg/day in three divided doses) for the first 2 weeks. Methicillin susceptible *S. aureus* PIE in the presence of prosthetic material should be treated with at least 6 weeks of *cloxacillin* (or cefazolin) and *rifampin* plus *gentamicin* for the first 2 weeks.

Treatment of PIE Caused by *S. pneumoniae* [57]

Optimal therapy for PIE caused by this organism has not been established. When treating PIE caused by this organism, it is important to determine if other sites (such as the meninges) have been seeded and to determine the antimicrobial susceptibilities of the organism. Once these have been determined, a treatment regimen can be developed. If the organism is susceptible to penicillin (MIC ≤2 μg/ml), and there is no meningitis, 4 weeks of therapy with *penicillin G* (200,000 units/kg/day in four to six divided doses) or *ceftriaxone* (100 mg/kg/day) for 4 weeks have been used successfully. If the organism has an MIC >2 μg/ml to penicillin and there is no meningitis, ceftriaxone over a 4 week course has been used successfully. If meningitis is present with PIE, and the organism is highly resistant to penicillin, a third generation cephalosporin such as *cefotaxime* (200 mg/kg/day in four divided doses) or parenteral *ceftriaxone* (100 mg/kg/day in two divided doses) can be used for 6 weeks. If the organism is intermediate or resistant to cefotaxime (MIC ≥2 μg/ml) and meningitis is present, consider the addition of *vancomycin* and *rifampin* to cefotaxime or ceftriaxone [87–90].

Treatment of PIE Caused by Enterococci [57]

The treatment of PIE caused by enterococci can be challenging. These organisms are resistant to the cephalosporins, relatively resistant to penicillin and vancomycin, and impermeable to the aminoglycosides. All *E. faecium* are resistant to amikacin and tobramycin, while *E. faecalis* are often resistant to amikacin. Monotherapy only inhibits growth – combination therapy is required for bactericidal effects. Combinations may include penicillin G or vancomycin plus gentamicin. Penicillin or vancomycin damages the cell wall, giving gentamicin access to the cytoplasm where it then targets the ribosomes and works synergistically to kill the bacterial cell [82].

Treatment of PIE caused by penicillin and gentamicin susceptible enterococci when no prosthetic material is present consists of a minimum of 4–6 weeks of penicillin G or Ampicillin at high doses (300,000 u/kg/day in four to six divided doses for *penicillin* G; 300–400 mg/kg/day divided in four to six doses for ampicillin) plus *gentamicin* for the entire course (3 mg/kg/day in three divided doses – once daily dosing is not recommended) [91]. If the child cannot tolerate penicillin, vancomycin may be used (dose 40 mg/kg/day in two or three divided doses to target trough concentrations of 15–20 μg/ml), in combination with gentamicin. However, because of vancomycin's decreased activity against enterococci, 6 weeks minimum therapy with both drugs is required.

If prosthetic material is present with enterococcal PIE, the same antimicrobials should be used but the duration of treatment should be a minimum of 6 weeks.

Treatment becomes more challenging when enterococci are resistant to the recommended antimicrobials. The duration of therapy is usually extended to a minimum of 6 weeks, and antimicrobial susceptibility testing is very important in guiding therapy. If the organism is penicillin susceptible but gentamicin resistant, then *streptomycin* can be used in combination with penicillin. The dose of streptomycin is 30–40 mg/kg/day in two equally divided doses. Enterococci that are resistant to penicillin, but sensitive to other antimicrobials can be treated with *vancomycin* and *gentamicin*. Few therapeutic options exist for multiply resistant enterococci and vancomycin resistant enterococci (VRE). *Linezolid* is one option (at a dose of 30 mg/kg/day divided into three doses for at least 8 weeks), and a critical review of 18 case reports, 9 case series and 3 clinical trials showed that linezolid was safe and effective in the off label treatment of resistant gram positive bactremias and endocarditis in children [92].

Treatment of PIE Caused by Gram Negative Organisms [57]

Therapy for HACEK organisms consists of a 4 week course of a third generation cephalosporin such as parenteral *ceftriaxone* (100 mg/kg/day) alone, *ciprofloxacin* (20–30 mg/kg/day in two divided doses) or *ampicillin* (300 mg/kg/day in four to six divided doses) plus *gentamicin* for the first 2 weeks [57].

Therapy for other gram negative organisms must be guided by their susceptibility profile, and combination therapy for a minimum of 6 weeks is usually needed.

Treatment of PIE Caused by Fungi [57]

Candida species are the most common cause of fungal endocarditis. Children tolerate conventional amphotericin better than adults, and the recommendation for therapy is amphotericin B (1 mg/kg/day) and valve replacement. The amphotericin should be continued for a minimum of 6 weeks, and if the child cannot tolerate amphotericin B, a lipid formulation may be considered with or without 5-fluorocytosine (5-FC) (100–150 mg/kg divided four times) [93]. Echinocandins

have shown favorable results in adults with candidal endocarditis, but there is less data with children [94]. Because these fungal infections can relapse years later, lifelong suppressive therapy with an oral azole in those who did not have surgery for native or prosthetic valve infection is prudent [95].

Treatment of Culture Negative Endocarditis [57]

In some cases of PIE, blood cultures are negative. Common reasons for this include: previous antibiotic use, inadequate blood culture samples or unusual organisms that require specific lab techniques for diagnosis. When an etiologic agent is not identified, therapy should be aimed at the most common organisms causing PIE (streptococci, staphylococci and HACEK organisms). A third generation cephalosporin combined with gentamicin offer good coverage, and if Staphylococci are suspected, addition of cloxacillin or vancomycin should be considered. If the child has animal exposures or contact with contaminated milk, they may be at risk for organisms such as *Bartonella spp*., *Coxiella spp*., *Pasteurella spp*. or *Brucella spp*. Therapy may need to be modified if these organisms are suspected [57].

The Role of Anticoagulants and Thrombolytics in PIE Therapy

Dissolution of the fibrin mesh in the vegetation may offer some theoretical advantages in the treatment of PIE. Indeed, when further vegetation formation is inhibited with anticoagulants, organisms are eradicated more rapidly. In vitro data examining the use of tissue plasminogen activator shows that it does not enhance the effect of antimicrobials. However, there have been case reports in extremely low birth weight infants with PIE who have been successfully treated with recombinant tissue plasminogen activator (rTPA) and prolonged antibiotics [14]. However, adult observational data shows an increased risk of cerebral hemorrhage and death in patients with endocarditis who received oral anticoagulation, and an adult double blind placebo controlled trial showed that aspirin also increased the risk of cerebral bleeding episodes [96, 97].

Surgery in PIE Therapy

Surgery is necessary for some children with PIE, because medical therapy alone will not be adequate. High risk clinical situations include children with: PIE caused by certain organisms (fungi or *S. aureus*); PIE on prosthetic material (valves and conduits); PIE and CHD (cyanotic CHD or systemic-to-pulmonary shunts); prolonged signs and symptoms of PIE (longer than 3 months); large vegetations involving the aortic or mitral valve (especially if valvular function is compromised); recurrent PIE and a poor response to medical therapy alone [57].

Prevention

Vaccines

The pneumococcal conjugate vaccine has been shown to decrease the rates of invasive *S. pneumoniae* disease, including bacteremia. Since 80 % of the isolates from children with *S. pneumoniae* PIE would have been covered by the vaccine, widespread use of the vaccine may lead to decreased pneumococcal PIE [98]. More recent data from Europe shows a decline in invasive pneumococcal disease, especially that caused by vaccine serotypes [99]. With the introduction of the 13-valent pneumococcal conjugate vaccine, there will likely be a further drop in invasive pneumococcal infections [100]. Presently, there are no vaccines to cover the other common etiologic agents of PIE.

Antibiotic Prophylaxis

Antibiotic prophylaxis has become more controversial in the past decade. While some national groups recommend prophylaxis for the prevention of IE, others do not [4, 101]. North American healthcare providers must approach the issue of antibiotic prophylaxis on an individual basis. They must take into account the degree to which the child's underlying heart defect creates a risk of PIE, the risk of bacteremia with the procedure and the potential adverse effects and cost of the prophylactic agent to be used [102].

Children at high risk for PIE include those with: prosthetic cardiac valves (including bioprosthetic and homograft valves), prosthetic material used for valve repair, a past history of PIE, unrepaired cyanotic congenital heart disease including palliative shunts and conduits, repaired congenital heart defects with prosthetic material within 6 months of surgery, repaired congenital heart defect with residual defects at or near the surgical repair, valvulopathy in a transplanted heart [4].

The risk of bacteremia varies with different procedures. Dental work and oral procedures put the child at risk for bactremia with viridans streptococci, and amoxicillin or intravenous ampicillin is an appropriate choice. Alternatives include first generation cephalosporins or ceftriaxone and clindamycin or vancomycin if there is a history of severe reactions (i.e. anaphylaxis) to beta lactams. Prophylaxis is recommended for procedures associated with manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa. Other procedures involving the respiratory tract, gastrointestinal and genitourinary tract no longer warrant antimicrobial prophylaxis to prevent PIE. But it is reasonable to provide prophylaxis to children at risk for PIE who require surgery for infected skin or soft tissue infections targeting *S. aureus* and beta hemolytic streptococci [4].

Conclusion

This chapter described the epidemiology, etiology, diagnosis, treatment and prevention of pediatric infective endocarditis – focusing on children with congenital heart defects. Surgical and medical advances have allowed children to overcome severe heart defects,

extreme prematurity and illnesses requiring indwelling lines. Unfortunately, many of the interventions that allow these children to survive put them at risk for PIE. In the future, the incidence of PIE will likely continue to increase and the etiologic agents will likely become more difficult to treat as antimicrobial resistance increases. Research is needed in the areas of primary prevention of PIE, improved diagnostic methods for PIE and effective therapies for PIE caused by multidrug resistant pathogens. In the interim, health care providers need to be cognizant of PIE in children with CHD because early diagnosis and therapy can decrease morbidity and mortality.

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Systemic Embolism in Endocarditis: Incidence, Risk Factors, Clinical Significance and Treatment Strategies

13

Omid Salehian and Kwan-Leung Chan

Abstract

Systemic embolism remains a vexing problem in patients with infective endocarditis. This complication affects about 30 % of these patients and generally occurs in the early stage of the disease. The size of the vegetation is the best echocardiographic predictor of the embolic risk, but there is considerable overlap in vegetation size between patients with and without embolic events. Early cardiac surgery appears to reduce the risk of embolism in patients with large vegetations and severe valvular dysfunction. Prompt diagnosis and effective antibiotic therapy remain the best way to prevent this serious complication of endocarditis.

