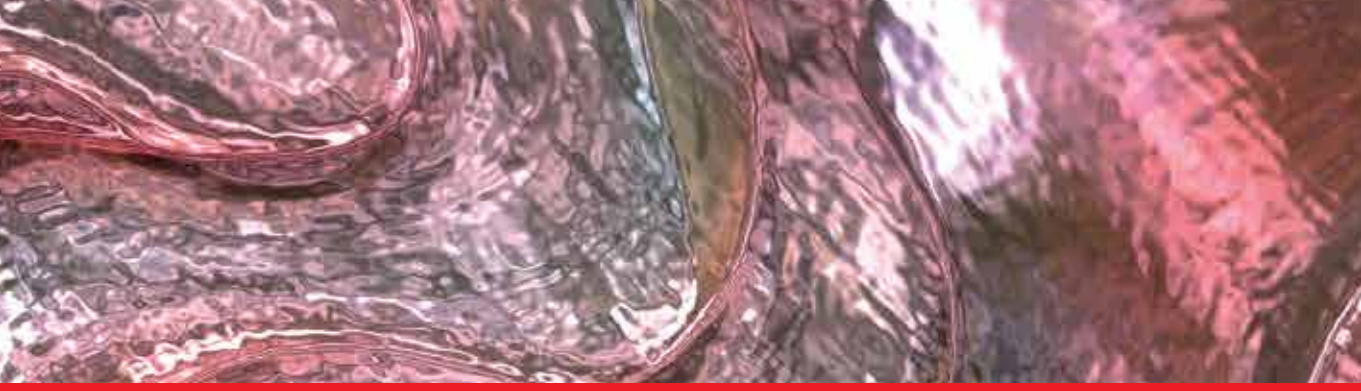

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Advanced Concepts in Endocarditis

Edited by Michael S. Firstenberg

ADVANCED CONCEPTS IN ENDOCARDITIS

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Meet the editor

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He has lectured worldwide and written more than 100 peer-reviewed articles, numerous textbook chapters, and edited several books. In addition, he is active in numerous professional societies, clinical research projects, and multidisciplinary leadership committees.

Contents

Preface

Endocarditis is an infection of the heart and is often characterized by the involvement of the cardiac valves, other intracardiac structures, or implantable devices that support cardiac function. Infections are defined by the involvement of either native cardiac structures or prosthetic or artificial materials or implants. Systemic complications, acute heart failure, and sepsis are common presenting signs and symptoms. The advances in imaging technologies such as echocardiography, computed tomography, and magnetic resonance imaging have facilitated the diagnosis and management of patients with suspected and proven infections. Nevertheless, the management of infected patients remains a formidable challenge. While patients often require a prolonged course of antibiotic (or antifungal) therapy, many cases require surgical intervention to appropriately "cure" them of their infections. The difficulty is in determining the timing of surgical intervention, often in the setting of recent or ongoing bacteremia, embolic complications such as recent stroke, acute heart failure, or evidence on worsening infection despite appropriate medical antibiotic therapy. Historical paradigms of care suggested a prolonged period of antibiotics with the goal of sterilization of the infected structures prior to surgery; however, this often resulted in substantial morbidity and/or mortality in those awaiting surgery. The obvious selection bias that occurs from withholding surgical therapy, while reasonable in patients for whom surgery is deemed to be too high risk or who show signs of improvement, has been shown to potentially deprive some patients of the chance of a definitive cure. Hence, currently, treatment plans will often consider early surgical intervention-even in those patients historically viewed as having high-risk characteristics. In fact, it is often those high-risk factors (as mentioned above) that serve as strong indicators that surgery should be considered. The growing difficulty in the current era of endocarditis management is the ethical dilemma in dealing with patients with infections, and sometimes reinfections, that are the result of "undesirable" (as viewed by some) social habits or lifestyle choices, such as intravenous substance abuse (IVDA). Such patients can be extremely difficult to manage in the acute (or perioperative) phase and their endocarditis can be very difficult to eradicate long-term. Without a doubt, patients with IVDA are at an extremely high risk for recurrence of their infections. Regardless of whether such abuse is viewed as a medical problem, a social problem, or a lifestyle decision, much debate is focused on how much time, energy, and resources should be devoted to treat a patient who many view as having an incurable problem-namely, their substance abuse and tendencies toward noncompliance.

In addition, there is a growing recognition of unusual causes of cardiac infections. Historically, a small subset of patients, despite imaging and clinical evidence of an infection, does not have positive cultures that can be used to guide antimicrobial therapy. With advances in genetic testing, molecular and biological markers, and other sophisticated techniques for growing and detecting unusual organisms, clinicians have better tools to use in adequately identifying causative agents and, therefore, allowing for more appropriate and targeted therapies.

As experience grows in the diagnosis and management of cardiac infections, there has also been a greater recognition of the presenting acute and chronic comorbidities that can be used to predict short- and long-term outcomes. While certain populations, such as those with implantable cardiac devices such as pacemakers, defibrillators, and left ventricular assist devices or those with advanced end-organ dysfunction, such as end-stage renal disease, have long since been recognized as being at high risk for poor outcomes, there is a growing recognition (as referenced above) that those patients with right-sided disease involving the tricuspid valve might warrant a change in how their disease has been traditionally managed. Historically, tricuspid disease has rarely been viewed as a surgical problem and most patients who underwent prolonged medical treatments — and often as a function of the baseline comorbidities (i.e., IVDA) or untreated, or undertreated, right-sided heart failure or pulmonary septic complication-did very poorly. As such, with greater recognition of the catastrophic complications associated with right-sided disease, there has been growing interest in better defining the guidelines for both medical and surgical management. In addition, as more patients, with more comorbidities, who are older, sicker, frailer, are offered surgical or catheter-based therapies for their structural heart disease, combined with better diagnostic tools, the incidence and sheer number of endocarditis cases are increasing rapidly.

The challenges in the diagnosis and medical and surgical management of patients with endocarditis clearly illustrate the value of developing and engaging a multidisciplinary team. Such a team of dedicated providers, as with many areas of cardiovascular case, help navigate a patient through a very difficult, and often unpredictable, disease course. Effective and efficient team communication is critical and can often be the definitive factor in achieving clinical success. The topic of "endocarditis" in itself can be overwhelming and, almost by definition, a singular book would quickly become both out of date and incomplete. It is hence the goal of this book, as a continuation of the previous volume on this topic, to highlight some of the current controversies and difficulties in this extremely complex topic.

As the Editor of this book, I want to extend my deepest appreciation to not only those who contributed to this volume, but also to the countless providers who care for, what are often, very sick, complex, and difficult patients. In addition, most importantly, I want to thank my family and close friends who supported me during the countless hours needed not only to manage these patients but also to share my interests in educating, mentoring, and supporting those who contributed to this text.

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Introduction

Chapter 1

Introductory Chapter: Introduction to Advanced Concepts in Endocarditis

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Additional information is available at the end of the chapter

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1. Introduction

Infective endocarditis is a broad topic that encompasses various types of infections of the heart and is typically used to describe abscess cavities, infectious or inflammatory vegetations on cardiac structures such as valves or implanted prosthetic devices, fistulae, or areas of localized infectious tissue destruction. Without a doubt, infectious problems involving the heart or cardiac structures represent a formidable diagnostic and therapeutic clinical problem. Furthermore, despite advances in medical and surgical therapies—some of which are highlighted in this text—there are concerns that there are significant increases in the number of cases reported. Even more concerning are some of the issues that have resulted in the increased incidence of endocarditis case and what impact these issues might have on how individual patients are managed and how society approaches this complex (and expensive) medical, surgical, and—now—social problem.

It is also becoming more apparent that even relatively minor procedures are associated with a risk of infecting both native and prosthetic cardiac structures [1]. Historically, it was assumed that procedures, such as dental work, had a significant role in the development of endocarditis and other procedures, such as endoscopic evaluations, had a minimal role, and therefore prophylactic antibiotics before all such "minor" procedures were not necessary. However, recent evidence suggests that there is a much greater risk for post-procedure endocarditis than initially thought—especially those with inherently abnormal cardiac structures, such as mitral valve prolapse or bicuspid aortic valves [2].

The epidemiology of infections reflects not only the dark side of the progresses in medical therapy but also some of the social problems that plague modern society. The changing microbiology also reflects how this complex disease has also paralleled the advances in medicine. Diagnostic tools continue to evolve with not only improvements in imaging technologies but also our understandings on how to appropriately use them to better understand the overall clinical picture. In addition, the role of therapies—especially early surgical intervention—has

been demonstrated to have a significant impact on the management and outcomes of infected patients. The goal of this text is to highlight some of the current concepts in the clinical characteristics, the presentation, the diagnosis, and the management options.

2. Epidemiology

There has been a significant increase in the overall incidence of infectious endocarditis—and there are many reasons for this. The two, probably, most important fundamental reasons are the growing number of patients with substantial comorbidities who are receiving therapies involving prosthetic material implanted into their hearts. Many of these patients have comorbidities that historically might have contraindicated advanced cardiac therapies (including heart valve surgery) years ago. Such comorbidities included not only frailty and advanced age but end-stage renal disease, history of solid or bone marrow transplantation, chronic high-intensity immunosuppression, and multiple previous cardiac procedures. In addition, the fact that medical advances have resulted in these "sick" patients living longer, even if the absolute rate (i.e., cases/year) did not change, the total number of cases would increase as the overall population at risk over time has increased.

The second growing population of patients at risk for developing endocarditis are patients with a history of intravenous substance abuse—and even more so, those who continue to abuse IV drugs having already undergone a surgical procedure to repair/replace an infected cardiac valve [3, 4]. The global burden of substance abuse and the impact of infectious endocarditis are only recently been the sources of focused investigation with a growing appreciation of the magnitude of the problem [5]. Many of these patients tend to be younger—and as a function of their greater physiologic reserve, difficulties in getting appropriate access to healthcare and the means in which they become infected can result in this population presenting much later in the course of an infection with advanced cardiac structural destruction and are more likely to have polymicrobial or fungal infections. As many of these patients have received suboptimal therapy for their nonspecific presentations and symptoms, late presentations after weeks, or even months, of therapies for "viral syndromes," "community acquired pneumonias," or even "cellulitis" from local infections at the site of infection are not uncommon. Noncompliance with medical therapy, combined with mistrust in the healthcare system, in this population might also predispose them to presenting late in their disease. Nevertheless, as more patients receive advanced cardiac therapies—such as catheter-based valve replacements, implantable cardioverter defibrillators, pacemakers, intravascular remote pressure monitors, and ventricular assist devices—the risks for developing device-related infections are substantial and growing [6, 7]. Unfortunately, the growth in the overall utilization of these devices in sicker patients has exceeded our overall understanding of how to reduce, prevent, or provide prophylaxis against potential infections [8–10]. Furthermore, with the growing understanding of the natural history of endocarditis, risk factors for developing infections, the management of specific types of infections and their presenting complication, long-term outcomes of both medical and surgical therapies, and the overall heterogeneous

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spectrum of clinical presentation, medical and surgical teams are becoming better at individualizing care plans.

3. Microbiology

A growing challenge has also been the "war" between evolving resistant bacteria, multidrug-resistant organisms, polymicrobial infections, and opportunistic fungi and the drug therapies that are available to safely and appropriately treat these infections. Such infections clearly have been shown to be predictors of poor outcomes and are often primary indications for urgent surgical intervention [11]. While advances in techniques used for testing of genetic techniques and cellular markers have improved the ability to define a causative agent, this does not inherently imply that such infectious are any easier to treat [12]. In addition, the growing recognition of "sepsis" and aggressiveness toward early treatment and diagnostic evaluations might have a secondary effect on the earlier recognition and overall incidence of diagnosing endocarditis. Nevertheless, without a doubt, the growing and routine use of immune modulating medications for common diseases such as rheumatoid arthritis, inflammatory bowel disease, and psoriasis (just to name a few) has also increased the incidence of unusual bacterial and fungal infections—of which progressing to endocarditis is common [13]. Another growing population is those adults with congenital heart disease. Many of these patients have had multiple previous surgical procedures involving prosthetic material and are, in general, living longer—both are risk factors for developing endocarditis [14, 15]. In addition, while the overall focus tends to be on infectious causes, there is clearly much to learn about noninfectious causes of endocarditis such as marantic or Libman-Sacks endocarditis [16].

4. Diagnosis

While it is often believed that positive blood cultures are the sine qua non in the diagnosis of endocarditis, it must be recognized that patients can often present with extensive destruction, and involvement of their cardiac structures has negative cultures. The original Duke Criteria has for many years provided the foundation for the diagnostic criteria of endocarditis [17]. However, advances in imaging technology and broader application of such technology have also proven to be extremely useful in the management of infected patients and guiding therapy [18]. Historically, transthoracic and transesophageal imaging were considered and still are first-line diagnostic tests to evaluate patients with suspected endocarditis—and current guidelines and appropriateness criteria continue to support their liberal use [2, 12]. The role of other imaging modalities, such as 3D echocardiography, computed tomography (CT), magnetic resonance imaging, and positron-emission tomography (PET) is expanding [19, 20]. Furthermore, not only is early use of advanced imaging well established in the diagnosis and management of endocarditis; it is clear that there should be a low threshold for repeat imaging to follow the response to medical therapies or, more specifically, help identify those patients who are failing medical therapy and might benefit from surgical intervention.

5. Therapy

Early involvement of a multidisciplinary team, as discussed below, is critical to the successful management of these complex patients. As many of these patients will require prolonged course of targeted antibiotics, compliance can be an issue even in the most motivated patients. These patients often require close follow-up to ensure that recommended treatment plans are not only adhered to but, more importantly, successful in eradicating the infection resulting in symptomatic valvular destruction. While it might be easy for the provider to "prescribe" a prolonged course of antibiotic therapy, successful completion often involves a recognition of the multiple socioeconomic issues that are keys to success. Many patients do not have the ability or resources to comply with daily (or more frequent) outpatient therapies—and clearly, prolonged hospital stays to complete a course of antibiotics is no longer reasonable nor practical. As such, care teams are often forced to become "creative" in discharge and treatment planning to individualize therapy within the framework of social support, financial resources, and patient factors. Such care plans might not follow established guidelines strictly, but as long as all involved—especially the patient through shared decision-making—understand the risks, benefits, goals, and options, then unconventional plans might be more likely to clinically succeed in the long run than guideline-based therapies that are, at an individual level, unreasonable and unlikely to succeed.

Probably one of the most important aspects in the management of endocarditis is identifying those patients who might benefit from surgical management. While current guidelines, as discussed below and in several chapters in this text, can help provide indications for surgery, the decision to operate is not always so simple. Patients often present critically ill, neurologic complications such as embolic strokes are common, and often there are complex comorbidities and surgical technical issues (i.e., previous cardiac surgery) that must be considered in the decision-making process of when to operate—and, just as importantly, what operation to perform.

Case by case surgical judgment (and experience) is often required to determine which structures can and should be preserved as opposed to which structures might require aggressive debridement and replacement. Surgeons must caution against the concept of "exercises in technique over judgement." While repairing an infected valve might limit the risk of reinfected prosthetic material or the need for re-intervention for a failing (or infected) artificial heart value, it must be also recognized that failed repairs are not without short- and long-term risks and complications either both in terms of reinfection from inadequate debridement of infected tissue and from the development of heart failure or structure complications from valvular dysfunction. A significant challenge is also the timing of surgery in the setting of systemic infections and complications—especially neurologic complication [21]. As discussed, each case requires a delicate balance when evaluating the potential risks and benefits of early versus delayed surgical therapy. However, without a doubt, early and aggressive intervention has been shown to improve overall outcomes at both the individual and population level. Such changes in the paradigm from delayed surgical management to earlier intervention are well established in current European and American Society guidelines, based upon randomized trials and extensive clinical experience, and discussed in further detail throughout this text [22–24].

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Even though there is some variability in the specific indications, and level of evidence to support for surgical therapy, in general early surgery should be considered in those patients who present with the following signs and symptoms [25]:

1. Early surgery is recommended for those patients with fungal infections or highly resistant organisms.
2. Valvular dysfunction resulting in signs or symptoms of acute heart failure.
3. Those patients who present with cardiovascular complications directly associated with their infections including new heart block, aortic or root, or annular abscess cavities or penetrating infectious complications such as fistula might benefit from early surgery.
4. Surgery is indicated in the setting of persistent bacteremia or fever greater than 5–7 days in the absence of another identifiable primary source in the setting of appropriate targeted antibiotic therapy.
5. Enlarging vegetations despite appropriate antibiotic therapy or evidence of recurrent embolic complications.
6. Vegetations that are mobile and greater than 1 cm and/or with evidence of severe valve regurgitation.
7. Mobile vegetations that are greater than 1 cm especially in the setting of other relative indications for surgery and when involving the anterior leaflet of the mitral valve.

Similar recommendations are used to guide therapy in patients with prosthetic valve endocarditis [26]. As discussed at length in the chapter on prosthetic valve infectious, it must be recognized that medical management is rarely successful, and despite what might be considered prohibitive surgical risks, the best chance at a long-term durable cure of infected prosthetic material often requires removal and replacement.

As previously mentioned, the worldwide substance abuse epidemic has resulted in a significant increase in patients presenting with right-sided endocarditis (i.e., involvement of the tricuspid valve). Because of historical concerns of relapse, noncompliance, and unclear indications for surgical intervention, many of these patients were treated medically—with treatment failures often blamed on the patient's social issues. However, as more and more patients present with right-sided disease, there is a growing body of the literature focusing on how to best treat this difficult patient population. Contemporary guidelines and indications for right-sided interventions follow those for left-sided disease [27]. Nevertheless, the specific surgical procedures considered for these patients, despite decades of experience, remain unclear [28, 29]. Options included "vegectomy," "valvectomy," valve repair, and valve replacement [30]. The historical literature on simply removing the infected tricuspid valve and leaving the patient with "wide-open" tricuspid regurgitation is still frequently utilized despite concerns for the development of severe right-heart failure and its devastating pathophysiologic consequences [31]. Even though there are a small subset of patients who not only survived this surgical approach AND complete a course of drug rehabilitation AND are deemed to be reasonable surgical candidates for eventual valve replacement AND have an uncomplicated surgical course, some advocate

(including this author) that this approach is completely against surgical and medical wisdom, inappropriate ethically, and predisposes patients to unreasonable postoperative complications and that operative intervention must involve appropriate debridement of all infected tissues but, as importantly, not predispose the patient to the catastrophic sequelae of "wide-open" tricuspid regurgitation. The technical and ethical aspects of right-sided disease and the management of patients with substance abuse are discussed in this text. Rarely is right-side infections managed with procedures that result in severe regurgitation—a pathophysiology that is often the initial indication for intervention.

6. Social implications

The growing population of patients who abuse intravenous drugs, as discussed, has resulted in a significant increase in those patients presenting with endocarditis. There has been a reported twofold increase in the number of active heroin users between 2006 and 2013 [32]. The implications of this cannot be ignored. While it is unclear if it is infected needles, skin contamination, or infected drugs being injected—or a combination of events—the consequences are the same. In addition, as a function of their substance abuse, often these patients present with underlying, and often untreated, hepatitis B, hepatitis C, and the human immunodeficiency virus (HIV) [33]. These patients often have chronic pain syndromes and high levels of tolerance to narcotics associated with their drug addictions, not to mention associated personality and psychological disorders, all of which challenge the short- and long-term care and management options for this population. Long-term compliance with medical therapies, such as anticoagulation for mechanical valves, might predispose these patients to early tissue valve failure and the need for reintervention. Such decision-making must also consider existing comorbidities, such as liver dysfunction from untreated hepatitis or recent embolic strokes. As such, it is easy to appreciate that even a single episode of endocarditis can have tremendous lifelong ramifications [34]. As such, having a good understanding of the long-term outcomes of these patients is important in decision-making at the time of their index event. For example, one study reported that between 2002 and 2014, there was a two times increase in the number of patients requiring surgery for infected endocarditis at their institution space (14.8% in 2002 to 26% in 2012). Of the 436 patients studied over a mean follow-up of 29 months, adverse events occurred in 20%, including 10% developing reinfections—often as a function of continued substance abuse. Even though there was a lower operative mortality in patients with drug abuse mainly due to their age, a propensity score analysis demonstrated that IV drug abuse was associated with an almost fourfold increase in valve-related complications and a 6.2-fold increase in the risk for reinfection. Unfortunately, because of the biased beliefs (some of which might be valid) of relapse of drug abuse, noncompliance, limited access to chronic healthcare, and poor socioeconomic status of many of these patients, surgery in the setting of long-standing drug abuse is often viewed as intervening on an end-stage disease that is often imminently fatal. Some clinicians view attempts at curing these patients of their infections and substance abuse as being futile. The consequence of this, as discussed in the chapter on the ethics of surgery, is the issue of what to do with patients who reinfected their prosthetic heart

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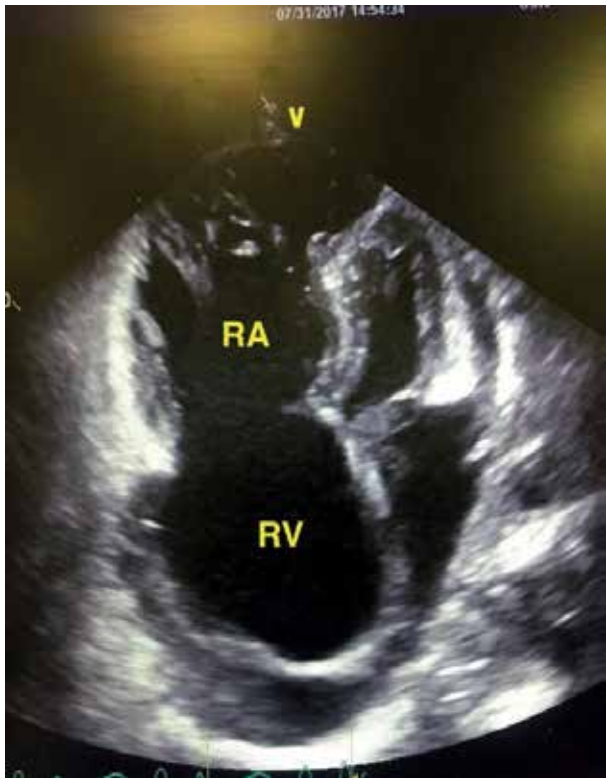

Figure 1. Echocardiogram of a 28-year-old mother of two with a long-standing history of substance abuse and multiple admissions over several years for tricuspid valve endocarditis. Surgery was not offered on multiple occasions due to concerns of recurrence and noncompliance and her substance abuse. She presented with severe right ventricular (RV) failure, severe right atrial (RA) enlargement, and a nonexistent tricuspid valve, ascites, and hepatic congestion, and was deemed to be inoperable by a multidisciplinary team. A palliative care consult was obtained, and she was referred to hospice. She died of right-sided heart failure several months later.

valves in the setting of ongoing substance abuse. Until more objective data and experiences are available to guide such decision-making, clearly prior to withholding potentially high-risk, lifesaving, re-operative surgery, a referral to palliative care and ethics team is indicated—not to mention an open and honest (and well-documented) discussion with the patient and family regarding the severity of the issue at hand. Many surgical teams will force the patient to sign a plan of care contract prior to surgery acknowledging that noncompliance and valve reinfection might result in withholding further or future therapies (**Figure 1**).

7. Conclusions

Improvements in technology and a greater awareness of the problem have resulted in a substantial increase in the diagnosis of infectious endocarditis. Furthermore, as patients present with

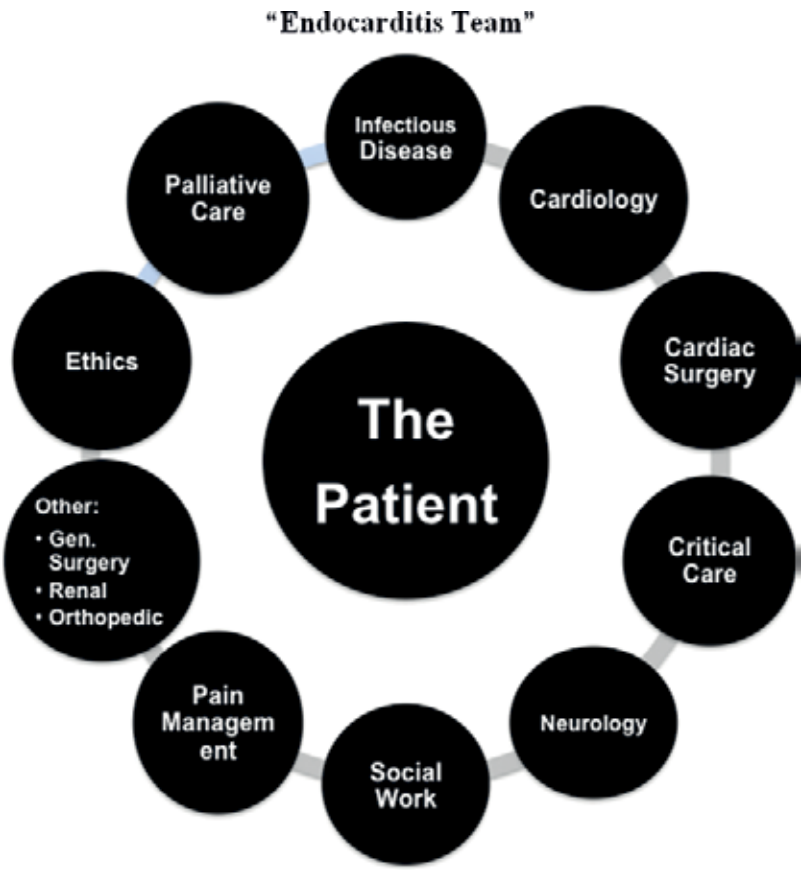

Figure 2. Structure of an "Endocarditis Heart Team" (adopted from Firstenberg [25]).

more complex and high-risk comorbidities, difficult social problems—such as intravenous substance abuse—and a wider utilization of invasive cardiac therapies, the risk for developing infectious complications has also increased. Without a doubt, the management of endocarditis —regardless of the presentation—continues to be an evolving and difficult problem. As such, much like many other complex medical and surgical problems, there is growing evidence that a team approach to both short- and long-term management is a foundation to success (**Figure 2**) [35, 36].

The goal of this text is to provide some valuable insights into some of the ever-evolving topics and controversies and by no means is it intendent to be the definitive reference—the area is too complex and the science is moving too quickly. Nevertheless, hopefully with a greater awareness and understanding, there can be ongoing improvements in the prevention, diagnosis, and treatment of this devastating problem.

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Section 2

Diagnosis and Medical Management

Chapter 2

The Role of Modern-Era Echocardiography in Identification of Cardiac Risk Factors for Infective Endocarditis

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Additional information is available at the end of the chapter

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Abstract

This chapter provides an updated overview of the scientific literature on cardiac pathology predisposing to infective endocarditis and the estimated risk associated with selected lesion-specific abnormalities, in an era of changing epidemiology and advanced echocardiographic imaging. Importantly, with the evolution of modern-era echo, subtle changes in valve structure and function are now easily detectable and a proportion of cases of apparently 'normal' valves involved with IE, may in fact have subtle pre-existing pathological and/or haemodynamic abnormalities. The chapter will have a clinical focus with an aim to provide the Physician with up-to-date and practical information on cardiac risk factor identification for infective endocarditis.

Keywords: echocardiography, infective endocarditis, risk factors, valvular heart disease, congenital heart disease, degenerative valve disease, rheumatic heart disease, cardiac pathology, disease incidence, modern-era

1. Introduction

Infective endocarditis (IE) risk is strongly associated with underlying cardiac disease. This chapter will review the pathology, mechanisms and estimated risks according to lesion-specific groups. Echocardiographic predictors of IE will be discussed along with the increasingly reported occurrence of IE in 'normal valves'.

2. Predisposing cardiac disease: a changing epidemiology

Since mid-last century, the epidemiology of IE has continued to change across high-income countries (HIC), from predominantly young patients with rheumatic heart disease (RHD) to the current era of an ageing population with IE, infrequent RHD and prevalent degenerative valve disease (DVD). A history of acute rheumatic fever (ARF) in patients with IE had declined from ~38 to 22.5% in the 30 years up to 1967 [1]. By the 1980s, this had reduced to 6% [2]. According to data from the International Collaboration on Endocarditis—Prospective Cohort Study (ICE-PICS), DVD is the most common underlying pathology in IE, with significant mitral regurgitation (MR) and aortic regurgitation (AR) accounting for 43.3 and 26.3% of cases, respectively, compared with rheumatic mitral valve, present in only 3.3% cases. Prosthetic valve endocarditis (PVE) accounts for up to 22.2% of cases [3], whilst the prevalence of cardiac device-related infective endocarditis (CDRIE) has increased along with health-care associated IE (HCAIE) [4]. Endocarditis patterns in congenital heart disease (CHD) have changed due to patients surviving into adulthood with more complex disease, the availability of improved surgical techniques and implantation of prosthetic material [5, 6].

The 2015 European Society of Cardiology IE management guidelines now consider the following cardiac conditions to pose the highest risk of IE: (i) prosthetic cardiac valves and/or repairs with prosthetic material, (ii) previous IE, (iii) cyanotic CHD, and (iv) any CHD that has been repaired for up to 6 months post procedure or indefinitely if a residual defect or valve incompetence persists. Repair or intervention includes both surgical and transcatheter procedures. Antibiotic prophylaxis is recommended for these patients when exposed to procedures considered high-risk [7].

3. Estimating risk of infective endocarditis: methodological issues

There are methodological challenges with investigating risk of acquiring IE. Two major limitations are: i) low incidence of IE in the general population and ii) selection bias associated with tertiary referral hospitals. Variations in study design and methodology also contribute to the difficulties faced in drawing generalised conclusions.

4. Pathogenesis of infective endocarditis with underlying cardiac disease

The major predisposing categories of underlying cardiac pathology are DVD, CHD and RHD. Platelet-fibrin aggregates form on damaged or inflamed endothelium, resulting in nonbacterial thrombotic endocarditis (NBTE), a precursor of IE [8]. Microorganisms are able to attach to this nidus via adhesion molecules and stimulate a host inflammatory response [8].

Regurgitant valves are at higher risk of IE than stenotic valves [9]. In a large clinical-pathological study on native valve endocarditis (NVIE), 84% of valves were regurgitant [10]. Another found the majority of cases of IE presenting to surgery were for regurgitant valves compared to a control-group of non-IE cases undergoing surgery (9% of regurgitant bicuspid aortic valves (BAV), 1.2% of calcified BAVs, 1.6% of calcified trileaflet aortic valves (AV) and 7% of mitral valve prolapse (MVP)) [11]. Aortic regurgitation (AR) is a predisposing lesion in 17–36% of cases of IE, whilst mitral regurgitation (MR) accounts for 10–18% [12].

The pathogenesis of IE in structural cardiac abnormalities is characterised by the hydrodynamic theory [13]. A high velocity turbulent jet exerts a shearing effect on endothelium, at the site of a restrictive orifice (e.g. ventricular septal defect (VSD) or MR jet) and/or a distal point of contact (jet lesion). The narrowest diameter of flow is the vena contracta (VC), just distal to the restricted anatomical orifice. This is where the pressure is minimal and retrograde flow may occur, permitting platelets and bacteria to deposit [13]. The typical location of vegetation is on the upstream side of the valve, that is, the atrial aspect of the MV, tricuspid valve (TV) and ventricular aspect AV, pulmonary valve (PV) [9].

Structurally normal native right-sided valves in the absence of significant pulmonary hypertension, are exposed to lower pressure flows and are far less commonly involved with IE. In children, without CHD, native right-sided IE involving normal valves is rare but may occur in association with trauma to the valve from central lines or catheters [14, 15]. Other factors are important in risk of acquiring IE and include an interplay between microorganism virulence, altered host defence mechanisms, predisposing systemic illness, and environmental and social factors [16].

5. Structurally normal native cardiac valves

Infective endocarditis does occur in some patients without pre-existing known structural abnormalities. Whether the valves were completely normal is uncertain. Early degenerative changes can be present without clinical detection [17]. Modern-era echo with high image resolution and careful scrutiny of valve morphology and function, has the potential to shed more light on this research question.

There is an increasing prevalence of IE involving structurally normal cardiac valves, accounting for 26–43% of native left-sided IE cases [2, 18, 19]. Sun et al. [18] reported the commonest underlying cardiac predisposition was mitral valve prolapse (MVP) followed by normal valves (26%). Olmas et al. [20] found in an IE cohort, normal left-sided native valves in 39.8% of patients aged >65 years and in 53.8% of those aged ≤65 years, whilst DVD comprised 23.4% of the cohort. However, details regarding Doppler valve function were not available. This is important, for even normal valves may be regurgitant, exposing endothelium to shearing forces. Limitations include assessing valves for pre-existing pathology when already involved by infection and absence of pathological correlation to exclude subtle underlying pathology. In vitro studies have demonstrated certain microorganisms can attach to and/or be internalised by healthy valve endothelium, however in vivo, animal studies have required trauma to the endothelium to initiate IE following an inoculum of bacteria [9]. This raises the

question—are the valves 'normal' or are there subtle pathological changes or haemodynamic disturbance, which predispose to IE. This was also raised by Que and Moreillon [21] and Baddour et al. [9].

To assess normal valve thickness according to age, 200 normal valves were reviewed at autopsy [22]. There was approximately double the thickness of the aortic cusps and mitral leaflets with age [22]. In a separate study, transoesophageal echo (TOE) identified normal MV thickness overall to be ≤3 mm and AV≤2 mm in those aged <60 years [23]. The prevalence of normal valves with physiological regurgitation was investigated in a retrospective echocardiographic study of 1333 patients without a history of cardiac disease or hypertension [24]. Physiological MR and TR were defined as structurally normal valves on 2-D imaging, with a regurgitant jet area occupying <20% of the left atrial (LA) area and <5 cm^2 within the right atrium (RA), respectively. Aortic regurgitation with jet to LVOT width ratio <25% and normal leaflets was considered physiological. Non-organic MR was detected in 1/3rd or patients aged 10–19 years and approximately 2/3rd of persons aged >30 years. Non-organic TR was identified in over 4/5th of persons across all age cohort groups (10–89 years). Non-organic AR was present in <10% of patients under 50 years, with an increase in prevalence corresponding to each decade, up to 46% of those aged 80–89 years [24].

5.1. Risk of endocarditis in normal valves with physiological regurgitation

Data is not readily available on the risk of IE in patients with left-sided non-organic regurgitation. However, one study did assess the risk of IE in structurally normal right-sided cardiac valves in adult patients with CHD and pulmonary hypertension (PHTN) [25]. Both TVs and PVs had physiological regurgitation. The presence of PHTN was responsible for increased regurgitant velocities across the valves and thought to mimic the haemodynamic forces experienced by incompetent left-sided valves. High velocity flow was defined as PR jet ≥3.2 m/s and TR≥4.7 m/s. A small subset of valves was inspected at necropsy with the majority of TVs and minority of PVs revealing mild nodular degenerative changes along leaflet closure margins. The echocardiograms were said to be normal in appearance. There were 0.61 and 7.17 cases of IE per 1000 patient-years in the normal valve group compared to the CHD control group, respectively. The risk was therefore small, but inconclusive due to insufficient patient numbers [25].

6. Degenerative valve disease

6.1. Degenerative disease of the aortic valve

The prevalence of nonrheumatic AS increases with ageing [26]. In a cohort of older patients with IE, the prevalence of acquired MR and AS was reported as 57 and 28% respectively, compared with 38 and 10% in patients <65 years [26, 27].

6.1.1. Fibro-calcific degeneration

Age-related findings often begin on the aortic valve in early or middle adulthood and include the following: (i) noduli arantii—fibroelastic proliferation on the ventricular surface of the

cusps, from early adulthood, most pronounced on the noncoronary cusp, (ii) ridge-like thickening at the base of cusps where mechanical forces are highest; occurs in early adulthood in 20–40% persons, and (iii) commissural adhesion, due to fibroelastic hyperplasia, affecting 10–20% of older persons [28]. With ageing, endothelial dysfunction and hemodynamic stress lead to degenerative changes, inciting an inflammatory process, not unlike atherosclerosis. Histological changes include subendothelial thickening, lipid and protein accumulation, inflammatory cell proliferation, fibrosis and calcification within the valve fibrosa [29]. The process is accelerated over the age of 55 years, and onset in males is marginally earlier than females [28]. Initially there is no significant restriction to cusp opening and the diagnosis of aortic sclerosis is confirmed with echo.

6.1.1.1. Aortic sclerosis and echocardiography

The presence of aortic sclerosis (focal thickening, no commissural fusion, peak velocity <2.0 m/s) is associated with an increased risk of death [30]. Caution should be exercised not to over diagnose sclerosis on echo [31]. Artefactual thickening and echogenicity can appear with harmonic imaging and over-gained signals. Optimising transthoracic (TTE) image settingsand use of both harmonic and fundamental frequencies can overcome these limitations [31]. Transoesophageal imaging has higher resolution and anatomical detail is superior [31].

6.1.1.2. Aortic stenosis and risk of endocarditis

Eventually large calcified deposits occupy the body of the leaflet and can extend into the ventricular septum, the ventricular surface of the anterior mitral valve leaflet (AMVL) and are associated with mitral annular calcification (MAC). Cusp motion becomes restricted and aortic stenosis (AS) ensues. Ulcerations and thrombi may form, being a potential mimicker of IE [16, 32], and may form a nidus for infective endocarditis. There is a paucity of data on IE occurring with aortic sclerosis, although empirically, the risk is very small. Endocarditis of calcific trileaflet AS is relatively uncommon. According to Delahaye [33] 27/366 cases of native valve IE were pure AS. Risk is higher in patients with BAV and/or AR. In a study from the Mayo clinic [10], 310 native valves were excised for IE and it was reported 59% had no calcification. Mild-moderate and severe calcification was present in 37% and 5%, respectively. The most common underlying cardiac structural abnormalities were BAV (38% of 170 aortic valves) and MVP (43% of 120 mitral valves). This finding would suggest that IE is less common in severely calcified valves [10]. Another study with pathologic correlation found pre-existing calcification present in 27% of valves with IE, though numbers in the study were small [11].

Acquired degenerative changes of the AV leaflets can occur secondarily in the context of conditions leading to annuloaortic dilatation. In this pathology, the leaflets come together at the free edges rather than the zone of coaptation, leading to focal thickening, and increased risk of NBTE and IE [17].

6.1.1.3. Fenestrations

Acquired age-related fenestrations form within the lunular region of the aortic semilunar cusps, adjacent to the commissures, often in association with myxomatous AV disease.

Fenestrations are found in approximately 5% of females and 10–20% of males, mostly present from the age of <45 years with a minor increase in prevalence over time, in males [28]. They are not routinely identified on echo because of their location above the line of closure. Fenestrations result in valvular regurgitation in the following circumstances: (i) spontaneous rupture resulting in a flail cusp, (ii) fenestration enlarges to extend below the zone of coaptation and/or (iii) reduced leaflet coaptation, such as prolapse or root dilatation, when the fenestration is no longer 'sealed-off' within the cusp closure zone [34, 35]. The risk of IE associated with fenestrations or valvular perforations is unknown.

6.1.1.4. Lambl's excrescences

Lambl's excrescences increase in prevalence with age and may become incorporated into the noduli arantii [28]. They are located along the lines of cusp closure of left-sided (high pressure) valves. They are composed of a fibro-elastic core with an endothelial layer covering the surface. There is associated turbulence and relative stasis of blood flow, which predisposes to formation of NBTE and IE [34]. Although the risk of IE is unknown, empirically it is uncommon. Occasionally Lambl's excrescences can mimic vegetation and lead to a false-positive diagnosis of IE. However, Lambl's are usually identified as thin single or multiple filamentous strands on echo, which help differentiate them from typical vegetations and papillary fibroelastomas.

6.1.2. Myxomatous degeneration

Primary myxomatous degeneration (PMD) of the AV is less common than of the MV. In cases of significant 'pure' AS, it has been said to be the primary underlying pathology in up to 10–36% of subjects [38], however other pathological studies examining excised regurgitant aortic valves have reported much lower rates of PMD, at 2% [36] and in a more recent clinicopathological correlation study from China, 3% (35 of 1080 excised aortic valves) [37]. Histological findings include degeneration of the fibrosa layer, disruption of collagen fibres and deposition of mucopolysaccharides [37]. The cusps are susceptible to developing fenestrations adjacent to the commissures and with time, the prolapsing cusps develop thickening of the free margin, thought secondary to chronic trauma from the regurgitant jet [38]. The incidence of endocarditis with this pathology is unknown, however empirically, high velocity regurgitant jets increase the risk of IE.

