

# INFECTIVE ENDOCARDITIS

## Relevant Guidelines

### **ESC 2023 guidelines on infective endocarditis**

2023 ESC Guidelines for the management of endocarditis. *Eur Heart J*. 2023.

### **ACC/AH 2020 guideline on valve disease**

2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease *J Am Coll Cardiol*. 2020

## Relevant Scientific Statements and Position Papers

### **AHA 2015 statement on infective endocarditis**

Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications: A Scientific Statement for Healthcare Professionals From the American Heart Association. *Circulation*. 2015;132:1435-86.

### **AHA 2016 Statement on Vascular Graft Infections, Mycotic Aneurysms, and Endovascular Infections**

Vascular Graft Infections, Mycotic Aneurysms, and Endovascular Infections: A Scientific Statement From the American Heart Association *Circulation*. 2016;134:e412-e460

### **AHA 2021 statement on streptococcal endocarditis prevention**

Prevention of Viridans Group Streptococcal Infective Endocarditis: A Scientific Statement From the American Heart Association. *Circulation*. 2021:CIR0000000000000969.

### **AHA 2024 Scientific Statement on Implantable Device Infection**

Update on Cardiovascular Implantable Electronic Device Infections and Their Prevention, Diagnosis, and Management: A Scientific Statement From the American Heart Association: Endorsed by the International Society for Cardiovascular Infectious Diseases. *Circulation*. 2024;149:e201-e216.

# INFECTIVE ENDOCARDITIS

## Definition

**Infective endocarditis (IE)** denotes infection of the endocardial surface of the heart. It most commonly involves heart valves (especially mitral and aortic) but may also occur at the site of a septal defect, on the chordae tendineae, or on the mural endocardium.<sup>1</sup> The characteristic lesion, a vegetation, is composed of a collection of platelets, fibrin, microorganisms, and inflammatory cells.<sup>2</sup> IE is either acute or subacute–chronic and is usually classified in four categories: native valve endocarditis, prosthetic valve endocarditis (early ie <1 year after valve surgery or late), infective endocarditis in intravenous drug users, and nosocomial infective endocarditis.

**Non-bacterial thrombotic endocarditis (NBTE)**, formerly recognized as marantic endocarditis, represents a rare cardiovascular pathology intricately linked with hypercoagulable states, notably malignancy and autoimmune disorders. It is characterized by the development of sterile vegetations comprised of fibrin and platelets on cardiac valves.<sup>3</sup>

## Epidemiology

The incidence of IE ranges within 3–10 episodes/100 000 person-years, and has not changed over the past two decades.<sup>1,4</sup> In the western world there is an increasing incidence of IE associated with a prosthetic valve and a possible decrease in patients with underlying rheumatic heart disease, which is more frequent in underdeveloped countries. New at-risk groups in developed countries include injection drug addicts, elderly with valvular sclerosis, people with prosthetic valves, patients on hemodialysis, and those with nosocomial exposure. IE is now more often an acute disease, most cases occur in patients over 60 years old and men are more likely to be affected than women.<sup>5</sup> Prosthetic valve endocarditis is the most severe form of IE and occurs in 1–6% of patients with valve prostheses, with an incidence of 0.3–1.2% per patient-year.<sup>5</sup> Although endocarditis is an uncommon coexisting condition in bacterial meningitis (in 2% of patients and usually due to *Streptococcus pneumoniae* and *Staphylococcus aureus*), it is associated with a high rate of unfavorable outcome.<sup>6</sup>

## Aetiology

According to the International Collaboration on Endocarditis-Prospective Cohort Study, a multinational and multicenter study of 2781 adults with IE conducted at 58 sites in 25 countries, *Staphylococcus aureus* is now the most common cause of IE in much of the world, followed by *viridans streptococci*, *enterococci*, and *coagulase-negative staphylococcus*.<sup>5</sup> This finding was confirmed by the more recent report of the ESC-EORP EURO-ENDO Registry.<sup>7</sup> However, in a recent population-based nationwide study from Spain, streptococcal endocarditis was still more frequent than *Staphylococcus*

