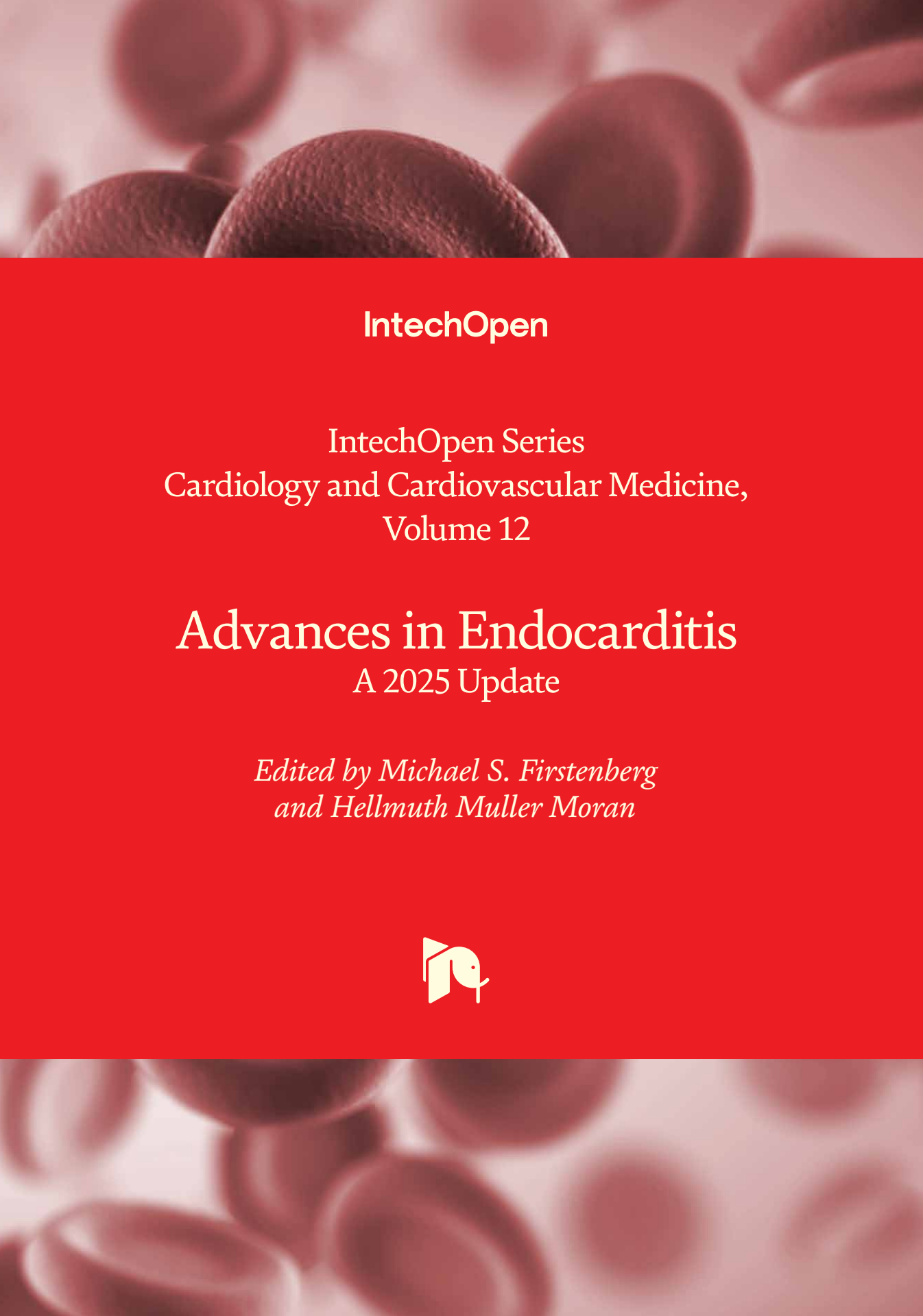


A microscopic view of red blood cells, showing their characteristic biconcave disc shape. The cells are in various stages of focus, with some in sharp foreground and others blurred in the background, creating a sense of depth. The color is a deep, natural red.

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Advances in Endocarditis

A 2025 Update

*Edited by Michael S. Firstenberg
and Hellmuth Muller Moran*



Advances in Endocarditis - A 2025 Update

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Meet the Series Editor



After completing his studies at the Medicine Faculty of Istanbul University in 1990, Prof. Kaan Kirali fulfilled his mandatory medical service and commenced his residency training at Koşuyolu Heart and Research Hospital in 1992. Following five years of assistant education, he pursued further training in England and the USA in 1998. Specializing in laparoscopic and minimally invasive cardiac surgery, he earned the titles of consultant cardiovascular surgeon in 1998, Assistant Professor in 1999, Associate Professor in 2002, and Chief in 2005 at the same hospital. Prof. Kirali also developed an interest in preventive medicine, obtaining an MSc in Public Health from Istanbul University in 2000. Over the past two decades, he has concentrated his scientific pursuits on cardiovascular repairs requiring specialized experience. With his expertise in coronary artery surgery, minimally invasive cardiac surgery, valve repair, and aortic root surgery, he has established new methods for awake coronary bypass revascularization, a new surgical approach for AVR during first and re-operations, aortic valve-sparing procedure, and radiofrequency ablation. Notably, he pioneered awake complete coronary artery bypass grafting (CABG) with bilateral internal mammary arteries (BIMA) and played a crucial role in advancing aortic root surgery with a new aortotomy incision, simplifying aortic valve interventions. Since the year 2000, Prof. Kirali has expanded his interests to heart transplantation, and in recent years, to left ventricular assist devices. He has served as the head of the transplantation department since 2015 and currently continues his work as the director of Koşuyolu High Specialization Education and Research Hospital in Istanbul, Turkey. In his prolific career, he has authored numerous papers in SCI journals, contributed to various book chapters, and served as an editor and reviewer for multiple academic journals. Additionally, he has edited several international books in the field of cardiovascular medicine.

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Preface

Infective endocarditis (IE) continues to pose a challenge to clinicians across various disciplines. Despite advances in antimicrobial therapy, imaging modalities, surgical techniques, and multidisciplinary care models, IE remains a deadly condition with significant morbidity and mortality. The risks are particularly concerning in patients with prosthetic valves, congenital heart disease, intravenous drug use, and immunocompromising conditions. Our ongoing difficulties in optimally diagnosing and managing this challenging disease, along with its complex associated problems, reflect the evolving nature of both the host-pathogen relationship and the healthcare systems tasked with providing appropriate and timely management.

This book, *Advances in Endocarditis – A 2025 Update*, was conceived as a collective effort among leading clinicians and researchers in cardiovascular medicine, infectious disease, imaging, cardiothoracic surgery, and critical care. This text seeks to offer both a contemporary review of emerging research and a practical foundation for clinicians confronting IE at the bedside. The reader will find novel insights, multidisciplinary perspectives, and above all, an unwavering commitment to the patient.

Precision in Diagnosis: The Foundation of Success

Accurate and timely diagnosis is the cornerstone of successful endocarditis management. After a short brief Introduction section, the second section, *Diagnosis of Endocarditis*, addresses three essential topics are addressed—each adding more insight to a critical aspect of our diagnostic armamentarium.

Quendo and Acosta start with a comprehensive analysis of multimodal imaging. As echocardiography evolves, so too does its integration with cardiac CT, MRI, and PET-CT, enabling more nuanced visualizations of vegetation, abscesses, and complications related to prosthetic valves. Their chapter emphasizes the growing importance of a combined approach—leveraging the strengths of each modality to reduce diagnostic uncertainty.

Peneva, Kunev, and Avramov focus on echocardiography, which remains the first-line tool in IE diagnosis. Despite its familiarity, transthoracic and transesophageal echocardiography continue to evolve with the advancement of 3D rendering and strain imaging. The nuances of interpretation, especially with prosthetic valve endocarditis, demand both technical skill and clinical insight.

Brangi et al. introduce the role of positron emission tomography (PET) in IE. While once relegated to oncologic imaging, PET-CT has emerged as a powerful modality in identifying low-grade infections and prosthetic valve complications, especially when standard imaging is equivocal. Its incorporation into the modified Duke Criteria has been a significant advance, redefining what constitutes a “definite” diagnosis.

These chapters emphasize a pivotal truth: diagnosis is no longer a binary concept. It is a spectrum that combines radiographic probability, microbiologic certainty, and clinical insights. In this age of data abundance, interpreting these signs with wisdom and restraint remains a deeply human endeavor.

Treatment Dilemmas: Balancing Art and Science

Section 3, *Treatment Options in Endocarditis*, transitions the discussion from detection to intervention. Each contribution reflects the challenges and opportunities in modern endocarditis management—from individualized care pathways to emerging technologies.

Hoover et al. explore the management of tricuspid valve IE—a topic gaining prominence due to the opioid crisis and the epidemic of IV drug use. The authors delve into the surgical versus medical debate, the duration of antibiotic treatment, and the role of valve repair versus valve replacement. Their discussion emphasizes the complexity of managing patients who are often young, socially vulnerable, and prone to recurrence.

Pavone and colleagues describe the creation of a dedicated endocarditis team—a model increasingly adopted across centers of excellence. Much like heart failure or stroke teams, these multidisciplinary units integrate cardiologists, infectious disease experts, surgeons, pharmacists, and case managers. The goal is unified Team decision-making by reducing delays, aligning goals, and minimizing interdepartmental silos.

Cornea et al. present state-of-the-art perspectives on ventricular assist device (VAD)-associated IE. As mechanical circulatory support becomes more common, the incidence of device-related infections rises. These are some of the most complex infections to manage, involving high stakes, biofilm formation, and difficult decisions regarding device explantation versus suppression. Their chapter provides both sobering reality and cautious optimism.

Griselli et al. revive an under-discussed topic: the Ross procedure in the context of IE. In young patients with aortic valve infection, the autograft approach can offer excellent hemodynamic outcomes and infection control—but not without trade-offs. Their insights invite a rethinking of what is possible when innovation meets experience. The insights in this chapter emphasize the importance of tailoring therapies to the specific presentations and demographics of patients – essentially, individualizing care models by recognizing that a “one size, fits all” approach is not always ideal.

Stawicki, Aultman, and Firstenberg address a harrowing complication: septic embolism. Whether cerebral, pulmonary, or systemic, emboli remain one of the most feared consequences of IE. Embolic complications are often the signs and symptoms that raise the index of suspicion for diagnosis and can, despite their clinical impact and risk, drive the indications for early surgical interventions. Their chapter synthesizes imaging strategies, anticoagulation controversies, and especially the timing of surgery in the face of neurological complications—issues that often test the courage and consensus of any heart team.

Finally, Laimoud et al. tackle the intersection of heart failure, mechanical circulatory support, and endocarditis. Their work emphasizes the fluid boundaries between infectious and structural cardiac disease. For some patients, heart transplantation may become the only path forward—requiring courage, clarity, and ethical reflection.

Future Directions

While this volume is rich in data, algorithms, and technical nuance, the essence of endocarditis care remains human, requiring individualization and a mindset towards lifelong management. Each patient's story is one of fragility and resilience, risk and recovery, and sometimes a reflection of the social challenges that are, unfortunately, becoming more common. It is impossible to read these chapters without being reminded of the stakes. IE is not merely a disease of the valves—it is a challenge to the entire healthcare system, to our ethics, and to our empathy.

In preparing this book, I am greatly appreciative of the contributors' commitment to excellence. Many of these authors are not only leaders in their fields but also stewards of collaborative care. They remind us that we do not face this disease alone. Whether through shared guidelines, joint surgeries, or compassionate bedside moments, we are at our best when we work together, with the best interests of the patient as our priority.

As we look toward the future of endocarditis management—incorporating artificial intelligence, molecular diagnostics, and minimally invasive interventions—the core question remains unchanged: “What is best for this patient, right now?” and how can we plan for the future.

I hope that *Advances in Endocarditis – A 2025 Update* will serve as both a reference and a source of reflection. May it guide your decisions, challenge your assumptions, and—above all—remind you of the privilege we have in caring for patients with this formidable disease.

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Section 1

Introduction

Introductory Chapter: Advances in Endocarditis

Michael S. Firstenberg

1. Introduction

Infective endocarditis (IE) has evolved from a relatively infrequent, subacute, rheumatic-valve-associated infection to a complex, complicated, challenging, and dynamic, multisystem disease disproportionately affecting patients with exposure to the healthcare system (s), prosthetic material, cardiac implantable electronic devices (CIEDs), acute/chronic immune system dysfunction (either through advanced diseases, such as cancers and autoimmune disorders, or medication induced), and substance use disorder (SUD). Currently, progress in rapid molecular diagnostics, hybrid imaging, selective oral step-down antimicrobial strategies, and earlier, protocolized surgery, implemented through formal “endocarditis teams” and professional society guidelines, has refined standards of care. Yet, fundamental challenges persist: culture-negative disease, antimicrobial resistance, device- and transcatheter valve-related infections, and the ethical dilemmas surrounding re-operative surgery in patients with ongoing IVDU. In addition, most importantly is the difficulties in patient selection when deciding about options for medical management vs. interventions that are becoming high-risk, more complicated, and associated with significant morbidity and/or mortality. This text synthesizes key advances, emphasizes decision-making at the bedside, and proposes a pragmatic research agenda aimed at closing the remaining gaps.

Few cardiovascular diagnoses demand the speed, precision, and humility of infective endocarditis. The disease requires timely decision-making and execution on therapies and furthermore, and there is no one-size-fits-all dogma. The contemporary IE patient is more likely to have a prosthetic valve, a transcatheter valve, a CIED, an indwelling line, or an active substance use disorder than a history of rheumatic fever. Rapidly expanding the use of immune modulating medications for common medical auto-immune medical problems, such as rheumatoid arthritis, has contributed to a growing incidence in complicated cases of IE. Fortunately, in response, our diagnostic and therapeutic options have expanded: Molecular tools more effectively identify pathogens from culture-negative specimens; PET-CT refines prosthetic and device infection diagnosis; selective oral step-down strategies challenge the “six-weeks IV for all” rule; and earlier surgery (with better surgical techniques and tools) is increasingly recognized as a determinant of survival when heart failure, uncontrolled infection, or embolic risk loom large. What ties these threads together is not a single drug or device, but a system—an IE team—that can integrate infectious diseases, cardiology, cardiac surgery, imaging, addiction medicine, and palliative care into coherent action.

2. The evolution of epidemiology: Devices, prostheses, and drugs

Epidemiologic data over the last decade document a clear migration from classic native-valve disease to healthcare-associated and device-related IE, as well as a surge tied to the opioid and methamphetamine epidemics [1–3]. Prosthetic valve endocarditis (PVE) and CIED infections now account for a substantial and growing proportion of cases, often with coagulase-negative staphylococci, *Staphylococcus aureus*, and *Enterococcus faecalis* being the most common [ii]. The rapid adoption of transcatheter aortic valve replacement (TAVR) has generated a new substrate for infection with diagnostic and operative challenges—peri-annular complications, leaflet destruction difficult to visualize on transthoracic echocardiography (TTE), and frail hosts with limited surgical options [4].

3. Diagnostics beyond cultures: Molecular tools and hybrid imaging

3.1 Molecular microbiology

Culture-negative endocarditis (CNE) remains a diagnostic landmine, particularly in pre-treated patients or infections with fastidious organisms. Broad-range 16S rRNA PCR and next-generation sequencing (NGS) have emerged as decisive tools, especially when applied to resected tissue, embolic material, or explanted devices [5]. These modalities shorten the time to organism identification, support antimicrobial tailoring, and reduce empiricism—especially crucial when resistance patterns or unusual pathogens (e.g., *Tropheryma whippelii*, *Coxiella burnetii*) are in play.

3.2 PET-CT

Few tools over the years have revolutionized that diagnosis and guided the management of IE as PET-CT. For prosthetic material, TEE alone can be nondiagnostic. 18F-FDG PET-CT, when available, has become central to the diagnostic algorithm for PVE and CIED infections, improving sensitivity for peri-annular complications, low-grade infection, and extracardiac septic emboli or metastatic foci [6, 7]. In many centers, PET-CT findings are now effectively “major criteria” adjuncts, strongly influencing both guideline-directed diagnosis and surgical timing. Cardiac MRI, WBC-SPECT/CT, and evolving radiotracers broaden our armamentarium but are not yet as widely standardized as PET-CT.

In suspected PVE/CIED IE, early PET-CT can be live-saving by accelerating surgical decision-making and uncovering occult foci of infection(s) that mandate adjuvant therapies, longer or broader antibiotic coverage.

4. Antimicrobial therapy: Precision, stewardship, and selective oral step-down

IE therapy has traditionally defaulted to prolonged intravenous (IV) regimens. The POET trial challenged that paradigm, demonstrating that carefully selected, clinically stable patients with left-sided IE could complete therapy orally with

outcomes noninferior to continued IV therapy [8]. While not universally generalizable, especially regarding *S. aureus* bacteremia with complications, uncontrolled infection, or PVE—the concept of “risk-stratified oral step-down” has gained traction, especially when combined with therapeutic drug monitoring and close outpatient follow-up.

In parallel, antimicrobial stewardship is no longer optional. Rising resistance (e.g., vancomycin-tolerant *Enterococcus*-species), drug toxicities, and catheter-related complications all argue for more nuanced regimens, frequent reassessment, and—where possible—shorter, evidence-based courses [2, 3].

5. Surgery: The earlier, the better; team-driven, and ethically challenging

5.1 Timing and indications

Over the years, the pendulum has clearly swung toward “early surgery” in well-defined scenarios: heart failure from valve destruction, uncontrolled infection (abscess, fistula, persistent bacteremia), large vegetations with recurrent emboli, and PVE with dehiscence or hemodynamic compromise [2, 9, 10]. The long-held concern that early surgery risks neurologic deterioration after stroke has softened as data suggest that, outside of large hemorrhagic events, waiting rarely improves outcomes and may worsen them by allowing further embolization or structural deterioration. Obviously, patient-selection is key, as many patients with advanced co-morbidities, frailty, and prohibitive risks might ultimately be deemed “too sick” for surgery and a focus on comfort-care, palliative-care, and end-of-life goals might be the best direction.

5.2 Technical strategies

Complex root reconstructions, homografts, and valve-sparing approaches (when feasible) are part of the contemporary surgeon’s toolkit. However, such tools and advanced skills might not always be available and, therefore, often a “do the best we can” approach might be the only reasonable option and “good enough” might, given the circumstances, be good enough [11]. While minimally invasive or robotic approaches are intriguing, they remain niche, should not delay or compromise source control, and probably are not ideally suited for the complex pathologies and anatomical challenges associated with IE.

5.3 The ethics of reoperation in intravenous drug abuse (IVDU)

Few topics ignite as much debate as repeat valve replacement for patients with active IVDU. National data confirm the frequency—and poor outcomes—of redo surgeries in this population [12]. The ethical pendulum has shifted from “should we reoperate?” to “how do we combine addiction treatment, harm reduction, and shared decision-making into the decision-making pathway so that surgery is not an isolated, futile act?” Rigid exclusion policies risk abandoning treatable patients; indiscriminate reoperations without integrated addiction care risk perpetuating a harmful cycle. A principled framework—transparent criteria, addiction-medicine engagement, palliative care involvement, and institutional oversight—is essential [13].

6. The endocarditis team: From guideline suggestion to operational necessity

Echoing successful heart team models in structural heart disease, **formal IE teams** demonstrably improve adherence to guidelines, accelerate surgical referral, and reduce mortality [2]. The optimal team includes infectious diseases, cardiology (imaging and interventional), cardiac surgery, addiction medicine, neurology, nephrology, and palliative care—with standardized triggers for escalation (e.g., persistent bacteremia at 72 hours, vegetation >10 mm with embolic event, new conduction abnormality suggesting abscess). Real-world success requires operational details: 24/7 consult pathways, PET-CT access, rapid surgical slots, and clear discharge plans that include antimicrobial stewardship and addiction support [14].

7. Future directions

Despite all of the rapid progress over the years in the diagnosis and management of IE, there is still much to learn and improve on, especially as patients get sicker and their medical (and sometimes social) co-morbidities become more complex. As such, there are clearly areas to pursue with future directions. Some examples, just to consider a few, include:

- Molecular diagnostics at scale: Prospective trials to define when such data changes management and outcomes.
- Optimizing PET-CT criteria: Standardized uptake value thresholds, timing relative to surgery, and interpretation frameworks across centers.
- Oral step-down in broader cohorts: Especially with *S. aureus*, PVE, and device-related IE. Namely, who is safe, and how should they be monitored for early complications or failure of therapy?
- Long-acting antibiotics: Define roles as step-down, bridge, or salvage therapy.
- Addiction-integrated surgical care: Evaluate bundled pathways that embed contemporary substance-abuse practices such as medication-assisted treatment (MAT), harm reduction, and social services.
- Catheter-valve (i.e., TAVR)-associated IE: Better risk stratification, prophylaxis strategies, and operative algorithms for frail, high-risk patients.

Without a doubt, each of these topics can be a chapter or text in itself and hopefully this list can inspire others.

8. Conclusion

Advances in IE care in 2025 are less about a single breakthrough than about integration of current tools of multi-disciplinary care: of diagnostics that see what echocardiography cannot, of antimicrobial strategies that are individualized and

measured, of surgery and invasive procedures that is timely and comprehensive, and of systems that acknowledge the social and ethical reality of the patients we treat including the potential for futility of care. The “answer” to endocarditis is not only better drugs or sharper scalpels—it is a coordinated, compassionate, data-driven infrastructure that aligns them.

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Section 2

Diagnosis of Endocarditis

Advancements in Multimodal Imaging for Improved Endocarditis Diagnosis and Management

Gabriel Velez Oquendo and Giancarlo Acosta

Abstract

Infective endocarditis (IE) is a life-threatening condition characterized by infection of the endocardial surface of the heart. The pathogenesis of this condition involves microbial infection or non-infectious insults that trigger immune activation, myocyte damage, and myocardial remodeling. It remains a serious condition with high morbidity and mortality despite advancements in diagnostics and treatment. Multimodal imaging is pivotal in diagnosing, assessing complications, and guiding treatment decisions. This chapter presents a comprehensive overview of endocarditis, focusing on its definition, etiology, pathophysiology, evaluation, and management. Discussion on how diagnostic challenges arise, particularly in blood culture-negative IE, and how advanced imaging modalities other than Echocardiography, such as Fluorodeoxyglucose positron emission tomography scan FDG-PET and cardiac computed tomography angiography (CCTA), enhance diagnostic accuracy. Moreover, FDG-PET is invaluable for evaluating prosthetic valve endocarditis, cardiac device infections, and disseminated disease. Combining CCTA with TEE improves vegetation detection and delineates structural abnormalities. Integrating these multimodal approaches into diagnostic strategies ensures comprehensive evaluation and optimizes IE patients' management. This chapter concludes with a discussion elucidating the role of various imaging modalities, their specific clinical applications in diagnosing and managing endocarditis, and potential future advancements that could enhance diagnostic accuracy and therapeutic outcomes.

Keywords: bacterial endocarditis, infective endocarditis, bacteremia, cardiac computed tomography angiography, echocardiography, fluorodeoxyglucose positron emission tomography with computed tomography

1. Introduction

Infective endocarditis is an infection of the inner lining of the heart or the heart valves, which makes it a serious and sometimes fatal condition [1, 2]. The most affected areas of the heart are the heart valves, congenital heart defects, and

Cardiac conditions	Comorbidities
• Bicuspid aortic valve • Rheumatic valve disease • Mitral valve prolapse • Intracardiac devices • Prosthetic heart valves • Prior infective endocarditis	• Advanced age • Uncontrolled diabetes mellitus • Chronic kidney disease • Intravenous drug use • Malignancy • Immunocompromised state

Table 1.
Risk factors for infective endocarditis.

intracardiac devices [3]. Although the annual incidence of IE is low at 10/100,000, it has a mortality rate of up to 30% within 30 days of diagnosis [4]. The clinical presentation can vary and may be acute, subacute, or chronic, depending on the causative organism, underlying cardiovascular conditions, and associated comorbidities [5]. Most patients present with fevers, night sweats, fatigue, and weight loss, among other symptoms [5].

Furthermore, the diagnosis of infective endocarditis should be considered in patients with predisposing factors, new heart murmurs, vasculitis, and embolic events associated with infective endocarditis [5]. Risk factors, including valvular heart disease, intracardiac devices, and advanced age, among others, predispose patients to IE (**Table 1**) [6]. Unfortunately, despite improvements in diagnostic and imaging techniques, exceptional attention should be paid to prior antibiotic administration, as this is the most prevalent cause of culture-negative infective endocarditis, resulting in untargeted antimicrobial therapy and diagnostic uncertainty [5]. This chapter will discuss the etiology, pathophysiology, and multimodal imaging modalities for diagnosing and managing infective endocarditis.

2. Pathophysiology

2.1 Etiologies of infective endocarditis

Gram-positive streptococci, staphylococci, and enterococci bacterial infections cause most cases of infective endocarditis [2]. These groups account for approximately 90% of the cases worldwide, with *Staphylococcus aureus* accounting for 30% of these cases [2]. Additionally, other common colonizing bacterial organisms in the oropharynx known as “HACEK” organisms (*Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella*) can be the culprit bacteria less frequently [7]. HACEK organismal endocarditis mainly affects patients with previous heart disease and/or artificial heart valves, and has an insidious course with a mean diagnostic delay of approximately 1–3 months [7]. Lastly, fungal endocarditis primarily represents less than 1% of cases but can be fatal in the immunocompromised population [7].

Patients’ risk factors and the environmental setting of bacterial acquisition can provide hints about the underlying infectious etiology [7]. Healthcare-related infective endocarditis cases emerge in the setting of early prosthetic valve endocarditis (within the first 60 days of surgery) or following recent vascular hospitalization, extracardiac procedures, hemodialysis, and vascular catheterization [7]. In these

cases, *Staphylococcus aureus* is usually the predominant organism (50% of cases) as compared to less virulent coagulase-negative staphylococci like *Staphylococcus epidermidis* that usually originate from indwelling vascular devices and/or recently implanted prosthetic heart valves; with enterococcal infection occurring in about 15% of cases [7, 8].

Infections acquired in the community usually develop secondary to intravenous drug use, degenerative valve disease, rheumatic heart disease, and patients with immunosuppression [7]. Notably, 10% of cases of infectious endocarditis occur due to intravenous drug use, suggesting repeated inoculation with skin flora such as *S. aureus*, streptococci, and *S. epidermidis* [7].

2.2 Pathological stages

A healthy endocardium is typically resistant to bacterial seeding [9]. The development of infective endocarditis requires prodromal endocardial injury that leads to the release of tissue factors and inflammatory cytokines associated with fibronectin expression that leads to the formation of platelet-fibrin thrombi. These thrombi and damage to the endothelium caused by valve sclerosis, rheumatic valvulitis, or direct bacterial activity eases bacterial adhesion [10]. Adhesin proteins such as fibronectin and bacterial clumping factors are key mediations of adherence, with bacterial colonization triggering cycles of endothelial injury and thrombus deposition [9].

The predilection of vegetation to form on the ventricular surface of the aortic valve and the atrial surface of the mitral valve demonstrates that hemodynamics plays an important role in the pathogenesis of infective endocarditis [11]. Furthermore, infectious endocarditis is more commonly associated with stenotic valves due to the presumption that high-pressure flow creates more local damage. The injured endocardium acts as a site for platelet aggregation and triggers the coagulation system, promoting the development of thrombotic vegetations, which can become colonized when bacteremia occurs [11].

3. Diagnosis

3.1 Clinical features

The clinical presentation of infective endocarditis is diverse and non-specific. It should be considered in patients with sepsis of unknown origin or fever in the presence of risk factors. Moreover, it can be associated with complications, particularly stroke or systemic embolic events [12]. Furthermore, patients with persistent unexplained bacteremia should be investigated for infective endocarditis.

The initial evaluation of a patient with suspected infective endocarditis includes assessing risk factors and obtaining a detailed history and physical examination [12]. Clinical findings can vary, with fever and cardiac murmurs being the most frequently observed signs. Other supportive indicators include splenomegaly and cutaneous manifestations such as petechiae or splinter hemorrhages. Osler's nodes, Janeway lesions, and Roth spots may be less commonly present. Signs of complications, including heart failure, stroke, or metastatic infection, are more frequently encountered in these patients. However, given individual clinical signs' low sensitivity and specificity, infective endocarditis cannot be ruled out based solely on physical examination [12].

Clinical suspicion is supported by consistent microbiological data and documentation of IE-related cardiac lesions demonstrated by imaging techniques [12]. Importantly, admission evaluation with an electrocardiogram is essential since new conduction disease suggests an extension of the infection into the paravalvular or myocardial tissue.

Diagnosing infective endocarditis requires a comprehensive approach integrating clinical evaluation, microbiological evidence, and imaging findings.

The modified *Duke criteria* provide a structured framework by categorizing diagnostic elements into major and minor criteria (**Table 2**) [13]. A definitive diagnosis is established with either two major criteria, one major plus three minor criteria, or five minor criteria. Additionally, when pathological specimens are available, confirmation can be achieved through histological examination or positive culture of samples taken from vegetation or abscess tissue. It is important to note that the *Duke criteria* may have limited sensitivity in cases involving prosthetic valve endocarditis, right-sided infective endocarditis, and cardiac device-related infections, further indicating that this criteria is necessary for use as a diagnostic tool rather than a replacement for clinical judgment [14].

3.2 Laboratory findings

Routine laboratory investigations in infective endocarditis are generally non-specific, often revealing elevated inflammatory markers. The primary microbiological

Major criteria	Minor criteria
1. Positive blood cultures: • Typical microorganisms consistent with infective endocarditis from two separate blood culture bottles: ◦ <i>Staphylococcus aureus</i>, <i>Viridans streptococci</i>, <i>Streptococcus bovis</i>, HACEK (<i>Haemophilus</i>, <i>aggregatibacter</i>, <i>cardiobacterium</i>, <i>Eikenella corrodens</i>, <i>Kinsella</i>), group, or community-acquired enterococci, in the absence of a primary focus ◦ Or ◦ Microorganisms consistent with infective endocarditis from persistently positive blood cultures • At least two positive blood cultures from blood samples drawn >12 h apart or • All of three, or most of >4 separate cultures of blood (within first and last sample > 1 h apart) or • Single positive blood culture for <i>Coxiella burnetii</i> or phase 1 IgG antibody titer >1:800 2. Evidence of endocardial involvement. Echocardiography is positive for infective endocarditis. • Defined by the presence of vegetation, abscess, or new partial dehiscence of prosthetic valve New valvular regurgitation • An increase or change in pre-existing murmur is not sufficient.	1. Predisposing heart condition, intravenous drug use. 2. Fever: temperature > 38°C 3. Vascular phenomena include significant arterial emboli, septic pulmonary infarcts, mycotic aneurysms, intracranial hemorrhages, conjunctival hemorrhages, and Janeway lesions. 4. Immunological phenomena: glomerulonephritis, Osler's nodes, Roth spots, rheumatoid factor. 5. Positive blood culture that does not meet a major criterion or serological evidence of active infection with an organism consistent with infective endocarditis.

Table 2.
Duke criteria for diagnosis of infective endocarditis [13].

diagnostic tool is blood culture, with three sets detecting bacteremia in 96–98% of cases; therefore, blood samples should always be obtained before initiating antibiotic therapy [14, 15]. However, approximately 10% of patients with infective endocarditis have negative blood cultures, complicating the diagnosis. This may be due to prior antibiotic use, infection with fastidious bacteria or fungi, or alternative conditions such as non-bacterial thrombotic endocarditis [16].

A causative organism can be identified in approximately two-thirds of patients through additional microbiological testing [17]. In cases of culture-negative endocarditis, serological testing for **Coxiella** and **Bartonella** should be performed first. If these results are negative, further testing for **Brucella**, **Mycoplasma**, **Legionella**, and **Chlamydia** is recommended [18]. When excised valve material is available, molecular techniques play a complementary role. Broad-range polymerase chain reaction (PCR), a highly sensitive method that amplifies conserved bacterial or fungal DNA, allows for precise organism identification through sequencing [19]. This approach is advantageous in patients with prior antibiotic exposure, as bacterial DNA often persists despite negative cultures.

4. Imaging modalities

Imaging plays a crucial role in diagnosing and managing infective endocarditis, with the detection of characteristic lesions as a major diagnostic criterion. Transthoracic Echocardiography is considered the first-line imaging modality, essential for diagnosing IE and evaluating structural and functional cardiac damage. Additionally, echocardiographic findings have prognostic significance and assist in guiding clinical decision-making and patient monitoring during antibiotic therapy [20]. While Echocardiography remains the primary tool for diagnosis, specific clinical scenarios require additional imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and nuclear imaging to confirm or exclude IE, assess the extent of cardiac involvement, and identify extracardiac complications [21]. However, each imaging technique has specific strengths and limitations, and the choice of modality depends on availability and expertise. When appropriate, a multimodality imaging approach should be strongly considered to optimize diagnostic accuracy and patient management.

4.1 Echocardiography

Transthoracic Echocardiography (TTE) and transesophageal Echocardiography (TEE) are the first and key imaging techniques to diagnose IE [22]. TTE must be performed first because it provides valuable information for diagnosis and assessment as a non-invasive technique [23]. TEE should be performed in most patients with suspected infective endocarditis, as it offers superior image quality and greater sensitivity for detecting perivalvular involvement [23].

Vegetation characteristics and size, perivalvular complications, intracardiac fistulas, and leaflet perforation are the main echocardiographic findings, but knowledge of the anatomical features of IE is fundamental to understanding better, analyzing and describing these echocardiographic findings [23].

The echocardiographic examination should assess three key anatomical features commonly present in infective endocarditis: vegetations, valve lesions, and abscesses. Vegetations typically form on the low-pressure side of the valve and, when large and

mobile, have a higher risk of embolization and, less commonly, valve or prosthetic obstruction. Valve lesions, often associated with vegetation, can lead to complications such as aneurysms, perforations, prolapse, severe regurgitation, and heart failure. Abscesses are frequently observed in aortic and prosthetic valve endocarditis and may be further complicated by pseudoaneurysm or fistula formation [23].

Typical vegetations appear as oscillating masses attached to a valvular structure, moving independently of the valve. However, some vegetation may present as non-oscillating masses in atypical locations. The diagnostic sensitivity of transthoracic Echocardiography (TTE) for detecting vegetation is approximately 75%, whereas transesophageal Echocardiography (TEE) offers higher sensitivity, ranging from 85% to 90% [24].

Transesophageal Echocardiography (TEE) is valuable in various clinical scenarios, mainly when transthoracic Echocardiography (TTE) cannot detect perivalvular complications, small vegetations, or vegetations associated with cardiac devices. TEE is strongly recommended for patients with an inconclusive TTE, those with a negative TTE but high clinical suspicion of infective endocarditis, and patients with a positive TTE to assess for local complications. Delays in initial echocardiographic evaluation are associated with more significant valvular damage, higher rates of peripheral embolic events, and an increased likelihood of requiring valve surgery [25].

While Echocardiography is essential for diagnosing infective endocarditis and provides a definitive diagnosis in most cases, atypical or inconclusive findings can occur, especially in the early stages of the disease and in patients with intracardiac devices or prosthetic materials [23]. Nevertheless, Echocardiography remains a critical tool for guiding clinical decision-making, particularly regarding potential surgical intervention and mortality risk assessment. Recent advancements in three-dimensional imaging have further enhanced its role in evaluating patients with infective endocarditis. However, echocardiographic findings should always be interpreted in the context of the patient's overall clinical presentation [23].

4.2 Cardiac computed tomography (CT)

Over the years, cardiac computed tomography (CT) has become increasingly important in the diagnosis and management of infective endocarditis, with recommendations for this imaging modality to be used in both native and prosthetic valve endocarditis, even being emphasized in the ESC 2023 guidelines as a class I recommendation for detection of valvular lesions in possible endocarditis [26]. Additionally, cardiac CT has been recommended to detect paravalvular and periprosthetic complications in cases where echocardiographic evaluation is inconclusive and when symptoms suggest extracardiac complications [27].

In suspected prosthetic valve endocarditis, cardiac CT plays a crucial role in assessing potential complications and overcoming the diagnostic limitations of Echocardiography. A non-contrast-enhanced acquisition allows for evaluating calcifications and differentiating surgical materials from paravalvular abscesses [28]. This is followed by ECG-synchronized computed tomography angiography (CTA), which enables the assessment of valve function using images reconstructed in both diastole and systole across the entire cardiac cycle [29]. Lastly, a delayed-phase acquisition covering the entire chest helps identify extracardiac complications such as septic emboli, underlying causes of endocarditis, and even coronary artery disease.

Additionally, CT imaging can detect various signs of endocarditis, including vegetations, valve perforations, fistulas, paravalvular leakage or dehiscence, abscesses,

and mycotic aneurysms [30]. A recent advancement in cardiac CT imaging is photon-counting computed tomography (PCCT), which offers advantages in evaluating coronary artery disease while reducing blooming artifacts. PCCT shows promise in minimizing metal artifacts, improving the assessment of prosthetic heart valves, and enhancing diagnostic accuracy in patients with suspected infective endocarditis [31].

Finally, in patients where infective endocarditis (IE) has been ruled out or remains uncertain, whole-body CT can be instrumental in identifying alternative infectious sources. The role of CT is increasingly recognized in both native and prosthetic valve endocarditis, and its use is now recommended in clinical guidelines for comprehensive diagnostic evaluation [32].

4.3 Cardiac magnetic resonance imaging (MRI)

The use of cardiac MRI for diagnosing infective endocarditis (IE) is limited by its relatively low spatial resolution and signal void artifacts caused by certain prosthetic materials, which can hinder the evaluation of prosthetic valve anatomy and function [33]. However, MRI offers superior sensitivity compared to CT for detecting neurological lesions, enhancing the identification of neurological complications in patients with IE, specifically embolic phenomena.

Brain MRI has been shown to significantly impact the diagnosis of infective endocarditis (IE) by serving as a minor diagnostic criterion, even in patients without neurological symptoms who have a non-definitive IE diagnosis. Furthermore, brain MRI can reclassify up to 25% of patients with an inconclusive diagnosis, leading to a more definitive diagnosis and facilitating earlier clinical decision-making [34].

Cardiac MRI is a valuable diagnostic tool for detecting vegetation in suspected infective endocarditis (IE) patients. It provides important diagnostic and prognostic insights by highlighting features such as antegrade versus retrograde dissemination, paravalvular tissue extension, and subendocardial and vascular endothelial tissue involvement. Additionally, the 2023 ESC guidelines recommend incorporating cardiac MRI into the diagnostic algorithm for infective endocarditis [12, 33].

4.4 Nuclear imaging (PET/CT and SPECT/CT)

Nuclear imaging techniques, such as [¹⁸F] Fluorodeoxyglucose positron emission tomography and computed tomography (FDG-PET/CT), are recommended for suspected prosthetic valve endocarditis, especially in inconclusive echocardiography findings. More importantly, a recent meta-analysis demonstrated an 86% specificity for prosthetic valve endocarditis, compared to 31% for native valve endocarditis [35]. The improved detection of prosthetic valve endocarditis from this nuclear imaging technique results from the higher frequency of valve vegetations in prosthetic valve endocarditis, as opposed to paravalvular involvement in native valve endocarditis, which leads to a stronger inflammatory response and increased [¹⁸F] FDG uptake. This makes the ability of FDG-PET/CT to detect septic emboli particularly valuable in such cases [36].

Imaging modalities like [¹⁸F]-FDG-PET/CT are especially useful in the evaluation of not only prosthetic valve endocarditis but also cardiac implantable electronic device infections. Additionally, it can be used to establish the presence of an infection in the endocardium directly or to find evidence for disseminated infection or portals of entry in IE disease. When diagnosis remains uncertain, findings of extracardiac foci of infection may help establish the diagnosis and can significantly impact treatment decisions [37].

A recent meta-analysis examining native valve endocarditis found that [18F] FDG PET/CT has poor sensitivity for diagnosis, though its specificity is very high at 99% [38]. Due to its low sensitivity, negative intracardiac findings on [18F] FDG PET/CT cannot rule out native valve endocarditis. However, if the imaging shows evidence of intracardiac infection, it is highly predictive of the diagnosis, particularly in cases where other diagnostic methods have not yet confirmed the condition. As a result, some experts recommend using [18F] FDG PET/CT in suspected cases of native valve endocarditis to detect disseminated disease [39].

For prosthetic valve endocarditis, [18F] FDG PET/CT demonstrates high sensitivity and specificity in detecting intracardiac infections. Recent studies report a pooled sensitivity of 86% and specificity of 84% [38]. In addition to identifying intracardiac infections, PET/CT can also reveal disseminated disease, which is particularly valuable since Echocardiography is often limited by prosthetic valve-related artifacts, reducing its diagnostic accuracy in this patient population [40].

For cardiac device-related infection, [18F] FDG PET/CT has improved performance with a high overall pooled sensitivity and specificity (87% and 94%, respectively) according to the most recent studies, including meta-analysis on this indication, with better performance for identification of pocket infections [41]. Furthermore, recent studies have shown that for patients with suspected left ventricular assist device (LVAD) infections, the sensitivity and specificity of this type of imaging were 97% and 99%, respectively [39]. In conclusion [17], FDG PET/CT results can accurately diagnose prosthetic valve endocarditis and cardiac electronic implantable device infections.

5. Multimodal imaging integration/management

Management of patients with infective endocarditis is a clinical and logistical challenge, as optimal care requires a good infrastructure with the involvement of a team composed of specialists that includes cardiologists, surgeons, and infectious disease physicians, among other teams. Multidisciplinary teams can optimize diagnosis, management, and early decision-making to improve clinical outcomes [25].