Keywords

Endocarditis • Embolism • Stroke • Aspirin • Vegetation size • Guideline • Cardiac surgery

Key Points

1. Systemic embolism is a common complication occurring in about 30 % of patients with IE.
2. Embolic events occur early in the course of the disease.
3. Morphologic parameters of vegetation particularly size appear to be a predictor of the embolic risk, but they have limited clinical usefulness in individual patients.

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4. Fibrinolytics, anticoagulants, and antiplatelet agents have not been shown to reduce the embolic risk, but they likely enhance the risk of bleeding.
5. Early diagnosis with prompt initiation of antibiotic therapy remains the most effective means to reduce the embolic risk.

Case Studies

Case 1

19-year-old man presented at the emergency department with sudden onset of right hemiplegia and dysphasia, after having had fever and malaise for several weeks. A brain computed tomogram showed left cerebral hemorrhagic infarct. He underwent emergency surgery to evacuate the intracranial hematoma. A transthoracic echocardiogram showed vegetations on a congenitally bicuspid aortic valve and moderate aortic regurgitation. A transesophageal echocardiogram showed a large vegetation on the aortic valve. Blood cultures subsequently grew S*taphylococcus aureus*.

Case 2

A 56-year old man with no history of valvular disease had fever, chills, and fatigue for 1 week and was diagnosed to have infective endocarditis (IE) after blood cultures grew S*taphylococcus aureus*. He responded well to treatment and did not develop significant valvular dysfunction. He was well for 1 year before the sudden occurrence of left upper quadrant abdominal pain due to splenic infarct confirmed by gallium scanning tomography. He did not have fever and blood cultures were negative. A transesophageal echocardiogram showed a 6-mm diverticulum on the posterior mitral leaflet which communicated with the left ventricle via a narrow neck and contained small echo densities within its cavity likely the source of the non-infective splenic infarct.

Embolic events in IE usually occur early and can be the presenting symptom as illustrated by Case 1. The differential diagnosis in patients suffering an embolic event should always include IE. Case 2 shows that embolic event can be a late complication as a result of unusual sequelae of IE, and transesophageal echocardiography plays an important role in the assessment of these patients.

Introduction

Embolism is a dreaded complication in patients with IE, as it is a major contributor to mortality and morbidity in these patients. Cerebral embolism accounts for the majority of systemic embolic events and most commonly affects the territory of the middle

cerebral artery resulting in severe disability. Cerebral microemboli are also common but more difficult to recognize since the manifestations may be subtle or absent. Embolism to other organs is often clinically silent and confers less aggregate morbidity or mortality compared to cerebral embolism. The incidence of systemic embolism is about 30 %, although various studies have reported a wide range from 10 % to 50 %. This high incidence has not decreased significantly over the years despite improvements in medical and surgical treatments. Embolic events tend to occur early in the course of the disease, frequently present in patients before the diagnosis of endocarditis has been made. Indeed embolic events such as stroke may be the presenting symptom such that endocarditis should always be in the differential diagnosis when dealing with a patient who has suffered an embolic event. After proper antimicrobial treatment has been initiated, the risk of embolism is lower with most events occurring within the first 2 weeks of treatment. This chapter reviews the risk factors and potential therapeutic treatments for systemic embolism in endocarditis.

Risk Factors Associated with Embolic Events

Infecting Organism

Many case series have showed that the risk of systemic embolization is related to the infecting organism. For example, a higher incidence of embolic events is well documented in patients with Staphylococcal endocarditis [1, 2]. In one of the early studies Pruitt et al. reviewed the records of 218 cases of IE and reported a total of 86 (39 %) neurologic complications [3]. There were 49 cases of *Staphylococcus aureus* IE, 53 % of which had neurologic complication, of which 13 cases (26.5 %) were due to cerebral emboli, representing the highest embolic risk among all the infecting organisms. In a more recent study, Heiro et al. reported that in 218 cases of IE over a 17-year period (1980–1996) in a teaching hospital in Finland there were 55 patients (25 %) with neurologic complications, 23 (42 %) of which had cerebral embolic events documented on an imaging study or at autopsy [2]. They also reported a higher incidence of neurologic complications in patients with *S. aureus* IE, accounting for 29 % of the 55 cases of neurologic complications. Neurologic complications in this study included embolic events (n = 13), transient ischemic attacks (n = 10), cerebral hemorrhage (n = 4), meningitis (n = 9), brain abscess (n = 1), toxic encephalopathy (n = 11), and headache (n = 7). It is not clear from this study if *S. aureus* was associated with a higher risk of embolic events alone.

In the study by Di Salvo et al. there were a total of 43 patients with Staphylococcal endocarditis, 23 of whom (53 %) suffered an embolic event compared to 32 % in patients with IE due to other organisms (P = 0.023) [1]. However on multivariate analysis, infection due to Staphylococci was no longer a significant predictor of embolic events, whereas vegetation size and mobility remained as independent predictors of embolic events. A more recent study by Thuny and colleagues suggests that embolic events are more common in IE patients with *Streptococcus bovis* or *Staphylococcus aureus* infection [4].

Fungal endocarditis, although relatively rare, carries a high mortality and morbidity. The association between fungal IE and embolic events has been well established with often devastating complications due to the occlusion of major arteries by large emboli [5]. In an excellent review of the world literature covering a 30- year span (1965–1995) of 270 cases of fungal endocarditis, Ellis et al. reported that 45 % of the patients had major arterial embolization, and cerebral emboli occurred in 47 patients, which was 17 % of the total population [6]. A further 24 patients had non-focal neurologic findings. In cases of fungal endocarditis, most clinicians advocate early surgical intervention to avoid systemic embolic events.

Valve Location

A number of studies suggested a higher risk of systemic embolization in patients with mitral valve endocarditis. Pruitt et al. reported a higher rate of cerebral as well as other systemic embolization in patients with IE affecting the mitral valve in their study of 218 patients with IE [3]. There were 74 cases of aortic valve endocarditis 10 of which developed major cerebral emboli (13 %), while 23 of 81 cases of mitral valve endocarditis (27 %) had major cerebral emboli. These authors hypothesized that the higher rates of embolic events associated with mitral valve endocarditis might be due to the associated enlarged left atrium with lower flow leading to a more congenial environment for production of larger and more friable vegetations. Cabell et al. reported that in 145 patients with IE, mitral valve endocarditis was associated with a greater risk of stroke (32.5 % vs 11.3 %, $P=0.003$) [7]. However, vegetations on the mitral valve were also significantly larger than those on the aortic valve. Hence, the higher incidence of embolic events with mitral valve endocarditis might be due to the larger and more mobile vegetations, rather than inherent differences of specific valve location. It is also unclear whether this difference in vegetation size between mitral and aortic valve endocarditis may be related to a difference in the duration of infection. The multicenter European study reported no difference in the rate of embolization between mitral and aortic valve endocarditis. Embolic events occurred in 70 of 191 patients (37 %) with mitral valve endocarditis and 67 of 214 patients (31 %) with aortic valve endocarditis [4].

The incidence of embolic events in patients with right-sided endocarditis is likely considerable but remains not well defined. Embolism has been estimated to be 70 % in patients with isolated pulmonary valve endocarditis. Large vegetation size (>15 mm) appears to be associated with recurrent embolization and persistent infection despite antibiotic treatment [8].

Vegetation Morphology

Vegetation is not only the hallmark of endocarditis but also the substrate for embolic events which are usually the result of fragmentation and embolization of the vegetation. The embolic risk is low but not nonexistent in patients with no vegetations on

echocardiography. There have been ongoing efforts to relate the embolic risk to various morphologic parameters of the vegetation such as size, extent, and mobility. This is best exemplified by the study of Sanfilippo et al. [9], who studied 204 patients with endocarditis, 85 of whom had left-sided native valve endocarditis. Clinical cerebral embolic events were detected in 22 % of patients with left-sided native valve endocarditis. They used a semi-quantitative grading system that incorporates multiple echocardiographic parameters (Table 13.1). They found that vegetation size, vegetation mobility, and valve location (mitral compared to aortic) were independent predictors of complications including death and heart failure. In addition, the derived vegetation score utilizing vegetation size, mobility and extent was a predictor of adverse outcomes.

Among all of the parameters, vegetation size is the one that has been most extensively studied. There is now a considerable body of evidence showing a positive association between vegetation size and risk of systemic embolization. One frequently cited study is by Mugge et al. who prospectively studied 105 patient with active IE [10]. There were a total of 33 (31 %) major embolic events, 28 (27 %) of which involved the central nervous system. When patients were stratified based on the size of the vegetation, the 47 patients with vegetations >10 mm had a higher incidence of embolic events (46.8 %) than that of the 58 patients with small or no detectable vegetations (18.9 %, $P<0.05$). On multivariate analysis, only vegetation size larger than 10 mm predicted systemic embolization, particularly in patients with mitral valve endocarditis. There was, however, considerable overlap in vegetation size between patients with and without embolic events (Fig. 13.1), so that in an individual patient the clinical usefulness of vegetation size is limited.

Di Salvo et al. also showed a significant relationship between vegetation size and embolic events in a retrospective study of 178 patients with IE assessed by transesophageal echocardiography (TEE) [1]. Embolic events were more frequent in patients with very large vegetations, with 70 % of the embolic events occurring in 43 patients with vegetation length >15 mm compared to 27 % of embolic events in 135 patients with vegetation size ≤15 mm. There was also a significant relationship between vegetation mobility and embolic events in this population. Of the 73 patients with moderate and severely mobile vegetations 45 (62 %) had embolic events compared to 21 events (20 %) seen in the 105 patients with low mobility scores ($P<0.001$).

Table 13.1 Vegetation scoring system from Sanfilippo et al. [13]

Score	1	2	3	4
Size (mm)	<6	7–10	11–15	>15
Mobility	Fixed	Fixed base with a mobile free edge	Pedunculated	Prolapsing
Extent	Single vegetation	Multiple vegetations limited to a single valve leaflet	Involvement of multiple valve leaflets	Vegetations that extend into extravalvular structures

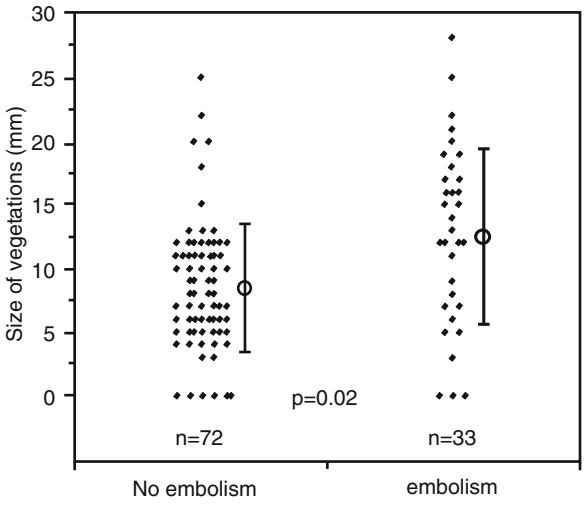

Fig. 13.1 This plot shows that there was a large overlap of vegetation size between patients with and without embolic events, even though there was a statistical difference in vegetation size between the two groups (Reprinted with permission from *J Am Coll Cardiol* (Ref. [10]) with permission)

In this study of the 30 patients who had both severely mobile and large vegetation (>15 mm), 83 % had embolic events. On multivariate analysis, vegetation size, and mobility were the only predictors of embolic events.

