Review Article
E Clinical Research 2025;(01):40-57
eISSN 3023-3399

Emerging Clinical Research ECR

Infective Endocarditis, a Nidus for Blood Stream Infection and Vertebral Osteomyelitis. Case Report with Literature Review

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Abstract

Infective endocarditis (IE) is a life-threatening infection of the endocardial surface of the heart, most commonly affecting the heart valves. It is a complex clinical entity characterized by a wide spectrum of presentations, evolving epidemiology, and a broad range of potential complications. While IE traditionally manifested in patients with pre-existing valvular disease, recent data highlight a shift toward healthcare-associated and device-related infections, often caused by *Staphylococcus aureus*, particularly in older adults and individuals with prosthetic heart valves or indwelling intravascular devices.

This case-based review discusses a rare but serious complication of IE—vertebral osteomyelitis—arising from hematogenous seeding of the spinal column by bacteremia. The patient, a 69-year-old female with multiple comorbidities and prior untreated *Staphylococcus aureus* bacteremia, presented with altered mental status and was later diagnosed with mitral valve IE complicated by vertebral osteomyelitis. Diagnosis was confirmed using transesophageal echocardiography and supported by magnetic resonance imaging findings.

This article emphasizes the diagnostic challenges and clinical implications of subacute infective endocarditis, particularly when classic signs are absent. It underscores the necessity of maintaining a high index of suspicion for metastatic infections such as vertebral osteomyelitis in patients with persistent bacteremia. The revised 2023 Duke-ISCVID diagnostic criteria and a multidisciplinary approach involving infectious disease and cardiology consultation are central to effective management. Early detection and prolonged intravenous antimicrobial therapy can prevent further complications and improve patient outcomes.

Introduction

Infective endocarditis (IE) is an infection of the endocardial surface of the heart, typically involving the heart valves—whether native or prosthetic—but it may also affect the mural endocardium, septal defects, or implanted cardiac devices. The pathogenesis of IE involves microbial colonization of damaged endocardial surfaces, often leading to vegetation formation composed of platelets, fibrin, and embedded microorganisms, ultimately resulting in progressive tissue destruction, embolization, and systemic complications [1].

IE can be classified based on the type of affected valve and the setting in which it was acquired. **Native valve endocarditis (NVE)** refers to infection involving a patient's original cardiac valves, while **prosthetic valve endocarditis (PVE)** involves infections that develop in surgically implanted mechanical or bioprosthetic valves. Furthermore, based on the context of acquisition, IE can be stratified into **community-acquired IE (CA-IE)** and **healthcare-associated IE (HA-IE)**. Community-acquired IE is diagnosed within 48 hours of hospital admission in individuals without recent exposure to healthcare settings. In contrast, healthcare-associated IE occurs ≥48 hours after hospitalization or in patients recently exposed to invasive medical procedures or prolonged indwelling devices [1].

Epidemiological trends reveal a shifting landscape, with a notable rise in healthcare-associated and device-related infections due to increased use of invasive procedures and cardiac prostheses. Although rheumatic heart disease was once the primary risk factor, degenerative valvular disease, intravascular catheter use, and cardiac

implantable electronic devices have emerged as significant contributors in recent years [2,3].

Early recognition and prompt diagnosis of IE are critical, as the disease carries a high risk of morbidity and mortality. Delayed diagnosis may result in severe cardiac complications such as valvular insufficiency, heart failure, and systemic embolism. One of the most significant metastatic complications of IE is **vertebral osteomyelitis**, which arises from hematogenous dissemination of microorganisms to the vertebral column. This often-overlooked manifestation may present with subtle or nonspecific symptoms such as back pain, fever, or neurologic deficits. In some cases, vertebral osteomyelitis may even serve as the initial presentation of an otherwise clinically silent endocarditis [39].

Given these diagnostic challenges, the need for heightened clinical vigilance cannot be overstated—particularly in elderly or immunocompromised patients presenting with bacteremia of unclear origin, musculoskeletal symptoms, or neurologic findings. Incorporation of advanced imaging modalities and adherence to established diagnostic frameworks, such as the Duke-International Society for Cardiovascular Infectious Disease (ISCVID) criteria, are essential in identifying both typical and atypical presentations of IE [54,55].

3. Epidemiology

The global and national burden of **infective endocarditis (IE)** has shown a steady increase over the past two decades, reflecting changing patient demographics, evolving microbial patterns, and increased exposure to healthcare interventions. In the United States, data from a large retrospective study revealed a significant rise in the incidence of IE—from 11 cases per 100,000 population in the year 2000 to 15 cases per 100,000 population by 2011—highlighting a growing public health concern [2]. A similar trend was observed in another comprehensive analysis using state data from California and New York, which confirmed a persistent increase in IE-related hospitalizations and demonstrated that this rise was primarily driven by infections caused by *Staphylococcus aureus* and a growing number of cases related to intravenous drug use and prosthetic devices [3].

The rising incidence of IE is not confined to the United States. A population-based study in France reported an annual incidence of 33.8 cases per million, with the highest burden observed among men aged 75 to 79 years [4]. Notably, the majority of these individuals had no previously known heart disease, and 27% of cases were classified as healthcare-associated endocarditis, reflecting the increasing role of hospital-based exposures such as indwelling catheters, surgical interventions, and cardiac implantable devices. Similarly, a Spanish observational study covering the years 2003 to 2014 documented an increase in IE incidence from 2.72 to 3.49 cases per 100,000 annually, with a disproportionate rise among the elderly population [5].

This epidemiological shift can be largely attributed to multiple factors, including population aging, the increasing prevalence of chronic comorbid conditions, and the expanding use of invasive medical devices. Elderly patients, who are more likely to have structural heart disease and undergo procedures such as valve replacement or dialysis, now represent a significant proportion of new IE diagnoses. Furthermore, healthcare-associated IE, including nosocomial and non-nosocomial healthcare-associated cases, now comprises a substantial fraction of overall IE cases, ranging from 25% to 35% in various studies [4,5].

The demographic shift also correlates with a change in microbiologic etiology. In contrast to earlier decades when viridans group streptococci dominated as causative organisms, *Staphylococcus aureus* has emerged as the leading pathogen, especially in healthcare-associated and device-related infections [4]. This pathogen not only accounts for a more aggressive clinical course but also portends higher rates of metastatic complications and mortality.

These findings underscore the need for enhanced surveillance, prevention strategies focused on high-risk groups, and early diagnostic intervention, particularly in aging populations and those frequently interacting with the healthcare system.

4. Risk Factors

The development of **infective endocarditis (IE)** is multifactorial, with risk factors broadly categorized into **personal characteristics** and **comorbid medical conditions**. Understanding these risk factors is essential for early identification, targeted screening, and timely intervention, particularly in vulnerable populations.

a. Personal Factors

Several demographic and behavioral traits increase an individual's predisposition to IE. These include:

1. **Advanced Age:**

Age is among the most significant risk factors. More than half of all IE cases in developed countries occur in individuals over 60 years of age. This age group often has age-related degenerative valvular changes, increased likelihood of prosthetic valve implantation, and greater exposure to invasive medical procedures [12,13]. The aging immune system and cumulative comorbidities further exacerbate susceptibility.

2. **Male Sex:**

A consistent male predominance has been observed in IE across epidemiological studies, with reported male-to-female ratios ranging from 3:2 to as high as 9:1. The reasons for this gender disparity are not entirely understood but may relate to higher rates of underlying cardiac disease and intravenous drug use among men [12].

3. **Intravenous Drug Use (IVDU):**

IVDU remains a major risk factor, especially for right-sided IE involving the tricuspid valve. Frequent breaches in skin integrity allow entry of skin flora such as *Staphylococcus aureus* into the bloodstream, which may seed the endocardium. Additionally, contaminants and particulate matter in injected substances may cause endothelial injury, facilitating bacterial adhesion [14]. The rising incidence of IVDU-related IE has become a major public health issue, particularly in North America.