Centralized care, which combines advanced diagnostic imaging, surgical expertise, and high patient throughput, is particularly beneficial for managing complex cases and may offer widespread advantages. Additionally, the effectiveness of centralized care in improving decision-making, reducing time to surgery, enhancing cure rates, and improving both short- and long-term outcomes could be effectively evaluated through a retrospective-prospective study [42].

6. Conclusion

The accurate diagnosis and effective management of infective endocarditis hinges on imaging advancements. Although Echocardiography remains the first-line imaging technique for evaluating IE, integrating cardiac computed tomography and other imaging modalities has proven pivotal in enhancing diagnostic precision, especially for evaluating prosthetic valves and cardiac electronic implantable device infections. Future advancements in imaging techniques, alongside the increasing emphasis on interdisciplinary team collaboration, promise to refine the diagnostic process further and optimize treatment strategies, ensuring a tailored and effective management plan

for each patient. By fostering a comprehensive and dynamic approach, we can aspire to improve diagnostic accuracy and enhance therapeutic outcomes for those afflicted by this challenging cardiac condition.

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Echocardiography in the Diagnosis of Endocarditis

Mila Peneva, Boyan Kunev and Danail Avramov

Abstract

Infective endocarditis (IE) is a devastating infectious disease with high morbidity and mortality, despite advancements in diagnosis and management. Both transthoracic and transesophageal echocardiography are the primary imaging modalities for initial evaluation and further surveillance. Evidence of a vegetation, perivalvular extension with either an abscess, pseudoaneurysm or fistula, dehiscence of a prosthetic valve, or a new regurgitant lesion serves as major criteria for definite IE. Dynamic assessment of haemodynamic consequences and detailed characterisation of valvular damage determine the management—either conservative or surgical. Transesophageal echocardiography is an invaluable tool for characterisation of prosthetic valve endocarditis or for assessment of perivalvular complications, otherwise predominately invisible by a routine transthoracic exam. The advancements in interventional cardiology with the transcatheter implantation of valves have opened a new field in endocarditis, with some peculiarities differentiating them from standard prosthetic valves. The incorporation of 3D echocardiography into routine everyday practice will enable better differentiation of valvular damage and morphology by the infectious process and guide the optimal surgical approach.

Keywords: endocarditis, echocardiography, vegetation, regurgitation, intracardiac mass, surgery

1. Introduction

Infective endocarditis (IE) is a challenging diagnosis with an often dismal prognosis, despite major advances in its contemporary management. Several registries from Western Europe and the USA estimate its prevalence to be around 3–14/100,000 patients annually [1]. Male predominance in a ratio of 2:1 to females is reported, and the mean age of diagnosis is around the sixth decade [2]. Major predisposing conditions include degenerative valve disease (30% of cases), in particular mitral valve disease, and a lower percentage of rheumatic valvular lesions, mainly in developing countries [2]. Increasing reports of healthcare-associated IE, due to the presence of prosthetic valves, conduits, cardiac-implantable electronic devices (CIED) and indwelling catheters are expected to shift the epidemiology of the disease. Drug abuse remains a key risk factor, especially for young males

Major criteria	Minor criteria
1. Blood cultures positive for IE	1. Predisposing conditions
2. Imaging positive for IE - TTE/TEE; CT; [18F]-FDG-PET/CT; SPECT/CT	2. Fever >38°C
	3. Embolic vascular dissemination (major systemic and pulmonary emboli/infarcts and abscesses, hematogenous osteoarticular septic complications, mycotic aneurysms, intracranial ischaemic/haemorrhagic lesions, conjunctival haemorrhages, Janeway's lesions)
	4. Immunological phenomena (glomerulonephritis, Osler nodes and Roth spots, rheumatoid factor)
	5. Microbiological evidence - positive blood culture but does not meet the major criteria, positive serological evidence

Table 1.
Duke criteria for IE. Definite IE—two positive major criteria, one major and three minor criteria, five minor criteria.

with concomitant hepatitis C and human immunodeficiency virus (HIV), and is associated with poor prognosis [3]. In the developed world, an acute *Staphylococcus aureus* infection is the leading cause of IE, mainly due to the ageing of the population, nosocomial contact and intravenous drug abuse, while younger patients with rheumatic disease in developing regions often present with a subacute-onset IE caused by Viridans group streptococci [4].

The European Society of Cardiology (ESC) guidelines from 2023 rely on the modified Duke criteria and define definite IE in the presence of two major criteria—positive blood cultures for a typical microorganism and imaging evidence for IE—or one major and three minor criteria or five minor criteria, as presented in **Table 1**. IE develops in a susceptible host in the presence of bacteraemia or fungaemia and targets the disrupted endocardium whenever there is a predisposing condition, leading to a high-velocity jet and turbulence such as valvular lesions, congenital heart defects or prosthetic valves [5]. The shear stress leads to loss of the protective endocardial surface and renders it a target for the blood pathogens. Further attraction and adhesion of platelets, fibrin, neutrophils and other products form a vegetation, which continuously grows in size and becomes a mobile, oscillating, sometimes pedunculated mass with a high risk for embolisation.

Echocardiography has been the cornerstone of diagnosis ever since the first M-mode depiction of vegetations by Dillan and colleagues in 1973 [6]. Both transthoracic (TTE) and transesophageal echocardiography (TEE) are the first-line imaging modalities, as a dynamic and concise haemodynamic assessment, apart from vegetation size and mobility monitoring, determines the therapeutic management—conservative or surgical. The advancement in echocardiography, in particular 3D TEE, provides in-depth visualisation of valvular lesions such as leaflet perforation, chordal rupture, perivalvular extension (abscess or pseudoaneurysm) and, in severe cases, intracardiac fistula formation. TEE has a Class I indication in the case of prosthetic valve IE, especially for a new partial dehiscence and paravalvular leak or for the visualisation of vegetations on CIEDs. Complementary techniques such as computed tomography (CT), positron emission tomography (PET) and magnetic resonance imaging (MRI) may supplement the diagnosis and further delineate the extent of perivalvular extension or assess for embolic complications.

2. Basic echocardiographic characteristics of IE

According to the modified Duke criteria, the key diagnostic echocardiographic findings for IE include vegetations, perivalvular extension with either an abscess, pseudoaneurysm or fistula, dehiscence of a prosthetic valve or a new regurgitant lesion [7]. ESC and American College of Cardiology (ACC) guidelines recommend TTE as a first step in a suspected IE case or in the case of a septic condition with a positive blood culture for *St. aureus*, streptococci or *Enterococcus faecalis*. A low threshold for TEE should be maintained when TTE is inconclusive, especially for right-sided IE or CIED-related [5, 8]. TEE has a better image quality with a higher sensitivity and specificity compared to TTE due to the close proximity to cardiac structures and more proper delineation of perivalvular extension.

Different registries report native IE in 72% of the cases, prosthetic IE in 21% and a lower percentage for indwelling catheters or implantable devices. The mitral valve was affected in 41%, the aortic valve in 28% and the tricuspid one in 12% of the patients [2]. Advancement in percutaneous techniques and the rising percentage of transcatheter valvular replacements, in particular aortic and pulmonary, have changed the epidemiological statistics for prosthetic IE. IE of transcatheter aortic valve replacement (TAVR) was documented at a similar rate to surgical aortic valve replacement (SAVR) and varies from 0.3 to 2.0 per 100 person-years [9]. A concerning observation is the higher incidence of late IE after transcatheter pulmonary valve implantation (TPVI) by Melody valves, with a rate from 1.3 to 9.1% per patient-year [10].

Vegetations are detected in almost 90% of definite IE cases [2]. They are predominantly located on the valvular free edge but may also appear on the subvalvular apparatus, prosthetic rings and pacemaker leads or indwelling catheters, i.e., wherever high turbulent jets are present. A key remark is their precise localisation on the low-pressure side of high-velocity jets, i.e., on the atrial aspect in the case of atrioventricular (AV) valve IE and on the ventricular side given semilunar valve involvement. They begin as a microscopic source of infection that gradually grows in size, becoming an irregularly shaped, sessile or pedunculated, highly mobile echogenic mass. Fungal lesions often appear larger than those in bacterial IE. TTE can easily differentiate vegetations with a size above 3–4 mm, while TEE has a better resolution size of 1–2 mm and thus higher sensitivity 87% and specificity 91% [11–14]. Non-standard views are encouraged for detailed assessment of the valves and for precise localisation and measurement of the infectious masses. A distinguishing feature is their independence of the valve motion, with an echocardiographic appearance of an oscillating or fluttering structure. Vegetations may present a heterogeneous structure with either echolucent or echodense areas; however, most often they resemble mid-myocardial echogenicity. IE usually causes tissue destruction and thus some degree of valvular dysfunction, predominantly a new regurgitation and rarely a stenotic obstruction. **Figures 1–4** depict cases of IE.

Differential diagnosis includes Libmann-Sacks or non-infective endocarditis, tumours, calcific nodules, Lambl excrescence or a thrombus. Libmann-Sacks endocarditis commonly develops in systemic lupus erythematosus and is characterised by complete involvement of the valves, i.e., their whole surface and thickness (both atrial and ventricular sides of the AV valves, ventricular and aortic sides in the case of the aortic valve). Characteristic features include thickened leaflets, granular vegetations in clusters, most commonly found in the coaptation zone, with a heterogeneous appearance due to the presence of both active and healing regions [15]. Lambl excrescences are benign, thin, hypermobile, long fibroelastic projections

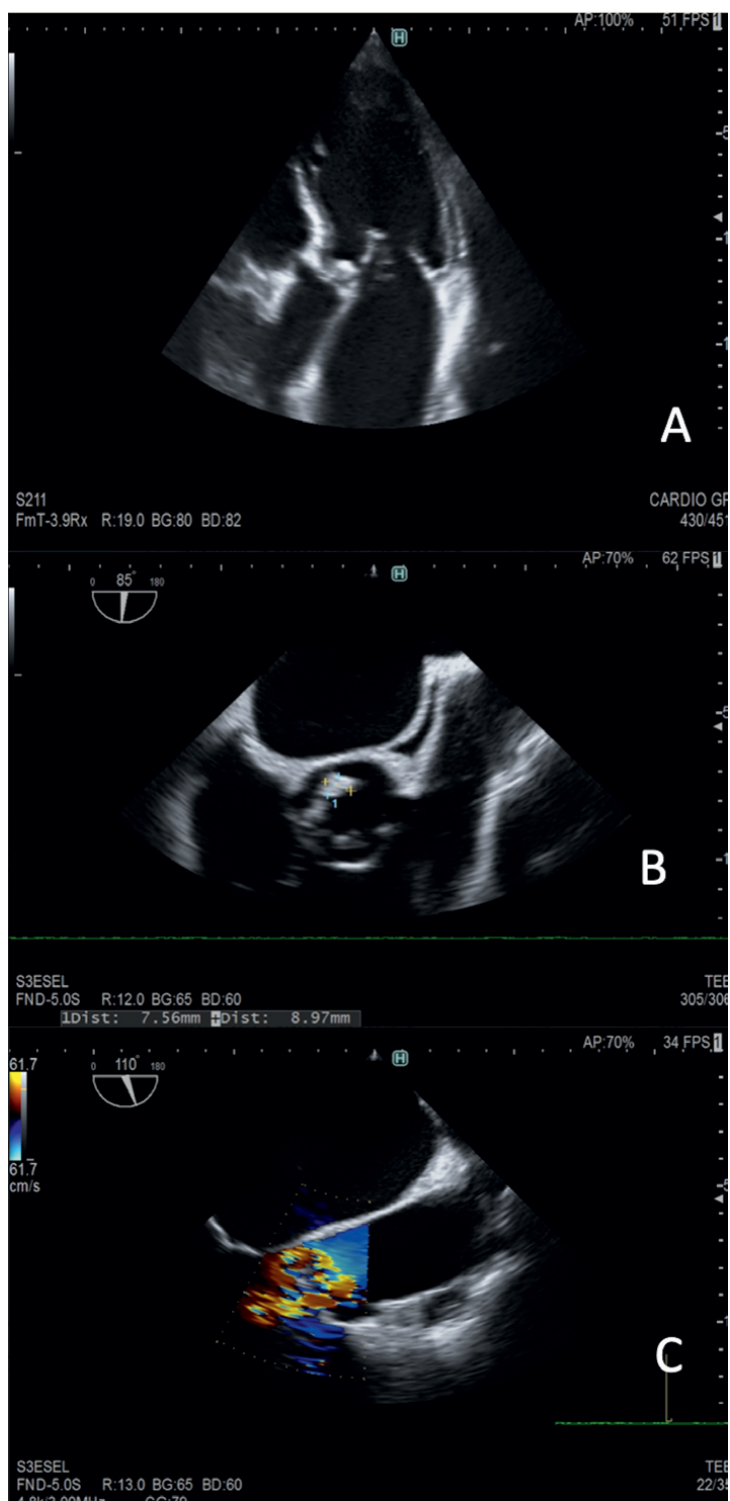


Figure 1.
A case of native aortic valve IE—a vegetation with a size of 7.6/9 mm is visible on the right coronary cusp with perforation and significant regurgitation. A - TTE, B and C - TEE.

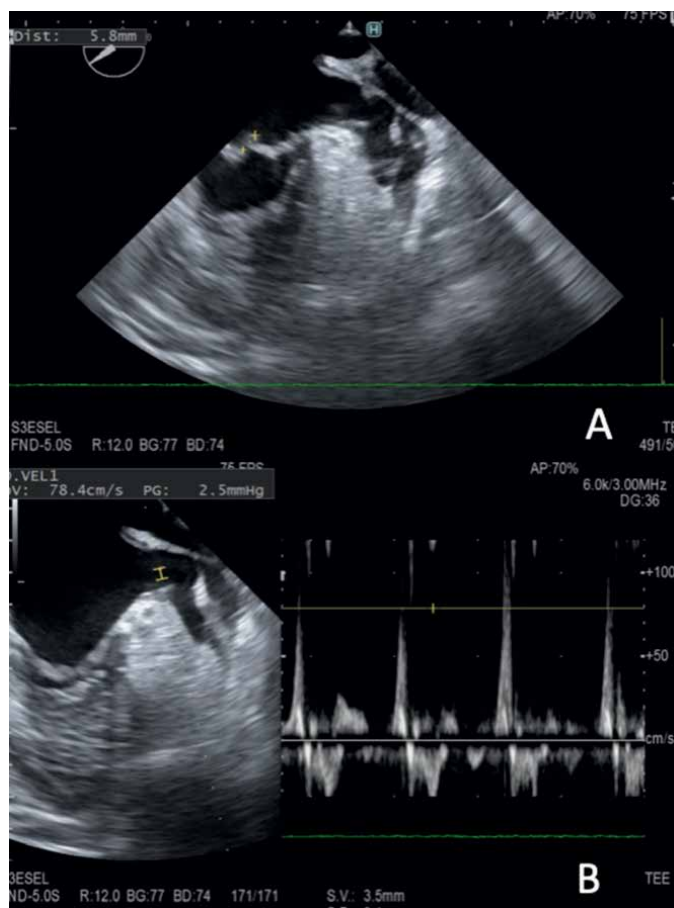


Figure 2.
A case of native mitral valve IE, complicated by embolic stroke. A - TEE exam with evidence of vegetation with a size of 6 mm is visible on the atrial side of the valve, with extension of the vegetation into the left atrial appendage. B - again TEE, with evidence of normal left atrial appendage velocity, partly excluding the risk of thrombosis, given the patient also had no history of atrial fibrillation.

arising from the coaptation zone, predominantly from the aortic valve, and pose a high risk for embolisation [16, 17]. TEE is of crucial diagnostic significance for proper identification and differentiation between the above-mentioned cardiac masses and IE **Figures 5 and 6**.

However, the echocardiographic findings are not conclusive for establishing a diagnosis of definite IE. The clinician should remain cautious and interpret the whole spectrum of available data with special attention to the sole medical history and physical examination of the patient [18–20].

3. Complications of IE

New-onset or worsening heart failure (HF) due to local valvular destruction may complicate the course in at least one third of the documented cases of IE and is the leading cause of urgent cardiovascular surgery in 50–60% of them. Native valve IE

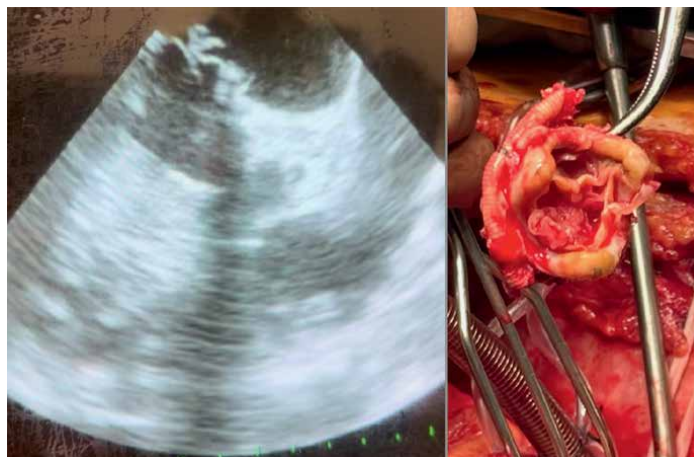


Figure 3.
A case of prosthetic biological mitral valve IE. A - TEE exam with evidence of mobile vegetation. B - intraoperative specimen.

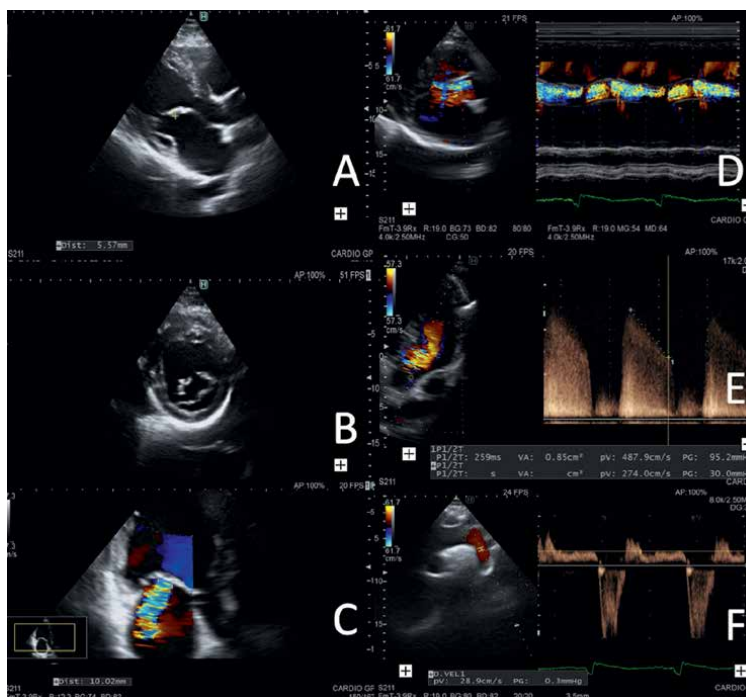


Figure 4.
A case of an acute aortic valve IE in a 21-year-old patient with surgically corrected balanced atrioventricular septal defect (AVSD), complicated by systemic embolism. The atrial and ventricular septum are intact, with no shunt through both patches and no evidence of vegetations. A - parasternal long-axis view (PLAX) of a dysplastic mitral valve with no definite signs of an oscillating mass. B - parasternal short-axis view of the mitral valve with evidence of a cleft of the anterior leaflet, typical for AVSD; differential diagnosis with a leaflet perforation is necessary. C - 2-chamber view of the severity of the mitral valve regurgitation. D - PLAX view of the severe aortic regurgitation due to perforation of the right coronary cusp. E- apical view, demonstrating the aortic regurgitation severity estimated by continuous wave Doppler with a short pressure half-time. F - suprasternal view, demonstrating flow reversal in the descending aorta by colour Doppler and an end-diastolic flow velocity > 20 cm/s as evidence for severe aortic regurgitation.



Figure 5.
A case of Libmann-Sacks endocarditis. A TEE exam with evidence of two masses with a heterogeneous appearance at the coaptation zone of the mitral valve.



Figure 6.
A TTE case of left atrial myxoma.

is three times more common than prosthetic valve IE, with reported incidences of haemodynamically significant valvular lesions for aortic valve IE (30%), mitral valve (20%) and tricuspid valve (<10%). Echocardiographic surveillance is crucial in IE treatment, and a prompt diagnosis of a newly developed murmur or deterioration determines the surgical indication. ESC and ACC guidelines recommend emergent

valve intervention whenever refractory pulmonary oedema or echocardiographic evidence of poor haemodynamic tolerance is present [5, 8].

The main mechanisms of regurgitant lesions are perforation, chordal rupture with a subsequent flail leaflet, cusp fenestration, and interference of the vegetation with leaflet closure. TTE combined with pulse, continuous and colour Doppler examination is crucial for precise haemodynamic assessment. For instance, acute aortic regurgitation due to leaflet damage is characterised by a short pressure half-time due to the rapid equalisation with the end-diastolic pressure of the unadjusted left ventricle (LV). The severe regurgitant jet often leads to premature closure of the anterior mitral valve leaflet, depicted on M-mode by a typical fluttering motion. Diastolic LV function is one of a restrictive filling pattern with elevated left atrial pressure. Careful evaluation of the mitral valve, in particular the ventricular surface of the anterior leaflet, for concomitant involvement by the infectious process and the formation of an aneurysm and a subsequent perforation is obligatory, and the operator should be cautious in the case of combined regurgitant lesions [21–23].

The mechanism of mitral insufficiency should be evaluated by both TTE and TEE, as the latter is much more sensitive for detection of leaflet perforation (45% vs. 90%). Perforation is reported in the range of 10–30% and may be suspected whenever a flow convergence zone and a jet traversing the leaflet in a direction towards the left atrium is depicted by colour Doppler. However, 3D TEE is much more accurate for precise evaluation and preoperative choice of the appropriate surgical approach—valve repair or replacement [13, 24, 25]. Engagement of the subvalvular apparatus with a subsequent chordal rupture and a flail leaflet leads clinically to acute severe mitral insufficiency and often refractory pulmonary oedema. The echocardiographic findings include a floating cord or cords in the left atrium, no leaflet coaptation, and a large eccentric jet in a direction opposite to the damaged leaflet. Signs of severity also include high E velocity above 1.5 m/s, higher D than S wave or systolic reversal from the pulmonary venous Doppler flow. The eccentricity of the jet may underestimate the quantitative evaluation of the mitral regurgitation by the proximal isovelocity surface area (PISA) method; however, one should bear in mind that effective regurgitant orifice (EROA) above 0.3–0.4 cm², a regurgitant volume above 45–60 ml and a regurgitant fraction around and above 50% indicate a severe lesion [26, 27]. Another qualitative feature of significance is the truncated triangular shape of the regurgitant jet on continuous wave Doppler. Carpentier classifies mitral regurgitation due to IE as type I due to perforation (normal leaflet motion) and type II in the case of a flail **Figures 7 and 8** [28].

Due to the acuteness of the infectious process in acute IE and a newly developed significant left-sided valvular lesion, the LV is typically unadapted and thus has normal size and hyperdynamic function. In the case of a subacute infection, the left ventricle may have remodelled and displays a different degree of dilatation and dysfunction due to the chronicity of the regurgitant lesion. Assessment for pulmonary hypertension by the tricuspid insufficiency jet and right ventricle size and systolic function may support the evaluation of the severity and duration of the lesion and thus prompt a more urgent need for surgery.

In prosthetic valve IE, haemodynamic deterioration is often due to dehiscence of a prosthetic valve and portends a dismal prognosis with high morbidity and mortality. On echocardiography, dehiscence may be suspected whenever one observes a rocking motion of the valve with excursion above 15% in one direction. The resultant para-valvular regurgitation is often severe and of poor clinical tolerance and necessitates timely intervention. One may suspect such a complication by the measurement of high transvalvular gradients on TTE. However, TTE is not sufficient for diagnostic

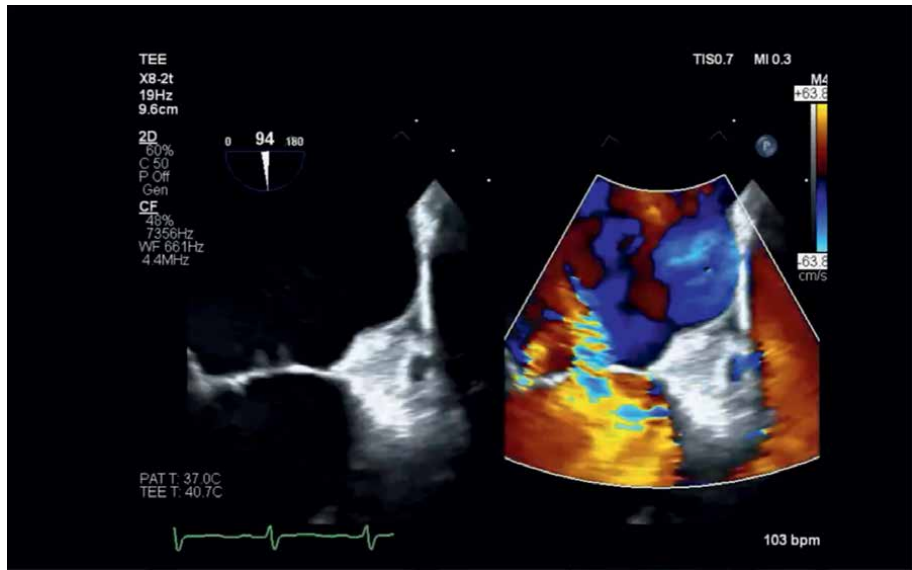


Figure 7.
A TEE case of mitral valve IE with a perforation of A1-A2 segments of the anterior leaflet.



Figure 8.
A TTE case of mitral valve IE with a perforation of the posterior leaflet.

assessment and may not differentiate any vegetations on the prosthetic valve. TEE is the method of choice, and paravalvular regurgitation due to IE is most precisely evaluated by 3D TEE by visualisation of the crescent defect between the native annulus and the sewing ring **Figures 9 and 10** [28–30].

Perivalvular extension of the infectious process is the second most common indication for urgent cardiovascular surgery. Data from contemporary registries report its incidence to be around 10–30% for native valve IE and 30–55% for prosthetic valve IE [25, 31]. Predictors of infectious perivalvular spread include a prosthetic valve,

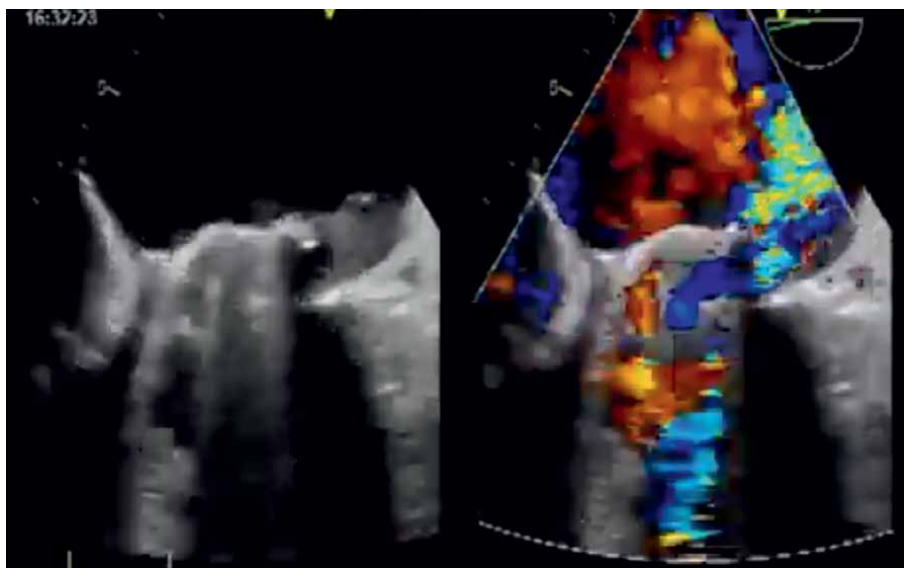


Figure 9.
A TEE case of prosthetic mitral valve IE. The case clearly demonstrates the rocking motion of the mechanical prosthesis with a significant paravalvular leakage.



Figure 10.
A TTE case of TAVR-IE.

aortic valve IE and staphylococcal infection. Predilection for the bicuspid aortic valve is reported with 50% of the reported cases and 20% for tricuspid valves. An interesting finding is the lower incidence of periannular abscess in TAVR patients [5, 32]. Perivalvular extension may appear as an abscess, mycotic pseudoaneurysm or fistula. Persistent fever and positive blood cultures despite appropriate antibiotic treatment and newly developed heart block should alert the clinician to such a complication. On TTE, thickening around the aortic annulus may raise suspicion for an abscess.

However, due to the low sensitivity of TTE, TEE is the gold standard for establishing a diagnosis, with a sensitivity of around 90%. A heterogeneous mass with echodense and echolucent zones around the aortic annulus or the myocardium and evidence of flow depicted by colour and pulse-wave Doppler is noteworthy for an abscess. In the case of posterior mitral annulus involvement, a differential diagnosis with calcification is necessary **Figure 11** [20, 33].

Another serious and potentially lethal complication is the formation of a mycotic false aneurysm or pseudoaneurysm due to the constant exposure of the abscess to high intravascular pressure and further invasion of the infection. The mitral-aortic intervalvular fibrosa (MAIF) is the region between the non-coronary aortic cusp



Figure 11.
Two TEE cases of complicated aortic valve IE with perivalvular extension and abscess formation.

and the anterior mitral leaflet and is one of the least vascular cardiac regions, which renders it quite susceptible to the infectious spread and pseudoaneurysm formation. The echocardiographic features include systolic expansion of the echolucent areas, and the communication may be depicted with colour flow Doppler from the subvalvular LV outflow tract. These may further be complicated by the development of a fistula, compression of the proximal left coronary arteries and subsequent myocardial ischaemia, rupture into the pericardial cavity and embolisation. Aorto-atrial and aorto-ventricular fistulas complicate 1.6% of native valve IE and up to 3.5% of prosthetic valve IE. All three sinuses of Valsalva are equally engaged, with a turbulent jet from the left or non-coronary cusp flowing most commonly into the right ventricle, causing a significant left-to-right shunt, while the jet from the left sinus of Valsalva is predominantly directed towards the left atrium, causing further volume overload of the LV. Such fistulae may be observed on TTE from the parasternal short-axis view and alternative imaging planes; however, TEE is again the imaging modality of choice for precise visualisation [28, 34, 35].

4. Special cases of IE in congenital heart diseases, right-sided, CIED-related and TAVR

Congenital heart diseases (CHD) act as a nidus for IE and are a major risk factor for both children and adults, with reported incidences of 4.1/10,000 and 11/10,000 patient-years, respectively. The most susceptible patients are those with ventricular septal defect (VSD), patent ductus arteriosus (PDA), tetralogy of fallot (TOF) and bicuspid aortic valve (BAV). However, the risk of IE drastically declines after 6 months of definite surgical correction without residual defects, especially for PDA, VSD and arial septal defect (ASD). Complex intracardiac repairs and palliative shunt procedures, however, act as a major predisposition. Different registries report the highest incidence for right ventricle-to-pulmonary artery valved conduits in 27% of radically corrected lesions and infected aorto-pulmonary shunts in 80% of palliative repair cases. Furthermore, cyanotic CHD, irrespective of the surgical treatment, remains the most vulnerable group. Despite lower procedural risk and percentage of early complications, the novel techniques of percutaneous valve implantation, in particular TPVI, pose a significant threat for IE compared to the standard surgical approach. Both types of prosthetic IE have comparable survival rates [36–41]. In the case of IE on a restrictive VSD, the vegetations are located on the right ventricular side of the septum. If PDA is infected, the sonographer may observe a mass floating from the pulmonary side of the ductus into the main pulmonary artery, with a high risk for embolisation. IE of the Eustachian valve is a relatively rare and an easily missed diagnosis during a TTE exam. Clinically, it may lead to relapsing pulmonary embolism with infarct pneumonia. In this case, and especially for prosthetic intracardiac materials, both TTE and TEE should be used as first-line imaging tools.

Right-sided IE occurs in 5–10% of IE cases in association with intravenous drug use (IDVU), implantable devices and central venous catheters. The lower incidence compared to left-sided IE stems from the lower velocities and pressure gradients across the tricuspid and pulmonary valves, lower right ventricular wall stress, and lower oxygen content of the returning venous blood [18, 42]. IE due to IDVU accounts for the majority of patients, with evidence of tricuspid valve involvement in 90%. Repetitive IDVU leads to valvular thickening, prolapse and regurgitation easily imaged by TTE. Optimal imaging of the tricuspid valve, however, necessitates atypical views for imaging of the

posterior leaflet from the parasternal long-axis, focused right ventricle view, and modified views for right ventricular inflow and outflow tracts. Important normal structures such as the moderator band in the right ventricle, crista terminalis, Eustachian valve, Thebesian valve and Chiari network in the right atrium should be differentiated from potential vegetations. Complications of right-sided IE are divided into valvular and non-valvular. The former include valvular regurgitation, more commonly of the tricuspid than the pulmonary valve, stenosis, leaflet perforation and annular abscess formation. Subsequent embolic episodes lead to septic pulmonary embolism with subsequent infiltration, exudates and risk for abscess and cavitation. Whenever evidence of systemic embolism appears, a patent foramen ovale should be excluded. TEE, particularly the bicaval view, is the method of choice. However, lowering the Nyquist limit may enhance imaging of a right-to-left shunt through the foramen ovale from the subxiphoid position. Newly developed high-grade atrioventricular block is highly suspicious for perivalvular extension and abscess formation. Nonetheless, advanced imaging techniques such as nuclear scans, computer tomography and, rarely, magnetic resonance should be used to precisely evaluate the scope of IE **Figure 12** [43].

CIED-IE is a major concern in the developed world with the advancement of different cardiac devices for pacing, defibrillation and ventricular support. The current definition includes three distinct scenarios: 1. bacteraemia with a valve vegetation, 2. bacteraemia with a device lead vegetation and 3. bacteraemia without evidence of vegetation. Correct identification of a vegetation is crucial, as it determines the clinical management, which most commonly involves CIED extraction. Valvular engagement is not uncommon and occurs in around 37% of the cases, with predominant involvement of the tricuspid valve; concomitant left-sided valve infection occurs in up to 15%. This clinical scenario is associated with higher hospital mortality. Diagnostic imaging examination begins with TTE, despite its lower sensitivity due to the artefacts created by the metallic electrodes. Information on valvular function, concomitant masses and overall cardiac performance should be reported. TEE is



Figure 12.
A TTE case of tricuspid valve IE - subxiphoid view.

recommended in all cases of CIED-IE and in cases of positive blood cultures for *St. aureus*. TEE sensitivity is higher despite its lesser proximity to the right-sided heart structures compared to TTE; however, vegetations in the upper segments of the superior vena cava or the coronary sinus may still be missed. Differential diagnosis is to be made with thrombi or fibrin strands attached to the surface of the pacemaker leads, as the right-sided cavities are characterised by much slower flow than left-sided ones, which predisposes to such a phenomenon. For optimal visualisation and characterisation of a vegetation, 3D echocardiography may be of additional support. In cases of high clinical suspicion for IE and negative echocardiography, other imaging tools such as computer tomography, positron emission computed tomography (PET-CT) with fluorine-18 fluorodeoxyglucose (18F-FDG), and scintigraphy should be performed. The treatment approach depends on the clinical scenario and consists of complete device extraction in most cases **Figures 13** and **14** [44, 45].

TAVR-IE is a type of prosthetic valve IE which occurs at a similar rate to SAVR, as mentioned earlier (0.3–2.0 per 100 person-years). Early prosthetic IE, especially <100 days after implantation, is six times more frequent than late IE, with a reported incidence of 2.6 per 100 person-years. The predisposition to infection stems from both patient-related (male, younger age, diabetes mellitus, chronic pulmonary disease, obesity, chronic kidney disease) and procedure-related factors. The latter include residual at least moderate aortic regurgitation, higher gradient post-implantation, valve-in-valve procedure, low TAVR placement, more than one prosthetic valve implantation, lack of balloon valvuloplasty beforehand and intraprocedural bleeding. Echocardiography, both TTE and TEE, remains a first-line imaging modality despite its much lower combined sensitivity and specificity—67.8% compared to 73% for SAVR-IE and around 90% for native valve IE. Different reports estimate inconclusive findings in one third of positive TAVR-IE. On the one hand, atypical presentation



Figure 13.
A TTE case of vegetation on a pacemaker lead without tricuspid valve involvement.



Figure 14.
Transverse sections of removed thrombotic vegetations around the pacemaker lead.

with lesions such as leaflet thickening or obstruction may obscure the diagnosis. Current data state practically no difference in the incidence of IE for both balloon-expandable (BEV) and self-expandable valves (SEV)—1.25 vs. 0.95%; p 0.33. There exists a different vegetation predilection depending on the TAVR platform design—the most common in both BEV and SEV are the leaflets; SEV often present also with stent frame involvement in 34% of cases. Around one third of TAVR-IE patients have at least two structures involved, with the most common being the mitral valve (48%), CIED (3.9%) and right-sided IE (1.4%). Multimodality imaging with CT, PET-CT and cardiac magnetic resonance imaging (CMR) is essential, as positive evidence of vegetation of the TAVR detected by PET-CT was missed by echocardiography in 33% of reported cases [9].

5. IE management and follow-up

Echocardiography is the primary diagnostic imaging modality for IE. The presence of vegetations, newly developed regurgitation of a native valve or dehiscence of a prosthetic one serves as a major criterion. Current ESC guidelines recommend TEE as a standard approach and TEE in the case of prosthetic valves, CIED or inconclusive TTE in the presence of high clinical suspicion for IE. During initial antibiotic treatment, TTE is not necessary in uncomplicated cases; however, newly developed AV

block or murmur, heart failure, ongoing fever and bacteraemia, or embolism require emergent echocardiography [5].

Either conservative or operative management depends on the clinical picture, along with imaging and laboratory exams. Echocardiographic evaluation should focus on the haemodynamic significance of the valvular lesion and its consequences: for left-sided valves, the presence of pulmonary hypertension and diastolic left ventricular dysfunction; for right-sided valves, in the case of severe tricuspid insufficiency, measurement of right ventricular size, systolic function and evidence of volume overload. ESC guidelines 2023 recommend emergent/urgent surgery in the case of refractory pulmonary oedema or ongoing heart failure and evidence of a poorly tolerable lesion. In the case of right-sided IE, operative management is indicated whenever the tricuspid regurgitation is significant and unresponsive to diuretics. The vegetation size also matters, as in the case of embolic accidents, a size >10 mm for left-sided valves warrant urgent surgical intervention. Evidence of vegetations >20 mm for the tricuspid valve and relapsing septic pulmonary emboli, otherwise detected by higher mean pulmonary blood pressure, also requires urgent surgical management with class Ib. The latter is graded by the right ventricular outflow tract acceleration time or the pulmonary diastolic regurgitant jet, whenever present. In the mentioned case, the systolic pulmonary pressure assessment by the tricuspid insufficiency jet is inappropriate, as it probably combines several mechanisms: primary damage by IE with perforation and secondary damage by the developed right ventricular dysfunction due to pulmonary hypertension. TTE is able to capture masses above 4 mm, while TEE has better resolution and clearly defines vegetations above 1–2 mm. Based on recent reports, the sensitivity for detection of vegetations by TTE and TEE in native and prosthetic valves is 70 and 50%, 96 and 92%, respectively. In all cases, 3D TTE/TEE would support better differentiation of the exact location, size and structural damage to the valves. In comparison of 2D TEE to 3D TEE, the former has lower specificity, 88 vs. 91.6%, despite similar sensitivity. Nonetheless, it is to be reminded that around 10% of the IE cases are not recognised no matter the imaging method [5].

Intraoperative TEE is with a class I C recommendation, as it guides the surgical management—valve repair or replacement surgery. Follow-up in the postoperative period and during conservative management with antibiotics also requires dynamic surveillance, especially at the end of the treatment, for assessment of valvular function and morphology and residual vegetations.

6. Conclusion

Echocardiography is an invaluable and cost-effective imaging modality for both the diagnosis and management of IE. Further advancement with the introduction of 3D TEE would guide the optimal surgical approach. However, either TTE or TEE only serves in correspondence with the clinical findings, especially in the case of prosthetic valve IE and CIED-related cases.

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The Role of Positron Emission Tomography (PET) in Management of Endocarditis

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Abstract

Endocarditis is a condition associated with high mortality and still often represents a diagnostic challenge due to the variability of its clinical manifestations. The 2023 ESC Guidelines for the management of endocarditis incorporate, within the modified Duke's criteria, new imaging modalities elaborated and published by the International Society for Cardiovascular Infectious Diseases (ISCVID): 18F-Fluorodeoxyglucose Positron Emission Tomography (18F-FDG-PET)/Cardiac Computed Tomography (CT). This technique combines the advantages of whole-body 18F-FDG-PET with the spatial resolution of CT, offering good sensitivity and specificity (0.74—CI 0.70–0.77 and 0.88—CI 0.86–0.91, respectively) for all cases of endocarditis, with improved performance, particularly in prosthetic valve endocarditis, positioning itself as a promising tool in this field. This chapter aims to review the role of 18F-FDG-PET)/CT in comparison with other imaging techniques, highlighting its potential use as an important diagnostic method in different clinical settings of endocarditis.

Keywords: 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET)/cardiac computed tomography (CT), endocarditis, diagnosis, Duke's criteria, imaging

1. Introduction

Infective endocarditis (IE) is a life-threatening cardiac infection and a major public health challenge [1], with an incidence of ~3–10 per 100,000 people. It is associated with high morbidity and mortality [2], with the overall mortality at ~25% [3].