*aureus* endocarditis.<sup>8</sup> There is evidence that the risk of endocarditis is dependent on the infecting streptococcal species. The highest endocarditis prevalence is observed in *S mutans*, *S gordonii*, *S sanguinis*, *S gallolyticus*, and *S mitis/oralis* bloodstream infections.<sup>9</sup> Gram-positive organisms account for >80% of all cases (Figures 1 and 2). *Candida* is the most frequent cause of fungal endocarditis, and culture-negative IE comprise 5-12% of all cases. Contrary to previous assumptions, IE in drug abusers is not limited to right-heart native valve infections by *S. aureus*. Left-sided and prosthetic valve endocarditis and non-staphylococcal organisms are relatively common.<sup>10</sup>

Cardiac abnormalities that are associated with high risk of IE are prosthetic cardiac valves or prosthetic material used for cardiac valve repair, previous infective endocarditis, congenital conditions unrepaired or repaired with prosthetic material, and cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve (see Prophylaxis). Infective endocarditis after left-sided heart valve replacement is not uncommon and occurs in about 1/20 over 10 years. Male, bioprosthetic valve, and heart failure were among factors associated with IE in MVR patients while male, bioprosthetic valve, and implantable devices were among factors associated with IE in AVR patients.<sup>11</sup> However, 50% of cases of infective endocarditis develop in patients with no known history of valve disease.<sup>1</sup> Between 15% and 30% of patients with antiphospholipid syndrome have valvular heart disease, known as Libman-Sacks endocarditis or nonbacterial thrombotic endocarditis.<sup>12</sup>

Infections of cardiac implantable electronic devices (CIED) are discussed in the Chapter on Complications of CIED.

Malignancy and autoimmune disorders are considered to be the causes of Non-bacterial thrombotic endocarditis.<sup>3</sup>

## Pathophysiology

The primary event is bacterial adherence to damaged endocardium. Excoriation of the endothelium triggers coagulation, and is colonized by bacteria that attract monocytes to produce tissue factor and cytokines.<sup>2, 13</sup> Cytokines and procoagulant factors contribute to continuing enlargement of the infected coagulum that eventually creates the vegetation. Organisms such as *Staph aureus*, *streptococci* and *enterococci* have surface adhesins that mediate attachment to the vegetation. *Staph aureus* also carries fibronectin-binding proteins on its surface that are adhered to the endothelium through the affinity of integrins, proteins that are produced as a response of endothelial cells to local inflammation, with fibronectin.<sup>2</sup> Microorganisms become enveloped within the vegetation and trigger further tissue factor production and platelet activation that both kills bacteria through microbicidal proteins and has procoagulant effects. Tissue invasion and abscess formation then follows. Infective endocarditis is more often due to gram-positive than gram-negative bacteria possibly because of differences in adherence to damaged valves or because of differences in their susceptibility to serum-induced

killing.<sup>2</sup> Bacterial adherence is completed within minutes during transient bacteremia that can be caused by microsurgical actions such as dental procedures. There is now evidence that most cases of infective endocarditis are not attributable to an invasive procedure, and bacteremia resulting from daily activities is much more likely to cause infective endocarditis than bacteremia associated with a dental or other procedure.<sup>13</sup> Thus, antibiotic prophylaxis in this setting is not mandatory.

Malignancy and autoimmune disorders, such as lupus and antiphospholipid antibody syndrome, and, more recently, COVID-19 contribute to endothelial dysfunction, hypercoagulability, and hypoxia in Non-bacterial thrombotic endocarditis.<sup>3</sup>

## Presentation

More than 90% of patients present with **fever**, often associated with systemic symptoms of malaise, anorexia, myalgias, and weight loss. It may be absent or minimal in patients with congestive heart failure, chronic renal or liver failure, previous use of antimicrobial drugs, or infective endocarditis caused by less virulent organisms, in the elderly and in immunocompromised patients.