In a retrospective study of 145 patients with aortic or mitral valve endocarditis, Cabell et al. showed vegetation length >7 mm to be an independent predictor of stroke (OR 1.21; 95 % CI 1.02–1.44, P = 0.03) [7]. Vegetation size was also an independent predictor of mortality at both 30 days and 1 year. In the study by Deprele et al. data from 80 patients with endocarditis diagnosed using TEE were analyzed [11]. On univariate analysis, vegetation mobility and vegetation size >10 mm were risk factors for systemic embolization but on multivariate analysis, only vegetation mobility remained an independent risk factor for embolization. In the study by Steckelberg et al. transthoracic echocardiograms were performed prior to initiation of antibiotics in 207 patients with left- sided IE [12]. In their study only 27 patients (13 %) had an embolic event from the time of initiation of effective antibiotic therapy to completion of therapy, death, cardiac surgery, or hospital discharge. They did not find a relationship between the size of the vegetation and risk of embolic events. There was no significant difference in the risk of embolic events among patients with vegetations >10 mm compared to those with smaller or absent vegetations. A prospective study on 384 patients with endocarditis reported that vegetation size (>10 mm) and severe mobility were predictors of new embolic events, even after adjustment for etiologic agent such as *Staphylococcus aureus* [4]. Vegetation size (>15 mm) was also a predictor of 1 year mortality.

Tischler and Vaitkus published a meta-analysis of ten studies published in the English language of embolic events in left-sided IE patients to assess if vegetations ≥10 mm increased the risk of complications [10, 12–21]. The pooled odds ratios for systemic embolization (in ten studies with total of 738 patients) and death (in six studies with total of 476 patients) in the presence of vegetations ≥10 mm were 2.80 (95 %CI 1.95–4.02, P < 0.01) and 1.55 (95 % CI 0.92–2.60, P = 0.1), respectively.

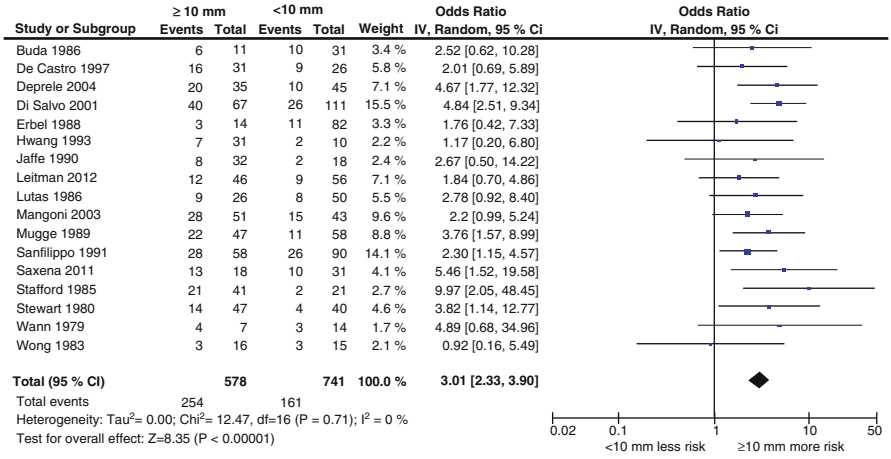

Fig. 13.2 Pooled analysis of 17 studies examining the effect of vegetation size on the risk of systemic embolism. Odd ratio (*OD*) and 95 % of confidence intervals (*CI*) are shown

Seven of the studies in this meta-analysis used transthoracic echocardiography alone for detection of vegetations, but the pooled odds ratio for systemic embolization from these seven studies, 2.85 (95 % CI 1.86–4.38), was similar to the pooled odds ratio from the three studies, 2.66 (95 % CI 1.36–5.24) that used both transthoracic and transesophageal echocardiography [9, 10, 14–21]. Since the publication of this meta-analysis in 1997, there have been additional studies involving patients with endocarditis in which vegetation size and embolic events were recorded [1, 7, 11, 22–25]. We performed a meta-analysis including a total of 15 studies: 10 from the original meta-analysis by Tischler and Vaitkus, one study by Wann and colleagues not included by Tischler and Vaitkus, and four recent studies [13, 26]. Our analysis of 1,319 patients in 17 studies with 415 systemic embolic events reveals a pooled odds ratio for systemic embolization with vegetations ≥10 mm of 3.01 (95 %CI 2.33–3.90, P<0.001) (Fig. 13.2).

Echocardiographic parameters of vegetations convey useful prognostic information in patients with IE, but clinical decision as to whether to proceed with surgery should not be based on echocardiographic findings alone because considerable differences are present among the studies, no standardized method of measuring vegetation size is generally accepted and there is a large overlap in vegetation size between patients with and without embolic events.

Age

Older patients with IE have a higher mortality and morbidity than younger patients. Overall most studies showed that the rates of embolic events are similar between the older and the younger patients, although cerebral embolization is a much stronger predictor of mortality in older patients [27].

Abnormalities of Coagulation and Fibrinolysis

Patients with IE have abnormalities in the coagulation cascade. Systemic bacterial infections in the absence of any cardiac involvement is an independent risk factor for embolic events, which may be related to inflammation-induced procoagulant changes in the endothelial lining, and increased levels of antiphospholipid anti- bodies [28–31].

Kupferwasser et al. showed that IE patients with embolic events had significantly higher levels of antiphospholipid antibodies [32]. They reported that patients with elevated antiphospholipid antibodies (14.3 % of the population) had a higher risk of embolic events compared to those with undetectable levels (61.5 % vs 23.1 %, P = 0.008). Patients with elevated antiphospholipid antibody levels and embolic events also had higher levels of thrombin and plasminogen activator inhibitor, as well as reduced levels of activated protein C. It is biologically plausible that this intravascular milieu of increased thrombin generation combined with impaired fibrinolysis would lead to an increased risk of thromboembolism.

Recently research has focused on the potential role for soluble adhesion molecules in the pathophysiology of IE [33, 34]. Soluble forms of P and E-selectins have been shown to be secreted from activated platelets and endothelial cells and appear to be early mediators of endothelial dysfunction in the setting of inflammatory response. Korkmaz et al. reported elevated levels of both P and E-selectins in IE patients with embolic events [35]. This study included 76 patients with IE, 13 of whom had an embolic event (17.1 %). Patients with embolic events had higher P-selectin levels than patients without events and normal controls. E-selectin levels were similarly elevated in patients with IE and embolic events. This increase in E-selectin may reflect the endothelial dysfunction secondary to injury, with induction of a pro-adhesive and pro-thrombotic surface leading to thrombus formation, and the higher P-selectin levels are associated with enhanced platelet activation, which has a direct impact on thrombin generation.

These data support the notion that IE patients with embolic events have a sustained hypercoaguable state which likely contributes to the development of embolic events as a result of increased systemic coagulation activation, enhanced platelet activity, and impaired fibrinolysis. Despite the above-mentioned abnormalities of coagulation and fibrinolysis which promote thrombus development, patients with IE are also at significant risk for bleeding secondary to consumptive coagulopathy as well as a decrease in production of coagulation factors by the liver [36]. The coexistence of a hypercoagulable state and increased propensity of bleeding is a formidable clinical challenge in the management of patients with IE.

Strategies to Decrease Embolic Risk

Antibiotic Therapy

Effective antibiotic therapy reduces but does not abolish the risk of events. A reduction in vegetation size is associated with a lower rate of embolic complications. Rohmann et al. prospectively studied 183 patients with IE and valvular vegetations

detected by TEE, who were treated with appropriate antibiotic regimens [37]. A total of 16.4 % of these patients suffered an embolic event during the follow-up period of 76 weeks. A significant reduction in vegetation size during antibiotic treatment was associated with a reduction in embolic events and mortality. A reduction in vegetation size >49 % was associated with no risk of embolic events ($P < 0.05$). In patients with a decrease in vegetation size >37 %, there was no mortality. Thus antibiotic therapy remains the most effective treatment to prevent embolic events in patients with IE.

Fibrinolytic Therapy

Since vegetations contain a significant amount of thrombin and fibrin, the use of fibrinolytic therapy might be helpful in breaking down vegetations leading to a decrease in embolic events. Another potential benefit of fibrinolytic therapy is a synergistic effect with antibiotics. Exposing the bacterial surfaces normally buried in the fibrin-platelet rich matrix of the vegetation to antibiotics may enhance the effectiveness of antibiotics [38, 39]. Animal studies have shown a substantial reduction in vegetation size with a high proportion of cure and less damage to the valves in animals treated with fibrinolytic therapy but this reduction in the vegetation size occurs at a cost of more and larger cerebral infarcts likely as a result of embolization of the vegetation fragments [40].

There are reports of successful treatment using fibrinolytic agents in children with IE and large vegetations [41, 42]. Levitas et al. prospectively examined the effect of treatment with tissue plasminogen activator in seven infants with enlarging vegetations despite intensive medical treatment, including antibiotics [43]. In all patients, fever resolved within 2–3 days, blood cultures became sterile thereafter, and vegetations diminished in size and were no longer seen after 4 days. No embolic or hemorrhagic complications in this population were reported. There are few case reports of fibrinolytic therapy in adults patients with IE with mixed results [44, 45]. The use is mostly in patients with coronary artery embolization. There may be a limited role for fibrinolysis in very selected cases of IE such as those with prohibitive surgical risks and enlarging vegetations despite appropriate antibiotic therapy, because intracranial hemorrhage and death are real concerns. This therapy should be undertaken only after careful consideration has excluded the possibility of surgical therapy.

Anticoagulant Therapy

Given the previously described abnormalities in soluble adhesion molecules and other humoral factors leading to a hypercoaguable state, it would be logical to suspect that anticoagulant therapy in patients with IE may decrease the risk of embolic events. Warfarin treatment is postulated to decrease fibrin generation and its adhesion to the valve surfaces, which may then decrease the bacterial colonies adherent to the valve surface. Using a rabbit model of IE with *Staphylococcus epidermidis,* Thörig and co- workers showed that warfarin treated rabbits needed a larger

bacterial inoculum to induce infection [46]. Despite this reduction in infectivity there was a significant reduction in survival in the warfarin-treated rabbits mainly as a result of pulmonary hemorrhage. Other studies have also shown this increase in mortality associated with warfarin treatment in animal models of IE [47, 48].