The incidence and severity have remained stable despite advancements in diagnostic and therapeutic strategies, primarily due to the growing number of elderly patients with more severe conditions and an increase in infections related to prosthetic valves or devices [2].

Infective endocarditis poses a diagnostic challenge due to its different clinical manifestations.

Sepsis or unexplained fever, when associated with risk factors, should raise concern. The initial clinical evaluation should involve assessing risk factors, considering the clinical context, and performing a physical examination. Laboratory tests include blood

tests (complete blood count, white blood cell count, and markers of inflammation) along with blood cultures. Positive blood cultures are essential for diagnosing infective endocarditis, as they help identify the causative organism and determine its antibiotic susceptibility. However, some cases of endocarditis are classified as blood culture-negative endocarditis, where no pathogen can be detected using standard blood culture techniques [1]. Imaging studies are fundamental and have a central role in the diagnostic workup of infective endocarditis, including first-level methods, such as transthoracic echocardiography (TTE), and second-level methods including transesophageal echocardiography (TOE), cardiac computed tomography (CT), and magnetic resonance imaging (MRI). Furthermore, nuclear medicine diagnostic methods have an increasingly important role in the diagnosis of infective endocarditis, such as radiolabeled leukocyte (SPECT/CT) and 18-FDG Positron emission tomography (18-FDG-PET/CT).

2. Diagnosis in endocarditis: Duke's criteria

Clinical, microbiological, and imaging findings have been integrated with the modified Duke criteria. Historically, the original Duke's criteria were published in 1994. We were used to diagnose infective endocarditis (IE), which was modified in 2000. However, the clinical presentation of IE can be very different, and some significant limitations of the modified Duke criteria have become especially evident when prosthetic material is involved. As a result, the 2023 ESC Guidelines for the management of endocarditis incorporate new imaging criteria elaborated and published by the International Society for Cardiovascular Infectious Diseases (ISCVID) [4]. In fact, while maintaining the original classification system of “definite,” “possible,” and “rejected” cases, several modifications and additions have been made to both the major and minor criteria. Among the most significant changes is the inclusion of a new “surgical criterion” within the major criteria, now listed alongside the existing “microbiological” and “imaging” criteria. Furthermore, this document has given a key role to nuclear imaging, such as 18F-fluorodeoxyglucose Positron emission tomography (18F-FDG-PET/CT)/cardiac computed tomography (CT) and white blood cell single-photon emission tomography/computed tomography (WBC SPECT/CT) in addition to both transthoracic and transesophageal echocardiography [1]. 18F-FDG-PET/CT imaging for IE is given by ESC 2023 infective endocarditis guidelines [1], a class I recommendation (level of evidence B) and is therefore recommended in cases of possible prosthetic valve IE to both detect valvular lesions, as well as confirm the diagnosis of IE or in cases of suspected CIED-associated IE to detect pocket infection and pulmonary embolism. They have also given a class I recommendation (level of evidence B) for brain and whole-body 18F-FDG-PET/CT and/or MRI imaging to detect peripheral lesions for patients with either native or prosthetic valve IE [1].

Moreover, a new consensus document for updating Duke criteria expands the minor criteria category. In particular, the criterion “endovascular implantable cardiac electronic devices” has been added to the list of predisposing factors, joining established categories such as prosthetic heart valves and use of injectable drugs, congenital heart disease, hypertrophic cardiomyopathy, previous valve repair, mild or more severe valvular regurgitation, and stenosis (**Figure 1**) [4].

2.1 Transthoracic and transesophageal echocardiography

Transthoracic echocardiography (TTE) is the first-level imaging test of choice for diagnosis and can provide important information about characteristics and size of

MAJOR CRITERIA

- A. Microbiologic Major Criteria
 - (1) Positive blood cultures
 - i. **Microorganisms that commonly cause IE^a isolated from 2 or more separate blood culture sets (Typical)^b**
or
 - ii. **Microorganisms that occasionally or rarely cause IE isolated from 3 or more separate blood culture sets (Nontypical)^b**
 - (2) Positive laboratory tests
 - i. **Positive polymerase chain reaction (PCR) or other nucleic acid-based technique^c for *Coxiella burnetii*, *Bartonella* species, or *Tropheryma whipplei* from blood**
or
 - ii. *Coxiella burnetii* antiphase I immunoglobulin G (IgG) antibody titer >1:800 [24]^d, or isolated from a single blood culture
or
 - iii. **Indirect immunofluorescence assays (IFA) for detection of IgM and IgG antibodies to *Bartonella henselae* or *Bartonella quintana* with immunoglobulin G (IgG) titer ≥1:800 [24, 25]^d**
- B. Imaging Major Criteria
 - (1) Echocardiography and **cardiac computed tomography (CT) imaging**
 - i. Echocardiography and/or **cardiac CT** showing vegetation,^e valvular/leaflet perforation,^f valvular/leaflet aneurysm,^g abscess,^h pseudoaneurysm,ⁱ or intracardiac fistula^j
or
 - ii. Significant new valvular regurgitation on echocardiography as compared with previous imaging. Worsening or changing of preexisting regurgitation is not sufficient.
or
 - iii. New partial dehiscence of prosthetic valve as compared with previous imaging [52]
 - (2) **Positron emission computed tomography with 18F-fluorodeoxyglucose ([18F]FDG PET/CT imaging)**
Abnormal metabolic activity^k involving a native or prosthetic valve, ascending aortic graft (with concomitant evidence of valve involvement), intracardiac device leads or other prosthetic material^{l,m}
- C. Surgical Major Criteria
Evidence of IE documented by direct inspection during heart surgery neither Major Imaging Criteria nor subsequent histologic or microbiologic confirmationⁿ

MINOR CRITERIA

- A. Predisposition
 - **Previous history of IE**
 - Prosthetic valve^o
 - Previous valve repair^o
 - Congenital heart disease^p
 - More than mild regurgitation or stenosis of any etiology
 - **Endovascular intracardiac implantable electronic device (CIED)**
 - Hypertrophic obstructive cardiomyopathy
 - Injection drug use
- B. Fever Documented temperature greater than 38.0 °C (100.4 °F)
- C. Vascular Phenomena Clinical or radiological evidence of arterial emboli, septic pulmonary infarcts, **cerebral or splenic abscess**, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions, purulent purpura
- D. Immunologic Phenomena Positive rheumatoid factor, Osler nodes, Roth spots, or immune complex-mediated glomerulonephritis^q
- E. Microbiologic Evidence, Falling Short of a Major Criterion
 - 1) Positive blood cultures for a microorganism consistent with IE but not meeting the requirements for Major Criterion^r
or
 - 2) **Positive culture, PCR, or other nucleic acid based test (amplicon or shotgun sequencing, *in situ* hybridization) for an organism consistent with IE^r from a sterile body site other than cardiac tissue, cardiac prosthesis, or arterial embolus; or a single finding of a skin bacterium by PCR on a valve or wire without additional clinical or microbiological supporting evidence [51]**
- F. Imaging Criteria
Abnormal metabolic activity as detected by [18F]FDG PET/CT within 3 mo of implantation of prosthetic valve, ascending aortic graft (with concomitant evidence of valve involvement), intracardiac device leads or other prosthetic material
- G. Physical Examination Criteria^s
New valvular regurgitation identified on auscultation if echocardiography is not available. Worsening or changing of preexisting murmur not sufficient

Figure 1.
International Society for Cardiovascular Infectious Diseases (ISCVID).

vegetation and on the complications such as abscesses, pseudoaneurysms, and partial dehiscence of prosthetic valves of infective endocarditis. Also helps to guide decision-making and patient follow-up while receiving antibiotic therapy and during the peri-operative and post-operative periods [5]. However, TTE is generally not enough, especially in detecting perivalvular complications, small vegetations, prosthetic valve endocarditis (PVE), and vegetations related to cardiac implantable electronic devices (CIED). In fact, while TTE offers good specificity, its sensitivity is low in comparison

to transesophageal echocardiography (TOE) [6]. So, TOE becomes essential in various clinical situations and is crucial for complete and confirmatory diagnosis and better-identifying complications [5, 7, 8]. According to the 2023 ESC Guidelines, it is strongly recommended for patients with a negative or inconclusive TTE result but with a high suspicion of infective endocarditis (IE), as well as for those with a positive TTE, to rule out local complications [1]. However, while transesophageal echocardiography (TEE) shows almost perfect sensitivity (around 99%) for diagnosing native valve endocarditis, its accuracy drops to about 90% in cases of endocarditis related to cardiac implantable electronic devices (CIED) [8, 9]. This reduction in sensitivity highlights the need for supplementary imaging techniques to enhance diagnostic precision, particularly in CIED-related endocarditis. So, other imaging modalities, including CT, nuclear imaging, and magnetic resonance imaging (MRI), are crucial for confirming the diagnosis and identifying extracardiac complications [9].

2.2 Computed tomography (CT) and magnetic resonance imaging (MRI)

Cardiac CT is a useful tool to support the diagnosis of infective endocarditis and to define perivalvular and periprosthetic complications such as abscesses, pseudoaneurysms, and fistulas. It is also a valuable element in assessing the systemic complications of endocarditis, such as septic embolism (a minor diagnostic criterion for diagnosis). Finally, CT is a key element in decision-making regarding surgical intervention [10–12] by evaluating valvular and myocardial anatomy, cardiac walls, and valvular planes [13].

MRI plays a central role in diagnosing neurological complications related to infective endocarditis, offering greater sensitivity than CT in this context. Additionally, it can be useful in cases with uncertain diagnosis, as the presence of cerebral lesions without neurological symptoms constitutes a minor diagnostic criterion to support the diagnosis of IE. It is also important for diagnosing spinal lesions, with diagnostic accuracy ranging from 89% to 94% for cases of spondylodiscitis and osteomyelitis [1]. However, MRI has a limited role in diagnosing IE due to its relatively poor spatial resolution and the absence of signal from certain heart valve prostheses [14, 15].

2.3 Nuclear medicine: Radiolabeled leukocyte SPECT/CT

Single-photon emission computed tomography (SPECT)/CT imaging with radio-labeled leukocytes is a diagnostic modality for visualizing infectious processes within the body [13]. This technique has a sensitivity ranging from 64% to 90% and a specificity between 36% and 100% [16, 17]. The increased specificity of leukocyte scintigraphy imaging may be explained by WBC imaging, which specifically targets infection [18], while 18F-FDG-PET/CT imaging evaluates glucose metabolism, which can be increased in a variety of conditions (including both infection and inflammation) [19]. The diagnostic ability is significantly higher in the presence of periprosthetic abscesses. In fact, a low spatial resolution and low signal intensity limit the detection of small infective foci (smaller than 1 cm) and those caused by non-pyogenic germs [20–22]. However, SPECT/CT imaging is not part of the major or minor criteria for the diagnosis of infective endocarditis according to the modified Duke criteria [1]. Therefore, a positive scan result by itself does not qualify as a diagnostic criterion.

2.4 Positron emission tomography (PET)/CT

Fluorodeoxyglucose Positron emission tomography/computed tomography (18F-FDG-PET/CT) is a diagnostic imaging technique that combines Positron emission tomography (PET) and computed tomography (CT) to provide both metabolic and anatomical information.

Fluorodeoxyglucose (F-FDG) is a radiopharmaceutical analog of glucose that is labeled with fluorine-18. It is injected into the patient's body and taken up by cells that are metabolically active, such as cancer cells, which have an increased rate of glucose consumption. PET detects the radiation emitted by the fluorine isotope as it decays, providing information about the metabolic activity of tissues. CT provides detailed anatomical images that are fused with the PET data, offering a precise localization of abnormal metabolic activity.

It is widely used in oncology, neurology and cardiology primarily for the diagnosis, staging, and monitoring of various diseases. This imaging modality has significantly improved the ability to assess cardiac disease, including:

- Coronary artery disease (CAD) and myocardial viability: assessment of myocardial perfusion and metabolism, helping to detect regions of the heart with reduced blood flow or ischemia by integrating coronary anatomical information provided by CT, refining risk stratification in patients, and guiding therapeutic decision-making.
- Inflammatory disease, such as myocarditis or inflammation related to atherosclerosis.
- Infective endocarditis: plays a crucial role in diagnosing infective endocarditis (IE) in patients with cardiac implants, such as prosthetic valves and devices (e.g., pacemakers or defibrillators) [23].

2.4.1 Patient preparation and standardization

Standardization in image acquisition and patient preparation is essential for a high-quality examination. Guidelines for standardization have been established by the European Association of Nuclear Medicine (EANM) and the European Association of Cardiovascular Imaging (EACVI) [22, 24]. The primary goal of patient preparation is to maximize the tracer uptake in the target tissue. FDG, a glucose analog, is absorbed by tissues based on their metabolic activity. Therefore, in infective endocarditis (IE), FDG is typically taken up by myocardial cells, and the patient preparation in IE aims to minimize myocardial metabolic activity [25].

A high-fat, low-carbohydrate (HFLC) diet for 12–24 hours prior to the scan is recommended to optimize suppression of the physiological glucose metabolism in the myocardium. Additionally, fasting for at least 12 hours before the examination is advised [26–28].

Medications can be taken, except corticosteroids, which should be postponed until after the FDG-PET/CT and reduced to the lowest possible dose within the 24 hours preceding the examination due to their interference with glucose metabolism [24].

Furthermore, beyond the diet, some studies [29] aimed at optimizing preparation have suggested that the intravenous administration of heparin 15 minutes before the

examination to promote lipolysis and the availability of free fatty acids may have an additive effect on the physiological myocardial FDG uptake. However, conflicting data exist regarding the use of heparin before the examination [30]. Therefore, in the absence of contraindications to heparin, a dose of 50 IU/kg may be considered as a complement to the HFLC diet.

The time interval between the FDG injection and the start of the scan should be 60 minutes. In the case of performing semi-quantitative analyses (e.g., standardized uptake values, SUV), documentation of the exact interval is necessary and is considered acceptable within the range of 55–75 minutes [25]. For visual analysis, the exact timing is of lesser importance and is acceptable within the range of 60–90 minutes [24].

Some data suggest that delayed imaging may increase the diagnostic accuracy of 18FDG-PET/CT. Leccisotti et al. [31] suggest that delayed imaging is associated with higher accuracy in diagnosing electrocatheter infections (70% vs. 51%, $p = 0.024$) compared to the standard protocol (1-hour post-injection) [32]. However, there is no data on delayed acquisition in native and prosthetic heart valves, where a possible increase in false positives is observed [33].

2.4.2 18-FDG-PET/CT analysis and clinical interpretation

18FDG-PET image processing is based on various reconstruction protocols and attenuation correction of photons emitted by the radiotracer, typically performed using CT [13]. Images must be evaluated in all 2D planes as well as in 3D cine mode with maximum intensity projection (MIP), considering both the intensity of FDG uptake in the target lesion and the uptake pattern [25].

The evaluation of non-attenuation corrected images is particularly important, especially in the presence of prosthetic valves or cardiac devices. Artifacts due to scatter or beam hardening caused by prosthetic valves or implanted cardiac devices can lead to false-positive results. Therefore, increased FDG uptake should always be confirmed on non-attenuation corrected images to further support the suspicion of prosthetic valve or device-related infection [24].

Proper image orientation along appropriate anatomical planes is essential for accurate visualization and interpretation of the structures of interest [34]. Interpretation focuses on both qualitative (visual) and quantitative analyses:

- **Qualitative analysis:** visually, attention should be directed to the distribution of hypermetabolism (on PET), which helps differentiate inflammatory from infectious patterns, and to the presence of anatomical lesions (on CT), which support the diagnosis of endocarditis—such as vegetations, abscesses, fistulas, and pseudoaneurysms [33].
- **Quantitative analysis:** Quantitative assessment is performed using standardized uptake values ($SUV = [^{18}F]FDG$ uptake in the region of interest/injected dose/patient weight) [35]. While semi-quantitative metrics using SUV are well established in oncology, their use in infective endocarditis (IE) is less common [25]. SUV values are obtained by placing a region of interest (ROI) or volume of interest (VOI) over the area of maximum metabolic activity. It has been shown that the maximum SUV (SUV_{max}) can aid in differentiating infectious ($SUV_{max} 7.91 \pm 3.63$) from inflammatory processes [36].

2.4.3 18-FDG-PET/CT: Diagnosis role

This imaging modality is a new imaging exam included in the 2023 Duke-ISCVID IE criteria. It addresses the diagnostic limitations of other imaging techniques, like echocardiography, in particular evaluating prosthetic material [5].

However, a significant difference is observed in specificity and sensitivity according to the subtypes of IE. In fact, F-FDG-PET/CT has a high specificity for all subtypes of infective endocarditis, but the sensitivity is much lower for native valve IE than prosthetic valve or cardiac implantable electronic devices IE. As suggested by Wang et al. [37] by a systematic review and meta-analysis aiming to evaluate the diagnostic accuracy of PET/CT in infective endocarditis diagnosis, the pooled sensitivity and specificity were 0.74 (95% CI 0.70–0.77) and 0.88 (95% CI 0.86–0.91) for all cases of endocarditis. However, for native valve infective endocarditis, the sensitivity was 0.31 (95% CI 0.21–0.41) with a specificity of 0.98 (95% CI 0.95–0.99). For prosthetic valve IE, the sensitivity was 0.86 (95% CI 0.81–0.89) with a specificity of 0.84 (95% CI 0.79–0.88). For cardiac implantable devices IE, the sensitivity was 0.72 (95% CI 0.61–0.81) and specificity was 0.83 (95% CI 0.75–0.89).

2.4.4 FDG-PET/CT in prosthetic valve endocarditis

The current indication for 18-FDG PET/CT [38, 39] is in patients with a high clinical suspicion of PVE and nondiagnostic echocardiography [4]. Consequently, it allows for the reclassification of suspected prosthetic valve endocarditis (PVE) cases from “possible” to “definite” IE, with an overall sensitivity of 0.86 (0.81–0.89) and specificity of 0.84 (0.79–0.88) [37].

According to the ISCVID Working Group, focal/multifocal or heterogeneous radiotracer uptake on the prosthetic valve is included as a Major Criterion [40]. Due to difficulty in distinguishing post-operative inflammation from an infectious phenomenon within the first 3 months after implantation [25], PET/CT results with [18F]FDG during this period are considered a minor criterion until more data become available regarding the routine use of early PET/CT scans [4]. However, it is important to emphasize that the distribution pattern of the metabolic signal may be differentiate these two aspects [1]: a homogeneous, diffuse and mild activity surrounding the ring is compatible with post-operative changes, while the presence of focal activity would be considered abnormal, indicating a potential case of endocarditis [41]. Nevertheless, the persistent host immune response to the biomaterial coating of the prosthetic valve’s sewing ring may continue for years after implantation and should be carefully considered as a potential source of diagnostic misinterpretation [33].

Furthermore, 18F-FDG-PET/CT is a useful diagnostic tool for patients with suspected transcatheter-implanted aortic valve infective endocarditis (TAVI-IE). In fact, it is difficult to diagnose when relying on the Duke criteria. Wahadat et al. [42] assess the additional diagnostic value of 18F-FDG-PET/CT in suspected TAVI-IE. A multicenter retrospective analysis was performed in 30 patients with suspected TAVI-IE. Patients were first classified with Duke criteria, and after adding 18F-FDG-PET/CT, which supported the reclassification of 10 of the 22 possible cases as “definite TAVI-IE” or “rejected TAVI-IE.” This changed the final diagnosis to 20% rejected (from 3% using the modified Duke criteria), 40% possible (from 73% using the modified Duke criteria), and 40% definite (from 23% using the modified Duke criteria) TAVI-IE.

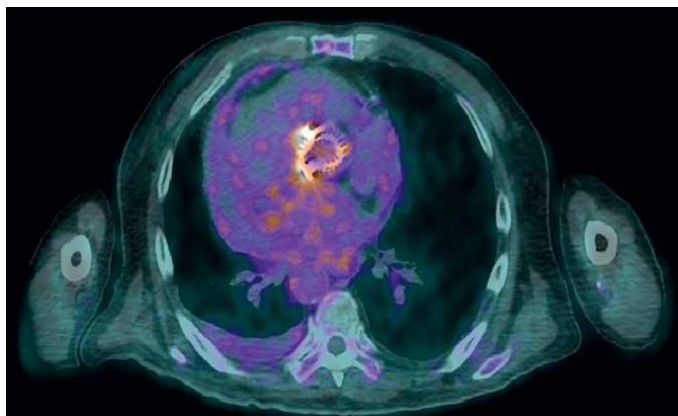


Figure 2.
Aortic prosthetic valve infection.

As a single-center retrospective study demonstrated, FDG-PET/CT could have a role in the evaluation of prosthetic aortic valve implantation and ascending aorta replacement infection. In fact, a focal pattern of the uptake of 18F-FDG or tracer uptake with soft tissue extension may identify suspected Bentall infection with a good sensitivity (86%) and specificity (80%). However, more data are needed in this specific setting of patients (**Figure 2**) [43].

2.4.5 18-FDG-PET/CT in cardiac implantable devices and leads infections

Abnormal uptake on CIED catheters is a major diagnostic criterion. It is useful in the setting of possible CIED-related IE to detect pocket infection and pulmonary embolism (recommendation class: I) [1]. This method has a good sensitivity and specificity (93–96% and 97–98%, respectively) for detecting generator and pocket infection [37]. However, for electro-catheter infection, the sensitivity and specificity are lower (65–76% and 83–88%, respectively) because of the smaller size of the vegetations and their lower metabolic activity [18, 25, 44]. Therefore, a negative scan cannot exclude infection in cases of high diagnostic suspicion [4]. Furthermore, given that general inflammation can cause increased uptake on 18F-FDG-PET/CT imaging, the results must be interpreted with caution if the device was implanted within 6 weeks of imaging [1].

Left ventricular assist devices (LVADs) are increasingly used in the management of advanced heart failure, yet device-related infections remain challenging to diagnose. In a meta-analysis involving 230 patients with suspected LVAD-related infections, a total of 256 [18F]FDG-PET/CT scans were performed. The findings demonstrated an overall sensitivity of 97% and specificity of 99% for driveline infections, and an overall sensitivity of 97% and specificity of 93% for infections involving central device components [25]. These results highlight the potential diagnostic value of [18F]FDG-PET/CT in this setting. However, larger prospective studies are needed to further validate these findings (**Figure 3**) [13].

2.4.6 [18]FDG-PET/CT in native valve endocarditis

In native valves, this imaging modality is not considered sensitive enough to rule out infective endocarditis (sensitivity, 0.31 [0.21–0.41]) but has a high positive

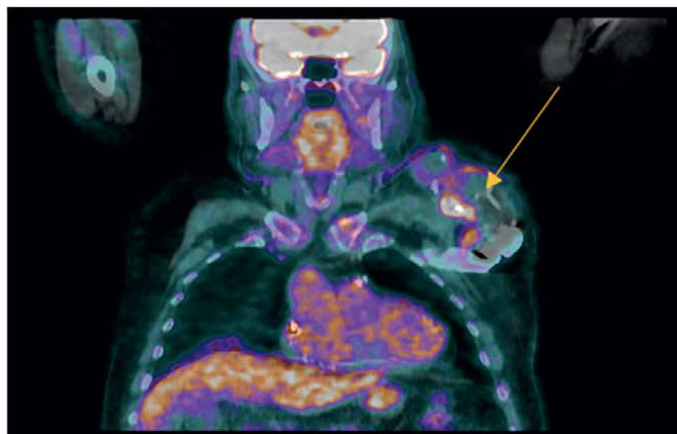


Figure 3.
Pacemaker pocket infection.

predictive value [4]. Thus, a significant and abnormal uptake on native valves has been included as a Major Criterion [37, 41].

Lower sensitivity in native valve infective endocarditis (IE) may be explained by several factors [19]. First, the biofilm formed on prosthetic valves is thought to be more inflammatory, making it easier to detect with 18F-FDG-PET/CT, compared to smaller and avascular vegetations typically found in native valve IE [45]. Additionally, prosthetic valves have a thicker valvular apparatus and struts, which are more easily imaged and visualized with 18F-FDG-PET/CT than the thin, highly mobile leaflets and vegetations of native valves [37]. Finally, a histological study showed that native valve IE tends to have a lower degree of polymorphonuclear cells and a higher degree of fibrosis compared to prosthetic valve IE [41].

An additional important aspect of 18F-FDG-PET/CT imaging for infective endocarditis (IE) is the ability to obtain whole-body images rather than just focusing on the heart. This has two significant implications: on one hand, it allows for a comprehensive view of potential extracardiac involvement, detecting clinically silent disseminated infectious disease, identifying primary infection source and/or septic

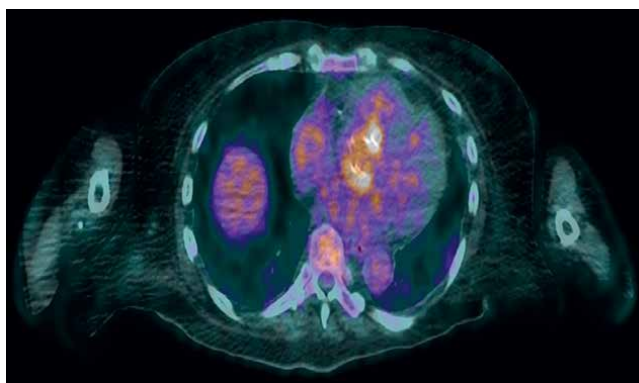


Figure 4.
Native aortic valve infection.

embolism, which can be crucial for diagnosis and patient management [13]. On the other hand, it provides supporting elements that can aid in diagnosing the condition [19]. In fact, several supportive features in 18F-FDG-PET/CT imaging for IE can assist in diagnosing the condition. For example, increased splenic and bone marrow activity can serve as indirect signs of IE. The immune response triggered by the infectious event leads to an increase in glycolytic metabolism, which is reflected in enhanced FDG uptake in both the spleen and bone marrow [46]. A splenic-to-liver ratio greater than 1 supports the diagnosis of IE [47]. However, hepatic steatosis, insulin resistance, metabolic syndrome, and other factors can also lead to increased FDG uptake, potentially generating false positives (**Figure 4**) [19].

3. Limitations

18-FDG-PET/TC uptake pattern is important for diagnosis, and many factors and conditions can contribute to both false-positive and false negative results. Homogeneous uptake indicates reactive nonspecific inflammation. Heterogeneous and/or multifocal uptake and propagation to surrounding soft tissues and/or metabolically active lymph nodes in the adjacent sites it is suggestive of infection [24].

False positives may occur due to conditions such as valve thrombosis or the use of surgical adhesives (e.g., biological glue and Teflon sutures), which can lead to focal increased FDG uptake [36, 39].

On the other hand, false negative results may arise from factors such as prolonged intravenous antibiotic therapy before the scan. Additionally, small isolated valvular vegetations without significant periannular involvement can also lead to false negatives [36, 39, 48].

4. Future perspectives

Artificial intelligence (AI) and machine learning are in continuous expansion and development and are becoming increasingly important, particularly in oncology [49]. A promising area of development would be to evaluate whether AI-based approaches can differentiate between physiological uptake, reactive or post-surgical inflammation, and infection in cases of suspected infective endocarditis (IE) [25]. Such advancements could significantly enhance the clinical utility of this imaging technique.

The elimination of motion artifacts, for instance, through ECG gating in PET imaging, could potentially increase the sensitivity of PET/CT in native valve endocarditis (NVE) and cardiac implantable electronic devices (CIED), thereby facilitating the identification of vegetations on valvular leaflets or intracardiac leads [25].

The implementation of integrated hybrid PET/MRI systems enables dynamic motion correction using MRI data, while also providing superior soft tissue characterization and functional imaging capabilities [50]. This approach could be particularly valuable in the assessment of native valve endocarditis, a setting in which PET/CT currently shows limited sensitivity [25].

Furthermore, an emerging and promising role of 18F-FDG-PET/CT is in patients with confirmed IE, where it may be used to monitor the response to antimicrobial therapy. This approach is already well established in oncology and inflammatory diseases, and growing evidence suggests its potential applicability in monitoring invasive infections. However, data on the use of 18F-FDG-PET/CT for treatment monitoring in IE are currently limited.

5. Conclusions

The use of 18F-FDG-PET/CT is a well-established diagnostic method, primary in the identification of prosthetic valve endocarditis. It is also useful diagnostic support in native valve endocarditis and cardiac implantable devices, especially in pocket infections. This method allows for making an infective endocarditis diagnosis and detecting cardiac complications, the sources of bacteremia, and monitoring response to antimicrobial treatment.

The implementation of promising imaging techniques within the modified Duke criteria [4] and 2023 ESC Guidelines for the management of infective endocarditis [1] enables an improved diagnostic approach to disease, thereby reducing the likelihood of underdiagnosed or late-diagnosed infectious events. We expect an increasing use of these techniques in clinical practice, ensuring timely diagnosis and enabling early pharmacological therapy for a disease still associated with high mortality.

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Section 3

Treatment Options in Endocarditis

Advances and Ongoing Challenges in the Management of Tricuspid Valve Infective Endocarditis

*Erin Hoover, Edward Hauptmann, Paige DeBlieux,
Lakisha Haran, Raghav Chandra and Suresh Keshavamurthy*

Abstract

Tricuspid valve infective endocarditis (TVIE) comprises 5–10% of all endocarditis cases and is more prevalent with the recent and ongoing opioid and intravenous drug epidemic, as well as increased placement of intracardiac devices. New technologies have been developed to manage tricuspid valve (TV) vegetations in an evolving population. In this chapter, we provide comprehensive review of age-old treatment modalities for TVIE as well as a discussion of advanced TV repair and replacement modalities and alternatives to surgery. We examine critical management nuances including optimal surgical technique based on a variety of patient-related factors, ideal operative timing, medical and surgical management of septic emboli, managing patients with prior percutaneous TV interventions and current TVIE, and emerging treatment techniques for TVIE. We aim to provide a framework for the multi-disciplinary care of TVIE in a changing patient and technology landscape.

Keywords: tricuspid valve endocarditis, tricuspid valve replacement and repair, intravenous drug use, septic emboli, AngioVac, T-TEER, intracardiac devices

1. Introduction

Right-sided infective endocarditis (IE) comprises 5–10% of all endocarditis cases. Ninety percent of this subset involves the tricuspid valve (TV) [1]. While *Staphylococcus aureus* is most commonly implicated in TVIE, other *Staphylococcal*, *Streptococcal*, and fungal pathogens may also be involved. Currently, the Duke Criteria, which include echocardiography findings, blood culture data, major and minor clinical criteria, predisposing conditions, and clinical sequelae, are used to establish a diagnosis of TVIE. Still, diagnosis can remain elusive given the vague clinical manifestations.

Due to the ongoing challenge of the opioid epidemic and associated high incidence of intravenous drug use, TVIE continues to be a major public health concern with

elevated morbidity and mortality. Furthermore, the utilization of intracardiac devices and central venous catheters also contributes to the high incidence of TVIE. Despite the overall rarity of the condition, TVIE remains clinically and socially significant. Patients diagnosed with TVIE may suffer from tricuspid regurgitation/insufficiency (TR) or stenosis (TS) leading to right heart strain/failure, or perivalvular abscess and damage to the electrical conducting system of the heart leading to high degree atrioventricular block. Septic emboli to the pulmonary vasculature may lead to clinically-significant pulmonary embolism or infarct, pulmonary cavitation and pleural effusion. Moreover, paradoxical emboli via a patent foramen ovale or intracardiac shunt may lead to systemic emboli, infarcts, cerebrovascular accident (CVA) septic shock, and multiorgan failure [1, 2]. The multitude of complications confers high morbidity and mortality on those diagnosed with TVIE with an unmeasured negative effect on quality of life.

Given its complexity, established guidelines for the medical and surgical management of TVIE are evolving. This chapter aims to review and discuss age-old treatment modalities for TVIE, advanced TV repair and replacement modalities, and alternatives to surgery such as AngioVac therapy. We examine critical management nuances including optimal surgical technique based on a variety of patient-related factors, ideal operative timing, medical and surgical management of septic emboli, managing patients with prior percutaneous TV interventions and current TVIE, and emerging treatment techniques for TVIE. We provide a comprehensive framework for the multi-disciplinary care of TVIE in a changing patient and technology landscape, with the understanding that this area of cardiac medicine and surgery is ripe for growth in the realms of clinical care and research (**Figure 1**).

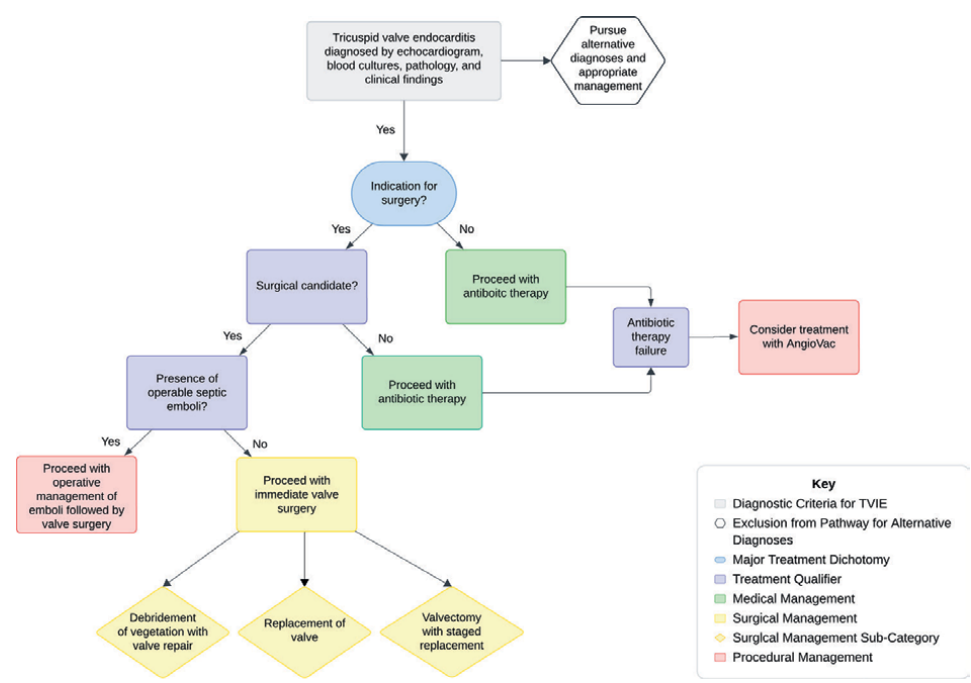


Figure 1.
Suggested clinical treatment pathway for the management of TVIE.

2. Indications for early surgery

In contrast to left-sided IE, TVIE is primarily a consequence of intravenous drug use (IVDU), indwelling cardiac devices, or long-term central catheters [1, 3]. Physiologically, regurgitation with right-sided IE is typically better tolerated with lower right heart pressures, and distal embolic phenomenon are primarily into the pulmonary circuit, as opposed to systemic sequelae seen with left-sided IE [4]. Additionally, in the IVDU, there is a high recurrence rate of TVIE due to continued drug use [5]. As such, most cases of TVIE are managed medically, and less than 4% of TVIE patients require surgical intervention [6]. Due to the relative infrequency of operations for TVIE, there are no well-defined guidelines for timing operative interventions. However, the 2015 European Society of Cardiology (ESC) guidelines on the management of infective endocarditis recommend surgical intervention for TVIE in the following situations: right heart failure due to tricuspid valve regurgitation that is refractory to medical therapy, persistent bacteremia for greater than 1 week or IE caused by fungi or other organisms that are notoriously difficult to eradicate, tricuspid valve vegetations >20 mm, and recurrent pulmonary septic emboli [1]. Since *S. aureus* is associated with valve destruction, larger vegetations and more frequent emboli, many consider early surgical intervention pertinent in the setting of a multidrug-resistant *S. aureus* [7]. The presence of a patent foramen ovale (PFO) is not a discrete indication for surgical intervention in cases of infective endocarditis. However, atrial septal structural defects correlate with an increased incidence of recurrent systemic septic emboli which constitutes an indication for surgery [8].

The 2020 American Heart Association (AHA) guidelines for management of valvular heart diseases recommends early surgical intervention (defined as surgery during the index hospital course and before completion of a full course of antibiotics) for the indications listed above, as well as for IE patients with heart block, annular abscesses, and extension of infection through the mitral valve or aortic noncoronary sinus [9–12]. Prosthetic valve endocarditis (PVE) is more likely to spread beyond the valve attachments and lead to complications such as perivalvular abscess or valve dehiscence, carries a higher mortality rate, and requires surgical intervention in around 50% of cases [13, 14]. Surgery for PVE, in combination with medical therapy, was shown to improve survival at 30 days, 2 years, and 3 years post-operatively compared to medical therapy alone [13]. For IE in the setting of indwelling cardiac devices, it is recommended to completely extract the device and leads, even if the infection appears to be limited to the generator pocket site [9]. A prospective cohort study of 141 patients demonstrated a survival benefit at 1 year with cardiac device removal at the initial hospitalization (HR: 0.42; 95% CI: 0.22–0.82) [15]. Alternatively, patients without right ventricular dysfunction, vegetations <1 cm, and non-severe TV regurgitation may be treated with antibiotics and observation if asymptomatic [12, 16].

Septic embolism resulting in cerebrovascular accidents is a particularly challenging clinical scenario, regardless of the presence of hemorrhagic conversion. The decision to proceed with early surgical therapy must be individualized to each patient's clinical status and hemodynamic stability. Traditional teaching recommended delaying cardiac surgery for 4 weeks after a cerebrovascular accident (CVA) based on a retrospective study published in 1995 that found a higher rate of neurological deterioration, including cerebrovascular-specific mortality, in patients undergoing cardiac surgery within 1 week of CVA when compared to surgery after a four-week delay [17].

These findings have been further corroborated by a retrospective study which demonstrated significant exacerbation of neurologic symptoms if early surgery within 2 weeks was pursued vs. >2 weeks [18]. Recent studies, however, have questioned this dogma. Kremer et al. performed a retrospective review of 688 patients with IE from a single institution over the course of 20 years and reported no significant difference in post-operative new CVA, post-operative neurologic recovery, in-hospital mortality, or long-term survival between cohorts of patients undergoing early cardiac surgery (less than 7 days after CVA) and late cardiac surgery (greater than 7 days after CVA) [19]. This data may be skewed by the fact that patients in the early surgery group were often further decompensated in terms of cardiac physiology due to valvular destruction and peri-valvular lesions and patients with hemorrhagic conversion of ischemic brain matter were more often placed in the delayed surgery cohort. While this study addresses patients with left-sided endocarditis, its findings may be generalized to cases of right-sided endocarditis in the setting of a PFO or atrial septal defect (ASD) resulting in neurologic emboli. Furthermore, stroke severity and region of infarct also impact outcomes. Moderate-to-severe ischemic, not hemorrhagic, CVA is associated with worsened functional outcomes 1 year after the inciting event [20]. Infarcts involving the middle cerebral artery are associated with reduced probability of neurologic recovery and only 50% of patients may return to a pre-stroke baseline level of function [21]. Still, the data suggests that in the correct patient population, where the benefits of halting ongoing heart failure and dissemination of septic emboli outweigh the risks of a deteriorating clinical state and post-operative sepsis, earlier valve surgery may be safe [19, 22]. Despite the trend toward earlier surgery in patients with cerebral septic emboli, one must account for each patient's medical complexities, the nuances of which are discussed below in the "Patients with septic emboli" section.

3. Surgical options

The primary goals for surgery for TVIE are debridement of all infected tissue and vegetations, as well as restoration of valve function when possible [1]. Generally, reducing or eliminating TV regurgitation and avoiding implantation of prosthetic material is optimal [23]. If possible, a vegetectomy can be performed by removing existing vegetations. If there is significant residual TR following vegetectomy, a TV repair should be employed [23, 24].

When a valve is salvageable, tricuspid repair with pericardial patch, cone repair technique, or suture versus sutureless annuloplasty can be utilized. Small defects may be amenable to direct closure with an autologous pericardial patch [25]. Pericardial patches may also be utilized for cusp augmentation, cusp replacement, and commissural reconstruction [26]. Replacement of resected chordae in the setting of infection with subvalvular extension may be achieved using artificial polytetrafluoroethylene neochords [12]. Cone repair, traditionally utilized to correct Ebstein's congenital anomaly, is also a viable option for salvage of tricuspid valve leaflets damaged by IE. Cone reconstruction, as first described by Da Silva, consists of clustering tricuspid leaflet tissue in a 360-degree formation (a "cone" shape) about the right atrioventricular junction, followed by reattachment of this tissue to the valve annulus in normal anatomic location. This method facilitates leaflet coaptation and restores proper valve function [27]. Suture annuloplasty may be used as a method of TV repair, or as an adjunct to alternative TV repair techniques, by reducing the tricuspid orifice area and approximating remaining valvular tissue. For example, the De Vega annuloplasty

includes placement of two semi-circular purse string sutures from the anteroseptal commissure to the posteroseptal commissure, which results in inward folding of the valve leaflets [28]. This results in leaflet coaptation, while avoiding excess tension on the valve [23]. After complete or near complete resection of a leaflet, Kay's annuloplasty may be used, which consists of suture placement in the segment of the annulus corresponding to the resected tissue, resulting in bicuspidization of the valve and significant reduction in the valvular orifice area [29]. It is worth noting that Kay's annuloplasty is not used in septal leaflet excision due to the risk of inducing atrioventricular block [23, 29]. When used in the posterior leaflet of the tricuspid valve, Kay's annuloplasty obliterates the space that resulted from leaflet excision but stops short of the posteroseptal commissure and is not likely to interfere with the cardiac conduction mechanism. Lastly, Carpentier's remodeling annuloplasty uses a prosthetic ring, which restores the normal annular shape and allows for normal valve function [30]. Suture annuloplasty overall is associated with higher rates of tricuspid regurgitation and post-operative annular dilation in comparison to Carpentier's annuloplasty [1, 31, 32]. Furthermore, a study by Dawood et al. reported no cases of recurrent TVIE in patients who underwent TV repair with an annuloplasty ring when compared to a re-infection rate of 21% when TVIE was managed with tricuspid valve replacement [4].