6.2. Degenerative disease of the mitral valve

6.2.1. Mitral valve sclerosis and age-related changes

Mitral valve sclerosis is commonly encountered in the elderly and characterised by leaflet thickening. In patients >60 years, the leaflets are at least twice the thickness compared to early adulthood [22]. The following changes are frequently noted on the anterior leaflet: (i) senile sclerosis - nodular thickening on the atrial surface of the closing edge, up to age of 65 years, (ii) atheromatosis—age-related lipoid deposition (yellow plaque) on the ventricular aspect of the base of the leaflets extending towards and sometimes involving

the chordal apparatus [28]. The following changes may be noted at the posterior leaflet: (i) puckered scars—infrequent at 3–5%, > 65 years, (ii) fibro-elastic hyperplasia (mitral opacity) of the atrial surface in ~20%, >65 years and, (iii) mucoid or myxomatous degeneration (~ 5–10%) ± prolapse, with increased proteoglycans in the spongiosa layer [28]. The condition shows a slight increase with age in the milder forms. Severe forms of mucoid change were not related to age [28]. Fibroelastic deficiency (FED) is seen more commonly in the elderly and can lead to leaflet prolapse and/or chordal rupture.

Mitral annular calcification (MAC) is common in the elderly though can occur prematurely in certain other conditions such as hypertrophic cardiomyopathy (HCM), PMD, diabetes and renal disease. MAC commonly involves the posterior annulus and parallels AV calcification, with a sharp rise >55 years [28]. Normal sphincteric action of the annulus is altered and MR ensues [17]. Inflammation accompanies MAC and complications such as ulcerative erosion, thrombus formation, systemic embolic, liquefaction necrosis, infected vegetations and abscess formation occur with increased frequency [34, 39]. With large protruding MAC deposits, it is theorised there is alteration of local blood flow, predisposing to NBTE and IE [39]. Mitral stenosis can also occur as calcium encroaches on the leaflets. Vegetations form at the base of the mitral leaflet [39] rather than the leaflet closure line, as seen with typical regurgitant lesions [17] and are localised accurately with 3-D echo. Although MAC predisposes to IE, the exact risk is unknown.

6.2.2. Myxomatous mitral valve disease and prolapse

Mitral valve prolapse (MVP) most commonly occurs due to PMD. Secondary myxomatous degeneration can occur in other conditions, such as RHD and age-related degeneration. Additional causes of prolapse include congenital and papillary muscle dysfunction. The 'middle' tissue layer of healthy valves, the spongiosa, normally thickenings towards the leaflet/cusp margins and this is not a pathological finding [16]. With pathological myxomatous changes, there is diffuse increase in deposition of glycosaminoglycans in leaflets, cusps, chords and annuli and thrombi may form [16]. In a study from China, echocardiography (either TTE or TOE) correctly identified valve prolapse and thickening in 85% of patients in which myxomatous disease was confirmed pathologically [37].

6.2.2.1. Prevalence of mitral prolapse and regurgitation in healthy individuals

In a landmark study, data was collected from a healthy population comprising the offspring of the original Framingham study group [40]. Echocardiographic criteria (2-D) used in the study were as follows: (i) prolapse - superior displacement of the mitral leaflet(s) >2 mm above the atrioventricular annular plane in the long-axis window, (ii) classic MVP - at least 2 mm prolapse with leaflet thickness ≥5 mm and, (iii) non-class MVP – ≥2 mm prolapse with leaflet thickness <5 mm [40]. A total of 2.4% met criteria for prolapse. Classic MVP was found in 1.3% of persons and non-classic MVP in 1.1% [40], with mean age mid 50s and a slight female preponderance. Mean MR volume was mild in the classic group and a trace in the non-classic and control groups. Severe MR was only found in the classic groups and comprised 7% of cases [40].

6.2.2.2. Prevalence and risk of mitral prolapse in endocarditis

Mitral valve prolapse occurs in 7–30% of cases of native valve IE, nearly always in the presence of MR and associated with redundant leaflets. Of note, NBTE forms on atrial aspect of thickened, redundant leaflets [17]. In a large clinicopathological correlation study of 120 native mitral valves excised due to IE, 43% had a history of prolapse [10]. The estimated risk of IE is shown in **Table 1**. Recent data published by Katan et al. [41] found a higher incidence of IE in MVP compared to earlier publications, thought in part due to the previous overestimation of true MVP in healthy individuals using less stringent diagnostic methods [41].

6.2.2.3. Mitral prolapse—echocardiographic predictors of endocarditis risk

Mitral regurgitation confirmed on echo and/or typical murmur, has been shown to be a predictor of risk in studies that have specifically assessed this variable (**Table 1**). In the study by Katan et al. [41], no cases of IE occurred in patients without a history of MR during follow-up. Nishimura et al. [47], found redundant leaflets (i.e. M-mode thickness ≥5 mm) were associated with IE, though numbers were small. Marks et al. [48] also confirmed classic MVP with leaflet thickening ≥5 mm (2-D echo) and redundancy was associated with IE risk over non classic MVP.

6.3. Degenerative disease of the right-sided cardiac valves

Gross degenerative changes of the right-sided valves are uncommon compared to the higher-pressure environment of left-sided valves. The TV often undergoes only minimal change, with nodular thickening along the closing edge of the anterior valve leaflet. Mild diffuse leaflet thickening may occur in middle age; though in a minority of patients (>65 years), may become moderate or severe [28]. Myxoid degeneration of TV leaflets occurs occasionally [49], with TV prolapse (TVP) and PMD occurring in about 4% of cases [37, 40] . The risk of IE in TVP is unknown.

The pulmonary valve (PV) remains translucent and thin in the vast majority. Nodular thickening (noduli Morgani) along the centre part of the closing margin occurs in <50% of subjects,

	Overall incidence of IE in MVP (risk per 1000 patient-years)	MVP with regurgitation (risk per 1000 patient-years)	Overall incidence of IE in MVP with murmur (risk odds ratio – 'OR')
Katan et al. [41]	0.87	0.63[1]; 2.9[2]; 7.16[3]	
Clemens et al. [42] and Tay and Yip [43]	0.38	n/a	15.1
Retchin et al. [44]	0.3	n/a	n/a
Hickey et al. [45]	0.14	n/a	5.3
Danchin et al. [46]	n/a	n/a	14.5

[1]Less than moderate MR.

[2]At least moderate MR.

[3]Flail leaflet.

Table 1. Risk of infective endocarditis associated with mitral valve prolapse and regurgitation.

increasing gradually with age [28]. The mild age-related degenerative changes of the PV are not typically associated with IE.

7. Congenital heart disease

7.1. Overall incidence of endocarditis in congenital heart disease

Recently published research estimates the incidence of adult congenital heart disease (ACHD)-associated IE is 1.0–1.33 cases per 1000 patient-years and in children (0–18 years), 0.41 cases per 1000 patient-years. Cumulative first incidence of IE, from birth to 18 years, was shown to be 6.1/1000 [5, 50, 51]. According to published data from the USA, the estimated incidence in children is lower, at 0.05–0.12 cases per 1000 patient-years [52, 53]. Interestingly, Marom et al. found 18% of children with IE had no underlying structural heart disease and no identifiable risk factors, compared to earlier published rates, ranging from 2.5–19% [54].

7.2. Incidence of endocarditis in complex congenital heart disease

Incidence rate in complex CHD has recently been published by Kuijpers et al. [5], 2017. Incidence of IE (per 1000 patient-years) reported according to lesion-specific pathology include: pulmonary atresia (PA) with ventricular septal defect (VSD), 7.84; double outlet right ventricle (DORV), 3.59; Marfans, 2.35; univentricular heart (UVH), 1.9; Tetralogy of Fallot (ToF), 1.8; congenitally corrected transposition (cTGA), 0.93; transposition, 0.89; and Ebstein's anomaly, 0.7.

7.3. Endocarditis in simple shunts

7.3.1. Ventricular septal defect

Overall estimated incidence of IE with a VSD in ACHD is 1.0–1.33 and for children, 0.41 per 1000 patient-years (**Table 2**). In another study, the incidence was reported at 1.86 in adults and 1.06 in children, per 1000 patient-years ($p = 0.06$) [55]. The majority of studies have identified the following risk factors: i) unrepaired VSD ii) co-existent AR and, iii) residual defect at site of VSD repair. It has not been unequivocally proven a restrictive defect carries a higher risk. A VSD associated with AR carries a 2x relative risk (incidence increase from 1.25 up to 3.48/1000) [55], whilst a VSD that has undergone secondary aneurysmal transformation to form a Gerbode defect (LV-LA shunt) carries a risk of 5 per 1000 patient-years [56]. In one study, non-operated VSD's carried a 2.6x risk (0.73 versus 1.87/1000 patient-years) [55].

7.3.2. Atrial septal defect

Secundum ASD IE incidence is estimated at 0.23 for children and 0.28–0.64/1000 patient-years in adults (**Table 2**). A higher than expected risk was likely due to concomitant valve disease or misdiagnosed primum defects [50]. Isolated ASD is rarely associated with infective endocarditis [57]. The risk in adults with atrioventricular septal defect (AVSD) is estimated at 0.89 per 1000 patient-years (**Table 2**).

		CHD	ASD; VSD; AVSD; PDA	Left-sided[1] Right-sided[2]	Cyanotic (complex/conotruncal)[3] Cyanotic (conotruncal/single ventricle)[4]
Kuijpers et al. [5] (ACHD; Included prosthetic valves)	Incidence (per 1000 pt. years)	1.33	0.64; 0.82; 0.89; 0.0	1.89; 0.57	1.94 n/a
	Adjusted HR (95% CI)	n/a	n/a n/a n/a n/a	n/a n/a	n/a n/a
Mylotte et al. [51] (ACHD; Excluded prosthetic valves; Included conduits and repairs)	Incident IE (per 1000 pt. years)	1.0	0.28; 0.65; n/a; 0.24	1.61; 0.35	n/a 1.17
	Adjusted OR[5,] (95% CI)	n/a	n/a; 2.81 (1.87–4.21); n/a; n/a	5.11 (3.6–7.25); n/a	n/a 4.82 (3.12–7.46)
Rushani et al. [50], (Paediatric)	Incidence (per 1000 pt. years)	0.41	0.23; 0.24; n/a; 0.35	0.44; 0.29	n/a 2.07
	Adjusted Rate Ratio (95% CI)	n/a	n/a; 0.97 (0.56–1.66); n/a; 1.25 (0.5–3.13)	1.88 (1.01–3.49); 1.22 (0.52–2.86)	n/a 6.44 (3.95–10.5)

[1]Left-sided includes: coarctation, aortic and mitral disease (Mylotte et al. and Rushani et al.); or LVOTO (left ventricular outflow tract obstruction), Marfan, BAV, CoA, MV defect, other LVOT (Kuijpers et al).

[2]Right-sided includes: Ebstein, anomaly of pulmonary artery/valve, TV disease (Mylotte et al. and Rushani et al); or Ebstein, RVOTO (right ventricular outflow tract obstruction), other (Kuijpers et al).

[3]Cyanotic (complex/conotruncal) includes: PA + VSD, DORV, UVH, ToF, TGA, Other (Kuijpers et al).

[4]Cyanotic (conotruncal/single-ventricle): ToF, TGA, truncus, hypoplastic left heart and univentricular heart (Mylotte et al. and Rushani et al.)

[5]Odds ratio when referenced to ASD, PDA, R-sided groups.

Table 2. Contemporary estimates of incidence and risk hazard ratios for infective endocarditis in children and adults with congenital heart disease, across selected lesion-specific groups.

7.3.3. Ductus arteriosus

The estimated risk of IE with patent ductus arteriosus (PDA) is 0.24 and 0.35 per 1000 patient-years in adults and children, respectively, whilst other data have shown for an unrepaired PDA, the IE risk is 0.35–1.4 per 1000 patient-years, in a mixed adult and paediatric cohort [12, 50]. According to one study, the risk of IE was only present <4 years of age, likely due to ligation procedure essentially eliminating IE occurrence in older children [50].

7.3.4. Echocardiography

Echo assessment of a VSD should include identification of vegetations or other IE complications, whether involving the defect, the valves or mural endocardium. Also, imaging must define shunt anatomy, efficacy of closure (where present), cardiac chamber size and function, pulmonary artery pressure and haemodynamics. Aneurysmal formation and Gerbode defect should be excluded. Echo is fundamental in the routine and peri-procedural assessment of ASD and other shunts. It is also important to note the presence or absence of an ASD (or other shunt) in valvular endocarditis. For example, an infected TV may be a source of paradoxical embolism. The direction of the regurgitant jet and shunt, along with the size and mobility of a vegetation are important factors when assessing the risk of embolisation.

7.4. Bicuspid aortic valve and aortic coarctation

Bicuspid aortic valve (BAV) is a common congenital abnormality and undergoes accelerated degenerative change and dystrophic calcification [17]. Only a minority develop 'pure' regurgitation. Prevalence of BAV is as high as 1–2% of the population, more common in men and a pre-existing lesion in approximately 20% of cases of IE [12]. The estimated hazard ratio (HR) for adults with a BAV, of acquiring IE up to middle age is 6.3 (CI, 3.0–13.4), with an incidence of approximately 2 per 1000 patient-years [5, 58]. According to Kiyota et al. [59], BAV carries a relative risk (RR) of 23.1 times that of a tricuspid aortic valve for acquiring IE. With aortic coarctation (AoC), the incidence of IE is <1 per 1000 patient years [12, 58]. At 25 years out, the cumulative incidence of IE in another study was 3.5% (563 pts. with median age at time of surgery, 1.9 years) [60].

7.5. Congenital aortic stenosis

Incidence of IE in congenital aortic stenosis is estimated at 2.0–2.71 per 1000 patient-years [12, 61]. Echocardiographic predictors of risk of endocarditis include AV gradient and a non-statistically significant increase in the presence of regurgitation. In the Second Natural History Study (NHS-2), Gersony et al. [55], found patients with peak gradient (PG) across the aortic valve of <50 mmHg had an IE rate of 0.45 per 1000 person-years versus 5.44 per 1000 person-years in those with gradient ≥50 mmHg. When the stenotic valve was associated with aortic regurgitation (AR), rates of IE increased from 1.98 up to 3.43 per 1000 patient-years (not statistically significant, $p = 0.105$) [55]. In those managed medically and with a PG < 50 mmHg, the

risk of IE was 0.27 per 1000 person-years and for patient with aortic valve replacement (AVR), follow-up rate of IE was 1.53 per 1000 person-years [55]. In a different study, the cumulative risk was 13.3% out to 25 years post-surgery (median age of surgery 7.0 years) in patients where follow-up was available. This equates to a higher annualised incidence of 7.2 per 1000 patient-years [60].

7.6. Pulmonary valve and tetralogy of Fallot

Pulmonary stenosis (PS) is usually related to congenital valve stenosis, sometimes in association with genetic syndromes. Pulmonary regurgitation (PR) due to congenital disease is mostly seen following previous repair of ToF or valvotomy [62]. Endocarditis of the PV is relatively uncommon both pre and post-surgery [55, 57, 60], except in palliative shunts [60]. In PS, a rate of 0.09 per 1000 person-years has been reported [55]. Tetralogy of Fallot carries a risk of approximately 1–2.3 per 1000 patient-years [12, 58].

7.7. Post-surgical and catheter intervention

In the Kuijpers et al. study [5], the following were noted: (i) 8 cases of IE with closed ASD, but of those, 6/8 were associated with a valve abnormality; (ii) 13 cases of IE with VSD, where 9/13 were open, and (iii) no cases of IE with PDA (83.6% were closed). A large population-based registry study of children who underwent surgical repair of congenital heart lesions reported no patient developed IE after surgical repair of PDA (620 patients, median age 2.6 years) and likewise in an ACHD population, no IE was reported [58]. The annualised risk of IE post repair of AoC has been estimated at 1.2 per 1000 patient-years [60]. Very uncommonly, early (<6 months) IE occurs after closure. Late onset IE is very rare and is usually due to delayed endothelialisation [63–65]. In fact, in a surgical follow-up study by Morris et al. [60], no children who underwent repair of an isolated secundum ASD developed IE following surgery. Small numbers were seen with primum ASD and complete AVSD. After 6 months post-surgical closure of ASD, VSD and PDA, the risk of IE is virtually eliminated. The same holds true for transcatheter closure, although with residual defects, the risk is not eliminated [52]. After definitive surgical repair of ToF, the risk is estimated at 0.7 per 1000 patient years but is much higher for a palliative shunt, at 8.2 per 1000 patient-years [60].

In a study by Rushani et al. [50], from the age of 0–6 months, unoperated cyanotic disease had an adjusted rate ratio (using ASD as a reference) for IE of 7.56, compared with the operated group at 9.22. For unoperated left-sided cardiac lesions, the rate ratio of IE was 2.35, though data was insufficient in the operated group to calculate the ratio [50].

In one study, the risk of IE was 5x increased early (<6 months) after any cardiac surgery in children [50] and 9.07x increased in adults up to 6 months after any non-valvular cardiac surgery [51]. Kuijpers et al. [5] reported valved-prosthetics in ACHD carry a hazard ratio (HR) of 17.29 (at 6 months), 15.91 (6-12 months) and 5.26 (>12 months) post-surgery. Non-valve containing prosthetics and repairs were associated with a HR of 3.34 at 0–6 months but no increase risk >6 months. The current European endocarditis prophylaxis guidelines (referred to elsewhere in this chapter) and US guidelines, accordingly recommend antibiotic prophylaxis for 6 months after complete closure of a defect with prosthetic material, regardless of whether it be percutaneously or surgically treated [57, 61].

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8. Hypertrophic cardiomyopathy

8.1. Pathophysiology and diagnosis

Hypertrophic cardiomyopathy (HCM) is an inherited genetic disorder characterised by myocardial thickening. Often this is asymmetric with marked involvement of the ventricular septum. In this setting, increased gradients are generated through the left ventricular outflow tract (LVOT) and if sufficient, result in systolic motion of the anterior mitral leaflet (SAM). Repeated trauma from contact between endocardial surfaces, results in formation of plaques on the ventricular septum, at the point of contact with the MV leaflet. There are altered mechanical and haemodynamic forces acting on the MV, AV and LVOT. This predisposes to endothelial trauma and inflammation, with the potential formation of NBTE and IE at multiple sites [17].

8.2. Echocardiographic diagnosis and predictors of endocarditis risk

Modern echocardiography is readily utilised to diagnose hypertrophic obstructive cardiomyopathy (HOCM). Typical criteria include an unexplained septal thickness of ≥15 mm and LVOT obstruction as a resting or provoked gradient of ≥30 mmHg. In one study [66], the incidence of IE was 1.4 per 1000 patient-years. Echocardiographic predictors of IE risk included: (i) resting LVOT obstruction with incidence of 3.0 per 1000 patient-years, and (ii) marked left atrial dilatation (in presence of resting LVOT obstruction) with incidence of 9.2 per 1000 patient-years. Left ventricular wall thickness was not associated with increased risk [66].

There is overall conflicting data, with some studies finding IE is related to LVOT gradient and a propensity for MV infection, whilst other studies have found the contrary, with no particular relation to LVOT gradient or predilection for AV or MV [67].

9. Postinflammatory valve disease

9.1. Background and pathologic changes

The most common type of postinflammatory valve disease occurs as a sequela of rheumatic fever, leading to RHD. As discussed earlier in this chapter, the incidence has dramatically reduced in high-income countries, except in certain indigenous populations and remains a major global health burden across middle and low-income countries. In Australia, the estimated rate of ARF in young indigenous Australians aged 5–14 years is 150–380 per 100,000 person-years [68].

Rheumatic AV changes include thickening of the cusps, extending to the free margins and associated with commissural fusion. Calcification may eventually develop and occurs predominantly at the commissures and cusp margins. Concomitant changes at the MV are usual and involve thickening and retraction of the leaflets and chords along with commissural fusion. With 'pure' aortic regurgitation, there is cusp fibrosis with leaflet retraction. Fusion of the cusps may mimic a congenital BAV and a 'fish mouth' appearance of the MV on echo. Systemic lupus erythematosus and other inflammatory and autoimmune conditions can mimic rheumatic changes [16]. Rheumatic heart disease may involve all cardiac valves, but

the mitral is most commonly affected. Stenosis is more commonly present at the mitral valve and regurgitation involving the aortic [49].

9.2. Echocardiographic diagnosis of rheumatic heart disease

The revised Jones Criteria [69] for diagnosis of ARF, importantly has now incorporated Doppler echo for both acute and chronic valvulitis. In the previous guideline (1992), cardiac involvement was based on clinical auscultation. Modern-era echo has been validated for diagnosis of subclinical carditis. Echo may either help confirm or exclude carditis when a murmur is present, or it may detect subclinical carditis. The most common cardiac changes are cardiac valve involvement (valvulitis) and may be accompanied by a pancarditis with or without a myopericarditis [69].

9.2.1. Echocardiographic diagnosis: Doppler haemodynamics and 2D features

With acute rheumatic mitral and aortic valvulopathy, functional and haemodynamic changes are readily diagnosed by Doppler echocardiography. The regurgitation must be demonstrated in at least 2 views with a peak jet velocity of >3 m/s, a pan systolic or diastolic jet respectively and a jet length of ≥2 cm for MR and ≥1 cm for AR. Morphological changes may or may not be present early during infection [69]. The morphological change(s) seen at the MV during acute valvulitis/carditis include: (i) annular dilatation, (ii) chordal elongation/rupture, (iii) leaflet prolapse and/or (iv) beading/nodular thickening of the leaflet tips. Chronic changes of the mitral valve apparatus include: (i) thickening of the leaflets/chords, (ii) chordal fusion, (iii) restriction of leaflet motion and/or (iv) calcification [69]. Acute and chronic aortic valve changes of rheumatic valvulitis/carditis demonstrated with 2-D echo include: (i) irregular and/or focal thickening of the leaflets, (ii) leaflet retraction/restriction with or without coaptation defects and/or (iii) leaflet prolapse [69].

9.2.2. Risk of endocarditis

Incidence of IE in persons with RHD is 3.8–440 per 1000 patient-years [61]. Data published from the National Health Service in England [70], revealed a marginally lower incidence of 3.05 cases per 1000 patient-years, compared with nonrheumatic valve disease at 2.73 per 1000 patient-years in the same study. The incidence of IE in rheumatic mitral stenosis is estimated at 0.17 per 1000 patient-years. Severity of valvular haemodynamics in RHD and risk of IE is not well described.

10. Intravenous drug use

Intravenous drug use (IVDU), along with cardiac-devices, CHD and vascular access catheters, are the major risk factors for RSIE. Right-sided IE constitutes 5–10% of IE cases and approximately 90% of RSIE involves the TV [71]. Overall, IVDU use accounts for 5–10% of all cases of IE [3, 72]. The median age at time of infection is 30–40 years, not infrequently seen in patients

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with human immunodeficiency virus (HIV). The majority of cases (right-sided > left-sided) are thought to involve structurally normal cardiac valves [8, 72]. Staphylococcus is the usual microorganism however infections are not infrequently polymicrobial [57]. Various fungi and pseudomonas are noteworthy for severe cases of IVDU-associated IE [8]. Interestingly, streptococci and enterococci more commonly affect left-sided valves, often with underlying structural abnormalities [73, 74].

According to Mathew et al. [75], the overall incidence of left-sided cardiac involvement was similar to right-sided IE, with a minority involving both right and left-sided valves [75]. Others have reported a predominance of right-sided lesions in patients with IVDU [72, 76]. The overall incidence of IE in IVDU is estimated at 0.7–20 cases per 1000 patient-years [74, 77].

The increased risk of IVDU patients acquiring IE is likely attributable to a multitude of factors. Proposed explanations include: (i) particulate matter injury to endothelium from substance injection, (ii) drug-induced thrombus formation and vasospasm, (iii) immune complex deposition on valves, (iv) altered host immune function, (v) frequent exposure to high volume bacterial inoculation, (v) increased prevalence of staphylococcal skin carriage, and (vi) sympathomimetic -induced PHTN resulting in an increase in valvular regurgitation velocity and endothelial trauma. A preference for right-sided involvement of structurally normal valves may also be related to altered host and microorganism factors [71, 74, 78]. It is theorised particulate matter up to 8–10 μm in size can transit across the normal pulmonary vasculature and potentially traumatise left-sided valvular endothelium [75]. However, the relatively high prevalence of left-sided valve involvement in the IVDU cohort without apparent underlying valve disease, may not be completely explained by the above theories and warrants further research.

Transthoracic echocardiography is often very useful in IVDU patients for excluding predisposing underlying structural heart disease and providing confirmation of IE, especially for TV endocarditis. Patients with IVDU are often younger and with satisfactory acoustic windows. In addition, the TV is located anteriorly within chest, being in close proximity to the imaging transducer. The use of TOE is preferred for complicated cases of right and left-sided IE, such as periannular extension, prosthetic valves, nondiagnostic TTE, CHD and for excluding infection at other sites within the right heart, such as the Eustachian valve, atrial wall or vena cavae.

11. Prosthetic cardiac valves, devices and risk of endocarditis

11.1. Surgical valves

The estimated risk of prosthetic valve endocarditis (PVE) overall is 0.3–1.2% per patient year (3–12 per 1000 patient-years) [57]. Recent study data from the National Health Service in England [70] reported an incidence of 4.64 cases per 1000 patient-years. In a landmark early study from the 1980s, the risk for mechanical valve IE was shown to be higher in first 3 months post-surgery, whilst for porcine valves, the IE risk was higher >12 months. The cumulative risk by 5 years was not significantly different between mechanical and porcine [79].

A large study recently published, incorporating contemporary valve data, has found bioprosthetic valves do carry a higher risk for IE than mechanical valves, with a multivariable-adjusted hazard ratio of 1.65 (CI, 1.16–2.37) for early (<12 month) and 1.53 (CI, 1.25–1.86) for late (>12 months) IE. The crude incidence rates were 11.7 vs. 7 per 1000 patient-years for early IE and 6.0 vs. 4.3 per 1000 patient-years at 1–5 years (post-surgery) for bioprosthetic and mechanical valves, respectively. Similar rates were seen out to 15 years of follow-up in both groups. The overall combined incidence for PVE was 0.57% (5.7/1000) per patient-year [80]. It was suggested structural deterioration of prosthetic valves is a contributing risk factor, but this requires further investigation. Another study found a higher risk of IE with bioprosthetic over mechanical AVR, where the incidence of re-hospitalisation for IE was at 2.2% versus 1.4%, over 12 years follow-up, with adjusted hazard ratio of 1.6 (CI, 1.31–1.94). This difference was seen across all groups, except those aged 75–80 years and patients with renal failure [80].

11.2. Valve repairs

Valve repairs with prosthetic material carry a reported incidence of 4.71 cases per 1000 patient years [70]. In a pooled analysis (24 studies), recurrence of IE after mitral valve repair versus surgical replacement was 1.8% compared to 7.3% (p 0.0013), with a mean follow-up of approximately 50 months [81].

11.3. Transcatheter valves

The incidence of IE in transcatheter aortic valve replacement (TAVR) is similar to surgically placed prosthetic valves. There is no reported significant difference between self-expanding and balloon-expanding IE rates. Residual moderate or severe regurgitation was associated with higher rates of IE at 16.3 per 1000 patient-years versus 9.3 per 1000 patient-years for mild or no aortic regurgitation [82].

For pulmonary transcatheter valve (Medtronic Melody™), one study [83] reported a rate of IE of 3% per patient-year for a median follow-up of approximately 2 years. With regard to valved-conduits, the incidence of IE with RVOT homografts was lower at 0.8% per patient-year compared to Contegra-Melody conduit rate of 2.7–3.0% per patient-year. In patients with an infected Melody valve, 4/8 had a peak gradient >40 mmHg, whilst only 5/99 in the non-IE group had a similar gradient ($p < 0.05$) [83]. This suggests a possible increased risk of IE with residual post-procedural gradients, but numbers are insufficient and further studies are required to confirm or refute this assertion.

11.4. Device-related endocarditis

Ventricular assist devices (VADs) carry an incidence of IE of 5.8 cases per 1000 patient-years [70]. In one study investigating VAD infections, the following rates (cases per 100 LVAD-years) were found: i) all infection types –32.8 (CI, 26.7–39.9), ii) IE 1.6 (CI, 0.5–3.8) and iii) bloodstream – VAD-related, 7.5 (CI, 4.7–11.2) [84].

Implantable pacemakers (PPM) and cardiac defibrillators (ICD) have a reported incidence of IE ranging from 0.68–1.9 cases per 1000 patient-years [57, 70]. Cardiac device-related infective endocarditis accounts for 10–23% of device infections [85]. Numerous risk factors have been identified, including previous device-related infection, however information on risk related to underlying structural cardiac or TV pathology is uncertain. From the ICE-PICS data [86], 6.4% of all cases of IE were CDRIE. Over one-third of cases had associated valvular involvement, most commonly the tricuspid valve.

11.5. Recurrent native and prosthetic valve infective endocarditis

One of the most important cardiac risk factors for endocarditis is a prior history of IE. In the ICE- PCS cohort, recurrent IE occurred in 4.8% of patients, given an odds ratio of 2.8 (CI, 1.5–5.1) [87]. This is concordant with findings from other published studies with rates between 3.3 and 11.7% [88, 89]. In a recent study, the risk for recurrent IE was 14.36 per 1000 patient-years [70]. In a different study, the risk of recurrence (in patient-years) was estimated as follows: (i) history of previous IE, 7.4 per 1000, (ii) prosthetic valve surgery for native valve IE, 6.3 per 1000 and, (iii) prosthetic valve surgery for prosthetic valve IE, 21.6 per 1000 [61]. In a meta-analysis comparing biological versus mechanical valve for IE surgery, recurrence of IE in mechanical valves was 3–9% and for biological valves 7–29% [90] . Other studies have found equal rates of reinfection of bioprosthetic and mechanical valves.

Renzulli et al. [91], interestingly reported there was no association with previous perivalvular extension and recurrent risk [91]. In a study focussing on aortic homografts, Flameng et al. [92] found the recurrence rate of IE was relatively low at 7% at a mean follow-up of 8 ± 5 years. A significant downside is the high rate of structural deterioration of aortic homografts, with a rate of 40% at 10 years [92].

Shimokawa et al. [93] reviewed long term outcomes of mitral valve repair following IE in patients with prolapse and found good outcomes when compared with repair for degenerative MVP without IE. In this study, there were no recurrences of IE [93]. In another meta-analysis, comparing MV replacement with MV repair in the setting of IE, the 5 year risk of recurrent IE was favourable in the repair group with OR 0.39 (0.10–1.58) [94].

12. Conclusion

The three main categories of cardiac disease predisposing to infective endocarditis are degenerative valve disease, congenital heart disease and less commonly in high-income countries, rheumatic heart disease. The changing epidemiology has been associated with an ageing population, increased prevalence of prosthetic valves, devices and shunts, and health-care exposure. This chapter has outlined the underlying pathology, risks and echocardiographic predictors for IE associated with a selection of lesion-specific cardiac pathologies. The chapter also addressed the observation of structurally ‘normal’ cardiac valves accounting for a rising proportion of IE cases. Whether this relates to microorganism virulence, host factors, early structural and

functional changes associated with degenerative valve disease, or a combination of all of the above, is unproven. Only further focused research using modern-era high resolution imaging and clinicopathological correlation, will provide new insight into this interesting question.

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Chapter 3

Endocarditis Caused by *Abiotrophia* and *Granulicatella* Species

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Additional information is available at the end of the chapter

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Abstract

Endocarditis caused by *Abiotrophia* and *Granulicatella* species, formerly known as nutritionally variant streptococci (NVS) is rare. It is associated with increased complications such as heart failure, systemic emboli, valve replacement surgery, treatment failures and mortality. The diagnosis of these infections is challenging due to specific nutritional growth requirements although modern techniques such as 16S rRNA sequence analysis and Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) are particularly useful. Penicillin resistance among these organisms is a growing problem. Penicillin and gentamicin combination or alternatively Vancomycin alone are the recommended treatment options, however there is increasing data regarding susceptibilities to other antibiotics. Varying susceptibilities to antibiotics among different species of NVS needs to be studied further.

Keywords: *Abiotrophia* and *Granulicatella* endocarditis, aorto-right ventricular fistula, *Abiotrophia* endocarditis

1. Introduction

Nutritionally variant (deficient) streptococci (NVS) were first described by Frankel and Hirsch in 1961 [1]. These gram positive bacteria resembled streptococci but had specific nutritional growth requirements. Since their first identification, over the years nomenclature of NVS changed several times based on DNA-DNA hybridization studies and 16S rRNA sequence analysis. They were first included in the genus *Streptococcus*, then genus *Abiotrophia*, and finally they were recognized as two separate genera; genus *Abiotrophia* and genus *Granulicatella*. Genus

Abiotrophia consists of *Abiotrophia defectiva* and genus *Granulicatella* consists of *Granulicatella adiacens*, *Granulicatella elegans*, *Granulicatella balaenopterae* and *Granulicatella para-adiacens*.

NVS are members of the normal flora of human pharynx, human urogenital and intestinal tracts [2].

Infective endocarditis caused by NVS is rare, causing approximately 2% of all cases of infective endocarditis [3]. Over 125 cases of infective endocarditis caused by *Abiotrophia* and *Granulicatella* spp. have been reported to date. It is estimated that approximately 5–6% of all cases of streptococcal endocarditis are caused by NVS [4]. Due to the fastidious nature of these organisms and difficulties in diagnosis, it is possible that endocarditis caused by NVS may be under-recognized. NVS are among the organisms causing culture negative endocarditis. The main reservoir of infective endocarditis inducing NVS is oral cavity as in the case of other viridans streptococci [5].

Although endocarditis and bacteremia are the most common infections associated by *Abiotrophia* and *Granulicatella* spp., the literature for infections caused by *Abiotrophia* and *Granulicatella* spp. has been growing with new sites of infections being reported as our awareness of these bacteria heightens and our diagnostic capabilities improve.

Ophthalmological infections have been encountered, ranging from keratitis to endophthalmitis [6]. NVS are known to cause corneal ulcers [7], vitreous infections [8] and infectious crystalline keratopathy [9]. Orthopedic infections, including prosthesis infection, septic arthritis, discitis and sacroiliitis have been reported [10–12]. Synovial biopsy sample from a patient with culture negative endocarditis also yielded NVS [13]. NVS are also associated with central nervous system infections; more commonly brain abscesses but rarely meningitis [14], subarachnoid hemorrhage [15] and intracranial aneurysms [3] have been reported. CNS infections have been commonly linked to embolic phenomena, neurosurgical instrumentation and immunosuppression [10, 16]. NVS have been isolated from patients with otitis media [1], otitis externa [2], sinusitis [17], parapneumonic effusion [18], cirrhosis [19], peritonitis [20], pancreatic abscess [21], bacteremia associated with postpartum or postabortal sepsis [19], tuboovarian abscess [22], breast implant associated infection [23], wound infections, and vaginal discharge [24]. Endarteritis caused by *A. defectiva* involving the main pulmonary artery in a patient with asymptomatic patent ductus arteriosus has been reported [25].

2. Microbiology

Nutritionally variant streptococci were first described by Frenkel and Hirsch in 1961 from blood cultures of cases of subacute bacterial endocarditis and from otitis media. These cell wall deficient, L form 'streptococci' were noted to grow in satellite colonies around other bacteria requiring substances secreted by other bacteria for growth [1]. 'Abiotrophia' means life nutrition deficiency, referring to the need of specific nutrients in media for growth of these bacteria [26]. They are catalase-negative, oxidase-negative, facultative anaerobic gram positive bacteria [27]. They often form white-gray, non-hemolytic colonies. These organisms hardly grow in culture media that streptococci ordinarily grow, such as sheep blood agar. They require supplementation of L-cysteine or pyridoxal HCl. In the absence of these supplements, NVS can also grow forming satellite colonies adjacent to streaks of helper bacteria such as *Staphylococcus aureus* or *Staphylococcus epidermidis*.

Bouvet et al. in 1989 showed that NVS could be divided into two groups, *Streptococcus defectivus* and *Streptococcus adiacens* by DNA–DNA hybridization studies. They noted that there was less than 10% DNA homology with the reference streptococcus species [28].

In 1995, Kawamura et al. proposed that these distinct species be transferred to a new genus, *Abiotrophia*, as *Abiotrophia adiacens* and *Abiotrophia defectiva* by using 16S rRNA gene sequencing. Subsequently two new species were added to this genus; *Abiotrophia elegans* [29] isolated from a patient with endocarditis and *Abiotrophia balaenopterae* [30] from a minke whale (*Balaenoptera acutorostrata*).

Finally, in 2000, Collins et al. proposed the taxonomy of NVS that we use today. They pointed out that genus *Abiotrophia* consisted of two distinct lines. *Abiotrophia defectiva* and a robust group consisting of *A. adiacens*, *A. balaenopterae* and *A. elegans*. They reclassified *A. adiacens, A. balaenopterae* and *A. elegans* into genus *Granulicatella* (*small chain of small grains in Latin*) and *Abiotrophia defectiva* into genus *Abiotrophia* [27]. Shortly before this taxonomy revision, Kanamoto et al. proposed a new strain, *Abiotrophia para-adiacens*, related to *Granulicatella adiacens* which is rarely reported but not widely published [31, 32].

3. Pathophysiology

Bacterial attachment to damaged heart valves is the key factor in infective endocarditis. Intact vascular endothelium can resist the development of endocarditis [33]. Experimental animal models showed that when catheter induced endocardial damage is produced; these endocardial lesions can be infected by direct inoculation of bacteria or by intravenous inoculation [34]. Pathophysiology of infective endocarditis typically would start with endothelial cell denudation, followed by exposure of underlying extracellular matrix (ECM) and finally binding of fibrin and platelets [33]. Extracellular matrix proteins are exposed during damage to the cardiac endothelium providing potential sites of attachment for virulent organisms [35] *Granulicatella* and *Abiotrophia* spp. have the ability to bind to fibronectin and other extracellular matrix proteins. The ability to bind to extracellular matrix proteins appears to correlate with the degree of infectivity of NVS [5].

Some groups of NVS are more pathogenic and other groups are less pathogenic. Highly pathogenic *G. adiacens* has high fibronectin binding ability. Highly pathogenic *A. defectiva* strains also have strong ability to bind to fibronectin and other ECM proteins whereas less pathogenic *G. para-adiacens* and *G. elegans* strains show low ability to bind to fibronectin and all other ECM proteins [5]. Similarly, among non-NVS streptococci that are commonly associated with infective endocarditis, *S. mutans*, *S. mitis*, *S. sanguis* and *S. fecalis* also have the ability to bind to the extracellular matrix [35].

By binding to the extracellular matrix proteins, bacteria are able to adhere to the damaged endocardium and subsequently producing colonization and infection. ECM binding ability however is not the sole indicator of pathogenicity. Some strains of NVS have high infectivity without significant binding to the ECM proteins suggesting other mechanisms involved in pathogenesis. Other mechanisms of endocardial infectivity of NVS remains to be discovered [5].

As a group, NVS have heterogenous properties of pathogenicity. *A. defectiva* has higher pathogenicity compared to other species of NVS [5]. About 73% of all NVS isolates from patients with bacterial endocarditis are *Abiotrophia defectiva*. *G. para-adiacens* and *G. elegans* strains are less virulent than *A. defectiva* and *G. adiacens* [5].

Okada et al. noted that [5] NVS isolates from endocarditis patients and from normal oral flora both had the ability to cause infective endocarditis.

4. Diagnosis

Identification of *Abiotrophia* and *Granulicatella* spp. in blood cultures is extremely difficult. NVS do not grow well in subcultures and may be regarded as contaminant bacteria. Their extreme pleomorphism may lead to misidentification of these bacteria as other bacteria, even fungi [36, 37]. Christensen and Facklam [38] studied 101 NVS isolates and reported that isolates were gram variable and pleomorphic, forms varied from bacilli with spore like swellings to cocci predominantly in pairs and chains when gram stain preparations were made from agar plates. NVS can demonstrate bulbous swelling and filament formation and they can form rough colony morphology on chocolate agar that can be suggestive of other microorganisms such as *Streptobacillus moniliformis* or *Erysipelothrix rhusiopathiae* [36].

NVS show morphologic variations depending on the pyridoxal concentrations in the growth medium [39]. Due to the difficulties in identification of these bacteria, it is crucial for microbiology staff to be vigilant and be aware of the pleomorphic nature of the NVS to prevent misidentification.

NVS should be suspected when gram stain shows microbial cells but cultures are negative [2]. Once their nutritional growth requirements are supplemented in media, NVS convert to streptococci-like cells [39] and gram positivity making them easier to identify, although it was also shown that correcting nutritional deficiency may not convert all abnormalities [40]. For *G. elegans*, addition of cysteine to growth media would have the effect of reversal of pleomorphic morphology but addition of pyridoxal HCl does not [29]. The difficulty in identifying these organisms leads to delays in diagnosis and thus timely initiation of appropriate antimicrobial treatment [41].

Contemporary blood culture methods enable *Abiotrophia* and *Granulicatella* spp. to grow routinely, visible colonies of these organisms appear in 48 h on subculture from positive blood culture media supplemented with *Brucella* and chocolate subculture media [3].

Cargill et al. noted that anaerobic blood culture bottles became positive sooner than aerobic blood cultures bottles; (3.56 h, standard deviation 8.49 h) although they noted that this was not significant or reliable [31].

Specific phenotypic characteristics of NVS can be identified by examining their patterns of production of α-galactosidase, β-galactosidase, β-glucosidase, N-acetyl-β-glucosaminidase and β-glucuronidase, and fermentation of trehalose, pullulan, tagatose and sucrose [32, 38].

A. defectiva produces α-galactosidase, β-galactosidase and produces acid from trehalose, sucrose and pullulan. Its acid production from tagatose is variable [38].