There have been no controlled randomized studies on the use of anticoagulants to prevent embolism in IE. An early study showed that the use of heparin or dicumarol did not reduce embolism but was associated with a high rate of cerebral hemorrhage [49]. Similar findings have been reported in the review by Pruitt et al. which showed that five of seven patients treated with anticoagulants developed embolic events, of whom three had hemorrhagic cerebral infarction, while only 10 of 211 patients not receiving anticoagulants had hemorrhagic cerebral infarction. Patients with prosthetic valve endocarditis are at a high embolic risk despite continuation of anticoagulation treatment, and the risk is higher in the absence of adequate anticoagulation. Wilson et al. retrospectively studied 52 patients with prosthetic valve (Starr–Edwards prostheses) endocarditis [50]. Central nervous system complications occurred in 10 of 14 (71 %) patients without adequate anticoagulation therapy and 3 of 38 (8 %) patients with adequate anticoagulation. Mortality was 57 % among the patients without adequate anticoagulation and 47 % among those with adequate anticoagulation. Autopsy findings showed that central nervous system complications were the primary cause of death in 63 % of the cases without adequate anticoagulation. In the study of Paschalis et al. patients already anticoagulated for prosthetic valves had the same embolic risk as those on no anticoagulation [51]. Davenport and Hart examined 62 episodes of prosthetic valve IE in 61 patients and found that the risk of embolic events was lower in patients with bioprosthetic valves than those with mechanical valves who were on anticoagulation [52]. The deleterious effects of anticoagulation should be considered in patients with prosthetic valve endocarditis, as these patients are at high risk for intracranial hemorrhage, which can result in death.

Despite the hypercoaguable state in patients with IE, anticoagulation does not provide significant protection against systemic embolization, and is potentially harmful. However, in patients who have other indications for anticoagulation, such as mechanical valves, venous thromboembolic disease, or atrial fibrillation, benefits of anticoagulation likely outweigh the risks of excessive bleeding, but these patients continue to have a high embolic risk despite adequate anticoagulation. Current guidelines by the American College of Chest Physicians on antithrombotic and thrombolytic therapy recommend discontinuation of vitamin K antagonists (Warfarin) in patients with mechanical valve endocarditis at the time of presentation until it is clear that invasive procedure will not be required and the patient has stabilized without signs or central nervous system involvement. Vitamin K antagonists can be reinstituted when patient is deemed stable without contraindications or neurologic complications [53].

Aspirin and Other Antiplatelet Agents

Damage to the valvular endothelial surfaces has been shown to promote adhesion of platelets to the collagen rich subendothelial surface [54]. Platelet activation and

continued fibrin deposition lead to larger and more friable vegetations, which have a higher risk for embolization. Hence there is a biological basis that platelet inhibitors such as aspirin could enhance vegetation resolution and reduce embolic events. Among the antiplatelet agents, aspirin has received the most attention and has been shown to be beneficial in animal models [55, 56]. The incidence of stroke and change in echocardiographic vegetation area were prospectively studied in a small study involving nine IE patients randomized to receive either low-dose aspirin (75 mg per day) in four patients or no aspirin in five patients [57]. During a follow-up of 343 days, two cerebral embolic events and one case of presumed embolic myocardial infarction occurred in the control group, compared with no events in the aspirin treated patients. There was a decrease in the mean vegetation area of 0.24 cm^2 in the aspirin treated group, compared to an increase area of 0.35 cm^2 in controls. In this study aspirin treatment was not associated with an increase in bleeding complications. This study, although small, provided the first human evidence of potential benefit of aspirin therapy in patients with IE.

This hypothesis was further tested in a larger randomized double-blind, placebo-controlled trial [22]. In this study 115 patients were randomized to receive 4 weeks of either 325 mg per day of aspirin (60 patients) or placebo (55 patients). Both native valve and prosthetic valve endocarditis were included. The overall embolic event rate was 29 % when the randomized and non-randomized patients were pooled. There were 17 patients (28.3 %) with embolic events in the aspirin group and 11 patients (20 %) in the placebo group. There was no significant reduction in embolic events with aspirin treatment but there was a trend towards a higher incidence of major and minor bleeding in the aspirin- treated group. One of the limitations of this study was that only 31 % of the target sample size was recruited and hence the trial may be under- powered to detect a small beneficial effect of aspirin therapy on the risk of embolic events. Another potential limitation is the low dose of aspirin used in the study. However, at the present time this trial is the largest randomized controlled study evaluating a therapeutic strategy to reduce systemic embolization in IE. Some investigators believe that there may still be a role for aspirin therapy in patients with IE due to *S.aureus*, as there are platelet binding sites for staphylococcal proteins providing a mechanism for interruption of bacterial cell adhesion to sites of vascular injury leading to thrombosis [33, 58].

There is evidence from experimental IE in animals models to support other antiplatelet agents such as thienopyridines alone or in combination with aspirin but there are no reported studies of thienopyridine therapy in patients with IE [59–61]. The potential benefits of antiplatelet agents must be balanced with the real risk of increased bleeding in patients already at an elevated risk for bleeding.

It is uncertain that patients already on aspirin before the development of IE may have a lower risk of embolic event, since contradictory results have been reported [62, 63]. Thus in patients who have been taking aspirin or other anti-platelet agents before IE onset, the indication, potential benefits and risks should be carefully considered to determine the appropriateness of continuation of anti-platelet therapy.

Surgical Therapy

There are a number of studies that suggest combined medical and surgical therapy for IE is superior to medical therapy alone and can decrease morbidity and mortality. Currently, the strongest indications for surgical therapy are congestive heart failure and uncontrolled infection despite optimal antimicrobial therapy. It has been suggested that surgical intervention may be considered in individuals with recurrent emboli and persistent vegetations despite appropriate antibiotic therapy.

There are significant sequelae of central nervous system embolization not the least of which is the risks to these patients during cardiovascular surgery. In a retrospective study of 181 IE patients with neurologic complications who underwent surgery, higher rates of postoperative morbidity and mortality were present in those patients operated within a short time span from their neurologic event [64]. When the surgical intervention was performed within 1 week after the neurological event, the risks of mortality and worsening neurologic deficit were 31.3 % and 43.8 %, respectively, compared to risks of 7.0 % and 2.3 % respectively when the operation was more than 4 weeks after the neurologic event.

Based on the available data one approach to left-sided native valve IE in patients who have suffered a cerebral embolic or hemorrhagic event is to delay the cardiac surgery, a minimum of 2 weeks after an embolic event and a minimum of 4 weeks after a cerebral hemorrhagic event [64–66].

When to perform surgery to prevent systemic embolism remains a difficult clinical decision. Although echocardiographic parameters of vegetations provide useful prognostic information, clinical decision-making should not be based on these findings alone but should include careful analysis of all the clinical variables. Early diagnosis with prompt initiation of appropriate antibiotics remains the most effective strategy in the prevention of embolic events. A recent prospective trial in early surgery in patients with native valve IE showed that early surgery led to a marked reduction in embolic events but no reduction in 6 month all-cause mortality. The patients all had vegetations >10 mm and severe left-sided valvular dysfunction [67]. Not surprisingly 77 % of the non-early surgery patients had valve surgery during the same hospitalization. These results support the notion that early surgery can reduce the risk of embolic events, although most patients with severe valvular dysfunction would require early surgery anyway.

Guidelines

The recent guidelines by the European Society of Cardiology (ESC) and the American Heart Association/American College of Cardiology (AHA/ACC) on the prevention and management of embolic events in IE are summarized in Table 13.2 [68, 69] Compared to the American counterparts, ESC placed more emphasis on the size of the vegetations. Large vegetations >10 mm in length and one or more embolic

Table 13.2 Summary of guidelines on the prevention and management of embolic events in infective endocarditis

Class of recommendations	AHA/ACC, 2014	ESC, 2009
I	Timing of surgery should be made by a multispecialty team	Vegetations >10 mm with one or more embolic events despite appropriate antibiotic therapy
		Vegetations >10 mm with heart failure or persistent infection or abscess
IIa	Early surgery is reasonable with recurrent emboli and persistent vegetations despite appropriate antibiotic therapy	
IIb	Early surgery may be considered in native valve IE with mobile vegetations >10 mm with or without embolic events	Vegetations >15 mm

AHA/ACC American Heart Association/American College of Cardiology, *ESC* European Society of Cardiology

events is a Class I indication in the ESC guidelines and a Class IIa indication for early surgery in the AHA/ACC guidelines. The other Class I indication in the ESC guideline in the setting of embolic events does not have significant clinical impact, because IE patients with serious complications such as heart failure, abscess or persistent infection should be considered for early surgery whether or not embolic events have occurred.

Conclusion

Despite advances in medical and surgical therapy, IE continues to have a high morbidity and mortality. The rate of systemic embolization has remained relatively constant over the past two or three decades. Risk factors such as vegetation size and mobility allow us to identify patients at a higher risk for embolic complications. However, no single therapy with the exception of prompt and appropriate antibiotic treatment has shown effectiveness in reducing systemic embolization, although early surgery in selected patients may be useful. Treatments to enhance vegetation resolution including fibrinolytics, anticoagulants and antiplatelet agents have shown no benefits but are associated with an increased risk of bleeding. Current recommendations reflect this lack of effective and safe therapy in these high-risk patients. When making a decision to proceed with cardiac surgery to reduce the embolic risk one needs to consider all the clinical variables. The decision should not be based solely on the echocardiographic findings.

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Neurological Complications of Endocarditis: Pathophysiologic Mechanisms and Management Issues

14

Christopher R. Skinner

Abstract

Endocarditis is a major threat to the nervous system. Early detection of neurological damage using neuro-imaging and treatment during the pre-embolic phase is essential to prevent serious morbidity and mortality.

MRI sequences such as GRE and SWI have great sensitivity to detect microhemorrhages in order to detect systemic sepsis affecting the CNS and subclinical embolic events. In the case of an acute neurological deficit in a patient known to have valvular disease, congenital heart disease or previous valvular surgery, embolization due to endocarditis must be considered high in the differential diagnosis. Serial imaging of the brain and brain vasculature using MRI/MRA and high resolution CT/CTA are required to monitor the formation and progression of infectious intracranial aneurysms.

Multi-disciplinary neurovascular consultation is required once infectious intracranial aneurysms have been detected. Once stabilized, infectious intracranial aneurysms often have a good prognosis.