In cases of multi-leaflet endocarditis, complete valve excision (valvectomy) is typically necessary [33]. In the original series reporting this procedure, Arbulo et al. reported a 64% survival rate 22 years after valvectomy in 53 patients with IVDU, with many deaths attributed to sequelae of IVDU rather than heart failure [33, 34]. A series of seven patients having undergone the Arbulo procedure (tricuspid valvectomy without replacement) noted the following post-operative physiologic effects: an average increase in mean right atrial pressure of 38%, an average increase in right ventricular end diastolic pressure of 59%, and a reduction of cardiac and stroke indices by 5% and 22%, respectively [35]. In about 33% of patients, clinically-significant sequelae such as right ventricle (RV) dysfunction, low cardiac output, ascites, and peripheral edema resulted, requiring TV replacement within 6 to 9 months [1, 33]. Hence, in patients with elevated pulmonary artery pressures, TV excision without replacement is contraindicated and a prosthetic valve must be implanted [5]. In the absence of preoperative exclusionary factors, this surgery historically is viewed as the operation of choice for IVDU as only 11% of patients over a 20-year period required prosthetic heart valve insertion to control medically-refractory right heart failure [34]. Valvectomy is a rare procedure only accounting for 7.2% of operations performed for TVIE in North America, whereas TV replacement was implemented for 53.8% of TVIE cases [36].

There are a variety of options available for TV replacement including bioprosthetic valve, mechanical valve, mitral valve homograft, and inverted stentless porcine aortic root prosthesis [37, 38]. Bioprosthetic heart valves are less thrombogenic than mechanical heart valves and are associated with improved cardiac hemodynamics. The two types of bioprosthetic valves are xenografts, valves derived from bovine or porcine pericardium and heart valves, and homografts.

The mitral valve or inverted pulmonary and aortic trunks of cadavers, and may be surgically implanted at the tricuspid valve location [39]. Bioprosthetic valves invariably undergo structural valve degeneration (SVD) which make them a less suitable option for younger patients with longer life expectancy. Indeed, a single center twenty-year experience with TV replacement demonstrated an estimated twenty-year survival of 54.8% after bioprosthetic valve replacement compared to 68.3%

with mechanical valve replacement due to leaflet and matrix disruptions resulting in hemodynamic dysfunction (SVD) [40]. While the incidence of recurrent TVIE after prosthetic valve replacement is high in IVDU (57%), the incidence of spontaneous recurrence remains relatively low (5.6–25%) [23, 41]. Mechanical heart valves are artificial objects derived from pyrolytic carbon, titanium or other polymers [42]. Mechanical valves are associated with increased durability and decreased reoperative rates (HR: 0.24; 95% CI: 0.08–0.72, $p = 0.001$) [43]. It must be considered that mechanical valves result in high shear stress and exhibit thrombogenic properties, requiring lifelong anticoagulation and precluding the future use of RV pacer leads or pulmonary catheters [1]. Downsides to TV replacement include increased infection risk from prosthesis implantation and the risk of causing atrioventricular block [23, 44]. Up to 16% of patients require pacemaker placement for heart block after TVR for all indications [1]. Other investigation note that 5.8% of patients after TVR required pacemaker implantation within just the post-operative year. Pre-operative TVR in the context of TVIE is independently correlated with developing atrioventricular block (AVB) and 34% of the TVIE subset required pacemaker implantation within 1 year post-operatively [45]. An alternative to traditional replacement techniques, with no reported incidences of post-operative heart block, is cylindrical reconstruction with a novel extracellular matrix, as described by Gerdisch et al. [46]. In this technique, the tricuspid valve is replaced with a cylinder sewn out of a proprietary extracellular matrix and attached to the existing papillary muscles and valve annulus. Case series demonstrated a 15% reoperation rate with well-functioning tricuspid valves in all patients post-operatively, making this another viable TV replacement option [46].

4. AngioVac therapy

The AngioVac system, which achieved FDA approval in 2014, is a minimally invasive mechanical suction device which utilizes a percutaneous venovenous circuit with a centrifugal pump, similar to extracorporeal membrane oxygenation (ECMO). The AngioVac system filters and aspirates intravascular debris and reinfuses blood to the patient. The system has demonstrated a clinical benefit in the setting of thrombotic or embolic disease, while use in the treatment of TVIE to debulk valvular vegetative burden is under recent investigation in patients with high-risk operative candidacy. A 2022 meta-analysis found the AngioVac device to be a safe and viable option for the removal of septic emboli in high-risk surgical candidates with right-sided infective endocarditis. Additionally, AngioVac therapy for the radical debridement of vegetations in the acute, infectious phase has exhibited a reduction in valve vegetation burden by greater than half in 89% of instances [45]. A decreased infectious load allows for improved penetration and efficacy of standard antimicrobials, which allowed 79% of patients to be free of bacteremia and with adequate valve function at 5 years after combined use of AngioVac and antibiotics [45]. AngioVac treatment may be an excellent option to bridge to definitive valvular surgery in the critically ill patient [47]. Furthermore, the AngioVac system may offer increased accessibility and ease of operation when compared to surgical intervention. Its development in 2014 aligned with a period in which society required widely applicable treatment for TVIE due to the increased prevalence associated with the simultaneous opioid epidemic. AngioVac is a less invasive, percutaneous alternative to cardiac surgery and can be performed by interventional cardiologists.

Despite promising results, there is a paucity of long-term data regarding usage, safety, efficacy, and cost-conscious care. This is in part because AngioVac for TVIE treatment is an unofficial indication for the device. One concern raised regarding the AngioVac device is the potential to inflict damage via mechanical force to the tricuspid valve. Fallon et al. describe a 65% increase in the prevalence of tricuspid regurgitation after AngioVac procedures [48]. Moreover, Voelkel et al. noted three of 33 patients in a 2017 study required elective tricuspid valve replacement after AngioVac therapy, although it is unclear if damage from the device or the natural history of TVIE contributed [49]. Although small in number, progression to surgical intervention is clinically-significant to those patients. Further investigation into the potential adverse effects of AngioVac use are warranted.

While there are few retrospective and single-center studies on AngioVac therapy for valve vegetations, as well as metaanalyses, there is a paucity of comparative data to control groups. Much is left to be discovered regarding AngioVac as a treatment modality for TVIE as either a stand-alone therapy or bridge to future surgery.

5. Special considerations for the management of infective endocarditis

The following subsections expound upon scenarios and patient-specific factors for which the treatment of tricuspid valve infective endocarditis is nuanced.

5.1 Patients with indwelling intracardiac devices

The prevalence of right-sided infective endocarditis is increasing, in part due to more frequent placement of cardiac devices—including pacemakers, mechanical valves, and defibrillator leads—and indwelling central venous catheters [50]. According to Elsaghir et al., implantable cardiac devices infections occur de novo in 0.5% of patients and 2% of patients undergoing device replacement [51]. A 25-year review of infective endocarditis cases found that cardiac implantable electronic device infective endocarditis (CIED-IE) was significantly more common than TVIE related to native and prosthetic valve infection [51]. Intracardiac devices are one of the more common causes of infective endocarditis, present in up to 10% of cases with a 1.9% embolic stroke risk [51]. As such, the Duke Criteria have been modified to include a history of implantable devices in the workup to rule out infective endocarditis [52]. CIED-IE can present as valvular, device lead, and bloodstream infections. Accurately diagnosing CIED-IE can be difficult given the broad clinical presentation and complexity of patients [52]. In 70–90% of cases, *Staphylococcus aureus* and *Staphylococcus epidermidis* are isolated as causative agents [53, 54]. Patients who develop CIED-IE have a poor prognosis with 3–14% mortality despite appropriate treatment with intravenous antibiotics and, if appropriate, device extraction [54].

To address the problem of CIED-IE, the European Heart Rhythm Association (EHRA) released a 35-page international consensus document in 2019 detailing infection prevention recommendations in the setting of CIED-IE [55]. An updated AHA expert consensus statement on the prevention, diagnosis, and treatment of CIED-IE was then published in 2023. The recommendations are as follows. *For the prevention of CIED-IE*: adhere to standard infection prevention measures, administer prophylactic preoperative cefazolin, practice surgical technique to prevent hematoma and superinfection, and consider an antimicrobial envelope for high-risk patients [52]. Regarding clinically-significant hematoma (CSH) formation, the BRUISE-CONTROL-1 and

BRUISE-CONTROL-2 trials were conducted to evaluate pre-operative adjustment of anticoagulation prior to pacemaker or defibrillator placement. These studies found that perioperative warfarin continuation or interrupted direct oral anticoagulant (DOAC) therapy, as opposed to heparin bridging, resulted in a significantly lower formation of CSH. Subsequent analysis determined that antiplatelet therapy, in combination with anticoagulation, doubled the risk of CSH in the peri-operative period of device implantation [56]. *For the diagnosis of CIED-IE:* examine the device pocket for signs and symptoms of infection, perform transesophageal echocardiogram (TEE) to evaluate for valvular vegetations if bacteremia is present, and consider computed tomography (CT) or positron emission tomography (PET) if the aforementioned evaluations are inconclusive or there is evidence of a lead-related mass on TEE. Future directions for diagnosis include device sonication and device surface molecular techniques to enhance microbial detection prior to clinical presentation of CIED-IE. *For the management of CIED-IE:* remove indwelling devices and perform transvenous lead extraction, provide chronic antimicrobial suppression for non-extraction candidates, only implant a new CIED once the original pocket has undergone adequate debridement and blood cultures are consistently negative, and consider subcutaneous implantable cardioverter defibrillator (S-ICD) and leadless pacemaker (LPM) for high-risk patients [52].

5.2 Patients with opioid use disorder and continued/recurrent drug use

TVIE is commonly associated with IVDU, and intravenous drug use-associated infective endocarditis (IVDU-IE) typically affects the tricuspid valve. The United States Opioid Epidemic first began in the 1990s, with second waves after 2006 and from 2010 to 2013 [57]. A 2020 review by Schranz et al. demonstrated a 238% increase in IVDU-IE hospitalizations from 2000 to 2013 [58]. This trend was paralleled in surgical management as tricuspid valve operations associated with IVDU, including repair and replacement, increased annually by 226% from 2012 to 2018 [59]. The typical IVDU-IE patient is younger and less comorbid than those with TVIE of other etiologies. Additionally, a higher proportion of this population experiences homelessness, poverty, and co-infection with Hepatitis C (RR: 1.55; 95% CI: 1.23–1.95) and Human Immunodeficiency Virus (HIV) (RR: 1.65; 95% CI: 1.44–1.90) [60, 61]. Degree of immunodeficiency correlates with incidence of IVDU-IE which is elevated and estimated to be between 6 and 30% in patients with HIV [61]. The prevention, recognition, and treatment of IVDU-IE places a financial, operational, and ethical strain on society [59].

Evidence-based guidelines to support treatment choices in IVDU-IE are lacking. Generally, there are three components to the management of IVDU-IE: medical management, surgical management, and addiction management. Medical treatment (conservative management) consists of two to six weeks of intravenous antibiotics. The duration and specific antimicrobial agent are dependent upon organism isolates and susceptibilities, the presence of intracardiac synthetic material, each patient's ability to tolerate the antimicrobial agent, and the ability of the antimicrobial to penetrate tissue [62]. According to Reisberg, when compared to the general population, IVDU-IE of the TV may develop at a higher incidence with gram-negative bacilli and fungal organisms, requiring tailoring of antimicrobial therapy [63]. Still, conservative management, without surgery, is favored until cessation of IVDU; and, data shows an equivalent two-year event-free survival rate in patients treated for TVIE with medication or surgery [57].

The implementation of surgical management, including timing and technique, for IVDU-IE of the tricuspid valve necessitates a risk-benefit analysis for each individual patient. Tricuspid regurgitation is the most common clinical presentation in those with IVDU-IE, and early surgery in this population has been associated with less long-term tricuspid regurgitation [64]. One advantage is that less comorbid patient population may have improved perioperative outcomes and lower 30-day mortality versus the typically older and less healthy cardiac surgery patient cohort. On the other hand, these patients, by nature of their addictions, have a much higher chance of re-infecting their surgical valve with some studies citing a four-fold increase in valvular complications, morbidity, and mortality [57]. Surgical options may include open valve repair and, more commonly, valve replacement. Additionally, tricuspid valvectomy with antibiotic therapy (a medical-surgical hybrid) is an acceptable initial management for patients with IVDU-IE when temporizing for eventual valve replacement [65]. When considering mechanical versus bioprosthetic valve, one should consider the following meta-analytic data: the average endocarditis recurrence rate in mechanical valves ranged from approximately 3–9% versus 7–29% in biological valves; mechanical valves demonstrated higher survival rates and are known to provide increased valve longevity when compared to biologic tissue valves; mechanical valves also demand life-long anticoagulation therapy which may be challenging in a patient population with high rates of non-adherence [66]. Much room for physician discretion exists, though, as similar meta-analyses find no significant difference between mechanical and biologic TV repairs when controlling for other patient-related risk factors [66]. Long-term data from which to draw conclusions regarding appropriate surgical management of IVDU-IE in the tricuspid valve is non-existent and opinions vary.

The final element to treatment of IVDU-IE is addiction management [62]. A 2024 comparative study in the American Journal of Medicine found decreased one-year mortality in patients with TV IVDU-IE associated with inpatient addiction medicine consultation [67]. Thus, a holistic approach to TVIE management in this population proves beneficial and prudent. Addiction medicine is a multi-disciplinary field of healthcare and further details are beyond the scope of this chapter.

One ethical and surgical dilemma in this population is the management of patients with recurrent IVDU who have re-infected previously-implanted prosthetic valves. Reoperation of prosthetic heart valves carries significant risk that must be weighed against potential patient benefit in cases of prosthetic valve endocarditis (PVE). Patient age and comorbidities are considered when determining appropriate candidates for redo TV repair. When the risk of reoperation is deemed inappropriate secondary to expected poor outcomes, resources are instead allocated to others whose disease processes are more amenable to valve surgery. One may question: should the continued use of intravenous drugs be an exclusionary factor when determining which patients are suitable for reoperative valve replacement? Makoto et al. completed a multi-center, prospective study in 2021 evaluating patient outcomes in those with IVDU-IE who were first-time valvular surgery (FVS) recipients versus those who received repeat valve surgery (RVS), with both groups sharing similar demographics. Significantly, 30-day mortality in the reoperative group was twice as high as the first-time group, with an unadjusted incidence of mortality increasing from 4.8 to 8.1% ($p = 0.049$) [68]. While the RVS group collectively had more comorbidities than the FVS cohort, RVS patients were not as likely to go into shock because of their endocarditis [68]. A retrospective analysis of the United Kingdom Heart Valve Registry from 1986 to 1996 looked at those patients who underwent bioprosthetic and mechanical

valve replacement for prosthetic valve endocarditis (PVE) and assessed 30-day and long-term survival [69]. Of the 341 cases of repeat replacement for PVE, 30-day mortality was found to be 20%, with age being the only independent risk factor [69]. In 2014, cardiologist Sarah Hull, MD wrote an opinion piece which eloquently parses this multi-faceted moral dilemma [70]. She describes that, just as patients with failing organs must undergo rigorous medical and psychosocial evaluation to be permitted a position on a transplant waitlist, certain criteria must be maintained regarding the limited time and resources for valve allocation. Although the use of illicit substances may not be considered equivalent to terminal disease, IVDU is a disease which may preclude benefit from a replaced valve, thus precluding allocation to a particular patient. She concludes that, just as one would not perform futile surgery on a palliative patient, one may consider the futility of re-replacement of the tricuspid valve in a recidivist user of intravenous drugs when deciding if surgery is a viable treatment option. If a patient is offered surgery, Talha et al. encourage a strict concomitant addiction therapy plan at the time of valve replacement which, as discussed earlier, remains a staple in the care of this patient population [71].

5.3 Patients with septic emboli

The incidence of septic emboli with TVIE is high, estimated at 44% of patients having major embolic events [1]. Tricuspid valve vegetations may embolize to the lungs via the pulmonary artery but may only embolize systemically with the presence of concomitant left-heart endocarditis or a PFO [72]. Inter-atrial communications (atrial septal defects) are visualized on echocardiogram bubble study [51]. There have been various case reports of previously-undiagnosed right-to-left cardiac shunts leading to septic emboli in TVIE. Hypothesis for new physiologic shunts include defects created in the inter-atrial septum due to severe tricuspid regurgitation jets, dilation of the thin-walled right atrium resulting in re-opening of the foramen ovale, and local destruction of tissue by vegetations. Hematogenous spread of bacteria and embolic clot can cause multi-system organ failure, disseminated intravascular coagulopathy, and septic shock [51, 73].

Up to 75% of TVIE cases present with clinical pulmonary manifestations [1, 51]. Heiro et al. report that 10.5% of patients with IVDU have pulmonary emboli on radiography, while other sources measure the incidence of pulmonary emboli in all comers of TVIE at 6.1% [51, 74]. Sequelae of septic pulmonary emboli include single or multiple, bi-pulmonary infarcts or abscesses, complicated by pneumothorax, pleural effusion, pulmonary edema, and empyema [1, 50]. Multiple septic pulmonary infiltrates may present as symptoms of pleuritic chest pain, cough, dyspnea, and fever. These symptoms mimic, and are often mistaken for, a lower respiratory tract infection [75]. However, an additional warning symptom may include hemoptysis [1]. Care must be taken not to dismiss such symptoms and to complete adequate diagnostic work up, especially in the IVDU population. Even so, radiographic findings on chest CT may be mistaken for pneumonia rather than septic emboli and one should consider empiric echocardiogram [1]. An additional sequela of septic pulmonary emboli includes increased pulmonary vascular resistance leading to right heart failure [1]. Although rare, elevated pulmonary pressure along with severe TR or TS from obstruction due to vegetations may lead to heart failure, although rare [1]. If severe, clinical repercussions of septic pulmonary emboli could lead to acute hypoxemic respiratory failure requiring intensive care unit stay and even mechanical ventilation. In the long term, septic pulmonary embolic could result in chronic cavitory lesions.

Treatment should focus on antibiotics, possible embolectomy, symptom management, and pulmonary rehabilitation [51].

As stated, systemic emboli arise from coexisting left heart endocarditis or so-called “paradoxical emboli” with a right-to-left shunt via a PFO. Literature estimates that 13% of TVIE patients have left heart involvement [75]. Types of systemic septic emboli are myriad and include neurologic, ocular, and cutaneous manifestations, as well as vascular and visceral organ involvement. Various categories of systemic septic emboli are detailed below.

Cerebral emboli occur in 26.3% of patients with infective endocarditis and are the most common form of systemic septic emboli [50, 51]. Due to this prevalence, the Duke Criteria account for whether a patient has suffered an intracranial hemorrhage as minor clinical criteria for the diagnosis of infective endocarditis. Often, brain emboli are clinically not diagnosed but may be noted radiographically in up to 80% of patients with infective endocarditis [51]. Neurovascular emboli are an independent predictor of mortality (with a 21% elevated mortality risk by some analyses) [51]. Diagnosis is via brain CT or magnetic resonance imaging (MRI) [51]. Often, patients present with stroke-like symptoms and are diagnosed before the presence of bacterial endocarditis is known; but, the presence of multifocal lesions should increase a clinician’s suspicion for an embolic cause. Presentation varies from asymptomatic (48% of patients with radiographic findings) to multifocal symptoms [51]. Specific neurologic deficits depend upon which portions of the central nervous system are impacted. Another deciding factor in one’s presentation is the severity of the insult—septic cerebral emboli may cause not only an ischemic insult by occluding vasculature or decreasing blood flow (stroke), but also cause an infectious and inflammatory insult with resultant edema and formation of abscesses [51]. Secondary intracranial mycotic aneurysms account for less than 10% of neurologic complications in patients with IE but are associated with very high morbidity and mortality [51]. The most challenging management factor related to septic cerebral emboli is the possibility of hemorrhagic conversion of infarcts when perioperatively anticoagulating a patient for cardiac valve surgery or when using thrombolytics for management of the acute ischemic stroke. As such, in the acute setting, early endovascular management with septic embolectomy by a neuroradiologist may be crucial for maximizing neurologic recovery [51]. Much of recovery after septic cerebral embolism focuses on rehabilitation and motor recovery [50].

Retinal emboli present as endophthalmitis and Roth or Litten spots visualized via ophthalmoscope or slit lamp as minute, red or pale retinal hemorrhages. These lesions are often subclinical [51]. As such, patients diagnosed with IE involving any valve should undergo prompt ophthalmologic evaluation with fundoscopy (**Figure 2**).

Few occurrences of *septic embolization to the coronary arteries* have been described and were successfully managed with aspiration thrombectomy [51].

Abdominal visceral emboli possible in all valvular types of IE, include those of the spleen and kidneys, with prevalences of 6.8 and 2.9% respectively [51]. These insults may result in thrombosis of blood supply, parenchymal infarction, hemorrhage, or abscess with subsequent end organ failure. Visceral emboli are diagnosed via ultrasound or CT and splenic emboli are identified more commonly. If involved, emboli to either organ may present with abdominal pain or specific clinical and laboratory findings related to inadequate perfusion and organ malfunction. Usual management includes antibiotics, procedural source control, and support of organ function. Renal replacement therapy, whether intermittent hemodialysis or continuous renal replacement therapy (CRRT), may be required to supplement kidney function [50].



Figure 2.
Roth spots as visualized on ophthalmologic exam [76].

Image-guided abscess drainage with interventional radiology or splenectomy and nephrectomy may be warranted on a case-by-case basis [51, 78].

Superior mesenteric artery emboli occur with unknown prevalence and may lead to two different presentations—septic occlusion and mycotic aneurysm, a focal dilation of an infected arterial wall due to septic emboli invading the vasa vasorum. These complications of infective endocarditis are visualized on arterial and venous duplex or CT scan. Septic occlusion may result in intestinal ischemia requiring resection, whereas acute occlusion without irreversible organ ischemia may be managed with endovascular embolectomy. Mycotic aneurysm is treated with removal of any mycotic thrombi and surgical resection of the aneurysmal segment. Prompt treatment of mycotic aneurysm is prudent as spontaneous thrombosis, rapid enlargement, and rupture may occur and hasten a patient's demise [51].

Peripheral vascular emboli contribute to acute limb ischemia in 2.2% of infective endocarditis patients [51]. Just as peripheral arterial disease (PAD) severity varies due to other etiologies, extremity ischemia due to septic emboli can have a wide spectrum of presentations from transient symptoms and partial occlusion managed with anticoagulants to complete vascular occlusion and critical limb ischemia requiring anticoagulation, revascularization with thromboembolectomy, and even amputation. Large lower extremity vasculature including the femoral vessels may be affected, as are more distal and smaller caliber vessels. Diagnosis is based on physical exam (appearance, temperature, sensorimotor function, and pulse examination) and CT angiography. With or without limb salvage, a pertinent management principle is the early inclusion of physical medicine rehabilitation physicians for therapies.

Dermatologic findings include Janeway lesions and ungual splinter hemorrhages [51]. Janeway lesions present as small, non-tender, maculopapular, red lesions on the volar surface of the hands/finger and plantar surface of the feet/toes. Dermatology evaluation is warranted in the setting of such septic microemboli (**Figures 3 and 4**).

The management of septic emboli in patients with TVIE is multifactorial. The tenets of treatment include prolonged intravenous antibiotics (~4–6 weeks); surgical management of valvular disease, possible PFO closure, and possible intracardiac device removal for source control; and, care of extracardiac affected organs. The optimal timing of interventions in patients with multiple organ systems affected by septic emboli requires an interprofessional approach [80]. Early cardiac surgery within days of admission has been shown to decrease infective embolic risk [50, 51]. Cardiac complications on infective endocarditis including valvular regurgitation,



Figure 3.
Ungual splinter hemorrhages [79].



Figure 4.
Janeway lesions present on the soles (A) and hand (B) [77].

pseudoaneurysm, fistula, abscess, and heart failure may lead to cardiac instability, providing another reason to pursue early cardiac intervention before these comorbid findings may establish [50]. Alternatively, some argue that neurologic embolic insults should be managed acutely and prior to definitive valve surgery as anticoagulation during cardiopulmonary bypass may result in hemorrhagic conversion. Likewise, anticoagulation for limb salvage may have the same effect. Yet, there is no data to support the ideal sequence of treatment events in patients with TVIE and embolic stroke [50]. This balance is complicated by the fact that neurologic embolic events may occur prior to presentation and patients may be treated for acute stroke symptoms

without having yet identified the causative infective endocarditis. Further nuance lies in the fact that one third of patients with intracranial hemorrhage subsequent to septic emboli and will suffer significant neurologic decline. Studies citing this statistic recommend postponing cardiac valve surgery for 4 weeks to evaluate if further intervention would be futile [50]. The above complexities necessitate that the idyllic timing for multi-system and multi-disciplinary operative, procedural, and medical interventions should be decided on a case-by-case basis for each patient.

5.4 Patients infected with multi-drug resistant (MDR) organisms

There is a higher likelihood of multi-drug-resistant infections in TVIE due to the patient population. Methicillin-resistant *Staphylococcus aureus* (MRSA) is the most frequent organism to cause TVIE and is strongly associated with IVDU, as well as congenital heart disease and patients who received previous antibiotic therapy [61, 81]. The mainstay of MDR TVIE treatment is an extended venous antibiotic course (eight or more weeks) and surgery, while this patient population is at a higher risk of requiring reoperation [82].

Along with MRSA, *Enterococcus faecalis* is another gram-positive bacterium that has been implicated in MDR TVIE. Antibiotic regimens to manage these organisms, as reported in case-based literature, include a combination or variety of the following: vancomycin, daptomycin, gentamicin, linezolid, trimethoprim-sulfamethoxazole (Bactrim), and rifampicin [81, 83]. As *S. aureus* is a common pathogen in other infections, it is possible patients will have received prior directed antimicrobial therapy, resulting in antibiotic-resistant infectious strains of endocarditis. One case report describes a patient with prior vancomycin and teicoplanin-cotrimoxazole (glycopeptide antibiotics), rifampicin, and linezolid treatment for osteomyelitis (a non-cardiac infection). This patient's subsequent MRSA endocarditis and systemic infection was resistant to these medications and only successfully managed with quinupristin and dalbapristin [84]. As for *E. faecalis* endocarditis, the synergistic effect when ampicillin and daptomycin are combined is specifically effective [82].

Risk factors for gram-negative bacterial endocarditis include hepatic cirrhosis, prosthetic heart valves, and urosepsis [62]. *Escherichia coli* and *Pseudomonas aeruginosa* are the two most prominent organisms associated with gram-negative, MDR TVIE and both show a trend toward high morbidity including severe heart failure [62]. *P. aeruginosa* produces ring and annular abscesses, systemic emboli, and neurological manifestations. In the case of a burn patient secondarily infected with MDR *P. aeruginosa*, multiple tricuspid valve replacements via redo sternotomies were required. This case report, published in 2015, detailed the first placement of an aortic valve homograft as treatment for recurrent MDR TVIE after failed TV replacements with biologic tissue prosthetics. Antimicrobials directed at treating gram-negative bacteria causing MDR infective endocarditis include colistin, ciprofloxacin, and meropenem [85]. These cases of re-operative intervention for MDR TVIE highlight another complexity of the disease—MDR strains may remain latent in a patient (blood cultures and repetitive-PCR negative) for years and may result in higher mortality [84].

5.5 Patients with a history of tricuspid valve transcatheter edge-to-edge repair (t-TEER)

Tricuspid valve transcatheter edge-to-edge repair (t-TEER) is a novel method for treatment of tricuspid regurgitation in which a clip or clasp-like device is utilized to

restore tricuspid valve integrity. Since 2022, t-TEER has been an emerging treatment option for high-risk patients with symptomatic, severe TR [14]. In the United States, the TriClip device has been FDA-approved for t-TEER and is delivered to the tricuspid valve via a minimally-invasive transvenous procedure. TriClip captures and coapts the TV leaflets without the need for cardiopulmonary or induced cardiac arrest, resulting in a dramatic reduction in tricuspid regurgitation for those with severe presentations. In 2024, the landmark TRILUMINATE trial (the Clinical Trial to Evaluate Cardiovascular Outcomes in Patients Treated with the Tricuspid Valve Repair System), a prospective, randomized controlled trial evaluated the safety and efficacy of TriClip for t-TEER when compared with medical therapy for patients with severe TR and poor operative candidacy. The data demonstrated a significant reduction of TR severity—specifically a reduction to less than moderate regurgitation in 79% of patients and a reduction of at least 1 TR grade in 92% of patients. Furthermore, there was a decreased incidence of heart failure-related hospitalizations and symptoms, and an improvement in subjective quality of life. These benefits were also sustained over a three-year follow-up period, the lengthiest follow-up to date [86]. After the impressive success of the TriClip and the similar Pascal steerable catheter system utilized in Europe, various other percutaneous methods to increase TV coaptation have evolved and been shown to reverse right heart remodeling [87]. One such intervention, developed in 2023, is the K-Clip tricuspid posterior annuloplasty which boasts easier operations and more widespread availability when compared to the TriClip with comparable safety and efficacy [88]. The overall trend is that cases of percutaneous tricuspid valve repairs are increasing.

There is a paucity of data regarding management of TVIE after t-TEER therapy. Meta-analysis for infective endocarditis following transcatheter edge-to-edge repair of the mitral valve (m-TEER) estimate post-operative IE rates of 0–2.6%, with 75% of cases occurring in the first year and 40% of cases resulting in in-hospital mortality [87]. It is unclear whether this data can be extrapolated to estimate the rate of post-operative TVIE after t-TEER. Case reports for TVIE after t-TEER have been published, noting high morbidity and mortality in these patients with complications including septic pulmonary emboli, sepsis, and multi-organ failure, as well as ischemic neurologic strokes in patients with naturally-occurring or surgically-created atrial septal defects [14]. Clinically, device-related TVIE must be ruled out in the setting of systemic infections lacking a source. On an investigational basis, further studies are required to illuminate the incident and consequences of TVIE after t-TEER, especially if such a complication has the potential for high morbidity and mortality.

5.6 Patients with a history of transcatheter tricuspid valve replacement (TTVR)

Transcatheter tricuspid valve replacement (TTVR) is another form of percutaneous TV intervention to reduce or eliminate tricuspid regurgitation in patients with severe TR who remain symptomatic despite optimal medical therapy [89]. TTVR has been noted in the literature to be favorable when compared to t-TEER as replacement of the valve may completely abolish TR, whereas repair with t-TEER may reduce TR by 1–2 grades with 50% of patients reportedly having residual minimal to moderate TR [90]. Patient selection factors thus affect what type of minimally invasive procedure is performed, with either being a feasible intervention in patients with TV regurgitation.

A retrospective study performed by McElhinney et al. specifically evaluated the incidence of TVIE after TTVR, with further data specifically related to a subgroup

of patients with prior infective endocarditis resulting in damaged tricuspid valve leaflets. This retrospective cohort data evaluated 306 patients who underwent TTVR at 80 centers over a nine-year period. Over a three-year follow-up period, 2.6% of patients were diagnosed with post-procedural TVIE—with a single patient having a history of IVDU-related TVIE and seven patients with no prior TVIE—although a greater proportion of patients with a history of TVIE were lost to follow-up. The study an “estimated cumulative endocarditis incidence” of 1.7% at 1 year and 4.2% at 3 years post-TTVR with an annualized incidence rate of 1.5% and no association with prior TVIE and the development of post-TTVR TVIE. Per this singular study evaluating endocarditis and TTVR, the overall risk of TVIE after TTVR is low and not related to a personal history of TVIE. Furthermore, there is no data to suggest an increased risk of mortality once having developed post-TTVR TVIE, although there is increased morbidity and need for reintervention including but not limited to valvuloplasty and surgical TV replacement [91].

6. Future directions/obstacles

Despite published consensus guidelines and procedural advancements, there are opportunities for further research and development in the realm of TVIE treatment. On a population level, TVIE is intricately linked to those who use intravenous drugs. There is a lack of long-term data and prospective evidence for the most appropriate type of TV repair in this cohort; however, challenges exist as many of these patients are lost to follow-up making it difficult to gather prospective data. Another deficiency exists in data regarding long-term outcomes after procedures t-TEER and TTRV, and further studies are warranted.

Upcoming topics in the management of TVIE include the treatment of biofilms and various adaptive surgical or procedural techniques. First, a biofilm is the organization of microorganisms in a protective environment of macromolecules and secreted polysaccharides which improves bacterial ability to tolerate systemic antibiotics and host phagocytic defenses [92]. The encapsulation of bacteria in such biofilms may lead to diagnostic difficulty as early blood cultures may result as negative. The mainstays of infective endocarditis treatment do not differ in the presence of biofilms, but the management paradigm may require higher dose or longer duration of antibiotic therapy [93]. New therapeutic strategies including bacteriophage treatment (lytic viruses that target, replicate within, and cause bacterial cell death), quorum sensing inhibitors (substance which disrupt bacterial-to-bacterial communication and thus disrupt the ability to form a biofilm), and hyperbaric oxygen therapy are emerging and require further investigation into their efficacy [8]. Surgical management may be increasingly indicated in the setting of biofilm formation. According to the American Association of Thoracic Surgery (AATS) guidelines regarding the surgical treatment of IE, “surgery not only removes infected tissue and foreign material, but also mechanically disrupts the biofilm and exposes residual live microorganisms to antimicrobials, antibodies, and immune cells” [94]. Next, scientific literature suggests sutureless valves, aortic homografts, stentless xenografts, and “Commando” procedures as budding surgical techniques for the treatment of TVIE [8]. Sutureless valves and aortic homografts are primarily utilized in aortic valve repair currently. Sutureless valves are reported to reduce aortic cross-clamp time and length of cardiopulmonary bypass, offering utility in patients at high-risk for general anesthesia. Aortic homografts for IE purport the benefits of biologic material and

improved outcomes with aggressive debridement with root replacement in cases of IE involving more than one-third of the valve annulus. Stentless xenografts reportedly resulted in decreased incidence of repeat endocarditis after valve replacement for IE and resultant decrease in reoperative rates. Next, the “Commando” procedure—concomitant mitral and aortic valve replacement along with reconstruction of the intervalvular fibrous body between the left and noncoronary aortic sinuses, the roof of the left atrium, and the anterior mitral leaflet—has been utilized for severe cases of IE, according to Rad et al. The incidence of clinical scenarios requiring this procedure is minimal and the surgery is associated with high morbidity and mortality (13.2%), as well as a 23.7% 20-year survival rate. Only small-scale studies have concluded that this surgery has a 50% reoperative rate and unclear clinical utility in the management of IE [8]. The details of the aforementioned procedures are beyond the scope of this chapter. Continued study of these developing methods may prove impactful in the care of patients with TVIE in the future.

7. Conclusions

The prevalence of TVIE has increased with the IVDU crisis and the increase in utilization of intracardiac devices and central venous catheters. The care of patients with TVIE is a common topic amongst cardiac surgeons and cardiologists. New methods like t-TEER, TTVR, and AngioVac augment the variety of existing surgical and procedural treatment options for TV endocarditis. These innovations are promising but lack long-term outcomes data and data regarding post-procedural reinfection rates. The management paradigm for TVIE may furthermore be complicated by systemic complications of the disease due to septic emboli and other patient-specific nuances and ethical dilemmas regarding the patient population. Additionally, as practices regarding TVIE evolve, so do the causative microorganisms with biofilm formation and antibiotic resistance making antimicrobial therapy in these patients evermore challenging.

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Endocarditis Team? Designing an Original and Tailored Clinical Pathway

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Abstract

Infective endocarditis (IE) is a complex and often misunderstood disease, carrying a substantial burden of morbidity and mortality. Over the past two decades, its incidence has risen steadily, accompanied by a growing predominance of highly virulent pathogens. Despite substantial advances in diagnostic tools, surgical techniques and perioperative management, IE continues to present major clinical challenges. In-hospital mortality remains extremely high, ranging from 15 to 30%, with a one-year mortality exceeding 40% in specific patient groups. In addition to its clinical impact, IE imposes a substantial economic burden, primarily due to prolonged hospitalization, extensive diagnostic work-ups, complex surgical interventions and long-term antibiotic therapy and follow-up. In such a complex scenario, delays in diagnosis and treatment are unfortunately common, often leading to fragmented and inefficient healthcare pathways, resulting in suboptimal patient management and compromised clinical outcomes. In response to these challenges, a dedicated Clinical Pathway (CP) for IE patients has been implemented to enhance interdisciplinary collaboration and ultimately improve patient outcomes.

Keywords: infective endocarditis, clinical pathway, perioperative management, clinical appropriateness, efficiency, multidisciplinary evaluation

1. Introduction

Infective endocarditis (IE) is a complex and often misunderstood disease that primarily affects native or prosthetic heart valves and, increasingly, intracardiac devices. Over the past two decades, its incidence has shown a worrying rise, now affecting approximately 13.8 individuals per 100.000 per year in the general

population [1]. This epidemiological trend reflects a multifactorial pathogenesis, involving both host- and microorganism-related factors. Contributing elements include the progressive aging of the population, the rising prevalence of chronic conditions (such as diabetes, chronic kidney disease, and malignancies), and the more frequent use of invasive medical procedures and intracardiac devices. The widespread adoption of prosthetic heart valves, through surgical or transcatheter approaches, and the increasing use of long-term intravascular catheters have further expanded the at-risk population.

The microbiological landscape has significantly shifted in recent decades. There has been a notable increase in the virulence of causative pathogens, particularly *Staphylococcus aureus*, *Enterococcus* spp., and non-HACEK Gram-negative bacilli, exhibiting more aggressive behavior [2].

Despite advances in diagnostic tools, including transesophageal echocardiography, PET/CT imaging and molecular microbiology techniques as well as improvements in surgical and perioperative management, IE remains a major clinical challenge. It is frequently associated with severe complications and carrying a substantial burden of morbidity and mortality and healthcare costs [3, 4]. In-hospital mortality remains high, ranging from 15 to 30%, while one-year mortality exceeds 40% in specific patient groups [3]. In addition to its clinical impact, IE imposes substantial economic burden, primarily due to prolonged hospitalization, intensive care requirements, repeated imaging and diagnostics evaluations, surgical procedures, and long-term antibiotic therapy and follow-up. Recent studies have also highlighted the psychological distress and reduced quality of life experienced by survivors, underscoring the need for a comprehensive, multidisciplinary care approach [5]. IE often evolves aggressively, with both local and systemic complications. Destructive infections may extend to the fibrous skeleton of the heart, frequently leading to heart failure, uncontrolled infection, and multiple septic embolisms, scenarios that are unfortunately common in clinical practice. The clinical presentation of IE is highly heterogeneous, ranging from asymptomatic form to life-threatening cases of septic shock and multiple organ failure. This variability is influenced by several factors, including the virulence of the causative microorganism, the presence of preexisting heart disease, prosthetic valves or intracardiac devices, and the overall clinical status of the patient [1]. Data from the EURO-Endo registry show a drastic shift in the epidemiological profile of IE and provide an accurate picture of IE disease today [6]. Historically affecting younger patients with rheumatic or congenital heart disease, IE now predominantly involves older patients, with a mean age of 60.97 ± 17.36 years and 12.0% of cases occurring in those aged ≥ 80 years. Furthermore, nosocomial IE represents the majority of cases (60.8%), occurring most frequently in hospitalized, frail patients with underlying comorbidities and recent exposure to invasive procedures. Additionally, 30% of patients had a history of prior heart valve surgery [6]. Delays in diagnosis and/or treatment often lead to fragmented and inefficient care pathways, particularly to frail patients with multiple comorbidities and high surgical risk. Such a “patchy” approach may result in a suboptimal patient management, compromise outcomes, and highlight the need for more structured management strategies. In light of the growing clinical and economic burden of IE, and inspired by successful models developed for valvular heart disease [7, 8], a dedicated Clinical Pathway (CP) for IE patients was implemented at our Teaching Hospital in 2023. This initiative aims to streamline care delivery, enhance interdisciplinary collaboration, and ultimately improve patient outcomes.

2. A clinical pathway roadmap for infective endocarditis: Evolving scenarios and emerging challenges

2.1 Increasing virulence in endocarditis pathogens: When microbes strike harder!

Over the past five decades, the epidemiology of IE has undergone substantial transformation, with a notable shift in the microbiological profile towards more virulent pathogens, resulting in more aggressive clinical manifestations [2, 9]. In high-income countries, the incidence of IE associated with rheumatic heart disease has significantly decreased. Conversely, advances in healthcare and increased life expectancy have contributed to a rising incidence of IE among elderly, primarily due to degenerative valvular disease, prosthetic valve implantation, and the use of cardiovascular implantable electronic devices. Furthermore, the prevalence of community-acquired, nosocomial, and other healthcare-associated IE has increased substantially [6, 10]. Historically, *Streptococcus viridans* was the most common causative agent. However, *Staphylococcus aureus* and coagulase-negative staphylococci (CoNS) now account for the majority of IE cases, particularly in healthcare-associated infections and among patients with prosthetic valves or intracardiac devices [2]. *Staphylococcus aureus*, a pathogen with high virulence and a propensity for rapid tissue destruction, is associated with fulminant clinical presentations, systemic embolic events, heart failure, and increased mortality. Similarly, the incidence of *Enterococcus faecalis*-related IE has risen, often in association with nosocomial exposure, invasive procedures, and prosthetic or transcatheter valve implantation, developments that have important public health implications. IE caused by Gram-negative bacilli or fungal pathogens remains relatively uncommon but is usually linked to healthcare-associated procedures and presents significant therapeutic challenges [2]. Blood cultures-negative endocarditis occurs in approximately 10–30% of IE cases. This is most frequently due to prior or inappropriate antibiotic administration, though it may also be attributed to infections caused by intracellular pathogens that are difficult to isolate using conventional microbiological techniques, such as *Coxiella burnetii*, *Bartonella* spp., *Brucella* spp., and *Tropheryma whippiei*. In such cases, advanced diagnostic techniques, such as serologic assays and polymerase-chain-reaction (PCR) testing on blood or excised valve tissue, can facilitate pathogen identification in up to 60% of patients [11, 12].