G. adiacens produces β-glucuronidase and produces acid from sucrose and tagatose. *G. elegans* hydrolyses arginine. Its hippurate hydrolysis is variable. It produces acid from sucrose. *G. balaenopterae* hydrolyses arginine and produces acid from trehalose and pullulan. [38]

G. para-adiacens produces β-glucosidase, does not produce α- or β-galactosidase or arginine and does not ferment trehalose, pullulan or tagatose [32].

Molecular diagnostic techniques can be used for rapid and accurate diagnosis of NVS in blood or tissue samples. PCR amplification of 16S rRNA and restriction fragment length polymorphism (RFLP) for routine detection of NVS was developed by Ohara-Nemoto et al. in 1997 [42]. For culture negative infective endocarditis, molecular techniques appear to be more sensitive in resected valvular tissue compared to blood samples [43].

Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) is a fast, reliable and cost-effective technique used to identify microorganisms by utilizing MALDI-TOF MS devices in the clinical microbiology labs [44]. These devices carry the potential to complement or replace the phenotypic identification of various microorganisms including bacteria [44]. MALDI-TOF MS is a rapid and accurate diagnostic tool that has been used to identify and timely diagnose NVS [45].

In culture negative endocarditis, *Abiotrophia* and *Granulicatella* spp. should be suspected and supplemented media should be performed for the organisms to grow. Once the growth is achieved, PCR amplification of 16S rRNA or MALDI-TOF mass spectrometry can be utilized for rapid and accurate diagnosis [46].

5. Clinical presentation and complications

Endocarditis caused by NVS typically follows a slow and indolent course. Endocarditis develops as a result of bacteremia. *Abiotrophia* and *Granulicatella* spp. are causes of endocarditis with severe complications such as congestive heart failure, valvular destruction, systemic embolization in both immunocompetent and immunocompromised patients.

Mortality rate associated with endocarditis caused by NVS is 17% which is higher than that of viridans streptococci (0–12%) and enterococci (9%) [47].

Underlying valvular disease is commonly seen as a predisposing factor for development of endocarditis. Over 90% of the cases have preexisting heart disease and 10% of patients have prosthetic heart valves [48]. Newer data however, suggest that there is increased involvement of normal heart valves in the past decade [49].

Embolization is a common complication of Abiotrophia endocarditis affecting one-third of patients. Typical peripheral manifestations of endocarditis such as petechia, digital clubbing, Osler nodes are not frequently found [41].

It has been known that infective endocarditis caused by NVS carries a higher risk of embolization, treatment failure and increased mortality as compared to infective endocarditis caused by viridans streptococci [4].

Stein et al. reviewed 30 published case reports of endocarditis caused by NVS and found that 17% of patients had relapses after antibiotic therapy. Bacteriologic failure rate was 41% (defined

as positive blood cultures after 7 days of appropriate antibiotic therapy, relapse following a course of therapy with appropriate antibiotics, or a positive valve culture). It is notable that bacteriologic failure was seen despite the sensitivity of the organisms to the antibiotics used in two thirds of the cases. About 31% of the patients required surgery. Mortality rate was 17% which was higher than that of endocarditis caused by enterococci or viridans streptococci [41].

Similarly a more recent review of 29 cases of solely *Granulicatella* endocarditis by Adam et al. showed very high rates of complications and adverse outcomes. Incidence of heart failure was 30%, embolism was seen in 30% of patients and perivalvular abscess was seen in 11%. The mortality rate was 17%. The average vegetation size was 16 mm (31). They found that aortic (44%) and the mitral (38%) valves were the most commonly effected and multivalvular involvement was (13%) [50].

Large vegetation sizes are associated with increased risk of systemic embolism in infective endocarditis. Case studies reveal large vegetation sizes with infective endocarditis caused by NVS (greater than 10 mm in 7 out of 8 cases reviewed by Lin et al., and average vegetation size of 16 mm in a case series of 29 patients by Adam et al.) [50]. These findings correlate with the high rates of systemic embolism seen in endocarditis caused by NVS.

Endocarditis caused by NVS is associated with high rates of infectious intracranial cerebral aneurysms although the exact incidence is unknown. Having a low threshold for obtaining imaging of the CNS is reasonable even for patients with vague complaints such as severe localized headaches or mild confusion [3]. Many infectious intracranial cerebral aneurysms resolve by antibiotic treatment with reductions in size in the first 1–2 weeks. The risk of rupture decreases with time on antibiotic therapy [3].

Endocarditis caused by NVS is associated with 13% of aortic valve damage and 11% of mitral valve damage. If not recognized on a timely basis, these patients may present with congestive heart failure as the first presenting manifestation of the infection [51]. Congestive heart failure is a potential complication of valvular destruction which can necessitate heart valve replacement surgery.

Aorto-RV fistula is a rare complication of *A. defectiva* endocarditis that requires early surgical intervention for closure [52]. Development of hemophagocytic lymphohistiocytosis was reported in a previously healthy patient with *A. defectiva* endocarditis [53].

Endocarditis caused by NVS has rarely been reported in children. According to a review of 13 pediatric cases in children, 69% had underlying heart disease [54]. Similar to adult patients, endocarditis caused by NVS in pediatric populations also appears to be associated with high complication rates including severe valvular damage, surgical valve replacement and systemic embolization [54, 55].

6. Treatment

Antimicrobial susceptibility testing is very difficult for *Abiotrophia* and *Granulicatella* due to their fastidious nature. In addition, the results of susceptibility testing may not be accurate or

reliable. Microbiological cure is difficult and infective endocarditis caused by these organisms is associated with high rates of treatment failures. Therefore, AHA (American Heart Association) and British Society for Antimicrobial Chemotherapy (BSAC) Infective Endocarditis treatment guideline for *Abiotrophia defectiva* and *Granulicatella* species is very similar to treatment guidelines for enterococcal endocarditis [33, 56].

Recommended treatment regimen is Ampicillin (12 g/d in divided doses) or penicillin (18–30 million U/D in divided doses or by continuous infusion) plus gentamicin 3 mg/kg/d in 2–3 divided doses).

For those patients who are intolerant to penicillin, Vancomycin alone without the use of gentamicin can be given for therapy. This is in contrast to enterococcal endocarditis treatment where Vancomycin is combined with gentamicin [33].

The duration of treatment for *Abiotrophia* or *Granulicatella* endocarditis needs to be determined by consultation with an infectious disease expert. As a general guidance, AHA recommendations for treatment durations for enterococcal endocarditis are as follows:

The treatment duration is 4 weeks for native valve endocarditis with symptoms or illness ≤3 months. 6 week therapy is recommended for patients with symptoms >3 months. For prosthetic valve or other prosthetic cardiac material infections, minimum 6 weeks of antibiotic therapy is recommended [33].

Historically, in animal models it was shown that Penicillin alone was inferior to Penicillin plus aminoglycoside or Vancomycin alone for the treatment of infective endocarditis caused by NVS [57, 58]. it was shown that penicillin plus low dose (0.32 mg/kg) vs. high dose (1.05 mg/kg) gentamicin treatment results were virtually identical [57].

There is encouraging data to suggest that shortened courses of aminoglycosides in the treatment regimens (median 15 days) may result is similar clinical outcomes in treatment of enterococcal endocarditis. However this particular issue requires further study and it is not yet known how this would apply to treatment of infective endocarditis caused by *Abiotrophia defectiva* or *Granulicatella* species. [49].

Given the growing concerns over antibiotic resistance among NVS, poor treatment outcomes and high rates of treatment failures it is important to look into data for susceptibilities of a broad range of antibiotics. There is however limited data available regarding the antibiotic susceptibilities of *Granulicatella* and *Abiotrophias* spp. due to the rare nature of the infections, the specific nutritional growth requirements and difficulties in standardization of testing methodologies.

7. Penicillin

NVS have the highest in vitro penicillin resistance compared to any other streptococci. The rate of penicillin resistance among NVS appears to be rising over the years. While an earlier study by Cooksey and Swenson in 1979 [59] and Gephart and Washington in 1982 [60] showed no isolates had a penicillin MIC >1 μg/ml, subsequent studies showed significantly increasing penicillin resistance; Bosley and Facklam in 1990 [61] noted 9% rate of resistance

to penicillin and Alberti in 2016 [62] reported 14% rate of penicillin resistance among NVS. It is also notable that the method of penicillin susceptibility testing has changed over the years. Douglas et al. (1994) [63] found that while historical method of penicillin susceptibility testing by reference dilution method did not find penicillin resistance, when same NVS isolates were tested with E test, 7% penicillin resistance was detected. The high rate of penicillin resistance among VNS appears also to be consistent among NVS isolates from pediatric infections [64].

According to antibiotic susceptibility testing of 132 isolates by Albierti et al. in 2016, only 33% of the 132 isolates were susceptible to penicillin and 14% were resistant with an MIC ≥4 μg/ml. The remaining 53% of the isolates had penicillin MICs in the intermediate category (0.25–2 μg/ml) [62]. Liao et al. reported 50% of their isolates (14 out of 28 isolates) had intermediate susceptibility to penicillin [65].

There appears to be differences in penicillin susceptibilities among different species of NVS. Albierti et al. showed that penicillin susceptibility is much less among *A. defectiva* compared to *G. adiacens* (10.8% vs. 38.9%). *G. elegans* isolates are highly susceptible to penicillin with MIC of 0.03 μg/ml (n = 5) [62].

In an earlier study by Touhy et al. in a review of 39 isolates from 1995 to 1999, similar to Albierti et al.'s findings, *G. adiacens* penicillin sensitivity was higher than that of *A. defectiva*; 55 vs. 8% respectively. [66].

7.1. Penicillin tolerance

It is notable that clinical failures of treatment have frequently been described even for penicillin susceptible strains when appropriate antibiotics are given. Holloway et al. described a phenomenon of penicillin tolerance among NVS which minimum bactericidal concentration (MBC) significantly exceeded (greater than 32) the minimum inhibitory concentration (MIC) that would lead to a slower antibiotic effect and potentially a worse clinical response. In addition to the usual nutritional supplements of vitamin B6 and cysteine to the plates, by adding penicillinase to the subculture medium and a staphylococcal streak across the plates they showed that even though all tested isolates were susceptible to penicillin (MICs of the strains ranged from 0.05 to 0.4 U of penicillin per ml), 100% of the isolates were penicillin tolerant. The isolates did not show any penicillin tolerance if the subculture was supplemented only with pyridoxal and cysteine [67]. Therefore, in order to identify penicillin tolerance and not misidentify the strains as penicillin sensitive, it is necessary to add penicillinase to the medium in addition to the usual growth supplements, pyridoxal HCl, cysteine and staphylococcal streak.

The slow growth rate of NVS is also thought to be responsible from poor response to antibiotic treatment. NVS generation time is 2–3 h while viridans streptococci generation time is 40–50 min [2, 41, 68].

7.2. Susceptibility testing

According to the latest consensus guidelines from the Clinical and Laboratory Standards Institute (CLSI) for antimicrobial susceptibility testing for infrequently isolated or fastidious bacteria, disk diffusion test for *Abiotrophia* and *Granulicatella* species is not recommended.

Instead, broth microdilution MIC testing by laboratories experienced in such testing is recommended. CLSI suggests broth microdilution MIC testing in Cation adjusted Mueller-Hinton broth with 2.5–5% lysed horse blood and 0.001% pyridoxal HCl [69].

E test is proven to be a rapid and simple method for MIC estimation for NVS, comparable to broth microdilution MIC testing [63].

CLSI consensus guidelines also emphasize that cases of *Abiotrophia* or *Granulicatella* infections can be managed by following the treatment recommendations in the medical literature without antimicrobial susceptibility testing. The antimicrobial susceptibility testing can be reserved for those cases where there is persistent infection, clinical failure, allergy or intolerance to the drugs of choice and possible resistance to the drugs that might be prescribed. Infectious disease specialists or other expert clinicians should make all susceptibility testing decision and test interpretation [69].

7.3. Cephalosporins

Penicillin resistance is often associated with resistance or decreased susceptibility to other beta-lactam antibiotics including ceftriaxone [66].

However, overall cephalosporin susceptibility among NVS appears to be higher compared to penicillin. In addition, A. *defectiva* appears to have higher susceptibility to 3rd generation cephalosporins compared to *G. adiacens*. According to a large review of susceptibilities of antibiotic susceptibility testing for 132 clinical NVS isolates from blood cultures that were isolated from 2008 to 2014 at Los Angeles hospitals by Albierti et al., Ceftriaxone susceptibility was 61.4% and Cefotaxime susceptibility was 43.2% among all isolates. *A. defectiva* was more susceptible than *G. adiacens* to the third generation cephalosporins (94.6% vs. 18.9% for Cefotaxime and 100% vs. 43.3% for ceftriaxone). Ceftriaxone susceptibility breakpoint was MIC ≤1 μg/ml as per CLSI M45 [62, 69]. Touhy et al. had found a similar susceptibility pattern of susceptibility for ceftriaxone; they had observed that 83% of the *A. defectiva* isolates and 63% of *G. adiacens* isolates were susceptible to Ceftriaxone by using MIC ≤0.5 susceptibility breakpoint [66]. Zheng et al. reported that out of 15 isolates of *Abiotrophia* and *Granulicatella*, 9 were resistant to Ceftriaxone (MIC of >2 μg/ml), 13 were resistant to Cefuroxime (MIC of >2 μg/ml) [64]. All six isolates of *G. adiacens* in their review were resistant to Ceftriaxone [64].

Albierti et al. noted that some of the isolates that were resistant to ceftriaxone still remained susceptible to Ceftaroline. (51.6% of *G. adiacens* isolates resistant to ceftriaxone with an MIC ≥4 μg/ml had Ceftaroline MICs of ≤1 μg/ml). On the other hand, 32% of *G. adiacens* isolates that were resistant to ceftriaxone (MIC ≥4) had Ceftaroline MICs ≥4 μg/ml. These isolates were noted to be resistant to penicillin (MIC ≥4 μg/ml). The Ceftaroline MIC90 for all isolates were lower compared to Cefotaxime or Ceftriaxone (2 versus >4 μg/ml) [62].

Resistance to higher generations of cephalosporins have been reported such as Cefepime (2 out of 21 isolates) [70] and Cefotaxime (7 out of 28 isolates were resistant) [65].

Species related differences of penicillin or cephalosporin sensitivities in determining antibiotic choices remains to be investigated. The high rates of ceftriaxone resistance among *G. adiacens* isolates appear to be fairly consistent across various studies.

European Society of Cardiology (ESC) Clinical Practice Guidelines include Ceftriaxone in their recommendations for treatment of endocarditis caused by *A. defectiva* or *Granulicatella* slightly differing from AHA recommendations. ESC recommendation for treatment of IE caused by *A. defectiva or Granulicatella* is Penicillin G, Ceftriaxone or Vancomycin for 6 weeks, combined with an aminoglycoside at least for the first 2 weeks [71].

8. Vancomycin

Iv Vancomycin is recommended as an alternative regimen to iv penicillin for those patients who are not able to tolerate penicillin or ampicillin [33].

Bouvet et al. by using an experimental animal model found that Vancomycin alone was as good as combination of Vancomycin and Gentamicin for treatment of endocarditis caused by NVS [58].

Vancomycin susceptibility breakpoint is typically MIC <1 μg/ml and no resistance to Vancomycin among NVS has been reported thus far [62, 64, 66]. It is notable however that MIC90 for Vancomycin is 2 times higher for *G. adiacens* compared to *A. defectiva* or *G. elegans* [62, 66].

9. Aminoglycosides

NVS remains susceptible to aminoglycosides (MICs for Gentamicin and streptomycin ≤4 μg/ml), high level aminoglycoside resistance has not been reported. As per AHA and BSAC guidelines for treatment of infective endocarditis caused by *Abiotrophia* or *Granulicatella* species, iv gentamicin is combined with iv penicillin (first line treatment) [33, 56].

10. Macrolides

Macrolide resistance is common among *Abiotrophia* and *Granulicatella species* (49.2% of all isolates sensitive to erythromycin vs. 87% of all isolates sensitive to Clindamycin) [62]. Resistance mechanisms include efflux among *mef*(A) positive isolates and *erm*(B) gene causing resistance to both Erythomycin and Clindamycin [64]. It was shown that *erm*(B) gene is located on Tn916-related transposon in *A. defectiva* similar to the pneumococcal transposon Tn3872, enabling Abiotrophia to act as a donor and recipient of antibiotic resistance [72]. Macrolide resistance pattern of NVS is suggestive of constitutive macrolide-lincosamide-streptogramin B (cMLSB) phenotype. Zheng et al. noted that all three isolates of NVS that carried erm(B) (*G. adiacens* and *G. elegans*) also carried *tet*(M), tetracycline resistance gene which is carried on the same transposon as ermB gene [62, 64].

11. Carbapenems

Resistance to Meropenem or Imipenem among *Abiotrophia* and *Granulicatella species* is rare. Review of 132 isolates by Albierti showed 100% sensitivity to Meropenem and Imipenem

(MIC ≤0.06 μg/ml for both antibiotics) [62]. Touhy et al. [66] found that 3 isolates of *A. adiacens* (out of 27 total isolates) and 7 isolates of *G. defectiva* (out of 12 total isolates) had increased MICs of Meropenem (0.5 μg/ml). These isolates also had penicillin MICs ≥0.5 μg/ml. One of their isolates of *A. adiacens* had a high MIC for Meropenem (MIC of 1 μg/ml) which was isolated from a patient with suspected intervertebral disc space infection who had received a prolonged course of various antibiotics including beta-lactams. This particular isolate was also resistant to penicillin and ceftriaxone (MICs ≥8 μg/ml).

12. Quinolones

Resistance to quinolones among NVS is rare. 8 *G. adiacens* [62] and one *G. elegans* [70] isolates have been reported to be resistant to Levafloxacin. The case of *G. elegans* resistant to Levafloxacin was isolated from a patient with neutropenic fever with bacteremia who had previously received Levafloxacin therapy. Mechanism of NVS resistance to quinolones is yet to be determined [62].

13. Daptomycin and linezolid

There are no CLSI defined sensitivity breakpoints for Daptomycin and Linezolid for NVS. Albierti et al. found that Daptomycin MICs appear to be relatively high for NVS. Daptomycin MIC90 was >4 μg/ml for *A. defectiva*, 4 μg/ml for *G adiacens* and 0.5 μg/ml for *G. elegans*. According to the CLSI breakpoint of susceptibility for viridans group Streptococci is MIC ≤1 μg/ml, majority of the tested isolates (89.4%) would be considered resistant to Daptomycin [62, 69]. The reason for relatively high Daptomycin MICs for *A. defectiva* and *G. adiacens* is not clear. This may be due to an inherent resistance of these bacteria to Daptomycin potentially due to differences in cell wall composition [62]. In a prior study a smaller number of NVS isolates (n = 10) were found to have MICs ≤0.125–2 [73]. The reason for the discrepancy in the findings of these two studies is not known and merits further investigation.

When the breakpoint of Linezolid susceptibility for viridans group streptococci (MIC ≤2 μg/ml) is applied to NVS, all NVS would be considered susceptible to Linezolid according to one study of 132 isolates [62, 69]. It was noted that *G. adiacens* MIC90 for Linezolid is higher (2 μg/ml) than that of *A. defectiva* and *G. elegans* (1 μg/ml) [62].

14. Rifampin

Rifampin appears to be one of the most effective antibiotics against NVS although the data is limited. It was shown that Rifampin had a minimal bactericidal concentration of 2 μg/ml while that of penicillin was 1 μg/ml [60]. Combination of Vancomycin and Rifampin showed synergy

in in vitro studies [74]. According to one review of 15 isolates of *Abiotrophia* and *Granulicatella* species, all isolates were found to be susceptible to Rifampin with MICs ≤0.012 μg/ml [64].

15. Role of surgery

Endocarditis caused by NVS is associated with high rates of complications including heart failure, embolization and valvular damage. The need for surgery and time of surgery remains to be determined. However based on outcomes of several cases published in the literature, the rate of surgical treatment is very high especially due to development of heart failure.

he rate of valve surgery is high; 51% (in a review of 29 cases of *Granulicatella* endocarditis by Adam et al.) [50], 48% (review of 23 cases of endocarditis caused by NVS by Guiliano et al.) [49], 38% (review of 30 cases of endocarditis caused by NVS by Stein et al.) [41], 44% (review of 9 cases of *A. defectiva* endocarditis by Hashimoto et al.) [75].

A vegetation size of 10 mm or more is associated with increased mortality and increased risk of embolic events [76]. EASE Trial showed that early surgery in infective endocarditis in patients with large vegetations significantly reduced the mortality, risk of systemic embolism or recurrence of infective endocarditis (3% in the early surgery group vs. 28% in the conventional treatment group) [77]. Lin et al. [68] reported 7 out of 8 cases of endocarditis caused by NVS had large vegetation sizes (10 mm). In the same review, 7 out of 8 cases required surgery (4 out of 8 cases required early valve replacement due to severe heart failure, while 3 cases underwent mitral valve repair 2,4, and 7 months after the diagnosis of endocarditis).

Combined approach with antibiotic treatment and surgery provides the best outcomes in endocarditis caused by NVS. Specifically, early surgical intervention should be considered for those patients with heart failure due to valvular destruction [68], hemodynamic compromise [49] or large vegetation sizes [68, 77].

16. Conclusion

Infective endocarditis caused by NVS has posed tremendous diagnostic and therapeutic challenges and continue to do so even in the era of modern medicine. Delays in diagnosis due to difficulties in identification frequently cause delays in treatment and poor treatment outcomes. Treatment failure and high complication rates associated with *Abiotrophia* and *Granulicatella* endocarditis is at least partially attributable to the pleomorphic nature of the organisms, lack of growth in subcultures and specific nutritional requirements in media along with the need for the microbiology lab staff to have heightened awareness of these microorganisms. Their fastidious nature of NVS makes the antibiotic susceptibility testing fairly difficult, causing delays in initiation of timely and effective antibiotic treatment.

Interpretation of the medical literature of *Abiotrophia* and *Granulicatella* spp. and its application to current clinical practice is challenging as the names of these organisms have been changed several times and not uncommonly the two genera were addressed together. There is

lack of large clinical studies and our knowledge about these organisms is based on relatively small number of reported cases.

Differences in pathogenicity and susceptibility to antimicrobials have been demonstrated among these heterogeneous group of bacteria. More studies are needed to determine if there are further species specific differences of these fascinating microorganisms which would help us improve our understanding, diagnosis and the treatment outcomes of infections caused by NVS.

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Chapter 4

Blood Culture-Negative Endocarditis

Mio Ebato

Additional information is available at the end of the chapter

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Abstract

Blood culture-negative endocarditis is often severe and difficult to diagnose. Infective blood culture-negative endocarditis is classified into three main categories: (1) bacterial endocarditis with blood cultures sterilized by previous antibacterial treatment; (2) endocarditis related to fastidious microorganisms in which prolonged incubation is necessary; (3) true blood culture-negative endocarditis, due to intra-cellular bacteria that cannot be routinely cultured in blood with currently available. There are two major etiologies for noninfective endocarditis: (1) nonbacterial thrombotic endocarditis and (2) endocarditis related to systemic diseases (SLE and Behcet disease). Team approach including cardiologists, infection disease (ID) specialists, microbiologists, pathologist and immunologist is crucial for diagnosis and management of blood culture-negative endocarditis as it needs elegant and high-quality modern technics of histology, molecular analysis and essential epidemiological information.

Keywords: blood culture-negative endocarditis, fastidious microorganisms, intra-cellular bacteria, noninfective endocarditis

1. Introduction

Blood culture-negative IE (BCNIE) refers to infective endocarditis (IE) in which no causative microorganism can be grown using the usual blood culture methods. BCNIE accounts for 5–10% of all cases of endocarditis [1]. This variation is caused by differences in the diagnostic criteria and sampling strategies used. A European study included 820 cases indicated 20% of

patients with confirmed IE had negative blood cultures [2]. BCNIE often produces considerable diagnostic and therapeutic dilemmas, which result in poor prognosis.

2. Main etiologies of BCNIE

There are three main causes for BCNIE.

1. Administration to antimicrobial agents before blood culture.
2. Endocarditis related to fastidious microorganisms in which prolonged incubation is necessary.
3. True blood culture-negative endocarditis, due to intra-cellular bacteria that cannot be detected by currently available routine blood culture system.

If all microbiological assays are negative, noninfective endocarditis is considered, and systematically differential diagnosis should be performed. Nonbacterial thrombotic endocarditis (marantic endocarditis) in patients with malignant tumor and systemic diseases such as SLE and Behçet are two main causes of noninfective endocarditis.

3. Diagnostic approach

Definitions of the terms used in the European Society of Cardiology 2015 [4] modified criteria adapted from modified Duke Criteria [3] were shown in **Table 1**. Diagnosis of IE is drawn as follows:

3.1. Definition

Pathological criteria: Microorganisms demonstrated by culture or on histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or pathological lesions; vegetation or intracardiac abscess by histological examination showing active endocarditis.

Clinical criteria: two major criteria; or one major criterion and three minor criteria or five minor criteria.

Possible IE: One major criterion and one minor criterion or three minor criteria.

Rejected IE: Firm alternate diagnosis; or Resolution of symptoms suggesting IE with antibiotic therapy for ≤4 days; or No pathological evidence of IE at surgery or autopsy, with antibiotic therapy for ≤4 days; or Does not meet criteria for possible IE, as above.

When blood culture is negative, systematic diagnostic approach should be performed for rapid and correct management of BCNIE. Diagnostic work-up in blood culture-negative endocarditis is shown in **Figure 1** [1, 4].

Major criteria

1. Blood cultures positive for IE

a. Typical microorganisms consistent with IE from two separate blood cultures

**Streptococcus viridance*, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus*

*Community-acquired enterococci, in the absence of a primary focus

b. Microorganisms consistent with IE from persistently positive blood cultures defined as follows

*>2 positive blood cultures of blood samples drawn >12 h part; or

*All of 3 or a majority of >4 separate cultures of blood (with first and last samples (drawn>1 h apart)

c. Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titer>1:800

2. Imaging positive for IE

a. Echocardiogram positive for IE: vegetation, abcess, pseudoaneurysm, intracardiac fistula, valvular perforation or aneurysma, new partial dehiscence of prosthetic valve

b. Abnormal activity around the site of prosthetic valve implantation detected by 18F-FDG PET/CT (only if the prosthesis was implanted for 3 months) or radiolabeled leukocytes SPECT/CT.

c. Definite paravalvular lesion by cardiac CT.

Minor criteria

1. Predisposition such as predisposing heart condition, or injection drug use.

2. Fever defined as temperature > 38°C

3. Valvular phenomena (including those detected by imaging only) major arterial emboli, septic pulmonary infarcts, infectious (mycotic) aneurysm, intracranial hemorrhages, conjunctival hemorrhages and Janeway's lesions.

4. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE

CT, computed tomography; FDG, fluorodeoxyglucose; HACEK, Haemophilus parainfluenzae, H. aphrophilus, H. paraphrophilus, H. influenzae, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae, and K. denitrificans; IE, infective endocarditis; Ig, immunoglobulin; PET, positron emission tomography; SPECT, single photon emission computerized tomography.

Table 1. Definitions of the terms used in the European Society of Cardiology 2015 modified criteria adapted from modified Duke criteria.

3.2. Past history and clinical examination

A precise interview about epidemiological factors, history of prior infections, exposure to antimicrobials, should be made in all patients with suspected BCNIE [1, 4].

Previous exposure to antibiotics is the most common cause of BCNE, and even a short course of antibiotics can cause long-lasting suppression of bacterial activity. A history of animal exposures may predispose to certain microbiologic etiologies. Immunosuppression or prolonged antibiotic therapy suggests endocarditis due to fungi. The epidemiological clues for defining the etiology of BCNIE are shown in **Table 2** [1].

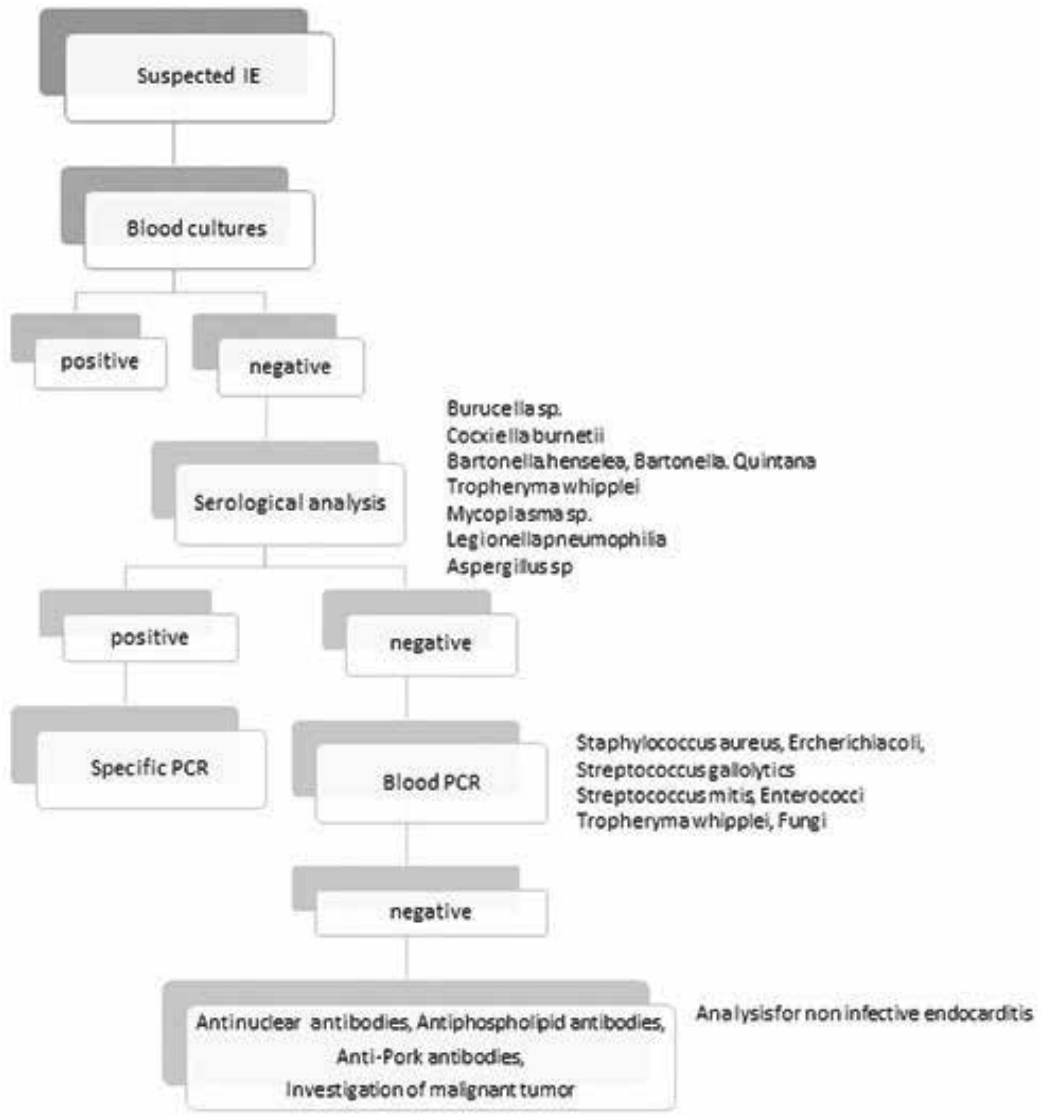

Figure 1. Diagnostic workup in blood culture-negative endocarditis.

3.3. Blood culture

BCNIE occurs frequently (45–60%) by common and easily grown staphylococci or streptococci in patients with preceding administration of antibiotics as it reduces the recovery rate of bacteria by 35–40% [5, 6]. In these cases, withdrawing antibiotics and repeating blood cultures are preferable methods to diagnose if the patient status allowed. The use of specific blood culture bottles for fastidious microorganisms is not recommended recently [1, 4, 5]. The extended incubation is applied only when cultures remain sterile after 48–72 h. Sophisticated automated systems allow isolating most pathogens that can grow slowly including Candida sp., deficient streptococci and HACEK group bacteria(Haemophilus, Aggregatibacter (previously

Epidemiological feature	Suspected microorganisms
Alcoholism, Cirrhosis	*Bartonella sp., Aeromnas sp., Listeria sp.*
Burn	*S. aureus*, Aerobic Gram-negative bacilli, Fungi
Chronic skin disorders	*S. aureus*, β-hemolytic streptococci
Genitourinary disorders	Enterococcus, GroupB streptococci, aerobic Gram-negative bacilli, *Neisseria gonorrhoeae*, Listeria monocytoogenes
Intravenous drug use, cardiovascular medical devices	*S. aureus*, CNS, Aerobic Gram-negative bacilli, β-Hemolytic streptococci, Fungi
Prosthetic valve replacement	Early(<1y): CNS, *S. aureus*, Aerobic Gram-negative bacilli, Fungi, *Corynebacterium sp., Legionella sp.*, Late(>1y): CNS, *S. aureus*, Viridance *Streptcoccus sp.*, Enterococcus sp., Fungi, Corynebacterium
Exposure to dog and/or cat	*Bartonella sp.,Pasteurella sp.*
Contact with contaminated milk or farm animal	*Brucella sp.*, Cociella bumetii
Homeless, body lice	*Bartonella sp.*
Gastrointestinal lesions	*S. gallolytics* (bovis), *Enterococcus sp.*, Clostridium spectrum
Dog or cat exposure	*Bartonella sp., Pasteurella sp., Capnocytophaga sp.*
Homeless, body lice	*Bartonella sp.*
Contact with contaminated milk or infected farm animals	*Brucella sp., Coxiella bumetii, Erysipelothrix sp.*
Diabetes mellitus	*S. aureus*, β-Hemolytic streptococci, *S. pneumoniae*
AIDS	*Salmonella sp., S. pneumoniae, S. aureus*
Organ transplantation	*S. aureus, Aspergillus fumigatus, Enterococcus sp., Candida sp.*

Table 2. Epidemiological clues for defining the etiology of blood culture-negative infective endocarditis *S. aureus*, *Staphylococcus aureus*; CNS, coagulase -negative staphylococci; *S. gallolytics*, *Streptococcus gallolyticus*; *Streptococcus pneumonie*.

Actinobacillus), Cardiobacterium, Eikenella, Kingella). Extending culture beyond 5 days is not contributive [1, 4–8]. The popular pathogens such as staphylococci, streptococci and enterococci are usually identified within 48 h. The European guidelines recommend that clinicians require prolonged incubation of vials only in the rare cases of cultures remaining negative at 48–72 h and if the diagnosis of IE remains plausible [4, 8].

3.4. Serology

The list of serological tests to be performed in case of blood culture-negative endocarditis used to include: *Legionella pneumophila*, *Mycoplasma hominis*, *Chlamydophila pneumoniae*, Brucella sp., *Coxiella burnetii* (*C. burnetii*), and Bartonella sp. Two major series showed that only Bartonella sp. and *C. burnetii* serological tests are contributive: 348 cases of suspected BCNIE were investigated between 1983 and 2001, the diagnosis was documented by serological tests in 268 cases (77%),

including 266 cases of *C. burnetii* (n = 167) or Bartonella sp. (n = 99) [5]. The same team reported a second series of 745 patients presenting with suspected BCNIE having received a panel of serological tests between 2001 and 2009. They documented the predominance of Q fever and Bartonellosis. A total of 354 of the 356 cases documented by serological tests were positive for *C. burnetii* (n = 274) or Bartonella sp. (n = 80) [6]. In other words, if only Bartonella sp. and *C. burnetii* serological tests had been used, only 4 out of 624 diagnoses obtained by serological tests would have been missed. A review of endocarditis caused by fastidious pathogens shows that Mycoplasma sp. endocarditis is very rare (<10 reliable observations published to date, mostly due to M. hominis), as well as Legionella sp. endocarditis [7]. Moreover, most cases of endocarditis supposedly due to Chlamydophila sp. are probably cross-reactions with a Bartonella sp. In 2015, the only routinely recommended serological tests in case of negative blood cultures are tests for Q fever and Bartonellosis [4]. Brucellosis serological tests can be added in case of risk factors (living in endemic areas, occupational exposure, consumption of nonpasteurized dairy products). Serological tests for Mycoplasma sp. and Legionella sp. are still recommended in the 2015 ESC guidelines [4].

3.5. Evaluation of valve tissue

The more frequent use of valve replacement in the acute phase of infective endocarditis and the advent of molecular biology techniques have revolutionized the diagnosis of blood culture-negative endocarditis:

PCR systems based on universal bacterial 16S ribosomal RNA have demonstrated excellent sensitivity and specificity [8, 9], as well as PCR targeting bacteria specifically responsible for endocarditis with negative blood culture: Bartonella sp., *C. burnetii* [10] and *Tropheryma whipplei* (*T. whipplei*) [11].

Moreover, the microscopic examination of valves after Gram staining, and cultures on appropriate media provide important information not only for the identification of the pathogen involved when the data were not available preoperatively [12], but also information on its viability at the time of valve replacement, which will impact the duration of post-replacement treatment [11, 13]. The histological analysis of valves is not contributive to diagnose except some rare diagnoses such as porcine bioprosthesis endocarditis mediated by allergy to porcine proteins [22, 23]. Summary of diagnostic procedure of rare pathogens of BCNIE is shown in **Table 3**.

Pathogen	Diagnostic procedures
Brucella sp.	blood cultures, serology, immunohistology, PCR of surgical materials
Coxiella burnetii	serology (IgG phaseI >1:800, tissue culture, immunohistology, PCR of surgical materials
Bartonella sp.	blood cultures, serology, culture, immunohistology, PCR of surgical materials
Tropheryma whippplei	hystology and PCR of surgical materials
Mycoplasma sp.	serology, culture, immunohistology, PCR of surgical materials
Legionella sp.	blood cultures, serology, culture, immunohistology, PCR of surgical materials
Fungi	blood cultures, serology, immunohistology, PCR of surgical materials

Table 3. Summary of diagnostic procedure of rare pathogens of blood culture-negative infective endocarditis.

4. Treatment

4.1. Empirical therapy

Selection of medical therapy for patients with BCNIE is difficult. Some of the laboratory-based diagnostic techniques to define fastidious or rare pathogens are not available in most clinical laboratories. It consumed considerable time for completion of testing if specimens are sent to a referral laboratory. Patients with BCNIE are often treated empirically for the more common bacterial causes of IE during the waiting time. There is a need to provide empirical antimicrobials for all likely pathogens, though certain therapeutic agents, including aminoglycosides, have potentially toxic effects. Consultation with an ID specialist to define the most appropriate choice of therapy is recommended. Once additional clinical and laboratory data were brought, initial empirical therapy should be changed to more specific treatment. For patients with acute (days) clinical presentations of native valve infection, coverage for S aureus, β-hemolytic streptococci, and aerobic Gram-negative bacilli is reasonable. Empirical coverage could include vancomycin and cefepime as an initial regimen [1, 4, 14]. For patients with a subacute (weeks) presentation of native valve IE, empirical coverage of *S. aureus*, Viridance group streptococci (VGS), HACEK, and enterococci is reasonable. One treatment option could include vancomycin and ampicillin-sulbactam to provide some coverage for these organisms [1, 4, 14]. For patients with culture-negative prosthetic valve IE, coverage for staphylococci, enterococci, and aerobic Gram-negative bacilli is reasonable if the onset of symptoms is within 1 year of prosthetic valve placement. A regimen could include vancomycin, rifampin, gentamicin [1, 4, 14]. If symptom onset is >1 year after valve placement, then IE is more likely to be caused by staphylococci, VGS, and enterococci, and antibiotic therapy for these potential pathogens is reasonable [1, 4, 14]. One initial treatment option could include vancomycin and ceftriaxone. If subsequent blood culture results or other laboratory methodologies define a pathogen, then empirical therapy should be changed to focused therapy that is recommended for the specific pathogen identified.

4.2. Antibiotic treatment for fastidious microorganisms

HACEK Gram-negative bacilli are fastidious organisms, and the laboratory should be made aware that infection with these agents needs consultation to specialist. Because of slow growth, standard MIC tests may be difficult to interpret. Some HACEK-group bacilli produce beta-lactamases, and ampicillin is therefore no longer the first-line option. They are susceptible to ceftriaxone, other third-generation cephalosporins and quinolones; the standard treatment is ceftriaxone 2 g/day for 4 weeks in native valve endocarditis and for 6 weeks in prosthetic valve endocarditis. If they do not produce beta-lactamase, ampicillin (12 g/day i.v. in four or six doses) plus gentamicin (3 mg/kg/day) divided into two or three doses for 4–6 weeks is an option [1, 4, 13]. Ciprofloxacin (400 mg/8–12 h i.v. or 750 mg/12 h orally) is a less well-validated alternative. Clinical outcome of HACEK endocarditis is favorable.

In cases with fungi, mortality is very high, and treatment necessitates combined antifungal administration and surgical valve replacement. Antifungal therapy for Candida sp. includes liposomal amphotericin B with or without flucytosine or an echinocandin at high doses; and for Aspergillus spp., voriconazole is the drug of choice and some experts recommend the addition

of an echinocandin or amphotericin B. Suppressive long-term treatment with oral azoles (fluconazole for Candida and voriconazole for Aspergillus) is recommended [1, 4, 14]. Consultation with an infectious doctor specialist in the Endocarditis Team is recommended.