4. **Poor Dental Health and Oral Hygiene:**

Oral flora, particularly viridans group streptococci, can enter the bloodstream during routine activities such as tooth brushing or invasive dental procedures, especially in individuals with poor dentition or periodontal disease. These microorganisms are known to have a predilection for cardiac valves, especially in those with pre-existing valve abnormalities. Therefore, dental hygiene is a modifiable risk factor for IE [15].

b. Comorbidities

In addition to personal risk factors, numerous medical conditions significantly elevate the risk of developing IE:

1. **Structural and Valvular Heart Diseases:**

Conditions such as mitral valve prolapse with regurgitation, aortic stenosis, and rheumatic heart disease predispose individuals to IE by creating turbulent blood flow and endothelial disruption, which facilitate microbial colonization. In one cohort, over 75% of IE patients had structural cardiac abnormalities at the time of diagnosis [7,27]. A Danish study among more than 3,000 patients with hypertrophic cardiomyopathy also revealed a significantly elevated IE risk compared to the general population [16].

2. **Prosthetic Valves and Cardiac Devices:**

The implantation of prosthetic valves, both mechanical and bioprosthetic, and cardiac implantable electronic devices (CIEDs), such as pacemakers and defibrillators, has been linked to a heightened risk of IE. These foreign materials provide surfaces for microbial adhesion and biofilm formation. Infections involving prosthetic valves tend to be more severe and often require surgical intervention [6,8,16].

3. **Congenital Heart Defects:**

Patients with congenital anomalies such as bicuspid aortic valve, ventricular septal defects, and coarctation of the aorta are at increased risk due to abnormal blood flow patterns and increased shear stress across the endocardium, facilitating bacterial adherence [18].

4. **Immunosuppression and Chronic Illness:**

Patients with conditions such as HIV infection, cancer, diabetes mellitus, or those on chronic immunosuppressive therapy have compromised immune responses that reduce their ability to clear bacteremia. Hemodialysis patients, for instance, face frequent intravascular access and often have valvular calcifications, further increasing the risk of IE [22,23].

5. **Prior History of Infective Endocarditis:**

Recurrence is not uncommon in patients with a history of IE. Studies estimate recurrence rates ranging between 2.5% and 9%, with higher risk in patients with persistent risk factors or incomplete treatment during the initial episode [19,20].

6. **Invasive Healthcare Exposure:**

Hospitalized patients or those undergoing invasive procedures involving vascular access, cardiac surgery, or indwelling catheters are at elevated

risk of healthcare-associated IE. These exposures introduce both a microbial source and mechanical disruption of the endothelium [21,26,27].

These risk factors highlight the importance of pre-procedural prophylaxis in select high-risk individuals, rigorous aseptic technique in medical care, and the need for patient education regarding hygiene, especially dental care. A comprehensive understanding of both personal and clinical risk factors is critical in reducing the burden of infective endocarditis.

5. Etiology

Infective endocarditis (IE) is caused by a wide array of microbial agents, though the majority of cases are attributed to a few key bacterial species. The ability of these organisms to adhere to damaged endocardial surfaces and form resilient vegetations plays a crucial role in pathogenesis. The **three most common pathogens** implicated globally are ***Staphylococcus aureus***, **viridans group streptococci**, and **enterococci**, each with distinct clinical and epidemiological implications.

5.1. Major Pathogens

Staphylococcus aureus is now the **leading cause** of IE in high-income countries, accounting for approximately 30% to 40% of all cases. It is particularly prevalent in **healthcare-associated endocarditis**, and among patients with **intravascular devices**, **prosthetic valves**, or those who inject drugs. *S. aureus* causes a rapidly progressive and destructive form of endocarditis with high metastatic potential and mortality. Methicillin-resistant *S. aureus* (MRSA) further complicates management due to limited therapeutic options [33].

Viridans group streptococci, predominantly *Streptococcus sanguinis*, *S. mitis*, and *S. mutans*, are part of the normal oral flora and classically associated with **subacute community-acquired IE**, particularly in patients with poor dental hygiene or undergoing dental procedures. These organisms are relatively slow-growing and less virulent than *S. aureus*, but may cause insidious damage over weeks if untreated [33].

Enterococci, particularly *Enterococcus faecalis* and *E. faecium*, account for approximately 10%–15% of IE cases. These are typically healthcare-associated pathogens, frequently encountered in older adults with **genitourinary or gastrointestinal tract manipulations**. Enterococci are inherently resistant to many antibiotics, making treatment more challenging and often requiring combination therapy [33,34].

5.2. Other Notable Microorganisms

Other significant, though less frequent, pathogens include:

- **Coagulase-negative staphylococci** – Frequently associated with prosthetic valve endocarditis.
- **Streptococcus bovis** (now *Streptococcus gallolyticus*) – Strongly associated with colonic neoplasia and mandates gastrointestinal evaluation in affected patients.
- **HACEK organisms** (*Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, and *Kingella*) – Fastidious Gram-negative bacilli historically linked with culture-negative IE.
- **Fungi** – Seen in immunocompromised hosts or prosthetic valve IE, particularly *Candida* and *Aspergillus* species.
- **Non-HACEK Gram-negative bacteria** – Such as *Pseudomonas aeruginosa*, especially in injection drug users.
- **Culture-negative cases** – Often due to prior antibiotic exposure or infection by fastidious organisms (e.g., *Bartonella*, *Coxiella burnetii*, *Tropheryma whipplei*) [35–36, 56–57].

5.3. Microbiological Distribution in Large Cohorts

In the **International Collaboration on Endocarditis-Prospective Cohort Study** involving 2,781 patients across multiple centers, the distribution of pathogens was documented as follows:

Pathogen	Frequency (%)
Staphylococcus aureus	31
Viridans group streptococci	17
***Enterococcus* spp.**	11
Coagulase-negative staphylococci	11
Streptococcus bovis	7
Other streptococci	5
Fungi	2
HACEK group organisms	2
Non-HACEK Gram-negative bacilli	2

Culture-negative or mixed flora	10

Source: Murdoch et al., 2009 [33]

5.4. Role of Healthcare-Associated Infections

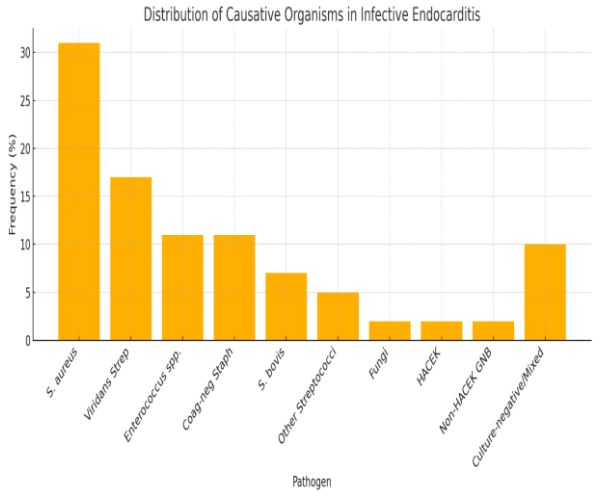
The modern era of medical care has witnessed a rise in **healthcare-associated infective endocarditis (HA-IE)**, driven by widespread use of central venous catheters, hemodialysis, cardiac devices, and invasive procedures. HA-IE now accounts for an estimated **25%–35%** of all IE cases. These infections are predominantly caused by *S. aureus*, coagulase-negative staphylococci, and enterococci, all of which can form biofilms on prosthetic material and are often multidrug-resistant [4,5,28].

Recent nationwide data from Denmark have also shown that patients considered at moderate cardiovascular risk—such as those with mitral valve prolapse or bicuspid aortic valve—have elevated IE incidence when exposed to healthcare interventions (Østergaard et al., 2019) [16].