Marantic endocarditis is rare. The prognosis often depends mainly on the clinical course of the underlying malignancy.

Institutions need to develop and implement structured approaches to the detection and treatment of IE.

Keywords

Endocarditis • Embolism • MRI • MRA • GRE • SWI • CT • CTA • Marantic • Endovascular

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Key Points

1. Endocarditis either IE or ME is a major threat to the nervous system
2. Early detection of neurological damage using neuro-imaging and treatment during the pre-embolic phase is essential to prevent serious morbidity and mortality. MRI sequences such as GRE and SWI have great sensitivity to detect subclinical embolic events and micro-hemorrhages associated with systemic sepsis affecting the CNS.
3. In the case of an acute neurological deficit in a patient known to have valvular disease, congenital heart disease or previous valvular surgery, embolization due to endocarditis must be considered high in the differential diagnosis.
4. Serial imaging of the brain and brain vasculature is required to monitor the formation and progression of infectious intracranial aneurysms. Both MRI/MRA and high resolution CT/CTA are appropriate tools to use for this purpose.
5. Multi-disciplinary neurovascular consultation is required once infectious intracranial aneurysms have been detected
6. Once stabilized, infectious intracranial aneurysms often have a good prognosis
7. Marantic endocarditis is rare. The prognosis often depends mainly on the clinical course of the underlying malignancy.
8. Institutions need to develop and implement structured approaches to the detection and treatment of IE.

Introduction

The occurrence of a neurological event due to infective endocarditis (IE) is often unexpected, sudden and catastrophic. It is frequently perceived as an unfortunate but generally unavoidable event. However, when one looks at the sequence of the pathophysiologic process of the disease, often there are telltale systemic and neurological signs and symptoms prior to the main event, which could be essential in making an early diagnosis. Early diagnosis may lead to interventions, which could be useful to mitigate the catastrophic sequence of events resulting in neurological damage and death.

This chapter is an attempt to document the sequence of the pathophysiological processes in which the nervous system gets progressively involved in the disease process of IE. Infective endocarditis will be the primary focus, but a brief discussion of marantic endocarditis is also included.

Full appreciation of the different neurological events in IE must take into consideration the pathophysiological processes, the etiological agent and the neurological localization over the dimension of time from pre-clinical events to the specific events resulting in neurological deficits and to further progression of neurological

complications. This chapter provides a neurological diagnostic framework for the practicing clinician based on the current literature.

Historical Perspective

The clinical triad of fever, heart murmur and stroke were recognized by Osler and others before him to indicate the presence of IE [1, 2]. Present-day clinicians strive to recognize the endocarditis complex before permanent damage to heart, brain and other target organs occurs. Despite the use of modern imaging, there continues to be significant delays in diagnosis and treatment in many IE patients.

The major historical milestones in the diagnosis and treatment of endocarditis have been the development of antibiotics, cardiac imaging including angiography and echocardiography, and the various options of surgical treatment from valve replacement or repair to extensive reconstruction of aortic or mitral annulus.

In everyday neurological practice, advancements in neuroimaging including computed tomography (CT), magnetic resonance imaging (MRI) and digital cerebral angiography have helped enormously in terms of the timely localization of lesions in the central nervous system (CNS) in order to initiate real-time treatments which can improve recovery, especially from ischemic and hemorrhagic events. These investigations are usually employed after the defining event has occurred. In order to improve outcomes in IE, more attention has to be paid to the use of these tools earlier in the course of the disease to provide information which may reduce mortality and morbidity. Specific treatments may include in highly selected cases the use of thrombolytic agents to hasten resolution of a septic embolus and the use of valve surgery to prevent an impending embolic stroke.

The use of neurological interventional techniques to deal with septic aneurysms has led to the development of aneurysm hardware for coiling and clipping infectious intracranial aneurysms. There are many case reports on treatment of these aneurysms using neuroradiological interventional techniques. However there are few clinical trials to assist the clinical determination of the best treatment of infected intracranial aneurysms from a risk benefit standpoint.

Despite advances in neurological imaging, the key to early diagnosis remains a high index of suspicion bearing in mind the protean manifestations of IE. The risk of CNS embolic event diminishes rapidly following the initiation of appropriate antibiotic therapy. A delay in the diagnosis and treatment must be avoided to improve the outcome of these patients. Thus the occurrence of an acute neurologic event in the context of constitutional symptoms should alert the clinician to the possibility of IE.

Epidemiology

The occurrence of neurological complications in IE is from 20 % to 40 %, with an average of 37 % [3]. Neurological deficits have been reported in up to 40 % of patients with endocarditis of the left side of the heart [4]. Once neurological damage

has occurred a mortality rate of 50 % has been reported versus 21 % in patients with endocarditis without neurological complications [5]. Therefore, prevention of neurological complications must become a priority.

Neurological complications were either the chief complaint or one of the major presenting symptoms in 28 % of patients with IE. The presence of congestive heart failure and non-cardiac shock with neurological damage increases the mortality and morbidity significantly [6, 7].

Pathophysiological Mechanisms and Clinical Manifestations

The first matter to consider is the sequence of the pathophysiological processes by which endocarditis affects the nervous system either directly or indirectly (Table 14.1). The life history of endocarditis starts with the development of damage to the endocardium, in particular the heart valve and surrounding tissue, with the initiation of an inflammatory process on the surface of a valve, which then leads to progressive destruction of the endocardial, then myocardial and conducting system tissue.

In the early stages, the inflammatory process does not usually lead to the formation and liberation of thromboembolic material, but rather initiates non-specific systemic inflammatory responses, which affect the nervous system indirectly. In the pre-clinical event stage, there is release of inflammatory cytokines such as interleukin-8 and tumor necrosis factor as well as other humoral responses. These humoral factors can affect the brain, often causing non-specific encephalopathic responses such as fatigue, anorexia and malaise. The detection of the presence of such cytokines could be used as markers of early disease activity. The cytokines probably interact with areas of brain, which are sensors of systemic disturbance such as the area postrema, hypothalamus and pineal glands. The symptoms of encephalopathy are difficult to explain in terms of precise localization, but these humoral factors are present in 30–50 % of patients subsequently developing clinical neurological events. Cerebrospinal fluid (CSF) markers of cerebral damage such as glial fibrillary acidic protein (GFAP) and neurofilament protein have been measured in combination with MRI scanning increasing the sensitivity of detecting CNS damage up to 73 % [8].

The second preclinical pathophysiological process, which results from the initial inflammatory process, is the development of diffuse vascular inflammatory reaction or vasculitis. This is usually a small vessel process, which affect all areas of cortex leading to non-focal signs and symptoms of cognitive decline, such as inattention, character changes, somnolence and irritability. At this stage endocarditis can masquerade as CNS vasculitis or vice versa [9]. When confronted with this non-specific clinical picture rarely do clinicians look to the heart for the underlying cause and order cardiac imaging such as echocardiography.

Diagnostic investigations which may be of help at this stage include a detailed history, especially for prodromal infectious symptoms, and physical examination with particular attention to the presence of a new heart murmur, splenomegaly and the presence of peripheral embolic events such as Roth spots or Janeway lesions.

Table 14.1 Symptoms, signs and pathological changes in different stages of neurological involvement in infective endocarditis

Stage	Symptom	Signs	Echo	Neuroradiology	Electrophysiology	CNS pathology
Pre-event early	Fever, malaise, weight loss, encephalopathy	Inattention, personality change	Normal, pre-existing valvular disease or prosthetic valve, VSD, ASD, PFO	Normal	Normal, possible intermittent slowing corticothalamic synchronization disturbances	Vasculitis, cytokine effects, increased inflammatory cells, CSF markers
Pre-event late	Increased systemic symptoms	Increased deterioration of mental status, seizures	Valve thickening and micro thrombus formation	Areas of increased signal on T2, SWI, GRE and FLAIR at cortex/white matter junction	EEG slowing, sleep fragmentation, intermittent localized spike and wave activity	Vascular thinning, Immunoglobulin and complement deposition on blood vessels
Initial event	Focal numbness weakness or visual loss, sudden headache	Loss of visual field, weakness, sensory loss, brain stem findings	Progressive valve destruction, friable thrombus on valve	Areas of increased signal in brain parenchyma or subarachnoid space	Focal slowing or periodic lateralized epileptiform discharges (PLEDS)	Ischemic and or hemorrhagic infarction, pyogenic destruction of medium sized distal vessels, infectious intracranial aneurysms
Secondary event	Severe headache, numbness, weakness, loss of consciousness	Coma, loss of brain stem reflexes, brain death	Progressive valve destruction, friable thrombus on valve	Signs of midline shift and uncal/tonsillar herniation	Loss of background rhythm, burst suppression, electrocerebral silence	Multiple areas of ischemic necrosis with and without hemorrhage with uncal/tonsillar herniation
Late effects	Loss of functional status, inability to ADLs or work	Permanent deficits of mental status vision, sensation, motor	Sequellae of infected valve or replacement prosthesis	Encephalomalacia in areas damaged by hemorrhage or infarct, hydrocephalus due SAH	Focal slowing, focal seizure focus in areas of cortical damage, sleep fragmentation decreased SWS, PLMs	Areas of gliosis and hemosiderin deposition. Encephalomalacia, axonal disruption, permanent vascular damage, hydrocephalus

ADL activity of daily living, *ASD* atrial septal defect, *FLAIR* fluid attenuated inversion recovery, *PFO* patent foramen ovale, *PLM* periodic limb involvement, *SAH* subarachnoid hemorrhage, *SWS* slow wave sleep, *VSD* ventricular septal defect

Laboratory investigations should include serum for immune complexes, protein electrophoresis and complement studies. MRI of the brain with and without gadolinium may demonstrate increased contrast in the small vessels of the cortex-white matter junction, which is quite distinctive from other inflammatory patterns. The electroencephalogram (EEG) may show non-specific changes of bilateral slowing. There are animal models of IE in pigs which have demonstrated areas of focal encephalitis [10]. Sleep disruption in this stage has not been well studied but fragmentation of sleep architecture and lack of slow wave sleep might be expected.

The so-called immune complex vasculitis, which can predate or accompany endocarditis, involves small blood vessels in the brain and elsewhere often leading to other complications such as glomerulonephritis and renal dysfunction. Approximately 20 % patients with IE are referred to nephrologists for underlying renal disease based on the presence of proteinuria and active sediment [11]. Recognition and prompt antibiotic treatment at this stage can potentially prevent serious neurologic deficits.

Neurological Embolic Events

The next stage of evolution at the endocardial level consists of progressive destruction of endocardium to the point of producing thromboembolic material which then affects the nervous system directly. The size and infectivity of this material depends on the duration of infection, the degree of destruction and the pathogenicity of the organism.