4.3. Specific therapy for true culture-negative microorganisms

The recommended therapy for true culture-negative microorganisms in the European guidelines 2015 is shown in **Table 4** [4, 12]. Consultation with ID specialist is highly recommended for the treatment of these special organisms. This is an area with a very limited level of evidence. The treatment of *T. whipplei* endocarditis has not been standardized. Doxycycline + hydroxychloroquine for 12–18 months, with monitoring of plasma levels of these two agents (objective: achieving plasma concentrations of 0.8–1.2 mg/L for hydroxychloroquine, and < 5 mg/L for doxycycline), and of negativation of samples initially positive for *T. whipplei* was proposed. The treatment of Bartonella sp. endocarditis is a beta-lactam antibiotic (amoxicillin or ceftriaxone) or doxycycline for 4 weeks in combination with gentamicin for the first 2 weeks [1, 4, 14] the treatment of *C. burnetii* endocarditis, is doxycycline + hydroxychloroquine until a phase1 antibody rate <800 is reached for IgG, and <50 for IgM and IgA [1, 4, 14].

4.4. Surgical treatment of blood culture-negative IE

There is no specific recommendation for surgical treatment of BCNIE: cardiac surgery indications rely on the same criteria that apply for any type of endocarditis (heart failure, uncontrolled infection, risk of embolism [1, 4, 15]). However, an additional argument for the surgical treatment of BCNIE is the ability to harvest valve tissue, which often finally allows microbiological documentation.

Pathogens	Standard therapy	Treatment outcome
Brucella sp.	Doxycycline (200 mg/day) + contrimocazole (960 mg/12 h) + rifampicine (300~600 mg/day for ≥3~6 months orally	Treatment success defined as IgG < 1:60
Bartonella sp.	Doxycycline (100 mg/12 h) orally for 4 weeks + gentamicin (3 mg/day) iv for 2 weeks	Success rate > 90%
Coxiella.burnetii (Q fever)	Doxycycline (200 mg/day) + hydroxychloroquine (200–600 mg/day) orally for ≥18 months	Treatment success defined as phase I IgG < 1:200 IgM, IgA < 1:50
Legionella sp.	Levofloxacin (500 mg/12 h) iv or orally for ≥6 weeks or clarithromycin (500 mg/12 h) iv for 2 weeks, then orally for 4 weeks + rifampin (300–1200 mg/24 h)	Optimal treatment unknown
Mycoplasma sp.	Levofloxacin (500 mg/12 h) iv or orally for ≥6 weeks	Optimal treatment unknown
Treaponema whipplei (Whipple's disease)	Doxycycline (200 mg/day) + hydroxychloroquine (200–600 mg/day) orally for ≥18 months	Long-term treatment, optical duration unknown

Table 4. Recommended therapy for true culture-negative microorganisms in the European guidelines 2015.

5. Noninfective endocarditis

When all microbiological assays are negative, the diagnosis of noninfectious endocarditis should systematically be considered (**Figure 1**).

5.1. Nonbacterial thrombotic endocarditis

Nonbacterial thrombotic endocarditis (marantic endocarditis, Trousseau syndrome) is observed in 1.2% of patients with active cancer at autopsy [16]. Usually, the single or multiple small vegetation-like lesions are observed predominantly on the mitral and aortic valves with no underlying valve diseases. These are associated with an underlying hypercoagulable state that justifies routine anticoagulation. Control of pathologically altered coagulation mechanism is essential for the treatment and the prognosis is poor without resolving the problem. The differential diagnosis with an infectious cause of BCNIE is often difficult, and the prognosis is poor [17]. The initial lesion is usually breast, lung, prostate, ovarian or colon cancer. However, it should not be forgotten that undiagnosed infective endocarditis is also common in cancer patients with sterile blood cultures and/or fastidious organisms that are difficult to identify by conventional methods.

5.2. Systemic diseases

Inflammatory diseases can cause endocarditis and produce a syndrome similar to culture-negative IE. Perhaps the one most often encounter is antiphospholipid antibody (APA) syndrome [18], which has been described as both a primary and a secondary syndrome of systemic lupus erythematosus(SLE) and malignancies. Sterile valvular vegetations form and often embolize, clinically mimicking in many respects with IE. The mitral valve is most often affected, and valvular regurgitation is the frequent functional abnormality. To complicate matters, the APA syndrome may also develop secondary to IE [19].

In patients with SLE, valve abnormalities are common (15–75% of autopsy series, depending on the severity of the disease), but rarely progress to a clinical stage of Libman-Sacks endocarditis [20]. The patients are usually young individuals with a very severe lupus poorly controlled by treatments. Immunological manifestations (Osler nodes) and embolism (stroke, often in combination with an antiphospholipid syndrome) may be observed. Valve lesions are mainly found in the left heart. Endocardium involvement may occur in Behçet's disease [21]. It is a disease of young ± male patients with a predominantly aortic involvement. Endocardium involvement in Behçet's disease is a poor prognostic factor. The treatment is of course should be targeted on the systemic disease (immune-suppressants, immune-modulators) with lifelong curative anticoagulation. Checkup for antinuclear antibodies as well as antiphospholipid antibody {anticardiolipin antibodies [immunoglobulin (Ig) G and anti-b2-glycoprotein 1 antibodies [IgG and IgM]} should be performed for the patients who are suspected to have noninfective endocarditis.

5.3. Allergy for porcine valve

When the patient has a porcine bioprosthesis implanted during last 6 months, anti-pork antibodies should be sought [22, 23] to consider allergy for the valve.

6. Conclusion

Blood culture-negative endocarditis is still a clinical challenge with heterogeneous pathology. Remarkable progress has been made in methodologies to evaluate the main etiologies in past two decades. Team approach including cardiologists, infectious disease specialists, microbiologists and immunologist is crucial for the correct diagnosis that is able to reach rapidly the new diagnostic microbiological techniques, and high-quality epidemiological information.

Conflict of interest

There is no conflict of interest for the theme.

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Chapter 5

Prediction of Embolic Events in Infective Endocarditis Using Echocardiography

Luminita Iliuta

Additional information is available at the end of the chapter

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Abstract

Aim: Defining the echographic parameters which can help in identifying the high-risk groups for embolic events (EE) in patients with infective endocarditis (IE). ***Material and method:*** 236 patients with IE followed up 3 years with ECO parameters measured on the vegetations (VEG). ***Results:*** (1) the incidence rate of the EE was 51.27% without any significant differences for EE occurrence from the point of view of clinical parameters. (2) There was a significant correlation between the embolia occurrence and IE with staphylococcus, IE of the right heart, the length and mobility of VEG. The only independent predictors for EE were: the maximum length >15 mm and the increased mobility of VEG with the maximal angle >60.7. (3) In 23.14% of the patients with big and very mobile, EE occurred after starting the antibiotic treatment. ***Conclusions:*** (1) the VEG dimension and mobility determined by TEE are important predictors for the prognostic and are correlated with the embolic risk. (2) Significant ECO predictors of the EE occurrence were: VEG length >15 mm, neck/thickness ratio >0.69, and maximal angle of displacement of VEG in the cardiac cycle >60.7. (3) During the antibiotic treatment, the embolic risk depends only on VEG mobility and dimension.

Keywords: infective endocarditis, transesophageal echocardiography, embolic events, echocardiography, vegetation

1. Introduction

In general population, the infective endocarditis incidence has been estimated between 2 and 6 cases per 100,000 patient years, but it is significantly higher in patients with valvular heart disease and those with intravenous drug abuse. In 22–50% of cases of IE occurs systemic embolization [1–4] and up to 65% of EEs involves the central nervous system which

are associated with a higher mortality rate. The incidence of embolic complications is higher in IE located on aortic and mitral valve and in IE due to *Staphylococcus aureus*, Candida species, HACEK and Abiotrophia organisms. The highest rate of embolic events is seen within the first 2–4 weeks of antimicrobial therapy [5], and it drops dramatically during the first 2 weeks of successful antibiotic therapy, from 13 to <1.2 embolic events per 1000 patient-days. Prediction of individual patient risk for embolization has proven extremely difficult. Echocardiography is the main investigation used in a lot of studies to identify a high-risk subset of patients with IE who might benefit from early surgery in order to avoid embolization. Higher embolic rates revealed by several studies using transthoracic echocardiography (TTE) and TEE were seen with the increase of the VEG dimensions [6]. Vegetation mobility has not been shown to be an independent risk factor for embolic events, probably because it is strongly correlated with VEG size [5]. In other studies, the embolic complications were by the infecting organism and the number of VEG, the number of valves involved and VEG characteristics.

That is why the first objective of our study was to identify the echographic parameters which were associated with the presence of an EE in patients with IE. Using these variables we tried to define the echographic parameters which can help in defining the high-risk groups for EE in IE patients and to evaluate the real value of the TEE for the EE prediction in these patients. Finally, we examined the relationship between the incidence of an EE occurrence during the antibiotic treatment and the type of antibiotherapy and the echographic predictors for a new EE during antibiotherapy.

2. Materials and method

A prospective study was performed on 236 consecutive patients diagnosed with IE according to Duke criteria [7] in our institute. The study protocol was approved by the institute management and Ethics Committee. All patients included in the trial gave written, informed consent. The study was in accordance with the Declaration of Helsinki regarding the human rights. The follow-up period was extended 3 years after randomization or until cardiac surgery whatever occurred the first and included clinical and echocardiographic examination for each visit.

The study protocol was completed with demographic data, the clinical status of the patient, VEG echographic parameters, EE occurrence, the antibiotic treatment efficacity and duration. The main echographic parameters measured on the VEG were: the maximum length (L), the maximum (tmax) and minimum (tmin) thickness, the narrowest diameter, the presence of the neck and its dimensions (lneck) and the mobility defined as the angle of displacement of long axis of vegetation throughout the cardiac cycle (**Figure 1**). The data base was done using Visual Fox Pro program.

The main prediction variables used were: NYHA class for heart failure, Duke criteria used for IE diagnosis (fever, new regurgitation murmur, blood cultures, inflammatory tests,

leukocytosis, anemia), type of IE (on native valve or prosthetic) and the type of the surgical intervention. The main outcome variables were: the presence and the type of EE, death occurrence and its causes.

The characteristics of the studied group were as follows:

- 58% male, the mean age was 47.8 ± 6 years;
- 77.12% of the patients were in NYHA class III;
- 86.96% of the patients had fever >38°C;
- a significant regurgitation murmur was present on 56.78% patients;
- 69.91% of the patients presented positive blood cultures (24.58% with *Staphylococcus aureus*);
- 38.14% of the patients presented anemia;
- 2.12% of the patients had prosthesis endocarditis;
- cardiac surgery was performed on 96.16% patients.

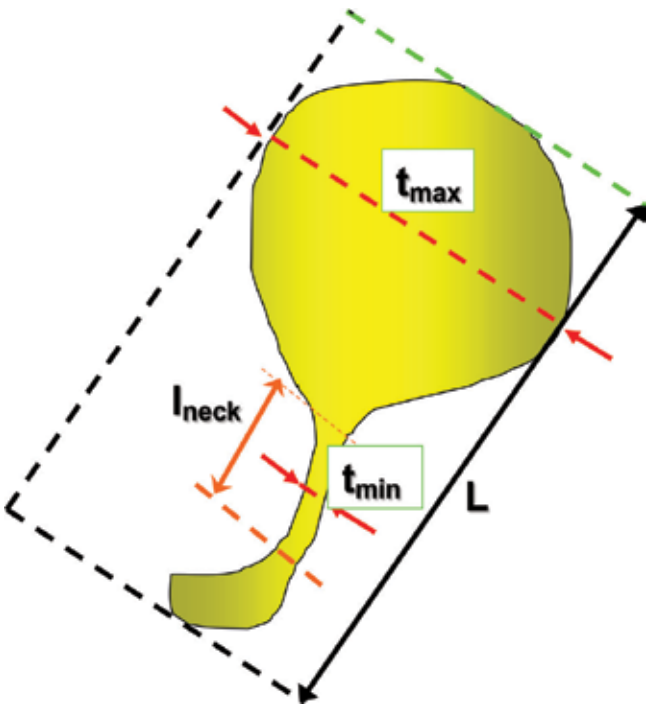

Figure 1. The echographic parameters measured on the vegetations.

The data collected represented the fields of a database in the Visual Fox Pro program. Data were processed using the Excel, Epi Info, Systat and SPSS programs for measurement of the power association between the prediction and outcome variables using the following tests:

a. for qualitative variables CHI square test or Fischer exact test (if expected cell size was less than 5)

b. for quantitative variables: T test (Student test), ANOVA test or U test depending on the samples volumes and Kruskal Wallis nonparametric tests.

The main methods of statistical correlation used in the study were the following:

- For quantitative variables analysis of simple linear and multivariate regression and correlation coefficient calculation;
- Relative risk calculation and the 95% confidence interval;
- Calculation of the positive and negative predictive value.

No sample size assumptions have been made. No confirmatory statistical hypothesis was prespecified, but a detailed analysis plan was defined before the database was locked. Continuous data are expressed as mean ± SD. Discrete variables are expressed as counts (percentages).

According to the exposure level to the risk factors, data were grouped on the presence of an EE and the type of the treatment (surgical intervention or medical therapy). For each exposure level, there were introduced the number of patients with an EE (cases) and the number of patients without an EE (controls). The confounders were controlled by stratification.

Data interpretation was performed taking into account the following hypothesis:

- a relative risk >1 was considered unfavorable; for these patients, the occurrence of an EE was increased due to the presence of the group characteristic by the RR value;

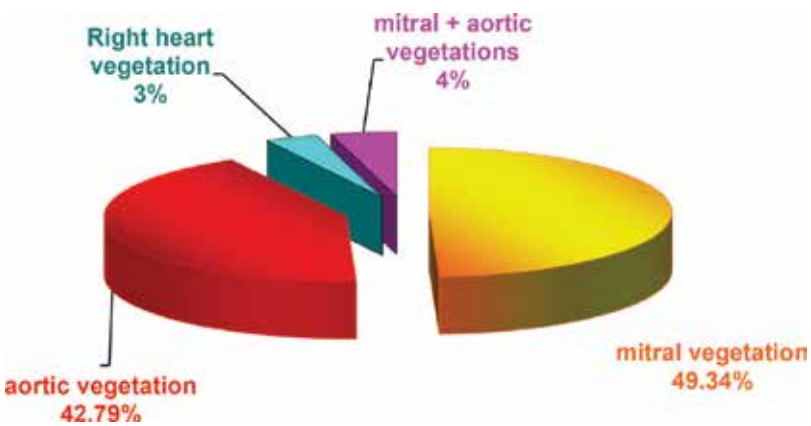

Figure 2. Patient distribution by vegetations site (229 patients).

- a relative risk = 1 included the patients subgroups classified as with no effect of the presence of group characteristic;
- a relative risk < 1 was considered favorable; for these patients, the occurrence of an EE was decreased due to the presence of the group characteristic by the RR value.

The patients were divided into two groups depending on the occurrence of the EE: group A—121 patients without an EE and group B—115 patients with an EE.

Depending on the VEG site, most of the patients (49.34%) had VEG on mitral valve, 42.79% on aortic valve, 4% both on mitral and aortic valve and 3% had right heart endocarditis (**Figure 2**).

3. Results

1. The incidence of the EE in patients with IE (diagnosed on Duke criteria) was 51.27% (121 patients). There were no significant differences for the occurrence of EE according to sex, age, fever presence, anemia, vegetation site or the presence of a significant regurgitation murmur (**Figure 3**).

2. The univariate analysis has shown a significant correlation between the EE presence and IE with staphylococcus, IE of the right heart, the length and mobility of vegetation. The only independent predictors for the EE revealed by the multivariate regression analysis were: the maximum length > 15 mm (RR = 4.92, p = 0.0001) and the increased mobility of the VEG with the maximal angle > 60.7 degree ± 12 (RR = 8.2, p = 0.003) (**Figure 4**). The univariate regression analysis has shown a significant correlation between the presence of an EE and the following parameters:

- IE with Staphylococcus ($R^2 = 0.71$, $p < 0.0001$);
- right heart IE ($R^2 = 0.43$, $p < 0.0001$);
- the maximum length of the vegetation ($R^2 = 0.921$, $p < 0.01$);
- the mobility of the vegetation ($R^2 = 0.48$, $p < 0.001$).

The multivariate regression analysis showed that the only echographic independent predictors of the EE were:

- the maximum length of the vegetation > 15 mm (RR = 4.92, p = 0.0001);
- the increased mobility of the vegetation—estimated as "the maximal angle of displacement of long axis of the vegetation throughout the cardiac cycle" more than 60.70 ± 12 (RR = 8.2, p = 0.003).

The maximum length of the VEG more than 15 mm increased the embolic risk by 4.92 times and its value between 10 mm and 15 mm by 1.84 times. Values less than 10 mm of the maximum length of the VEG turned out to be protective for EE, the associated RR being 0.92.

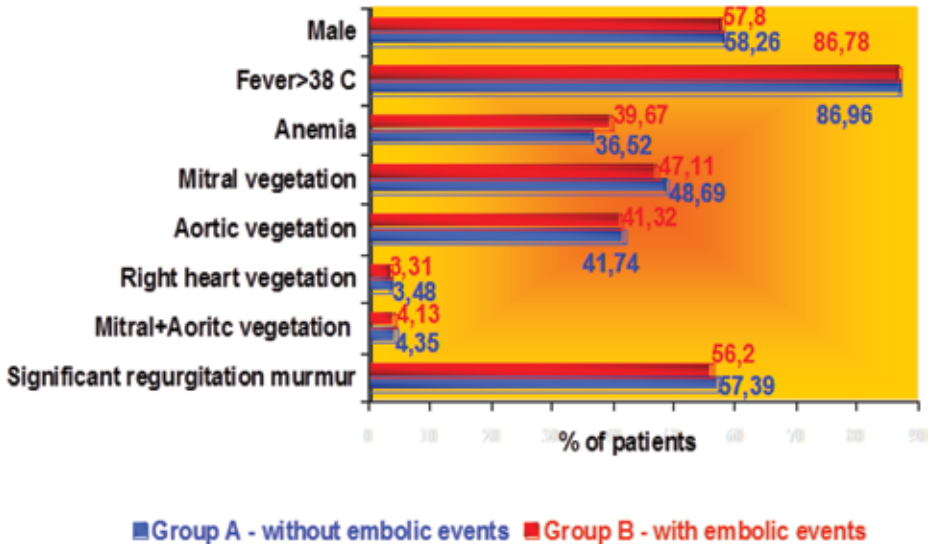

Figure 3. The occurrence of an embolic event depending on clinical parameters. Mean age: group A—48.7 ± 5 years; group B—46.9 ± 6 years.

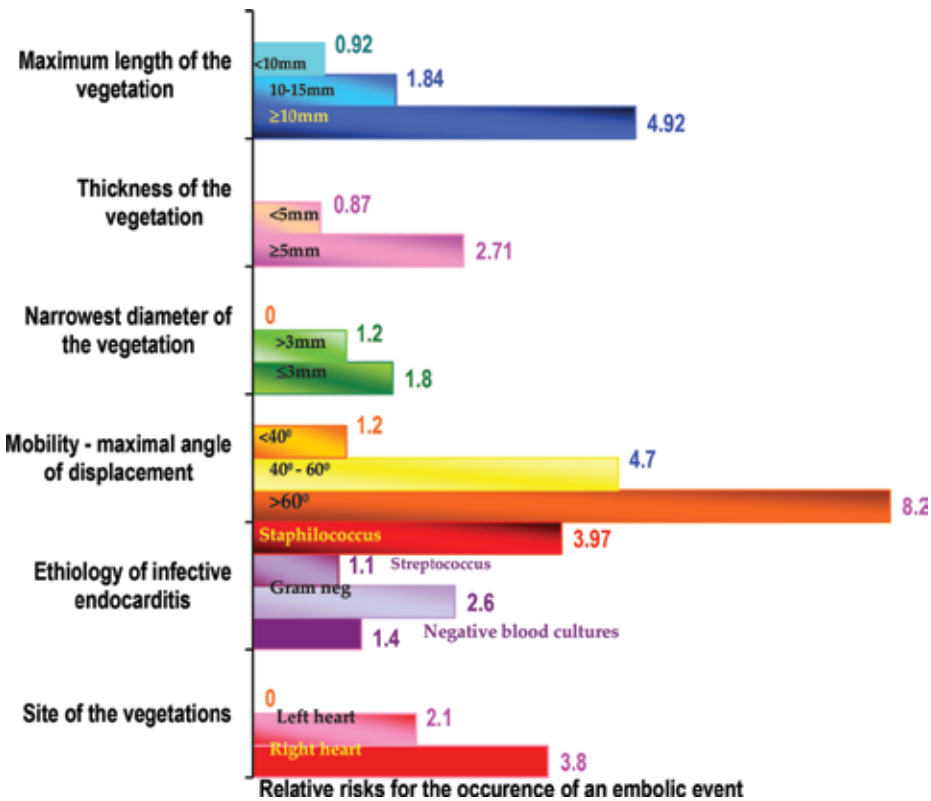

Figure 4. The relative risks for the occurrence of an EE depending on different echo parameters.

Values more than 5 mm of the maximum thickness of the VEG have increased the risk of the EE occurrence among our patients by 2.71 times. For thinner VEG, under 5 mm, the risk for EE was significantly reduced. The narrowest diameter (respectively the neck thickness—l_{neck}) less than 3 mm increased the risk for EE by 1.8 times. Regarding the mobility of the VEG, it significantly influenced the frequency of EE occurrence. Thus, the maximal angle of the VEG displacement between 400 and 600 increased by 4.7 times the risk for EE and for its values more than 600, by 8.2 times. The analysis by etiologic agent of IE showed a higher risk of EE in IE with *Staphylococcus aureus* and with Gram-negative bacteria. As other studies also showed, the likelihood of EE occurrence is higher in IE on right heart, the presence of infectious process on the tricuspid valve increasing the risk for EE by 3.8 times.

3. The differences between the patients with and without EE according to echocardiographic parameters of VEG are shown in **Table 1**.

Thus, the maximum length of the VEG was nearly twice in patients who suffered an EE compared with patients without an EE (about 12.6 mm and respectively about 6.2 mm).

In addition, the maximum thickness of the VEG measured by TEE was higher with about 3.3 mm in patients in group B. The ratio between the thickness of the VEG neck and the maximum thickness of the VEG was higher in patients without an EE (0.78 in group A respectively 0.42 in group B). In the same way, the VEG mobility (which was estimated by the measurement of the maximal angle of displacement of the vegetation was about three times bigger in patients who suffered an EE (25.1 degrees in group A and respectively 71.8 degrees in group B).

4. The rate of the EE occurred after starting the antibiotic treatment was 23.14% (28 patients) and simple linear and multivariate regression analysis found only in two independent predictors. These independent predictors for the occurrence of the EE, once antibiotic treatment has been started were the length of the VEG more than 15 mm and a high mobility of the VEG with maximal angle of displacement of long axis during the cardiac cycle >65 degrees (**Figure 5**). Thus, the maximum length of the VEG more than 15 mm increased the risk for EE occurrence by 7.1 times, the maximum width more than 5 mm increased the EE risk by 3.2 times and a neck/thickness ratio < 0.5 increased the EE risk by 3.5 times. Regarding the VEG mobility, the maximal angle of displacement values between 40 and 60 degrees increased the risk of the EE occurrence by 4.1 times and for its values >650, by 9.2 times. The IE due to a staphylococcal infection was associated with a more frequent EE occurrence, but the VEG localization on the right or left heart do not influence at the same level the EE risk as before the beginning the antibiotic treatment.

Echographic parameters	Embolic event		p value
	No	Yes	
Maximum length (mm)	6.2 ± 0.03	12.6 ± 0.04	<0.001
Maximum thickness (mm)	3.9 ± 0.01	7.2 ± 0.02	<0.003
Neck/thickness ratio	0.78 ± 0.2	0.42 ± 0.2	<0.001
Maximal angle of displacement of the vegetation	25.1 ± 10	71.8 ± 14	<0.0001

Table 1. Echographic differences between patients with IE who suffered or without EE.

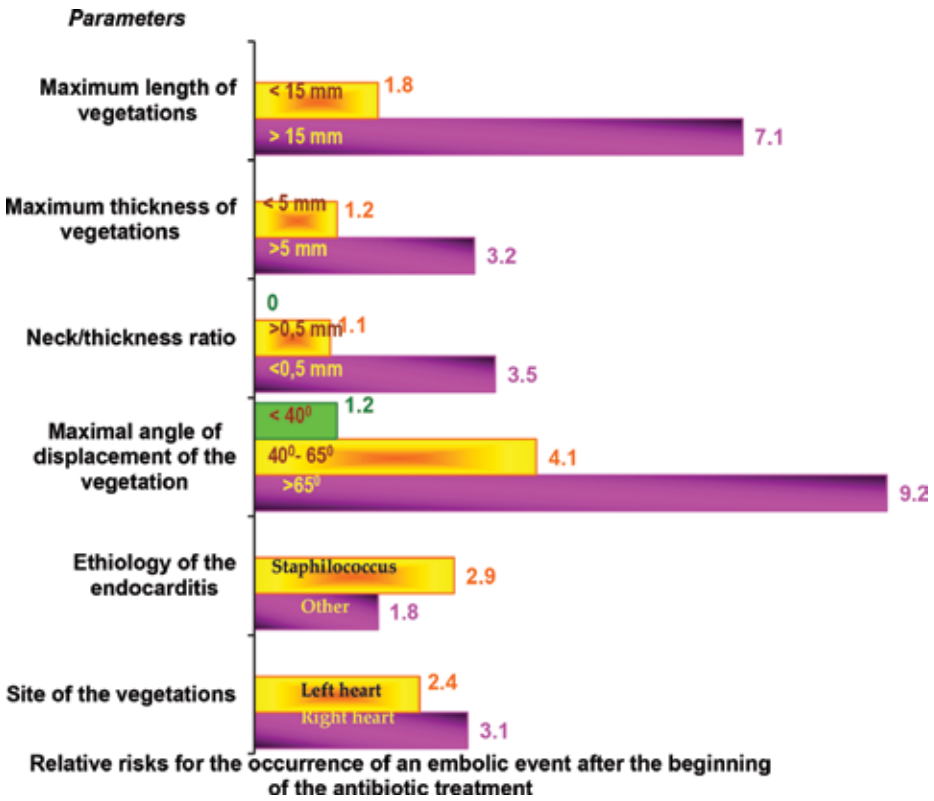

Figure 5. Correlation between clinical and echo parameters and the appearance of the embolic events after the antibiotic treatment has been started.

4. Discussions

The prediction of individual patient risk for embolization has proven extremely difficult. Many studies have attempted to use echocardiography to identify a high-risk subset of IE patients who might benefit from early surgery to avoid embolization [5, 6, 8–16]. In several studies using TTE was shown a trend toward higher embolic rates with VEG more than 1 cm in diameter located on the left heart [6]. In our study, the VEG dimension associated with a higher EE rate was about 15 mm probably because of a more precise measurement by TEE. Regarding the VEG diameter, in another study based on TEE, mitral VEG diameter more than 1 cm was associated with the highest incidence of embolism [6]. The association was strengthened when analysis was limited to those patients who had not yet experienced a clinical EE. Among such patients, the predictive accuracy for embolism with large mitral VEG was nearly 100% and in our study that value was about 94%. Mugge et al. had found particularly for patients with mitral valve IE, a VEG diameter greater than 10 mm was highly sensitive in identifying patients at risk for EE. On the other hand, VEG size was not significantly different in patients with and without severe heart failure

or in patients surviving or dying during acute IE. In addition, no significant correlation was found between VEG size and IE location or type of infective organism. VEG with a maximal diameter of >10 mm were associated with a 50% incidence of EE, compared with a 42% incidence of emboli in patients with VEG measuring less or equal to 10 mm. Inter observer variability was higher with respect to vegetation shape, mobility, and attachment characteristics. Echocardiographic VEG characteristics were not helpful in defining the risk of embolic complications in patients with IE [5].

Heinle et al. found that patients with a maximum VEG diameter > 10 mm had a significantly higher incidence of EE than those with < or = 10 mm ($p < 0.05$). There were no significant differences in the frequency of emergent valve replacement between patients with aortic value and mitral valve IE. The maximum size and total score reflecting mobility, extent and consistency of VEG using two-dimensional echocardiography provide useful information to predict the occurrence of EE in patients with IE [6].

Another prospective TEE study, however, found no clear correlation of VEG size with embolization, and transthoracic and TEE characteristics of VEG were not helpful in defining embolic risk in patients with IE [8].

De Castro used multivariate analysis and identified echocardiographic accessible risk factors for subsequent embolism a VEG size of more than 10 mm and mitral valve involvement [8]. Risk factors associated with in-hospital increased mortality rate were embolism, a vegetation size of more than 10 mm, and *Staphylococcus aureus* IE. Also, precise echocardiographic visualization of VEG helps to stratify patients into a high-risk sub-group, needing early prophylactic surgical intervention.

Overall, these data are compatible with previous observations that in general, mitral VEG, regardless their size, are associated with higher rates of embolization (25%) than aortic VEG (10%) [10]. On the other hand, the highest embolic rate (37%) has been seen in the subset of patients with mitral VEG attached to the anterior rather than the posterior mitral leaflet. In particular, mobile VEG attached to the mitral valve with a maximal diameter > 10 mm may be prone to EE [10]. In a retrospective study, Deprele et al. analyzed the risk factors for systemic emboli in IE [13]. They found that the risk of emboli was 57% when the VEG measured >10 mm and only 22% when it was <10 mm ($p = 0.003$). The mobility of the VEG was also a risk factor: 48% if the vegetation was mobile; and 9% if fixed ($p = 0.003$). Sex, age, pathogen, antibiotic treatment, type of valve and the number and position of the VEG were not found to be risk factors. With multivariate analysis, only mobility was identified as a risk factor.

The effect of VEG size on embolic potential was specific to the infecting organism, with large VEG independently predicting EE only in the setting of streptococcal IE [13, 17–19]. In contrast, staphylococcal or fungal IE appears to carry a high risk of embolization that is independent of the VEG size.

The evolution of VEG size revealed by TEE appears to predict EE; however an increase in VEG size revealed by TEE over 4–8 weeks of antibiotic therapy. In patients with IE and increasing VEG size, the EE rate among was twice that of patients with static or decreasing VEG size. In

addition, a second peak of late EE occurred at 15–30 weeks after diagnosis of IE, and it was associated with failure of a VEG to stabilize or diminish in size as defined by echocardiography [5, 6].

Because of the known decrease in embolic risk over the first 2 weeks of antibiotic therapy, the benefit of surgery in avoiding catastrophic embolic events is the greatest early in the course of the IE. Early surgical intervention may preclude a primary or recurrent major EE but exposes the patient to both the immediate and the life-long risks of valve replacement. That is why, the strategy for surgical intervention to avoid systemic embolization in IE still remains specific to the individual patient, benefit being the greatest in the early phase of IE when embolic rates are the highest and when other predictors of a complicated course are present (i.e., recurrent embolization, congestive heart failure aggressive, antibiotic-resistant organisms or prosthetic-valve IE). Surgical options must be considered when large VEG are detected on the mitral valve, particularly the anterior leaflet. Failure of a VEG to stabilize or diminish in size on TEE during clinically adequate therapy may also predict later EE.

5. Conclusions

1. The unfavorable prognostic in IE is predicted by the VEG dimension and mobility measured by TEE and is correlated with the EE.
2. The most important echographic predictors of the EE occurrence were: VEG length > 15 mm, neck/thickness fraction > 0.69, maximal angle of displacement of VEG throughout of the cardiac cycle > 60.7 degrees.
3. During the antibiotic treatment, the embolic risk depends only on the VEG mobility and dimension, and it does not depend on infectious agent and on the VEG site.
4. Early TEE in IE can identify the patients with high risk for an EE and who are candidates for the early surgical treatment (patients with very mobile VEG and with VEG length > 15 mm).

Conflict of interest

There is no conflict of interest.

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Section 3

Surgical Therapy

Chapter 6

Surgical Management of Mitral Valve Endocarditis

Fabian Andres Giraldo Vallejo

Additional information is available at the end of the chapter

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Abstract

Before the antibiotic era and cardiac surgery, infective endocarditis (IE) was a predominantly fatal disease. In-hospital mortality persists relatively high despite development in medical and surgical treatment. Adequate timing and surgical management of the infected valve help prevent substantially early and late mortality. The surgical approach of mitral valve endocarditis should be based on extension of the disease and annular involvement. When the valve and annulus are severely affected, the best option is to perform a complete excision and mitral valve replacement (MVR). Only if the disease is limited to the valvular tissue, mitral valve repair is the preferred surgical option.

Keywords: infective endocarditis, epidemiology of infective endocarditis, mitral valve surgery, mitral valve repair, periannular abscess

1. Introduction

The term *infective endocarditis* (IE) refers to infection of the endocardial surface of the heart. Infection may affect heart valves mainly but may occur within a septal defect, in chordae tendinae, or in the mural endocardium. Shunt infections (e.g., arteriovenous shunts, arterioarterial shunts (patent ductus arteriosus)) or coarctation of the aorta is similar in presentation to IE. The main site of cardiac involvement is on the line of closure of a valvar surface. Most affected sites are the atrial side of the atrioventricular valves or on the ventricular surface of the semilunar valves [1].

Perhaps the most convincing hypothesis for the pathogenesis of IE has been given to Rodbar in which high velocity flows from a high-pressure source form in an orifice and enter a low-pressure sink. Bacteria are deposited through *Venturi currents* beyond the orifice to form vena contracta creating mechanical erosion and deposition of platelets and thrombin [2].

Diagnostic criteria for IE were published in 1982 by von Reyn et al. (the Beth Israel Criteria), but these criteria did not include echocardiographic findings in the case definitions [3]. Including the important role of echocardiography in the evaluation of suspected IE, new case definitions and diagnostic criteria were proposed in 1994 [4], modified in 2000 and broadly used since then [5]. The usefulness of echocardiography in the diagnosis of IE is clearly known [6]; transesophageal imaging has superior sensitivity and specificity, is cost-effective, and should be done when transthoracic approach is negative and the patient has a high clinical suspicion of IE.

Even though the infected aortic valve is difficult to repair, well-known repair techniques can be applied to patients with mitral valve endocarditis. Advantages of mitral valve repair compared with replacement are well established for noninfectious mitral valve disease and include low perioperative mortality, preserved left ventricular function, no need for long-term anticoagulation, less long-term thromboembolic complications, lower risk of IE, freedom from reoperation, and improved long-term survival [7].

2. Clinical features and diagnostic criteria

Investigators at Duke University modified the terms introduced by Jones (rheumatic fever); these criteria include major and minor signs and symptoms, echocardiographic findings, iatrogenic and nosocomial factors (indwelling catheters), and history of IV drug abuse (**Table 1**) [5]. The most common clinical manifestation of IE is fever, which can be present in 95–100% of patients. Fever may present as low grade or spiking following peak of bacteremia. It is important to draw two sets of blood cultures from different sites in any patient at risk of having IE who presents with fever of unknown origin for more than 48 h. Once blood cultures have been obtained, antibiotics should be started until proper identification of causative organism [8]. When IE is confirmed by echocardiography, surgery, or autopsy, positive blood cultures are obtained in 95% of cases when two blood specimens are obtained and are positive in 98% of cases with four blood specimens [9]. However, when dealing with prosthesis valve endocarditis (PVE), a negative-culture endocarditis can rise to about 10% of cases on most surgical series [10, 11]. The diagnosis of IE should be investigated in any patient with sepsis of unknown origin or fever associated with risk factors. Sepsis can present in a variety of forms and can range from malaise to shock depending on the virulence of the pathogen and the host immune response [12, 13]. Stroke or systemic embolism can also be present as a complication of IE. Whenever a patient presents with persistent or unexplained bacteremia, the diagnosis of IE should be ruled out. *S. aureus* bacteremia is associated with IE in 25–30% of cases, and all patients should undergo echocardiography [14, 15]. Risk factors for developing IE include previous IE, a prosthetic valve or cardiac device and valvular or congenital heart disease, indwelling intravenous lines, intravenous drug use, immunosuppression, and a recent dental or surgical procedure. Popular known signs like Osler's nodes, Janeway lesions, and Roth spots are rare; their absence does not rule out infective endocarditis. Heart failure, stroke, or metastatic infection (osteomyelitis, peripheral abscess) are much more common. Routine laboratory tests are usually nonspecific. Admission electrocardiogram is useful since new disturbances may suggest paravalvular or myocardial extension of infection [16].

Definite infective endocarditis

Pathologic criteria

- Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen
- Pathologic lesions; vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis

Clinical criteria

- Two major criteria
- One major criterion and three minor criteria
- Five minor criteria

Possible infective endocarditis

- One major criterion and one minor criterion
- Three minor criteria

Rejected

- Firm alternate diagnosis explaining evidence of IE
- Resolution of IE syndrome with antibiotic therapy for ≤4 days
- No pathologic evidence of IE at surgery or autopsy, with antibiotic therapy for ≤4 days
- Does not meet criteria for possible IE, as above

Major criteria

Blood culture positive for IE

- Typical microorganisms consistent with IE from two separate blood cultures: viridans streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus*
- Community-acquired enterococci, in the absence of a primary focus
- Microorganisms consistent with IE from persistently positive blood cultures, defined as follows:
- At least two positive cultures of blood samples drawn >12 h apart
- All of three or a majority of ≥ four separate cultures of blood (with the first and last samples drawn at least 1 h apart)
- Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer >1:800

Evidence of endocardial involvement

- Echocardiogram positive for IE (TEE recommended in patients with prosthetic valves, rated at least "possible IE" by clinical criteria or complicated IE [paravalvular abscess]; TTE as first test in other patients), defined as follows:
  - 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
  - Abscess
  - New partial dehiscence of prosthetic valve
  - New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)

Minor criteria

- Predisposition, predisposing heart condition or injection drug use
- Fever, temperature > 38°C (100.4°F)
- Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
- Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor
- Microbiologic evidence: positive blood culture but does not meet a major criterion as noted above* or serologic evidence of active infection with organism consistent with IE
- Echocardiographic minor criteria eliminated

HACEK, *Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* spp.; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography
Modified from Li et al. [5].

Table 1. Definition of infective endocarditis (IE) according to modified Duke criteria.

Diagnosis of IE includes the sum of clinical findings, microbiological analysis, and imaging results. A definite diagnosis includes two major modified Duke criteria, one major plus three minor and five minor criteria [5]. Alternatively the diagnosis can be made by specimen culture or histology (obtained by surgery or autopsy) of the vegetation or abscess. The physicist must note that Duke criteria were devised to help in the diagnosis but never to replace the clinical judgment [17].

Infection of the mitral valve and its supporting structures is less frequent than aortic valve endocarditis but may be more indolent in its course. When *S. aureus* is the infecting organism, the mitral valve is more frequently involved (± 40% of cases) followed by the aortic valve in 36% of cases [18]. Echocardiography plays a major role in diagnosis and detection of complications. A major criterion includes the presence of valvular vegetation or abscess or new dehiscence of a prosthetic valve [19]. Besides diagnostic, echocardiography also provides information on the hemodynamic status of the valve lesion and left and right ventricular function. In native valve endocarditis (NVE), transthoracic echocardiography (TTE) has a sensitivity of 75% and specificity of >90% for detection of a vegetation. Transesophageal echocardiography (TEE) has a sensitivity >90% and should be done in a patient with a negative or equivocal TTE and high clinical likelihood of infective endocarditis [19]. As for abscess, leaflet perforation or pseudoaneurysm TEE offers better detection than TTE [20, 21]. In patients with prosthetic valves, the sensitivity of TTE is lower (36–69%), and TEE is more accurate in detecting complications and cardiac device infections [22, 23].

3. Therapy

The management of patients with IE necessitates a multidisciplinary approach where cardiologists, cardiac surgeons, and infectious disease specialists are involved. There are no clinical randomized trials that guide the management decisions nor a level A evidence in international guides [8, 24].

3.1. Antibiotics

Antibiotics should be started once blood cultures have been acquired; nevertheless if the patient is stable, the physician could wait until final report is available [25]. Empirical antibiotic regimens for the native valve endocarditis and prosthetic valve endocarditis are outlined on definite guidelines by the British Society for Antimicrobial Chemotherapy (**Table 2**) [25]. Antibiotics can be modified according to culture results, local resistance patterns, virulence, and the presence or absence of prosthetic material. Because penetration of antibiotics to vegetations is difficult, prolonged parenteral antibiotic administration is advisable. Treatment for at least 4–6 weeks is usually necessary and longer for some cases (e.g., Q fever endocarditis).