**Embolic events** to the brain (>50% of emboli), spleen or lung occur in 15-30% of patients with IE and may be the presenting feature. They are associated with tricuspid or pulmonary IE, presence of a vegetation, and Staph aureus IE.<sup>7</sup> An embolic event is the most common presentation of Non-bacterial thrombotic endocarditis.<sup>3</sup>

**Native valve endocarditis.** Degenerative lesions such as mitral regurgitation and senile aortic stenosis are present in up to 50% of patients with IE older than 60 years.<sup>2</sup> Mitral valve prolapse predisposes patients to IE with an estimated incidence of 0.01% per patient-year of follow-up. The risk is significantly higher in the presence of flail leaflets and MR (1.5% per year).<sup>14</sup>

**Prosthetic valve endocarditis** is found in 5-20% of patients with IE.<sup>5, 15, 16</sup> It is *early* (within 2 months post-operatively, usually due to *Staph aureus*), or *late* (typically >12 months post-operatively), often due to *Streptococci*, and gram-negative bacteria of the *HACEK* group. Although mechanical valves probably have a higher rate of infection during the first three months after surgery, similar rates with bioprostheses are seen later.<sup>15</sup> Prosthetic valve endocarditis may be manifested as an indolent illness with low-grade fever, or it can be acute with new or changing murmurs and congestive heart failure. Unexplained fever in a patient with a prosthetic valve should prompt careful evaluation for prosthetic valve endocarditis.

In patients with **implanted devices**, clinical manifestations of pocket infection are present in the majority of patients with early lead-associated endocarditis (<6 months after device implantation). However, late lead-associated endocarditis should be considered in any patient who presents with fever, bloodstream infection, or signs of sepsis, even if the device pocket appears uninfected. Prompt recognition and management may improve outcomes.<sup>17, 18</sup> See Chapter 76 for a detailed discussion. In **IV drug addicts**, IE usually occurs in the absence of pre-existing valve lesions. The TV is affected

in >50% of cases but only 1/3 of patients have a murmur on admission. *Staph aureus* is the most common pathogen (up to 70%), followed by *streptococci*, *Pseudomonas aeruginosa*, and *polymicrobial* causes (including *anaerobes*).<sup>5, 17, 19</sup> In HIV positive IV drug abuser the risk is inversely related to the CD4 count (four-fold higher if CD4 < 200 cels/ $\mu$ L).<sup>20</sup>

**Nosocomial endocarditis** is defined as IE developing in patients hospitalized >48h prior to the onset of symptoms or signs of IE.

## Clinical Features

Most, but not all, patients present with **fever**.

**Heart murmurs** are found in up to 50% of patients, while worsening of old murmurs is found in 20% of patients.<sup>5</sup>

**Myoskeletal symptoms** (arthralgia, myalgia, back pain) may appear early with the disease.

**Peripheral stigmata** of IE are increasingly uncommon (2-8%), as patients generally present at an early stage of the disease, are not pathognomonic, and are virtually absent in tricuspid valve endocarditis.

**Splinter haemorrhages** (linear petechiae in the mid-nailbed)

**Osler's nodes** (tender, raised nodules on the pads of fingers or toes)

**Janeway's lesions** (nontender, slightly raised haemorrhages on palms and soles)

**Conjunctival haemorrhage**

**Roth's spots** (haemorrhagic spots with a central white area in the retina)

**Systemic embolism** usually occurs to the *brain*, *spleen*, and *kidneys* or other organs in left-sided IE, and to *lungs* in right-sided IE.

**Neurological findings** may be due to embolism or intracranial hemorrhage (see Complications).

**Heart failure** may be seen with ensuing valve destruction or chordal rupture.

## Diagnosis

Diagnostic schemes according to the **modified Duke criteria** as considered by AHA/ACC, as well as the modified ESC criteria are presented in Table 1. Patients should be managed by a dedicated endocarditis team (Table 2 and Figure 3). General recommendations for diagnosis in patients with native or prosthetic valves are provided in Tables 3 and 4, and Figures 4-7.

**Transthoracic echocardiography** has a sensitivity of 60-70% for detecting vegetations.

**Transesophageal echocardiography** is the first line imaging modality.. It increases sensitivity to 75-95% while maintaining specificity of 85-98%.<sup>15</sup> It is also more sensitive for detecting perivalvular extension of the infection, valve perforations and myocardial abscess.

**Cerebral angiography** or **Magnetic Resonance Angiography** are used for detection of intracranial mycotic aneurysms.

**CT** or **CMR** have limited value for diagnosing intracardiac infections, but can be useful for detection of cerebral bleeding and embolic events or splenic abscess.