The clinical context based on the neurological history of the embolic ictus is vitally important. Carotid or simple cardiac emboli usually arise abruptly without any encephalopathic prodrome. If altered mental status precedes a cerebral thromboembolic event for more than minutes, there should be a strong suspicion of an underlying systemic disease such as IE which has a propensity for embolic events. The presence of various risk factors for IE listed in Table 14.2 should heighten clinical suspicion for IE.

With respect to the brain, the site of embolization from a central source embolus such as a heart valve can involve any of the four arteries which supply the circle of Willis. As a general rule, the site of embolization for larger emboli tends to reflect

Table 14.2 Clinical risk factors for the development of infective endocarditis

Presence of a prosthetic valve
Intravenous drug use
Body piercing, especially the tongue
Congenital heart disease especially right to left shunts
Previous intra-cardiac surgery
Presence of intracardiac catheters, shunts, tubing or other prostheses
Immunodeficiency
Exposure to zoonotic infections

sites of higher flow such as the left middle cerebral artery territory which is the language dominant hemisphere in right-handed individuals.

The spinal cord and peripheral nerves remain relatively immune to peripheral embolization from the heart [12]. Occasionally emboli to skeletal muscle can occur and can present a sudden onset of an unusually severe localized non-radicular pain in an isolated muscle of any limb or the paraspinal muscles. In such a case, bloodwork shows unexplained high levels of creatinine kinase of skeletal muscle origin.

The issue of the timing of the emboli causing neurological deficits is an important one, as it may determine the decision with respect to surgical management of the valvular disease. Clinical observation suggests that in some patients with IE there is a bimodal distribution to the development of neurological deficit. The initial embolic event may be small and cause either a reversible event or minor deficit. Then, after a period of clinical improvement, a larger more devastating embolus often occurs 3–4 days later. This phenomenon may be a reflection of the relationship between the size of the valvular vegetation and the risk of embolization. Large vegetations of >30 mm have been shown to have a higher risk of embolization than smaller vegetations [9], implying that the longer the vegetation is allowed to grow on the valve, the more likely it is to embolize when it gets larger thus causing proportionally greater damage.

Recent MRI studies show that most transient focal neurological deficits lasting more than 30 min are in fact caused by small emboli, which cause changes on Diffusion Weighted Imaging (DWI) MRI sequences. Therefore the occurrence of any focal neurological deficit longer than 30 min in a patient with endocarditis should trigger rigorous search for the source and consideration of the merit of surgery in the presence of large vegetations with the usual precautions to rule out a hemorrhage. This is discussed in more detail in Chap. 13. MRI has been shown to be superior to CT scanning to perform disease staging and provide guidance for therapeutic decisions, [13, 14]. Newer techniques using Positron Emission Tomography (PET) scanning have been able to detect areas of ischemic damage related to tissue metabolic changes [15].

Therefore for large and small emboli, the pathophysiological mechanisms include ischemia due to blockage of vessels, hemorrhage into an area of ischemia, and infection of the area affected by the embolus.

The presence of small micro-hemorrhages on Gradient Echo (GRE) or Susceptibility Weighed Imaging (SWI) MRI imaging sequences is common in IE patients and may indicate active micro-emboli activity (Fig. 14.1) [16, 17]. One study showed that for every 1 mm increase in the size of the vegetation, there is a 10 % increase in the incidence of ischemic microbleeds. The presence of microbleeds on MRI poses a contraindication to the use of systemic anticoagulation [17, 18].

Ischemia from large emboli tends to be cortical and lobar, conforming to the flow pattern of the supplying artery. For instance, a large speech-dominant hemisphere middle cerebral artery infarct leads to the constellation of symptoms including aphasia and contralateral hemiplegia of the face, arm and to a lesser extent the leg. For small vessel ischemia, the pattern is much more random with cortical, subcortical and brain stem infarcts occurring concurrently. The presenting neurological signs and symptoms in this case are often discordant suggesting multiple localizations.

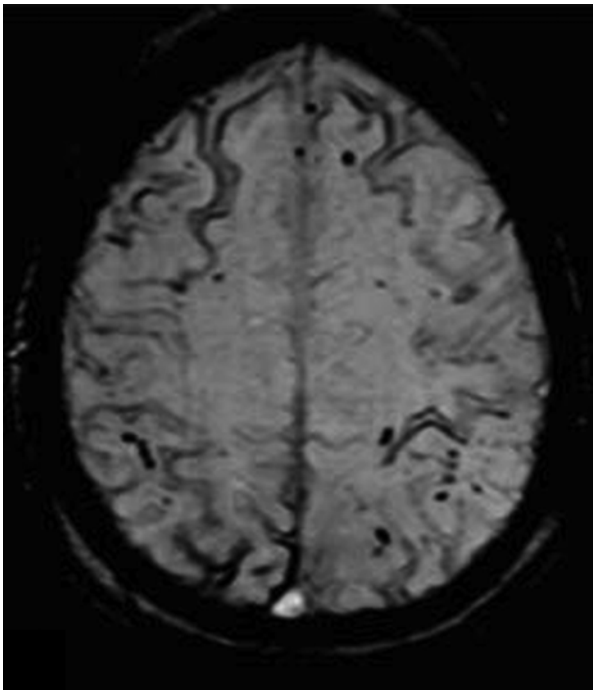

Fig. 14.1 Areas of increased magnetic susceptibility due to multiple micro-hemorrhages in sepsis (From Ref. [16] with permission)

Cardiac emboli, which travel through the vertebrobasilar system, tend to fragment on their journey up the basilar artery seeding the brain stem in several places and then fragment to either or both of the posterior cerebral arteries, the so-called "top of the basilar syndrome" (Fig. 14.2) [19].

A typical brainstem prodrome can present as an acute unexplained cranial neuropathy sometimes as simple as a Bell's palsy. On closer examination, the anatomical neighbors of the facial nerve, cranial nerves 5, 6 or 8 may be involved on the same side indicating more widespread pontine damage. This would then be a significant clue to prompt a search for a central source of emboli before a larger embolus is released.

Infectious Intracranial Aneurysm

Following the seeding of the nervous system with septic emboli, the next phase of damage occurs. This involves the vascular damage due to the infected emboli invading the blood vessels directly. The development of septic or infectious intracranial aneurysms (also known as mycotic aneurysms) in the brain should be considered a late complication in which there has been adequate time for the blood vessels, which are relatively resistant to infectious invasion, to be affected and develop weakening

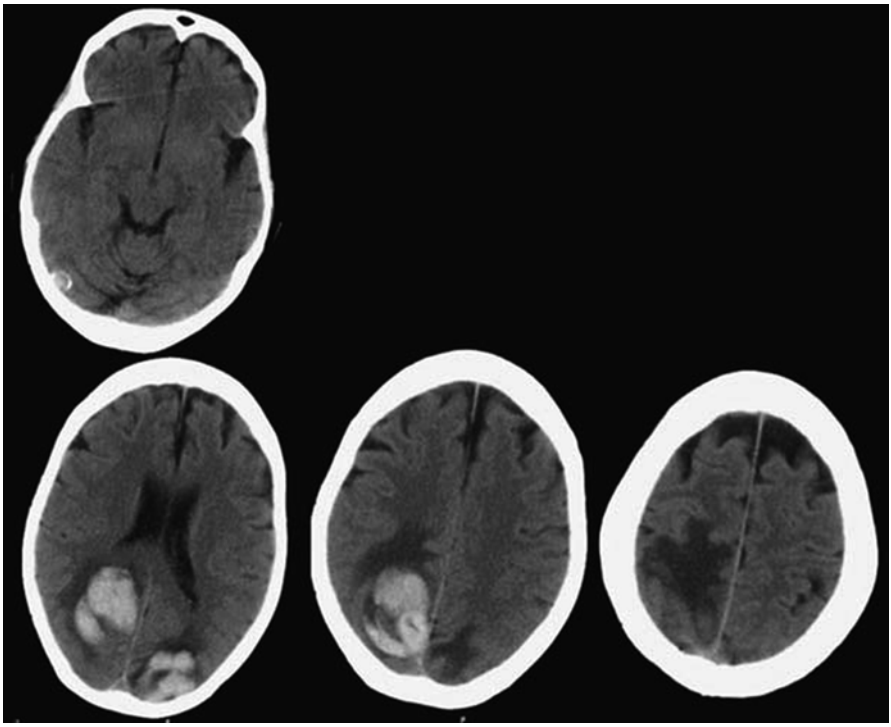

Fig. 14.2 This figure shows bilateral hemorrhagic infarction from an embolus traveling up the vertebrobasilar system and fragmenting into a left and right-sided occipital thromboemboli

of the collagen support structure (Figs. 14.3 and 14.4). The frequency of infectious intracranial aneurysms is 2–10 % in patients with IE [20].

There is no literature to suggest that individuals with qualitative abnormalities of collagen such as Ehlers-Danlos syndrome or polycystic kidney disease or fibromuscular dysplasia have a higher risk of infectious intracranial aneurysms than the normal population. Common sense would dictate that cerebral vessels of these individuals may have more severe tissue destruction when affected by septic emboli.

The use of MRI and magnetic resonance angiography (MRA) has improved our ability to diagnose infectious intracranial aneurysms, which are often clinically silent until they reach a size which causes mass effect or rupture. The usual rules concerning the size of aneurysm and the risk of rupture do not apply to infectious intracranial aneurysms. Once an infectious intracranial aneurysm is identified, serial angiography is recommended to follow aneurysm growth [21]. The advances in CT angiography provide the ability to image both the interior and exterior anatomy of the vessels in three dimensions to allow examination of these serial changes. The neuroradiologist needs to be alerted to the clinical problem under investigation as the various types of rendering such as volume rendering may be inappropriate when maximum projection rendering may be more appropriate to visualize the interior of the vessel.