These evolving microbiological patterns highlight the necessity for early recognition and timely initiation of pathogen targeted antimicrobial and surgical interventions tailored to the increasingly severe clinical presentations observed in contemporary IE cases [13]. The emergence of multidrug-resistant organisms, including methicillin resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and ESBL-producing Gram-negative bacilli, complicates treatment strategies. These infections often necessitate the use of broad-spectrum or combination antimicrobial therapies, particularly in developing countries where routine susceptibility testing may not be feasible [14, 15].

2.2 Infective endocarditis in the polymorbid and frail elderly population: A growing clinical concern

Within the spectrum of patients affected by IE, older patients represent a particularly vulnerable cohort population. The incidence of IE is particularly high among patients aged over 70 years, reflecting the radical demographic and epidemiological

shifts observed over recent decades and is expected to rise further due to the global aging population and to the increasing use of invasive medical interventions [16]. Patients over 80 years of age present a significantly high burden of comorbidities, including malignancies, diabetes mellitus, and chronic kidney disease, as reflected by elevated Charlson Comorbidity Index and EuroSCORE values [17]. Notably, advanced age represents an independent risk factor for IE, with elderly patients exhibiting an approximately fivefold higher risk compared to younger population [17]. The presence of CIEDs and prosthetic valves—particularly following transcatheter aortic valve implantation (TAVI)—is more common in older adults and represents a significant predisposing factor for IE. These conditions not only elevate the risk of infection but are also associated with poorer prognostic outcomes. Frequent healthcare system interactions further increase risk of nosocomial infections and colonization with multidrug resistant microorganisms [15, 18]. A notable increase, up to fivefold, in IE incidence has been observed in elderly patients diagnosed with colorectal cancer compared to those with other malignancies such as lung, breast, or prostate cancer [19]. Several hypotheses have been proposed to explain this association, including the routine use of colonoscopy in the diagnostic workup for *Streptococcus gallolyticus* IE, and more recently *Enterococcus faecalis*-related cases [20]. Furthermore, colonoscopy itself may also facilitate IE development by disrupting the intestinal mucosa and promoting bacterial translocation. The co-occurrence of IE and malignancy significantly increases non-cancer-related mortality and can influence oncological treatment decisions based on patients' predicted survival and clinical frailty [21]. The clinical presentation of IE in the elderly patients often deviates from the classical signs and symptoms. It is frequently characterized by nonspecific constitutional symptoms, such as lethargy, fatigue, malaise, anorexia, and unintentional weight loss. In some cases, delirium may represent the only manifestation of IE [22]. Vascular complications, including embolic events, appear to be less common in this population, a trend that may be partly attributed to the widespread use of antiplatelet and anticoagulant therapies in older adults [23]. These findings underscore the complexity of managing IE in elderly and frail patients, where age-related physiological changes, multimorbidity, and polypharmacy intersect with heightened infectious risk and atypical clinical presentations [6]. A tailored, multidisciplinary approach is essential to ensure timely diagnosis, optimize therapeutic strategies, and balance the risks and benefits of invasive procedures. As the aging population continues to grow, the integration of geriatric assessment into IE management pathways will be increasingly critical to improve outcomes and preserve quality of life in this vulnerable patients' population [24].

2.3 Cancer patients and infective endocarditis: An increasing recognized condition

According to the EURO-ENDO registry, IE in the oncology population is a complex and increasingly recognized condition, accounting for 11.6% of all IE cases [25]. Within the oncology population, two key factors contribute to an elevated risk of developing endocarditis: firstly, cancer treatments, including chemotherapy and immunotherapy, often induce immunosuppression, thereby increasing patients' susceptibility to infections; secondly, the necessity for the implantation of indwelling medical devices (such as central venous catheters) for prolonged intravenous therapies creates potential routes for pathogen entry [26]. Several studies have reported increased nosocomial or healthcare-associated IE in cancer and elderly populations. The patients frequently had undergone a non-dental procedure before

the development of IE, with *Enterococcus* being the most prevalent pathogen following gastrointestinal or genitourinary interventions. Conversely, *Staphylococcus* species are most commonly implicated after invasive procedures such as tissue biopsy, central venous catheterization, chemo-port implantation, and percutaneous drainage catheter insertion [19, 27].

The occurrence of endocarditis held significant prognostic value in this cohort, as IE was a major reason for the discontinuation of antitumor therapy and the denial of further aggressive treatment in nearly all oncology patients who died. The management of IE generally involves prolonged antibiotic therapy and surgical treatment. However, in these patients, surgery may be more complex due to frailty, immunosuppression, and an increased risk of complications. Although the theoretical indications for cardiac surgery are not significantly different from those in the general population with endocarditis, surgery was performed less frequently due to the high surgical risk (80.2% vs. 54.0%, $P < 0.001$), patient death prior to surgery (17.3% vs. 22.9%, $P = 0.260$), or patient refusal (16.0% vs. 19.3%, $P = 0.486$), respectively. Unfortunately, the prognosis for these patients is often poor, with higher mortality rates due to the combined effects of both the cancer and the infection, as well as the impact of cancer progression [25].

2.4 From surgical valve prostheses to percutaneous cardiac devices IE population: A growing clinical challenge

Characteristics of patients with IE have dramatically changed over recent decades, with a growing number of cases occurring in patients with intracardiac prosthetic material, including surgical or percutaneously implanted valves and cardiac implantable electronic devices (CIEDs). These changes are particularly evident in the elderly population, who now represent a growing proportion of IE cases and often present with atypical features and increased clinical complexity [6]. As the use of TAVI and CIEDs continues to expand, particularly among older and higher-risk individuals, a new clinical paradigm is emerging, characterized by evolving microbiological profiles, diagnostic challenges and unique therapeutic considerations.

2.4.1 Prosthetic valve endocarditis (PVE)

Prosthetic valve endocarditis (PVE) represents the most severe form of IE, occurring in 1–6% of patients performing a valve surgery and accounting for 20–30% of all cases of IE, with a worryingly increasing trend in the last few years. Based on the time since valve surgery, two main subgroups of patients may be recognized: early PVE (within 6 months of valve surgery) and late PVE (≥ 12 months post-surgery) [28, 29]. These subgroups are associated with different outcomes even though specific pathogens and clinical conditions may be prognostically more important [30]. Clinical presentation is frequently atypical, particularly in the early postoperative period in which fever and inflammatory syndromes may occur even in the absence of clear imaging findings [31]. The PVE is associated with higher in-hospital mortality (20–40%) and morbidity as well as reduced long-term survival compared with native valve IE. Early surgical intervention is generally considered the best therapeutic option for PVE, especially in cases with severe prosthetic dysfunction, heart failure, local complications (dehiscence or paravalvular abscess/fistula formation) or high embolization risk [32–34]. Despite strong evidence, data from the EURO-ENDO registry show that surgery was only performed in 73% of patients with a clear surgical

indication, therefore emphasizing the treatment difficulties in this high-risk population. In contrast, medical therapy may be a reasonable option in elderly patients with uncomplicated non-staphylococcal late PVE [35].

2.4.2 Transcatheter aortic valve implantation infective endocarditis

Patients undergoing transcatheter aortic valve implantation represent an emerging challenge in the IE population. Technological advances, procedural simplification, as well as reproducibly favorable results have contributed to the wide adoption of TAVI, which has become the treatment of choice for elderly patients at high and intermediate surgical risk [36]. Clinical presentation is frequently atypical, and diagnosis may be challenging due to anatomical or clinical conditions. Imaging is particularly challenging: the extensive metallic stent frame surrounding the valve leaflets can obscure vegetations, with transesophageal echocardiography (TEE) failing to detect lesions in up to 60% of cases [37]. Prognosis and treatment of post-TAVI IE is complicated by older age and a higher patient risk profile. According to a recent multicenter registry, in-hospital mortality reaches 41.8 and 66.7% at a 2-year follow-up [38]. Similar to surgical PVE, early cardiac surgery is recommended in the presence of complex clinical scenarios, such as severe prosthesis dysfunction, uncontrolled infection, or heart failure [31]. Nevertheless, surgery is performed in about 20% of cases, a much lower rate compared with NVE and surgical PVE [39]. The characteristics of the TAVI population, with often advanced age and high or prohibitive surgical risk, along with the potential difficulties associated with the removal of a large amount of stent frame frequently adherent to the ascending aorta, may play a role in the low rate of surgical interventions. Therefore, the decision to proceed with surgery should be individualized, balancing surgical risks against the limited effectiveness of medical therapy alone [31].

2.4.3 Cardiac implantable electronic device infections (CIED)

The use of CIEDs has grown considerably in recent years accompanied by a rising incidence of CIED-infective endocarditis (CIED-IE) [40]. Data from the Euro-Endo registry indicate that CIED-IE accounts for about 10% of all cases of IE [6]. In-hospital mortality ranges from 5 to 8%, with higher rates observed in older patients and in those with multiple comorbidities or systemic infections. Optimal management requires early and complete device removal [41] combined with initial empirical antibiotic therapy while awaiting identification of the pathogen. Indeed, in the real world, device removal is often postponed in favor of initial antibiotic therapy largely due to a perceived procedural risk in patients with severe comorbidities and an estimated high surgical risk. Percutaneous extraction is the preferred procedure and should be performed in specialized centers with onsite surgical backup. On the other hand, surgical extraction should be considered in case of large vegetations and/or when concomitant valve surgery is indicated. Importantly, all patients with CIED-IE should immediately be referred to a tertiary care center where a local endocarditis team can provide a multidisciplinary evaluation considering surgery even in challenging clinical scenarios [42].

2.5 Infective endocarditis in people who injection drugs: A recurring challenge

Endocarditis in people who inject drugs (PWID) remains an ongoing issue today, with a consistently rising incidence. Repeated intravenous injections introduce

contaminated particles into the bloodstream, which can infect the tricuspid valve and right-heart chambers, potentially leading to infections in left-heart structures, worsening the prognosis [31, 43]. Managing IE in PWID is challenging due to high long-term morbidity and mortality in a young population, as well as psychosocial and environmental factors that contribute to recurrent substance use [44]. Additionally, IE surgical treatment is complicated by concerns over prosthetic valve reinfection. Due to the complexity of this marginalized patients group, a multidisciplinary approach, including specialists in addiction medicine, cardiology, infectious diseases, cardiac surgery, case management, social work and psychiatry, is mandatory [45]. The majority of IE in PWID can be treated successfully with antibiotic therapy, because mostly involved right heart valves. Mortality rates of PWID are relatively low, even when surgery is required, probably due to the patient's young age and fewer coexisting comorbidities. Unfortunately, lower short-term mortality does not translate into favorable long-term outcomes [46, 47]. Relapse or recurrent episodes of endocarditis accounted for 55% of deaths, suggesting that adverse outcomes were primarily due to ongoing infection [48]. For both medically and surgically managed patients, 30-day readmission is most frequent for endocarditis (18.1%) and septicemia (14.0%), possibly indicating persistent drug use. Although we cannot distinguish between new and recurrent infections, the fact that over 25% of medically managed PWID-IE patients were ultimately readmitted with endocarditis highlights a fundamental challenge in the current management of this specific patient subset [44].

2.6 Sex difference in infective endocarditis: An underrecognized dimension of risk

Female patients represent a distinct subgroup in the context of IE. Multiple studies have consistently demonstrated a lower incidence of IE among women compared to men. Women typically constitute approximately one-third of IE cases, a pattern observed across various patient subpopulations and geographic regions [6, 31, 49]. Several hypotheses have been proposed to explain this disparity. These include a potential protective effect of female sex hormones, particularly estrogens, which are known to support endothelial function and reduce cardiovascular risk [50]. Other contributing factors may include underdiagnosis, referral bias in published studies, and a lower prevalence of known IE risk factors in women, such as bicuspid aortic valve disease and previous valve replacement surgery [31]. However, not all findings are consistent. A notable 25-year nationwide study from Scotland, in fact, reported a similar incidence of IE between sexes, challenging earlier conclusions [51]. Contradictory observations have also been made regarding the impact of sex on clinical outcomes. Female sex has been associated with a higher mortality after routine cardiac surgery [52] and, particularly, in the IE population. Some studies have reported higher in-hospital mortality for women compared to men (32% vs. 23%), while others have reported similar mortality rates among the two sexes [53, 54]. The exact reasons behind these disparities are yet not entirely understood. The higher mortality rates for women might be attributed to several known risk factors, including older age, a more frequent mitral valve involvement, more *Staphylococcus Aureus* infections, and a higher prevalence of neurological complications and preoperative hemodialysis [50]. Additionally, a higher perceived surgical risk in female patients may lead to lower surgical referral rates, potentially contributing to poorer outcomes [55, 56]. Despite the reported sex-based differences, further research is necessary to clarify these findings and better understand the underlying mechanisms driving them. Understanding the biological, clinical, and systemic factors that contribute to

such disparities may be essential for developing more personalized diagnostic strategies, optimizing treatment decisions, and ultimately improving outcomes for all patients affected by IE.

2.7 Infective endocarditis in adults with congenital heart disease: Clinical complexities and evolving risks

The population of adults with congenital heart disease (ACHD) is steadily increasing, as a result of advances in surgical and medical therapies that have substantially improved survival into adulthood [57, 58]. This patient population is highly heterogeneous, encompassing a wide spectrum of congenital cardiac anomalies, ranging from simple lesions such as atrial septal defects to complex forms of congenital heart disease, including tetralogy of Fallot, transposition of the great arteries, and univentricular physiology. The diversity in anatomical and physiological presentations, compounded by differences in surgical and medical histories, contributes substantially to the clinical complexity observed in the ACHD cohort.

Among the long-term complications faced by this population, IE remains a critical concern. Incidence rates range from 0.9 to 1.26 cases per 1000 patient-years [59]. In-hospital mortality is considerable, ranging between 6% and 9%, and is further exacerbated by complications such as neurologic events, renal failure, *Staphylococcus aureus* infection, and delayed or denied surgical intervention [60–63]. Surgical management is frequently required but carries substantial risk, attributable to the cumulative burden of prior interventions, the presence of prosthetic materials, and the high prevalence of syndromic comorbidities.

The risk of IE varies significantly according to the type of congenital lesion. While simple defects—such as secundum atrial septal defects, patent ductus arteriosus, and isolated pulmonary valve stenosis—confer a relatively low risk, more complex or unrepaired cyanotic heart defects markedly elevated susceptibility, particularly when prosthetic materials or residual shunts are present [59].

Pathogen profiles in ACHD-associated IE are comparable to the general population, with *Streptococcus* spp. and *Staphylococcus aureus* being the most frequently identified organisms [31, 61–64]. Given the anatomical and clinical complexity of ACHD-related IE, accurate diagnosis and comprehensive treatment planning are required [62, 65]. A substantial proportion of cases require valve replacement or additional corrective procedures [59, 60, 66].

Although perioperative risk is markedly elevated in this cohort, conservative management is associated with significantly poorer outcomes, highlighting the necessity of prompt and individualized intervention strategies. Optimal care for these patients should extend beyond the standard Endocarditis Team to include multidisciplinary collaboration within specialized congenital heart disease centers, to improve clinical outcomes and to guide the decision-making process in this high-risk population [31].

2.8 Operative risk assessment in infective endocarditis: Challenges, limitations of conventional scores, and the need for tailored prognostic tools

According to the Euro Endo survey [6], 69.3% of patients diagnosed with infective endocarditis (IE) met the criteria for cardiac surgery; however, only 74% of these patients ultimately underwent the procedure. In the remaining cases, surgical intervention was not performed due to an unacceptably high operative risk. This highlights the gap between guideline recommendation and real-world scenarios, which often

depends on the patient's clinical condition, frailty, comorbidities, and individual surgical risk assessment. Operative risk assessment and evaluation of the risk–benefit ratio of surgical intervention are therefore critical components of the overall treatment strategy.

Risk scores provide numerical clarity and support decision-making, especially in high-risk patients requiring aggressive perioperative planning. Standard risk scores such as the European System for Cardiac Operative Risk Evaluation (EuroSCORE) and the Society of Thoracic Surgeons (STS) scores, predict mortality across general cardiac surgery populations but fall short when applied to IE. These models do not fully account for the unique pathophysiology, higher morbidity, and elevated mortality associated with endocarditis surgery.

Recognizing these limitations, several IE-specific prognostic models [67–74] have been proposed over the past decade. These tools incorporate patient characteristics, microbiological data, and disease-specific variables to more accurately predict in-hospital mortality. However, variability in their design and validation raises questions about their clinical reliability and generalizability. Despite their potential, the real-world impact of these IE-specific scores remains unclear [31].

2.9 Endocarditis surgery specific scores

2.9.1 STS score for infective endocarditis

Gaca *et al.* [67] developed a simplified risk scoring model tailored to patients undergoing surgery for IE, using data from the Society of Thoracic Surgeons (STS) database. The model incorporates 13 variables independently associated with post-operative mortality, including prior CABG, urgent/emergency surgery, cardiogenic shock, use of preoperative IABP or inotropes, multiple or prior valve surgeries, diabetes (insulin- and non-insulin-dependent), hypertension, chronic lung disease, active endocarditis, renal dysfunction (creatinine >2.0 mg/dL), and arrhythmias. Each variable was weighted based on its impact, with emergency status and cardiogenic shock emerging as the strongest predictors, followed by renal dysfunction. The model demonstrated good discrimination, but limitations include the need for external validation and concerns related to sample size and generalizability.

2.9.2 The De Feo: Cotrufo score

De Feo *et al.* [68] developed a risk model to estimate operative mortality in patients undergoing surgery for IE. Six independent predictors of mortality were identified: 1) age, 2) NYHA class IV, 3) preoperative renal failure, 4) preoperative mechanical ventilation, 5) peri-valvular involvement, and 6) positive blood cultures immediately before surgery. Each variable was assigned a score, allowing patients to be stratified into four risk categories: very low risk (0–5 points), low risk (7–13 points), high risk (14–19 points), and very high risk (≥ 20 points). The De Feo score showed strong predictive accuracy even though its applicability is limited by the small sample size and a limited number of patients with healed IE.

2.9.3 RISK-E score

The RISK-E score [69] is a validated tool for estimating in-hospital mortality in patients undergoing cardiac surgery for active left-sided infective endocarditis (IE).

A notable strength of this model is the inclusion of microbiological data as independent predictors of mortality, setting it apart from traditional scores.

2.9.4 PALSUSE score

PALSUSE [70] is an acronym for seven clinical variables: 1) prosthetic valve, 2) age > 70, 3) large intracardiac destruction, 4) *Staphylococcus* species, 5) urgent surgery, 6) female gender, and 7) EuroSCORE > 10. Validated primarily for in-hospital mortality and perioperative complications in IE, PALSUSE demonstrates fair predictive capacity. While it aligns well with EuroSCORE II in terms of calibration, its overall discriminatory ability is limited.

2.9.5 APORTEI score

The APORTEI score [71] was derived from pooled estimates of a systematic review and meta-analysis, identifying risk factors specifically associated with in-hospital mortality following surgery for IE.

2.9.6 AEPEI score

The AEPEI score demonstrated good internal and external validity, with calibration and discrimination comparable to EuroSCORE II. However, its development was limited by a relatively small sample size (361 patients) and a restricted variable set, potentially excluding relevant mortality predictors [72].

2.9.7 ANCLA score

The ANCLA score was derived from a cohort of 138 patients undergoing IE surgery [73]. Five independent predictors of in-hospital mortality were identified via multivariate analysis 1): anemia, 2) NYHA class IV, 3) critical preoperative state, 4) large intracardiac destruction, and 5) Thoracic aorta surgery. Despite its simplicity, the ANCLA score demonstrated strong predictive performance, outperforming several IE-specific models and showing comparable accuracy to EuroSCORE II. In subsequent analyses, it consistently showed higher discriminative ability than STS, De Feo, PALSUSE, RISK-E, and EndoSCORE, and performed similarly to the AEPEI score ($p = 0.077$). However, its utility remains limited by the lack of external validation.

2.9.8 STOP score

The STOP score developed by Habberthuer *et al.* in 2021, targets a growing subset of IE patients—those with drug-induced endocarditis. Designed to reflect the distinct clinical profile of drug-related IE—typically younger patients with unique comorbidities—the STOP score provides a tailored approach to risk assessment. While it accounts for procedure-specific and patient-related factors, further studies are needed to confirm its predictive superiority over more generalized models [74].

2.9.9 COSTA score

The COSTA score, developed by da Costa *et al.* [75] in 2007, was among the first models aimed at estimating in-hospital mortality in patients undergoing surgery for

infective endocarditis (IE). Based on a retrospective cohort of 186 surgical patients, the score was derived through multivariate analysis identifying seven independent predictors of mortality, each assigned by a trained Endocarditis Team.

2.9.10 Limitations

Current models do not account for several critical factors that should be considered, including clinical elements (e.g., embolic events, liver disease, frailty), imaging findings (e.g., right ventricular function, right ventricular systolic pressure, left atrial size, complications from endocarditis), as well as laboratory and perioperative parameters. Additionally, risk models should be designed and validated to predict outcomes beyond operative mortality, including in-hospital morbidities and long-term survival.

In light of the above, reliance on these risk scores without individualized, case-specific assessment by a specialized Endocarditis Team may inadvertently result in the inappropriate exclusion of patients from potentially life-saving surgical intervention. Therefore, determining when operative management for a specific patient is futile requires compassionate multidisciplinary insight along with consideration of the patient's and family's wills.

2.10 Early surgical management of infective endocarditis: When evidence meets clinical practice

The concept of early surgery in IE constitutes a major paradigm shift, fundamentally redefining management strategies for this high-risk condition. Historically, surgery during the acute phase of infection was largely avoided, due to the perceived high surgical risk and the heightened likelihood of relapse [75]. However, advances in perioperative care management and surgical techniques have redefined clinical practice, establishing early surgery as a viable—and often preferred—therapeutic option even in the early stages of infection. This evolution reflects a critical transformation in clinical practice, prioritizing timely intervention to prevent irreversible structural damage and improve outcomes [76].

While early intervention during the acute or active phase of IE in the presence of uncontrolled sepsis, shock, and organ failure raises concerns about high operative mortality and the risk of relapse due to implantation of prosthetic material in an infected field, delaying surgery until completion of antimicrobial therapy may result in extensive cardiac tissue destruction possibly leading to more complex surgical repairs, progressive cardiogenic shock, organ failure, and increased operative mortality [77].

Compared to previous recommendations [78], the 2023 European Society of Cardiology Guidelines for the management of IE place an even stronger emphasis on the role of surgical treatment, particularly underscoring the benefits of early surgery in the management of heart failure, the prevention of embolic events, and, most critically, in cases of uncontrolled infection [31].

Notably, the guidelines provide clearer definitions of surgical timing: emergency surgery (to be performed within 24 hours, irrespective of preoperative duration of antibiotic treatment); urgent surgery, now redefined to occur within 3 to 5 days, markedly narrowing the previous early surgery window of up to 7 days, and non-urgent surgery (to be performed within same hospital admission) [31]. This update reflects an effort to promote earlier surgical intervention in this high-risk population

and to optimize clinical outcomes. In fact, surgical intervention performed within 2–3 days of meeting indication criteria has been shown to significantly reduce the risk of embolic events and mortality, particularly in patients with large mobile vegetations, severe valvular regurgitation, or persistent infection despite optimal antibiotic therapy, compared to conventional medical therapy [76, 79]. Nonetheless, in daily clinical practice, systematic application of early surgical intervention, even when indicated, remains fraught with difficulty [78].

Multiple factors may contribute to the delay in the timely performance of surgery in patients with IE. A central issue is diagnostic uncertainty, particularly in atypical presentations or cases of culture-negative endocarditis, often resulting in hesitation to initiate consultation due to the lack of a definitive diagnosis [80]. Furthermore, clinical presentation may be nonspecific and subacute, particularly in elderly or immunocompromised patients, complicating early diagnosis and delaying surgical indications. In addition, logistical barriers including delayed transfers to tertiary care centers, limited access to specialized surgical teams, and prolonged preoperative assessments may significantly hinder prompt surgical intervention [81]. The situation is further complicated in frail or elderly patients, where a perceived high operative risk often leads clinicians to adopt a conservative or delayed strategy, even in the face of clear surgical indications [82]. In this context, it is essential to raise awareness among healthcare providers about the prognostic implications of surgical timing and to promote adherence to evidence-based criteria for early referral. These measures are crucial components of quality improvement initiatives. Despite these barriers, clinical evidence supports the efficacy of early surgical intervention in improving clinical outcomes when appropriately used. Therefore, efforts should be made to minimize diagnostic and logistical delays, enhance early surgical referral, and integrate multidisciplinary care pathways to maximize the benefits of early intervention. This discrepancy between guidelines and real-world practice is particularly pronounced in healthcare systems burdened by resource limitations, logistical inefficiencies or inadequate interdisciplinary coordination. In these settings, early identification of the causative pathogen, prompt initiation of targeted antimicrobial therapy, and the establishment of streamlined diagnostic and referral pathways are essential to facilitate timely surgical intervention.

3. From rough roads to dedicated clinical pathways: As is!

To date, we have conducted a comprehensive analysis of the main challenges associated with IE, highlighting its persistent relevance as a complex and insidious clinical condition. Despite advances in diagnosis and treatment, IE continues to exert a considerable socioeconomic burden, particularly in terms of adverse clinical outcomes—such as in-hospital and long-term mortality—and healthcare resource management, including the high costs of hospitalization and antimicrobial therapy. The wide spectrum of clinical presentations often requires specialized expertises, and management by nonexpert physicians may result in delayed diagnosis and suboptimal treatment approaches. Delays in diagnosis and treatment make these care pathways often fragmented into multiple and, sometimes, dangerous steps that may result in suboptimal patient management, especially in the subset of frail patients with important concomitant diseases and high surgical risk. While looking at the tools that might

change the efficacy in delivering high quality of care, heart valve centers are required to have to main structures:

1. A standardized clinical care pathway, which ensures consistent, evidence-based management of IE patients
2. A multidisciplinary team with established expertise in cardiac infections, encompassing specialists in infectious diseases, cardiology, cardiac surgery, anesthesiologist, and other relevant fields, as recommended in international guidelines [31]

The clinical pathways (CPs) were first introduced in the 1980s at the New England Medical Center in Boston, in response to the introduction of Diagnosis Related Groups (DRG), as a framework for balancing cost and quality of care. By the end of the 1990s, more than 80% of US hospitals implemented CPs, just as in the UK, they were introduced as tools to define care processes, to implement clinical governance and to improve quality of care, when escalating medical costs pressured physicians to decrease resource use, without jeopardizing patient safety or clinical outcomes [83]. They are also known as “critical pathways,” “integrated care pathway,” “care maps,” and “care pathways,” and they are being embraced in many systems and have nowadays been implemented in hospitals across the globe [84–86]. CPs are evidence-based, multidisciplinary care plans designed to support shared decision-making and streamline the organization of care for a clearly defined group of patients over a specific time frame. They outline the essential steps of the healthcare process—from diagnosis to treatment and rehabilitation—ensuring comprehensive management of patients from hospital admission to discharge. The goal is to optimize both patient and hospital outcomes by reducing postoperative morbidity, shortening the length of stay, improving team communication, and controlling costs. Additionally, CPs enhance clinical appropriateness and efficiency, contributing to more structured and effective care processes [83, 86]. Compared to other forms of process management, CPs allow translation of international guidelines into protocols specifically tailored to the local hospital structures, systems, and time frames [87]. CPs have the advantage of ranking priority among interventions and health outcomes, drawing attention to the fact that the true aims of a healthcare organization are not the outputs, but the outcomes [83]. According to continuous quality improvement principles, the introduction of CPs could be an effective strategy for healthcare organizations to reduce or at least to control their processes and clinical performance variations, in order to improve clinical effectiveness and efficiency [88].

Various studies provide evidence that CPs positively affect patient outcomes (mortality, length of stay) and efficiency of care, thus lowering costs in the cardiovascular field. In fact, variations in diagnostic and therapeutic prescriptions, protocol implementation, and so on were shown in sites where pathways were implemented successfully [89, 90]. The overall purpose of clinical pathways is to improve outcome by providing a mechanism to coordinate care and to reduce fragmentation, and ultimately cost. The implementation of CPs by healthcare organizations has allowed a significant shift in the traditional healthcare paradigm, moving the focus from merely treating disease (“to cure”) to a model that emphasizes the importance of a holistic and personalized approach to patient care (“to care”). This transformation has been made possible through the adoption of care maps that prioritize personalized treatment, promote collaboration among specialists, and integrate patient preferences into the decision-making process [83].

4. A referral hub-spoke clinical pathway for the patient with infective endocarditis: To be!

At our Institution, in 2023, a working group composed by healthcare managers, infectious disease specialists, cardiac surgeons, cardiologists, anesthesiologists, geriatricians, and other professionals involved in the care of IE patients have defined and elaborated a shared pathway, suitable for our institution and local contest. The creation of the CP for IE followed three phases (**Figure 1**): in the first phase, the working group (1) reviewed literature over the latest Evidence-Based Medicine and Best Practice for IE care and (2) defined standards of quality of care for CP. The next phase was characterized by (3) the establishment of a highly specialized multidisciplinary Endocarditis Team; (4) definition of inclusion criteria to enroll patients in the CP and creation of an algorithm for IE diagnosis and treatment, both in the emergency and/or elective setting; and (5) detailed description of clinical episodes (initial framing, evaluation/staging, treatment, rehabilitation, follow-up/monitoring) within different care settings (home, general practitioner's practice, inpatient at hospital or long-term care facilities). In the final phase, the key steps included (6) the monitoring of volume, process, and outcome indicators (**Table 1**) and (7) the analysis of gaps in quality of care, through the identification of targeted improvement actions and specific timeframes for audit and evaluation.

The aims were:

- improving the quality of care with an evidence-based medicine approach, tailored to each patient's needs and expectations

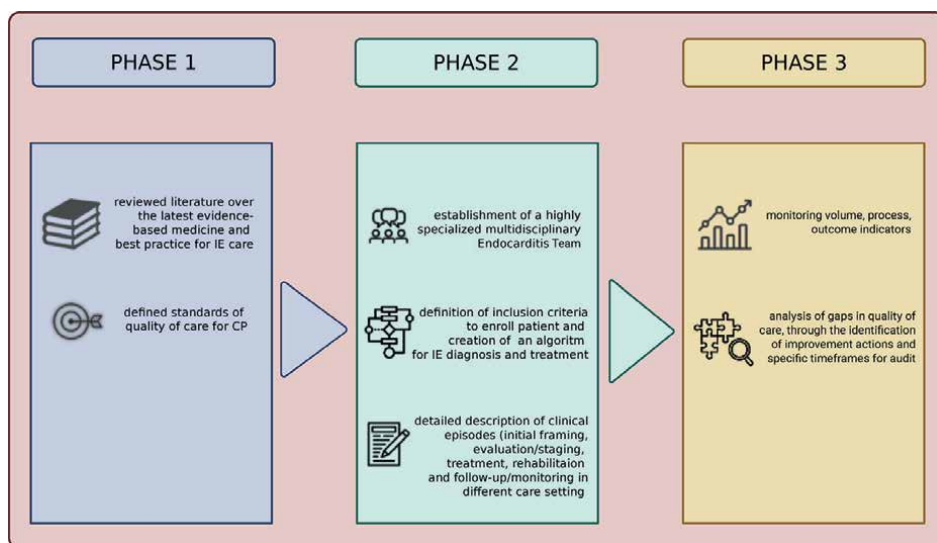


Figure 1.

Phases of the creation of the Clinical Pathway for Infective Endocarditis. The development followed three main phases: (1) conceptualizing: literature review and definition of quality standards; (2) structuring: creation of a multidisciplinary Endocarditis Team, definition of patient inclusion criteria, development of a diagnostic and therapeutic algorithm, and detailed description of clinical care pathways across settings; (3) monitoring: analysis of volume, process, and outcome indicators, and identification of quality gaps and improvement actions. CP: Clinical Pathway; IE: Infective Endocarditis.

- taking care of each patient from the early time of diagnosis to discharge, delivering care in a timely fashion (within optimized time frames)
- optimizing the hub-spokes network to support community physicians in the appropriate management of patients with IE
- providing the patient complete information at any time of the care process
- data collection in a dedicated Research Electronic Data Capture (REDCap), monitoring the outcomes and evaluating of process and performance indicators

	Indicator	Domain	Operational definition
1	Volume of IE admissions	Accessibility	All discharges with infective endocarditis ICD-9-CM codes
2	Appropriate ward allocation from Emergency Department	Interface/ governance	IE patients from ED admitted to pathway wards ÷ all IE ED admissions
3	Preoperative length of stay – elective	Efficiency/Quality	$\Sigma(\text{days from admission to surgery}) \div \text{elective IE surgical patients}$
4	Endocarditis-Team consultations	Accountability	Count of inpatient episodes with ≥ 1 Endocarditis-Team consultation
5	Compliance with early surgery criteria	Efficiency	$\text{Surgery} \leq 7 \text{ days in pts. meeting ESC "early" criteria} \div \text{eligible pts}$
6	In-hospital mortality rate	Outcome	$\text{IE deaths during admission} \div \text{IE Total IE admission}$
7	One-year all-cause mortality	Outcome	$\text{Deaths} \leq 365 \text{ days post-discharge} \div \text{IE discharges}$
8	30-day postsurgical Emergency Department readmission	Outcome	$\text{IE patients returning to ED} \leq 30 \text{ days} \div \text{all IE surgical discharges}$
9	30-day reoperation / re-intervention	Outcome / Safety	$\text{Repeat valve surgery or transcatheter intervention} \leq 30 \text{ days} \div \text{initial IE surgeries}$
10	Time-to-targeted antimicrobial therapy	Technical quality	Median hours: positive blood culture → first pathogen-directed antibiotic
11	BCNIE molecular diagnostics use	Efficiency / Innovation	$\text{BCNIE cases with PCR/16S sequencing} \div \text{total BCNIE cases}$
12	Outpatient Parenteral Therapy (OPAT) success rate	Interface / Continuity	$\text{Completed OPAT without unplanned visit/readmission} \div \text{OPAT starts}$
13	Change in EQ-5D-5L (discharge→6 mo)	Patient-reported outcome measure	Mean Δ HRQoL index between discharge and 6 months
14	Median PPE-15 score	Patient-reported experience measure	Median patient-experience (PPE-15) at discharge

ICD 9 CM: Classification of Diseases, 9th revision - Clinical Modification; IE: infective endocarditis; ED: Emergency Department; ESC: European Society of Cardiology; BCNIE: blood culture negative infective endocarditis; OPAT: Outpatient Parenteral Therapy; HRQoL: Health-related quality of life; PPE 15: Picker Patient Experience Questionnaire.

Table 1.
 Evidence-based key-performance indicators (KPIs) for the infective endocarditis clinical pathway.

5. The endocarditis team: The operating arm of a dedicated clinical pathway

The model of multidisciplinary teams was first introduced as standard practice in oncology and has since expanded across various medical fields, including cardiovascular settings. Initially conceived for the management of complex coronary artery disease [91], the Heart Team now plays a central role in the multidisciplinary approach to a wide range of cardiovascular conditions, such as valvular heart disease, heart failure, and grown up congenital heart disease [92, 93].

Recently, international guidelines [31] have emphasized the need for a new standard of care for patients with IE, highlighting the critical role of the Endocarditis Team. In a Heart Valve Center dedicated to the management of valvular heart disease, it is mandatory to identify a multidisciplinary team of IE experts for the appropriate management of this complex subgroup of patients [13, 31]. Composed of specialists from various disciplines, the Endocarditis Team takes in charge every patient admitted to the hospital with suspected IE, ensuring a timely diagnosis and tailored treatment strategies. A recent ESC position paper [13] has strengthened the necessity for a structured Endocarditis Team, defining the specific roles and contributions of each member within the evidence-based decision-making process.

- Cardiologist plays a central role in the early diagnosis and cardiac evaluation. As imaging expert, the cardiologist conducts an accurate echocardiographic assessment, offering essential information about the valvular lesions, the extent of periannular complications and the hemodynamic status in both native and prosthetic valve dysfunction. In fact, the transthoracic echocardiogram, including transesophageal, is the milestone for the detection, assessment, and treatment of IE.
- As a cornerstone of the Endocarditis team, infectious disease specialist provides essential clinical expertise throughout both the diagnostic workup and the therapeutic management. He prescribes targeted antibiotic therapies, guided by microbial sensitivity tests, clinical status, and comorbidities such as renal and hepatic dysfunction. The specialist also manages empirical antibiotic therapy in culture-negative cases, steers further diagnostic investigations when clinical suspicion remains high, and directs suppressive antibiotic strategies in patients for whom surgery is not indicated.
- Cardiac surgeons, as a third core member of multidisciplinary team, is responsible to confirm the surgical indication, determining the appropriate type of surgical intervention—repair, replacement, or reconstruction—based on the type and extent of the IE lesion and identifying the optimal timing for surgery, particularly in complex or high-risk cases. He shares concerns about a possible surgical intervention with the team. In collaboration with the infectious disease specialist, when surgery is contraindicated or not feasible, the cardiac surgeon explains the rationale for this decision to the patient and their family, outlining the available therapeutic alternatives.

Endocarditis is a complex condition that involves both infectious disease and cardiovascular fields, potentially requiring either structured—antibiotic and surgical—therapy or antibiotic therapy alone. In the context of a CP, the infectious disease specialist and the cardiac surgeon assume the role of co-coordinators within the

multidisciplinary team. They act as spokespersons for team decisions, interfacing with other specialists and communicating with the patients and the families.

- Another key member of the team is the cardiac anesthesiologist, whose responsibilities span preoperative risk stratification, intraoperative optimization, and postoperative management. The anesthesiologist prescribes targeted measures to correct reversible vulnerabilities—such as coagulation abnormalities, iron-deficiency anemia, and impaired renal or respiratory function—thereby lowering perioperative morbidity and improving surgical outcomes. Beyond the acute phase, the cardiac anesthesiologist coordinates the early rehabilitation pathway. Acting as a linchpin for continuity of care, the anesthesiologist works with physiotherapists, consults with therapists, and dietitians to identify the optimal window for early, even minimal, rehabilitation interventions, tailored to each patient's clinical status. Once the acute phase is stabilized, the anesthesiologist contributes to post-acute care planning, facilitates transfer to specialized rehabilitation facilities and maintains clinical oversight in complex cases. This comprehensive knowledge of the patient's perioperative course ensures that rehabilitation is timely, effective, and safe.

While in other models described in the literature [94, 95], the core of the Endocarditis Team typically consists of the cardiologist, infectious disease specialist, and cardiac surgeon; in our model, the anesthesiologist is also an integral core member, serving as a clinical gatekeeper. This four-member structure is mandatory for the appropriate and personalized selection of the therapeutic strategy. Other key contributors to the Endocarditis Team include:

- Microbiologists identify the causative microorganism through blood cultures and in analyzing intraoperative tissue samples using both culture methods and PCR. The latter becomes particularly crucial in complex cases of blood culture-negative endocarditis or when there is a discrepancy between microorganisms isolated from blood and those detected in excised valve tissue. Moreover, when all valve culture tests are negative, despite histological evidence of acute inflammation, the PCR-based identification of microorganisms may guide the recalibration of antimicrobial therapy.
- Radiologists provide essential imaging pre- and postoperatively support, contribute to disease staging, confirming or excluding the presence and distribution of septic emboli and offering detailed information on the extent of cardiac involvement. In fact, radiological findings are integrated with echocardiographic imaging to enhance diagnostic accuracy, particularly in identifying perivalvular complications such as abscesses, pseudoaneurysms, and extensions of the infection into the fibrous skeleton of the heart.
- Neurologists. Neurologic complications occur in about 20–30% of IE, and the majority of these are ischaemic embolic strokes [31]. The presence of neurological complications has traditionally represented a major determinant in the decision-making process regarding the optimal timing of surgery. This is largely due to concerns that cardiopulmonary bypass could precipitate a hemorrhagic transformation of recent ischemic lesions or exacerbate ongoing cerebral damage. While recent guidelines [31] recommend early surgery in patients with nonhemorrhagic

stroke, cases involving hemorrhagic stroke require individualized assessment. Accordingly, neurologist involvement is of paramount importance.

- Geriatricians. As previously highlighted, the incidence of IE among elderly population continues to rise. The higher surgical risk is due not only to their comorbidities but also to frailty. The latter is defined as “impaired or reduced resistance to external stressors, posing the individual at increased risk of adverse health outcomes.”¹⁶ In accordance with the guidelines, all patients older than 70 awaiting a procedure have their frailty assessed by a geriatrician. The assessment is performed through a multidimensional approach based on the computation of the Rockwood frailty index [96], the Mini Nutritional Assessment [97], the 4-min walk test [98], and the handgrip strength test [99]. Special attention is devoted to conditions that are potentially amenable to interventions, such as malnutrition and sarcopenia.
- Electrophysiologist. The increasing incidence of CIED infections, whether manifesting as pocket infections or systemic infection, necessitates the on-call involvement of an electrophysiologist, who has expertise in device extraction. Despite current evidence strongly supporting a Class I indication for complete device and leads removal in patients with confirmed CIED-IE, the adherence to CIED infection management protocols remains suboptimal [41, 42]. Similarly, in cases of IE related to substance use, psychological evaluation is systematically required, with the primary objective of delineating the patient’s psychological profile. This evaluation is crucial for assessing the patient’s capacity for adherence to medical therapy, the risk of relapse and the feasibility of long-term treatment plans following surgical or medical management [43].
- Psychologist. Given the complexity of disease, we integrated a psychologist into our team to assess anxiety and depression and to provide emotional support to patients and their families throughout the process of adapting to the diagnosis and hospitalization. This intervention also plays a key role in promoting treatment adherence and improving overall patient outcomes.