The transition in microbial epidemiology toward more virulent and drug-resistant organisms emphasizes the importance of **early pathogen identification** using blood cultures, serology, and molecular tools, as well as **targeted antimicrobial therapy**.

Figure 1: Distribution of Causative Organisms in Infective Endocarditis

Figure 1. Pathogen distribution based on data from the International Collaboration on Endocarditis-Prospective Cohort Study (Murdoch et al., 2009). The most common organisms are Staphylococcus aureus (31%), followed by viridans group streptococci (17%) and enterococci (11%).



6. Pathophysiology

The pathogenesis of infective endocarditis (IE) is a multistep process involving **endothelial injury**, **microbial adherence**, **vegetation formation**, and **immune evasion**. These mechanisms interact dynamically with both host defenses and microbial virulence factors, culminating in the formation of a characteristic vegetation—composed of fibrin, platelets, and microbial colonies—on the endocardial surface.

6.1. Endothelial Injury and Microthrombus Formation

The initial event in the development of IE is **injury to the endocardial surface**, particularly on heart valves. This injury may be caused by turbulent blood flow (from structural defects), direct trauma (from catheters or devices), or even toxic effects of circulating inflammatory mediators. The damaged endothelium exposes underlying **subendothelial collagen and tissue factor**, triggering **platelet aggregation** and **fibrin deposition**, which leads to the formation of a **sterile thrombotic nidus**—known as **nonbacterial thrombotic endocarditis (NBTE)** [37].

6.2. Bacterial Adherence and Colonization

Transient bacteremia—arising from activities such as dental procedures, catheter insertions, or intravenous drug use—introduces microbes into circulation. **Adhesins** on the surface of certain bacteria (such as **fibronectin-binding proteins** in *Staphylococcus aureus*) enable these pathogens to attach to fibrin-platelet matrices at sites of endothelial damage [38].

Once adhered, these organisms **evade phagocytosis and immune clearance**, especially within the protected matrix of the thrombus. The immune system is unable to access organisms within vegetations effectively due to lack of vascularity and the shielding effect of fibrin layers.

6.3. Vegetation Maturation

Following microbial adherence, the bacteria proliferate within the thrombus, further promoting **platelet deposition**, **fibrin accumulation**, and **biofilm formation**. This leads to the expansion of a mature **infected vegetation**, which is the hallmark of IE. Vegetations are friable and can fragment, leading to **systemic emboli** and **metastatic infections** such as **vertebral osteomyelitis**.

In *Staphylococcus aureus* IE, this process occurs rapidly and is associated with **greater virulence** and a **higher incidence of metastatic complications** due to the organism's potent arsenal of toxins and immune evasion mechanisms [38].

6.4. Host Immune Response and Tissue Destruction

Chronic infection leads to **local immune activation**, cytokine release, and infiltration by neutrophils and macrophages. However, the immune response is often ineffective due to bacterial shielding. Over time, the infection may erode valve tissue, cause **abscesses**, and result in **valvular perforation**, **chordae tendineae rupture**, or **pseudoaneurysms**, leading to progressive heart failure.

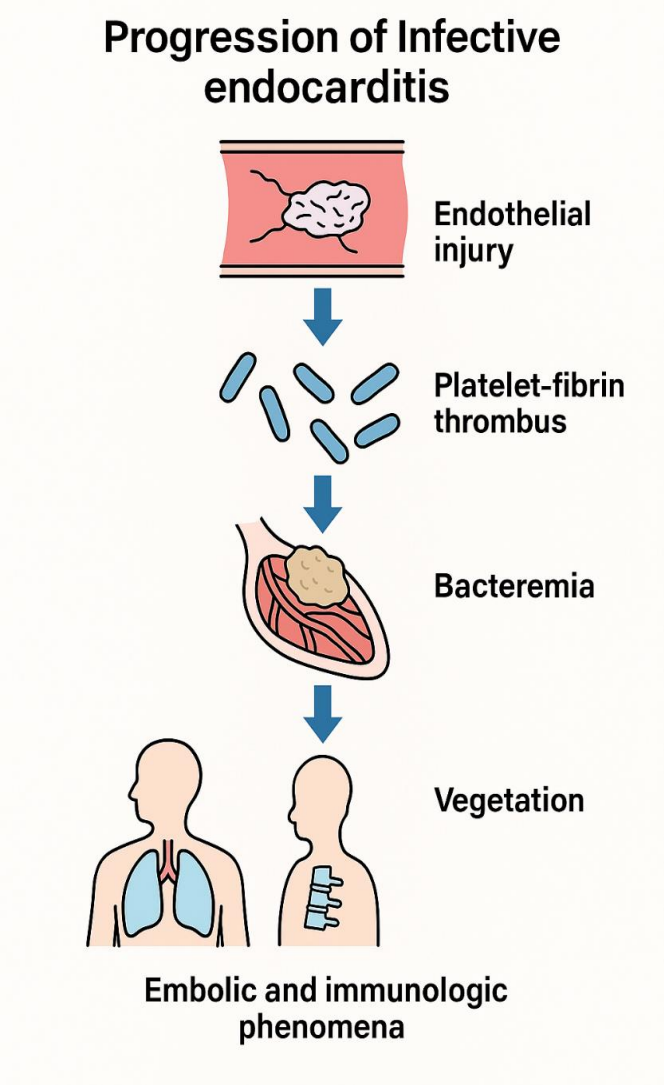
Table 1: Stages in the Pathogenesis of Infective Endocarditis

Stage	Description
Endothelial Injury	Caused by turbulent flow, trauma, or prosthetics; exposes subendothelial tissue
Platelet-Fibrin Thrombus	Forms a sterile nidus (NBTE) on damaged endocardium
Microbial Seeding	Transient bacteremia introduces pathogens; adhesion via microbial surface proteins
Colonization and Biofilm	Pathogens multiply within fibrin mesh; form biofilm; resist host defenses
Vegetation Formation	Infected thrombus matures into friable mass with high embolic risk
Immune Evasion and Damage	Inflammation and tissue destruction with ineffective immune clearance

Sources: Nappi et al., 2018 [37]; Nappi & Singh, 2023 [38]

Figure 1. Progression of Infective Endocarditis

Figure 1 illustrates the sequential stages in IE development, starting with endothelial injury, followed by thrombus formation, bacteremia, vegetation growth, and eventual embolic/immune complications such as septic pulmonary or spinal infection.



7. Clinical Presentation

The clinical presentation of **infective endocarditis (IE)** is notoriously variable, ranging from a fulminant illness to a subtle, indolent condition. This variability reflects the **nature of the causative organism**, the **host's immune response**, and whether the infection involves **native or prosthetic valves**.

7.1 Acute vs. Subacute IE

IE classically presents in two forms: **acute** and **subacute**.

- **Acute IE** typically occurs in healthy valves and is most often caused by **virulent organisms** such as *Staphylococcus aureus*. It presents

abruptly with **high-grade fever**, **chills**, **septicemia**, and **rapid valve destruction**, often progressing to **heart failure** or **systemic embolization** within days [39].

- **Subacute IE** is usually associated with **less virulent pathogens**, such as viridans group streptococci. It affects abnormal or damaged valves and unfolds **gradually** over weeks. Symptoms are often nonspecific and include **low-grade fever**, **malaise**, **fatigue**, **arthralgias**, and **weight loss**. Because of its insidious onset, subacute IE is more likely to be missed during early stages [40]

7.2 Constitutional Symptoms and Signs

Common nonspecific features include:

- **Fever** (present in up to 90% of patients)
- **Chills, night sweats**
- **Fatigue and malaise**
- **Weight loss**
- **Myalgias and arthralgias**
- **Headache, anorexia**
- **Dyspnea (in advanced or valvular cases)**

On auscultation, a **new or changing murmur** is a hallmark, found in up to **85% of cases**, and often the earliest clinical clue [39].