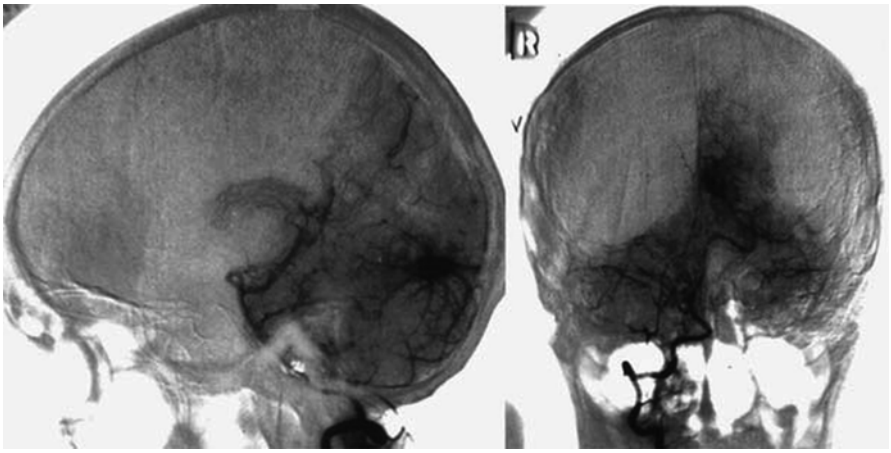

Fig. 14.3 This cerebral angiogram shows a nidus a distal branch of the left posterior cerebral artery, which caused a subarachnoid hemorrhage, and was subsequently resected (Courtesy Dr. H. Lesiuk)

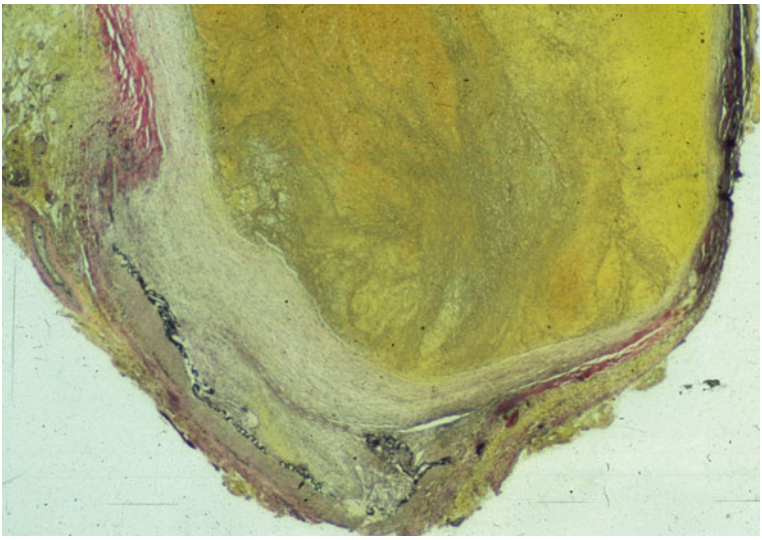

Fig. 14.4 This is the photomicrograph of the mycotic aneurysm shown above that was resected surgically. There is a collection of purulent necrotic material in the aneurysm, which spread through the intima and media to the point of failure of the arterial wall (Courtesy Dr. H. Lesiuk)

Infectious intracranial aneurysms of the vertebrobasilar system are rare but have been reported on the posterior cerebral artery [22]. Extracranial arteries can be affected to cause neurological deficits such as in the iliofemoral system. Infectious aneurysms of the extracranial carotid arteries are rare but have been reported in the extracranial portion of the internal carotid arteries [23, 24].

Brain Abscess and Meningitis

Other complications to the nervous system following seeding, infarction and infection include the development of seizures from areas of damaged cortex, brain abscesses, meningitis, subdural hematomas and ventriculitis [25]. Both brain abscess and meningitis are uncommon accounting for 0.6 % and 5 % respectively of the neurological complications in 340 patients who experienced such complications in a multi-centre study of 1,345 episodes of left-sided IE [26]. Staphylococcus aureus was the most common etiologic agent. The treatment for intracerebral abscess in IE patients should include a search for infectious intracranial aneurysms which frequently co-exist in these patients. Most solitary brain abscesses, however, are not caused by IE [27]. Among 1,025 episodes of meningitis from 2006 to 2012 in the Netherlands, IE was identified in 24 episodes (2 %). The common organisms were Streptococcus pneumonia and Straphylococcus aureus. The prognosis is poor due to frequent systemic and neurologic sequalae [25].

Intracranial Hemorrhage

The relative neurological damage from any of these processes depends on the localization and the severity combined with the effect of age and other medical comorbidities. The presence of hyperglycemia, hypertension or hypotension may increase the severity of ischemic damage caused by thromboemboli especially if these are septic. Hemorrhage complicating septic emboli can lead to sudden rapid herniation syndromes and brain death (Fig. 14.5). Long-term neurological complications of thromboembolic events and sepsis in the brain beside the focal deficits caused by local destruction of brain tissue include seizure disorders, movement disorders, personality changes, cognitive dysfunction and dementia.

Subarachnoid hemorrhage (SAH) from infectious intracranial aneurysms occurs in approximately 1–1.7 % of cases of IE [28] with a mortality rate of 80 % [20]. The occurrence of SAH in the context of IE is highly predictive of the presence of an

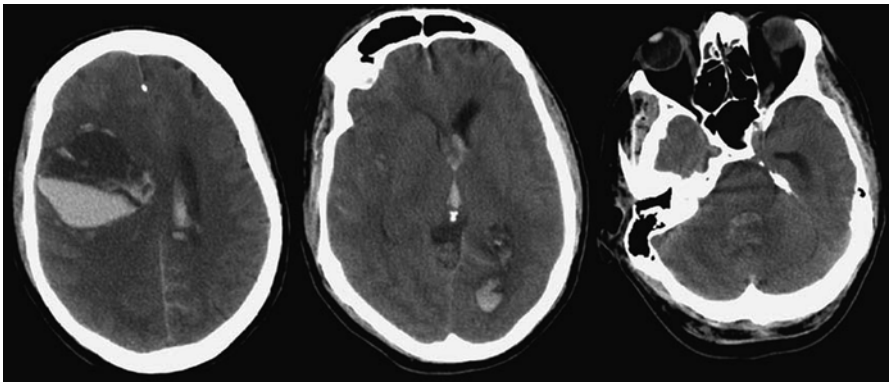

Fig. 14.5 CT scan of 45-year-old man with mechanical aortic valve with Staph aureus endocarditis develops sudden left sided weakness and brain death in 36 h. CT scan shows large right hemisphere infarct with hemorrhage extending into the lateral third and fourth ventricles

infectious intracranial aneurysm by angiography [29]. Some authors have suggested that subarachnoid hemorrhage in the context of endocarditis may have alternate mechanisms such as leakage from damage due to pyogenic necrosis instead of rupture of infectious intracranial aneurysms. Infectious intracranial aneurysms should be considered in the differential diagnosis of non-traumatic subdural hematoma [30, 31]. Infectious intracranial aneurysms when successfully treated either medically or with neuro-interventional techniques can resolve over time and usually present no long-term risk of rupture after stabilization.

IE is associated with multiple types of neuropathological lesions and activation of cells of monocyte-microglial lineage throughout the brain [32]. One study of the histopathology of intracranial hemorrhage due to IE found that hemorrhagic transformation of the ischemic infarct due to septic emboli is the most frequent mechanism leading to intracerebral hemorrhage in patients dying of IE and that rupture of pyogenic arteritis or infectious intracranial aneurysms is an alternative mechanism in other cases [33].

Etiological Agents

One of the major factors determining the outcome of neurological events due to IE is the metastatic infectivity of the etiological agent. *Streptococcus pneumoniae* and *Staphylococcus aureus*, common organisms causing IE, often resulting in multifocal cerebral and systemic septic emboli [25].

There is a paucity of literature that links the pattern of thromboemboli with specific organisms, although more virulent organisms associated with large vegetations can cause thromboemboli earlier in the course of the disease as opposed to a more subacute clinical courses by less virulent organisms such as *Streptococcus viridans*. Some organisms such as non-typhi Salmonella are more prone to cause septic aneurysms of large vessels such as the aortic arch with the potential for shock and significant downstream damage leading to a poor outcome [34].

Different organisms may produce different profiles of cytokine and humoral proinflammatory responses. It remains to be determined whether detection of these molecules could be used for the purpose of early diagnosis of IE in the context of new onset, unexplained mental status change.

Neurological Localization

The approach to localization in patients with IE with neurological involvement should mirror the time course of the pathophysiological processes listed above. The pathophysiological mechanism of the early involvement of cortical and subcortical structures to produce confusion or personality change and altered levels of consciousness is not well understood. The liberation of systemic cytokines is known to affect the sleep and attention centers in the hypothalamus. Close attention has to be paid to the history of an abrupt change in mental status with no other medical

explanation in terms of systemic illness or change in medication. Often this prodrome can precede the thromboembolic events by many days or weeks and therefore offers a long potential window for intervention.

The various brain localizations mentioned above include territories served by middle cerebral, vertebrobasilar and anterior cerebral vessels. When the neurological localization conforms to one of these patterns, the presence of large vessel emboli is most likely. The appearance of concurrent multi-focal localizations would suggest the liberation of small emboli to multiple territories in the nervous system, which can include the spinal cord, peripheral nerves and muscle.

The appearance of dysfunction of the neuromuscular junction in a patient with culture-negative endocarditis should raise the possibility of marantic endocarditis and a paraneoplastic etiology for the neurologic manifestation. A search should be considered for a neoplasm most likely a small cell tumor in the lung. Antibody assays are available to assist in the search of paraneoplastic causes [35].

Clinical History

The clinical history is essential to assist in determining the presence of risk factors for the development of endocarditis (Table 14.2). The suspicion of endocarditis should raise the following crucial questions: what is the source of the infection, what is the most likely organism, and to where in the CNS has the vegetation embolized?

Symptoms can be non-specific such as low back pain and hematuria [36, 37]. The occurrence of TIA or stroke prior to the acute illness is essential in terms of determining a baseline neurological status. In the patient with new onset of fever and encephalopathy, family or friends can be the richest source of information to guide the search for the source of the infection and to provide information on baseline mental state. The cheapest test is always more history.

When reviewing a patient with IE and recent cardiac surgery other factors must be considered in determining the cause of the neurological deficits. In particular there are factors relating to other cardiac conditions and the surgical procedure itself, which may have a role in causing the deficits (Table 14.3).

Table 14.3 Potential causes of stroke in patients who have undergone cardiac surgery

Intracardiac thrombus or intracardiac shunts
Embolism of fragments of valve tissue or calcium
Air emboli
Aortic atherosclerosis, which is a source of emboli during surgery
Embolism of thrombus formed at aortic cannulation sites
Watershed stroke due to hypotension during the procedure

Treatment Methods to Prevent Embolic Stroke

From a neurological standpoint, treatment options depend on many factors, such as which phase of the illness the patient is in, the pre-existing CNS status and the severity of CNS damage caused by IE. In the pre-event phase, it would be most desirable to diagnose the presence of IE and to commence treatment to prevent the growth and propagation of valvular vegetation. Conventional treatment with antibiotics is appropriate. The risk analysis for treatment with anticoagulants has to take into consideration all the variables. These would include the presence of arrhythmias, presence of prosthetic heart valves and the presence of previous cerebral damage from stroke or hemorrhage. Anticoagulants should be continued in patients in whom it is indicated prior to IE, but there is no evidence for its use to prevent embolism in IE patients. The presence of diffuse microvascular disease or microbleeds detected by MRI with SWI protocols are known risk factors for cerebral hemorrhage with anti-coagulants.