3.2. Surgery

About 40–50% of patients with IE undergo surgical therapy [26, 27]. Goals of surgery are removal of infected tissue and drainage of abscess, restoration of ventriculoarterial or atrioventricular continuity, and reversion to hemodynamic stability. In children, this process may

	Empirical antibiotic regimen and dose	Comment
Native valve endocarditis—indolent presentation	Amoxicillin (2 g, every 4 h, intravenously) + gentamicin* (optional; 1 mg/kg of actual bodyweight)	Better activity than benzylpenicillin against enterococci and many HACEK bacteria; the use of gentamicin before availability of culture results is controversial
Native valve endocarditis— severe sepsis (without risk factors for multiresistant enteric Gram-negative bacilli, *Pseudomonas*)	Vancomycin* (dose as per local guidelines) + gentamicin* (1 mg/kg of ideal bodyweight, every 12 h, intravenously)	Activity against staphylococci (including meticillin-resistant *Staphylococcus aureus*)
Native valve endocarditis—severe sepsis (with risk factors for multiresistant enteric Gram-negative bacilli, *Pseudomonas*)	Vancomycin* (dose as per local guidelines) + meropenem (2 g, every 8 h, intravenously)	
Prosthetic valve endocarditis—pending blood cultures or with negative blood cultures	Vancomycin* (1 g, every 12 h, intravenously) + gentamicin* (1 mg/kg, every 12 h, intravenously) + rifampicin (300–600 mg, every 12 h, orally or intravenously)	

Adapted from Gould et al. [25].
All antibiotic doses are adjusted according to renal function. HACEK=*Haemophilus* spp., *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kinga*.
*Regular measurement of serum concentrations needed to monitor and adjust dosing.

Table 2. Empirical treatment for different clinical scenarios in patients with suspected infective endocarditis.

require repairing of the underlying malformation. Valve repair and replacement are options for reconstruction, and there is no evidence that favors a bioprosthetic valve over a mechanical valve. *Heart failure* caused by valvular obstruction or regurgitation is the most common indication for surgery. A dismal prognosis is ensued when refractory pulmonary edema or cardiogenic shock is present and no emergent surgery is done [28, 29].

There is limited evidence to guide clinical practice when the patient has well-tolerated severe valve regurgitation and postpone surgery until stabilization with antibiotics. *Complex or uncontrolled infection* is the second indication for surgery. The complications include abscess, pseudoaneurysm, fistula, or atrioventricular block. A pseudoaneurysm is a perivalvular cavity that communicates with the cardiac chambers (evidenced by Doppler color), whereas an abscess is a pus-filled perivalvular cavity that does not communicate [19]. If perivalvular infection progresses, a fistula can be created (usually aorto-cavitary) which can have a mortality as high as 41% even with surgery [30]. *Prevention of embolism* is the third indication for surgery. This complication can affect 25–50% of patients [31]. Stroke is the most common presentation, but embolism resulting in end-organ infarction (kidney, spleen, coronaries, mesentery, and limbs) can also be present. Most emboli occur in the first 2 weeks after diagnosis with risk decreasing rapidly after antibiotics are instituted [32, 33]. Embolism is more likely when the vegetation is large (>10 mm), highly mobile, and located in the mitral valve [34]. *Persistent or relapsing infection* and infection caused by antibiotic-resistant microorganisms (e.g., *S. aureus*, *S. lugdunensis*, *Pseudomonas*, fungi) are also indications for surgery [27].

Surgery for IE is done through partial or full median sternotomy. Suppurative pericarditis suggests a previous perforation at the aortic or mitral ring or ring abscess [35, 36]. It is recommended to use bicaval cannulation to facilitate the procedure in the presence of burrowing abscess, acquired septal perforation, unexpected right-sided valve involvement, or complex aortic root reconstruction. Intraoperative TEE plays a major role in diagnosis and treatment guidance. When left-sided IE is present, minimal manipulation of the heart is important to avoid migration of embolic material. Ample excision of infected tissue is performed with drainage of abscess and closure of defects [37]. When mitral endocarditis is present, aortic valve involvement should be considered. Although absence of echocardiographic anomalies in the aortic area argue against the presence of vegetations and inspection of the aortic valve is not necessary. Reconstruction on mitral valve area can be accomplished when the vegetation is healed or small and the tensor apparatus is mostly uncompromised. Usual sites of native valve endocarditis are drop lesion of anterior leaflet or leaflet vegetation and ring abscess of posterior portion (**Figure 1**). Small perforations may be closed using autologous pericardium or bovine pericardial patch, or otherwise the defect may be closed using continuous suture (**Figure 2**). Reconstruction of the mitral valve represents a challenge if major involvement of the valves is present. Most of the times, a replacement is considered; nevertheless, the risk for PVE is greater especially in ongoing positive blood cultures. If commissural areas are compromised by the infection, a sliding annuloplasty can be performed. Partial leaflet resection, pericardial patch replacement of mid-leaflet areas, or both may be used [37]. The remaining orifice size after reconstruction must be large enough (25 mm in an adult, z-score − 2 or greater in children) to prevent mitral stenosis [37]. Suture annuloplasty is preferable over prosthetic ring in active IE, but a biodegradable annuloplasty ring has been suggested by some authors [38]. In the absence of active IE (e.g., negative blood cultures, no inflammation), classical reconstruction techniques may be used for the mitral valve. Quadrangular resection of a portion of the posterior leaflet (**Figure 3**) or triangular resection of a portion of the anterior leaflet may be done, followed by the insertion

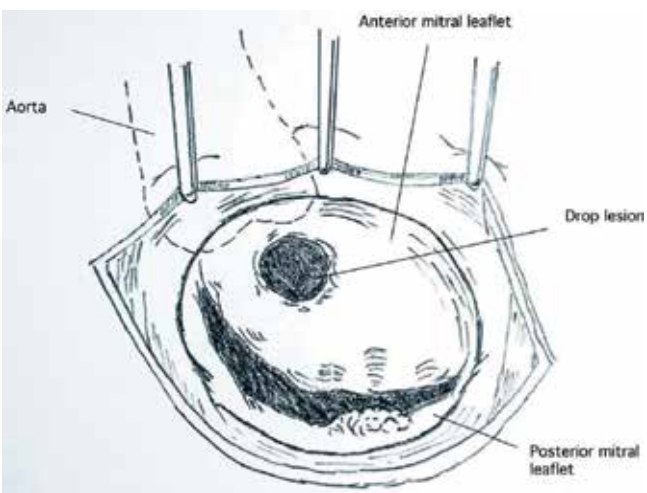

Figure 1. Drop lesion of anterior leaflet and leaflet vegetation and ring abscess of posterior leaflet.

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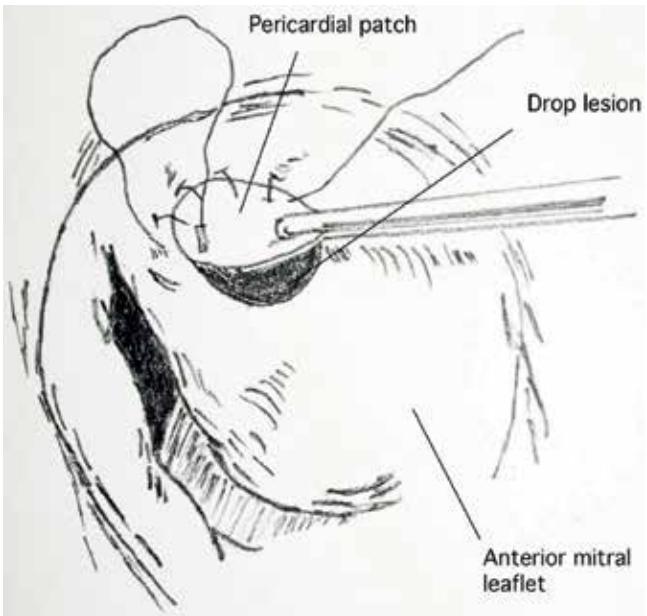

Figure 2. Pericardial patch used to close a drop lesion of the anterior leaflet.

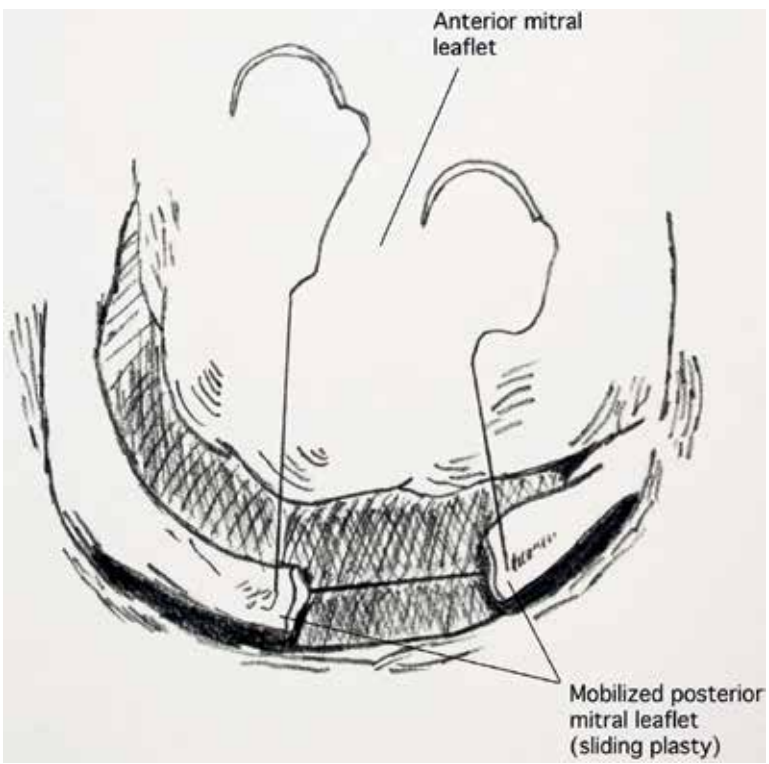

Figure 3. Limited quadrangular resection and sliding plasty of posterior leaflet.

of a partial or complete annular ring. When resecting the mitral valve, the posteroinferior zone of the mitral annulus should be inspected because myocardial ring abscess usually occurs in this location [39, 40]. When left atrioventricular discontinuity is present in mitral valve IE, a small variation of the usual valve replacement can be used. After thorough debridement of the affected tissue in the mitral ring, interrupted horizontal mattress sutures are anchored with felt or autologous pericardium pledgets to the ventricular aspect of the mitral annulus, brought up through the left atrial aspect and then through the prosthetic sewing ring. Deep bytes are performed [37]. When extensive ring abscess is present (**Figure 4**), a different approach is done. The atrioventricular discontinuity is reconstructed using an autologous or bovine pericardial patch. The ventricular aspect is anchored to the myocardium and endocardium using deep bytes of continuous 3-0 or 4-0 polypropylene suture. The superior aspect of this patch is anchored to the left atrial side with a continuous suture (**Figure 5**). The prosthesis is anchored to the ventricular aspect of the suture line using interrupted horizontal mattress sutures supported with felts pledgets (**Figure 6**) [37]. Using antibiotic, antiseptic solutions (e.g., povidone-iodine), or antifungal agents to impregnate the prosthesis and the affected area has been described to help in the management of this entity [41–43]. Mitral valve repair for IE continues to be challenging and much less commonly performed than valve replacement [44]. Repairing tissues that may be infected in the acute stages and the durability of repairing inflamed tissues are the main concerns influencing the decision [45–47]. Several studies have reported excellent results for mitral valve repair in IE [48–51].

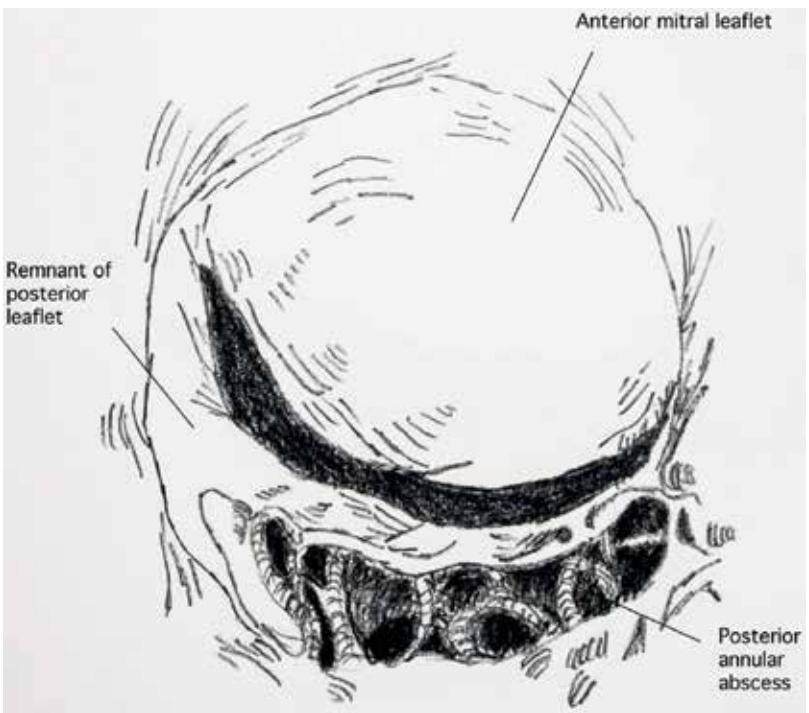

Figure 4. Infective endocarditis with ring abscess compromising the posterior leaflet of mitral valve.

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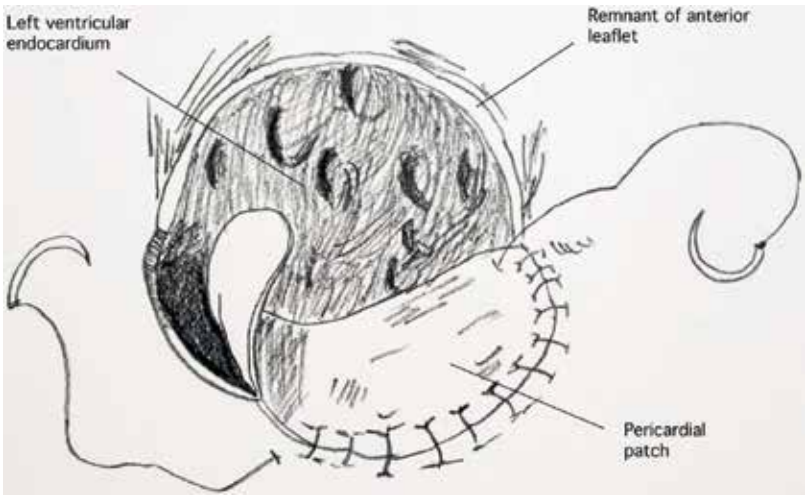

Figure 5. The defect is covered by a pericardial patch anchored within the left ventricle and extending up across the base of the posterior leaflet. Stitches then are placed to the left atrial wall.

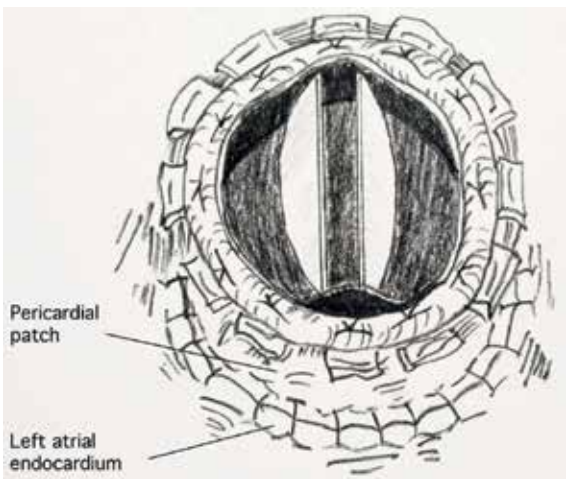

Figure 6. Prosthesis is placed in position. The posterior suture line is on the patch in this case. Eventually the prosthesis may be seated below the patch on ventricular wall.

4. Results

Hospital mortality for valve operations in patients with IE varies widely (4–30%) [52–57]. This variation can be due to several factors, especially the difference in risk between the acute phase of IE and the healed stage. A study from Richardson reported a mortality of 14% in surgically treated patients versus 44% in those medically treated. Operative mortality was affected by urgency of operation. Mortality for elective operations (next convenient day), was 5%, for urgent operations (next day), 16% and for emergent operations in patients with cardiogenic shock (immediately), 33% [58].

Freedom from reoperation is higher when the mitral valve is involved (compared with the aortic valve) probably for less annular involvement. In a series from Brigham and Women's Hospital (Boston) reporting freedom from reoperation for mitral valve IE, the results found 92 and 62% at 5 and 10 years for acute endocarditis and 94% and 84% for healed endocarditis (p = 0.7), respectively [59]. A serious complication after valve replacement for IE is a new or worsening neurologic deficit. Friable vegetation may dislodge and cause CNS deficits. Moreover, an existing CNS deficit is aggravated by operation. A study from university of Illinois found evidence of cerebral septic emboli in 42% of patients who underwent valve replacement for IE. Complications included postoperative strokes in 6%, brain abscesses in 2%, and seizures in 1% [60].

5. Indications for operation

Indications for operation are based in the hemodynamic state of the valvar lesion or defect. When active NVE is present, a lack of consensus exists about some of the specific indications for surgery [61]. General indications for operation, however, exist from both the American and European societies (**Table 3**) [8, 24]. As for timing of surgery, specific recommendations are outlined in **Table 4** [26]. However it is important to remember that no randomized controlled

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Congestive heart failure*

- Congestive heart failure caused by severe aortic or mitral regurgitation or, more rarely, by valve obstruction caused by vegetations
- Severe acute aortic or mitral regurgitation with echocardiographic signs of elevated left ventricular end-diastolic pressure or significant pulmonary hypertension
- Congestive heart failure as a result of prosthetic dehiscence or obstruction

Periannular extension

- Most patients with abscess formation or fistulous tract formation

Systemic embolism†

- Recurrent emboli despite appropriate antibiotic therapy
- Large vegetations (10 mm) after one or more clinical or silent embolic events after initiation of antibiotic therapy
- Large vegetations and other predictors of a complicated course
- Very large vegetations (15 mm) without embolic complications, especially if valve-sparing surgery is likely (remains controversial)

Cerebrovascular complications‡

- Silent neurological complication or transient ischemic attack and other surgical indications
- Ischemic stroke and other surgical indications, provided that cerebral hemorrhage has been excluded and neurological complications are not severe (e.g., coma)

Persistent sepsis

- Fever or positive blood cultures persisting for >5 to 7 days despite an appropriate antibiotic regimen, assuming that vegetations or other lesions requiring surgery persist and that extracardiac sources of sepsis have been excluded
- Relapsing IE, especially when caused by organisms other than sensitive streptococci or in patients with prosthetic valves

Difficult organisms

- *S. aureus* IE involving a prosthetic valve and most cases involving a left-sided native valve
- IE caused by other aggressive organisms (*Brucella, Staphylococcus lugdunensis*)

- IE caused by multiresistant organisms (e.g., methicillin-resistant *S. aureus* or vancomycin-resistant enterococci) and rare infections caused by Gram-negative bacteria
- *Pseudomonas aeruginosa* IE
- Fungal IE
- Q fever IE and other relative indications for intervention

Prosthetic valve endocarditis

- Virtually all cases of early prosthetic valve endocarditis
- Virtually all cases of prosthetic valve endocarditis caused by *S. aureus*
- Late prosthetic valve endocarditis with heart failure caused by prosthetic dehiscence or obstruction or other indications for surgery

[*]Surgery should be performed immediately, irrespective of antibiotic therapy, in patients with persistent pulmonary edema or cardiogenic shock. If congestive heart failure disappears with medical therapy and there are no other surgical indications, intervention can be postponed to allow a period of days or weeks of antibiotic treatment under careful clinical and echocardiographic observation. In patients with well-tolerated severe valvular regurgitation or prosthetic dehiscence and no other reasons for surgery, conservative therapy under careful clinical and echocardiographic observation is recommended with consideration of deferred surgery after resolution of the infection, depending upon tolerance of the valve lesion.
[†]In all cases, surgery for the prevention of embolism must be performed very early since embolic risk is highest during the first days of therapy.
[‡]Surgery is contraindicated for at least 1 month after intracranial hemorrhage unless neurosurgical or endovascular intervention can be performed to reduce bleeding risk.
Adapted from ACC/AHA 2014 Guidelines [8].

Table 3. Indications for surgery for infective endocarditis.

Emergency surgery (within 24 h)

- Native (aortic or mitral) or prosthetic valve endocarditis and severe congestive heart failure or cardiogenic shock caused by:
  - Acute valvular regurgitation
  - Severe prosthetic dysfunction (dehiscence or obstruction)
  - Fistula into a cardiac chamber or the pericardial space

Urgent surgery (within days)

- Native valve endocarditis with persisting congestive heart failure, signs of poor hemodynamic tolerance, or abscess
- Prosthetic valve endocarditis with persisting congestive heart failure, signs of poor hemodynamic tolerance, or abscess
- Prosthetic valve endocarditis caused by staphylococci or Gram-negative organisms
- Large vegetation (10 mm) with an embolic event
- Large vegetation (10 mm) with other predictors of a complicated course
- Very large vegetation (15 mm), especially if conservative surgery is available
- Large abscess and/or periannular involvement with uncontrolled infection

Early elective surgery (during the in-hospital stay)

- Severe aortic or mitral regurgitation with congestive heart failure and good response to medical therapy
- Prosthetic valve endocarditis with valvular dehiscence or congestive heart failure and good response to medical therapy
- Presence of abscess or periannular extension
- Persisting infection when extracardiac focus has been excluded
- Fungal or other infections resistant to medical cure

Adapted from Prendergast et al. [26].

Table 4. Timing of surgery.

trials are available to guide current practice. Among the indications for surgery in IE, operation for acute heart failure provides the greatest survival benefit [62, 63].

Infective endocarditis is a serious condition associated with significant morbidity and mortality. Adequate management requires intervention of multiple specialists. Correct and timed diagnosis and antibiotics are necessary, but an important percentage of patients still require surgery. Surgical mortality is high, but long-term results continue to improve with increased number of patient undergoing valve conserving surgery.

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Chapter 7

Surgical Treatment for Tricuspid Valve Infective Endocarditis

Takashi Murashita

Additional information is available at the end of the chapter

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Abstract

Isolated tricuspid valve infective endocarditis is relatively rare. However, the frequency of tricuspid valve infective endocarditis in the United States is rapidly increasing, mainly due to the epidemic of intravenous drug use. A medical treatment is the first choice for this disease; however, surgical intervention is required when the patients suffer from heart failure, large vegetation, or persistent bacteremia despite appropriate medical treatment. Several techniques for tricuspid valve reconstruction have been proposed, and their outcomes have been reported to be good. However, in the cases of severe valve destruction, tricuspid valve replacement is required. Post-surgical management of drug-induced infective endocarditis is challenging due to its poor compliance to medication and high rate of reinfection. There is an ethical controversy as to surgical indication for reinfection induced by relapse of drug use. In addition, because reoperation for tricuspid valve carries high risk, there is also a controversy regarding valve choice in drug users.

Keywords: tricuspid valve infective endocarditis, intravenous drug use, surgical outcomes

1. Introduction

Infective endocarditis carries high mortality and mortality. Murdoch et al. studied 2781 adults with definite infective endocarditis admitted to 58 hospitals in 25 countries [1]. They reported that surgical treatment was performed in 48%, and in-hospital mortality was 18%. Nevertheless, surgery during the current endocarditis episode was associated with decreased risk of in-hospital death (odds ratio, 0.56; 95% confidence interval, 0.44-0.69).

Tricuspid valve infective endocarditis was relatively rare and accounted for 5 to 10% of all infective endocarditis [2]. In the study of Murdoch et al. which was reported in 2009 [1], tricuspid valve infective endocarditis was found in 12% of the entire cohort. However, the frequency of tricuspid valve infective endocarditis is rapidly increasing along with the epidemic of intravenous drug use. Seratnahaei et al. reported that the incidence of tricuspid valve infective endocarditis was 6% between 1999 and 2000, and it markedly increased to 36% between 2009 and 2010 [3]. Also reported history of intravenous drug use increased from 15 to 40%.

2. Surgery for tricuspid valve infective endocarditis

2.1. Epidemiology

The key predisposing factors for tricuspid valve infective endocarditis include intravenous drug use, cardiac implantable electronic devices, long-term central venous access catheters, and congenital heart disease [4].

In the study of Murdoch et al. [1], current intravenous drug use was found in 16% of the cohort of North America, chronic intravenous access accounted was found in 25%, implantable cardiac devices accounted was found in 12%, and congenital heart disease accounted was found in 25%.

Moss et al. reported that 41% of injection drug users with bacteremia had the evidence of endocarditis [5].

Athan et al. performed a prospective cohort study which described a 6.4% incidence of cardiac device-related infective endocarditis among 2760 patients [6]. There was coexisting valve involvement in 37.3% patients and predominantly tricuspid valve infection (24.3%). Concomitant valve infection was associated with higher mortality than no valve infection (odds ratio, 3.31; 95% confidence interval, 1.71–6.39).

2.2. Indications for surgery

The most recent guidelines from the American Heart Association stated that the surgical intervention is reasonable for patients with certain complications with class IIa recommendations, and they also stated that it is reasonable to avoid surgery when possible in patients who are intravenous drug users [7]. The 2015 European Society of Cardiology guidelines for the management of infective endocarditis stated that surgery should be considered in the following situations with class IIa recommendations: [1] right heart failure secondary to severe tricuspid regurgitation with poor response to diuretic therapy, [2] infective endocarditis caused by organisms that are difficult to eradicate (e.g. persistent fungi) or bacteremia for at least 7 days despite adequate antimicrobial therapy, and [3] tricuspid valve vegetations >20 mm that persist after recurrent pulmonary emboli with or without concomitant right heart failure [8].

Hecht et al. followed the clinical course of 121 patients with right-sided infective endocarditis caused by intravenous drug use, and reported that vegetations greater than 20 mm were associated with increased mortality [9].

Kiefer et al. performed a prospective, multicenter study enrolling over 4000 patients with infective endocarditis and known heart failure status [10]. In-hospital mortality was lower in the patients undergoing valvular surgery compared with medical therapy alone (20.6 vs. 44.8%, $p < 0.001$), and 1-year mortality was also lower in patients undergoing surgery compared with medical therapy alone (29.1 vs. 58.4%, $p < 0.001$).

2.3. Timing of surgery

The early surgical intervention for left-sided infective endocarditis has been well suggested [7, 11, 12]; however, the surgical indications for right-sided infective endocarditis are not well defined.

Akinosoglou et al. suggested that the timing of surgical management depends on the following factors: [1] cause of endocarditis (e.g. urgent in pacemaker and prosthetic infective endocarditis), [2] causative infective factors (e.g. fungal and *Staphylococcus aureus*), [3] coexistent left-sided infection, [4] response to antibiotic therapy, [5] toxicity of medical treatment, and [6] complications of disease (e.g. abscess and increased vegetation size) [13].

Early surgery should be considered if the causative organism is *Staphylococcus aureus*, which often results in large vegetations, massive valve destruction, and embolic manifestations [14]. Remadi et al. reported that early surgery was associated with reduced mortality in *Staphylococcus aureus* infective endocarditis [15].

Taghavi et al. compared the outcomes between surgical management and medical treatment for tricuspid valve endocarditis [16]. They found that patients treated surgically had clear blood cultures sooner, defervesced earlier, and demonstrated a complete resolution of vegetations. They concluded that the early surgery is warranted for patients with tricuspid valve endocarditis when they are bacteremia and/or systemically infected despite optimal medical treatment.

In contrast, Gaca et al. reviewed the surgical outcomes for isolated tricuspid valve endocarditis using the Society of Thoracic Surgeons Database, and reported that patients in the healed tricuspid valve endocarditis had lower complications rates, shorter overall length of stay, and a trend toward lower operative mortality compared with active endocarditis [17].

2.4. Tricuspid valve reconstruction

Akinosoglou et al. suggested that, in intravenous drug users who run a high risk of complications, vegetectomy and valve repair, avoiding artificial materials should be considered as that can improve late survival rate [13].

Successful surgical intervention requires radical debridement of infected tissue first [4]. In case of leaflet perforation or small defects localized to one or two leaflets can be repaired by either direct closure or patch plasty using an autologous pericardial patch [18] (**Figure 1**).

In case of limited infection on the posterior leaflet, bicuspid valve formation of the tricuspid valve can be performed by excising the posterior leaflet and mobilizing the anterior and septal

leaflets [18] (**Figure 2**). Ghanta et al. reported good mid-term outcomes of suture bicuspidization of the tricuspid valve [19].

Artificial chordae using expanded polytetrafluoroethylene sutures can be applied after the resection of infected chordae [20].

Tricuspid annuloplasty is performed either with prosthetic rings or with non-prosthetic suture annuloplasty such as Kay's or De Vega's annuloplasty [13]. Although suture annuloplasty has an advantage of avoiding prosthetic materials in the setting of infection, several studies

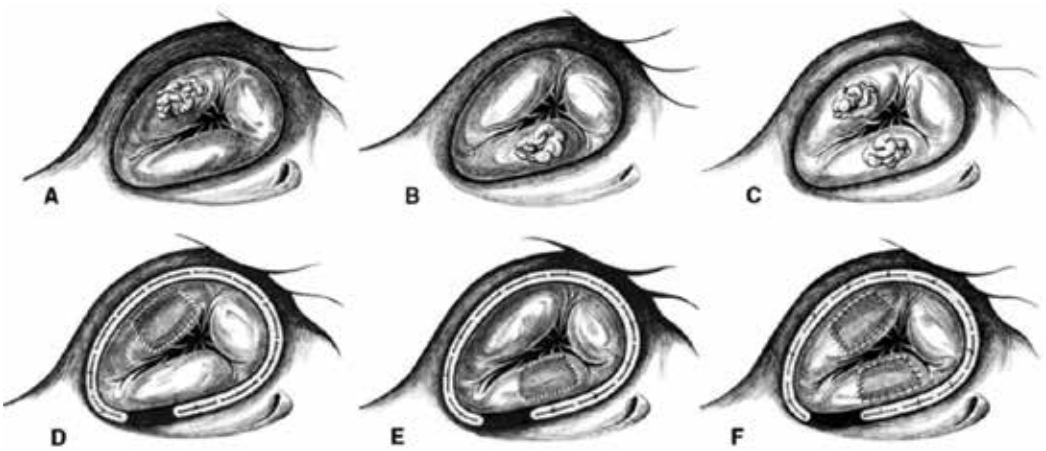

Figure 1. Endocarditic lesion on the anterior leaflet (A), the posterior leaflet (B), or on both (C), anterior and septal leaflet (D–F) after the excision of the endocarditic lesion, patch plasty, and stabilization of the valve with a tricuspid annuloplasty ring.

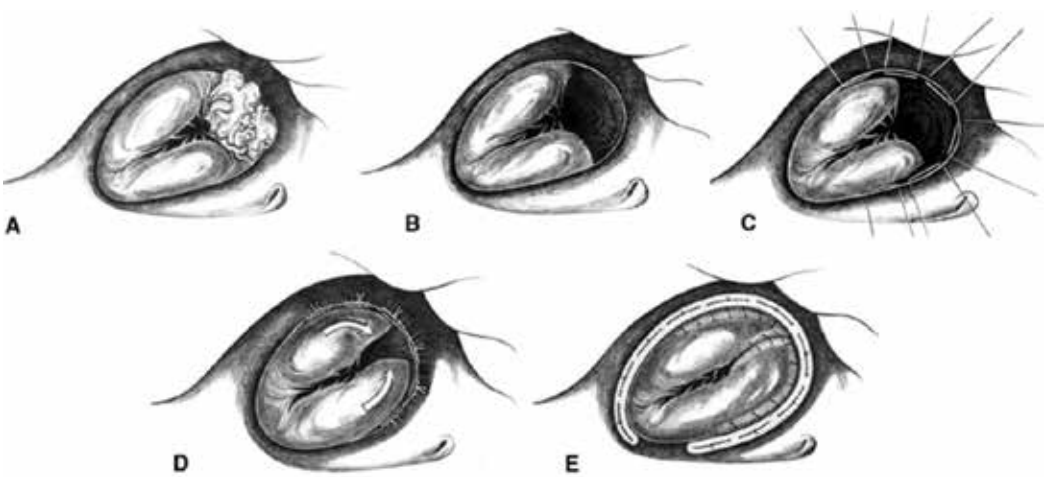

Figure 2. (A) Endocarditic lesion on the posterior leaflet. (B) Excision of the posterior leaflet. (C) Partial mobilization of the anterior and septal leaflet and preparation of plication sutures. (D) Bicuspid leaflet formation of the valve. (E) Stabilization of the valve with a tricuspid annuloplasty ring.

showed that the ring annuloplasty is superior to suture annuloplasty in terms of recurrent tricuspid regurgitation or reoperation [21–24].

2.5. Tricuspid valve replacement

In case of severe valve destruction, valve replacement is performed using either a mechanical valve or tissue valve.

Cho et al. compared surgical outcomes of mechanical tricuspid valve replacement (n = 59) and tissue tricuspid valve replacement (n = 45), and found that there was no difference in long-term valve-related complications such as thromboembolic or bleeding events [25].

Hwang et al. also reported that there was no difference in long-term survival, cardiac death rates, and thromboembolic and bleeding complication rates between mechanical and tissue tricuspid valve replacements [26].

Liu et al. performed a meta-analysis to review the results of mechanical and bioprosthetic valves in the tricuspid valve position [27]. They did not find difference in survival, reoperation, or prosthetic valve failure between two valve types.

2.6. Surgical outcomes for tricuspid valve infective endocarditis

The surgical outcomes for tricuspid valve infective endocarditis are listed in **Table 1**. Overall good surgical outcomes were reported, and the durability of tricuspid valve reconstruction was good.

Study	Year	Number of pts	Surgical technique	Mortality (%)	Recurrence of regurgitation	Recurrence of infection
Musci et al. [28]	2007	51	31 reconstructions, 17 tissue TVR, 3 mechanical TVR	11.3% for reconstruction, 12.5% for TVR	—	2 patients had reoperation due to reinfection after the tricuspid reconstruction.
Gottardi et al. [18]	2007	22	18 reconstructions, 3 tissue TVR, 1 mechanical TVR	0	3 patients had grade 1–2 TR	2 patients had recurrent endocarditis, which were treated conservatively.
Baraki et al. [29]	2013	33	15 reconstructions,14 tissue TVR, 4 mechanical TVR	9	2 patients had grade > 2 TR	3 patients underwent reoperation for recurrent endocarditis
Gaca et al. [17]	2013	910	354 reconstructions, 66 valvectomies, 490 TVR	7.6% for reconstruction, 12.1% for valvectomy, 6.3% for TVR	—	—

TVR, tricuspid valve replacement; TR, tricuspid regurgitation.

Table 1. Surgical outcomes for tricuspid valve endocarditis.

Musci et al. reported a 20-year single institution surgical experience for right-sided infective endocarditis [28]. They performed 31 tricuspid valve reconstructions and 20 valve replacements. The 30-day, 1-, 5-, 10- and 20-year survival rate after the operation was 96.2, 88.4, 73.5, 70.4 and 70.4%, respectively, for isolated right-sided infective endocarditis. The survival rate was significantly better than the patients with combined right- and left-sided infective endocarditis. Survival was not different between valve reconstruction and replacement.

Gottardi et al. performed 18 tricuspid valve repair and 4 tricuspid valve replacements for active infective endocarditis, and there was no mortality [18]. During the follow-up, three patients presented with grade 1–2 tricuspid valve regurgitation after the valve reconstruction.

Baraki et al. reviewed 33 tricuspid valve surgeries for endocarditis, which included 14 tissue valve replacements, 4 mechanical valve replacements, and 15 tricuspid valve repairs [29]. Thirty-day mortality was 9%, and advanced age, EuroSCORE, and *Staphylococcus aureus* were associated with a less long-term survival rate. Residual tricuspid valve regurgitation grade ≥2 was found in two patients.

2.7. Intravenous drug user

Intravenous drug abuse is increasing dramatically in the United States [30]. Of many medical complications caused by drug use, infective endocarditis is one of the most challenging issues given the significant risk of acute mortality as well as late recidivism, reinfection, and poor social situations.

The infection caused by the drug use can be found both on right- and left-sided heart or even on both sides. Even though the prognosis of right-sided infective endocarditis is better than left-sided, surgery may be required in at least 25% of patients [31].

The surgical outcomes for drug-induced endocarditis are summarized in **Table 2**. Overall, the short-term and long-term survival was not different between drug users and non-drug users; however, the rates of late reinfection and reoperation are higher in drug users.

The choice of valve prosthesis for intravenous drug users is controversial [32]. Rabkin et al. reported that the median survival of intravenous drug users was only 3 years, and therefore tissue valves are justified even for young patients [33]. Kaiser et al. used tissue valves more frequently in drug users than non-drug users (75 vs. 52%), even though drug users were younger [34].

In the meantime, several previous studies showed that the postoperative survival rate of drug users is similar to non-drug users [34–37]. That may imply that intravenous drug users receiving tissue valves will live long enough to require a reoperation for valve degeneration. Given the fact that the redo surgery for tricuspid valve carries high risk [38], the use of mechanical valve may be justified for selected patients who can be compliant with anticoagulation. Mechanical tricuspid valves have a risk of thrombosis with an incidence of ≤3.3% of patient-years [39].

2.8. Reinfection after surgery

Patients with intravenous drug use are high risk of reinfection. The surgical outcomes for redo tricuspid valve surgery have been reported to be poor.

Study	Year	Number of pts	Hospital	Findings
Shrestha et al. [35]	2015	536; 41 (8%) were drug users	Cleveland clinic	Short-term mortality was not different between drug users and non-drug users; however, a hazard of death or reoperation between 3 and 6 months after the operation was 10 times higher in drug users compared with non-users.
Kim et al. [36]	2016	436; 78 (17.9%) were drug users	Massachusetts General Hospital and Brigham and Women's Hospital	Operative mortality was lower among drug users; however, overall mortality was not different. Drug users had higher risk of valve-related complications principally because of higher rates of reinfection.
Rabkin et al. [33]	2012	197; 64 (32.5%) were drug users	University of Washington Medical Center	Survival was lower in drug users than non-drug users (at 30 days, 1 year, 5 years, and 10 years; 91.2 vs. 93.6%, 77.5 vs. 83.0%, 46.7 vs. 71.1%, and 41.1 vs. 52.0%, respectively, $p = 0.027$). Intravenous drug use was an independent risk factor for diminished survival ($p = 0.03$). 8 of 64 (12.5%) of drug users experienced recurrent infective endocarditis.
Kaiser et al. [34]	2007	346; 62 (17.9%) were drug users	Washington University	Long-term survival and perioperative complications were not different between drug users and non-drug users; however, reoperation for recurrent infection was higher in drug users (17 vs. 5%, $p = 0.03$).
Carozza et al. [37]	2006	39 drug-induced infective endocarditis and 85 non-drug-induced infective endocarditis	Second University of Naples	Although hospital and long-term survival did not significantly differ between two groups, the rate of recurrence of infection was higher in drug users.

Table 2. Surgical outcomes for drug-induced infective endocarditis.

Jeganathan et al. reviewed 68 patients who had previous history of tricuspid valve surgery and underwent reoperations on the tricuspid valve, and in-hospital mortality was 13.2% [38]. They also reported high incidence of postoperative bleeding, low cardiac output syndrome, stroke, and renal failure.

Musci et al. reported that 6 out of 79 patients underwent reoperation due to reinfection after the correction of right-sided active infective endocarditis, and only 1 of them (16.7%) survived the reoperation [28].

The prognosis of prosthetic valve infection without surgical intervention is dismal. Ivert et al. reported that 64% of the patients with prosthetic valve endocarditis died, and most deaths occurred within 3 months of the first evidence of infection [40]. Nevertheless, the surgical treatment for prosthetic valve endocarditis is also challenging [41].

Luciani et al. performed multicentre study for surgical outcomes for prosthetic valve endocarditis [42]. Among 209 patients who underwent surgery for prosthetic valve endocarditis, the in-hospital mortality was high (21.5%). Grubitzsch et al. reviewed 149 patients who underwent redo surgery for prosthetic valve endocarditis [43]. The operative mortality was 12.8%.

In the setting of high risk of surgical treatment for reinfection, a dilemma exists regarding the surgical indication for patients who are non-compliant to medical treatment, and develop reinfection due to relapsing of drug use [44]. There is a controversy as how many chances surgeons should give to non-compliant patients.

Hull et al. proposed that the patients who have a history of intravenous drug use should be encouraged to sign a contract agreeing to undergo drug rehabilitation and make a good faith effort to abstain from substance abuse in the future [45].

3. Conclusions

The incidence of tricuspid valve infective endocarditis is increasing along with the epidemic of intravenous drug use. Surgical treatment would be necessary when the patients suffer from heart failure, large vegetation, and persistent bacteremia despite appropriate antibiotic therapy. Tricuspid valve reconstruction is desirable as artificial material can be avoided; however, in cases of severe valve destruction, tricuspid valve replacement is warranted. Management of patients with intravenous drug users is challenging due to late recidivism, reinfection, and poor social situations. The operation for reinfection carries high risk. There is an ethical controversy regarding the surgical indication for reinfection induced by relapse of drug use. Surgeons can play a role by bringing the problem of epidemic of drug use to public consciousness.