6. The decision-making process: Insights from a comprehensive matrix model

The Endocarditis Team must meet on a frequent basis, at least once a week and work with standard operating procedures and the local clinical governance arrangements [31]. Since 2023, our Endocarditis Team has convened regularly twice a week (Tuesdays and Thursdays) to assess surgical eligibility and determine the appropriate timing of intervention in cases of definite IE, to rationalize a negative result when the clinical suspicion is high, and to define follow-up strategies for patients deemed unsuitable for surgery. In addition, in a hub-spoke network, the team evaluates all patients with a definite or suspected diagnosis of IE, admitted to other referring hospitals, offering support to physicians in the choice of diagnostic tests and in therapeutic management or transferring the patient in the case of surgical treatment or failure to respond to the antibiotic therapy, in order to avoid unnecessary delays. The Team should share protocols with the physicians from the referring hospitals and should facilitate their continuing education. Referral modalities to the Team may

The modified Duke criteria provide the basis for the decision-making process and, with combined clinical, microbiological, and echocardiographic data, remain the standard for classifying IE as definite, possible, or rejected.

Therapeutic management of IE requires a dedicated, multidisciplinary “endocarditis team” to coordinate and optimize patient care, including the timing of surgery and choice of medical therapy. Antibiotic treatment must be tailored to the specific pathogen and administered intravenously for a typical duration of 4 to 6 weeks.

Surgical intervention, according to 2023 ESC guidelines, should be considered early in the disease course in the presence of heart failure, uncontrolled infection (e.g., abscess, persistent bacteremia, or large vegetations), prosthetic valve involvement, or to prevent systemic embolization. The timing of surgery is critical: Emergency (within 24 hours) in cases of severe heart failure or uncontrolled infection, Urgent (3–5 days) for patients at high risk of embolism, and nonurgent when the patient is clinically stable, but anatomical correction is necessary.

For patients who have no indication for surgery, close clinical monitoring is essential to detect any worsening condition while continuing targeted antibiotic therapy. Patients in whom surgery is not feasible—due to comorbidities, advanced age, or refusal—should receive close follow up and prolonged, targeted intravenous antibiotics. The outpatient parenteral antibiotic therapy (OPAT) program can allow safe treatment continuation at home under medical supervision. Post-discharge follow-up is crucial to detect relapses, monitor for late complications, and manage long-term sequelae. Patients should be educated on the importance of maintaining excellent oral hygiene and avoiding unnecessary invasive procedures. Antibiotic prophylaxis is advised for high-risk individuals undergoing high-risk procedures.

Long-term cardiologic follow-up is recommended to monitor valve function, assess symptoms of heart failure, and evaluate the potential need for late surgical intervention.

In a Heart Valve Center, a successful Endocarditis Team requires long-term commitment and active participation from its members. The effectiveness of the team depends not only on its ability to ensure timely diagnosis and individualized treatment strategies for each patient and management of complex cases but also on the integration of different expertise and on improving outcomes. Equally important should be active involvement in the promotion of clinical research and a strong commitment to continuous professional development. Only through this structured and sustained synergy can a truly effective and innovative approach to the management of IE be achieved [94].

7. Conclusions and take-home messages

7.1 Conclusions

Over the past 50 years, the epidemiology of IE has undergone profound changes. The aging population, the widespread use of prosthetic valves and intracardiac devices, and the intensification of invasive medical procedures have contributed to a rising incidence of IE, particularly among frail populations. At the same time, the emergence of highly virulent pathogens and multidrug-resistant microorganisms, has led to more severe clinical manifestations and has complicated therapeutic management. Despite strong evidence supporting the benefits of surgical intervention, surgery remains underused in clinical practice, particularly in high-risk patients, underscoring a persistent gap between guidelines recommendations and real-world management.

In this evolving landscape, the establishment of structured CPs and dedicated Endocarditis Teams is a crucial strategy to ensure standardized evidence-based care, minimize diagnostic and therapeutic delays, and optimize patient outcomes. The contemporary management of IE thus requires an integrated, dynamic, and personalized model of care, capable of adapting to the increasing clinical complexity and the continuous evolving microbiological profiles.

Looking to the future, the widespread implementation of standardized clinical pathways, the consolidation of efficient hub-spoke networks, and strengthening of interdisciplinary collaboration will be essential not only to improve the prognosis of patients with IE but also to reduce the significant socioeconomic burden of a disease that, although rare, represents an increasingly important public health challenge.

7.2 Take home messages

7.2.1 Evolving epidemiology

The epidemiology landscape of infective endocarditis (IE) has changed dramatically in recent decades, with a decrease in rheumatic disease-related cases and a rising incidence of nosocomial and healthcare-associated infections.

7.2.2 Microbiological profile

Staphylococcus aureus, coagulase-negative staphylococci, and *Enterococcus faecalis* are now the predominant pathogens, often associated with prosthetic valves and CIED infections.

7.2.3 Rise in frail populations

The aging population, often with multiple comorbidities, and intracardiac devices represent a growing and particularly vulnerable population, with atypical and complex clinical presentations.

7.2.4 Early surgery

Despite strong evidence supporting surgical intervention, especially in cases of heart failure, uncontrolled infection, or high embolic risk, surgery remains underutilized in routine practice.

7.2.5 Multidisciplinary management

Optimal care of IE requires implementation of multidisciplinary teams (Endocarditis Teams) and evidence-based clinical pathways to ensure coordinated, timely, and tailored interventions.

7.2.6 Advanced diagnostics

Molecular techniques (e.g., PCR) and serological assays are indispensable in diagnosing culture-negative IE and tailoring antimicrobial therapy, especially in complex or atypical cases.

7.2.7 Addressing clinical disparities specific

Patient subgroups—including oncology patients, people who inject drugs, women, and adults with congenital heart disease—exhibit distinct risks and outcomes that demand individualized care strategies.

7.2.8 Standardized pathways improve care

The integration of structured clinical pathways enhances diagnostic accuracy, reduces variability in treatment, improves outcomes, and ensures a more efficient use of healthcare resources.

Conflict of interest

The authors declare no conflict of interest.

Acronyms and abbreviations

IE	infective endocarditis
CP	clinical pathway
HACEK	haemophilus, aggregatibacter, cardiobacterium, eikenella, kingella
PET/CT	positron emission tomography/computed tomography
CoNS	coagulase-negative staphylococci
PCR	polymerase chain reaction
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
VRE	vancomycin-resistant enterococci
CIEDs	cardiac implantable electronic devices
TAVI	transcatheter aortic valve implantation
PVE	prosthetic valve endocarditis
NVE	native valve endocarditis
PWID	people who inject drugs
ACHD	adults with congenital heart disease
STS	society of thoracic surgeons
IABP	intra-aortic balloon pump
NYHA	New York Heart Association
DRG	diagnosis related groups
ESC	European society of cardiology
TTE	transthoracic echocardiography
TEE	transesophageal echocardiography
OPAT	outpatient parenteral antimicrobial therapy

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Recent Innovations in the Management of Endocarditis in Ventricular Assist Device (VAD) Patients

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Abstract

The chapter will address the latest advancements in the management of endocarditis among patients with durable left ventricular assist devices (VADs). The discussion will encompass a wide array of innovations in diagnostic modalities, antimicrobial therapies, surgical approaches and techniques and preventive strategies and best practices. The advances in surgical therapies including device replacement or removal of infected VADs, heart transplantation by different new surgical approaches will be reviewed. The multidisciplinary approach to management is highlighted to drive innovation in the management of endocarditis in VAD cohort of patients. The chapter key points will focus on integration of the new approaches and developments in clinical practice to improve the patient outcomes.

Keywords: ventricular assist device infection, infective endocarditis, surgical interventions, heart transplantation, innovative approaches

1. Introduction

As ventricular assist devices (VAD) use continues to expand for patients with heart failure, tackling infectious complications remains a critical challenge. Recent advancements in diagnostic imaging, molecular pathogen identification, biofilm-target treatments, and device design are paving the way for more effective and personalized approaches to managing VAD-related infections.

1.1 Brief overview of the significance of endocarditis in VAD patients

Despite the increasing use of VADs for end-stage heart failure, infection remains a significant risk factor for morbidity and mortality.

1.2 Definition of VAD-related infective endocarditis (IE) (possible, rejected, definite)

In 2020, the MCS Academic Research Consortium updated the definition of ventricular assist device (VAD) infection, categorizing it into two distinct groups: MCS-specific infections and non-MCS-related infections [1]. The revised definition provided by the Academic Research Consortium (ARC) is specifically focused on infections associated with durable mechanical circulatory support (MCS) devices. According to this definition, left ventricular assist device (LVAD)-associated endocarditis is characterized by infection involving the cannula or pump, confirmed by a positive culture obtained from an explanted LVAD, in conjunction with the presence of vegetations or other pathological findings consistent with the modified Duke criteria [2].

After the 2023 Duke-ISCVID criteria update, the diagnosis of VAD-related infective endocarditis (IE) requires either microbiological confirmation or pathological evidence of active IE from operative or postmortem specimens. The major clinical criteria now include microbiologic, imaging, and a newly introduced surgical category. The surgical major criterion is defined by direct intraoperative evidence of IE, even without subsequent histologic or microbiological confirmation.

The microbiologic major criteria [2] for diagnosing ventricular assist device (VAD)-associated endocarditis include:

- Positive blood cultures.
- Detection of pathogens through polymerase chain reaction (PCR) or other nucleic acid-based techniques, specifically for *Coxiella burnetii*, *Bartonella* species, or *Tropheryma whippelii*.
- Serologic evidence, such as elevated IgG antibody titers from blood cultures or indirect immunofluorescence assays detecting IgM and IgG against *Bartonella henselae* or *Bartonella quintana*.
- PCR and next-generation sequencing (NGS), which are particularly valuable for identifying causative organisms in culture-negative cases, are used when conventional microbiological cultures fail, due to prior antibiotic administration or presence of fastidious microorganisms.

The imaging major criteria comprise:

- Echocardiographic or cardiac computed tomography (CT) findings indicative of infective endocarditis, including vegetation, valvular perforation, abscess formation, or pseudoaneurysm.
- Positron emission tomography (PET) using 18F-fluorodeoxyglucose (18F-FDG) demonstrates abnormal metabolic activity in native valves, prosthetic materials, or VAD components, such as the pump or cannula [2].

The minor criteria [2] include:

- Predisposing factors: A history of infective endocarditis (IE), the presence of a prosthetic valve, an endovascular cardiac implantable electronic device (CIED), hypertrophic obstructive cardiomyopathy (HOCM), or intravenous drug use.

- Fever: A body temperature exceeding 38°C.
- Vascular phenomena: Manifestations such as arterial emboli, septic pulmonary infarcts, cerebral or splenic abscesses, and mycotic aneurysms.
- Immunologic phenomena: The presence of purpura, Janeway lesions, or other immune-mediated manifestations.

1.3 Diagnostic categories for LVAD-related endocarditis

- Definite endocarditis: Confirmed either by microbiologic evidence (isolation of microorganisms from cardiac tissue, vegetation, or an explanted prosthetic valve) or by histological findings of active IE. Clinically, a diagnosis is established based on [2]:
 - Two major criteria (e.g., a positive blood culture and imaging evidence of vegetation).
 - One major and three minor criteria.
 - Five minor criteria.
- Possible endocarditis: Defined by the presence of one major criterion and one minor criterion.
- Rejected endocarditis: Determined when there is insufficient evidence to meet the diagnostic criteria for IE.

These revised diagnostic criteria enhance the accuracy of identifying VAD-related endocarditis by integrating microbiologic, imaging, and intraoperative findings, thereby facilitating more precise clinical decision-making.

2. Advanced methods in diagnosing VAD endocarditis

Advancements in diagnostic techniques have significantly improved the detection and management of ventricular assist device (VAD)-associated endocarditis. Among these, molecular diagnostics, particularly polymerase chain reaction (PCR) and next-generation sequencing (NGS), play crucial roles in identifying pathogens, especially in culture-negative cases.

2.1 Molecular diagnostics

2.1.1 16S rDNA polymerase chain reaction (PCR)

PCR is a highly sensitive technique that utilizes Bacterial DNA detection to identify pathogens in culture-negative endocarditis [3]. It provides rapid results within hours and is particularly effective in detecting known pathogens and resistance genes. While PCR is cost-effective and well-suited for VAD-associated endocarditis due to its targeted approach, it is limited by the necessity of prior knowledge of the target genes, making it less effective for unknown or rare pathogens.

2.1.2 Next-generation sequencing (NGS)

NGS offers a broader-spectrum approach, capable of detecting all microbial DNA/RNA, including previously unidentified or rare pathogens. Unlike PCR, it does not require prior knowledge of target genes and can identify both bacterial and fungal species, making it valuable for polymicrobial infections. However, NGS requires 12–48 hours [4], making it slower than PCR, and is also more expensive. Given its ability to detect all known and novel resistance genes, NGS is particularly useful in complex culture-negative cases with unexpected pathogens. The incidence of blood-culture negative endocarditis 31–35% [4]. These advanced molecular methods have enhanced the speed and accuracy of VAD endocarditis diagnosis, enabling earlier intervention and targeted treatment strategies, ultimately improving patient outcomes. This method is recommended for patients with negative blood cultures and high suspicion of IE [4].

3. New imaging techniques in VAD endocarditis diagnosis

Accurate diagnosis of ventricular assist device (VAD)-associated endocarditis relies on advanced imaging techniques to detect vegetation, abscesses, and infected device components. Traditional echocardiography remains the primary imaging modality, while newer methods, including multidetector computed tomography (MDCT) and fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT), provide additional diagnostic insights.

3.1 Echocardiography

Transthoracic (TTE) and transesophageal echocardiography (TEE) continue to be fundamental in diagnosing VAD-related infective endocarditis (IE).

TEE, with superior sensitivity compared to TTE, is more effective in detecting vegetation, abscesses, and other structural abnormalities. However, echocardiographic findings can be false-negative, particularly in cases with small vegetations or device-related shadowing artifacts, necessitating complementary imaging.

Additionally, false-positive findings can occur due to structures mimicking vegetations, such as pannus, thrombi, or noninfected prosthetic material. Importantly, a negative TTE does not exclude VAD-IE, highlighting the need for further investigation in cases with strong clinical suspicion. Advanced echocardiographic techniques, including three-dimensional (3D) echocardiography (in defining the size and dimensions of vegetation) and contrast-enhanced echocardiography, offer improved visualization of complex structures, aiding in the differentiation of infection-related and non-infectious lesion [5].

3.2 Multidetector computed tomography (MDCT)

MDCT is particularly useful for evaluating localized infections, detecting fluid collections, gas pockets, and soft tissue abnormalities surrounding the VAD [6].

However, the presence of metallic components in the device can create artifacts, limiting visualization of certain cardiac structures.

MDCT is more effective in detecting thrombosis in the outflow graft or inflow cannula than in directly identifying infection. Despite these limitations, its high-resolution imaging capabilities make it a valuable adjunct to echocardiography in cases where infection is suspected but not clearly identified.

3.3 Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT)

FDG-PET/CT has emerged as a promising tool in the diagnosis of VAD infections, leveraging increased glucose metabolism in inflamed tissues to identify infected areas. This technique was recently incorporated into VAD endocarditis diagnostic strategies, with studies demonstrating a 92% sensitivity and 83% specificity in detecting VAD-related infections [7].

In a small study of patients with suspected LVAD infections, FDG-PET/CT successfully mapped the extent of infection on both the device and adjacent structures, providing crucial information for guiding treatment decisions [7].

While further validation through larger studies is needed, FDG-PET/CT has the potential to improve clinical outcomes by detecting both localized and distant infectious foci, aiding in early intervention and targeted antimicrobial therapy.

3.4 Cardiac magnetic resonance imaging (CMR)

CMR shows valvular vegetations and perivalvular involvement, but there are few studies showing the utility of this procedure because the artifacts can make diagnosis difficult [8].

- Advantages:
 - Provides detailed soft tissue contrast without ionizing radiation.
 - Useful in identifying myocardial involvement, abscess formation, and valve destruction.
 - Can differentiate infected thrombi from sterile thrombi, aiding in diagnostic accuracy.
- Limitations:
 - Metallic artifacts from the VAD can degrade image quality.
 - Contraindicated in patients with certain metallic implants or non-MRI-compatible devices.
 - Limited use in unstable patients due to longer scan times.

3.5 Dual-energy computed tomography (DECT)

It is an advanced computed tomography imaging technique that uses two different X-ray energy levels to differentiate materials with similar densities.

- Advantages:
 - Reduces metal-related artifacts, improving visualization of soft tissue infections around the VAD [9]

- Enhances detection of inflammatory changes, abscesses, and prosthetic material infections.
- Limitations:
 - Limited availability in routine clinical practice.
 - Requires specialized software and expertise for interpretation.

3.6 White blood cell (WBC) scintigraphy (SPECT/CT with 99mTc-HMPAO-Labeled leukocytes) in VAD-related endocarditis

- Advantages:
 - Directly detects active infection by imaging labeled white blood cells accumulating at the injection site.
 - Can differentiate infectious from non-infectious inflammatory processes.
- Limitations:
 - Requires specialized radiopharmaceuticals and extended imaging times.
 - Sensitivity is lower than that of FDG-PET/CT for detecting VAD infections.
 - Guidelines recommend that SPECT/CT with 99mTc-HMPAO-Labeled Leukocytes may be an additive tool in positive blood cultures with negative echocardiography [10].

3.7 Intravascular ultrasound (IVUS) and intracardiac echocardiography (ICE)

- Advantages:
 - Provides high-resolution imaging inside the heart and vascular structures.
 - Can help visualize vegetations, thrombi, and prosthetic valve involvement in challenging cases [11].
- Limitations:
 - Invasive technique, requiring catheter-based imaging.
 - Used primarily in research or complex cases.

3.8 Emerging techniques

- Artificial intelligence (AI)-Assisted imaging analysis: AI algorithms are being developed to enhance automated detection of vegetations, abscesses, and infections in VAD patients [12].
- Hybrid imaging approaches: Combining FDG-PET/CT with MRI or SPECT/CT could improve sensitivity and specificity in challenging cases.

While echocardiography, MDCT, and FDG-PET/CT remain the primary imaging modalities, additional techniques such as CMR, DECT, WBC scintigraphy, IVUS, and ICE can play complementary roles. The choice of imaging should be tailored to each patient, integrating multiple modalities for accurate and early diagnosis of VAD-associated endocarditis.

4. Clinical manifestations of VAD-associated infective endocarditis

4.1 Clinical presentation

The most common symptom is fever, accompanied by anorexia, chills, dyspnea, night sweats, and myalgia. On physical examination, findings may include splenomegaly, splinter hemorrhages, and the emergence of a new heart murmur. Additionally, characteristic dermatological and ophthalmological manifestations, such as Osler's nodes, Janeway lesions on the palms, and Roth spots on the retina, may be observed [13].

4.2 Pathogenic mechanisms

The infection may initially involve the driveline (**Figure 1**), which possesses a velour texture due to incomplete tissue incorporation or mechanical trauma, such as traction or torsion. These factors facilitate biofilm formation, allowing bacterial colonization of the driveline and enabling microorganisms to persist in a latent state for extended periods [14].

Pump infections can be classified as either extravascular or endovascular [13]. The primary mechanisms underlying pump infection include systemic bacteremia or direct contamination during device implantation (**Figure 2**).

4.3 Diagnosis

The diagnosis of endovascular pump infection is based on clinical signs and symptoms, positive blood cultures, and imaging findings. The infection can manifest with general signs as fever, leukocytosis and hemodynamic instability or inflow outflow



Figure 1.
The drive line and outflow graft after the HeartMate 3 implant.



Figure 2.
HeartMate 3 pump implanted on the apex of left ventricle.

cannula obstruction. Presence of vegetation with systemic emboli can also occur (19). Systemic infection can produce systemic inflammatory response syndrome (SIRS) are not markers for local infections as drive line infection. Elevation of other markers of inflammation as CRP or procalcitonin are not relevant for VAD endocarditis. The evaluation may answer to the question if there is a superficial or a deep infection caused by drive line infection or bloodstream infection. Transthoracic echocardiography (TTE) or transesophageal (TOE) has a crucial role in assessing intracardiac masses or abscess formation. Additionally, computed tomography (CT) scanning and fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT) provides enhanced diagnostic accuracy. Definitive confirmation is achieved through histopathological analysis of tissue samples obtained during surgical VAD removal [13]. For extravascular pump infections, diagnosis relies primarily on positive blood cultures in conjunction with intraoperative microbiological cultures obtained during surgical intervention.

5. Innovative therapeutic approaches

5.1 Antimicrobial strategies

- Antimicrobial lock therapy (ALT): Can be used in cases of catheter-related infections to eradicate biofilms within device components, potentially preserving the VAD while clearing the infection [15]. While ALT is not a first-line therapy for deep-seated VAD infections, it can be useful as an add-on in superficial infections or as a salvage therapy in non-surgical candidates.
- Biofilm-disrupting agents: Aspirin, Dabigatran (direct inhibitor of thrombin), hyperbaric oxygen therapy, and bacteriophages are good adjuvants, allowing antibiotics to penetrate and eliminate bacteria more effectively [16].
- Nanotechnology-based antimicrobials: Nanoparticles delivering antibiotics directly to biofilms on VAD surfaces may enhance treatment efficacy while reducing systemic toxicity [17].

5.2 Management strategies for VAD-associated infective endocarditis

The treatment of ventricular assist device (VAD)-associated infective endocarditis (IE) is based on four key pillars (See **Table 1**) [6]:

- Identification of the causative microorganism to guide targeted antimicrobial therapy.
- Classification of the infection type, such as infective endocarditis, mediastinitis, or localized VAD infection.
- Localization of the VAD-specific infection site, including the pump (endo or extravascular infection), cannula, or driveline, and address properly the antibiotics (local or systemic) to the area involved (19).
- Assessment of transplant candidacy, determining whether the patient is a candidate for heart transplantation (bridge to transplant) or is receiving long-term support with the device (destination therapy).

5.3 Microbial etiology and antimicrobial therapy

Pseudomonas aeruginosa has been reported as the most frequently isolated pathogen from explanted VADs in cases of infective endocarditis, followed by *Staphylococcus epidermidis* [18].

In bloodstream infections, the most isolated organisms include *Enterococcus* species, coagulase-negative *Staphylococcus*, and methicillin-sensitive *Staphylococcus aureus* (MSSA).

The most frequent diagnosis pattern was a combination of clinical signs, trans-esophageal echocardiography, positive blood cultures and LVAD explant cultures [18].

Pump and cannula infections are rare (4.3% of all VAD-specific infections, 19), and it is difficult to distinguish VAD-related endocarditis in which we may prove vegetation, outflow cannula dehiscence, or implanted material.

The treatment approach for VAD-related IE involves a combination of antibiotic and antifungal therapy, with surgical intervention considered when necessary. Once the antibiotics regimen is selected, it is important to establish if limited (fixed duration) or continuous antibiotics are necessary. For the infections affecting the pump or cannula and in VAD endocarditis, parenteral antibiotics are indicated for 6 weeks and consecutive suppressive antibiotics are strongly recommended (19). To control the source of infection, the VAD exchange or VAD removal should be considered (see **Table 1**). Patel et al. [18] reported a median duration of 91 days between LVAD implantation and the onset of endocarditis. Because of biofilm formation, which is difficult to resolve by antibiotics, complete device removal can be a viable option. Heart transplantation is another option for severe VAD infection and may be considered the only definitive therapy for chronic infections [19]. The patients with VAD support as a bridge to transplant should receive suppressive antibiotic therapy until the time of transplant. If infection is suspected at the time of transplant intraoperative cultures and samples from pump pocket, internal and external components of VAD, or fluid collections or tissue may be taken to help in target antibiotic therapy management. All the material of the VAD may be removed because it is a source of recrudescence infection. Pretransplant infections are risk factors for posttransplant infections (19) and are correlated with lower survival.

Type of infection	ISHLT classification	Microbiology	Pathogenesis	Clinical manifestations	Diagnostic microbial-imaging	Management antibiotics	Management source control
1. Infections on external surfaces of VAD-superficial DLI	VAD-specific	Gram-positive skin flora, Coryneform, Gram-negative bacteria including pseudomonas	Local trauma and subsequent superinfection	Erythema, Induration, Tenderness, Purulent discharge	Exit site culture Imaging: none	Oral antibiotics for a minimum 14 days. Suppressive therapy may be considered for recurrent infections	None usually required
Deep DLI	VAD-specific	Like superficial DLI	Progression of superficial DLI	Like superficial DLI, more associated with more associated symptoms	Exit site culture Blood cultures Imaging: Bedside US, CT, or nuclear imaging	Parenteral infections for 4–8 weeks. Suppressive antibiotics should be strongly considered.	Driveline debridement, and percutaneous aspiration of collection Drive repositioning
Pump-pocket infection	VAD-specific	Like DLIs, but a greater representation of enterococcus, Gram-negative bacteria and Candida	Inoculation of microorganisms at the time of implantation, ascending DLI, or hematogenous seeding from BSI	Like deep DLI, it may also have erosion of the device with the development of sinus tracts in the chest or abdominal wall	CT or nuclear imaging	Parenteral antibiotics for 4–8 weeks Suppressive antibiotics are recommended.	Surgical debridement of pump pocket or percutaneous aspiration Antibiotic beads surgically placed on pocket Pump exchange or removal for severe cases
Mediastinitis	VAD-related	Gram-positive skin flora less Gram-negative	Contiguous extension of sternal wound or pump-pocket infection or secondary contamination	Systemic symptoms fever, chest pain, sternal wound drainage or dehiscence	CT or nuclear imaging	Parenteral antibiotics for 4–8 weeks. Suppressive antibiotics are recommended.	Surgical debridement

Type of infection	ISHLT classification	Microbiology	Pathogenesis	Clinical manifestations	Diagnostic microbial-imaging	Management antibiotics	Management source control
2. Infections on internal surfaces of the VAD-bloodstream infection (BSI)	VAD-related or non-VAD-related	Depends on primary source	Microorganisms' translocation from a site-specific focus of infection	Fever, symptoms of low cardiac output, localizing symptoms of the primary focus of infection	TEE site-specific imaging guided by underlying clinical syndrome	Parenteral antibiotics for 2–6 weeks (depending on infecting organism and various patient factors) Suppressive antibiotics are recommended.	Remove any foci on infection (drain,) or debridement infection and remove indwelling catheter
Pump/cannula infections and VAD endocarditis	VAD-specific	Depends on primary source of BSI	Hematogenous seeding from a BSI (rare early-onset infections may be due by inoculation at the time of VAD implantation)	Fever, symptoms of low cardiac output, embolic phenomena	Blood cultures TEE, CT, nuclear imaging	Parenteral antibiotics for 6 weeks. Suppressive antibiotics are recommended.	Device exchange or removal

Table 1.
Infectious disease syndromes associated with VAD (19).

5.4 Surgical and interventional innovations in VAD-associated endocarditis

Surgical intervention for VAD-associated IE includes VAD exchange or heart transplantation. However, studies have reported conflicting outcomes regarding the superiority of surgical intervention over conservative antimicrobial therapy. While some reports suggest no significant survival benefit with VAD exchange [20], others indicate that surgical intervention may improve patient survival compared to medical therapy alone [18]. Pretransplant VAD infection is a risk factor for post-heart transplant outcomes being associated with lower survival. Mediastinitis, retrosternal abscess drive line, or pump-pocket infections before transplant had a postoperative risk of infection of 58.8% [19] and usually developed in the first month after transplantation.

5.4.1 Left ventricular assist device exchange

The most used durable VADs include HeartWare (HVAD), HeartMate 2, and HeartMate 3. Due to reliability concerns with the HVAD system, including its failure to restart after accidental pump stops, Medtronic discontinued the HVAD system, with HeartMate 3 becoming the preferred alternative. Device exchange requires consideration of anatomical and technical differences between these systems, including variations in apical connector design, sewing ring configuration, and outflow graft diameter.

5.4.2 Surgical approaches for HVAD to HeartMate 3 exchange by open procedure

This procedure can be performed from a median sternotomy or by thoracotomy. Given the risks associated with redo sternotomy, including potential outflow graft injury due to adhesions, alternative surgical approaches, such as anterolateral thoracotomy, may be preferred. The procedure can be done open or by minimally invasive access.

The standard surgical procedure for open HVAD removal [20] and HeartMate 3 implantation includes:

- Complete excision of the HVAD, including the sewing ring, inflow cannula, and outflow graft.
- Insertion of the HeartMate 3 pump by securing a new sewing ring to the left ventricular apex.
- Anastomosis of the new outflow graft to the ascending aorta, which may require enlargement aortotomy due to the larger diameter of the HeartMate 3 graft. Cardiopulmonary bypass or extracorporeal membrane oxygenation (ECMO) are used to facilitate safe device exchange and minimize hemodynamic instability.

The determination of whether to explant all ventricular assist device (VAD) components or solely the pump along with the power cord is based on the absence of outflow tract obstruction or infection, as confirmed by computed tomography (CT) of the thorax. The procedure is performed *via* a left anterior Mini thoracotomy. Then advantage of thoracotomy resides in less bleeding, less risk for right ventricle injury and better exposure of the apex of LV [22].

5.4.3 Alternative surgical techniques in complex cases

In cases where complete HVAD removal poses a high risk of complications, alternative strategies [20] may be employed:

- Use of the existing HVAD sewing ring: The HeartMate 3 connector can be secured over the HVAD sewing ring, as its larger size allows for a stable fit.
- Sealing modifications: A sterile rubber seal may be placed around the HeartMate 3 inflow cannula to prevent leakage, reducing the need for extensive dissection to remove the original HVAD sewing ring.
- Other surgical approaches:
 - Anterolateral thoracotomy can minimize sternotomy-related risks but requires graft-to-graft anastomosis, leaving a portion of the original outflow graft in place.

Right upper anterior thoracotomy with graft tunneling provides an additional option, allowing anastomosis of the new outflow graft to the ascending aorta *via* the right chest.

5.4.4 Ventricular assist device implantation by minimally invasive approach

Minimally invasive approach for VAD insertion [21] is considered because of developments of new miniaturized VAD that can be implanted by smaller incisions with less bleeding or right ventricular dysfunction. At the same time, anterolateral thoracotomy offers an alternative for avoiding a redo sternotomy and risk of outflow graft injury. This approach described by Chen [21] consists on a 6 cm left anterolateral thoracotomy in fifth or sixth intercostal space and a 4 cm upper hemi sternotomy. Intraoperative echocardiography is used to identify the apex of the heart. The procedure is done usually on cardiopulmonary bypass, or an off-pump approach is possible as well. If CPB is used, the cannulation sites are the femoral vein (Seldinger technique) and distal ascending aorta. The main steps are starting cardiopulmonary bypass, coring the apex of LV, and insertion of the sewing ring. The VAD pump is connected, and the outflow graft is tunneled inside the pericardium to the right side of ascending aorta. Side-biter clamp is placed on ascending aorta and a 4–0 Polypropylene suture used to anastomose the outflow graft to the aorta. Pump is starting and deairing procedures are the same as in open access.

Minimally invasive approach reduces trauma, and when an off-pump procedure is used, this can avoid the CPB-related adverse effects [22].

5.4.5 Alternative surgical approaches for correcting aortic valve regurgitation in patients with ventricular assist devices (VADs)

5.4.5.1 Aortic valve repair

This is indicated in cases of significant aortic regurgitation (AR), which may compromise VAD function by creating retrograde flow into the left ventricle and diverting blood from the systemic circulation. One technique to mitigate AR is the Park stitch,

which involves placing a pledgeted 5–0 monofilament nonabsorbable polypropylene suture at the central coaptation point of all three cusps, specifically at the level of the Arantius node [23]. This approach has been demonstrated to effectively reduce regurgitation and improve valve competence.

An alternative method, described by Barac [24] utilizes the implantation of an internal geometric annuloplasty ring to address both AR and annular dilatation. This technique offers the advantage of preserving the native valve while minimizing the use of prosthetic material, thereby reducing the risk of infection. However, drawbacks include the necessity of cardioplegia and aortic cross-clamping, as well as potential adverse effects on right ventricular function. Despite these limitations, this approach may present a more favorable alternative to aortic valve replacement (AVR).

5.4.5.2 Aortic valve replacement

Remains a viable option, particularly in patients with aortic valve disease secondary to endocarditis. This procedure can be performed using either mechanical or bioprosthetic valves. When selecting a biological prosthesis, a bovine pericardial valve is often preferred due to its tendency to degenerate *via* progressive stenosis, in contrast to porcine prostheses, which are more susceptible to leaflet tears and recurrent aortic regurgitation [23].

5.4.6 Heart transplantation

The surgical treatment options for ventricular assist device (VAD) infections include left ventricular assist device (LVAD) explantation, replacement with a new LVAD, or heart transplantation. Among these approaches, heart transplantation is the only option that ensures the complete eradication of infection sites. The most important principle is to try to remove all the infected VAD components before sepsis and other complications occur [25]. Long-term antibiotics play a very important role after the transplant and if the recipient benefits from a good donor heart, the long-term outcomes are similar with noninfected recipients.

The immunosuppressive medication regimen may be modified to exclude induction therapy, and patients in this group often require increased inotropic support. In cases of active ventricular assist device (VAD)-related infection, heart transplantation remains the only life-saving treatment option.

6. Conclusions

The management of VAD-associated infective endocarditis is complex and requires a multidisciplinary approach, incorporating antimicrobial therapy, proper selection of surgical procedures, and careful patient selection. Device exchange strategies must consider the technical complexities of VAD systems, patient's clinical status, and the risks associated with a redo procedure.

Ongoing research is essential to refine surgical techniques and improve outcomes for patients with VAD-associated infections.

Conflict of interest

The authors declare no conflict of interest.

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The Role of Ross Procedure in Aortic Valve Endocarditis

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Abstract

Replacement of the aortic valve is the most common surgical procedure employed across the world for infective endocarditis. Among the various options, the vast majority of patients receive conventional mechanical or stented bioprosthesis. However, when the aortic infection is more extensive, involving the aortic root or the aorto-mitral continuity, the use of aortic homograft is preferred, with the possible alternatives consisting of prosthetic stentless bio-roots or prosthetic valved conduits with mechanical or biological valves. In a very small minority of cases, for localized infections, aortic valve repair has been performed as well. The aortic valve replacement with pulmonary autograft, commonly known to the cardiac surgical community as the Ross procedure (RP), has been performed in infective endocarditis both in the adult and pediatric populations. The Ross procedure, in general, is a more complex surgical procedure, involving two valves, and is particularly recommended in high-volume centers with dedicated surgical expertise. In this chapter, we aim to discuss the role of the Ross procedure in infective endocarditis in adults and children, the indications and contraindications, the risks and benefits, and the results in comparison with the alternative options.

Keywords: aortic valve endocarditis, surgical aortic valve replacement, Ross procedure, adult, pediatric

1. Introduction

Infective endocarditis (IE) is a disease of the endothelium of the heart, typically involving the left-sided valves. It is a rare disease with an annual incidence ranging from 3 to 10 per 100,000 of the population. Despite the improvement in the diagnosis and treatment, the mortality has not changed in the last 20 years, approaching 30% at 1 year. The epidemiology of IE has changed over the years, from young or middle-aged adults to older people, particularly with comorbidities, and with prosthetic valve replacement, indwelling cardiac devices, hemodialysis, intravenous drug abuse, and immunosuppression being the main risk factors. As a consequence, *Staphylococcus aureus* has become the most common cause of IE, as reported in the recent literature. Preventive strategies have been developed worldwide, particularly to avoid health-care-associated IE, with a continuous refinement of the guidelines across different

countries. The medical approach to IE is based on bactericidal antibiotic treatment able to provide microbial clearance and balancing the effect of the treatment with the risk of antibiotic-related toxicity and prolonged hospital stay. Surgical treatment becomes necessary when we find progressive valvar and cardiac tissue destruction, failure of antibiotic treatment to control infection, and risk of embolism. The aim of surgery is to remove all infected valvar and paravalvular tissues, debride abscesses and cavities with the reconstruction of cardiac anatomy, and valvar replacement. Several types of valve prosthesis are available depending on the extent of infection, surgical and center expertise, and clinical profile of the patient, and for the aortic valve, one of them is represented by the RP.

2. The Ross procedure

The Ross procedure (RP) is a surgical technique described more than 50 years ago by Donald Ross in the *Lancet*, where the pulmonary valve (pulmonary autograft) is used to replace a damaged aortic valve [1]. However, extensive research was done earlier by Shumway and colleagues regarding the usage of the pulmonary valve as a substitute for the aortic and mitral valves [2, 3]. A donated human pulmonary valve (pulmonary or aortic homograft/allograft) is then used as a substitute for the pulmonary valve in the vast majority of cases. Ross's personal results were published in 1987 and in 1997, stimulating great interest in the procedure among the surgeons and reaching great popularity between 1990 and 2000 [4, 5]. However, the interest in the RP subsequently declined, reaching only 0.1% of aortic valve replacements (AVR) in the United States in 2010, and in the United Kingdom, between 2007 and 2009, only 2% of young adult patients who underwent elective AVR had an RP [4]. Arguments against the RP were the complexity of the operation with increased operative risk, particularly in small-volume centers; poor long-term outcomes with progressive failure of the aortic autograft or pulmonary homograft, or both; and the complexity of reoperations [5–7]. The lack of recognition of the value of the RP as an excellent option for AVR has been reported by Bonow in his editorial and by Yacoub in many of his publications [8–10]. However, many groups around the world not only continued to routinely perform the RP, but they also tried to understand the new “physiology” created by RP, with the pulmonary valve placed in the systemic circulation, and the modalities of failure of RP. This has pushed surgeons to re-elaborate and modify the surgical techniques, which has brought a reduction of complications experienced in the early years of RP. The great long-term results of RP reported in the last 5 years have therefore renewed the interest in RP, particularly as an excellent option for selected young and middle-aged adults. We need to stress that these data are coming from carefully selected patients and are performed by specialized high-volume centers dedicated to the RP. These centers have established a proper education regarding the RP among cardiologists and surgeons, allowing them to achieve excellent results, and the same education with proctoring is needed for medium- or low-volume centers to reach comparable results. We do not have an ideal aortic valve prosthesis, and despite the success of the transcatheter aortic valve replacement (TAVR), with the recent expansion in patient eligibility, TAVR is commonly not performed in patients below 60 years, where the RP remains an excellent option, as confirmed by recent reports in the literature. Progressive autograft dilation, annular dilation often associated with aortic valve insufficiency, has led the surgical techniques of RP to be progressively refined to prevent these complications. Paradoxically,

the first and most remarkable change was not advantageous in preventing the aforementioned complications, and it involved the implantation of the pulmonary autograft. This changed from its original scalloped “sub-coronary” technique described by Donald Ross to the “mini-root replacement” technique employed by the vast majority of surgeons these days [1]. The great advantage of the original technique is the support to the pulmonary autograft from the native aortic annulus and aortic wall. However, this technique could be technically very challenging, particularly when there is a size discrepancy between the pulmonary valve and the aortic valve, and requires great expertise from the surgeons. The “mini-root” technique is technically easier and reproducible, particularly when learned by a junior surgeon with a much less steep learning curve, but the pulmonary autograft lacks the annular support, resulting in progressive pulmonary autograft dilation. As a consequence, several modifications have been employed to avoid this complication. The so-called “inclusion technique,” where the pulmonary autograft is sutured within the native aortic root or supported within a Dacron tube or similar prosthetic material. In the last 10 years, usage of personalized external aortic root support (PEARS), developed in the United Kingdom and originally created to prevent dilatation of the aortic root in Marfan patients, has been extended to the RP as support for the pulmonary homograft. It involves surgical implantation of a bispaced mesh support modeled around the neo-aortic root and the ascending aorta with excellent long-term outcomes [11]. Furthermore, two more complications of RP were observed and tackled over time: annular dilation, particularly in patients with dilated aortic annulus pre-RP and aortic regurgitation, and distal dilation of the pulmonary autograft in patients with dilated ascending aorta. Solutions regarding the annular dilation were the reduction and fixation of the aortic annulus with sutures or annuloplasty reduction with peri-annular external Dacron. However, there is a general consensus regarding the importance of implanting the autograft within the native aortic annulus, as the pulmonary valve lacks true fibrous support. Regarding the second problem, a Dacron interposition graft or other type of prosthetic material sutured between the pulmonary autograft and the ascending aorta has been used to avoid distal dilation of the autograft. Therefore, considering these possible complications, for a long time it has been common knowledge among physicians that female patients below 50 years old with a small annulus and underlying aortic stenosis are the best candidates for RP. On the contrary, male patients with aortic insufficiency, dilated aortic annulus, and dilated ascending aorta are the worst candidates for RP. However, recent large series reported outstanding short- and long-term results in patients with aortic regurgitation, contradicting the above old-fashioned concepts, although it is always important to identify high-risk patients (dilated annulus $\pm$ aortic regurgitation and dilated ascending aorta) in order to apply these technical refinements [12]. Among less important modifications of RP described over the years, we are citing the one proposed by Elkins and colleagues where the left coronary artery button was not harvested completely but left in continuity with the distal ascending aorta [13]. The Ross procedure offers several advantages in comparison with the other valve prosthetic options for AVR. Compared with mechanical and bioprosthetic valves, which produce an expected obstruction due to the sewing ring, RP has a superb hemodynamic profile with flow patterns similar to normal subjects. However, compared to free-style xenografts and homografts, which are not stented and do not produce the intrinsic obstruction of mechanical and stented bioprosthetic valves, the RP maintains the same hemodynamic profile in the long term, while the gradients across the aortic homograft, for example, rise with time, although performances are similar in the short term.