<sup>18</sup>F-fluorodesoxyglucose (<sup>18</sup>F-FDG) **PET-CT** is also a promising modality for detecting infection.<sup>21-24</sup>

Novel cadmium-zinc-telluride (**CZT**) detector equipped SPECT systems improve the accuracy of molecular/cellular imaging, and with simultaneous multi-isotope imaging with <sup>111</sup>In and <sup>99m</sup>Tc are under study for the diagnosis of suspected endocarditis.<sup>25</sup> Multi-modality imaging is often necessary in IE.<sup>26</sup>

**ESR** and **CRP** (elevated in >60% of patients), as well as **leukocytosis**, **anaemia**, and **microscopic haematuria** may be present but are not specific.

**Blood cultures** In patients with possible infective endocarditis, three or at least two sets of cultures of blood (one aerobic and one anaerobic) collected by separate venipunctures should be obtained within the first 1 to 2 hours of presentation. Patients with cardiovascular collapse should have three cultures of blood obtained at 5-to-10-minute intervals and thereafter receive empirical antibiotic therapy.

Sampling from central venous catheters carries a high risk of contaminants (mainly staphylococci).

Positive blood cultures for *E. faecalis* and *S. aureus* have the highest prevalence of IE.<sup>27, 28</sup>

Epidemiological clues that may assist aetiologic diagnosis are provided in Tables 5 and 6.

**Culture-negative endocarditis** occurs in at least half of IE patients in the current era.<sup>28</sup> There are three main causes: 1. blood cultures sterilized by previous antibacterial treatment, 2. endocarditis related to fastidious microorganisms, such as *HACEK* bacteria, *defective streptococci* - *Gemella*, *Granulicatella*, and *Abitrophia* *sp* - *Propionibacterium acnes*, *Candida* *sp*. In these cases, prolonged incubation will allow identifying the causative pathogen in a few days, and 3. the "true" blood culture-negative endocarditis, due to intra-cellular bacteria that cannot be routinely cultured in blood with currently available techniques, such as *Bartonella* *sp*, *Coxiella burnetii* (both easily diagnosed by ad hoc serological tests), and *Tropheryma whipplei* (usually diagnosed by PCR on excised cardiac valve tissue).<sup>29</sup> Subacute right-sided IE, mural IE, and uremia are other causes. Serologic testing, valve or blood polymerase-chain-reaction (**PCR**) assay, and highly specialized microbiologic techniques lead to the identification of the pathogen in up to 60% of cases.<sup>1</sup> PCR amplification of the 16S ribosomal RNA gene that is specific for bacteria in tissue samples, including valves and peripheral emboli, can remain positive even after long-term treatment with antibiotics.<sup>30</sup>

*HACEK* group are fastidious, gram-negative bacilli that grow slowly in standard blood culture media, and recovery may require prolonged incubation. Thus, the microbiology laboratory should be asked to retain blood cultures for ≥2 weeks in all patients suspected of having IE but whose blood cultures are initially negative. Bacteremia caused by *HACEK* microorganisms in the absence of an obvious focus of infection is highly suggestive of endocarditis even in the absence of typical physical findings.

*HACEK* IE is very uncommon in North America.<sup>2</sup>

*Q* fever IE (*Coxiella burnetii*) and *Bartonella* IE are also more common in Europe than in North America.<sup>4</sup> *Q* fever IE (a zoonosis) is one of the most common causes of culture-negative IE. Serology

(IgG phase 2>1:800), tissue culture and immunohistology and PCR of surgical material are needed for diagnosis of Q fever IE. *Bartonella sp* (*B. Quintana* and *B. henselae*) IE is a subacute form that may present with heart failure due to AR. Predisposing factors are alcoholism, homelessness, and exposure to body lice. Blood cultures, serology, culture and immunohistology and PCR of surgical material are needed for identification of *Brucella* or *Bartonella* or *Legionella sp*.