7.3 Cutaneous and Immunologic Manifestations

Though uncommon in the era of early detection and antibiotics, **cutaneous findings** remain critical diagnostic clues when present. These reflect either **septic emboli** or **immune complex deposition**.

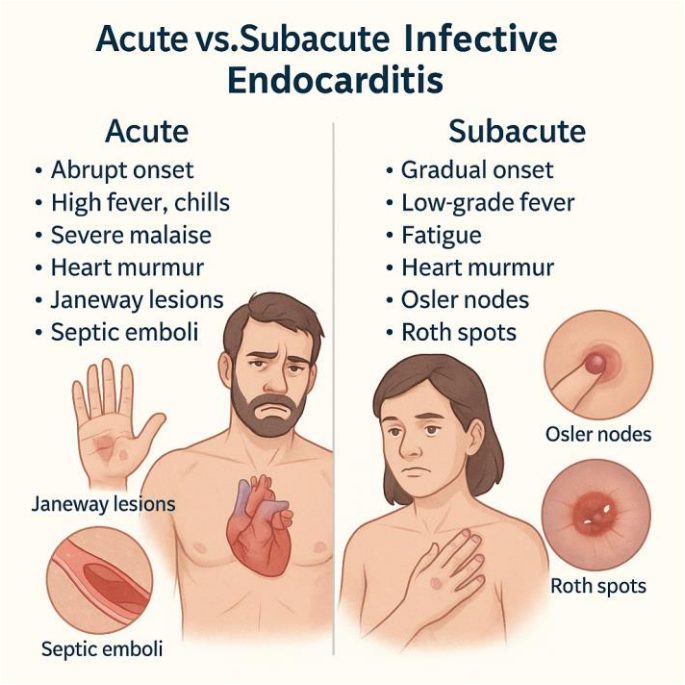
Table 1. Classical Peripheral Signs of Infective Endocarditis

Finding	Description	Pathogenesis	Prevalence
Janeway lesions	Painless, erythematous macules on palms/soles	Septic microemboli (microabscesses)	5–15%
Osler nodes	Painful, violaceous nodules on finger/toe pads	Immune complex deposition	5–10%
Roth spots	Retinal hemorrhages with pale centers	Immune-mediated vasculitis	~2%
Splinter hemorrhages	Linear reddish-brown streaks under the nails	Vascular injury or microemboli	Up to 20–40%
Petechiae	Small red/purple spots on mucosa or skin (palate, conjunctiva, extremities)	Capillary hemorrhage	~30%
Clubbing	Bulbous deformity of fingertips/toes	Chronic hypoxia or inflammation	Rare in acute phase

Sources: Baddour et al., 2015 [39]; Cahill & Prendergast, 2016 [40]

7.4 Visual Aid: Clinical Contrast Between Acute and Subacute IE

Figure 1. Visual comparison of acute and subacute infective endocarditis. The acute form features high fever, chills, Janeway lesions, and septic emboli, while the subacute form typically presents with fatigue, Osler nodes, and Roth spots. These peripheral stigmata, though infrequent, remain key diagnostic indicators in patients with vague systemic symptoms.



7.5 Neurologic, Musculoskeletal, and Other Organ Involvement

Up to **40%** of patients experience **neurologic symptoms** such as:

- Stroke (embolic)
- Intracerebral hemorrhage
- Brain abscess
- Meningoencephalitis

Musculoskeletal pain (especially back pain) may be the presenting complaint in cases of **vertebral osteomyelitis**, a metastatic infection from bacteremic seeding [39].

Other findings:

- **Splenomegaly** due to immune response or embolic infarction
- **Anemia of chronic disease**
- **Renal involvement**: hematuria, proteinuria, or **immune complex-mediated glomerulonephritis**

8. Complications

Infective endocarditis (IE) is associated with a wide range of complications that can significantly impact morbidity and mortality. These arise from three primary mechanisms: direct cardiac tissue destruction, systemic septic embolization, and immune-mediated injury. Complications may affect virtually every organ system, often leading to multisystem involvement. Early identification and intervention are essential to prevent permanent damage or death, especially in vulnerable populations such as the elderly, immunocompromised, and those with prosthetic heart valves [39].

8.1 Cardiac Complications

Cardiac manifestations are the most frequent and often the most life-threatening consequences of IE, observed in up to **50% of patients**. These include:

- **Valvular Regurgitation**: Resulting from leaflet perforation or rupture of chordae tendineae, leading to volume overload and heart failure.
- **Heart Failure**: Commonly develops due to acute valvular insufficiency, most often involving the mitral or aortic valves.
- **Perivalvular Abscess and Fistula Formation**: May occur particularly in prosthetic valve IE, requiring urgent surgical intervention.
- **Conduction Abnormalities**: Extension of infection into the conduction system can result in heart blocks or arrhythmias [39].

8.2 Neurologic Complications

Neurologic events occur in **20–40% of IE patients**, and they are a major determinant of prognosis. These include:

- **Ischemic Stroke**: Caused by embolization of vegetations to cerebral vessels.
- **Intracerebral Hemorrhage**: Often due to septic arteritis or rupture of mycotic aneurysms.
- **Brain Abscess**: Resulting from hematogenous spread or direct extension of embolic infarction.
- **Meningitis and Encephalopathy**: Particularly in immunocompromised or elderly individuals [39].

8.3 Embolic Complications

Septic embolization is a hallmark of IE, resulting from the detachment of infected vegetations. Emboli can lodge in various systemic arteries, leading to:

- **Renal infarction**, presenting with flank pain and hematuria.
- **Splenic infarction or abscess**, associated with left upper quadrant pain and sepsis.
- **Pulmonary emboli**, especially in right-sided IE, leading to pleuritic chest pain, dyspnea, or septic pulmonary infarcts [39].

8.4 Metastatic Infections

Hematogenous spread of the pathogen can cause **metastatic seeding** of distant organs. One of the

most important and often underdiagnosed examples is:

- **Vertebral Osteomyelitis**: Infection of the vertebral bodies, commonly presenting with back pain and localized tenderness. MRI is the diagnostic modality of choice. This complication may be the first clinical clue to underlying IE, particularly in subacute or culture-negative cases.
- **Septic Arthritis**, **psoas abscess**, and **epidural abscess** may also occur, complicating the course and management of IE [39].

8.5 Immunologic Complications

Immune responses to circulating microbial antigens can cause secondary inflammatory disorders such as:

- **Glomerulonephritis**: Often presenting with hematuria, proteinuria, and renal impairment due to immune complex deposition.
- **Osler Nodes**, **Roth Spots**, and **positive rheumatoid factor**: Classic but now relatively rare due to early antibiotic therapy [39].

Table 1: Major Complications of Infective Endocarditis

Complication Type	Manifestations	Prevalence	Clinical Significance
Cardiac	Valvular regurgitation, heart failure, abscesses, conduction blocks	~50%	Often necessitates surgery
Neurologic	Stroke, hemorrhage, abscess, meningitis	20–40%	High impact on morbidity and mortality
Embolic	Infarction of spleen, kidney, brain, lungs	~25%	May be presenting symptom
Metastatic Infection	Vertebral osteomyelitis, septic arthritis, psoas abscess	~10–15%	Often underdiagnosed; requires imaging
Immunologic	Glomerulonephritis, Osler nodes, Roth spots	<10%	Reflects systemic immune activation

Clinical Insight:
Vertebral osteomyelitis, as seen in the presented case, is a classic example of how IE may present with **extracardiac symptoms**—in this case, back pain and altered mentation—before classic cardiac signs such as murmurs or embolic stigmata appear. Awareness of this possibility is essential, particularly in elderly or immunocompromised individuals with bacteremia of unclear source.