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Chapter 8

Prosthetic Valve Endocarditis

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Additional information is available at the end of the chapter

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Abstract

The management of infections of the cardiac structures—specifically native heart valves—remains a difficult clinical challenge. Patients often present with a systemic infection that is made worse by embolic complications, such as strokes, along with pathophysiologic sequelae of acute valvular dysfunction. The timing of interventions has a significant impact on short- and long-term outcomes. The challenges and management decisions are even more complex when the infection involves a prosthetic valve—as risks of reoperative cardiac surgery can be substantial. The goal of this chapter is to discuss the history of prosthetic valve endocarditis, review the current literature on the management of specific valvular involvement (i.e., aortic and/or mitral), and illustrate the challenging problems and outcomes that drive clinical decision making. While many of the indications for surgery are similar to those associated with native valve infections, there is increased risk with reoperative surgery, often difficulties in clearing infection due to prosthetic material being in place. Unfortunately, antibiotics alone are not always effective, and frequent communications between the cardiac surgeon and infectious disease physicians are often necessary to find the "sweet spot" to perform the surgery.

Keywords: endocarditis, valve disease, aortic valve, mitral valve, cardiac surgery, prosthetic heart valves, infections

1. Introduction

Prosthetic valve endocarditis (PVE) is a rare, but serious complication of cardiac valve replacement surgery. As the prevalence of prosthetic valves increases, the incidence of PVE also rises. PVE constitutes approximately 20% of all cases of endocarditis, now greater than previous estimates of 1–5% [1]. The incidence of PVE is estimated at 0.3–1% per patient-year, with a

cumulative risk of 3% at 5 years and 5% at 10 years [1, 2]. The incidence of PVE in the aortic position is significantly higher than in the mitral position [3]. In comparison, the mitral valve is more commonly affected than the aortic valve in native valve endocarditis [4]. Patients undergoing simultaneous aortic and mitral valve replacement have an even greater risk of PVE than with a single valve replacement [5, 6].

2. Historical note

In 1885, Osler observed an association between perioperative bacteremia and endocarditis [7]. In 1935, Okell and Elliott noted that 11% of patients with poor oral hygiene had positive blood cultures for *Streptococcus viridans*, and that 60% of patients had bacteremia associated with dental extraction [8]. Not long after, initial reports of valve replacements by Starr and Harken, the first reports of PVE appeared in the literature [9, 10]. Before the routine use of prophylactic antibiotics, Geraci and Stein reported incidences of early PVE of 10 and 12%, respectively [11, 12]. The use of routine prophylactic antibiotics was noted to reduce the incidence of early PVE to 0.2% [11]. From the outset, the surgical management of PVE has been a formidable challenge. In the 1960s and 1970s, surgery for PVE was associated with an extremely high mortality rate. Discouraged by early operative experience, cardiac surgeons avoided intervention in cases of PVE despite recognition that antibiotic therapy alone was ineffective and often fatal. Surgery for PVE was reserved for high risk cases, and the surgical outcomes were predictably poor. Hence, a vicious cycle developed in which surgery was avoided for fear of poor surgical outcomes, and poor surgical outcomes achieved in high risk cases reinforced this fear.

In 1972, Ross successfully performed an aortic root replacement for PVE using an aortic homograft [13]. His report stressed surgical principles still true today: complete surgical debridement of all infected tissue, the use of homograft for reconstruction, and the minimal use of foreign material in the infected area [13]. In 1977, Olinger and Maloney reported replacement of an infected aortic prosthesis and external felt buttressing for correction of aortoventricular discontinuity [14]. In 1980, Frantz reported successful repair of an aortoventricular discontinuity from endocarditis and abscess formation by aortic root replacement using a synthetic valved conduit [15]. In 1981, Reitz successfully applied this technique to the treatment of prosthetic aortic valve endocarditis [16]. In 1982, Symbas combined aortic valve replacement with patch repair of a periannular abscess cavity [17]. In 1987, David and Feindel described techniques to reconstruct the mitral annulus with pericardium after debridement for PVE [18].

Surgical treatment of PVE remains a significant challenge, but outcomes improved in the 1990s. Factors that contributed to improved outcomes included:

1. widespread use of transthoracic and trans-esophageal echocardiography in making an early, accurate diagnosis,
2. an appreciation that, like surgical infections elsewhere, surgery for PVE requires radical debridement of infected and devitalized tissue,

3. improvements in myocardial protection, including routine use of retrograde cardioplegia, permitted longer and safer cardiac operations, and
4. cryopreserved homograft availability. Combined with resistance to reinfection, homografts provided flexibility in cardiac reconstruction after debridement. Currently, homograft aortic root replacement is considered the procedure of choice in the treatment of complex aortic PVE.

3. Risk

The risk of PVE to the patient is lifelong. However, as assessed by hazard function analysis, the risk of infection is greatest during the first 3 weeks after valve implantation [19]. Most deaths occur within 3 months of PVE development [18]. By clinical convention, PVE is classified as early or late [20]. Early PVE is acquired perioperatively and accounts for approximately one-third of all cases [20, 21]. Although traditionally defined as occurring within 60 days of initial valve replacement, the contemporary literature variably defines early PVE as occurring within 2, 6, or 12 months of initial valve replacement [20–22]. Late PVE results from infection unrelated to the initial valve operation and accounts for the remaining two-thirds [20]. The prognosis for early PVE is significantly worse than that of late PVE and often requires surgical intervention [20].

The distinction between early and late PVE provides insight into the acquisition of infection, expected clinical course, and appropriate management. Early PVE arises from the contamination of the valve during the perioperative period of valve implantation [20]. However, a patient with a prosthetic valve placed more than 12 months prior remains at risk for PVE commonly related to a healthcare-associated infection [20]. In a prospective, multicenter study of 171 patients with prosthetic heart valves by Fang et al., 43% developed endocarditis [23]. At the time, bacteremia was discovered, 33% had prosthetic valve endocarditis. These cases were described as having endocarditis at the outset. In comparison, 11% developed endocarditis at a mean of 45 days after the bacteremia was discovered. These cases were described as having new endocarditis. All cases of new endocarditis were health care associated with 33% developing bacteremia from intravascular devices [23].

Patients with central venous catheters are at particular risk for bacteremia. In the United States, approximately 80,000 central venous catheter-related cases of bacteremia are reported annually [24]. Urinary catheters are another source of bacteremia [25]. Catheter-associated bacteriuria develops at a rate of 8% per day in the first week of catheterization [25]. After the tenth day of catheterization, over 50% of patients are bacteriuric. Bacteremia develops in 0.4–4% of patients with catheter-associated bacteriuria [25]. Bacteremia per se does not invariably cause PVE. In a 10-year review of 890 patients by Parker et al., 3.6% undergoing cardiac valve replacement developed bacteremia in the early postoperative period. Only 6% of bacteremic patients developed PVE, though uniformly fatal [26]. Other authors have suggested that the risk of PVE may be significantly higher in cases of bacteremia; Murray reported an infective endocarditis rate of up to 25% in cases of *Staphylococcus aureus* bacteremia [27].

Although PVE secondary to candidemia is rare, accounting for 5–10% of all cases, it carries a high mortality rate [28]. In a retrospective study of 44 cases of nosocomial fungemia in patients with prosthetic heart valves by Nasser et al., 9% developed fungal endocarditis at a mean of 232 days after documented candidemia [29]. Hence, patients with candidemia must be treated aggressively in the acute setting and be provided close long-term follow-up.

Implantation of a prosthetic valve in the setting of native valve contamination without known active infection may increase the risk of PVE. For this reason, many surgeons routinely culture excised valve leaflets to ensure that the new valve is not contaminated at the time of implantation. In a study of 222 patients by Campbell et al., 14.4% who underwent elective valve replacement had positive valve cultures [30]. Coagulase-negative *Staphylococcus* was the most common bacterial isolate [30]. None of these patients had clinical evidence of infection. Only 3% of patients with positive valve cultures developed PVE. Most positive native valve cultures were thought to be false positives. Campbell concluded that positive cultures did not predict PVE and recommended against routinely obtaining native valve cultures [30].

Nonetheless, the potential morbidity and mortality of PVE may justify the practice of culturing excised valve tissue and treating patients with positive cultures. Intraoperative contamination at the time of valve implantation may occur from a variety of sources. Cardiac surgical procedures are complex and entail numerous intravascular monitoring devices as well as the circuit of the cardiopulmonary bypass machine. This complexity may contribute to the incidence of positive intraoperative blood cultures. In 1969, Ankeney and Parker reported positive intraoperative blood cultures in 19% of patients undergoing open cardiac surgery [31]. In a 1974 study of 66 patients undergoing open cardiac surgery, Kluge et al. reported a 71% incidence of positive intraoperative cultures from at least one site and a 20% incidence from two or more sites [32]. Several decades later, the issue remains unresolved.

In a 2004 study of 64 patients who underwent cardiovascular surgery, Shindo et al. reported positive intraoperative blood cultures in 16% of patients who underwent cardiopulmonary bypass [33]. Intraoperative blood salvage is routinely used in cardiac surgical procedures to avoid homologous blood transfusion. Autotransfusion is associated with lower risk of hypersensitivity reactions and infections compared to transfusion of homologous blood [33]. However, intraoperative blood salvage is associated with a high incidence of positive cultures. Shindo et al. reported positive blood cultures in 67% of cases using intraoperative blood salvage, excluding cardiopulmonary bypass [33]. In a 1992 study of 31 patients, Bland et al. reported positive cultures in 97% of cases using intraoperative blood salvage [34]. In a 1999 study of 10 patients by Reents et al., 90% of cases using a cell-saving device had bacterial contamination [35].

Hemodialysis has also been associated with endocarditis, particularly with the increasing prevalence of dialysis dependence. In a study of 329 patients with endocarditis by Cabell et al., 20.4% were hemodialysis dependent [36]. Hemodialysis was independently associated with the development of *Staphylococcus aureus* endocarditis. The frequency of hemodialysis dependence also significantly increased during the 7-year study period, from 6.7 to 21% [36]. There was a corresponding significant increase in *Staphylococcus aureus* endocarditis during

the study period, from 10 to 68.4% [36]. The prognosis of endocarditis in hemodialysis patients is poor, with in-hospital death rates of 25–45% and 1-year death rates of 46–75% [37].

Healthcare-associated infections are a significant source of PVE, accounting for 10–34% of all cases [38]. The majority of cases of healthcare-associated PVE develop more than 72 h following hospital admission [38]. The source of healthcare-associated PVE is frequently an intravascular device, such as a pacemaker or implantable cardioverter defibrillator. PVE is classified as healthcare-associated if it occurs within 1 year of device insertion [38].

4. Type of prosthesis

The incidence of PVE in mechanical and bioprosthetic valves is comparable [39]. Patients with mechanical prostheses have a higher risk of PVE in the first 3 months following valve replacement than those with bioprostheses [19]. The reason for higher risk of PVE in the early postoperative period with mechanical prostheses is unclear. Allografts lack prosthetic material and have a very low incidence of PVE in the early postoperative period. This suggests that mechanical prostheses have a tendency to develop early PVE, attributed to surface contamination at the time of surgery [19].

PVE in mechanical and bioprosthetic valves differs in anatomic involvement [40]. Infection of mechanical valves involves the junction between the sewing ring and annulus. This leads to the development of perivalvular abscesses, valve dehiscence, pseudoaneurysms, and fistulas. In comparison, infection of bioprosthetic valves is localized to the leaflets, leading to vegetations, cusp rupture, and perforation [40]. Endocarditis after mitral valve repair is rare. In a study of 30 patients, Gillinov et al. reported only 3% of cases of failed mitral valve repair as being caused by endocarditis [41]. In a study of 1275 mitral valve repairs over a 9-year period, Karavas et al. reported a 0.7% incidence of mitral valve endocarditis requiring surgical intervention [42]. The reason for this low incidence is likely related to less prosthetic material for potential infection with mitral valve repair than replacement.

4.1. Aortic valve prosthetic valve endocarditis

Aortic PVE is associated with substantial early morbidity and mortality. Regardless of the type of infected valve, mechanical or bioprosthetic, extensive tissue destruction may complicate aortic PVE. In a 20-year study of surgical treatment of aortic PVE by Perrotta et al., perivalvular abscess was reported in 83% of patients [43]. Comparably, Sabik et al. reported a 78% abscess rate in 103 patients with aortic PVE [44]. Abscess formation may be complicated by pseudoaneurysm and fistulisation [40]. Complete aortoventricular discontinuity has been reported in 40% of patients with aortic PVE [44]. Medical therapy alone has been associated with mortality rates as high as 70%, improved to 4–20% with surgical intervention. Significant risk factors for mortality include older age, higher preoperative creatinine, shorter interval from initial valve operation to reoperation for PVE, and fistula development. Mortality results from sepsis and multiple organ failure [44].

Aortic PVE is characterized by varying degrees of annular involvement. Extension of infection into the annular and periannular structures is a major determinant of both early and late surgical outcomes. The extent of valvular destruction relates to the virulence of the infecting organism and the duration of infection [45]. The inflammatory process of aortic PVE begins at the prosthetic sewing ring and extends through the aortic annulus, commonly in the region of aortomitral continuity [46]. The spectrum of periannular infection ranges from simple localized abscess to larger subannular aneurysm, with or without perforation into adjacent cardiac chambers. Progressive periannular infection may disrupt aortoventricular continuity or the aortomitral trigone, leading to intracardiac fistulae [44].

The goals of surgical intervention for aortic PVE include [44]:

1. complete debridement of infected and nonviable tissue,
2. repair of associated cardiac defects,
3. reconstruction of the aortic root, and
4. placement of a competent valve.

Reconstruction is complicated by severe destruction of the aortic root seen in PVE, characterized by development of abscesses, fistulas, aortoventricular discontinuity, and ventricular septal defects [47]. Achievement of the goals of surgical intervention for aortic PVE may require radical cardiac debridement. Failure to adhere to these principles poses significant risk for recurrent infection and valve dehiscence.

Following complete debridement, appropriate surgical reconstruction is guided by specific circumstances. In the majority of cases, an aortic root replacement is indicated [48]. A tension-free repair, excluding attenuated areas from high pressures, is essential [48]. If necessary, transmural sutures may be used to secure the conduit to the interventricular crest. Surgical principles dictate minimal use of synthetic material in the infected area. Aortic homograft is considered the replacement valve-conduit of choice in the treatment of aortic PVE [49]. Homograft vascular tissue is significantly more resistant to infection than prosthetic material. Aortic root replacement with homograft minimizes prosthetic material in the area of infection, thereby reducing risk of recurrent infection. The incidence of reinfection is low, ranging from 0 to 6.8% [49].

The use of allograft provides greater flexibility in the reconstruction of debrided areas [50]. Implantation may exclude abscess cavities from circulation by sewing the proximal anastomosis of the allograft to the inferior border of the abscess cavity [50]. Use of an aortic homograft with its attached mitral leaflet is particularly valuable in this regard [51].

The Ross operation, using pulmonary allograft, has been proposed as an alternative surgical option for the treatment of complex aortic PVE [51]. An initial study in 1994 by Joyce et al. of pulmonary allograft replacement reported success in six patients between 10 and 32 years of age with aortic valve endocarditis, with no mortality or reinfection [52]. In 2002, a retrospective study of 343 patients who underwent the Ross procedure by Takkenberg et al. reported

low operative mortality, but limited durability due to progressive dilation of the autograft root causing severe aortic valve regurgitation [53]. The Ross procedure is typically performed in critically ill patients and is used very selectively in PVE.

Morbidity and mortality associated with allograft aortic root replacement in the setting of PVE with involvement of the periannular region is significant [54]. A retrospective study of 32 patients with complicated aortic PVE who underwent allograft aortic root replacement by Dossche et al. reported annular abscess in 81%, aortomitral discontinuity in 43%, and aortoventricular discontinuity in 34%. There was a 9.4% operative mortality rate in this study, attributed to multiple organ failure and low cardiac output. The reported 5-year survival rate was 97.3%, and 5-year freedom from recurrent endocarditis was 96.5% [54]. As described, Sabik et al. reported similar rates of periannular abscess and aortoventricular discontinuity at 78 and 40%, respectively [44]. Reconstruction with cryopreserved allograft was associated with an in-hospital mortality rate of 3.9% in this study. Long-term survival rates at 1, 2, 5, and 10 years were 90, 86, 73, and 56%, respectively. Only 3.9% of patients required reoperation for recurrent PVE; 95% were free of recurrent PVE at 2 years [44].

Despite the advantages provided by allografts in the treatment of aortic PVE, their availability is limited. This has led to the use of mechanical valve-conduits for aortic root reconstruction with excellent results in the treatment of aortic PVE. Hagl et al. reported favorable results in a retrospective study of 28 patients who underwent aortic root replacement for PVE using prosthetic material rather than homograft [55]. Reported in-hospital mortality was 11%, and the incidence of recurrent endocarditis requiring reoperation was only 4% [55].

A study of 127 patients by Avierinos et al. compared the treatment of aortic endocarditis with aortic homograft in 43% and with conventional prosthesis in 57% [56]. In-hospital mortality was comparable between homograft and prosthesis at 11 and 8%, respectively. Prosthetic valve endocarditis was the only variable independently associated with in-hospital mortality. This mortality rate was not influenced by the type of valvular substitute, even in cases of annular abscess. There was no significant difference in endocarditis recurrence, prosthesis dysfunction, or cardiovascular mortality between aortic homograft and prosthesis at 10 years [56].

Aortic root replacement with stentless porcine xenografts has been developed as a surgical alternative in aortic PVE [57]. The stentless valve provides flexibility in reconstruction of the debrided myocardium. However, it places prosthetic material in the infected area, risking infection of the prosthetic valve-conduit. A study of 132 patients who underwent aortic root replacement with stentless porcine xenografts by LeMaire et al. reported a 7.6% mortality rate. There was a 6.8% incidence of late valve-related complications, including prosthetic endocarditis and annular pseudoaneurysm [57]. Reconstruction with cryopreserved allograft remains the preferred surgical strategy.

In addition to the difficulty associated with extensive resection of the prosthetic valve-conduit and surrounding tissue, two particular challenges must be overcome to replace the infected valve-conduit. The first challenge is reimplantation of the coronary artery ostia into the allograft. Scarring from the initial procedure may make it difficult to effectively mobilize

the left and right main coronary ostia for anastomosis to the allograft without undue tension. Raanani et al. described surgical reconstruction of the left main coronary artery using an autologous pericardial or saphenous vein patch [58]. The second challenge is achieving adequate resection and debridement of the distal graft-to-aorta anastomosis, which may require deep hypothermia and circulatory arrest. Furthermore, an allograft may not have sufficient length to reach the distal aortic anastomosis. Sabik et al. described the use of a second allograft to bridge the distance between the first allograft and the aorta [44].

High operative mortality rates have been reported for the replacement of infected valve-conduits, attributed to the degree of surgical difficulty. In a study of 11 patients with infected ascending aortic grafts who underwent composite valve graft placement by LeMaire and Coselli in 2007, a 30-day mortality rate of 46% was reported [59]. In comparison, a study of 12 patients who underwent composite replacement of the aortic valve and ascending aorta for infective endocarditis by Ralph-Edwards et al. reported an operative survival rate of 91.7% [60]. In this series, extensive debridement was performed, often requiring resection of the infected portion of the left ventricular outflow tract with circumferential reconstruction using bovine pericardium. It was often necessary to extend the length of the coronary arteries with saphenous vein or expanded polytetrafluoroethylene grafts to facilitate reimplantation as well [60]. As described, in a study of 23 patients who underwent ascending aorta and aortic valve replacement with the prosthetic material for acute PVE, Hagl et al. reported an 11% in-hospital mortality rate and a 4% incidence of recurrent endocarditis requiring reoperation at 4 months [55].

4.2. Mitral prosthetic valve endocarditis

Endocarditis is rare after mitral valve repair. The rate of freedom from endocarditis at 10 years following mitral valve repair is estimated at 95–99% [61]. Although native valve endocarditis can often be managed medically, PVE typically requires early operation. In a study of 22 patients with endocarditis after mitral valve repair by Gillinov et al., 68.1% underwent repeat mitral valve operations. Mitral valve replacement was required in 73.3%, and rerepair was performed in 26.7%. Following reoperation, 30-day, 1-year, and 5-year rates of freedom from reoperation were 65, 41, and 26%, respectively [61]. The principles of surgical management include the removal of all infected and devitalized tissue as well as the removal of the annuloplasty ring. If rerepair is not possible, replacement is necessary. Destruction of the mitral annular region is less common than periaortic annular destruction. Surgical debridement and resection of abscess formation in the posterior mitral annulus or in the region of aortomitral continuity is a significant surgical challenge, associated with a high operative mortality.

The mitral annulus may be reconstructed with autologous pericardium after debridement, as described by David and Feindel [62]. If the posterior mitral annular region requires reconstruction, this may be done with pericardium as well [15]. If necessary, the new mitral prosthesis may be translocated onto either the atrial or ventricular side of the annulus. If technically feasible, ventricular translocation may prevent exposure of the attenuated area to high pressure [15]. Aortomitral discontinuity is uncommon and particularly difficult to reconstruct. This trigonal region may be reconstructed using a modification of the technique described by Rastan et al. [63].

5. Operations with recent stroke

Neurologic sequelae occur in 25–70% of cases of infective endocarditis and portend increased mortality [64]. The mechanisms of neurologic injury include ischemic infarction secondary to embolization, hemorrhagic transformation of ischemic infarction, pyogenic arteritis, and rupture of intracranial mycotic aneurysm [65]. Systemic embolization occurs in 12.9% of patients with left-sided endocarditis after initiation of antibiotic therapy [66]. Of those with embolic events, 52% affect the central nervous system, and 65% occur within 2 weeks of initiation of antibiotic therapy [66]. Risk factors for embolization include vegetation size and mobility [66, 67]. There is no significant difference in incidence of embolization between native and prosthetic valve endocarditis. The risk of embolization is higher in mitral endocarditis than in aortic endocarditis [66].

The most common neurologic complication is ischemic stroke [65]. From a surgical perspective, the primary concern is hemorrhagic transformation of an ischemic infarct as a consequence of anticoagulation required during cardiopulmonary bypass [65]. Asymptomatic cerebral infarctions may occur in 30–40% of patients with endocarditis [64]. For this reason, it may be advisable to exclude an ischemic stroke with preoperative computed tomography. Clinically, silent or small infarcts should not delay cardiac surgery, since the risk of progression is low [64]. However, with the evidence of larger infarcts or intracerebral hemorrhage, surgical intervention should be delayed up to 4 weeks due to the associated risk of a significant neurologic event during cardiopulmonary bypass [64]. In such patients, the need for valve replacement should be balanced with high perioperative neurologic risk.

6. Indications for surgery

While there are a variety of resources available to assist in the decision making regarding interventions for prosthetic valve endocarditis, the key principles of therapy have been advocated by both American [68, 69] and European societies [70].

1. *Indications for surgery.*[1]

- Valve dysfunction resulting in symptoms of heart failure (Class I).
- Left-sided infectious endocarditis caused by S. aureus, fungal, or other highly resistant microorganisms (Class I).
- Relapsing infection (Class IIa).
- Recurrent emboli and persistent vegetations despite appropriate antibiotic therapy (Class IIa).

[1]Adapted from The American Association of Thoracic Surgeons consensus statement on the management of infectious endocarditis [68].

2. *Timing of surgery.*
   - Once an indication for surgery is established, the patient should be operated on within days (Class I). Earlier surgery (emergency or within 48 hours) is reasonable for patients with large, mobile vegetations (Class IIa).
   - Patients should be on appropriate antibiotic therapy at the time of surgery (Class I). Once a patient is on an appropriate antibiotic regimen, further delay of surgery is unlikely to be beneficial (Class IIa).
3. *Neurologic complications and surgery for PVE.*
   - An operative delay of 3 weeks or more is reasonable among patients with recent intracranial hemorrhage (Class IIa).
   - Patients with PVE and neurologic symptoms should undergo brain imaging (Class I); it is reasonable to screen patients with left-sided IE for possible stroke or intracranial bleeding prior to operation (Class IIa).
4. *Technical considerations.*
   - Aortic PVE. If the root and the annulus are preserved after radical debridement in prosthetic aortic valve IE, implantation of a new prosthetic valve (tissue or mechanical) is reasonable (Class IIa). If there is annular destruction and invasion outside the aortic root, then the root reconstruction and use of an allograft or a biologic tissue root are preferable to a prosthetic valved conduit (Class IIa).
   - Mitral PVE. When there are annular destruction and invasion, the annulus is reconstructed and the new prosthetic valve anchored to the ventricular muscle or to the reconstruction patch in a way to prevent leakage and pseudoaneurysm development (Class IIa).
   - Among patients on dialysis, normal indications for surgery are reasonable, but additional comorbidities must be factored into assessments of risks and outcomes (Class IIa). Shorter durability of bioprostheses and allografts may be considered in the choice of valve prostheses used (Class IIa).

7. Conclusions

Without a doubt, the incidence of native valve endocarditis is growing-the reasons for this are multifactorial and, in general, reflect a greater access to advanced cardiac surgical therapies. Sicker patients, older patients, and more patients are undergoing valve replacement surgery for an ever-expanding list of indications. Increased used of vascular access, be it for chronic electrical system therapies (i.e., pacemakers and defibrillators), medical therapies (i.e., chemotherapy, dialysis), or as an extension of intravenous substance abuse, all have contributed to a growing incidence of both native and prosthetic valve infections. Regardless, any prosthetic valve replacement leads to a life-time risk that these patients for the development of prosthetic

valve infections-either as a result of their initial operation, their ongoing (and potentially worsening) comorbidities, or simply as a function of patients living longer and with a cumulative annual risk. The development of prosthetic valve endocarditis is often, and appropriately so, viewed as a catastrophic event due to its association with devastating complications (i.e., strokes), substantial risk for operative morbidity and/or mortality, and baseline comorbidities and functional status at the time of presentation. More than most other medical and surgical therapies, a timely engagement by a multidisciplinary team is crucial to the establishment of a short- and long-term treatment plan. Clearly, much like native valve endocarditis, patients with prosthetic valve infections have shown benefit from early and aggressive surgical therapies-once established indications for surgery have been met or it has been demonstrated that optimized medical therapies have failed. Such therapies, despite substantial perioperative risks, must be focused on with aggressive debridement and elimination of all prosthetic and infected material. While prolonged courses of antibiotics and nonoperative management may have a role in select patients with limited disease burden, or for those in whom surgical reintervention is deemed to be a prohibitive, it must be recognized that the risk of treatment failure in such patients often results in worse complications or premature death. In conclusion, the medical and specific surgical decisions when dealing with a prosthetic valve infection must be individualized to provide the patient with the best opportunity for a cure.

Conflict of interest

None of the authors of this chapter have any disclosures or conflicts of interest to report in the context of the material presented.

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Section 4

Advanced Problems

Chapter 9

The Ethics in Repeat Heart Valve Replacement Surgery

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Additional information is available at the end of the chapter

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Abstract

The treatment of patients with intravenous drug use (IVDU) has evolved to include a wide range of medications, psychiatric rehabilitation, and surgical interventions, especially for life-threatening complications such as infective endocarditis (IE). These interventions remain at the discretion of physicians, particularly surgeons, whose treatment decisions are influenced by several medical factors, unfortunately not without bias. The stigma associated with substance use disorder is prevalent, which leads to significant biases, even in the healthcare system. This bias is heightened when IVDU patients require repeat valve replacement surgeries for IE due to continued drug use. Patients who receive a valve replacement and continue to use illicit drugs intravenously often return to their medical providers, months to a few years later, with a reinfection of their bioprosthetic valve; such patients require additional surgeries which are at the center of many ethical discussions due to high mortality rates, for many complex medical and social reasons, associated with continuous chemical dependency after surgical interventions. This chapter examines the ethics of repeat heart valve replacement surgery for patients who are struggling with addiction. Considerations of justice, the fiduciary therapeutic relationship, and guiding ethical principles justify medically beneficial repeat heart valve replacement surgeries for IVDU patient populations.

Keywords: replacement valve surgery, ethics, justice, addiction, intravenous drug use

1. Introduction

The treatment of patients with intravenous drug use (IVDU) has evolved to include a wide range of medications, psychiatric rehabilitation, and surgical interventions, especially for

life-threatening complications such as infective endocarditis (IE). These interventions, however, remain at the discretion of surgeons, and the healthcare team, whose treatment decisions are influenced by several medical factors, unfortunately not without bias. The stigma associated with substance use disorder is prevalent, especially toward IVDU, which leads to significant biases, even in the healthcare system [1]. This bias is heightened when IVDU patients require multiple or repeat valve replacement surgeries for IE due to continued drug use, which can be quite costly for healthcare institutions.

We explore various barriers when considering repeat heart valve surgeries, especially the implicit bias that can negatively influence the duty of physicians and their decision to provide comprehensive patient care. Patients who receive a valve replacement and continue to use illicit drugs intravenously, often return to their medical providers months to years later with a re-infection of their prosthetic valve; many of these patients have several medical comorbidities and require extensive care. The topic of multiple or repeat heart valve surgeries are the center of many ethical discussions due to the high mortality rates associated with both the inherent mortality from ongoing drug abuse and the risks of often complex and technically challenging high-risk re-operative cardiac surgery.

This chapter examines the ethics of repeat heart valve replacement surgery for patients who are struggling with addiction, and the important factors that ought to guide health care professionals in making future treatment decisions. Considerations of justice, the fiduciary therapeutic relationship, and guiding ethical principles justify medically beneficial repeat heart valve replacement surgeries for IVDU patient populations. We will present and analyze two cases, which were presented to a hospital ethics committee, and provide justification for a narrative-based ethical approach to identify those factors for when patients ought to receive multiple heart valves and the conditions for pursuing this surgical intervention despite chemical dependency challenges.

To better examine the ethical and social issues significant to discussions about heart valve replacement surgery among IVDU populations, particularly those seeking repeat surgeries due to chemical dependency relapse, it is important to understand the current climate in the United States with respect to IVDU and IE, as well as the need for comprehensive surgical and mental health care for patients who are committed to their recovery.

2. A brief examination of the literature

There is an increasing body of literature prompted by the rapid increase of prescription and non-prescription opioid drugs in the United States that emerged in the 1990s and is at epidemic levels today. In 2016, 64,000 Americans died from drug overdoses, which was a 21% increase from the year before [2]. Some states are struggling more than others to combat this leading cause of death among Americans under age 50 [2]. Unfortunately, there is more discussion about public health and law enforcement interventions, rather than focusing on individualized medical care in persons who are in critical need of comprehensive therapy,

which includes high-risk surgeries, detoxification programs, and extensive mental health care for chemical dependency among other related mental health disorders. Helping the addict is discussed less frequently as an important step to fight this epidemic [3], which is relevant to our ethical and social examination as to why we need to re-think the standards of medical care and treat patients holistically by incorporating mental health care into every aspect of their overall care. This is especially pertinent to the treatment of IE secondary to IVDU.

2.1. Relationship of intravenous drug use and infective endocarditis

With the rise of the opioid epidemic in the past few years, high-risk valve replacement surgeries have become a growing medical, financial, and ethical burden. Historically, IVDU represented a small percentage of patients with IE. In one study, the proportion increased from 14.8% in 2002–2004 to 26% in 2012–2014 during which time, heroin use doubled [4, 5]. Today, approximately 11% of IVDU are at risk for developing IE [6], which is characterized by infection of the inner lining of the heart, leading to the growth of vegetation on heart valves that disrupt the ability to pump blood. Overall, IE is an extremely morbid disease: in-hospital mortality rates range from 11 to 26% with an estimated 5-year mortality of up to 50% [7]. Complications include heart failure, valve insufficiency, embolic strokes, and intracerebral hemorrhage. IE secondary to IVDU is most commonly caused by bacteremia from *Staphylococcus aureus* and *Enterococcus faecalis* that are abundantly found on the skin and gastrointestinal tract, or by particulates in illicit drugs that cause micro-damage to tissues as they circulate [8, 9] following injection. Treatment is often sufficient using high-dose antibiotics, but 60 to 70% of severe cases require surgical intervention [4].

Studies have shown that patients with IE secondary to IVDU are younger than patients with no IVDU and more likely to be young Caucasian males, with some regional variability among populations [4]. The average age of patients who suffer from IE secondary to IVDU is 30 years old, and 90% of them are heroin addicts [7, 8]. Approximately 75% of individuals admitted to treatment for heroin abuse or dependency reported using injection as the primary method of drug use [10].

Despite IVDU representing a significantly younger patient population with less cardiovascular and comorbid risk factors, long-term outcomes are compromised by reinfection [4] and continued drug abuse. A patient who receives a valve replacement yet continues to use intravenous drugs is likely to re-infect their bioprosthetic or homograft valves, requiring additional valve replacement surgeries. However, such treatment opportunities may not be offered to this patient population due to high mortality rates. For example, studies have found that patients who resume IVDU after their initial valve replacement have high mortality compared to patients who abstain from drug use after their surgery [11]. A patient who resumes IVDU may get an extra 1–5 years of life out of their new valve rather than the 10–15 years of life that a new valve (mechanical or biological) can give without IVDU. Such decision-making must also be done in the setting of the overall poor and limited (but somewhat incompletely defined) life-expectancy of the habitual use of IV drugs.

2.2. Factors contributing to stigma and the refusal of care

In general, many surgical professionals identify repeat valve replacement surgery as non-beneficial for patients with IVDU, and thus, refuse or are reluctant to offer this procedure or refer patients to other surgeons who are willing to treat this patient population. Even when the valve replacement surgery may provide some benefit and give a few more years of quality life for patients, surgical professionals and the healthcare team may feel as though the financial burdens to patients and healthcare institutions is a reasonable justification for not replacing infected valves. This is especially true given the high relapse rates for IVDU and readmission with active IVDU. In addition, because the IVDU patient population contributes to increased unemployment and reliance on publicly funded insurance [12], some health care professionals may feel as though they have a duty to the community by not prolonging the lives of patients with IE secondary to IVDU, and thus adding additional financial burdens for communities and an already resource-limited health system.

Smyth et al. (2010) conducted a prospective study of patients who were dependent on opioids and admitted to a residential chemical dependency service for treatment. The authors found that 91% of 109 patients interviewed had relapsed; 59% relapsed just within one week of discharge [13]. Those who had earlier relapse were characteristic of our patient population; patients are younger in age, have a history of IVDU, did not complete the recommended length of time in the addiction program, and did not enter in or commit to aftercare programs. The authors also found that delayed relapse occurred among those who completed their entire program, as well as those individuals who were in a relationship with an opiate user, which was an unexpected finding and deserves further research [13].

Furthermore, given the significant rise of IVDU with the opiate epidemic in the United States, further research on relapse is needed, including the multitude of factors that contribute to relapse. Without addressing the factors that contribute to relapse, the rate will continue to rise, perpetuate stigma, fuel healthcare professionals' reluctance to provide multiple heart valve replacement surgeries, among other medical interventions. A study in China examined heroin addiction relapse and the effects of detoxification medications (methadone) combined with psychological counseling and social support measures, which were found to be essential to ongoing recovery and reduction of relapse rates along with patient compliance [14]. Additional studies have found that patients who recur to IVDU after the initial valve replacement procedure have very high mortality compared to patients who undergo rehabilitation [15].

From a medical perspective, the relationship between IE and substance use disorder is no different than nephropathy and diabetes, coronary artery disease and smoking, or the countless other chronic medical problems that are worsened by "life-style" choices. However, the negative connotations and stigma associated with IVDU lead to patients being treated differently in the health care system and among physicians, who deny life-saving care and devalue their patients as persons in need of advocacy and support to combat their addictions.

2.3. Gaps in the literature

Unfortunately, little research has been done on the value of extensive psychiatric and behavioral health interventions prior to, during, and following surgical treatment and the overall

clinical, psychosocial, and legal outcomes (e.g., improved medical compliance, reduced recidivism in drug use and criminal acts). One study found that only 7.8% of patients treated for IE were discharged with plans to receive medication-assisted treatment during the 10-year period of the study. In that same study, 25% of patients were readmitted with active IVDU [16]. Aggressive treatment for IE, including antibiotics and valve transplants, is neither effective nor advantageous without targeting the underlying addictive behaviors that contribute to poor health outcomes and mortality.

Addiction treatment, particularly for opioid users, is limited by factors that are beyond the control of physicians and drug users who may be willing to seek recovery. A study published by Jones *et al.* in 2015 reported that nationally, 96% of states (48 out of 50) had lower opioid treatment program capacity rates than their corresponding opioid abuse or dependence rates. The study also reported that 38 states had over 75% of their opioid treatment programs operating at an 80% capacity or more [17]. These numbers are indicative of a severe national shortage in treatment options, which could in part explain the ongoing struggle in IVDU achieving or maintaining their recovery.

Furthermore, little theoretical work has been done to identify the complex ethical issues surrounding this IVDU patient population who qualify for valve replacement surgery but who may be denied this life-sustaining intervention due to a number of factors including, but not limited to, financial cost, perceived poor quality of life, suspected non-compliance in post-surgical care and addiction treatment, and social worth. This chapter aims to start closing these gaps and to provide guidance to surgeons and healthcare teams when confronted with difficult medical, social, and ethical dilemmas.

Thus, through the presentation of two cases of IE secondary to IVDU, we will identify the medical, social, and ethical issues, recommendations for whether we should provide repeat valve replacements, and how we ought to treat patients who are struggling with mental health issues, including, but not limited to chemical dependency. Our case analyses will also identify the limits of justice and the duty of health care professionals in providing repeat heart valve surgeries.

3. Case presentation

The following two case presentations are based on actual patients with identifying information removed so as to protect their identities. These cases were presented to an ethics committee for an initial recommendation; however, the analysis and discussion presented here extends beyond committee consultation or even those guiding ethical principles that contribute to decision-making and resolution. These cases reveal a need for a narrative ethical approach to best understand individual patients and their medical, psychosocial, and value-based needs from diagnosis through recovery. The cases presented in this chapter are montages of health care team members' stories about their interactions with patients through medical evidence, patient interviewing, and clinical observation. However, there is an equal need for the medical team and the patient to co-author or construct a joint narrative of illness and medical care [18, 19]. These cases, however, do represent the multiple voices of the

multidisciplinary medical team about the patient in a brief, accessible case presentation. The features of these cases serve as valuable starting points for understanding the complexity of medical decision-making, unifying repeat heart valve replacement, post-operative care, and mental health treatment, and the need for ongoing recognition of the patient's story.

3.1. Case 1: a unified care model

A 24-year-old homeless, female patient is brought into the emergency department by a family member and presents for sepsis related to IVDA. The patient has a 10-year history of drug use with previous endocarditis, requiring cardiac surgery and debridement of an infected tricuspid valve approximately 14 months prior to the current admission. She has a history of untreated depression. The patient is admitted for complaints of joint pain, swelling, and general malaise. She reports injecting heroin and crack cocaine in her extremities (feet, arms, and hands) daily. The patient was drug-free for a short period of time with the assistance of residential treatment and hospitalization at a nursing facility where she received IV antibiotics for the endocarditis. However, the patient missed a dose of Suboxone (buprenorphine and naloxone) due to lack of transportation, did not seek support from health care professionals, and was unsuccessfully attempting to stop her persistent drug use on her own. Her continued drug use and failure of medical management have resulted in the need for pre-operative cardiac surgery for large vegetation in the tricuspid valve. The patient is willing to pursue addiction treatment following surgery and post-operative care and has had a history of taking Suboxone as an effort to stay clean and sober. An ethics consult is called to provide a recommendation on whether it is ethically permissible to re-operate in this patient with infective endocarditis from persistent IVDU. The ethics committee further weighed in on recommendations for achieving a unified care model in which the immediate medical needs namely, heart valve replacement, antibiotic therapy, and acute peri-operative pain management. Critical in the discussion was also providing a pathway that includes comprehensive mental health care for the patient's depression and addiction.

3.2. Case 2: resistance to IVDU treatment

A 29-year-old married male with a history of depression, multiple suicide attempts, poly-substance intravenous drug use (heroin and methamphetamines), and a history of endocarditis was brought to the emergency department by EMS following a suspected overdose. The patient was unresponsive until EMS delivered multiple doses of naloxone in route to the emergency department. Upon arrival, the patient was alert but had difficulty speaking. The patient's wife, who is a recovering addict, alerted EMS to her husband's overdose. Upon questioning the patient's current drug use, he admits to using methamphetamine cut with Fentanyl over the past week. The patient was drug-free for approximately 1.5 months after a prior hospital admission for septic mitral valve endocarditis due to IVDA, as well as renal failure, which was resolved following treatment. He received a bioprosthetic mitral valve and antibiotic therapy. Aside from his brief period drug-free, he has never been in treatment specifically for his chemical dependency and currently feels like he doesn't need such treatment. The patient suffers from multiple cerebral septic emboli with hemorrhagic

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transformation, aphasia, and distal limb emboli. He currently reports feeling feverish with body chills, headache, and joint pain; lab results show *Serratia* bacteremia, hypokalemia, transaminitis, anemia, and thrombocytopenia (I do not think we need these labs after *Serratia* bacteremia). An ethics committee is called upon to guide the treating surgeon whether this patient should receive a repeat valve replacement if he medically qualifies for this intervention. Additional ethical guidance is sought to determine what are the ethical obligations of the healthcare team when the patient does not believe he needs chemical dependency treatment and is likely to have repeated events of IE secondary to IVDU.