Serology, culture and immunohistology and PCR of surgical material are needed for *Mycoplasma spp*, and histology and PCR of surgical material for identification of *Tropheryma whipplei*. *Non-tuberculous mycobacteria* is a rare cause of endocarditis following cardiac surgery.<sup>31</sup> Blood cultures, serology and PCR of surgical material are needed for diagnosis of *fungal* endocarditis. Microbial cell-free DNA testing (Karius test) is necessary for identification of causative such as *M chimaera* that should be considered as a potential cause of infections after cardiopulmonary bypass surgery.<sup>32</sup>

## Therapy

Appropriate antibiotic therapy should be initiated and continued after blood cultures are obtained with guidance from antibiotic sensitivity data and infectious disease consultants. Patients with known valve disease should not receive antibiotics before blood cultures are obtained for unexplained fever. General recommendations on therapy are provided in Tables 7-9, and Figures 8-10. Detailed antibiotic schemes have been published by AHA and ESC.<sup>19, 33</sup> Therapy of IE is mostly based on expert opinion, since no large, randomized studies exist. Bactericidal antibiotics are indicated, and the choice of an optimum regimen is based on antibiotic susceptibility testing and minimum inhibitory concentrations (MIC) of the principal drugs for the infecting pathogens. Due to the inoculum effect, ie reduced antimicrobial activity on highly dense bacterial populations, the effective MIC can be much higher than anticipated by in vitro susceptibility tests.<sup>19</sup> Prolonged therapy (4-6 weeks) is usually necessary for the avoidance of relapses. Therapy can be switched to oral route once fever has subsided and blood cultures are negative.<sup>34</sup> In patients with left-sided endocarditis changing to oral therapy may be considered after 10 days of IV therapy (POET Trial).<sup>35, 36</sup> Catheter-based percutaneous mechanical aspiration (using catheters approved for thrombi and pulmonary embolus) is an emerging acute intervention for debulking infective vegetations in right-sided infective endocarditis.<sup>37</sup>

***Streptococci*** are common pathogenic agents in community-acquired native valve endocarditis. The taxonomy of these organisms is evolving, and certain species have biological characteristics that may complicate diagnosis and therapy.<sup>19</sup> Resistance to penicillin and other  $\beta$  lactams (intermediate resistance MIC: 0.12  $\mu\text{g/L}$ , high resistance: MIC>0.5  $\mu\text{g/L}$ ) may be seen in viridans group *streptococci* (a-hemolytic) and *S gallolyticus (bovis)*-a nonenterococcal group D *streptococcus*.

Traditionally, coagulase-positive ***staphylococci*** (*S aureus*) cause primarily native valve endocarditis, whereas coagulase-negative staphylococci (*S epidermidis* and various other species) cause primarily

prosthetic valve endocarditis, but considerable overlap exists. *S aureus* is now the most common cause of IE in the developed world.<sup>5</sup> **Methicillin-resistant staphylococci** (MRSA) are also resistant to most other antibiotics (including quinolones), and vancomycin resistance is also beginning to develop. No standard therapies exist for the treatment of *S aureus* IE caused by isolates that are not susceptible to vancomycin. Classification of these isolates has become complex and includes designations of reduced susceptibility (hVISA), intermediate resistance (VISA), and high-level resistance (VRSA).

Daptomycin is an effective alternative to vancomycin/gentamicin for MRSA endocarditis., and, linezolid, and quinupristin-dalfopristin, telavacin, and ceftaroline may also be effective.<sup>19</sup>

**Enterococcal** IE typically occurs in older male patients with urinary tract infection or instrumentation. Enterococcal endocarditis is increasingly frequent worldwide and the vast majority of cases are due to *E. faecalis*, which often affects prosthetic valves and less frequently pacemakers/defibrillators.<sup>38</sup> Although its clinical presentation may be less severe than nonenterococcal endocarditis, relapses are common. There is increasing resistance to aminoglycosides, and multidrug-resistant enterococci are also resistant to vancomycin (VRE) and cause infections of increased morbidity and mortality.

**Fungal** endocarditis is rare but can develop in a wide range of patients. The well-recognized risk factors associated with fungal endocarditis, such as IV drugs abuse and immunocompromised state, have become less prevalent compared with the presence of a cardiovascular device, including central venous catheters, permanent pacemakers and defibrillators, and prosthetic valves.<sup>19</sup> Valve replacement is usually needed (AHA 2015 statement on IE, I –B). In treated cases, chronic lifelong suppression with an oral azole is recommended (AHA 2015 statement on IE, IIa-B), especially in patients who were not suitable for valve replacement.

The management of **culture-negative endocarditis** is presented in Tables 8 and 9. Predictors of poor outcome are presented in Table 10.