These long-term performances are related to the pulmonary autograft, which represents the only living substitute to replace the diseased aortic valve, and it undergoes physiological changes due to the adaptation to new conditions created by the systemic pressure [14]. Despite the recent advances in manufacturing mechanical valves, which require a lower level of anticoagulation, these prostheses require lifelong anticoagulation, creating a substantial risk to patients with several complications, including bleeding episodes, thrombo-embolic phenomena, life-threatening complications that range between 1 and 4.5% per patient-year, etc. [15, 16]. With the RP, we can avoid these risks, and the RP is an excellent option for women of childbearing age and for those people who want to avoid anticoagulation for different reasons (occupational/sporting activities, etc.).

However, RP remains a complex surgical procedure with some risks, which are minimized when RP is performed in high-volume centers with known surgical expertise for the RP, and these centers have shown early outcomes similar to standard AVR with prosthesis. On the contrary, small centers reported suboptimal results with up to three times the operative mortality compared to classical AVR. Recently, systemic or pulmonary hypertension has been directly correlated with degeneration of both pulmonary autografts and homografts. These preoperative factors should be sought and treated aggressively in these patients, particularly in the postoperative period, mainly with β -blockers or angiotensin-converting enzyme inhibitors (ACEi) [17]. When aortic regurgitation and ascending aortic dilatation develop after RP, surgery is necessary following the same indications and principles as for a native aortic valve and aorta, although some surgeons have a lower threshold for re-intervening, mainly if the aortic valve is competent. Progressive pulmonary stenosis develops in some patients inside the pulmonary homograft following RP, and intervention is required if right ventricular dilation or dysfunction develops. Nowadays, the percutaneous transcatheter approach with valve insertion after dilation of the homograft is the procedure of choice, with surgery left for cases unsuitable for the percutaneous approach [18, 19]. Oversizing the homograft or choosing pulmonary homografts instead of aortic ones has been adopted by some surgeons in order to increase the longevity of the homograft, while other groups have been using other types of conduits, but we are missing long-term outcomes [20]. In summary, surgical procedures after RP are more complex and troublesome, with higher operative risks, but with better outcomes in high-volume centers.

Patients with prosthetic aortic valves have long-term higher mortality when compared to the matched general population [21–23], while patients with RP have a survival similar to the matched general population [24]. Comparing RP with prosthetic AVR or aortic homograft replacement, the RP showed a considerably higher long-term survival compared to aortic homograft (95 vs. 78% at 13 years), and compared with isolated mechanical prosthesis, RP showed the same early mortality with better survival at 20 years (94 vs. 84%) [25, 26]. Survival after RP was identical to that of the age- and sex-matched general population [26]. A study done in the United Kingdom looking at isolated AVR between 2000 and 2012 demonstrated that RP was associated with the longest event-free survival, better than mechanical replacement and much better than bioprosthetic valve replacement, and once again resulted in a similar survival to the matched general population [27]. There are different perspectives in the pediatric population because small prostheses are not available, and xenografts and homografts degenerate rapidly. Many groups around the world reported in the literature that the RP is the best surgical option in children with severe aortic valve

disease, and, in association with the Konno, when associated with left ventricular outflow tract obstruction [28, 29].

3. Ross procedure for adults with endocarditis

After an initial enthusiasm in the RP, during the years, there has been an underuse of the RP in the adult population. This has been due to the existence of many “simpler” surgical alternatives to the RP [10]. The use of biological tissue valves, mechanical valves, and also aortic homografts as alternative operations to the RP in adults was mainly because of the fast-learning curve compared to the RP, which is a technically demanding operation dealing with the base of the heart, vital structures, and both outlet semilunar valves [10].

The quest for the ideal tissue valve replacement has been an important task for the cardiac surgical community with the intent to find the ideal valve, which could potentially be a lifetime solution. The RP could have the potential to be the ideal long-term solution for the aortic valve due to the excellent hemodynamics and freedom from reoperation on both the left and the right side in the adult population, with data showing restored long-term survival compared with the general population [30, 31]. Since there is strong evidence worldwide now, there has been a reappraisal of the Ross operation in adolescents, young adults, and adults in many centers around the world. In our opinion, the RP is the ideal solution for problems regarding the aortic valve (even severe insufficiency with some technical adjustments) in this group of patients, extending the indication from the pediatric age up to 55 years old. This target population could benefit more in terms of growth, quality of life, and freedom from reoperation. Currently, no other valve substitute can match the results of the RP [31, 32].

Without being too extensive in describing all the benefits of the RP, which are described above and below in the text, we will focus on this paragraph on the use of the RP for IE in the adult population. What is the rationale for utilizing the pulmonary autograft (a living valve) in the aortic position in IE?

To cover this topic, we must remember that in the current era, IE is flourishing with a high incidence in native valves and also in prosthetic valves.

In fact, IE represents a challenging condition with an increasing incidence that reached 13.8 cases per 100,000 subjects per year in 2019 [33], and this rate is expected to be much higher in the near future due to the epidemiology and antibiotic resistance. Despite diagnostic and therapeutic advances, IE is associated with high early and long-term mortality and morbidity, with 14–22% in-hospital mortality rates and up to 50% mortality at 10 years [33, 34]. Surgery is required in 30–50% of the patients affected by IE, and surgical mortality ranges from 15 to 45%. Patients with prosthetic valve endocarditis have an in-hospital mortality rate that is twofold greater with more postoperative complications as compared with patients with native valve endocarditis [33, 34]. Since there are multiple alternatives for the type of valve to use in the setting of native or prosthetic valve endocarditis, actual guidelines recommend a tailored approach for each situation and do not favor any particular valvular substitute [34]. So, accordingly, it is recommended to choose based on multiple factors, thus considering patients preferences, lifestyles, ages, and types of pathology and extension of the IE on the surrounding structures of the left ventricular outflow tract (LVOT) (root abscess, cavitation, septal erosion, mitral involvement with or without left fibrous trigone destruction), surgeon, and center experience.

Also, for aortic valve endocarditis, the use of an autologous living valve is an ideal option in patients who are at high risk for recurrence, including intravenous drug users (IVDU).

In a recent study from Chauvette et al., nonelderly adults (≤ 60 years of age, mean 46 ± 11 years, 81% male) undergoing surgery for aortic valve IE had suboptimal mid-term survival. The aortic valve was replaced with a mechanical prosthesis (44%), a tissue valve (30%), a homograft (18%), or a Ross procedure (9%). Mean follow-up was 6.2 ± 4.6 years (92% complete).

Although non-IVDU patients with native valve endocarditis have better mid-term outcomes, survival remains lower than a matched population of elective AVR in nonelderly patients. RP, compared to the other valve substitutes, showed a trend of better outcome in terms of durability, quality of life, and rate of endocarditis recurrence [35].

Another recent study from Kehara et al. compared the results of the RP for IE to other conventional valve substitutes (biological, mechanical prosthesis, and aortic homograft). Freedom from the composite endpoint of death, reinfection, reoperation, and stroke at 1 and 3 years was $61.8 \pm 12.1\%$ and $46.3 \pm 16.2\%$ in the Ross group, respectively, and was $45.3 \pm 8.5\%$ and $31.1 \pm 8.4\%$ in the other group, respectively. Freedom from the composite endpoint was significantly better in the Ross group than in the other group ($P = 0.04$). The authors concluded that RP appears to be a better option for IE compared with conventional prostheses in the mid-term, but further follow-up is necessary [36].

Similar results, but in the long term, were found by Loobuyck and colleagues [37] and Chauvette and colleagues [38]. Loobuyck reported an estimated overall survival and freedom from recurrent endocarditis or reoperation of $84.2 \pm 6.6\%$ and $89.4 \pm 5.9\%$ at 10 years, respectively, with a median follow-up of 12 years [37]. Chauvette reported that actuarial survival and cumulative incidence of IE recurrence were $88 \pm 8\%$ and $13 \pm 8\%$ at 8 years, respectively. All these demonstrated the superiority of the Ross procedure for IE compared with conventional prostheses [38].

Numerous studies have reported a very low rate of IE after RP, either on the left side or on the right side, with a very low incidence of reoperation for IE after RP, thus adding more evidence in favor of the operation. Sievers et al. found an incidence rate of 0.36% per patient per year in a very large study from the German-Dutch Ross Registry (patients at risk: 2271) [39].

David et al. reported their long-term results of the RP in a cohort of patients followed prospectively for more than two decades. The analyses include 212 patients, and of these, only 7.1% (15 patients, of whom only two had active endocarditis) had an indication for IE. The recurrence of IE on the pulmonary autograft was not observed in this series, but there were only seven cases of IE on the pulmonary homograft at 20 years of follow-up, thus reporting a remarkable result of 96.6% freedom from valve-related endocarditis after RP. In this study, the cumulative mortality at 20 years was 10.8%. The cumulative probability of Ross-related reoperations at 20 years was 16.8%; on the pulmonary autograft, it was 11.5%, and on the pulmonary homograft, it was 8.2% [40].

The development of moderate or severe aortic insufficiency and pulmonary homograft dysfunction increased with time. At 20 years, the probability of aortic insufficiency was 13%, and of pulmonary homograft dysfunction was 19.7%.

Similar results were found by Luciani et al. [32], reporting the very long-term outcomes of the RP in 81 consecutive young patients with aortic valve disease who have reached more than two decades of follow-up. In the series, there were seven

late deaths in 80 hospital survivors (median follow-up 21 years, IQR 20–23), with $88 \pm 5\%$ survival at 25 years. Freedom from autograft reoperation was $46 \pm 6\%$, while freedom from autograft valve replacement was $60 \pm 7\%$, thanks to autograft valve-sparing techniques. Freedom from isolated right valve reoperation was $98\% \pm 4\%$. Young patients undergoing the Ross procedure enjoy unprecedented survival well into the third decade of follow-up, even when faced with reoperation. At 25 years, the risk of autograft reoperation is consistent, while negligible for homograft. Technical improvements at operation and valve-sparing at reoperation may prolong autograft valve durability [32].

Clearly, there is no perfect aortic valve substitute, and aortic valve replacement to treat aortic valve disease is a palliative procedure. Choosing the right substitute for the aortic valve for patients is particularly difficult in young adults and especially children. Both bioprosthetic and mechanical valves are associated with high rates of valve-related complications (bleeding, infections, stroke, structural deterioration, significant mortality at reoperation) [35, 36, 41].

Possible explanations for the survival advantage that the RP offers compared to other alternatives include accurate patient selection, referral to experienced, high-volume cardiac units, and close and regionalized follow-up after surgery. Nonetheless, pulmonary autografts have the ability to restore normal aortic valve and root function, imposing no afterload onto the left ventricle, and to protect from valve-related thromboembolic and hemorrhagic complications. Multiple reports, showing a freedom from cardiac-related mortality of over 90% at 25 years, are a finding still unmatched by any mechanical or biological aortic valve replacement series in young adults [32, 39–42].

Reoperation remains the Achilles heel of the Ross procedure, while other types of cardiac or cardiovascular adverse events are unlikely even when entering the third decade of follow-up. Freedom from autograft reoperation at 25 years in multiple series has proved unsatisfactory, with nearly half of the patients experiencing this complication over time, especially after the second and third decades after RP [32].

Reoperation has occurred mainly on the left side in the young adults, regardless of the technique of implantation of the autograft, root/mini-root vs. subcoronary intra-aortic implant, which are the principal techniques of autograft implant in the young adult. Implantation of the pulmonary autograft in the subcoronary position is more complex than aortic root replacement because it requires a greater knowledge of the functional anatomy of the semilunar valves and the surgeon's ability to match the geometry of the pulmonary valve cusps to a frequently abnormal aortic root. However, even when the aortic root replacement technique is used, the surgeon must apply the principles of functional anatomy to ensure that the diameters of the native aortic annulus and sinotubular junction match those of the pulmonary autograft and that the anatomy of the transplanted pulmonary root is not altered. Furthermore, the pulmonary-ventricular junction (pulmonary annulus) must be placed at the same level as, or immediately beneath, the aorto-ventricular junction, and no foreign material should be used in this anastomosis, especially in the setting of infective endocarditis [32, 40]. In this setting and in the presence of a large abscess of the root, the subcoronary implant could be even more challenging due to the lack of muscle beneath the pulmonary autograft, which should be kept minimal to avoid the quality of the valve implantation over time.

The benefits of external autograft support have recently led to a variety of technical modifications, including synthetic graft encasement of the graft (possibly to be avoided in the setting of IE), allowing the Ross procedure to be extended to patients with bicuspid valves and dilated aortic anuli without incurring a greater risk of

reintervention at 10 years [42]. It is our preference to utilize both techniques based on the anatomy of the patients. When using the root technique, it is crucial to leave the noncoronary sinus intact, the intracoronary pilaster for supporting the new autograft root, and to stabilize the new sinotubular junction by either interposing a vascular graft or a pericardial strip (the so-called supported root technique).

The prevalence of pulmonary homograft dysfunction has been gratifying in most series of RP in young adults, particularly when considering the negligible need for isolated right-heart valve reintervention. This issue is correlated with the use of greater conductors, older patients, and mainly the prevalent use of pulmonary homografts [32].

Regardless of the technique of implantation of the pulmonary autograft, it seems that after a long period of observation, the Ross procedure may eventually fail; thus, performing a regular follow-up in these patients is crucial for depicting the right time for reintervention and thus salvaging the autograft valve. Along with unprecedented survival, free from cardiac mortality, an unsurpassed quality of life is the trademark of the Ross procedure in young patients. The physiologic behavior of the autograft, allowing complete left ventricular remodeling, and the avoidance of oral anticoagulation enable a variety of activities (education, employment, physical exercise, pregnancy) vital in adolescents and young adults. The same are at risk with standard AVR, even in the best scenarios of optimal self-management of oral anticoagulation [10, 30, 32, 40, 42].

In summary, based on the evidence, the RP does have a role in the IE young adult patients, especially in those with active use of IVUDU and in dedicated cardiac units where an experienced Ross team exists. However, for IE, tissue or mechanical aortic valve replacement remains the standard of care in many units unfamiliar with the Ross procedure, with homograft aortic root replacement reserved mainly for those patients with significant periannular and subannular involvement [43].

4. Ross procedure for children with endocarditis

Aortic valve pathology is very common among congenital heart disease, with an incidence of 6% in children with cardiac disease. In the pediatric population, the valve choice can be a challenge due to the size required, the growth of the children, and the durability of the prosthetic valves. Therefore, we are dealing with the same options as for the adult population, and each option has advantages and disadvantages. Mechanical valves, if the size required is available, are durable, and procedures are normally not challenging but require anticoagulation and, as a consequence, increase the risk of life-threatening complications such as hemorrhagic and thromboembolic episodes. Bioprostheses are not routinely used in children because of their poor durability, and the same problem is observed with aortic homografts despite their better hemodynamic performance in the early stage. Furthermore, we should not forget that reoperations are required with the above options because of the development of patient-prosthesis mismatch. The Ross procedure represents a solution to all the problems discussed because it can be performed without size limitations, the pulmonary autograft grows with the patient, lasts longer than bioprostheses and homografts, does not require anticoagulation, and shows low endocarditis risk and excellent hemodynamic performance. However, detractors of the Ross procedure argue that it is a challenging procedure, turning the single valve disease into a double valve disease, with late complications, mainly neo-aortic root dilation with

development of aortic regurgitation, and risk of reintervention. Recent literature has provided us with two robust systematic reviews with meta-analyses focusing only on the Ross procedure in children: Moroi et al. in 2021 and Dib et al. in 2024 [44, 45]. In all reviews, primary end-points were early and late mortality, while secondary end-points were different in the two studies. Moroi reported an early mortality ranging from 0.0–17%, with the higher perioperative mortality associated with the neonatal and infantile groups, while most studies included in this review showed an overall early mortality between 1 and 5%. Dib showed a pooled early survival rate of 96%, and, again, higher mortality was present below the age of 1 year, with a pooled early survival rate of 86.8%. From both reviews, it emerges clearly that some studies included in the reviews consider an age of less than 1 year as a risk of mortality. The results, however, have been improving over the years in this subgroup, but recent analyses have demonstrated a significant correlation between low-volume centers and higher mortality [44]. The two reviews showed a very good late mortality for the Ross procedure in children: 0.04 to 1.83% reported by Moroi and pooled survival rates at 5, 10, and 15 years of 93.2, 91.1, and 90.1%, respectively, reported by Dib. Furthermore, Notenboom et al. from the Takkenberg group published a comprehensive meta-analysis on all pediatric aortic valve replacements supported by a microsimulation study model on life expectancy. In this review, early mortality after Ross was 3.7%, compared to 7.0 and 10.6% for mechanical AVR and homograft AVR, respectively. Pooled late mortality rates after Ross were 0.5%/year compared to 1.0%/year and 1/4%/year for mechanical AVR and homograft AVR, respectively [46]. These results are confirmed by three recent studies that reported a significantly better early and late mortality rate for the Ross procedure when compared with mechanical prosthesis, bioprosthesis, and homograft. Alsoufi et al. showed a superior early ($p < 0.001$) and late mortality ($p = 0.009$) in comparison with mechanical valves, with 2.3 vs. 6.1% in perioperative deaths [47]. Brown et al. reported a cumulative early and late mortality of 4% for the Ross group compared to 17% of other valve options with an actuarial survival rate of 94% at 20 years for the Ross compared to 81% of the non-Ross group, and Sharabiani et al. from the UK remarked on a better survival after the Ross procedure compared to mechanical and bioprosthetic valves, approaching the survival of the general population [48, 49]. In accordance with this statement, Takkenberg et al. reported a 15-year actuarial survival of 93.5% in children with a life expectancy up to 95% of the age- and sex-matched general population, and Sievers et al. declared that survival after the Ross procedure is similar to the age- and gender-matched population [50, 51]. Reoperations represent the long-term issue for the Ross procedure. We should distinguish between autograft and homograft/RVOT intervention. Autograft reinterventions are caused by the development of aortic valve incompetence associated with progressive neo-aortic root dilation. Reintervention rates on the autograft vary across the various studies. Donald et al. reported a freedom from autograft reoperation of 86% at 10 years, with a freedom from autograft reoperation much lower in children younger than 1 year compared to older children (84.4 vs. 97.6% at 5 years), while Nelson et al. showed a higher mortality in infants and neonates but a lower incidence of autograft reoperations when compared with older children [52, 53]. In the two systematic reviews discussed earlier, Moroi reported a neo-aortic failure rate between 0.37 and 2.81% per year, with risk factors being younger age and preoperative regurgitation, and annular dilation [44]. Dib showed a freedom from autograft intervention at 5, 10, and 15 years after the Ross of 96, 90.2, and 79%, respectively, with better but not statistically significant results in children older than 1 year [45]. Notenboom et al. reported an occurrence rate of aortic valve reintervention after the

Ross procedure of 1.3%/year and 1.1%/year in mechanical AVR, while these rates were significantly lower compared to homograft AVR with 4.6%/year [46]. Similarly to the adult group, various surgical techniques have been attempted to avoid the progressive neo-aortic dilation after the Ross procedure in the pediatric population. Among them, we should mention the subcoronary implantation, the inclusion technique, and bands like absorbable poly-(p-dioxanone) (PDS) around the sinu-tubular junction proposed by Tan Tanny et al., which resulted in less aortic insufficiency compared to the non-PDS group [54]. Annular and sinu-tubular junction fixations ± ascending aorta reduction/replacement and tight control of systemic pressure were strongly enforced by Brown et al. with improved outcome compared to their early experience [48].

Regarding reintervention on the homograft/RVOT, Moroi reported an annual failure between 0.34 and 4.76%, mainly caused by stenosis [44]. Younger children, particularly those less than 1 year old, had more reintervention on the homograft/RVOT compared to older children. The same conclusions were shown by Dib et al. in their review, with a freedom from intervention on the RVOT at 5, 10, and 15 years after the Ross of 92.1, 79.7, and 63.5%, but with a rate significantly higher in patients below 1 year ($p < 0.001$) [45]. Notenboom et al. noted that the high overall reintervention rate after the Ross (3.4%/year) was caused mainly by the RVOT reinterventions, with a higher rate in infants compared to older children (6.5%/year vs. 2.3%/year) [46]. Donald et al. had freedom from intervention on the RVOT at 5, 10, and 15 years after the Ross of 87.7, 74.1, and 54.5%, respectively, with age younger than 1 year being a risk factor, and Sharabiani et al.'s findings were also consistent with the above statement [49, 52]. On the contrary, Nelson et al. reported an overall 15-year freedom from RVOT intervention of 53% and the lowest among infants (19%) [53]. Again, strategies to avoid RVOT intervention have been employed, like upsizing the homograft when possible or using a decellularized homograft to diminish the immune response with preservation of the matrix as a scaffold for cellular repopulation. Considering other end-points in these reviews, it must be emphasized that the low thrombogenicity and low bleeding risk of the Ross procedure, also taking into account the avoidance of anticoagulation. More importantly, the Ross procedure has a lower incidence of endocarditis compared to non-Ross AVR (1.7 vs. 10%). In summary, the superiority of the Ross procedure as AVR in the pediatric population is well emphasized in these words from Dr. d'Udekem and colleagues: "There is now no more doubt that the Ross procedure is the best option for valve replacement in the pediatric population. A strategy of primary repair followed by the Ross procedure at a later age seems the only option that appears to be superior to the primary Ross procedure because it provides an increased longevity of the autograft. There is no doubt that the results of this procedure will improve as we have realized what the pitfalls of the technique were and identified the best way to prevent them. We must now figure out the best way to train the existing and future generations of surgeons on the subtleties of this procedure" [55].

There are limited reports in the literature regarding infective endocarditis affecting the aortic valve in the pediatric population and the recommended treatment. The Ross procedure has been widely used in the treatment of aortic valve endocarditis; however, the surgical results have always been mixed with other pathologies treated. Donald et al. reported 11 children (7.9%) among 140 who underwent the Ross procedure for infective endocarditis, with two early and one late death. The early deaths were in children younger than 1 year [52]. Alsoufi and colleagues reported 215 children who underwent the Ross procedure, with 8 (4%) for infective endocarditis, but details about the outcome in this subgroup are unavailable [56]. Binsalamah et al.

published a report on primary aortic root replacement in 206 children. Ninety-eight underwent the Ross procedure, and 5 (5%) for infective endocarditis, with no early or late deaths in this subgroup [57]. Rowe et al., in their analysis of the Ross procedure in children using the Society of Thoracic Surgeons Congenital Heart Surgery Database, reviewed 2805 children, and 2% (n = 56) underwent the Ross procedure for infective endocarditis. Although it does not appear to be a risk factor on the univariate analysis, infective endocarditis is an independent variable associated with operative mortality, neurological deficit persisting at discharge, or acute renal failure requiring a permanent pacemaker on multivariable analysis in this review [58]. Khoo and colleagues, reviewing 30-year experience outcomes for infective endocarditis among 138 children, found the Ross procedure was performed in 12 (8.7%) patients over a total of 39 with aortic valve endocarditis, with an all-valve mortality of 12.8% (5/39) [59]. A valuable contribution to this subject comes from Wu and colleagues. They reported 41 children who underwent aortic valve surgery for infective endocarditis. Ross procedure was performed in 13 (31.7%), and valve repair was the most common surgical procedure (16–39%). The Ross procedure had an operative mortality of 15.4% (2/13), compared to no mortality for the valve repair group, but better than the homograft replacement group (33.3%) and the mechanical valve group (33.3%). The Ross procedure had a freedom from reoperation of 100% at 5 years and 63% at 10 and 15 years, far better than the homograft replacement group, 26.5% at 5 and 10 years, with one early reoperation due to vegetations in the RVOT and three late reoperations, two for RV-PA replacement and one for mechanical aortic valve replacement. Their conclusions are in favor of the Ross procedure when repair is not feasible in infective endocarditis because of its excellent freedom from reoperation. They recommend an ideal approach, particularly for neonates and infants, consisting of a valve repair followed, if necessary, by the Ross procedure. Furthermore, they advocate urgent surgery if vegetation size is ≥ 10 mm, as the risk of embolization is quite high (40%) [60].

5. Discussion/conclusions

The RP is the only valve replacement performed with a living graft. After the initial enthusiasm, the RP usage dropped worldwide for several reasons, like the complexity of the operation, essentially a “two-valve” surgery, durability, and redo-surgery often being very challenging. However, better and more accurate patient selection (age, type of disease, life expectancy, etc.), recent refinements in the surgical expertise able to prevent possible early and late complications, and postoperative care have revamped the RP, particularly in centers where high-volume aortic root surgery is accomplished [60, 61]. From systematic review and meta-analysis literature, it is very evident now that the RP is used mainly in children (often the only possible option), young and middle-aged adults, usually up to the age of 50, and in selected older patients. In these patients, RP demonstrates its greatest advantages. First, the aortic root is replaced with a living substitute structurally and functionally similar to the native one, able to undergo adaptation and therefore having optimal hemodynamic performance, resulting in better long-term viability and, as a consequence, long-term clinical outcome [62]. RP allows avoiding anticoagulation necessary for mechanical valves, with all the thromboembolic complications that follow, making RP also a very good option for women of childbearing age. Another major advantage of the RP is the low rate of long-term related complications, including autograft and homograft deterioration and endocarditis, thromboembolic and

bleeding phenomena. The quality of life is also excellent in RP patients, considering the hemodynamics and the lack of anticoagulation. The drawbacks of RP are the technicality and the risks of the procedure, and the risks of long-term failure of autograft and pulmonary substitute. High-volume centers with great surgeon expertise report a very low mortality with excellent results compared to low-volume centers. Long-term failure of the two valves has been tackled with better patient selection, refinement of surgical technique, and improved postoperative care, particularly with tight control of systemic blood pressure. Furthermore, the challenges of reoperations after RP have been claimed as a substantial drawback for the RP, and again, high-volume centers produce excellent results for this surgery. To highlight the excellent outcome of RP in young and middle-aged patients, we should mention two comparative studies: the first comparing RP with homograft AVR and the second, which looked at all AVR performed in the UK between 2000 and 2012. Both studies demonstrated that the survival after RP was similar to that of the matched general population [25, 27]. The excellent results of RP are evident in the pediatric population as well, and are strongly advised by eminent surgeons as the best option for valve replacement in children.

When we look at the implementation of the RP in infective endocarditis, most of the literature reports mix the outcomes of all the different indications for RP; therefore, the specific results of RP in infective endocarditis are not always available, except in a few studies.

In the pediatric population, Wu and colleagues looked specifically at aortic valve surgery for infective endocarditis in children, where the RP was compared with other procedures, while Khoo et al. just reported the all-valve mortality for children undergoing aortic valve surgery for endocarditis.

In general, RP represents an excellent option for aortic valve replacement in children and young and middle-aged adults, and RP also seems to be a great choice in infective endocarditis of the aortic valve and root.

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Septic Embolism: A Dreaded Complication of Cardiac and Vascular Infections

*Elizabeth C. Stawicki, Julie M. Aultman
and Michael S. Firstenberg*

Abstract

Septic Embolism results in potentially severe clinical consequences and high morbidity rates, especially when associated with infective endocarditis (IE). Often caused by combinations of thrombus and infectious material, either bacterial or fungal, septic embolism (SE) can originate from various infected sites by local or systemic metastasis, but it can also start with primary cardiac valve infections. Several factors, either alone or in combination may lead to increased risk for IE – advanced patient age, the use of prosthetic valves, implantation of various intracardiac devices, intravenous (IV) drug use, and various healthcare associated infections that involve antibiotic resistant strains of bacteria - over the past two decades demonstrated high correlation with IE and SE incidence. In a typical clinical environment, IE may appear as clearly causative, but sometimes it may seem concurrent with the appearance of SE. Septic emboli tend to affect end-organs and organs with “filter-like” structure/function, often featuring a progressive change in vessel diameter (artery-arteriole-capillary-venule-vein). Although septic emboli to a wide range of anatomic locations have been described, most frequently involved organs are the liver, spleen, brain, and lower extremities. As with most infections, management requires prompt recognition, identification of offending microorganism(s), and the initiation of appropriate antibiotic regimen. The wide clinical spectrum of clinical presentation(s) makes diagnosis challenging. Multidisciplinary input requires cardiologists, cardiovascular surgeons, infectious disease specialists, microbiologists, radiologists (including interventional radiologists), and often neurologists. The emergence of complications, which may be severe, brings into the decision-making equation difficult risk-benefit dilemmas revolving around goals-of-care and quality of life determinations. Post identification, both interventional and non-interventional management is dependent on the presence and severity of complications, as well as on the acknowledgment of clinical bias and diagnostic inconsistencies. Aggressive treatment is essential in halting the progression of SE, reduction in morbidity and mortality, and ultimately functional restoration and full recovery.

Keywords: clinical management, ethical considerations, infection, infective endocarditis, management strategy, septic embolism

1. Introduction

The continuous challenges and frequently changing perspectives on IE diagnosis and treatment have evolved significantly since William Osler's discovery and the publication of criteria for infective endocarditis in the late nineteenth century [1]. Over time, the medical community adopted increasingly evidence-based diagnostic paradigms, including von Reyn's criteria, Duke's criteria, and now the Modified Duke's Criteria (MDC and subsequent updates) [2–4]. Despite the historical evidence of both diagnostic value and treatment benefits associated with the earlier published criteria (e.g., von Reyn and original Duke) in categorizing clinical findings, guiding pathological confirmation, and promoting echocardiographic examinations to improve diagnostic accuracy and guide IE management, an over-reliance on blood cultures, echocardiography, and reduced sensitivity in certain patient populations led to the introduction of the MDC [5] and their most recent updates [6]. The current gold standard, the MDC, has its own limitations [3, 7], one of which is the under-diagnosis of right-sided infective endocarditis (RSIE) affecting the tricuspid valve, common in intravenous drug users (IVDU) [8]. Additionally, a more recent surge in IE cases, combined with improved imaging detection suggests that "atypical" presentations and pathogens, device-related infections, and greater prevalence of chronic comorbidities, all appear to concurrently increase in incidence [9–11] and further lead to difficult risk-to-benefit dilemmas in clinical decision-making and patient care.

Recent clinical research shows that nearly half (47%) of IE cases can be considered to be healthcare infections, including hospital-acquired infections (HAI) and post-surgical IE being on the rise, with an associated 29–50% morbidity rate [12, 13] and despite nationwide organizational efforts to lower HAIs. The growth in antibiotic resistance is a notable factor in several population groups affected by IE, including individuals in the 4th to 6th decades of life [14, 15], as well as those suffering from chronic conditions such as renal failure and heart disease, further complicating both the diagnosis and treatment [16, 17]. The latter groups of patients often have a higher prevalence of additional comorbidities, presenting unique confounding factors and detection-related challenges, especially when considered in the context of routine blood cultures, echocardiography, and other non-standard clinical parameters [18, 19].

As microorganisms become increasingly resistant to first-line antibiotics, many infections become more difficult, and at times, impossible to treat [20, 21], especially in the setting of IE and SE. Rise of IE due to heroin usage and IV drug usage in general creates a population not only difficult, and expensive to treat, but often coincides with right-sided infective endocarditis (RSIE), an observed limitation of the MDC-based guidelines [4, 22]. Finally, it is important to recognize in recent years the presentation of IE has become more acute, making diagnosis and treatment more challenging, yet increasingly time-critical [23, 24]. Among key complications of acute IE, the development of potentially devastating SE may be observed in some patient populations. In this chapter, we focus on the pathophysiology, diagnosis, and management of SE in the context of IE, using a systematic anatomic approach that incorporates the most recent developments in this fast-changing area of cardiovascular infectious disease.

2. Pathophysiology of septic embolism

When examining the pathophysiology of SE, the presence of infection, sepsis, and systemic inflammatory response [25–27] are critical findings, followed by the

determination of the site or origin of a suspected infection [28, 29]. Clinicians must quickly identify an active infectious site within the host, correlating it to the bacterial (or fungal) infection, both from anatomical and microbiological standpoints, and looking for all potential sources – “from head to toes” [30–32]. Additionally in the context of IE, any underlying /potential associated factors, such as malignancy, prosthetic implants, among other causes, must be recognized along with any structural alterations of heart valves causing valvular inflammation leading to thromboembolic vegetations [33–35]. Finally, one must recognize the contrast between infectious and non-infectious valvular abnormalities, including important distinctions between “sterile emboli” and IE as a trigger for distant embolic complications (e.g., stroke, ischemic bowel, or acute lower extremity ischemia) [27, 36]. Such differentiation is essential to the immediacy of therapeutic management required in the setting of non-infectious embolism (e.g., stroke) [37]. The presence of infection, any associated inflammation/tissue ischemia, and dysfunctional clotting, significantly changes the therapeutic equation. It also highlights the importance of accurate early (or in some cases immediate) diagnostics and treatment of infectious sources, including any indwelling/implantable devices and other etiologic factors [38]. Because IE can occur in virtually any anatomic part within the human body, many instances – especially mild or asymptomatic ones - often are undiagnosed or only discovered at the height of morbidity [38–40]. This may include both peripheral emboli (e.g., Janeway lesions, splinter hemorrhages, and Osler’s nodes) and Septic Pulmonary Emboli (SPE) present in right sided infective endocarditis [36, 41, 42].

The genesis of SE is predicated on the aggregation of a thrombus in a critical cardiac, predominantly valvular location [43]. Valve endothelium exhibits high structural reliability and an inherent structural resistance to infection [44–46]. However, once a mechanical stressor begins to affect either a native valve, prosthetic valve, or implanted pacemaker lead(s), irretrievable loss of original tissue characteristics may emerge, with exposure of extracellular matrix proteins and resultant local inflammation, accumulation of fibrin and platelets, and subsequent increased vulnerability toward seeding from bloodstream infections [35, 47, 48]. What follows is a negative feedback loop that promotes platelet activation, additional fibrin formation and aggregation, further increasing the risk of subsequent infection [35]. These changes may contribute to the loss of the innate “infection resistance” and thus enable adhesion of bacteria to the endothelial surface, thrombus formation, and the progression of the infected material through adhesins [49, 50]. Thrombin, the product of the coagulation cascade, plays a bridging role in this process, called immunothrombosis [49–51]. Infectious organisms, combined with abnormal coagulation tendency, create an “opportunity window” that enables the emergence of IE and eventually SE (if IE is undiscovered or asymptomatic) [23, 52].

The presence of microorganisms and resultant inflammation attracts further accumulation of fibrin-platelet-microorganism complexes, leading to growth of infectious vegetations [36]. If such vegetations, in whole or in part, are released into the circulation, septic embolization is said to have taken place, either as a singular or pleural event, in various temporal iterations [26, 41]. The most common microorganisms responsible for such complications include methicillin resistant *Staphylococcus aureus* (MRSA) and various “Streptococci” groupings (Viridans group, *S. pyogenes*) with the most prominence in relation to acute IE with increased platelet and fibrin action within vegetative sites [53, 54]. Other microorganisms with lower prominence/incidence in relation to IE include: Enterococci, Pseudomonas, and *Candida albicans*, Beta-hemolytic Streptococcus, and HACEK (seen less frequently in IE cases): *Haemophilus*, *Actinobacteria*, *Cardiobacterium*, *Eikenella*, and *Kingella* [55, 56]. In general, the

occurrence of the above may be associated with the presence of infected pacemaker leads, implanted vascular catheters, prosthetic valves, or some form of anatomic (acquired or congenital) abnormality of the native valve. Bacterial species that feature specific adhesion matrix molecules are particularly prone to attach onto the damaged valvular surface, injured endocardium, or exposed prosthetic material [33, 57–60].

3. Anatomic origins of septic embolism

According to a 2022 study by Venepally et al., the most frequently affected valve was the aortic valve followed by the mitral, tricuspid, and pulmonary valves [61]. Development of SE often starts with bacterial endocarditis colonizing heart valve surface(s), often in patients with predisposing heart valve abnormalities, congenital defects, or in the presence of cardiac implantable electronic devices [57]. Once the initial adherence barrier is overcome, bacteria are able to colonize the valve surface and subsequently form vegetations [62]. Growing vegetations cause flow abnormalities, and if dislodgement of parts or entire vegetation occurs, a vascular obstruction can happen, leading to low blood flow and ischemic damage to downstream structures. In other words, these vegetations can detach and travel as an embolus through the bloodstream to various organs, causing potentially life-threatening sequelae [63].

Bacterial endocarditis, septic thrombophlebitis, periodontal, acute myocardial infarction, and central venous catheter-related SE may occur when bacteria, thrombi, or infected material lodges within distal organs during its systemic (re)circulation, leading to secondary infections typically following IE [64]. Most common of them is bacterial endocarditis, when infectious bacteria form clusters of infected tissue, causing vegetations along the cardiac lining and valves [65]. These vegetations can either stay within the heart or detach from the heart and travel through the bloodstream forming an embolus carried to any part of the body; most commonly the brain, kidneys, lungs, spleen, and lower extremities [66]. Other organs and body systems may also be involved, with associated lower incidence likely due to either asymptomatic presentations, organ-specific vascular tree (and blood flow) characteristics, or simply limited diagnostic accuracy (and thus under-diagnosis) [27]. Thus, it is imperative to enhance diagnostic accuracy and strengthen therapeutic guidelines to improve clinical outcomes. The scope of general diagnostic criteria must be diverse in character in order to properly overcome the diversity of potentially causative abnormalities.

4. General diagnostic considerations

As the landscape of IE diagnostics evolves, especially with the adoption of the Modified Duke Criteria (MDC), the overall framework is becoming much more structured, assisting clinicians in providing a more consistent and prompt treatment window for IE [67, 68]. The MDC remains the cornerstone of diagnosing both IE and SE, relying on major and minor criteria involving clinical, microbiological, and echocardiographic findings [6]. However, the challenges presented by a broad range of atypical cases, such as those with indolent or subacute courses, continue to complicate the diagnostic picture. The Modified Duke Criteria system for IE incorporates the presence of positive blood cultures and characteristic echocardiographic findings (i.e., vegetations), yet there are gaps in sensitivity, particularly in RSIE, where echocardiographic findings may be less pronounced or even absent in a significant

proportion of cases [69]. The failure to detect these cases, especially during the earlier stages of the overall pathophysiological process, due to technical limitations or atypical manifestations represents a persistent and critical diagnostic hurdle.

Additionally, one significant challenge in diagnosing SE is its wide range of possible clinical presentations and associated complications, especially those stemming from embolism involving various organs, such as the brain, kidneys, and lungs [70, 71]. This variability in presentation means that clinicians must maintain a high index of suspicion, especially in the context of these embolic events manifesting with a range of potential symptoms that are often non-specific and may be easily mistaken for representing other conditions [72–74]. This is where multidisciplinary collaboration, including input from cardiovascular experts, infectious disease specialists, and radiologists, becomes essential to ensuring accurate diagnosis and timely and appropriate treatment through shared decision-making.

Blood cultures, while essential for diagnosis of IE and SE, also present a challenge due to their limited sensitivity in certain forms of IE, such as culture-negative endocarditis or cases attributable to fastidious organisms such as *Bartonella* spp., which is a slow-growing, emerging pathogen species that challenges culture-based identification [75, 76]. While the MDC and its more contemporary modifications/updates rely heavily on blood culture positivity, the underdiagnosis or delayed diagnosis of such cases can occur when initial cultures fail to identify the causative pathogen [2, 4]. Therefore, alternative methods such as PCR testing or serological assays are increasingly being recommended to improve diagnostic accuracy [77, 78]. Still, despite significant progress being made, this challenging aspect of diagnosis and confirmatory testing related to IE and SE remains poorly explored and diagnostic technologies remain underdeveloped to improve sensitivity.

Of note, in septic endocarditis, the presence of peripheral manifestations such as Osler's nodes, Janeway lesions, and splinter hemorrhages, while potentially beneficial in the diagnostic context, can also be challenging to interpret, particularly in the early stages [79, 80]. These peripheral or “external” signs are often used as part of the minor criteria in the MDC, but their absence does not rule out the diagnosis [81, 82]. Clinicians must also be mindful of the increased risk of SE in intravenous drug users or immunocompromised patients, as these groups may present with atypical manifestations of SE, making early diagnosis more difficult [23, 83].

In terms of general diagnostic considerations, numerous guidelines and recommendations have been evolving to address the above challenges [84, 85]. Although beyond the scope of the current discussion, certain general aspects of these recommendations warrant a brief mention, such as the importance of timely imaging and the potential need for advanced imaging techniques like transesophageal echocardiography or cardiac MRI, particularly in difficult-to-diagnose cases such as culture-negative endocarditis, subacute or indolent IE, prosthetic valve endocarditis (PVE), fungal endocarditis, endocarditis in the immunocompromised, and RSIE [74, 86, 87]. In addition, prompt initiation of appropriate antimicrobial therapy remains a cornerstone of management, and these guidelines emphasize a stepwise approach to empiric antibiotic therapy while awaiting culture results [33, 85].