4. Ethics case analyses: a need for comprehensive just care and patient illness narratives

The above cases are representative of several medical, social, and ethical issues presented when patients are suffering from IE secondary to IVDU and who may require a repeat heart valve surgery and extensive mental health care for addiction and other related mental disorders (e.g., depression). In situations where patients have IE secondary to IVDU and need a new heart valve—their first surgical intervention—surgeons and others are more likely to treat the typical young patient with a probable successful surgical outcome without a need to seek ethical counsel. In our experiences, while most patients receive minimal chemical dependency treatment post-surgery, relapse (as discussed above) is likely, and a comprehensive mental health care program with monitoring, social support, and a recognition of the social determinants that contribute to the relapse are often not sufficiently addressed.

Thus, these patients return with IE and in need of a second, third, or more heart valve replacement surgeries. Surgeons and other healthcare professionals, particularly those working in community hospitals with limited financial resources, may question their duties to this patient population while considering their obligations to their medical community and society at large. Heart valve replacement surgeries, post-operative care, and addiction treatment are costly, and the financial burdens to patients, healthcare institutions, and the general community may deter surgeons from moving forward despite the patient's need. We can add the statistic about how the cost is increasing using the data from NC either here or in the paragraph with all the other statistics. Furthermore, the social stigma and biases against drug-addicted patients impact medical decisions, particularly when combined with the potential risk to health outcome measures, which can affect individual health care professional evaluations, work satisfaction, and trust among the general patient population.

The emotional impact of providing surgical care with the likelihood the patient will be back again for repeat heart valves due to IVDU can prompt moral distress, cynicism, and resentment of this patient population regardless of the moral obligations to treat when medically necessary, or beneficial. All of these considerations for repeat heart valve replacement surgeries should not be dismissed. They are essential for building a case for comprehensive just care, which is guided by core ethical principles of beneficence, non-maleficence, and justice, as well as a recognition of the individual patient's story through narrative medicine. Narrative

medicine prompts healthcare professionals to absorb, interpret, and co-author the dynamic story-telling in patient care. By co-authoring the illness narratives of patients, providers are able to acquire deeper insight into each patient's understanding of their illness, their goals for recovery, and the triggers that act as obstacles to recovery. Furthermore, through these illness narratives, providers will bear witness to the individuality of medical cases and recognize that some patients really can be helped even with the likelihood of relapse and future harm, which can reduce moral distress and clinical cynicism (e.g., "why try to help if these patients will end up abusing drugs again") [20–22]. However, the illness narratives need to be sustained; patients' stories do not end once they complete their post-operative care (e.g., antibiotic therapy).

It is our general position that repeat heart valves for patients with IE secondary to IVDU ought to be given if they are medically beneficial and if the patient is willing to commit to addiction recovery and ongoing, comprehensive mental health treatment that aims to address the social triggers, existing mental health disorders, and other factors that influence the chemical dependency. This is not the responsibility of the surgeon alone, but a medical team that has access to hospital and community resources, appropriate skills, knowledge to address the whole patient and their medical and psychosocial needs, and the ability to combat social stigma by treating the patient as a person with a very specific narrative. When repeat heart valves are not medically necessary or ethically beneficial, may cause undue suffering, and/or the patient is unwilling to commit to a comprehensive treatment program after thorough guidance by the health care team, then it is ethically justifiable to refuse surgery. However, each case is unique, and there may arise unique considerations that have not yet been previously addressed or ethically analyzed. Thus, it is essential that a narrative ethical approach that calls attention to the nuances of the case, i.e., the elements of the patient's story, is automatically part of the medical assessment and a sustainable chronic care plan.

4.1. Case I analysis: establishing standards of care

In this first case, there are a number of social factors that are contributing to the patient's current medical state. First, this is a young, homeless patient who does not have the means to acquire sustainable basic human needs. Regardless of whether her drug use led to the homelessness or vice versa, she is surviving in an unhealthy, unsupportive, and harmful environment, which is an obstacle to addiction recovery and overall health. When living in a residential treatment facility, she was able to have security, shelter, food, warmth, and community support, in addition to, medical treatment, all of which are essential for a recovering addict who, unfortunately, did not have these resources prior to her first valve surgery. However, these resources are limited; they are only available for the duration of her medical treatment for the endocarditis, and not for the ongoing recovery for her addiction. Her lack of essential resources, social instability, and homelessness are likely to have played a role in her subsequent relapse while on Suboxone; this demonstrates the necessity for holistic and comprehensive care in order to fully rehabilitate a patient with a chronic condition. Furthermore, this patient has a history of untreated depression—another significant factor that could have led to her current medical state.

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The use of IV drugs to combat feelings of depression and despair are not uncommon among untreated patients. Reasons for why she did not seek medical attention for her depression are unknown, but given the difficulties of navigating the health care system, federal insurance programs, and community programs that can aid a patient in accessing mental health care, it is not surprising that her depression went untreated. A person already addicted to IV drugs may have even more difficulty accessing mental health care due to the cognitive effects of the drugs, the stigma of drug use, and the lack of social support in seeking help. This patient tried to stop her drug use, but could not stop without the necessary social support and addiction therapy. Because she was previously successful at recovery, is a good surgical candidate for a medically indicated tricuspid valve replacement, and has a strong commitment to seeking post-operative care and addiction treatment, the surgical intervention should be granted. An ethics committee convened with this case and further recommended that it is critical for a team-based approach to be utilized for patients with IVDU who are seeking valve replacements.

A range of medical specialists and addiction experts, along with the surgical team, are essential for developing and implementing a treatment plan. It is also recommended that these patients sign a behavioral agreement in addition to the standard surgical consent form that details the patient's level of understanding about the risks and benefits of the surgery, addiction interventions, and any other medical and psychosocial care that promotes a good clinical outcome. Clinical outcomes are often determined by the success of the surgeries and post-operative care. However, we need to begin to look more critically at the long-term success of recovery, factors contributing to relapse, and how a team-based approach can aid the patient in quickly getting back into recovery. Recovery is a life-long process and a good clinical outcome may take years to fully measure and understand despite the more immediate surgical successes.

In the end, this patient did receive re-operative tricuspid and aortic tissue valve replacement. However, the behavioral contract, a non-legally binding contract, was not used. This contract prompts the patient to understand the need to get comprehensive treatment beyond a valve replacement, as well as empower the patient to take charge of her life, and maintain physical and mental health through ongoing counseling, therapy, and pharmaceutical interventions to treat her depression and addiction. The value of the contract is that it is a way to understand the patient's illness narrative and her commitment to recovery; although not used for this particular patient, it is a useful tool that can be beneficial for other patients. Of course, basic human needs (home, food, social support) are also needed, yet securing these resources for patients can be a challenge without having social work, nursing, and community support. There are limitations to what a surgeon can do beyond immediate surgical care, so it is critical for a wider health care community to recognize their ethical obligations to this patient population.

4.2. Case 2 analysis: a deeper understanding of medical need

In regard to the second case, this young male patient is struggling with mental health issues—particularly untreated depression and addiction—and is married to a recovering addict, who either can be a positive or negative influence in his recovery depending on their willingness

to work together toward mutual recovery. Without mental health treatment, his depression, suicidal ideations, and addiction will continue. One of the primary problems with this case is the patient's reluctance (which might be confounded by potential neurologic dysfunction due to his embolic strokes) to mental health treatment, feeling as though he does not need it despite the magnitude of health complications arising from his pervasive drug use. Specifically, the IVDU has led to multiple hospitalizations, a mitral valve replacement, and multiple, serious co-morbidities that have left him with ongoing physical pain and cognitive impairment. Prior to testing for valve functionality, this patient, too, was presented to an ethics committee, which prompted discussion regarding whether valve re-operation would be beneficial to this patient with serious comorbidities that may increase his surgical risk and lead to a poorer quality of life.

Similar to the first case, discussions surrounding addiction stigma, the need for social support, a need for the patient's commitment to seek addiction treatment, and a team-based approach to patient care were presented. However, unlike the first case, this particular patient is suffering from a number of medical issues that each need to be taken into consideration in the evaluation for a replacement valve, as well as an acknowledgment of the patient's lack of commitment to comprehensive mental health treatment. The ethical guidance sought is grounded in the principles of beneficence and non-maleficence, as well as a narrative-based justice approach that details the specifics of the patient's medical history, social support, quality of life, and his preferences and commitment to recovery. The goals of the medical team, from an ethical perspective, are to very carefully look at his medical condition, and whether he even has a chance for survival and future quality of life with a second valve replacement surgery. Second, it is critical for the medical team to revisit the topic of comprehensive mental health care, including treatment for depression and chemical dependency. Objective consideration must also be given if there are overwhelming evidence of medical/surgical futility—but this concept can be extremely difficult to determine in young patients.

The need for aggressive inpatient chemical dependency treatment is essential to this patient's recovery. However, unlike the first case in which valve replacement surgery and addiction treatment are simultaneously discussed as a holistic approach to patient care, for this patient, the addiction treatment becomes an interesting topic of discussion due to the gravity of his medical condition and his resistance to treatment. That is, the first case had less medical ambiguities in terms of the surgical candidacy for valve replacement combined with a clear indication of the patient's commitment to recovery. Thus, due to the immediate and justifiable medical need, the decision to move forward with surgery came simultaneously with a team-based plan and patient contract for recovery. Here, the patient's condition warrants an initial discussion about whether replacement valve surgery would be non-beneficial treatment. Causing further harm either during surgery or postoperatively should be avoided so as to ensure the best quality of life while living with a terminal condition. Furthermore, if the replacement valve surgery would be deemed beneficial, there remains the issue of the patient's lack of commitment to recovery. If there is persistent resistance to mental health care, ethically it would be unjust to proceed with a surgical intervention.

Following the ethics consult, the patient's valves with small vegetation were functioning, and his bacteremia was responding well to antibiotic therapy. The surgical team determined that after

he completed extended care, he then should seek aggressive inpatient chemical dependency treatment to limit the risk of relapse and recurrence. However, the medical team may be at an impasse given the patient's current resistance and lack of commitment to addiction recovery.

While it is recommended the medical team should have ongoing dialog with the patient to understand his reluctance at undergoing mental health treatment, and continuing to identify providers, care facilities, etc., that could aid in his recovery, additional steps may be needed before proceeding with any future medical interventions (e.g., valve replacement). If medical therapy alone fails e.g. progression of disease, worsening valve functioning, or recurrent emboli that lead to further complications, treatment options will need to be re-evaluated. Depending on his medical state, the patient may not be a future candidate for a replacement valve, and thus other medical resources and personnel, such as palliative care, may be required for the care of this patient.

In our first case, it is recommended the patient sign a behavioral contract to strengthen her existing commitment toward recovery, which further illustrates she does not have to go through recovery alone, i.e., the medical team will not give up on her if she maintains her commitment. In this second case, however, a behavioral contract may not be enough, since such non-legally binding contracts are symbolic gestures of the medical team's medical/social/legal relationship to a patient the shared responsibilities of both parties. When a patient is not willing to share responsibilities in the relationship and is resistant to addressing serious mental health disorders, the first step is to understand why.

4.3. Addressing the ethical and social problems of repeat valve replacements and the limits of justice

Valve replacements in IVDU must be administered regardless of the negative connotations associated with addiction or illicit drug use, with the patient's health, surgical success, and access to comprehensive addiction treatment being the goals of treatment. Both conscious and unconscious biases can affect clinical judgments that lead to unjust decision-making and disrespectful treatment of patients.

Similar to the health disparities we see in organ transplantation cases, where racial and ethnic biases have affected the length of time on a transplant waiting list, or lifestyle behaviors (e.g., alcohol addiction) have affected judgments about probability of success for organ replacement surgeries, medical judgments are not immune to bias when determinations about medical outcomes are being made. That is, it is all too easy for a surgeon to determine that her patient does not qualify for a valve replacement because of the high surgical risk, which may be based on the patient's untreated addiction, probability of relapse, and co-morbidities due to the effects of IVDU (e.g. the inherent risks of recurrent overdoses), rather than on the patient's survivability on the surgical table and success of the valve replacement itself. A surgeon may also exhibit conscious biases toward her patient when considering the continued burden of having to provide ongoing treatment, which increases the financial and personnel cost to the medical institution. Thus, such attitudes and feelings lead to a biased clinical judgment, but may also be generated out of concern for professional evaluation and outcomes-based, performance measures.

The first step in reducing the need for repeat valve replacement and improving patient health outcomes and survivability is to understand the patient's own unique story that prompted the IVDU, their goals for treatment, and their overall understanding of their own responsibilities toward successful, comprehensive treatment. By motivating them with a behavioral contract that speaks to the healthcare team's responsibility to the patient's care and the patient's own commitment, this may be a positive step.

Second, patients will not have a chance for successful recovery if they are not provided with needed resources and appropriate guidance to motivate them to seek long-term treatment. Such treatment should involve methods ranging from psychotherapy to pharmaceutical interventions.

Unfortunately, most current care is focused on the infective pathology; in IE patients only the acute problem is addressed, but no effort seems to be placed on preventing readmissions or improving the patient's quality of life. Addressing the lack of care and support IVDU patients are receiving, rather than trying to limit patient access to replacement procedures provides the just treatment these patients deserve, in addition to reducing the financial burden on healthcare systems and society. Health care providers often fail to identify addiction as the significant comorbidity that it is, and do not treat it as aggressively and appropriately using drugs that specifically target opioid use disorders; this results in under-treatment of addiction [16]. Such a limited care approach needs to change.

Third, surgeons and the healthcare team also require the support of ethics teams when complex social and ethical questions arise with patients. Personal biases lead to social stigmatization of patients with IVDU, influence medical decisions, lead to provider burnout, moral distress, and cynicism among health care providers. Having ongoing team-based discussions about these negative experiences, attitudes, and emotions is one step in the right direction, Recognizing the ethical and social issues that penetrate the medical problems can also help navigate and resolve dilemmas and elicit a deeper understanding of the individual patient and their illness narrative. It is important for healthcare providers to engage in self-care, and to have the opportunity to address issues before they devolve into negative emotions and attitudes that can be harmful to self and other.

Finally, it is critical for the health care team to know when additional treatment is futile. There are limits to justice. However, such limits to therapies must be based upon objective evidence supported by the medical literature rather than poorly grounded assumptions, biases, and outdated, or erroneous knowledge or datasets.

5. Conclusions

Unless physicians treat the chronic and acute illnesses in patients with IE due to IVDU, their ethical duties toward their patients remain unfulfilled, and they fail to provide just care. This issue becomes more precarious when considering patients who require additional valve replacements due to continued IVDU.

The American Medical Association's *Code of Medical Ethics* states that is the physician's ethical obligation "to place patients' welfare above their own self-interest and above obligations to other groups and to advocate for their patients' welfare" [23]. It is the duty of physicians to promote the health of their patients through comprehensive, beneficial treatment based on evidence-based medicine, and to respect them as persons with dignity, uninfluenced by social stigma and clinical bias. For patients with IE secondary to IVDU, it is important to treat both the psychiatric, social and infectious etiologies: the substance use disorder, homelessness, and food insecurity, as well as the IE, along with any additional comorbidities that are present. Although every patient with IE secondary to IVDU differs in the severity of presentation and comorbid conditions, patients with a positive prognosis should have the opportunity to achieve health and life with medical assistance.

Unfortunately, it is not unusual for patients with recurrent IE secondary to IVDU to experience social stigmatization and bias at the hands of the healthcare system and to be denied the comprehensive care that is needed in such cases. While some patients are justifiably denied due to a significant medical risk over benefit, patients are also denied simply because they are perceived as non-compliant, or because their potentially risky surgical treatments may negatively affect the health reviews and ratings of the surgeons performing the valve replacements. It is not ethically just to penalize viable surgical candidates when their addiction has neither been addressed nor treated. Citing high rates of treatment failure and non-compliance is not a valid excuse when the substance use disorder has not been treated as aggressively as the IE, especially when taking into considerations the lack of resources available for these patients to seek and maintain recovery.

Conflict of interest

The authors have no conflict of interest.

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Chapter 10

Septic Embolism in Endocarditis: Anatomic and Pathophysiologic Considerations

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Additional information is available at the end of the chapter

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Abstract

Septic embolism is a relatively common and potentially severe complication of infective endocarditis (IE). Septic emboli (SE), most often described as consisting of a combination of thrombus and infectious material—either bacterial or fungal—can be caused by hematogenous spread from virtually any anatomic site; however, it most commonly originates from cardiac valves. During the past two decades there has been a confluence of various risk factors that, both alone and in combination, led to greater incidence of both IE and SE, including increasing population age, greater use of prosthetic valves, implantation of various intracardiac devices, escalating intravenous drug use, and the high incidence of healthcare associated infections with antibiotic resistant microorganisms. From a clinical standpoint, SE can present at any time during the course of IE and may even be the initial presenting sign. SE may affect virtually any location in the human body, but some organs (e.g., liver, spleen, brain) and anatomic regions (e.g., lower extremity) tend to be more frequently involved. The most important aspect of management involves prompt recognition and proactive therapeutic approach. Given the broad spectrum of clinical presentations, symptoms and complications, SE can be challenging to diagnose and treat. Following the identification of SE, appropriate antibiotic coverage should be immediately instituted followed by supportive and/or interventional management, depending on the severity of presentation and the associated complications. In this chapter we explore the pathophysiology, anatomic origins, diagnostic tools, therapeutic measures, and new developments in SE, focusing predominantly on bacterial infections of cardiac origin.

Keywords: endocarditis, infective endocarditis, morbidity and mortality, septic embolism

1. Introduction

The collective understanding of infective endocarditis (IE) has changed significantly since its early characterization by Sir William Osler [1, 2]. In most low-and-middle income countries, rheumatic fever accounts for approximately two-thirds of all endocarditis cases [3–5], whereas in developed countries it is responsible for less than 10% of instances [6]. Over the past decade the incidence of IE has been increasing, with a recent study showing an overall increase of >30% between 2000 and 2011 [7]. The American Heart Association identified IE and associated complications as a major source of cardiovascular disability [8].

This surge in IE has been linked, in part, to recent medical advances, including increased use of implantable cardiac devices and a growing population of patients with chronic comorbidities [5, 9, 10]. Moreover, 10–35% of newly diagnosed cases of IE are thought to be healthcare associated infections, and hospital-acquired IE attributable to sources other than cardiac surgery is an emerging problem with mortality as high as 30–50% [11, 12]. The above observations can be explained, to some degree, by increases in antibiotic resistance including greater incidence of methicillin-resistant *Staphylococcus aureus* (MRSA), and higher prevalence of comorbidities in an increasingly aging population [2, 5, 12, 13].

In terms of intravenous drug use, injectable heroin has seen significant escalation [14, 15], with an associated incidence of IE growing by 58% between 2000 and 2013 [14]. In addition to the disease burden on individual patients and their families, the health-care system is further taxed with managing this difficult and expensive to treat population [14, 16]. Finally, it is important to recognize that recent years have seen IE presentations becoming more acute in nature, making diagnosis and treatment more challenging at times [5, 17, 18]. Among key complications of acute IE, the development of potentially devastating septic emboli (SE) may be seen. In this chapter, we will focus on the pathophysiology, diagnosis, and management of SE in the context of IE, using a systematic anatomic approach and outlining some of the most recent developments in this fast-changing area of cardiovascular infectious disease.

2. Pathophysiology of septic emboli

When discussing the pathophysiology of emboli of cardiac origin, one must consider both non-infective (Libman-Sacks or autoimmune, Marantic or related to wasting illnesses such as cancer) and infective (e.g., bacterial or fungal) endocarditis [19–21]. As an overarching theme, any condition that results in structural "damage or alteration" of cardiac valves has the potential to trigger an inflammatory reaction leading to the formation of valvular "vegetations" and thromboembolic complications [22]. In contrast to non-infectious valvular etiologies which lead to sterile emboli, IE has the potential to produce SE which typically are composed of a conglomerate of infectious organisms, inflammatory cells, platelets and fibrin [23]. In contrast to non-infectious emboli, SE have the potential to result in both vascular compromise and hematogenous spread of infection [24–26]. Evidence shows that as many as 50–82% of patients with IE may be affected by some form of SE, including both symptomatic and sub-clinical

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presentations [27–29]. In terms of valvular propensity for systemic (non-pulmonary) SE development, mitral valve is the most commonly involved [10, 30].

The genesis of SE is predicated on the appearance of a thrombus in a critical cardiac (usually valvular, **Figure 1**) location. This is usually associated with the presence of infected pacemaker leads, prosthetic valve, or some form of anatomic (acquired or congenital) abnormality of the native valve [30]. Bacterial species that feature specific adhesion matrix molecules are particularly likely to attach onto the damaged valvular surfaces, endocardium, or exposed prosthetic material [30–32]. Simultaneous presence of inflamed tissue and microorganisms leads to further accumulation of fibrin-platelet-microorganism complexes, contributing to the growth of infectious vegetations [33, 34]. If fragments of such vegetations—in whole or in part—are released into the circulation, SE is said to have occurred [5, 31, 32]. Microorganisms most often implicated include *Staphylococci*, *Beta-hemolytic Streptococci*, *Haemophilus*, *Actinobacteria*, *Caridobacterium*, *Eikenella*, and *Kingella*. The latter 5 are often listed under the acronym, "HACEK", and are less likely to cause IE than *Staphylococci* and *Streptococci* [10, 32, 35, 36]. Identifying the causative organism is critical to instituting prompt treatment with the most appropriate antibiotics. It is important to recognize that SE may affect any organ system or anatomic location, although certain patterns of involvement tend to be more common than others. This chapter will review key clinical evidence and developments regarding the diagnosis and management of SE. The authors will organize the current discussion according to regional/anatomic considerations in order to systematize and simplify the review process.

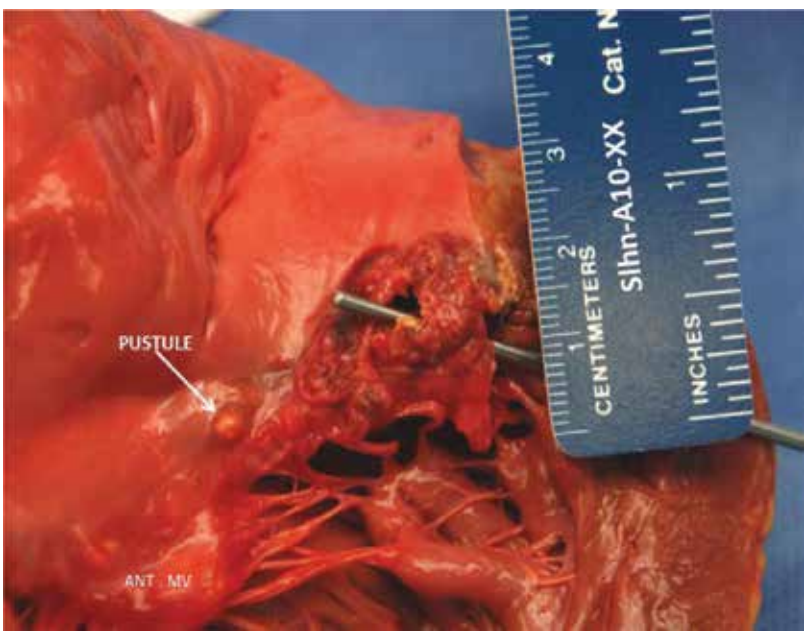

Figure 1. An example of a large necrotic bacterial vegetation, leading to the replacement of the entire posterior mitral valve leaflet. A pustule can be seen in the immediate vicinity of the vegetation. Also note the normal-appearing leaflet, chorda tendinea, and papillary muscles of the anterior leaflet (labeled as ANT. MV).

3. Head and neck

3.1. Brain

It is well known that there are many different central nervous system (CNS) manifestations of SE [37]. However, proving direct cause-and-effect relationship has been more challenging. Evidence suggests that septic cerebral embolic events may complicate as many as 40% of cases of IE, with recurrence rates for SE reaching 50% [38]. Cumulatively, manifestations of SE within the cerebral circulation can be divided into cerebral infarction (purely ischemic, purely hemorrhagic, or combined), CNS infection (encephalitis, meningitis, and abscess formation); and vasculopathy (vasculitis, mycotic aneurysm formation), with widely varied clinical presentations [38]. Summary of potential CNS manifestations of IE is provided in **Table 1**.

Involvement of SE within the CNS can be broadly categorized into cerebrovascular and non-cerebrovascular event types. Given that approximately 20% of cardiac output is dedicated to supplying the cerebrovascular system, it is no surprise that the brain is among the most commonly involved organs in IE. In fact, it is not uncommon for a cerebrovascular event to precede the formal diagnosis of IE, and to be the trigger for subsequent cardiac work-up [39]. Consistent with the above information, the greatest risk factor for a cerebral SE is left-sided IE, especially when due to *Staphylococcus aureus* infection. For embolic strokes, symptomatology heavily depends on the final resting point of the embolus. In one extreme case, complete cortical blindness followed the rupture of bilateral occipital mycotic aneurysms [40]. Even among patients with a limited duration of initial clinical symptoms, the risk of recurrent brain infarction may be as high as 80% [41]. **Figure 2** demonstrates septic embolism to the brain originating from mitral valve endocarditis.

Among patients experiencing CNS complications due to SE, approximately 50–60% have ischemic lesions, with the middle cerebral artery distribution being most commonly affected [42, 43]. Associated symptoms may include contralateral hemiplegia, homonymous hemianopia, dysarthric or aphasic speech, neglect, and sensory loss. It is difficult to differentiate

Cerebrovascular	Infections	Secondary complications	Rare complications
Ischemic stroke	Meningoencephalitis	Toxic-metabolic encephalopathy	Myeloradiculitis
Intracerebral hemorrhage	Cerebritis	Seizure	Spinal cord infarction
Subarachnoid hemorrhage	Abscess formation	Headache	Discitis/osteomyelitis
Mycotic aneurysm formation	Ventriculitis		Cranial neuropathies
	Ependymitis		Mononeuritis multiplex
			Myalgia

Adopted from Ref. [6].

Table 1. Central nervous system manifestations of infective endocarditis.

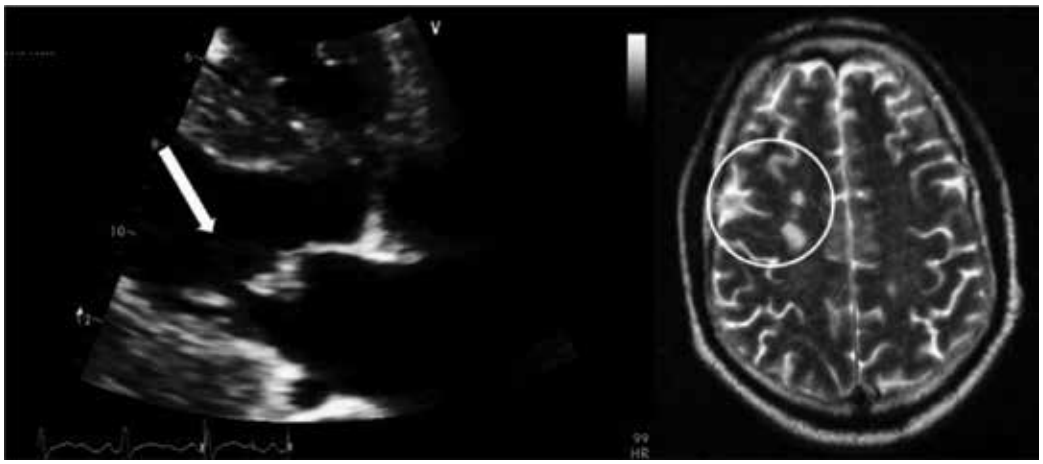

Figure 2. An example of septic embolization to the brain (circled) originating from an infected vegetation on the mitral valve (arrow) (source: Ref. [29]. Image used under the terms of the Creative Commons Attribution-Noncommercial-Share Alike 3.0 Unported license).

between intracerebral hemorrhage and ischemic infarction based on clinical symptoms alone, and importantly, the American Stroke Association recommends against the use of intravenous Alteplase in cases of suspected ischemic stroke due to SE because of elevated potential for hemorrhagic conversion [23]. At the time of this publication there is no specific recommendation for or against intra-arterial intervention (e.g., thrombectomy) in the setting of SE causing large vessel occlusion and cerebral infarction, and cases should be evaluated on an individual basis.

Risk factors for mortality in stroke caused by SE include MRSA infection, older patient age, and larger vegetation size [44]. Patients with right-sided IE can also experience cerebral SE although it is very uncommon and occurs through the so-called "paradoxical embolus" pathway [45, 46]. Prompt evaluation for cerebral SE is critical in any patient presenting with focal neurologic symptoms, and usually starts with computed tomography (CT) of the brain to rule out bleeding, and potentially CT-Angiography to evaluate the cerebral circulation for patency. One must keep in mind that, regardless of clinical symptoms, the majority of patients with IE have some evidence of cerebral SE on magnetic resonance imaging (MRI) [47, 48].

Patients with cerebral SE have elevated mortality rates compared to patients presenting with stroke from other etiologies. In fact, baseline mortality of approximately 8–9% may reach nearly 40% in the presence of meningitis, hemorrhage, or brain abscess [39]. In the setting of mild cerebral ischemia, immediate antibiotic therapy combined with valve surgery within 48 h results in improved outcomes, including fewer systemic embolic events and more favorable mortality profile [49]. Recent studies also suggest that an ischemic stroke secondary to IE is unlikely to transform into a hemorrhagic stroke [50]. Primary indications for surgery in the setting of IE include the emergence of heart failure, uncontrolled infection, and embolism prevention [49]. Note that antithrombotic therapy is somewhat controversial in this setting. The American Heart Association guidelines for surgical intervention state that in the absence of severe neurological deficits, cardiac surgery should be considered urgently [50, 51]. In cases

of severe ischemic stroke, it is recommended to delay surgery by at least 4 weeks, and with hemorrhagic stroke (usually a more severe complication) at least 4 weeks are recommended prior to proceeding with cardiac surgery [50].

3.2. Eyes

Septic embolization involving ocular and facial structures is extremely rare. There is, however, fragmentary case-based evidence for such occurrences. In one example, Dadu et al. [52], described SE involving the ophthalmic artery and the inferior muscular artery, resulting in diplopia due to medial rectus muscle paralysis. In that particular case, IE of the mitral valve was causative. In another rare occurrence, Cumurcu et al. [53], describe a case of a septic metastasis to the iris, resulting in iris abscess and endophthalmitis.

3.3. Thyroid

The possibility of SE to the thyroid has been proposed in 1959 by Richie while describing acute suppurative thyroiditis in a child [54]. Cabizuca et al. [55], reported an unusual case of IE leading to acute thyroiditis, presumably due to septic embolization. Although undoubtedly uncommon, the paucity of literature reports in this area is likely due to limited awareness and under-recognition of similar clinical presentations.

4. The thorax

Given the pathophysiologic factors discussed earlier in the chapter, SE of cardiac origin tend to follow the pattern of "cardiac output." Consequently, a generalization can be made that the higher the blood flow to a specific organ or anatomic region, the higher the chance of SE traveling there. Within the thorax, there are two commonly described types of septic emboli—those originating on the "left side" of the heart and involving the coronary arterial circulation or thoracic aorta [56, 57], and those originating from the "right side" and involving the pulmonary arterial circuit [58–60].

4.1. Coronary circulation

First described in the 1910s and 1920s, septic coronary embolism continues to be under-recognized as a cause of acute coronary ischemia [56]. These types of emboli predominantly originate from bacterial valvular vegetations [61]. A high index of clinical suspicion is required because electrocardiographic (ECG) and laboratory changes characteristic of myocardial ischemia can easily be misinterpreted as being due to more typical coronary artery thrombosis [29]. The diagnosis is established through the performance of a comprehensive work-up, including trans-thoracic and trans-esophageal echocardiography (TEE), with subsequent angiography as indicated [62, 63]. Management may include a variety of both non-interventional and interventional procedures, up to and including surgical cardiac revascularization at the time of valve replacement [29].

4.2. Thoracic aorta

Mycotic aneurysms of the aorta have been described as a consequence of septic emboli from infective endocarditis [64]. Clinical management of these lesions is challenging, partly due to the presence of active infection within the aneurysm itself, and partly due to the associated inflammatory changes and altered (e.g., diminished) structural integrity of the involved aorta [65]. Mycotic aortic aneurysms are associated with significant mortality and complications, including the potential for the development of aortoesophageal or aortotracheobronchial fistula [66, 67].

4.3. Pulmonary artery

Pulmonary artery aneurysms (PAA) of infectious etiology are among less frequently seen complications of endocarditis [68, 69]. They are similar to mycotic aneurysms, with the main difference being the location of occurrence [70]. PAAs (also referred to as Rasmussen's aneurysms) can be seen in patients with tuberculosis. However, there have been recent cases with PAAs being associated with endocarditis [70, 71]. These aneurysms require prompt surgical treatment given published mortality rates of approximately 50% [72]. Patients with aneurysms that are symptomatic or >6 centimeters in size are candidates for surgery [73]. Data regarding surgical treatment are limited; however, recent studies have shown that steel coil embolization may be applicable in this setting [70, 74–76]. While PAAs are uncommon in endocarditis, they should be considered in patients with IE that present with pulmonary symptoms.

4.4. Pulmonary circulation

Pulmonary SE are relatively common complications of right-sided IE (RSIE). As outlined in previous sections, any areas through which large volume of blood transits will be inherently susceptible to SE. The pulmonary arterial circuit is no exception in this regard. From an anatomic standpoint, evidence suggests that septic pulmonary emboli (SPE) involve both upper and lower lobes, with bilateral upper lobes involved in >70% of patients, and peripheral or subpleural zones involved in >90% of cases [58]. Centrally located lesions were noted in only about 25% of instances [58]. SPE are distinct from other types of pulmonary emboli because of their tendency to form cavitary lesions with air-fluid levels [77]. A significant proportion of patients with RSIE are intravenous drug users [78, 79], although there is an increasing number of patients with SPE who present with IE due to implanted cardiac devices [80, 81]. SPE in intravenous drug users can manifest with empyema, and is most likely to be associated with endocarditis due to *S. aureus* infection [82]. Other common complications of SPE include pulmonary abscess and pulmonary nodules [77]. If patients with either empyema or a pulmonary abscess are identified, it is crucial to continue intravenous antibiotics and preform an incision and drainage prior to any required valve surgery [83]. Waiting is not recommended as a strategy in these patients, mainly because of the risk of further complications associated with therapeutic delays [83, 84]. Pulmonary and perivalvular abscess should be suspected in intravenous drug users who fail to respond to antibiotic administration [84].

As with any other type of pulmonary embolism (PE), SPE can be life threatening [85–87]. It is important to note that it may be initially difficult to differentiate between the two types of PE. Consequently, diagnosis and management requires high levels of clinical suspicion, appropriate diagnostics (e.g., TEE), and immediate treatment (antibiotics, with surgery if indicated). Most SPE patients present with constitutional symptoms, dyspnea, chest pain, and cough (including hemoptysis) [58]. CT imaging may show the presence of cavitary lesions with an associated "feeding vessel sign," representing a pulmonary artery coursing directly into the infected area [88].

5. Abdomen and retroperitoneum

5.1. The spleen

Septic embolism to the spleen is well described as a complication of IE [10]. In fact, after SE to the central nervous system (>50%), spleen appears to be the second most commonly involved organ in terms of frequency (approximately 30%), with some variability across sources of reported data [18, 28, 89]. One of most common presentations of SE to the spleen is the appearance of single or multiple abscesses [90], including microscopic lesions that were difficult-to-detect until the advent of advanced CT imaging [89]. Abdominal CT and MRI are the gold standard for diagnosing splenic abscesses [8]. Infected splenic artery aneurysms attributed to embolic sequelae of IE have also been reported [91]. Clinical management involves splenectomy in about 50% of cases, with percutaneous drainage indicated for large isolated abscesses and patients who are poor surgical candidates [29]. In cases of splenic arterial aneurysm and infarction, prompt surgical intervention is recommended. Patients should undergo drainage of the abscess or splenectomy prior to any cardiac surgery. This may help prevent further propagation and/or distant spread of the systemic infectious process [8, 91]. An example of splenic SE is shown in **Figure 3** [92].

5.2. The liver

Septic emboli to the liver are relatively common, occurring in >10% of cases of IE [10]. Similar to SE to the spleen, SE to the liver have the potential to evolve over time, coalescing from smaller "micro-abscesses" into larger collections [10]. Hepatic abscesses can be present in association with either right-sided or left-sided endocarditis [93, 94]; however, it may be difficult to determine whether the origin of the infection is cardiac or extra-cardiac, especially when the involved microorganism has known affinity for both locations [94]. Clinical management should follow established guidelines and practices for the treatment of IE and hepatic abscesses [29]. Similar to splenic abscess management, hepatic abscess should be drained as soon as possible in order to prevent worsening and/or further spread of the systemic infectious process [95].

5.3. The pancreas

Due to its vague clinical presentation, SE to the pancreas has the potential to go unrecognized. This is partially because SE to the pancreas often co-occurs with SE to other organs, potentially leading to "clinical masking" of organ-specific symptoms and/or signs [96]. Clinically, septic emboli to the pancreas may result in a picture resembling acute pancreatitis, and are

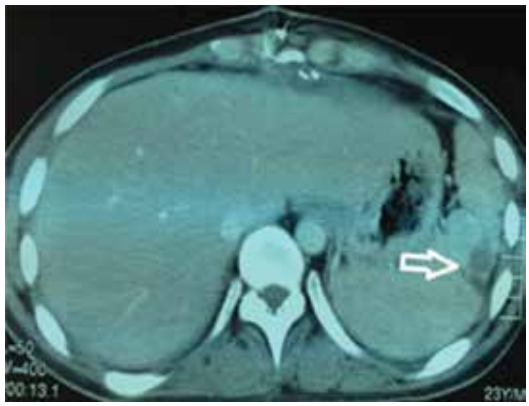

Figure 3. An example of septic embolus to the spleen. In this particular case, the embolus originated from *Corynebacterium diphtheriae* endocarditis (source: Ref. [92]. Image used under the terms of Creative commons Attribution-Noncommercial-NoDerivs Unported license).

usually characterized by leukocytosis, elevated pancreatic enzymes, peri-pancreatic "stranding" on CT scan, and acute abdominal pain [29]. Most often, pancreatic involvement in the setting of IE and SE tends to be self-limited [10]. At times, the finding of pseudoaneurysms involving adjacent arterial structures may provide a hint that the origin of the observed clinical syndrome is a result of SE [97].

5.4. The kidneys

Similar to the pancreas, SE to the kidneys is most often described in the setting of multi-visceral involvement [29]. Overall, renal SE are relatively frequent in the setting of IE, and their manifestations include infarcts in 31% of cases and glomerulonephritis in 26% [98]. Of interest, glomerulonephritis seen in association with IE has been shown not to feature immune complex deposition [98]. The co-occurrence of SE to other organs with arterial "high-flow" characteristics is exemplified by cases involving simultaneous cerebral, splenic, renal, and intestinal emboli [96]. Clinically, patients with renal SE may be found to have hematuria, glomerulonephritis, and evidence of renal failure [10]. Management focuses on preservation of renal function and is generally supportive, including antibiotic treatment, end-organ support (if required), and percutaneous or open interventions (in cases where abscess drainage is indicated) [98–100].

Etiology of renal injury in patients with IE is not always obvious, especially given the combined effect of cardiac dysfunction, sepsis, and concurrent treatment with potentially nephrotoxic antibiotics [98, 101]. Systemic infection can lead to acute tubular necrosis, while antibiotic treatment can lead to acute interstitial nephritis [102]. It is important to differentiate these conditions from the glomerulonephritis that is seen in IE, with an outline of important differentiating factors provided in **Table 2**.

5.5. The intestines including mesenteric involvement

Given its large surface area and rich vasculature, the bowel receives a significant amount of cardiac output and is highly susceptible to SE originating from IE [10, 29]. Fortunately, when compared to other organs and organ systems outlined above, arterial distribution to the

Type of kidney injury→	Glomerular	Interstitial	Tubular	Vascular
Typical causes	Bacterial endocarditis and vasculitis	Antibiotics	Sepsis and hypovolemia	Renal ischemia
Cast type	Red blood cell casts	White blood cell casts	Granular casts	Tubular epithelial cell casts
Clinical management	Treatment of underlying etiology	Remove inciting substance	Hydration and treatment of underlying condition	Surgical correction of underlying pathology

Table 2. Types of kidney injury, including their associated differentiating characteristics [102].

bowel appears to be less commonly affected (e.g., superior mesenteric artery in 3%, inferior mesenteric in <1%) [103]. This may be, at least in part, due to the presence of some degree of redundancy within the mesenteric vasculature, as opposed to a lack of such redundancy in the kidney or spleen. Occlusion of the superior mesenteric artery by SE is relatively well described in the setting of mitral valve endocarditis [104]. Mesenteric pseudoaneurysm attributable to SE has also been described [105]. In cases of acute arterial occlusion, bowel infarction may follow without prompt restoration of adequate blood flow to the involved segment(s) of bowel [106].