The management of **endocarditis related to cardiac devices (CIED)** is discussed in the relevant Chapter. These patients may need their devices removed even when endocarditis is apparently confined to a cardiac valve.

Endovascular therapy or neurosurgical intervention may be needed for **intracranial mycotic aneurysms**.<sup>39</sup>

Regardless of the source of infection, inpatients with IE should be thoroughly evaluated by a **dentist** familiar with the potential role of the mouth in these cases. The optimal timing for this evaluation may be after the patient's cardiac status has stabilized and early enough that all invasive dental procedures can be accomplished during intravenous antibiotic therapy. The clinical examination should rule out periodontal inflammation and pocketing around the teeth and caries that will eventually result in pulpal infection. A full series of intraoral radiographs is required for the identification of caries and periodontal disease (eg, bone loss, tooth fractures) (AHA 2015 statement on IE, I-C).

Criteria for **outpatient therapy** are presented in Table 10. Indications for **surgery** are

discussed in the section on Complications.

## Complications

**Heart failure** due to valve destruction, **uncontrolled infection**, and **embolic phenomena** are the most common complications of IE and constitute indications for valve replacement. Other indications for **surgery** are presented in Tables 11 and 12, and Figures 11, and 12. Other indication for surgery are IE due to organisms that are difficult to eradicate such as *Pseudomonas aeruginosa*, *brucella*, *Coxiella burnetii*, and *fungi*, and IE on prosthetic valves. Surgical mortality in active IE is 6-25%. When surgery is performed within the first week of antibiotic treatment, there may be increased risks of relapse and prosthetic-valve dysfunction.<sup>40</sup> However, in the EASE trial, early surgery was beneficial in patients with left-sided infective endocarditis, severe valve disease, and large vegetations.<sup>41</sup> There is now evidence of an association between early surgery and lower mortality in endocarditis.<sup>19</sup> Valvular surgery should be deferred when hemorrhage is present.<sup>42</sup> In mitral valve IE, repair may be feasible but in the aortic position valve replacement is usually needed. Mechanical and biological prostheses have similar outcome. If blood cultures are still negative at the time of surgery, a sample of valve tissue should be obtained for culture, and a broad-range PCR assay should be performed to help identify the causative microorganism. Approximately one fourth of patients with surgical indications did not undergo surgery in the international (ICE-PLUS) cohort. Factors associated with nonsurgical treatment were a history of moderate/severe liver disease, stroke before surgical decision, and *Staphylococcus aureus* etiology.<sup>43</sup>

Surgery may lead to a sudden release of inflammatory mediators, which is associated with postoperative organ dysfunction, but hemoadsorption despite reducing plasma cytokines at the end of cardiopulmonary bypass, did not result in any of the clinically relevant outcome measures.<sup>44</sup>

**Embolic events** are related to migration of vegetations. They are more often seen with large vegetations (>10 mm),<sup>45</sup> and *Staph aureus* or *Candida* IE. Age, diabetes, AF and embolism before antibiotics are also associated with embolism.<sup>46</sup> Reported incidence is 20-40% but much lower after initiation of suitable antibiotic therapy (6-12%). Aspirin does not reduce the risk of embolization.<sup>47</sup> The risk is higher during the first 2 weeks of treatment and with large (>10 mm, and especially >15 mm) and mobile vegetations. The role of anticoagulants in IE is controversial. Temporary discontinuation of anticoagulation until the septic phase of the disease is overcome is usually recommended, especially in cases of *S aureus* endocarditis.<sup>42</sup> Recommendations are provided in Table 13. Recent evidence suggests that, despite recommendations, surgery, when indicated, should be probably not delayed in the absence of severe neurological impairment.<sup>48</sup> Left-sided IE with vegetation size >10 mm are associated with more complications and higher mortality, but surgery during the index hospitalization results in lower 6-month mortality.<sup>49</sup>

**Neurological complications** may be due to emboli (usually middle cerebral artery), intracranial haemorrhage due to mycotic aneurysms that result from septic embolization of vegetations to the arterial vasa vasorum, or due to rupture of an artery related to septic arteritis at the site of embolism. Vegetation size  $\geq 3$  cm, *Staphylococcus aureus* as the causative microorganism, and involvement of the mitral valve are risk factors related to the development of neurological complications, whereas early and appropriate antimicrobial treatment reduced their incidence.<sup>42</sup> Unruptured aneurysms may resolve with antibiotic therapy alone, and patients should be followed with serial angiography performed to document the resolution of the aneurysm. Endovascular treatment should be pursued only if the aneurysm is very large (e.g.,  $>10$  mm) or if it is not resolving or is enlarging despite treatment with antibiotics.<sup>1</sup>

The management of neurologic complications is presented in Table 14.