In the pre-event stage, if encephalopathy is present, the treatment should be focused on maintaining optimal metabolic and nutritional balance with correction of any potential or pre-existing nutritional deficiency such as B12, folate, thiamine or thyroid in addition to appropriate antibiotic therapy. There is no evidence to support the prophylactic use of anti-convulsants at this stage.

The use of antiplatelet agents during this stage to prevent the formation and propagation of thromboemboli material from a damaged valve to decrease the risk of embolization has to be balanced against the risk of causing hemorrhage from potentially compromised cerebral vessels. A study comparing the use of ASA at a dose 325 mg versus placebo failed to show a positive effect for prevention of infarct but conferred a slightly higher risk of hemorrhage. ASA had no effect on vegetation resolution and valvular dysfunction [38].

Patients with IE and concomitant coronary artery disease may be taking dual anti-platelet agents such as clopidogrel and ASA. This combination has been found to confer a higher risk of spontaneous cerebral hemorrhage. Although studies in a population with IE treated with these agents have not been performed, great caution and close monitoring for bleeding are warranted in IE patients taking both agents.

Treatment After Occurrence of Stroke

After a neurological defining event such as an embolus has occurred, the treatment focus shifts to that of acute stroke care. There are a few series in which the use of thrombolytics has been safely carried out in children, but there is little evidence to support the safety of thrombolytics in adults in the acute state [39, 40]. The use of these agents in the face of endocarditis can have potentially disastrous results since the risk of bleeding is real particularly if there are unsuspected micro hemorrhages and infectious intracranial aneurysms which have already formed. This emphasizes the

need for urgent high-resolution imaging of the neurovascular tree prior to the initiating of thrombolytic therapy in any patient with an acute deficit with suspected IE.

The technology of clot retrieval in acute stroke presents options for using such devices in the context of stroke in IE [41].

The decision with respect to anticoagulation after an acute event in a patient with endocarditis requires weighing the risk of bleeding into an area of non-hemorrhagic infarction against the daily risk of embolization. Although published guidelines are helpful, they cannot supplant the discussion by a multidisciplinary team consisted of both medical and surgical specialists, in order to carefully assess the risks and benefits of continuation versus interruption of antithrombotic therapy is a given patient with IE and suspected CNS event. The guidelines of the American Heart Association/American College of Cardiology (AHA/ACC) and the European Society of Cardiology (ESC) are listed in Table 14.4 [42, 43]. The guidelines largely address the issue of continuation versus interruption of antithrombotic therapy in IE patients who have been on antithrombotic treatment prior to the diagnosis of IE. In IE patients not on antithrombotic therapy prior to IE, antithrombotic therapy including anticoagulants and antiplatelet agents are not indicated in this situation, because patients with IE have an increased risk of bleeding and there is no data to support a beneficial effect of antithrombotic therapy.

Whether to perform valve surgery in a patient with embolic stroke and persistent valvular vegetation is a clinical dilemma. The decision must be individualized. Valve surgery may be reasonable in a patient who has had a small cerebral infarct but still has large mobile valvular vegetations. Pre-operative MRI scanning is now recommended to document pre-existing lesions using DWI and ADC mapping to determine lesion age [44].

Table 14.4 Guidelines on the use of antithrombotic therapy in infective endocarditis

AHA/ACC guidelines	
IIa	Reasonable to temporarily discontinue anticoagulation when there are neurological symptoms compatible with embolism or stroke
IIb	Temporary discontinuation of VKA anticoagulation at the time of IE diagnosis
ESC guidelines	
I	Interruption of antiplatelet therapy in the presence of major bleeding
	In ischemic stroke without cerebral hemorrhage replacement of VKA by unfractionned heparin for 2 weeks
	In intracranial hemorrhage, interruption of all anticoagulation
IIa	In intracranial hemorrhage and mechanical valve, unfractioned heparin should be reinitiated as soon as possible following multidisciplinary discussion
IIb	In the absence of stroke, replacement of VKA by unfractionned heparin for 2 weeks in case of *S. aureus* IE may be considered

AHA/ACC American Heart Association/American College of Cardiology, *ESC* European Society of Cardiology, *IE* infective endocarditis, *VKA* vitamin K antagonist

The surgical treatment of infectious intracranial aneurysms presents technical challenges not present with berry aneurysms of the circle of Willis. The localization of infectious intracranial aneurysms is more difficult because they tend to be more distal, are more friable and may be obscured by hematoma. The basic surgical principle is to render the infectious nidus safe from further necrosis, breakdown and bleeding. This often requires taking the whole vascular apparatus including the feeding artery, the aneurysm and the draining vein. This type of surgery has a high risk of causing collateral ischemic damage in the area served by the vessel, which has to be sacrificed to make the aneurysm safe from further bleeding.

Newer techniques such as wand-guided MRI and MRA-guided frameless stereotaxy have been developed [45]. The use of stereotactic angiography to localize infectious intracranial aneurysms is described [46]. Advanced techniques such as stereoscopic synthesized brain-surface imaging can be used to precisely localize the aneurysm and minimize the size of the craniotomy [47].

Neuroradiological interventional techniques for treating infectious intracranial aneurysms include coiling, glue embolization or stenting. The options for treatment are multiple and there are few evidence-based guidelines to assist decision making in this regard. In many cases, it is a matter of reviewing the anatomy of the infectious intracranial aneurysm or aneurysms in a multi-disciplinary neurovascular forum to decide on the best course of action considering factors such as the size of the aneurysm, the location, the size of the neck, surgical accessibility and medical co-morbidities.

The debate concerning neurosurgical versus neuroradiological interventional techniques follows the same pattern as with berry aneurysm treatment. The location of the aneurysm, the size, the clinical stability of the patient and the availability of a facility with experience performing the available procedures all figure into the decision as to which might be a better choice. There are case reports of both surgery and coiling used for different infectious intracranial aneurysms in the same patient. In general, patients with endocarditis and infectious intracranial aneurysms, the infectious intracranial aneurysm should be properly treated before valvular surgery is performed.

With respect to the timing of cardiac surgery after a cerebral embolism, the risk depends on the size and location of the infarct and the risk of reperfusion injury after the patient comes off the bypass pump. Some studies suggest that patients with endocarditis who have suffered neurological deficits for whom surgery is delayed up to 3 weeks may have better outcomes [4, 48]). The current standard of practice is to delay cardiac surgery a minimum of 2 weeks after an embolic infarct with little or no hemorrhage and 4 weeks after a cerebral hemorrhagic event. Early cardiac surgery can be considered in younger patients with small neurological deficits without significant heart failure. Fukuda et al. suggested that infectious intracranial aneurysms should be dealt with before the cardiac surgery [49]. The ESC guidelines regarding the indications and timing of interventions listed in Table 14.5 provide a pragmatic and reasoned approach in dealing with these seriously ill patients [42].

Table 14.5 Management and timing of intervention in patients with infective endocarditis and neurological complication

Class I	After a silent cerebral embolism or transient ischemic attack, surgery is recommended without delay if an indication remains
	Following intracranial hemorrhage, surgery must be postponed for at least 1 month
	Neurosurgery or endovascular therapy are indicated for very large, enlarging, or ruptured intracranial aneurysm
Class IIa	After a stroke, indicated cardiac surgery should not be delayed as long as coma is absent and cerebral hemorrhage has been excluded by cranial CT
	Intracranial aneurysm should be looked for in any patient with IE and neurological symptoms – CT or MR angiography should be considered for diagnosis
	Conventional angiography should be considered when non-invasive techniques are negative and the suspicion of intracranial aneurysms remains

CT indicated cardiac, *MR* magnetic resonance

Marantic Endocarditis

Marantic endocarditis (ME) or non-bacterial thrombotic endocarditis is a rare clinical entity, which features the occurrence of sterile fibrin-platelet deposits on the surface of mitral, tricuspid or aortic valves [50, 51].

In patients with chronic diseases or malignancy, the occurrence of recurrent strokes should alert the clinician to the possibility of ME [52]. The presence of embolic material on a heart valve without evidence of infection should trigger a search for the primary malignancy. Gynecological neoplasms seem to have the highest potential for developing ischemic stroke related to microemboli due to marantic endocarditis [53]. The embolic events can precede any symptoms from the underlying malignancy for months to years. Occasionally treatment of the underlying malignancy leads to improvement of the endocarditis and the prothrombotic state [54]. Common neurological findings are altered mental status, seizures, and hemiplegia. Pneumonia, hypoxia, disorders of coagulation, and renal failure are frequently present in seriously ill patients.

Differences in the MRI appearance of infarcts in ME versus IE using DWI imaging is reported [55]. Infarcts due to the former have been found to show multiple, widely distributed, small and large strokes.

Summary

Unexplained acute neurological events in the presence of a subacute systemic illness, zoonotic exposure or a prosthetic valve should alert clinicians alert to the possibility of IE. The most cost effective investigation remains a comprehensive history of the illness, which should be gleaned from any and all sources including the patient, the family and the primary care provider. A high index of suspicion coupled with appropriate focused investigations including multiple blood cultures, imaging

the heart and the nervous system are essential to prevent further damage. The detection of IE should trigger an intense search for a source of infection such as gastrointestinal, dental or cutaneous source.

In the face of IE or ME, when a single defining neurologic event occurs, be on the alert for the second more devastating event.

Optimal care for these patients requires a team approach incorporating cardiac, cardiac surgical, neurological, neurosurgical and neuroradiological expertise. The occurrence of IE should have the same urgency and alert protocol similar to that for stroke and myocardial infarction. Some centers have adopted an endocarditis protocol such as "A Multi-Disciplinary Alert Strategy" [56].

Preventing progressive neurological complications in patients who have IE and stroke remains a clinical challenge. Early and frequent neuroimaging in the presence of IE is essential to prevent further injury. In the event of infectious intracranial aneurysms, early involvement of the neurosurgical and neuroradiological teams is essential to prevent further neurological damage. Once stabilized, infectious intracranial aneurysms present minimal long-term risk of rupture and rebleeding, given that the source of infection has been identified and rectified. A delay of 3–4 weeks between treatment for infectious intracranial aneurysms and cardiac valve surgery seems to be the standard of care for most patients. Compared to adults, children have better outcomes from the treatment of infectious intracranial aneurysms and the use of thrombolytic therapy.

Mortality and morbidity from IE remain high despite technological advances. What is required is a structured institutional approach for timely detection, treatment and research similar to that being currently used in acute stroke.

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