5.6. Reproductive organs

The involvement of reproductive organs in septic embolic complications is very uncommon. However, the authors believe that at least a brief overview of this under-recognized topic is warranted. In terms of testicular involvement, symptomatic presentation, including swelling, has been reported in conjunction with right-sided endocarditis [107]. It is thought that the this unusual clinical picture may result from SE [52, 107]. In another case, pneumococcal pulmonary valve endocarditis has been circumstantially linked to epididymo-orchitis and a scrotal abscess [108], although the directionality of causation may be difficult to prove except for the fact that *Streptococcus pneumoniae* isolated from the epididymo-orchitis is seldom a primary cause of scrotal infection. Equally uncommon, ovarian involvement has also been reported. In an exceedingly rare case, a female patient presented with a giant pyomyoma suggestive of ovarian neoplasm [109]. The origin of this presentation, however, was traced to *Streptococcus agalactiae* endocarditis and deep vein thrombosis of the right external iliac and femoral veins [109].

6. Extremities and musculoskeletal system

In general terms, extremity involvement in association with IE represents approximately one-third of all cases of SE, with clinical manifestations involving the musculature in approximately 40% cases and bones/joints in >10% of instances [10, 110]. Other than massive embolic events involving acute occlusion of arterial flow to an extremity producing significant ischemia, symptoms tend to be more “nebulous” in terms of clinical presentation, more self-limited in nature, and easily overlooked by clinicians [10, 100]. Pathognomonic signs such as Osler nodes

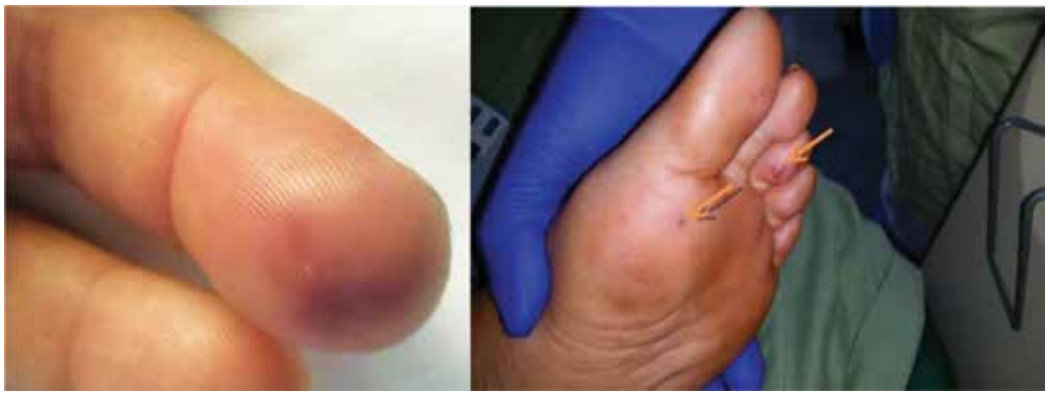

Figure 4. (A, left) An example of an Osler node in a patient with infective endocarditis (source: Ref. [112], image used in accordance with the terms of the CC BY 4.0 License); (B, right) Janeway lesions (see arrows) in a patient with aortic valve vegetation (source: Ref. [113], image used under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License).

and Janeway lesions are rare (2.7 and 1.6% cases, respectively) but highly suggestive of endocarditis [111]. **Figure 4A** shows an example of an Osler node, while **Figure 4B** demonstrates a Janeway lesion [112, 113].

6.1. Acute extremity ischemia

This potentially devastating presentation has been reported in the setting of more severe cases of IE, often involving valve replacement [114–116], with some patients experience multiple/recurring embolic events [114, 115]. In terms of clinical presentation, patients may exhibit a broad spectrum of complaints including pain, pallor, poikilothermia, and paresthesias with extreme cases threatening the viability of the limb itself [114]. Both surgical and thrombolytic management options have been reported [117, 118]. Prompt recognition of the cardiac source of SE is critical in preventing further embolic events.

6.2. Septic arthritis

Due to their non-specific nature and general commonality, joint-related complaints can be challenging to diagnose and easily misinterpreted. Not infrequently, multiple diagnostic tools must be utilized to successfully identify the cardiac source of the patient's original symptoms (and thus the proximal source of infection) [119]. In one case, it was the complaint of septic arthritis which led to the ultimate diagnosis of streptococcal endocarditis [120]. Similar to other embolic phenomena associated with IE, septic arthritis tends to be a manifestation of multi-focal metastases of infectious material [119, 121].

7. Uncommon neurologic presentations

This section will discuss a heterogeneous group of less common manifestations of SE affecting the CNS, including extracranial involvement. The paucity of published literature in this broad

topic area is likely due to limited awareness and under-recognition of such clinical presentations. Within the microcosm of SE associated with IE, approximately 30–40% of events involve neurological manifestations [10, 122]. Beyond the more commonly seen complaints (e.g., stroke, transient ischemic attack, meningitis, brain abscess) within this subset, less frequently reported clinical manifestations may include visual loss, seizures, acute mononeuropathy, and even spinal cord involvement [122–124]. Septic emboli can migrate to the spinal cord, causing segmental infarction [122, 123]. These exceedingly rare events have the potential to result in severe disability and often accompany additional, simultaneous SE to other anatomic regions [10].

8. Miscellaneous considerations

During the past two decades, significant increases have been noted in the number of valvular repairs, valve replacements, intracardiac devices and hemodialysis catheter placements [125–128]. Collectively, these procedures inherently create a small, but significant risk of IE, especially in patients with chronic comorbid conditions such as renal insufficiency, diabetes and autoimmune diseases [129–131]. Given the potential for major morbidity and mortality associated with IE in the setting of indwelling intravascular/intracardiac devices, the primary focus should be on prevention. Within this context, efforts include more selective device implantation policies and better modulation of known post-implantation risks [132].

In terms of general diagnostic considerations, numerous guidelines and recommendations have been published to date. Although beyond the scope of the current discussion, certain aspects of these recommendations warrant a brief mention [133, 134]. One very important highlight is the emphasis on prompt echocardiography in cases of suspected IE, with TEE recommended if the initial TTE is negative and clinical suspicion remains high [8]. Echocardiographic imaging can then be repeated in 3–5 days if clinical symptoms/suspicion persist [8]. It is also suggested that patients with vegetations >10 mm in size, embolic events while on antibiotic treatment, and patients with >2 embolic events should be evaluated for surgical intervention [8]. One unique diagnostic consideration is the inability to use magnetic resonance imaging (MRI) in patients with certain types of intravascular devices/implants. Amraoui et al. recently described the use of positron emission tomography (PET) as an alternative method of identifying foci of SE in patients with implantable cardiac devices, with limited success [135].

Treatment options start with intravenous antibiotics, however in certain cases prompt surgical treatment is necessary. The American Heart Association developed guidelines to assist with identification of patients who require prompt surgical intervention [136]. Patients with IE who develop decreased left ventricular ejection fraction (LVEF) or a new aortic or mitral valve murmur require prompt surgery [50, 136, 137]. Patients with preserved LVEF that are stable and adequately managed on medical therapy do not need an immediate corrective surgery [138]. However, a recent study demonstrated that surgical intervention in the setting of CHF can reduce mortality from approximately 60–85% to 15–35% when compared to medical therapy alone [139, 140]. Patients who present with valvular vegetations >10 mm in size, or with multiple vegetations on imaging, are likely to benefit from surgery [136]. Another important indication for surgery is lack of improvement after 7 days of appropriate antibiotic

therapy [136]. Any SE to end organs or associated arterial aneurysms also warrant immediate surgical evaluation and prompt intervention. As mentioned earlier in the chapter, emboli to different anatomic regions may require distinct plans and different timing in terms of surgical intervention [50]. The diagnosis of prosthetic valve endocarditis constitutes another major indication for surgical intervention. Patients who present within 60 days of discharge following the placement of a new prosthetic valve with persistent fevers should be evaluated for the presence of IE, and if proven to harbor such infection should undergo operative management. It is important to remember that roughly 25% of prosthetic valve patients may be at risk of IE [136, 141].

9. Conclusions

Despite significant clinical research and advances in clinical management, septic embolism associated with infectious endocarditis continues to be a diagnostic and therapeutic challenge. Given the increasing number of intravascular and intracardiac device implantations, as well as the greater prevalence of chronic comorbid conditions, it is not surprising that the incidence of both infectious endocarditis and septic embolism has followed suit. In this chapter, we outlined general pathophysiologic and anatomic considerations with which all physicians should be familiar. This important knowledge should serve to assist providers in maintaining a high level of clinical suspicion for potential IE and/or SE. Given the continued high rates of associated disability and mortality, more research is needed to better understand and treat these "low-frequency, high-impact" events.

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Chapter 11

Left Ventricular Assist Device Infections

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Additional information is available at the end of the chapter

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Abstract

Left ventricular assist device (LVAD) infections are important causes of morbidity and mortality in patients who receive these mechanical circulatory supports as a bridge to transplantation (BTT) or as destination therapy (DT) (for individuals who are not candidates for cardiac transplant). Infections are more common among persons who received pulsatile flow LVADs as opposed to newer continuous flow (CF) devices. Other risk factors for infection include obesity, renal failure, depression and immunosuppression. An LVAD infection increases the risk of infections in persons who undergo cardiac transplantation. Infections include percutaneous site, driveline, pump pocket and pump/cannula infections; sepsis, bacteremia, mediastinitis and endocarditis. Diagnosis is achieved by monitoring LVAD flow parameters and observing typical clinical and laboratory manifestations of infection. Imaging such as PET-CT or SPECT-CT imaging can be helpful to establish a diagnosis of pump pocket infection. Echocardiography may aid in detecting native valve endocarditis and thrombus associated with the LVAD. The most common pathogens include *Staphylococcus*, *Corynebacterium*, *Enterococcus*, *Pseudomonas* and *Candida* spp. Treatment requires targeted antimicrobials plus surgical debridement of infected tissue and device components. In cases of pump/cannula/LVAD endocarditis, especially if fungal pathogens or *Mycobacterium chimaera* are involved, LVAD removal/reimplantation vs. transplant is necessary, combined with extended antimicrobial therapy.

Keywords: left ventricular assist device, driveline infections, pocket infection, endocarditis

1. Introduction

Surgical management of heart failure has revolutionized the lives of patients with symptomatic end stage heart disease of all causes (reviewed in [1–3]). The first left ventricular assist device (LVAD) was implanted in 1963 by Liotta and Crawford ([4] and references therein),

followed by the implantation of the first artificial heart by Cooley in 1969, as a bridge to transplant. The famous Jarvik 7 artificial heart was implanted in 1984 by De Vries. It was not until 1994 that the FDA first approved the LVAD as a bridge to transplant, and only in 2010, was the HeartMate II LVAD, a continuous flow (CF) device, approved as destination therapy ([4, 5] and references therein). After January 2010, only continuous flow devices i.e. HeartMate II have been implanted. The HeartMate III, Heartware HVAD and the Jarvik 2000 LVADs are currently under study in clinical trials [6–8]. An increasing number of patients are receiving non-surgically deployed LVADs such as the Impella 5.0 (5 L/min flow) as they await a decision regarding cardiac transplantation versus destination therapy with a larger (10 L/min flow) standard device [9]. More and more patients who are not considered candidates for transplantation are receiving destination LVADs and have significant improvement in their NYHA functional class and quality of life despite the numerous potential complications that these patients often face [1, 10, 11]. As devices evolve, becoming ever smaller, more compact and potentially entirely contained within the patient, it is anticipated that many of the complications, particularly infectious complications, will diminish in frequency. However, with the current state-of-the-art, infectious complications including drive line infections, pocket infections, bacteremia and the most dreaded infectious complication, endocarditis and associated mycotic aneurysms, remain important causes of morbidity and mortality in LVAD recipients, both destination therapy (DT) and as a bridge-to-transplant (BTT). In this review, we will not consider complications of devices used in so-called "bridge to decision" therapy such as the Impella 5.0.

The continuous axial flow HeartMate II is now the most common LVAD in use in the US; between 2006 and 2016 a total of 17,008 CF LVADS have been implanted with 81% 1 year survival [12]. LVADs including HeartMate II and other devices have been reviewed in [1, 3, 4, 13–17]. Newer centrifugal flow devices, HeartMate III and HeartWare HVAD that are smaller and reportedly less prone to thrombosis and device failure are in clinical trials in the US [7, 8, 18] but have been utilized successfully in other parts of the world [19].

This review will focus on several aspects of LVAD infections including the rare complication of endocarditis, and will identify gaps in knowledge regarding diagnosis of LVAD infections, treatment and prevention of these infections. Differences in rates of infection in bridge vs. destination therapy will be discussed but the focus of review will be on destination therapy as that is where we see the most infectious complications. The epidemiology and microbiology of LVAD infections will also be addressed including risk factors and the impact of device related complications on post-transplant infectious complications. *Mycobacterium chimaera* LVAD infections will also be discussed.

2. Epidemiology and risk factors for LVAD infections

Several studies have looked at various aspects of LVAD candidates in terms of their risk of developing complications including infections. A significant reduction in infections has already been noted in a randomized trial comparing older pulsatile flow LVADs to current continuous flow (CF) LVADs [5]. The improvement in infection rates was felt to be due to the smaller size of the device and the driveline caliber [20]. An observational study of LVAD type

(pulsatile versus CF) spanning 2000–2009 in a single institution concluded that differences in infectious complications in that cohort were more related to when the device had been implanted, with more recent implantations showing fewer infections [21]. Subsequent innovations (axial to centrifugal flow) have not resulted in a reduction in infectious complications [7, 8] with an actual increase in sepsis with the Heartware HVAD device compared to HeartMate II control [7]. Studies have looked at factors including age [22], gender [23], body habitus including both small patients [24] and obesity [25], trauma [26], duration of LVAD support [27] as well as presence of comorbid conditions such as diabetes [28–30], depression and chronic kidney disease (CKD) [31], alcoholism and immunosuppression [29], and malnutrition ([32, 33] and references therein). In a Japanese multicenter trial looking at 300 patients receiving HeartMate II between April 2013 and December 2016, patients older than 60 had similar overall survival and risk of driveline and pocket infections [22]. An older study found that age and the presence of diabetes were associated with increased risk of LVAD endocarditis [34] with a median age of 59 among patients with endocarditis compared with a median age of 53 in those without ($p = 0.02$). Women receiving LVADs were often sicker (Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) cohorts 1 or 2) and had significantly higher bleeding complications, arrhythmias and right heart failure, but not infectious complications [23]. Driveline infections were slightly more common in smaller (body surface area (BSA) < 1.5 m^2) patients (13 vs. 12 patients, $p = 0.003$) but mediastinal infections occurred in 2 patient with BSA > 1.5 m^2 with no cases among smaller patients [24]. Clerkin et al. examined data from a BTT cohort of 3856 patients between 2004 and 2014, and found that patients with a body mass index (BMI) >35 kg/m^2 had a trend towards increased infection risk (hazard ratio 1.59, 95% confidence interval 0.99–1.94, $p = 0.058$) [25]. Diabetes mellitus as a risk factor for infection was studied among 341 individuals who underwent LVAD implantation at Mayo Clinic between 2007 and 2016 [28]. Thirty-eight percent of the LVAD recipients had diabetes, and those patients also had significantly more ischemic cardiomyopathy as a cause for LVAD implantation, more were receiving LVADS as destination therapy and these patients also had higher BMI than those without diabetes. Looking at a composite endpoint of stroke, pump thrombosis and infections, patients with diabetes were 2.1 times more likely to have a poor outcome. There was a 1.73 fold increased risk of all cause mortality among diabetic patients as well. Interestingly, pre-operative hemoglobin A1C (HgbA1c) levels were not related to adverse outcomes, and LVAD recipients experienced lower HgbA1cC levels and lower diabetes medication requirements post-implantation. A large prospective multicenter trial of 86 HeartMate II recipients identified depression and CKD as independent risk factors for infection [31], with adjusted hazard ratios of 2.8 ($p = 0.007$) and 1.7 ($p = 0.023$) respectively. A multicenter trial in France looked at 159 patients who received LVADs between 2007 and 2012 and found that 22.6% of the patients had at least one infectious complication [29]. LVAD infections in this cohort were associated with alcoholism in 33%, diabetes in 11% and other immunosuppression in 11%. Of note, a small case series of 4 HIV patients implanted with LVADs did not show an increased risk in infection and one of the patients was successfully transplanted [35]. The implantation of an LVAD itself seems to result in reduced cell mediated immunity with decreased interleukin-2 (IL-2) and tumor necrosis factor (TNF) production, and increased IL-10 by T-lymphocytes. Greater numbers of suppressive regulatory T-lymphocytes (T_{regs})

are found in these patients for an average of 6 months post-implantation ([36], also reviewed in [33]). LVAD induced immune deficits appear to resolve in CF devices as compared to older pulsatile devices ([33] and references therein).

2.1. Impact on post-transplant infections

Additional studies have looked at outcomes in transplant patients who developed LVAD infections either as BTT or DT (where the infection was treated in part by removal of the DT device, with subsequent receipt of an organ) [20, 30, 34, 37, 38]. In US studies, pre-transplant LVAD infections appear to influence outcomes in cardiac transplant patients, with more infectious complications in those with prior LVAD infectious complications. Other risk factors in multivariate analysis included age, ICU length of stay and use of an anti-thymocyte agent [38]. A sub-study of the Swiss Transplant Cohort Study found that pre-transplant LVAD infections did not have an impact on post-transplant outcomes with slightly lower rates of infection and slightly higher survival rates among LVAD BTT patients [37]. Enterococcal infections including with VRE and Staphylococcal infections were most common among LVAD associated post transplant infections [30, 34]. The presence of infections with molds such as *Aspergillus* spp. are felt to be a strong relative contraindication for transplantation [6].

3. Microbiology of LVAD infections

The microbiology of LVAD infections has been extensively reviewed [20, 26, 27, 29–31, 33, 34, 37, 39–43]. In the main, LVAD infectious etiology is related to the particular clinical syndrome e.g. driveline infection vs. pocket infection vs. endocarditis. The International Society for Heart and Lung Transplantation classifies infections as "VAD related" or "VAD specific" to refer to bacteremia, endocarditis and mediastinitis versus driveline, pocket and pump/cannula infections [13]. INTERMACS lists non-device related infections, device related infections (internal pump infections; percutaneous site infections and pocket infections (listed together)) and sepsis [12].

3.1. Bacteremia and sepsis

Bacteremia and sepsis are seen most frequently in the peri-operative period and often these infectious disease syndromes are associated with non-VAD infections such as central line associated blood stream infections (CLABSIs), ventilator and hospital associated pneumonia, urinary tract infections, *Clostridium difficile* associate diarrhea and colitis. The microbiology of these peri-operative non-VAD infections has been reviewed in the references above and will not be covered again in this chapter.

LVAD related bacteremias can also occur with associated sepsis, and may be related to device infections (pump pocket, pump/cannula), infective endocarditis and mediastinitis. The organisms detected in bacteremic patients (e.g. Staphylococci, Enterobacteriaceae, *Pseudomonas aeruginosa*, Enterococci, *Candida* spp.) are indicative of at least some of the possible device related organisms causing infection [20, 31, 34, 37, 40, 43, 44].

3.2. Driveline infections

Driveline infections are most common, and skin flora from patient's skin are the predominant pathogens detected (reviewed in [40]). Often, trauma of the driveline tunnel, due to rough manipulation of the driveline, and lack of skin fixation that reduces tension on the driveline, leads to infections. The microbiology includes *Staphylococcus aureus*, both methicillin susceptible (MSSA) and resistant (MRSA), coagulase negative *Staphylococci* (CNS) (*S. epidermidis*), *Corynebacterium* spp. [21, 26, 27, 33, 34, 45, 46], viridans streptococci [31], *Enterococcus faecalis* [31, 34], *E. faecium* including vancomycin resistant strains "VRE" [30], Gram negative enteric bacilli such as Enterobacteriaceae (*Enterobacter cloacae* and *E. aerogenese* [31] *Escherichia coli*, *Klebsiella* spp. [34], *Proteus mirabilis* [31], *Serratia marcescens* [21]), *Pseudomonas aeruginosa* [20, 26, 31] and *Stenotrophomonas maltophilia* [31]. There have been rare instances of fungal driveline infections with *Candida* spp. such as *C. albicans, glabrata* [20, 31, 34]. There have been recent series of reports of infections with *Mycobacterium chimaera*, related to open chest surgery and cooling units employed for cooling cardioplegia solution [47]. In rare cases, patients developed endocarditis in the setting of recent valvular surgery. To date, one case of a complicated LVAD driveline infection with abdominal wall abscess by *M. chimaera* has been reported [48].

Biofilm formation by many different organisms contributes to persistence of infections due to the poor efficacy of antibiotics against organisms within biofilms, even when drug resistance is not present [33, 40, 43, 49].

3.3. Pocket infections

Pocket infections can occur at the time of implantation, during trauma to the driveline and pocket from driveline manipulation or bleeding into the pocket from coagulopathies [20]. The microbiology of pocket infections is thus very similar to driveline infections, with skin flora such as Staphylococci and Corynebacteria predominating, as well as *Enterobacteriaceae*, Enterococci, *Pseudomonas* and *Candida* spp. [20, 26, 31, 40]. We are in the process of reporting on a patient with a HeartMate II LVAD for DT who cracked his driveline and had extensive hematoma formation in the pump pocket with subsequent persistent infection and bacteremia with *Enterobacter cloacae (*Skalweit, in preparation). Computed tomography images of this patient are shown in **Figure 1**, with hematoma, phlegmon and small air bubbles evident in the pump pocket (a) before debridement. **Figure 1b** is after debridement. **Figure 2a–c** shows the pump pocket wounds after debridement, with placement of a vacuum wound device and after closure of the defect. One case of a pocket infection with *M. chimaera* has been reported in a patient who developed a fluid collection contiguous with the pump pocket [48]. The patient underwent extensive debridement and omental flap coverage of the device. Operative specimens were routinely cultured and he was empirically treated with broad spectrum antibiotics but did not respond to therapy. Subsequent mycobacterial cultures revealed the pathogen and he was maintained on lifelong *M. chimaera* therapy.

3.4. Mediastinitis

As a direct extension of pocket infections or as a result of sternal wound infections, LVAD associated mediastinitis is rarely observed [34, 43, 48]. *S. aureus* (MRSA), CNS, and vancomycin

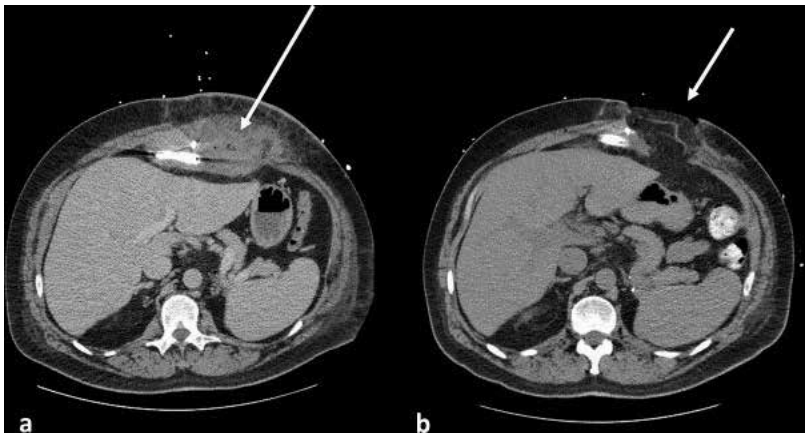

Figure 1. (a and b) Computed tomography (CT) images of pump pocket infection before (a) and after (b) surgical debridement. Solid arrows show the location of a complex hematoma, phlegmon and air bubbles. Operative cultures grew a susceptible *Enterobacter cloacae*.

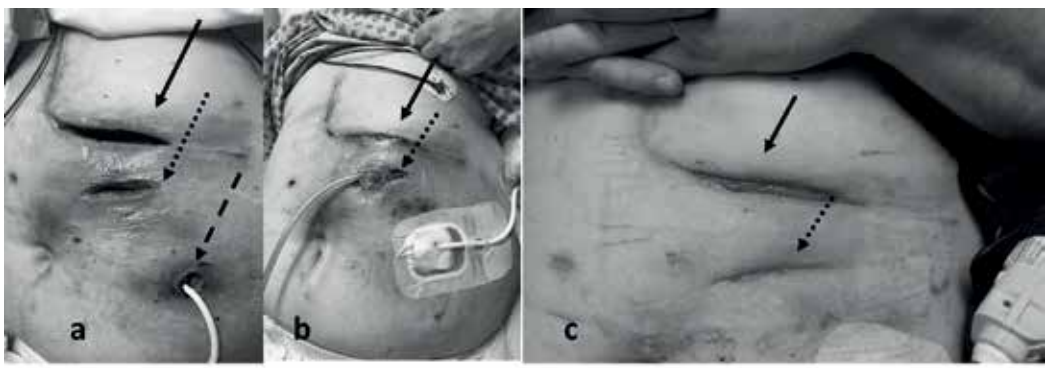

Figure 2. (a–c) Wound care in *Enterobacter cloacae* pump pocket infection, post debridement (a), with wound vacuum device placement (b) and after healing (c). Heavy and dotted arrows indicate the pump pocket wounds, dashed arrow is the driveline.

susceptible *E. faecalis* were the reported pathogens in five patients with LVAD mediastinitis [34]. A single case of fungal mediastinitis presenting with LVAD outflow obstruction caused by growth of *Syncephalastrum racemosum* has been reported [50]. The concern with mediastinal infection is always one of extension to involve the great vessels, the pericardium and bone, requiring potential additional source control and extended antibiotic therapy.

3.5. Infective endocarditis and pump/cannula infections

Endovascular infections can occur on native valves, prosthetic valves as well as in association with the LVAD pump body and cannula and are associated with high mortality [26]. Early case reports with older generation pulsatile flow devices described LVAD valve replacement on a Novacor N100 LVAD [51]; pathology revealed Gram positive cocci. A series of fungal LVAD

infections revealed that 3% met criteria for LVAD endocarditis (cultures of blood and explanted LVADs positive for fungal pathogens) [50]. *Candida albicans*, *C. parapsilosis* and *S. racemosum* were isolated in 3, 1 and 1 case respectively. More recently in the continuous flow era, LVAD associated endocarditis has been defined as "clinical evidence of pump and/or cannula infection along with the presence of vegetations on echocardiography or a vascular phenomenon as defined by modified Duke's criteria" ([26] and reviewed in [42]). *Staphylococcus aureus* (MRSA, MSSA) predominates, as well as CNS (MRSE, MSSE) and *Pseudomonas aeruginosa* (reviewed in [42]). Cases of linezolid resistant *Streptococcus sanguinis* [52] and *Listeria monocytogenes* [53] with associated leukocytoclastic vasculitis have also been reported.

3.6. Cerebrovascular microbleeds/stroke/mycotic aneurysm

Other complications related to LVAD infections can include hemorrhagic stroke and mycotic aneurysm. Patients with heart failure are already at risk of thrombosis, and increased infectious complications and coagulopathy associated with LVADs increases the risk of device thrombosis and stroke (reviewed in [54]). Aggarwal et al. [55] studied the relationship between bacteremia and stroke in LVAD patients in a retrospective chart review study. They studied 80 patients who had undergone LVAD placement in their institution, of whom 30 developed blood stream infections. Among those 30, 13 developed hemorrhagic strokes (43%) compared to 5/ 50 (10%) in LVAD recipients without bacteremia. In their report, the majority of BSI were caused by Staphylococci (CNS, MRSA). Yoshioka et al. found a similar association with hemorrhagic stroke in patients with either bacteremia or pump pocket infection [56, 57]. Organisms isolated among the nine patients in their study with hemorrhagic stroke included methicillin susceptible *S. epidermidis* (MSSE), MSSA, *Corynebacterium* spp., MRSA, CNS, *E. faecalis*, *Bacillus* sp. and *Campylobacter* sp. A rare complication in an LVAD recipient is mycotic aneurysm related to prior recurrent *Klebsiella rhinoscleromatis* bacteremia and subarachnoid hemorrhage [58].

3.7. Drug resistance

Prior treatment with antibiotics and extended therapy with narrow spectrum antibiotics did not appear to increase risk for LVAD infections with multidrug resistant organisms (MDRO) [59]; MDRO infections were related to indication (DTT > BT), obesity and driveline technique ("velour exposed" versus buried). However, a recent case series reported that high level daptomycin resistance in *Corynebacterium striatum* LVAD infections was selected for by using daptomycin as treatment [60].

4. Diagnosis of LVAD infections

LVAD infections can manifest in many ways from indolent infections in patients that are minimally symptomatic to septic patients requiring intensive care. Most sources [13, 27, 39, 40, 43, 61, 62] agree on general investigations that should occur in order to diagnose an LVAD related or device specific infection. If LVAD infection is suspected, driveline and three sets

of blood bacterial cultures before antibiotics are administered should be obtained, in addition to routine laboratories: complete blood count (CBC); complete chemistries including LDH; coagulation studies (fibrinogen, platelets, D-Dimer, Factor VIII, INR, PTT); erythrocyte sedimentation rate, C-reactive protein). Procalcitonin is elevated in the initial postoperative period and does not appear to be a useful marker of infectious complications [63]. Imaging of the driveline and pump pocket using ultrasound has been suggested by some groups to assess for fluid in the pump pocket or tracking along the driveline. Computed tomography (CT) scanning is of limited utility due to the reflective properties of the pump body. However positron emission tomography (PET-CT) [64]; or gallium single photon emission computed tomography (SPECT-CT) [64–66], reviewed in [40]) have been used to diagnose infection of LVAD components as well as to assess for metastatic sites of infection often found with prolonged bacteremia with pathogens such as *S. aureus* and *P. aeruginosa* (reviewed in [40, 67, 68]). Erba et al. [69] showed that ^{99m}Tc-hexamethypropylene amine oxime labeled autologous white blood cell (^{99m}Tc-HMPAO-WBC) SPECT-CT had 94% sensitivity at detecting cardiac implantable electronic device infections, with 95% negative predictive value in patients with other sources of infection. Inflammation from driveline trauma may result in a positive PET-CT image, even in the absence of infection. Transesophageal echocardiography is utilized in the setting of positive blood cultures to look for vegetations on native valves or on device components [26, 44, 62]. However, it has been previously acknowledged that echocardiography may be of limited use in evaluating for vegetations, due to reflections off of the device's reflective metal surfaces [50]. The role of echocardiography [70] and the application of newer techniques such as real time three dimensional (3D) echo has been reviewed [71] and discusses utility in evaluating native valves and presence of thrombus.

LVAD parameters such as flow rates may also be an indication of infectious complications [61]. Elevations of B-type natriuretic peptide (BNP) were also found to be a marker of serious adverse events in LVAD patients, including severe infections such as sepsis, mediastinitis and pump pocket infections [72]. Thrombosis, alteration in coagulation parameters, stroke, acute renal failure may also be early indicators of infection as well as more routine signs such as fever, leukocytosis and localizing signs and symptoms.

Additional microbiologic techniques such as fluorescent *in situ* hybridization (FISH) and polymerase chain reaction (PCR) have been used to identify additional pathogens in biofilm obtained from explanted LVADs and may provide supplemental information on which to base antimicrobial selection [73].

5. Outcomes in LVAD infections

Clinical outcomes for LVAD implantation have been extensively reviewed (see for example [10, 61, 74, 75]) including for infection. It is estimated that 15% of LVAD recipients die due to infectious complications, with the majority of deaths occurring within the first 30 days of receipt [76]. More than half of the data available for review is for patients receiving CF devices for BTT indications. Overall rates of infection for CF devices in trials and registries with more

than 100 patients were follows: local site infections 20–49%; driveline infections 12–22%; pocket infections 2–5%; sepsis 3–36%; other types of infections 26–35% [10]. It is estimated from the INTERMACS registry data [12] that there are 8 infectious complications per 100 patient-months in CF LVAD recipients. The European Registry for Patients with Mechanical Circulatory Support (EUROMACS), a European registry of LVAD recipients includes data from 52 hospitals from 2681 patients with 2947 implants since 2014 [77]. Overall serious infection rates were 6.18 per 100 patient months within the first 3 months of implantation. Three year survival was only 44% in patients with CF devices, and 20% of the deaths were attributable to infections. In a retrospective study of 88 CF LVAD implantations (22% DT) between 2006 and 2014 at the Toronto General Hospital, 129 readmissions occurred, of which 17% were related to infections [78]. Despite this readmission rate (63% with at least one readmission), outcomes were excellent with only 6 deaths. Other analysis of the INTERMACS registry revealed that 19% of LVAD recipients developed a percutaneous site infection within 12 months of receiving a CF LVAD [79]. Ten percent of patients with these infections died, with sepsis being the most common cause of death (26%) [79]. In general, DT is associated with greater infection risk, and recurrence of infection, especially driveline infections. The majority of these infections are driveline infections and outcomes are generally good (reviewed in [80, 81]). Fortunately with infection control techniques, rates of driveline infections appear to be decreasing [82]. Pocket infections are less common but can confer greater risks of morbidity including hemorrhagic stroke [56, 57]. In a large prospective study of infections after cardiac operations, Perrault et al. found that LVAD and transplant patients experienced 5.8 times higher rates of mediastinal infections (95% CI 2.36–14.33) with five times higher readmission and mortality rates [83]. Nearly all cases of LVAD endocarditis will require explanation and replacement of the device as well as prolonged antimicrobial therapy, and the risks associated with these [42]. Outcomes are improving overall however. Among 156 patients who survived more than 4 years in one center, the mean survival was 7 years with ~1 readmission per year [84]. In terms of overall quality of life, 92% of these patients were NYHA Class I or II. The most common reason for readmission was infection (10%).

6. Treatment and prevention of LVAD infections

Management of LVAD infections is related to the specific LVAD infectious clinical syndrome [13, 26, 27, 30, 31, 42, 43]. Typically, combined medical-surgical treatment is needed, with infectious disease consultation to determine the best selection of empiric and microbiologically driven antimicrobials. Site infections and driveline infections are typically managed with local wound care and a combination of intravenous then oral antibiotics if possible as dictated by the organism isolated from the infected site. Percutaneous site infections have even been treated with topical agents such as crystal violet [85]. Sometimes the tunnel must be excised, and a new tunnel created with the application of a vacuum wound device to close the defect. Certain infections have been prevented by reducing exposed driveline material (velour) by keeping it entirely in the subcutaneous tunnel [82]. Preventing trauma to the driveline by use of anchoring devices [86], and use of sterile technique when changing the driveline dressing are key in preventing driveline infections. Standardized strategies for driveline dressings, and

in overall LVAD infection control within hospitals are also helpful in preventing infections [86–88]. Pocket infections must typically be managed with surgical debridement in the operating room with techniques such as omental wrapping of the pump housing to cover exposed metal and to close surgical defects [89, 90]. In rare instances, extrapolating from the orthopedic surgery literature, antibiotic impregnated beads have been placed in the pocket (reviewed in [91, 92]) although this has not been studied in a rigorous manner. Arguably, tissue levels of parenteral antibiotics are sufficient to treat residual infection once source control has been achieved. Placement of an additional foreign body in the pocket may not be advised, especially since the antibiotic concentrations from the beads will eventually wane, requiring subsequent bead exchange or removal. Repeated exposure to sub-inhibitory concentrations of antibiotic can lead to selection of antibiotic resistant organisms. Indolent pathogens such as *M. chimaera* or in the case of fungal infections may necessitate exchange of the pump and other components that are involved. LVAD endocarditis requires explanation and extended antimicrobial therapy, potentially with lifelong suppression if re-implanted or if cardiac transplantation occurs [42, 48, 50].

Optimal peri-implant antibiotic prophylaxis has not been established in a rigorous trial. However, "best evidence" was provided in a review by Acharya et al. [93] and consists of antibiotic coverage for Staphylococci, Enterococci, *Pseudomonas* and *Candida* spp. They concluded that use of an extended spectrum beta-lactam plus vancomycin in areas where rates of methicillin resistant *S. aureus* are high, a fluoroquinolone, fluconazole and mupirocin ointment (nasal application) in the "peri/post-operative" period (~3 days) was recommended. Prophylactic antibiotics are not recommended to prevent driveline infection after the immediate post-operative period [94].

7. Future directions

The development of biventricular or LVAD devices with transcutaneous energy sources ("TETs") will eliminate driveline infections [95]. However, this remains the "holy grail" for developers of mechanical circulatory support devices [96, 97]. Magnetically levitated pumps help reduce the rates of reoperation (and attendant complications like infection) [7]. Changes in size and materials involved in these devices can also reduce risk of thrombosis and enable easier explanation and reimplantation should complications arise [98]. Minimally invasive procedures such as off-pump implantation and alternative implant sites may also lead to reduced infection risk [99].

8. Conclusions

Left ventricular assist device (LVAD) infections are important causes of morbidity and mortality in patients who receive these mechanical circulatory supports as a bridge to transplantation (BTT) or as destination therapy (DT) (for individuals who are not candidates for cardiac transplant). Infections are more common among persons who received pulsatile flow LVADs as opposed to newer continuous flow (CF) devices. Other risk factors for infection include obesity, renal failure, depression and immunosuppression although HIV positive LVAD recipients have not had increased rates of infection in the limited number of recipients to

date. An LVAD infection increases the risk of infections in persons who undergo cardiac transplantation. Infections include percutaneous site, driveline, pump pocket and pump/cannula infections; sepsis, bacteremia, mediastinitis and endocarditis. Diagnosis is achieved by monitoring LVAD flow parameters and observing typical clinical and laboratory manifestations of infection (fever, local induration, erythema, abdominal pain, high flow LAVD parameters, leukocytosis, elevated inflammatory markers such as ESR, CRP; markers of coagulopathy). Elevated BNP may herald severe infection such as sepsis and pump pocket infection. PCR and FISH microbiologic techniques increase diagnostic yield of specific pathogens in biofilm on drivelines and other device components. Imaging such as PET-CT or SPECT-CT imaging can be helpful to establish a diagnosis of pump pocket infection. Echocardiography may aid in detecting native valve endocarditis and thrombus associated with the LVAD. The most common pathogens include *Staphylococcus*, *Corynebacterium*, *Enterococcus*, *Pseudomonas* and *Candida* spp. Treatment requires targeted antimicrobials plus surgical debridement of infected tissue and device components. In cases of pump/cannula/LVAD endocarditis, especially if fungal pathogens or *Mycobacterium chimaera* are involved, LVAD removal/re-implantation vs. transplant is necessary, combined with extended antimicrobial therapy. The "holy grail" of future mechanical circulatory support is a fully implantable device that relies on transcutaneous energy supplies. Devices of the future would be less prone to infectious complications potentially but would not entirely eliminate infectious complications. Smaller devices with magnetically levitated pumps, minimally invasive techniques and uniform infection control practices are the state-of the art in preventing infectious complications of LVADs today.

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Conflict of interest

Dr. Skalweit is an employee of the Department of Veterans Affairs. The opinions expressed here are her own and not those of her employer. Dr. Skalweit has no conflicts to declare.

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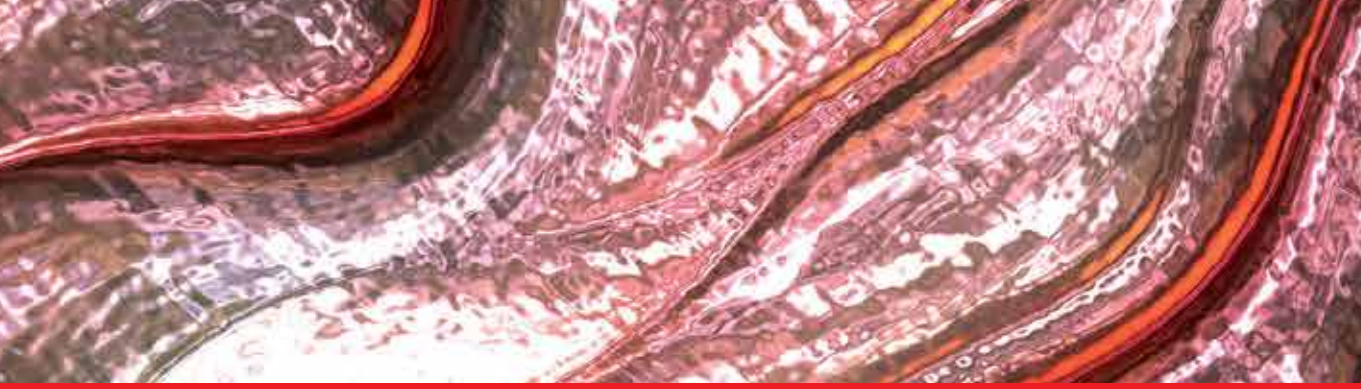

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Endocarditis is a disease process that involves an infection of the heart, cardiac structures, or implantable cardiac support devices and can be a difficult clinical problem. As patients get older and have more comorbidities, their risks for infection increase. In addition, the growing problem of intravenous substance abuse has led to a considerable increase in these patients developing endocarditis. Advances in medical technology have facilitated diagnosis and management, particularly with greater emphasis on early surgical intervention. Nevertheless, success requires a team approach and individualization of care in the setting of very complex medical, surgical, and ethical problems. The goal of this book is to illustrate some of the evolving challenges and controversies in managing these very complex and often extremely sick patients.

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