9. Diagnostic Approach

The diagnosis of **infective endocarditis (IE)** requires a combination of **clinical suspicion**, **microbiologic confirmation**, and **imaging evidence**. The challenge lies in IE's variable presentations, which may range from florid sepsis to subtle constitutional symptoms. Diagnosis is guided by **structured criteria**, the most updated being the **2023 Duke-International Society for Cardiovascular Infectious Diseases (ISCVID) criteria**, which supersede the modified Duke criteria of 2000 [54,55].

9.1 Laboratory Workup

a. Blood Cultures

Blood cultures are the **cornerstone of diagnosis** in suspected IE. Recommendations include:

- **At least three sets** of blood cultures from **separate venipuncture sites** drawn over 30–60 minutes before initiating antibiotics.
- Cultures should be repeated 24–72 hours after treatment initiation and then every 3 days until negative [43].

Persistent bacteremia, especially with *Staphylococcus aureus*, should raise concern for **endocardial involvement**.

b. Inflammatory and Immunologic Markers

- **Elevated ESR and CRP**: Sensitive but nonspecific markers of systemic inflammation.
- **Rheumatoid factor**: Positive in subacute IE (suggests immune activation).
- **Circulating immune complexes**, **cryoglobulins**, and **hypocomplementemia**: Reflect immune

complex deposition, commonly seen in glomerulonephritis.
- **Urinalysis**: May show **microscopic hematuria**, **proteinuria**, **red blood cell casts**, especially in immune-mediated renal involvement.

9.2 Imaging Modalities

a. Echocardiography

- **Transthoracic echocardiography (TTE)**:
  - Noninvasive and readily available.
  - Sensitivity ~60–75%; specificity ~90–95%.
- **Transesophageal echocardiography (TEE)**:
  - Gold standard for diagnosis.
  - Sensitivity ~90–100%, particularly for detecting **vegetations**, **abscesses**, and **prosthetic valve infections** [45–47].

TEE is preferred in:

- Prosthetic valve IE
- Prior IE
- Obesity or poor transthoracic window
- Negative or equivocal TTE with ongoing clinical suspicion

b. Electrocardiography (ECG)

- Useful for detecting **conduction abnormalities** (e.g., new AV block), suggesting **periannular extension** [44].

c. CT and FDG-PET/CT

- **Cardiac CT**:
  - Better for identifying **paravalvular complications** (abscesses, pseudoaneurysms).
  - Limited for detecting vegetations compared to TEE [48–50].
- **FDG-PET/CT**:
  - Useful in **prosthetic valve IE** and **device-related IE**.
  - Detects **metabolic activity** of infected sites and **distant septic foci** (e.g., vertebral osteomyelitis).
  - Sensitivity is higher in prosthetic valve IE than native valve IE [52,53].

d. Chest Radiograph & MRI

- **Chest X-ray**: Used to identify septic pulmonary emboli, particularly in **right-sided IE**.
- **MRI spine/brain**: For patients with neurologic symptoms or back pain, to detect **embolic infarcts**, **abscesses**, or **osteomyelitis**.

9.3 Diagnostic Criteria: 2023 Duke-ISCVID

The **2023 Duke-ISCVID criteria** incorporate microbiologic, imaging, and pathologic findings to stratify patients into **definite**, **possible**, or **rejected IE**. They offer improved sensitivity for prosthetic valve and device-related infections [54].

Table 1: Summary of 2023 Duke-ISCVID Diagnostic Criteria

Category	Criteria
Definite IE	- Pathologic criteria (e.g., organism in vegetation or valve histology)
	- **OR** Two major clinical criteria
	- **OR** One major + three minor **OR** five minor
Possible IE	- One major + one minor **OR** three minor criteria
Rejected IE	- Alternate diagnosis, no pathologic evidence after ≤4 days antibiotics, or failure to meet clinical criteria

Major Criteria

1. **Microbiologic**:
   - Two positive blood cultures with typical organisms (e.g., *S. aureus*, viridans strep, *Enterococcus*)
   - Serologic or molecular evidence of rare pathogens (e.g., *Bartonella*, *Coxiella burnetii*)
2. **Imaging**:
   - Vegetations, abscess, new regurgitation, valve perforation on echocardiography
   - FDG-PET/CT uptake consistent with infection
   - Intraoperative or gross evidence of endocardial infection

Minor Criteria

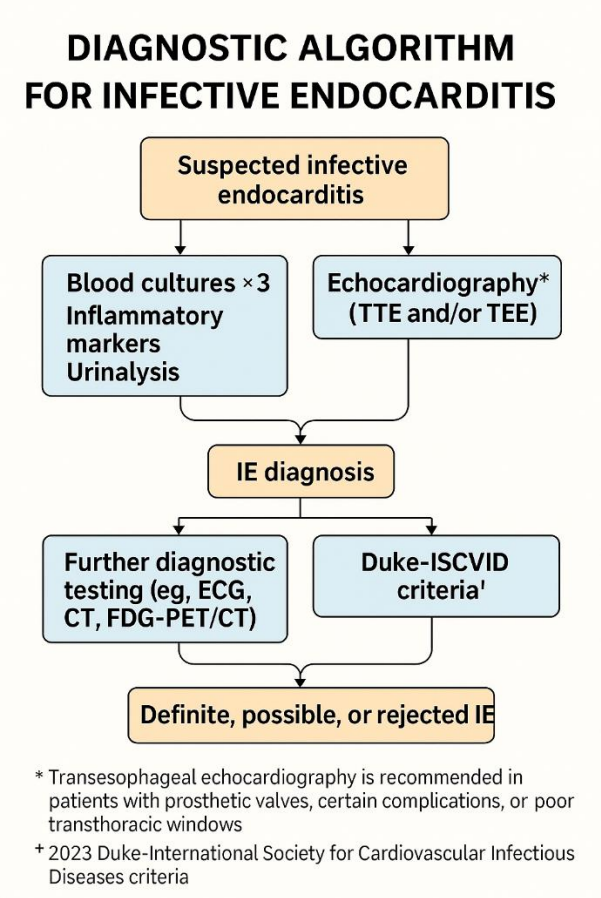
- Predisposing heart condition or IV drug use

- Fever ≥38.0°C
- Vascular phenomena (emboli, Janeway lesions, hemorrhages)
- Immunologic phenomena (Osler nodes, Roth spots, glomerulonephritis)
- Positive culture not meeting major criteria

Sources: Fowler et al., 2023 [54]; Li et al., 2000 [55]

Visual Summary: Diagnostic Algorithm for Infective Endocarditis

This flowchart outlines a practical diagnostic approach to IE, incorporating microbiologic workup, imaging, and application of Duke-ISCVID criteria. TEE is emphasized for prosthetic valve IE, while advanced imaging supports diagnosis in equivocal cases or to detect metastatic complications.



10. Case Report

This case highlights the diagnostic complexity and clinical consequences of **missed infective endocarditis**, emphasizing the value of **clinical vigilance**, **serial imaging**, and multidisciplinary collaboration in improving outcomes.

10.1 Patient Background

A 69-year-old African-American female with a medical history of hypertension, poorly controlled type 2 diabetes mellitus, peripheral vascular disease, and chronic back pain presented to the emergency department with **progressive altered mental status**, generalized weakness, and new-onset urinary incontinence. She had a known episode of **methicillin-sensitive *Staphylococcus aureus* (MSSA) bacteremia** six months prior, following a skin infection, but was discharged prematurely against medical advice and **did not complete antibiotic therapy**.

10.2 Initial Clinical Evaluation

Upon arrival, the patient was febrile (38.9°C), hypotensive (BP 88/50 mmHg), tachycardic, and disoriented (GCS 12). Physical exam revealed a **new systolic murmur** best heard at the apex, moderate tenderness along the lower lumbar spine, and poor dentition. There were no overt peripheral stigmata of endocarditis.