5. Septic embolism by affected end-organ

Septic vegetation associated with infectious/SE can metastasize to virtually any part of the body. The most impacted organs tend to consistently receive a significant

amount/percentage of blood supply, prominently including the spleen, liver, kidney, lungs, peripheral (e.g., extremity, bowel) locations, and brain [88, 89]; each associated with their own consecutive long-term outcomes, further contributing to mortality and morbidity associated with IE [27]. Such complications include splenic and renal infarction, hypoxia and pulmonary infarction in the lungs, cerebral mycotic aneurysm, seizure and rare brain abscess, peripheral (extremity) and mesenteric ischemia caused by peripheral embolization [26, 27, 70]. Finally, myocardial infarction events have been described as secondary consequences of coronary SE [90, 91].

5.1 Brain (intracranial)

One of the most frequent sites of septic embolization is the brain, with approximately 1 in 4 cases of infective endocarditis exhibiting cerebral involvement [92, 93]. Septic emboli lodging (and blocking or flow-limiting) cerebral arteries lead to distal ischemia, resulting in potential brain infarction. Septic cerebral emboli could result in ischemic stroke, brain abscess, seizures, and other neurological impairments commonly manifest with a broad range of infectious and non-infectious central nervous system pathologies [93, 94]. Following an ischemic infarction, there is a very real risk of conversion to hemorrhagic infarction, especially if anticoagulants are being used [95–97]. Long-term cognitive and motor impairments may present depending on the exact anatomic location and volume of the affected (e.g., infarcted) brain tissue [98, 99].

Sequelae of SE involving the central nervous systems (CNS) can be categorized into two general types based on the mechanism(s) and affected cerebral structures: cerebrovascular events (e.g., stroke) and other CNS complications (e.g., brain abscess, seizure) [100, 101]. Cerebrovascular events require prompt recognition, accurate anatomic diagnosis, and immediate treatment to prevent additional short- and long-term complications [102]. These events primarily involve hemorrhagic and ischemic strokes due to septic emboli blocking blood flow or leading to blood vessel ruptures [91]. On the other hand, non-hemorrhagic CNS events primarily include brain (and adjacent) abscesses, encephalitis/meningitis, hydrocephalus, and seizures [94, 103]. Although the clinical management focus is different and distinct from cerebrovascular events, the other (non-cerebrovascular) CNS events also require prompt recognition and treatment, as their associated mortality and morbidity rates may be lower with appropriate and timely therapeutic intervention.

5.2 Lungs

Septic pulmonary embolism (SPE) is a rare type of pulmonary embolism (PE) that leads to potentially severe complications and may be life-threatening, similar to the more commonly seen venous thrombo-embolic disease [104]. This type of SE is associated with bloodstream infections where an infected thrombus dislodges from the central vascular system and embolizes to the pulmonary artery. In addition, SE traversing the central venous system may also take on the appearance of primary embolism associated with infective endocarditis when cardiac septal defect is present [105, 106]. SPE may occur in the setting of indwelling central venous catheters and pacemakers, when the patient is high risk for infective endocarditis, and right-sided heart infections [107]. In cases of SPE, tissue damage may include localized tissue ischemia, secondary inflammation, as well as the more traditional cardio-pulmonary manifestations typically seen with venous thromboembolism [71]. Longer-term, pulmonary abscess may emerge [83]. Initial

symptoms may be nonspecific due to diagnostic overlap with various other cardiac, pulmonary and infectious conditions. Patients may present with shortness of breath, tachypnea, pleuritic chest pain, and other more severe symptoms up to and including hemoptysis and cardio-pulmonary collapse [108, 109]. Patients with preexisting lung or heart disease are particularly vulnerable to worsening respiratory function and other associated complications.

5.3 Abdomen and retroperitoneum: Kidney, spleen and pancreas

SE involving abdominal and retroperitoneal regions typically affects the kidneys and spleen [70]. Overall, splenic infarctions are observed in 6.8% of patients with IE and renal embolism in about 2.9% of cases. Both occurrences can lead to organ dysfunction, pain, abscess and potentially organ failure [41, 110]. The spleen is the most frequent abdominal site for SE, often leading to pain, potential secondary hemorrhage, and splenic abscess, requiring procedural (percutaneous or surgical) drainage to prevent the escalation of systemic infection [41]. Renal involvement often presents with hematuria, glomerulonephritis, and in more severe cases, renal failure [111]. Renal abscess may also develop [111]. Although technically intra-abdominal, SE involving the bowel will be discussed alongside other “peripheral” anatomic locations in the next section. Overall, pancreatic involvement is thought to be rare, with clinical manifestations similar to those of acute pancreatitis (see additional information below).

5.4 Peripheral (extremity) and mesenteric septic emboli

Peripheral embolization events, affecting extremities and the bowel, leading to distal ischemia and potential tissue infarction, are also relatively common complications of infective endocarditis [112]. Acute mesenteric ischemia (AMI) is associated with SE that dislodges and travels to mesenteric arterial arcades, usually manifesting as distal ischemia and resulting in segmental bowel infarction. Prompt recognition and operative intervention is required to prevent bowel necrosis, peritonitis with septic shock and multi-organ failure, and subsequent mortality [113, 114]. Similar general observations apply to omental septic emboli and ischemic sequelae thereof.

Distal extremity locations share physiological similarities to mesenteric locations, in that without prompt recognition and treatment, the risk of distal ischemia and tissue necrosis is significant, and larger (and thus more proximal) arterial extremity septic emboli will result in non-viable extremity without emergent intervention [115, 116]. In less extreme cases, embolic “showering” of distal tissues results in patchy ischemia, with or without tissue and/or functional loss [117, 118].

5.5 Other organs and organ systems

A detailed discussion of all organs and organ systems that can be potentially involved in SE secondary to infective endocarditis is beyond the scope of this chapter. However, for the reader's benefit, we do provide a general overview of all previously recognized and described published instances of less commonly involved organs and organ systems. The above may include SE involving the pancreas (with pancreatitis-like symptoms); the liver (usually presenting as transaminemia, likely with associated abscess); the eye (presenting as blindness or visual disturbances); and cutaneous (mentioned in previous sections) [26, 41, 119, 120].

6. General therapeutic guidelines

Multidisciplinary approaches are paramount when treating the often highly complex patients with SE and associated complications, including significant critical care needs and resources [26, 90]. After initial microbiology studies are obtained, immediate treatment with broad-spectrum, intravenous antibiotics, is mandatory; however, in certain cases where diagnostic data supports more aggressive management, prompt surgical treatment (cardiac, non-cardiac, or both) may be indicated and necessary [27, 85]. Various expert professional guidelines provide a useful and practical framework regarding which patients require immediate surgical intervention [121–123]. Of importance, patients with IE who develop acutely decreased ejection fraction or a new aortic or mitral valve murmur require immediate surgery [121–123]. Patients with preserved ejection fraction who are stable and adequately managed on medical therapy may not require immediate surgical intervention, but this may change. More patients may be offered and opt for surgical interventions when presented with a more precise diagnostic determination, lower risk of surgical interventions, and a clearer understanding of long-term consequences if/when surgery is postponed. More specifically, it has been shown that surgical intervention in the setting of new congestive heart failure can reduce mortality by approximately half when compared to medical therapy alone, with improved overall cure rates [33, 90]. In general, patients who present with valvular/intracardiac vegetations greater than 10 mm, or with multiple vegetations on imaging, will require surgery [124, 125].

Another important indication for surgery is lack of improvement after 5–7 days of appropriate antibiotic therapy [126, 127]. Any septic emboli to end organs or mycotic aneurysms within the arterial circulation also warrant prompt surgical intervention [128, 129]. As mentioned earlier in the chapter, emboli to different organs may require different timings in surgical intervention. Finally, the last major set of surgical indications we will consider is for prosthetic valve endocarditis (PVE) and for endocarditis in the setting of various indwelling cardiovascular devices [130–132]. Regarding the former (PVE), treating surgeons may encounter a unique set of challenges. More specifically, patients who develop PVE within 60 days of valve implantation are at increased risk for severe infection, often requiring surgical intervention. In these cases, early valve replacement may be necessary to control the infection and restore normal cardiac function [133, 134]. In addition, for patients with PVE, prolonged or ineffective antibiotic therapy can lead to significant complications, making early intervention preferable [135, 136].

Embolic events to end organs, such as the brain, kidneys, or lungs, also warrant immediate procedural (e.g., surgical or percutaneous) intervention, especially when they are associated with significant damage to the affected organ or risk of further embolism [41, 70]. Embolic phenomena can lead to devastating consequences, including strokes, organ infarction, or abscess formation, and surgical management is critical to reduce long-term morbidity and mortality [26, 27, 70]. As noted earlier in this chapter, the timing of surgery can vary depending on the organ affected, with prompt intervention being important in preventing further embolic damage depending on the probability of improving patient outcomes and overall quality of life.

7. New developments in septic embolism

Recent literature on the topics of IE and SE emphasizes the increasing importance of multidisciplinary treatment approaches, with some evidence suggesting

improved outcomes and reduction in morbidity and mortality, while providing the most effective treatment possible [137]. Another important trend in contemporary literature is the increase in the relative incidence of staphylococci, which can be attributed to a decrease in the incidence of rheumatic heart disease and a general increase in invasive procedures [138, 139].

On the diagnostic and risk assessment front, the European Society of Cardiology in partnership with the International Society for Cardiovascular Infectious disease (ISCVID) made important improvements in sensitivity to Duke's clinical criteria from 2015 to 2023 in IE diagnostics [140]. Finally, it is important to mention the ever increasing problem of IVDU and the associated propensity toward IE. There are significant efforts being implemented to address both the IVDU epidemic and to improve the safety and hygiene associated with IVDU, to help reduce the incidence of infective endocarditis (and thus its many complications, including septic emboli) [141, 142].

8. Conclusions

Despite significant clinical research and overall progress, SE associated with infective 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 IE and SE has followed suit. We hope that we successfully outlined general pathophysiologic and anatomic considerations of IE and SE with which all physicians should be familiar to guide diagnostic and treatment decisions, to better educate patients who may seek intervention much earlier, and to improve overall patient outcomes. Given the persistently high rates of associated disability and mortality, more research is needed to better understand and treat IE, SE, and various potentially devastating, associated complications.

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Management of Infective Endocarditis with Heart Failure and Role of Mechanical Circulatory Support

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Abstract

Infective endocarditis (IE) is a life-threatening condition that includes a complex interplay between sepsis and heart failure (HF), highlighting the challenges in diagnosing and managing these concomitant conditions. We will highlight the bidirectional relation between IE and HF, emphasizing the importance of multimodal and multidisciplinary approaches in identifying and managing IE with HF. We will discuss the potential role of mechanical circulatory support, especially extracorporeal membrane oxygenation, in managing patients with IE. Surgical intervention can be a life-saving option in complicated cases with IE, however, cardiovascular failure carries high risks of operative mortality. So, a multidisciplinary approach is crucial to considering the benefits and risks of surgery and the appropriateness of MCS.

Keywords: infective endocarditis, mechanical circulatory support, heart failure, cardiogenic shock, septic shock, sepsis, extracorporeal membrane oxygenation

1. Introduction

Infective endocarditis (IE) is a complex and life-threatening infection of the endocardial surface of the heart, including the heart valves, myocardium, and great vessels. IE can lead to devastating complications, including heart failure, embolic events, and mortality [1]. The coexistence of heart failure (HF) and IE presents a formidable clinical challenge, significantly worsening prognosis and complicating management. Up to 50% of IE cases can involve acute or chronic HF, while pre-existing HF predisposes patients to IE by fostering turbulent blood flow, endothelial damage, and immune dysregulation [2]. The management of IE requires a multidisciplinary management, involving cardiologists, infectious disease specialists, cardiothoracic surgeons, and intensivists. This chapter will provide an overview of the diagnosis and management of IE, highlighting the role of mechanical circulatory support which is

still debatable. The intersection of IE and HF necessitates a comprehensive understanding of their pathophysiology, diagnostic challenges, and therapeutic strategies.

2. Epidemiology

The reported worldwide incidence of IE was 13.8 cases per 100,000 persons per year with approximately 66,300 deaths [3, 4]. There are huge variations in the incidence, and mortality of IE across age groups, different regions of the world, and even within the same country which may be attributed to timing of diagnosis, appropriate management, and quality of care [3, 5]. The improvement of diagnostic tools resulted in increased rates of diagnosis of IE [4]. The use of cardiac devices, such as transcatheter valves, mitral clips, and implantable electronic devices including pacemakers and defibrillators, has revolutionized the treatment of structural and conduction abnormalities. However, these devices are associated with a growing incidence of device-related infective endocarditis (DRIE), which carries a high morbidity and mortality [4, 6].

3. Pathophysiology and clinical presentations

3.1 Bidirectional relationship

3.1.1 IE Leading to HF

- **Valvular destruction:** Vegetations on heart valves can cause severe regurgitation or stenosis, rapidly leading to left ventricular (LV) volume overload, pulmonary congestion, and systemic hypotension. Left-sided valves, particularly the aortic and mitral, are involved in most cases while right-sided valve vegetations are usually better tolerated [4, 7].
- **Sepsis-induced myocardial suppression:** Sepsis, presents in 30–50% of IE patients, impairs myocardial function through cytokine-mediated depression of contractility, mitochondrial dysfunction, and altered calcium signaling [8, 9].

3.1.2 HF predisposing to IE

- **Prosthetic valves and devices:** Prosthetic valves carry an annual IE risk of 1.5–2.5%, with *Staphylococcus aureus* and *Enterococcus faecalis* being the leading pathogens [4].
- **Immune dysregulation:** Chronic HF promotes gut dysbiosis and systemic inflammation, increasing susceptibility to bloodstream infections [7].

3.2 Mechanisms of heart failure

- **Acute valve regurgitation:** Rapid destruction of the valve leads to abrupt hemodynamic changes, including LV volume overload and cardiogenic shock. Mitral valve involvement is associated with rapid pulmonary edema, while acute aortic regurgitation can cause sudden LV decompensation [4].

- Sepsis-associated myocardial dysfunction: Elevated cytokines (e.g., IL-1, TNF- α) disrupt mitochondrial ATP production, reducing myocardial energy reserves [10].

3.3 Acute versus chronic heart failure

3.3.1 Acute HF in IE

- Presentation: Acute HF manifests with dyspnea, pulmonary edema, and hemodynamic collapse. It is often triggered by severe mitral or aortic regurgitation or septic shock.
- Management challenges: Differentiating sepsis-induced myocardial depression from valve-related HF is essential, as these require distinct management strategies. Surgical Indications: Approximately 80% of acute HF cases in IE necessitate urgent valve surgery to restore hemodynamic stability [4].

3.3.2 Chronic HF in IE

- Presentation: Chronic HF in IE develops insidiously, often in patients with recurrent IE or prosthetic valve infections. Symptoms include fatigue, fluid retention, and progressive dyspnea.
- Management: Long-term management requires adherence to ESC and AHA/ACC guidelines for HF, combined with prolonged antibiotic therapy to prevent recurrent infections [11].

4. Management

Managing HF in IE requires a multifaceted approach that balances hemodynamic stabilization, infection control, and long-term HF therapy. This section explores strategies for acute and chronic HF, with an emphasis on mechanical circulatory support (MCS) and evidence-based HF therapies.

The overlapping symptoms of HF and IE complicate diagnosis. Patients may present with fever, fatigue, and signs of decompensated HF such as dyspnea and orthopnea. Early suspicion is vital, particularly in patients with prosthetic valves, recent invasive procedures, or a history of intravenous drug use. The modified Duke criteria, while foundational, should be supplemented by a multidisciplinary approach for timely and accurate diagnosis [4].

4.1 Hemodynamic stabilization

Invasive hemodynamic monitoring using central venous catheterization, arterial catheterization, and serial blood gases analysis with close hemodynamic monitoring is crucial to early detect any deterioration and early start vasoactive drugs. Norepinephrine is the vasopressor of choice in patients with vasoplegia while dobutamine and epinephrine are used in patients with low cardiac output. Pulmonary artery catheterization helps to differentiate the hemodynamic profile due to cardiogenic shock (CS) or septic shock [12, 13]. Using blood lactate measurements,

oxygen-derived variables, and carbon dioxide gap during resuscitation helps to detect outcomes [14]. Invasive hemodynamic monitoring with vasoactive drug therapy helps to identify patients who need surgery and who will benefit from MCS.

4.2 Diagnostic modalities

- The diagnosis of IE in patients with HF requires a meticulous, multimodal approach, integrating patients' characteristics, clinical evaluation, laboratory markers, and imaging techniques. By understanding the complexities of this diagnostic process, healthcare providers can improve patient outcomes by ensuring timely and accurate identification of these intertwined conditions. Early multidisciplinary consultations including cardiologists, infectious disease specialists, and other relevant experts can help to guide the diagnostic process.
- Duke Criteria were defined in 1994 and modified in 2000 to be a widely accepted diagnostic framework, consisting of two major and five minor criteria. Major Criteria: Evidence of endocardial involvement (e.g., echocardiography, cardiac MRI) and Positive blood culture for IE. Minor Criteria: Fever $\geq 38^{\circ}\text{C}$, Microbiological evidence (e.g., positive serology), Immunological phenomena (e.g., glomerulonephritis, Osler's nodes), Vascular phenomena (e.g., mycotic aneurysm, embolism), and Echocardiographic findings (e.g., vegetations, abscesses) [15, 16]. Due to advances in diagnostic microbiology and imaging modalities, Duke criteria were modified, and new criteria were added including intra-operative evidence of IE as one of the major criteria of IE [4, 17].
- Imaging studies: Transthoracic echocardiography (TTE) is used for the assessment of cardiac functions and valves while transesophageal echocardiography (TEE) gives a more detailed evaluation, especially in prosthetic valve and device endocarditis. Echocardiography is crucial for identifying vegetation characteristics and local complications and following up during medical and peri-operative management [4, 18]. Recent guidelines recommended TTE as class IB initial diagnostic modality for patients with suspected IE and TEE as class IB in case of negative TTE or in patients with prosthetic valve or intra-cardiac device [4]. Cardiac computed tomography (CT) has been recommended as class IB in patients with prosthetic valve endocarditis (PVE) or native valve endocarditis (NVE) to diagnose the extent of valvular and perivalvular damage, especially in patients with surgical plan [4]. Positron emission tomography (PET) with fluorodeoxyglucose (FDG) has been recommended as class IB for NVE and PVE due to its diagnostic criteria, detect biofilms on cardiac devices and detect metastatic infections [4, 19]. Cardiac magnetic resonance imaging (MRI) has a limited diagnostic value compared to cardiac CT scanning and has limitations in patients with MRI-incompatible cardiac devices. However, brain MRI is useful to detect microbleeds and metastatic emboli especially in asymptomatic patients and in patients with unconfirmed IE diagnosis [4, 20, 21].

4.3 Antibiotic therapy

- Empiric therapy: Empiric antimicrobial therapy should cover common IE pathogens such as *Staphylococcus aureus*, viridans group streptococci, and Enterococcus. Vancomycin combined with ceftriaxone or gentamicin is

frequently employed as initial therapy, particularly in patients with a high risk of methicillin-resistant *S. aureus* (MRSA). In prosthetic valve IE, rifampin may be added to enhance biofilm penetration. The 3 sets of blood cultures should be drawn before the antibiotic therapy.

- Targeted therapy for resistant organisms: Once culture results are available, therapy should be modified according to the identified pathogen:
 - For MRSA: Vancomycin or daptomycin.
 - For vancomycin-resistant enterococci (VRE): Linezolid or daptomycin, with gentamicin in selected cases.
 - For culture-negative IE: Coverage should include *Coxiella burnetii*, *Bartonella spp.*, and fungal pathogens based on clinical suspicion and epidemiology.
- Duration of antibiotics course is 4–6 weeks in most cases, and close monitoring of renal functions should be done to avoid renal toxicity, especially in patients with HF [4].

4.4 Removal of infection source

Any patient admitted with IE should be managed by a multidisciplinary team to get the appropriate plan according to clinical and hemodynamic state. After hemodynamic stabilization and antibiotic therapy, removal of infected tissues is crucial including valves and pacemaker leads. The timing of surgical intervention depends on the clinical profile, echocardiographic findings, presence of neurological manifestations, and response to antibiotics. Emergency surgery within 24 hours has been recommended (Class IB) for patients who have mitral or aortic IE complicated with refractory cardiogenic shock. Urgent surgery within 3–5 days has been recommended (Class IB) for patients with left-sided IE and heart failure or uncontrolled local infection like abscess, large vegetations ≥ 10 mm, valve dehiscence, and new heart block [4]. Surgery for right-sided IE has been recommended in case of acute tricuspid regurgitation with right ventricular failure (Class IB), recurrent pulmonary emboli requiring ventilatory support (Class IB), tricuspid vegetations ≥ 20 mm (Class IC), and simultaneous left-sided IE (Class IC). Tricuspid repair has been recommended (Class IIa) than tricuspid valve replacement [4].

5. Role of mechanical circulatory support

5.1 Use of ECMO in severe life-threatening infections

Sepsis is a life-threatening dysregulated immune response to infection that can proceed to macro- and microcirculatory disturbances, impaired oxygen delivery, tissue hypoxemia, progressive lactatemia, multi-organ system failure, and high mortality [22]. Extracorporeal membrane oxygenation (ECMO) had been increasingly used to support circulation and ventilation as a rescue measure giving the clinicians enough time for decision-making and definite treatment. However, the benefits of ECMO are still debatable in patients with sepsis [23, 24]. There is a paucity of solid data about

Studies	Patients, study period	ECMO configuration	Source of sepsis	Organisms	outcomes
Cheng et al. [25]	151, 2001–2011, Median age: 51 (37,63) years SOFA score: 12.6 ± 4.6 Initial lactate: 7.2 ± 5.3 mmol/L	VA: 50 (33.1%) VV: 101 (66.9%) 24.5% of patients had cardiac arrest before ECMO. 19.2% had ECPR.	Respiratory: 76% Primary bacteremia: 22% Positive blood culture: 31.1% Abdominal: 12% Infectious myocarditis: 30%	GPC: 17.2% GNB: 33.8% Fungi: 6.6% Viruses: 17.2% Polymicrobial: 10.6%	ECMO removal: 68% Hospital survival: 29.8% Better outcomes were linked to respiratory sepsis rather than primary bacteremia and Gram-positive rather than Gram-negative sepsis.
Park et al. [26]	32, 2005–2013, Median age: 55 (44,63) years SOFA score: 16 (14,18) initial lactate: 8.9 (5.8,14.6) mmol/L	All received VA-ECMO. 14 (43.8%) had cardiac arrest before ECMO. 7 (21.9%) had ECPR	Respiratory: 34.4% Urinary: 12.5% Abdominal: 21.9% Positive blood culture: 62.5% Others: 31.2%	GPC: 34.4% GNB: 47% Fungi: 15.6%	Hospital survival: 21.9% 31.3% of patients received ECMO after ≥ 30.5 h of septic shock and died Predictors of mortality: CPR, CPR duration, SOFA score, and troponin peak level > 15 ng/mL.
Bréchet et al. [27]	14, 2008–2011 Median age: 45 (28,66) years SOFA: 18 (8,21) Lactate: 9 (2,17) mmol/L	All started VA. 5 cases converted to VV-ECMO. No cardiac arrest before ECMO.	Respiratory: 78.6% Positive blood cultures: 35.7% Abdominal: 14.3% Others: 7.1%	GPC: 64.3% GNB: 28.5% Fungi: 0%	Hospital survival: 71%
Huang et al. [28]	52, 2005–2010, Median age: 56.8 (42.7–63.6) years SOFA: 16 (13–18). Median lactate: 5.3 and 8.8 mmol/L in survivors and non-survivors, respectively.	VA-ECMO. 21 (40%) had ECPR	Respiratory: 48.1% Urinary: 9.62% Abdominal: 21.2% Others: 21.2% Positive blood culture: 44.2%	GNB: 59.62% GPC: 26.9% Fungi: 9.62% Others: 5.8%	Hospital survival: 15%
Choi et al. [29]	28, 2007–2013, Median age: 44 (33.5,67) years. SOFA: 15 (13,17). Lactate: 5.9 (4,9.5) mmol/L	VA: 21 (75%) VV: 4 (14.2%) V-VA: 3 (10.7) 14 (50%) had cardiac arrest. 6 (21.4%) ECPR.	Respiratory: 46.4% Urinary: 71% Abdominal: 14.3% Others: 32.1% Positive blood culture: 39.3%	GNB: 53.6% GPC: 35.7% Fungi: 3.6% Others: 32.1%	Hospital survival: 35.7% SAPS II < 80 was linked to better survival Acute Lower limb ischemia: 71% Acute kidney injury: 71.4% hypoxic brain injury: 71%
Vogel et al. [30]	12, 2014–2017, Age: 40.5 (23.75,50) years SOFA: 10 (7.5,11.25) Lac: 5.0 (3.85,6.05) mmol/L	VAV: 7 (58.3%) VV converted to VAV-ECMO: 5 (41.7%) 5 (41.7%) had cardiac arrest. No ECPR.	All cases had septic cardiomyopathy with a median LVEF: 16.25% (13.13,17.5).	NA	Hospital survival: 75%

Studies	Patients, study period	ECMO configuration	Source of sepsis	Organisms	outcomes
Yeo et al. [31]	8, 2013–2015, Median age: 50.9 (18,71) years Lactate: 7.8 (6.3,16.3) mmol/L	V-VA No cardiac arrest before ECMO. All patients had severe ARDS with a baseline median PaO ₂ /FiO ₂ : 57 (51.3,76.2)	Respiratory: 62.5% Others: 37.5%	NA	Hospital survival: 50%
Han et al. [32]	23, 2007–2017, Mean age: 56.0 (±12.3) years Median SOFA: 12 (10,13) in survivors, and 15 (13,18.3) in non-survivors. Median lactate: 4.4 (2.2,7.4) in survivors, and 6.8 (5.5,8.9) mmol/L in non-survivors.	All VA-ECMO No cardiac arrest before ECMO.	NA	GPC: 30.4% GNB: 8.7% Fungi: 4.3% Others: 56.6%	Hospital survival: 21.7%
Myers et al. [33]	32, 2009–2016, Median age: 46 (30,58) years Mean SOFA (95%CI): VV 8.9 (7.7–10.1) in VV, and 11.4 (9.7–13) in VA cases Mean lactate (95% CI): 71 (4.7–9.0) in VV, and 71 (2.4–6) mmol/L in VA cases.	VA 11(34.4%) VV 21(65.6) 12 (38%) had cardiac arrest. Mean PaO ₂ /FiO ₂ (95%CI):90 (52–128) in VA cases, and 65 (50–81) in VV cases	Respiratory: 72% Others:28%	NA	Hospital survival: 41%
Ro et al. [34]	71, 2005–2012, Age: 56.0(± 12.3) years SOFA:18.2(± 4.0) median lactate: 5.8 (4.3,5.9) mmol/L in survivors, and 11.6 (7.5,15.0) mmol/L in non-survivors.	VA-ECMO 9 (12.7%) had cardiac arrest. No ECPR	Respiratory: 69% Urinary: 5.23% Abdominal: 11.3% Primary bacteremia: 14.1% Positive blood culture: 42.3%	GPC: 19.7% GNB: 59.2% Fungi: 14.1% Mycobacteria: 5.6%	Hospital survival:7%
Banjas et al. [35]	From a total of 131, 19 patients had ECMO for septic shock, 2011–2016, Median age: 62 (55,73) years Median lactate: 5 (2,11) mmol/L median SOFA: 8 (6,12)	V-VA-ECMO 3 (16%) had cardiac arrest.	Respiratory: 52.6% Abdominal: 41.1% Soft tissue infections: 5.26%	NA	Hospital survival: 42%

Studies	Patients, study period	ECMO configuration	Source of sepsis	Organisms	outcomes
Bréhot et al. [36]	82, 2008–2018, Age: 48(±15) years Lactate: 8.9(±4.4) mmol/L SOFA: 16.6(±2.9)	VA: 62 (75.6%) V-AV: 8(9.76%) VV converted to VA: 12 (14.6%) No cardiac arrest before ECMO.	NA	NA	3-months survival: 60% ECMO decreased mortality [adjusted RR: 0.57, p = 0.0029]
Kim et al. [37]	37, 2007–2015, Median age: 51(35.5,64.5) years median SOFA:15(13,17)	VA 26 (70.3%) VV 8 (21.6%) V-VA 3(8.1%) 18 (48.6%) had cardiac arrest. 8 (21.6%) had ECPR.	Respiratory: 45.9% Abdominal: 13.5% Soft tissue: 13.5% Others: 27% Positive blood culture: 51.4%	GPC: 16.2% GNB: 43.2% Others: 40.5%	Hospital survival: 40.5%
Falk et al. [38]	37, 2012–2017 Age: 55 (45,66) years Lactate: 7 (3.6,10.5) mmol/L SOFA: 16 (15,18)	VA: 27(72.97%) VV: 4(10.8%) VV converted to VA: 6(16.2%) 7 (18.9%) had cardiac arrest. No ECPR.	NA	NA	Hospital survival was 64.7% in cases with distributive shock and 90% for septic cardiomyopathy.
Zha et al. [39]	31, 2017–2021, Mean age: 55(±24) years Mean lactate: 2.31(±2.64) mmol/L mean SOFA: 12(±3)	AI/VV-ECMO No cardiac arrest before ECMO.	Respiratory: 100% Positive blood culture: 45.2%	GPC: 6.5% GNB: 64.5% Fungi: 9.7% Viruses: 3.2% Others: 16.2%	30-day mortality: 38.7% 90-day mortality: 51.6%
Takauji et al. [40]	40, 2011–2013, Age: 66(±12) years Median APACHE II: 28 (21,33) Median SOFA: 13 (10,15) Median lactate: 3.4 (1.9,9) mmol/L	AI/VV-ECMO No cardiac arrest before ECMO.	Respiratory: 62.5% Non-respiratory: 375% Positive blood culture: 47.5%	GPC: 22.5% GNB: 20% Fungi: 5% Viruses: 2.5% Others: 50%	Hospital survival: 47.5%

APACHE, Acute Physiology and Chronic Health Evaluation; SAPS II, Simplified Acute Physiology Score II; CI, Confidence Interval; RR, Relative Risk; VV, Veno-venous; VA, Veno-arterial; ECPR, extracorporeal cardiopulmonary resuscitation; GNB, Gram-negative bacilli; GPC, Gram-positive cocci; SOFA, Sequential Organ Assessment Failure.

Table 1.
Studies of ECMO in septic shock.

outcomes with ECMO use in sepsis due to heterogeneity of study designs and indications of ECMO support and cardiac functions with sepsis. We reviewed the studies of ECMO use in sepsis and summarized the most significant variables in **Table 1** [25–40].

5.2 Indications of ECMO support in patients with sepsis

5.2.1 Sepsis with respiratory failure

Acute respiratory distress syndrome (ARDS) can occur with severe infections due to direct lung infections, septic pulmonary emboli, or as a part of the systemic inflammatory response syndrome (SIRS). For patients who fail to improve and exhibit refractory hypoxemia $\pm$ hypercapnia despite protective lung ventilation, recruitment maneuvers, and prone positioning, veno-venous ECMO (VV-ECMO) may be a life-saving solution [41].

5.2.2 Sepsis with ARDS and hemodynamic instability

Patients with ARDS may exhibit right ventricular dysfunction due to mechanical ventilation, hypoxemia, and hypercapnia resulting in vasoconstriction and microthrombosis of pulmonary circulation. Moreover, acidosis impairs cardiac contractility and vascular tone necessitating inotropic support [41, 42]. The underlying sepsis etiology may necessitate high vasopressor support. All these conditions may require respiratory and circulatory mechanical support like veno-arterial ECMO (VA-ECMO) or adding arterial cannula to the VV-ECMO to set V-VA configuration. Right ventricular assist device (RVAD)-ECMO configuration with the Protek Duo cannula draining blood from right atrium to the pulmonary artery is another promising option proving pulmonary and RV support [43, 44].

5.2.3 Sepsis with heart failure

Patients with sepsis can develop different patterns of hemodynamic collapse due to ARDS-related RV failure, low systemic vascular resistance (SVR) distributive shock, sepsis-induced myocardial depression, and mechanical complications of IE [45, 46]. Careful assessment of hemodynamic profile and cardiac function is crucial to identify the ideal supportive measures, need for mechanical circulatory support (MCS), and best machine required. Septic cardiomyopathy (SCM) refers to decreased myocardial contractility due to sepsis and can affect both ventricles as well as systolic and diastolic functions. SCM was reported in up to 83% of patients with sepsis and its pathophysiological mechanisms include mitochondrial dysfunction, cytokine storm, apoptosis, and endothelial dysfunction [47, 48]. SCM has been linked to increased mortality, however, it is reversible and expected to recover within 10 days which makes MCS a life-saving option till control of sepsis and recovery of cardiac functions [49].

5.2.4 Sepsis with circulatory failure but preserved cardiac function

Patients with sepsis can develop vasoplegia resulting in hemodynamic collapse with low SVR, disturbed cellular metabolism, and hyperlactatemia despite preserved or hyperdynamic cardiac contractility [14, 46]. This condition is always an area of debate among the treating team members regarding the potential benefits of VA-ECMO. Many strong reasons to avoid VA-ECMO include: (1) vasoplegia and

capillary leak results in extravasation and decreased effective blood volume that will impair ECMO flow; (2) VA-ECMO will not correct the cellular hypoxemia and mitochondrial dysfunction; (3) increasing ECMO flow will decrease venous return and increase afterload which will impair the cardiac functions; and (4) the extracorporeal circulation may result in further derangement of the coagulation system and breed the microbes which will exaggerate the sepsis and multi-organ failure.

Ling and his colleagues [50] conducted a systematic review of 468 patients from 14 studies and reported a pooled survival rate of 36.4% with worse outcomes in patients without significant cardiac dysfunction. Another systematic review by Sato and Kuriyama [51] included 245 adult patients with septic shock receiving VA-ECMO support from six studies and reported a mortality rate of 76.7%. The high mortality rates of VA-ECMO support in patients with sepsis-related cardiogenic shock or septic shock deny the potential benefits in these clinical conditions. VA-ECMO was not recommended in patients with septic shock and preserved cardiac functions unless the patients developed low cardiac index and preferred to be done in high volume ECMO centers [52].

5.2.5 Infective endocarditis

Infective endocarditis carries great risks of mortality and many morbidities due to sepsis, embolic infarcts, and hemodynamic instability. The complications include neurological events, renal failure, respiratory failure, heart failure, and multi-organ failure [53]. The reported incidence of acute heart failure reached 40% of patients with IE [1]. Recent guidelines recommended emergency surgery (Class IB) for acute

Articles, type	Reason for MCS	Surgery, timing of MCS	Outcomes
Handa et al. [55], Multicentre retrospective	585 patients with IE (2009–2017), 215 (36.8%) had HF without CS, 69 (12%) had CS with a median EuroSCORE II of 21.9 (IQR:13.6,31.1).	All patients had cardiac surgery 2/69(3%) had pre-operative VA-ECMO, 6/69(9%) had pre-operative IABP Postoperatively, 10/284 patients required VA-ECM, 18/284 patients had IABP.	Mortality occurred in 15/69(22%) and 27/215(13%). RRT was required in 24/69 (35%) and 35/215 (16%). MOF 10/69 (14%) and 14/215 (7%).
Li et al. [56], case report	A 48-year-old woman with mitral IE and CS.	Peripheral VA-ECMO, no surgery due to poor condition.	The patient died before surgery Multiple cerebral, splenic, and limb infarcts.
Kunioka et al. [57], case report	A 33-year-old woman with mitral IE. Coronary embolism with pulseless electrical activity.	VA-ECMO then coronary angioplasty and MVR. Failed ECMO weaning, upgraded to LVAD.	The patient survived. She developed coronary aneurysm that required surgical repair.
Usui et al. [58], case report	A 68-year-old woman with mitral and aortic IE.	VA-ECMO after cardiac arrest and resuscitation before emergency cardiac surgery due to coronary occlusion by vegetations.	The patient died 19 days after surgery due to MOF. The surgery was delayed due to cerebral bleeding from mycotic aneurysms that required embolization.
Edlin et al. [59], case report	A 43-year-old man with Australian syndrome (IE, meningitis, and pneumonia).	VA-ECMO was inserted after emergency surgery (MVR, AVR, and drainage of aortic abscess).	The patient survived.

Articles, type	Reason for MCS	Surgery, timing of MCS	Outcomes
Noyes et al. [60], case report	A 35-year-old man with mitral and aortic IE complicated with aorto-atrial fistula.	VA-ECMO was inserted before emergency surgery due to rupture of aortic valve.	The patient survived.
Bainiwal et al. [61], case report	A 39-year-old woman with SLE and mitral IE.	Emergency VA-ECMO due to PEA before MVR.	The patient survived. The patient had AKI and required RRT.
Ibrahim et al. [62], case report.	A 24-year-old man with adult congenital heart disease and pacemaker-related IE.	VA-ECMO after surgery then shifted to VV-ECMO.	The patient survived. Many complications happened including AKI requiring RRT, and pulmonary embolism.
John et al. [63], case report	Case 1: a 24-year-old man with tricuspid IE. Case 2: a 52-year-old woman with aortic IE. Case 3: a 36-year-old woman with aortic IE.	Case 1: VA-ECMO and no surgery. Case 2: VA-ECMO after AVR. Case 3: VA-ECMO and no surgery.	The three patients died after MCS and RRT.
Chen et al. [64]	A 55-year-old man with dilated cardiomyopathy and ICD-related IE.	First, ICD was removed and Impella was inserted then VA-ECMO was inserted. Failed weaning off MCS, heart transplantation was done.	The patient survived.

ECMO, Extracorporeal membrane oxygenation; HF, Heart failure; RRT, Renal replacement therapy; CS, Cardiogenic shock; MVR, Mitral valve replacement; IABP, Intra-aortic balloon pump; MOF, Multiple organ failure; AVR, Aortic valve replacement.

Table 2.
Published articles of MCS in patients with IE.

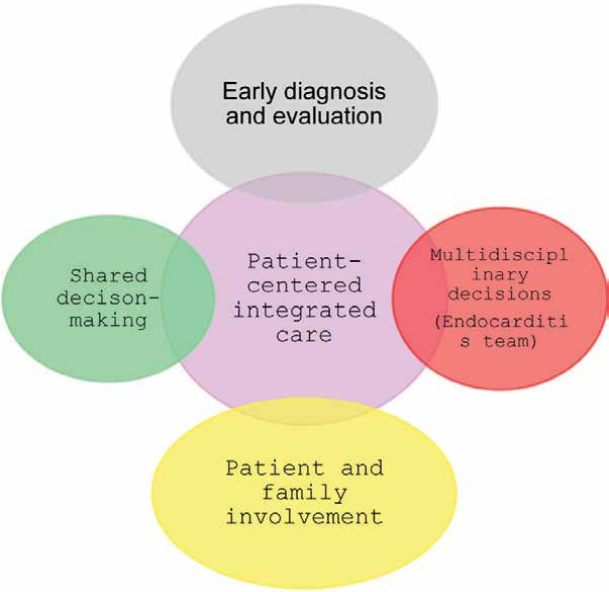


Figure 1.
The interplay of multidisciplinary teamwork, patients and family preferences, and shared decision-making to reach individualized integrated patient care.

IE complicated with cardiogenic shock and urgent surgery for uncontrolled infection with presence of large vegetations, valve dehiscence, heart block, or abscess (Class IB) [4]. Surgical intervention can be a life-saving option in complicated cases with IE, however, cardiovascular failure carries high risks of operative mortality [54]. So, a multidisciplinary approach is crucial to considering the benefits and risks of surgery and appropriateness of MCS. We reviewed the literature about the use of MCS in IE and almost all the publications are case reports (**Table 2**) [55–64].

Finally, delivery of integrated individualized patient-centered care requires collaboration and engagement between the medical team and patients with their family members and among the different specialties of healthcare. Sharing information about the risks, benefits, and potential complications of every step of management helps to reach the appropriate decision to get the best outcome (**Figure 1**).

6. Conclusions

Infective endocarditis is a serious condition, especially when associated with heart failure with or without sepsis. Careful clinical evaluation, use of advanced diagnostic imaging, and collaboration of multidisciplinary teams with engagement of patients will ensure appropriate patient-centered individualized care. VA-ECMO support in patients with sepsis-related cardiogenic shock or septic shock is associated with worse outcomes and should be carefully considered in cases of low cardiac output.

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Endocarditis, or infection of the heart, represents one of the most complicated diagnostic and therapeutic challenges in modern medicine. This book was conceived out of necessity as an effort to bring clarity and understanding to a disease that often challenges clinicians regarding diagnosis and treatment. Endocarditis, whether native valve, prosthetic, or device-related, is a condition that sits at the multidisciplinary crossroads of infectious disease, radiology, critical care, cardiology, and cardiac surgery. Its management requires not only a deep understanding of microbiology and pathophysiology, but also close coordination across disciplines and institutions. In my years caring for patients with this complex condition, I have seen how subtle signs can be missed, how delays in diagnosis can have devastating consequences, and how timely, aggressive intervention—medical and surgical—can be lifesaving. However, despite advancements in imaging, antibiotics, and surgical techniques, mortality remains unacceptably high. This book is not just a review of what we know, but also hopefully inspires all of us to be better and continue to advance the field of study. Chapters in this volume aim to provide clinicians, trainees, and students with a practical and up-to-date foundation in the pathogenesis, diagnosis, and management of endocarditis. Topics include evolving microbial trends, indications for surgery, the role of imaging, embolic complications, and special populations such as intravenous drug users, advanced co-morbidities, and those with implantable devices. Wherever possible, we have emphasized evidence-based practice and the rapidly expanding published literature, but also acknowledge the critical role of experience, judgment, and multidisciplinary collaboration. I am grateful to the many contributors whose expertise and dedication have shaped this text. May this book serve as a resource and a reminder: behind every case of endocarditis is a patient whose life may depend on our vigilance, precision, and compassion.

*Kaan Kivrali,
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