Initial labs demonstrated:

- WBC: 16.8 × 10⁹/L
- CRP: 192 mg/L
- ESR: 98 mm/hr
- Creatinine: 2.3 mg/dL (baseline 1.2)
- Urinalysis: hematuria, granular casts

10.3 Diagnostic Workup

Given the patient's fever, bacteremia history, and new murmur, **infective endocarditis** was suspected. Blood cultures were obtained and grew **MSSA** within 6 hours. Additional workup included:

- **Transthoracic echocardiogram (TTE):** inconclusive due to poor acoustic window.
- **Transesophageal echocardiogram (TEE):** revealed **a mobile vegetation (~9 mm)** on the **posterior leaflet of the mitral valve**, with moderate mitral regurgitation.
- **MRI Lumbar Spine:** demonstrated L3–L4 **vertebral osteomyelitis** and **paraspinal phlegmon**—confirming **metastatic seeding**.
- **FDG-PET/CT:** not performed due to renal function concerns.

10.4 Management

A multidisciplinary team involving infectious disease, cardiology, nephrology, and neurology initiated comprehensive management:

- **Antibiotic therapy:** Cefazolin 2g IV every 8 hours for 6 weeks (adjusted for renal function)
- **Supportive care:** IV fluids, tight glucose control, and delirium precautions
- **Surgical consult:** Cardiothoracic surgery deferred valve replacement due to hemodynamic stability and age-related risk
- **Serial echocardiography:** Follow-up TEE at week 3 showed **stable vegetation** with no worsening regurgitation or abscess formation

10.5 Outcome

The patient's mental status and inflammatory markers improved progressively. She completed a 6-week antibiotic course in a skilled nursing facility. At 3-month follow-up, she remained **afebrile**, **blood culture-negative**, and was undergoing outpatient physical therapy for residual back pain.

Table 1: Clinical Timeline of Events

Day	Clinical Event	Diagnostic Finding	Intervention
0	Admission with AMS, murmur, fever	Blood cultures: MSSA	Broad-spectrum antibiotics started
1	Blood culture positive	TTE inconclusive	Planned TEE
2	TEE performed	Mitral valve vegetation (9 mm), MR	Cefazolin initiated
3	MRI spine	L3-L4 osteomyelitis	Added back brace and pain management
5	Multidisciplinary review	Stable hemodynamics	Surgery deferred
21	Repeat TEE	No progression of vegetation	Continued antibiotics
42	Antibiotic course completed	Clinical and lab improvement	Discharged to SNF
90	Outpatient follow-up	Clinically stable, culture-negative	Continued rehab and monitoring

Teaching Points

- **Missed bacteremia** can lead to **silent IE with metastatic complications**, such as **vertebral osteomyelitis**.
- **Serial echocardiography**, particularly **TEE**, is indispensable when TTE is non-diagnostic.
- A **comprehensive and multidisciplinary approach** improves survival, even in frail elderly patients with comorbidities.
- MSSA remains **highly destructive** and requires prompt, full-course antibiotic therapy.

Cited as: Agho, 2025, case report.

11. Management

The management of infective endocarditis (IE) involves a coordinated **multidisciplinary approach** that includes timely initiation of **antimicrobial therapy**, careful **surgical risk assessment**, and often **infectious disease (ID) consultation**. Treatment decisions are guided by the **microbial etiology**, **valve type (native vs. prosthetic)**, **clinical severity**, and **presence of complications**.

11.1 Empirical and Directed Antimicrobial Therapy

Empirical therapy should begin **as soon as blood cultures are obtained**, especially in hemodynamically unstable patients. Therapy is tailored once the pathogen is identified and susceptibility results are available.

Empirical therapy recommendations vary by valve type and suspected pathogens:

Clinical Setting	Empirical Regimen	Rationale
Native valve IE (no device, community-acquired)	Ceftriaxone + Vancomycin	Covers strep, MSSA/MRSA, enterococci
Prosthetic valve or device-related IE	Vancomycin + Gentamicin + Cefepime	Broad Gram-positive & Gram-negative coverage
Suspected IV	Vancomycin	*S. aureus*

drug use-related IE	± Cefepime or Piperacillin-Tazobactam	(MSSA/MRSA), Pseudomonas

Directed therapy examples:

- **MSSA**: Cefazolin or nafcillin for 6 weeks
- **MRSA**: Vancomycin or daptomycin
- **Enterococcus**: Ampicillin + ceftriaxone or ampicillin + gentamicin
- **Viridans strep** (penicillin-sensitive): Penicillin G or ceftriaxone ± gentamicin for synergy

Antibiotic duration is typically **4–6 weeks**, depending on vegetation size, prosthetic involvement, and clearance of bacteremia [39].

11.2 Surgical Indications

Up to **50% of patients with IE** will require **surgical intervention** during the disease course. Indications are based on **hemodynamic deterioration**, **risk of embolization**, and **failure of medical therapy**.

Table 1: Major Indications for Cardiac Surgery in IE

Category	Indication
Heart failure	Valve dysfunction causing acute pulmonary edema or cardiogenic shock
Uncontrolled infection	Abscess, fistula, persistent bacteremia despite appropriate antibiotics
Embolic risk	Large (>10 mm), mobile vegetation, especially after embolic event
Prosthetic valve IE	Paravalvular leak, dehiscence, prosthetic dysfunction
Recurrent emboli	Despite appropriate antibiotic therapy
Fungal or resistant organisms	Candida, Brucella, or multidrug-resistant Gram-negatives

The **timing** of surgery is critical. In cases of severe heart failure or ongoing embolization, **early surgery (during active infection)** improves survival [39].

11.3 Importance of Infectious Disease Consultation

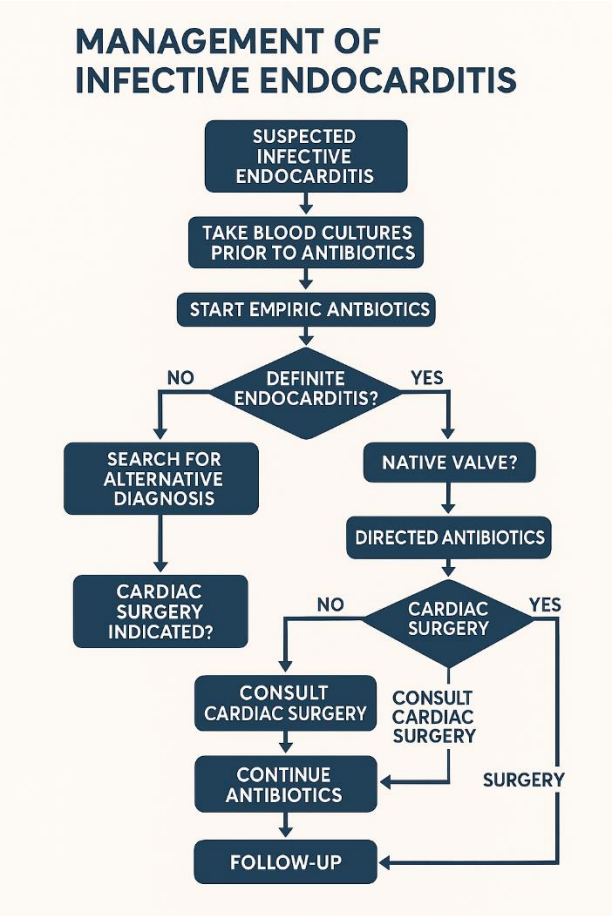
Multiple studies confirm that involvement of an **ID specialist** significantly improves outcomes, even in culture-negative or device-related cases. DeSimone et al. (2025) reported that **ID consultation reduced in-hospital mortality by 30%** and shortened time to effective therapy, particularly in prosthetic valve and *S. aureus* bacteremia cases.

Key roles of ID involvement:

- Guiding diagnostic workup for culture-negative endocarditis
- Recommending appropriate empiric and definitive therapy
- Evaluating for metastatic infection (e.g., vertebral osteomyelitis)
- Monitoring therapy duration and adverse effects
- Supporting decisions on valve surgery and long-term suppressive therapy

In **culture-negative IE**, the ID team facilitates specialized testing (e.g., *Bartonella*, *Coxiella*, *Tropheryma whipplei*) and helps initiate empirical regimens based on epidemiologic risk [39,56].

Figure Suggestion: "Decision Tree for IE Management"



Stepwise decision-making in the management of infective endocarditis (IE). After obtaining blood cultures, empirical antibiotics are started. Confirmed IE guides selection of directed therapy and consideration of surgery, with ongoing follow-up and multidisciplinary oversight.

Conclusion

Infective endocarditis (IE) remains a formidable clinical challenge due to its complex pathogenesis, variable presentation, and potential for severe complications. The disease begins with **endothelial injury** and progresses through **bacterial colonization**, **vegetation formation**, and **immune evasion**, leading to both localized cardiac destruction and systemic sequelae. The spectrum of complications includes **valvular regurgitation**, **embolic stroke**, **metastatic infections** such as **vertebral osteomyelitis**, and **immune-mediated glomerulonephritis**, underscoring the urgency of early recognition and intervention.

This case-based review illustrates how a delayed diagnosis of IE can result in **metastatic vertebral osteomyelitis**, a preventable yet often overlooked manifestation. The failure to recognize persistent *Staphylococcus aureus* bacteremia as a red flag contributed to a cascade of complications in the presented patient. However, with a structured diagnostic strategy and prompt treatment—including prolonged intravenous antibiotics and multidisciplinary care—the patient achieved a favorable outcome.

Timely diagnosis hinges on a **high index of suspicion**, particularly in patients with known bacteremia, prosthetic heart valves, or nonspecific systemic symptoms. The integration of **advanced imaging modalities** (e.g., transesophageal echocardiography, FDG-PET/CT) and **comprehensive laboratory workup** enhances diagnostic sensitivity, especially in complex or culture-negative cases.

Most importantly, the adoption of the **2023 Duke–ISCVID criteria** represents a critical advancement in the diagnostic framework of IE. These updated guidelines incorporate novel imaging findings and microbiologic tools, improving the detection of both native and prosthetic valve infections, and aligning clinical practice with modern capabilities.

Ultimately, early recognition, **pathogen-directed therapy**, **appropriate surgical intervention**, and **infectious disease consultation** are the cornerstones of effective IE management. Vigilance among clinicians—especially in interpreting subtle signs and leveraging diagnostic algorithms—is essential to prevent the devastating consequences of delayed or missed endocarditis.

References

1. Friedman ND, Kaye KS, Stout JE, et al. Health care--associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med 2002; 137:791.
2. Pant S, Patel NJ, Deshmukh A, et al. Trends in infective endocarditis incidence, microbiology, and valve replacement in the United States from 2000 to 2011. J Am Coll Cardiol 2015; 65:2070.
3. Toyoda N, Chikwe J, Itagaki S, et al. Trends in Infective Endocarditis in California and New York State, 1998-2013. JAMA 2017; 317:1652.
4. Selton-Suty C, Célard M, Le Moing V, et al. Preeminence of Staphylococcus aureus in infective endocarditis: a 1-year population-based survey. Clin Infect Dis 2012; 54:1230.

5. Olmos C, Vilacosta I, Fernández-Pérez C, et al. The Evolving Nature of Infective Endocarditis in Spain: A Population-Based Study (2003 to 2014). J Am Coll Cardiol 2017; 70:2795.
6. Wang A, Athan E, Pappas PA, et al. Contemporary clinical profile and outcome of prosthetic valve endocarditis. JAMA 2007; 297:1354.
7. Habib G, Erba PA, Iung B, et al. Clinical presentation, aetiology and outcome of infective endocarditis. Results of the ESC-EORP EURO-ENDO (European infective endocarditis) registry: a prospective cohort study. Eur Heart J 2019; 40:3222.
8. Khaloo P, Uzomah UA, Shaqdan A, et al. Outcomes of Patients Hospitalized With Cardiovascular Implantable Electronic Device-Related Infective Endocarditis, Prosthetic Valve Endocarditis, and Native Valve Endocarditis: A Nationwide Study, 2003 to 2017. J Am Heart Assoc 2022; 11:e025600.
9. Glaser N, Jackson V, Holzmann MJ, et al. Aortic valve replacement with mechanical vs. biological prostheses in patients aged 50-69 years. Eur Heart J 2016; 37:2658.
10. Glaser N, Jackson V, Holzmann MJ, et al. Prosthetic Valve Endocarditis After Surgical Aortic Valve Replacement. Circulation 2017; 136:329.
11. Bjursten H, Rasmussen M, Nozohoor S, et al. Infective endocarditis after transcatheter aortic valve implantation: a nationwide study. Eur Heart J 2019; 40:3263.
12. Hill EE, Herijgers P, Claus P, et al. Infective endocarditis: changing epidemiology and predictors of 6-month mortality: a prospective cohort study. Eur Heart J 2007; 28:196.
13. Cantrell M, Yoshikawa TT. Infective endocarditis in the aging patient. Gerontology 1984; 30:316.
14. Pericàs JM, Llopis J, Athan E, et al. Prospective Cohort Study of Infective Endocarditis in People Who Inject Drugs. J Am Coll Cardiol 2021; 77:544.
15. Lockhart PB, Brennan MT, Thornhill M, et al. Poor oral hygiene as a risk factor for infective endocarditis-related bacteremia. J Am Dent Assoc 2009; 140:1238.
16. Østergaard L, Valeur N, Wang A, et al. Incidence of infective endocarditis in patients considered at moderate risk. Eur Heart J 2019; 40:1355.
17. Cherubin CE, Neu HC. Infective endocarditis at the Presbyterian Hospital in New York City from 1938-1967. Am J Med 1971; 51:83.
18. Zegri-Reiriz I, de Alarcón A, Muñoz P, et al. Infective Endocarditis in Patients With Bicuspid Aortic Valve or Mitral Valve Prolapse. J Am Coll Cardiol 2018; 71:2731.
19. DeSimone DC, DeSimone CV, Tleyjeh IM, et al. Association of Mitral Valve Prolapse With Infective Endocarditis Due to Viridans Group Streptococci. Clin Infect Dis 2015; 61:623.
20. Tornos MP, Permanyer-Miralda G, Olona M, et al. Long-term complications of native valve infective endocarditis in non-addicts. A 15-year follow-up study. Ann Intern Med 1992; 117:567.
21. Carrel T, Schaffner A, Vogt P, et al. Endocarditis in intravenous drug addicts and HIV infected patients: possibilities and limitations of surgical treatment. J Heart Valve Dis 1993; 2:140.
22. Martino P, Micozzi A, Venditti M, et al. Catheter-related right-sided endocarditis in bone marrow transplant recipients. Rev Infect Dis 1990; 12:250.
23. Robinson DL, Fowler VG, Sexton DJ, et al. Bacterial endocarditis in hemodialysis patients. Am J Kidney Dis 1997; 30:521.
24. Nahass RG, Weinstein MP, Bartels J, Gocke DJ. Infective endocarditis in intravenous drug users: a comparison of human immunodeficiency virus type 1-negative and -positive patients. J Infect Dis 1990; 162:967.
25. Bestetti RB, Figueiredo JF, Da Costa JC. Salmonella tricuspid endocarditis in an intravenous drug abuser with human immunodeficiency virus infection. Int J Cardiol 1991; 30:361.

26. Riancho JA, Echevarría S, Napal J, et al. Endocarditis due to Listeria monocytogenes and human immunodeficiency virus infection. Am J Med 1988; 85:737.
27. Sax H, Bloemberg G, Hasse B, et al. Prolonged Outbreak of Mycobacterium chimaera Infection After Open-Chest Heart Surgery. Clin Infect Dis 2015; 61:67.
28. Hasse B, Hannan MM, Keller PM, et al. International Society of Cardiovascular Infectious Diseases Guidelines for the Diagnosis, Treatment and Prevention of Disseminated Mycobacterium chimaera Infection Following Cardiac Surgery with Cardiopulmonary Bypass. J Hosp Infect 2020; 104:214.
29. Østergaard L, Voldstedlund M, Bruun NE, et al. Temporal Changes, Patient Characteristics, and Mortality, According to Microbiological Cause of Infective Endocarditis: A Nationwide Study. J Am Heart Assoc 2022; 11:e025801.
30. Tleyjeh IM, Abdel-Latif A, Rahbi H, et al. A systematic review of population-based studies of infective endocarditis. Chest 2007; 132:1025.
31. Correa de Sa DD, Tleyjeh IM, Anavekar NS, et al. Epidemiological trends of infective endocarditis: a population-based study in Olmsted County, Minnesota. Mayo Clin Proc 2010; 85:422.
32. Fowler VG Jr, Miro JM, Hoen B, et al. Staphylococcus aureus endocarditis: a consequence of medical progress. JAMA 2005; 293:3012.
33. Selton-Suty C, Célard M, Le Moing V, et al. Preeminence of Staphylococcus aureus in infective endocarditis: a 1-year population-based survey. Clin Infect Dis 2012; 54:1230.
34. Murdoch DR, Corey GR, Hoen B, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. Arch Intern Med 2009; 169:463.
35. Téllez A, Ambrosioni J, Llopis J, et al. Epidemiology, Clinical Features, and Outcome of Infective Endocarditis due to Abiotrophia Species and Granulicatella Species: Report of 76 Cases, 2000-2015. Clin Infect Dis 2018; 66:104.
36. Das M, Badley AD, Cockerill FR, et al. Infective endocarditis caused by HACEK microorganisms. Annu Rev Med 1997; 48:25.
37. Ambrosioni J, Martinez-Garcia C, Llopis J, et al. HACEK infective endocarditis: Epidemiology, clinical features, and outcome: A case-control study. Int J Infect Dis 2018; 76:120.
38. Nappi F., Spadaccio C., Dreyfus J., Attias D., Acar C., Bando K. Mitral endocarditis: A new management framework. J. Thorac. Cardiovasc. Surg. 2018;156:1486–1495. doi: 10.1016/j.jtcvs.2018.03.159. [DOI] [PubMed] [Google Scholar]
39. *Nappi F., Avtaar Singh S.S. Host-Bacterium Interaction Mechanisms in Staphylococcus aureus Endocarditis: A Systematic Review. Int. J. Mol. Sci. 2023;24:11068. doi: 10.3390/ijms241311068.* [DOI] [PMC free article] [PubMed] [Google Scholar]
40. Baddour LM, Wilson WR, Bayer AS, et al. Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications: A Scientific Statement for Healthcare Professionals From the American Heart Association. Circulation 2015; 132:1435.
41. Cahill TJ, Prendergast BD. Infective endocarditis. Lancet 2016; 387:882.
42. GROSS NJ, TALL R. CLINICAL SIGNIFICANCE OF SPLINTER HAEMORRHAGES. Br Med J 1963; 2:1496.
43. Loughrey PB, Armstrong D, Lockhart CJ. Classical eye signs in bacterial endocarditis. QJM 2015; 108:909.
44. Fowler VG Jr, Sanders LL, Sexton DJ, et al. Outcome of Staphylococcus aureus bacteremia according to compliance with recommendations of infectious diseases

specialists: experience with 244 patients. Clin Infect Dis 1998; 27:478.
45. Meine TJ, Nettles RE, Anderson DJ, et al. Cardiac conduction abnormalities in endocarditis defined by the Duke criteria. Am Heart J 2001; 142:280.
46. Lindner JR, Case RA, Dent JM, et al. Diagnostic value of echocardiography in suspected endocarditis. An evaluation based on the pretest probability of disease. Circulation 1996; 93:730.
47. Irani WN, Grayburn PA, Afridi I. A negative transthoracic echocardiogram obviates the need for transesophageal echocardiography in patients with suspected native valve active infective endocarditis. Am J Cardiol 1996; 78:101.
48. Rasmussen RV, Høst U, Arpi M, et al. Prevalence of infective endocarditis in patients with Staphylococcus aureus bacteraemia: the value of screening with echocardiography. Eur J Echocardiogr 2011; 12:414.
49. Kim IC, Chang S, Hong GR, et al. Comparison of Cardiac Computed Tomography With Transesophageal Echocardiography for Identifying Vegetation and Intracardiac Complications in Patients With Infective Endocarditis in the Era of 3-Dimensional Images. Circ Cardiovasc Imaging 2018; 11:e006986.
50. Sifaoui I, Oliver L, Tacher V, et al. Diagnostic Performance of Transesophageal Echocardiography and Cardiac Computed Tomography in Infective Endocarditis. J Am Soc Echocardiogr 2020; 33:1442.
51. Feuchtner GM, Stolzmann P, Dichtl W, et al. Multislice computed tomography in infective endocarditis: comparison with transesophageal echocardiography and intraoperative findings. J Am Coll Cardiol 2009; 53:436.
52. Bruun NE, Habib G, Thuny F, Sogaard P. Cardiac imaging in infectious endocarditis. Eur Heart J 2014; 35:624.
53. Van Riet J, Hill EE, Gheysens O, et al. (18)F-FDG PET/CT for early detection of embolism and metastatic infection in patients with infective endocarditis. Eur J Nucl Med Mol Imaging 2010; 37:1189.
54. de Camargo RA, Sommer Bitencourt M, Meneghetti JC, et al. The Role of 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in the Diagnosis of Left-sided Endocarditis: Native vs Prosthetic Valves Endocarditis. Clin Infect Dis 2020; 70:583.
55. Fowler VG, Durack DT, Selton-Suty C, et al. The 2023 Duke-International Society for Cardiovascular Infectious Diseases Criteria for Infective Endocarditis: Updating the Modified Duke Criteria. Clin Infect Dis 2023; 77:518.
56. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000; 30:633.
57. Tattevin P, Watt G, Revest M, et al. Update on blood culture-negative endocarditis. Med Mal Infect 2015; 45:1.
58. Fowler VG, Durack DT, Selton-Suty C, et al. The 2023 Duke-International Society for Cardiovascular Infectious Diseases Criteria for Infective Endocarditis: Updating the Modified Duke Criteria. Clin Infect Dis 2023; 77:518.
59. Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyjeh IM, Rybak MJ, Barsic B, Lockhart PB, Gewitz MH, Levison ME, Bolger AF, Steckelberg JM, Baltimore RS, Fink AM, O'Gara P, Taubert KA: Diagnosis, Antimicrobial Therapy, and Management of Complications: A Scientific Statement for Healthcare Professionals From the American Heart Association. Circulation. 2015 Oct 13;132(15):1435-86. doi: 10.1161/CIR.0000000000000296. Epub 2015 Sep 15.
60. DeSimone DC, Garrigos ZE, Marx GE, Tattevin P, Hasse B, McCormick DW, Hannan MM, Zuhlke LJ, Radke CS, Baddour LM; American Heart Association Council on Lifelong Congenital Heart Disease and Heart Health in the Young;

Council on Clinical Cardiology; and Council on Quality of Care and Outcomes Research. Blood Culture-Negative Endocarditis: A Scientific Statement From the American Heart Association: *Endorsed by the International Society for Cardiovascular Infectious Diseases*. J Am Heart Assoc. 2025 Apr 15;14(8):e040218. doi: 10.1161/JAHA.124.040218. Epub 2025 Mar 17. Erratum in: J Am Heart Assoc. 2025 May 6;14(9):e10928. doi: 10.1161/JAHA.124.035178. PMID: 40094211; PMCID: PMC12132861.