**Heart failure** may be seen in up to 40% of IE cases and is most commonly associated with aortic than mitral regurgitation. Urgent surgery is indicated in unstable patients; otherwise stable AR or MR are dealt with after eradication of the infection.

**Endocarditis-related TR** is increasingly recognized due to IV drug abuse, and the use of AngioVac-assisted vegetation debulking is also increasing.<sup>50</sup>

**Uncontrolled infection** Fever associated with infective endocarditis often resolves within two to three days after the start of appropriate antimicrobial treatment in patients with less virulent pathogens, and defervescence occurs in the majority of patients by the end of the second week of treatment. The most common causes of persistent fever ( $>14$  days) are infection due to resistant organisms, extension of infection beyond the valve (often with myocardial abscess, pseudoaneurysm or fistula), other nosocomial infection, pulmonary embolism, and drug hypersensitivity (particularly if the fever resolves and then recurs). Perivalvular extension is suspected in cases of persistent fever or new AV block. Perivalvular abscess is more common in aortic IE, and, especially, in prosthetic valve IE (50-100%). The presence of persistent positive blood cultures is an independent risk factor for in-hospital mortality which doubles the risk of death of patients with left-sided endocarditis.<sup>51</sup>

**Glomerulonephritis** is immune complex-mediated (15% of patients with IE). Renal embolism may cause haematuria (25% of patients) but rarely azotaemia. Antibiotic-induced interstitial nephritis (mainly with aminoglycosides and vancomycin), or severe haemodynamic impairment may also contribute.

**Pyogenic spondylodiscitis, peripheral arthritis, and myo-pericarditis** may also be seen. Splenic emboli are common but **splenic abscess** is rare. CT angiography, magnetic resonance angiography, or digital subtraction angiography can be used for detection of intracranial or extracranial **mycotic aneurysms** (AHA 2015 statement on IE, IIa-B). Cerebrospinal imaging to detect intracranial mycotic aneurysms or CNS bleeding in all patients with IE or contiguous spread of infection who develop severe, localized headache, neurological deficits, or meningeal signs (AHA 2015 statement on IE, I-B).

In-hospital **mortality** is approximately 17% and more frequent with prosthetic valve endocarditis.<sup>7</sup> Recommendations for post-discharge follow-up are provided in Table 15.

## Prognosis

History of previous endocarditis, and endocarditis in patients with a cardiac electronic device or with congenital heart disease and shunts or conduits are at high risk of dying due to endocarditis.<sup>52</sup> Increased age, pulmonary edema, paravalvular complications, prosthetic valve IE, and staphylococcal IE are also prognostic factors for in-hospital mortality.<sup>2</sup> Mortality rates vary according to the offending organism and range from approximately 10% with viridans streptococci, 25–45% with *S aureus*, to >50% with fungi (mainly *Candida* and *Aspergillus*), and *P aeruginosa*. Q fever IE also carries a high mortality. Overall mortality is 30%, ranging from 10% for right-sided, to up to 40% for left-sided IE, whereas operative mortality again depends on the underlying condition and varies between 5 to 15%.<sup>1, 4, 5, 15</sup> Haemorrhagic stroke is the most powerful factor associated with in-hospital mortality with left-sided IE.<sup>45</sup> Relapses usually occur within 2 months of discontinuation of therapy, 2–6% of patients (Table 16).<sup>34</sup> Main risk factors are inadequate duration of antibiotic therapy or the presence of resistant organisms, persistent focus of infection (ie abscess), and prosthetic valve endocarditis.<sup>19 53</sup> An algorithm for differentiating relapse from reinfection is presented in Figure 13. In a report of the ENDOREA Study Group, factors associated with long-term outcomes were the severity of multiorgan failure (the strongest independent predictor), prosthetic mechanical valve IE, vegetation size  $\geq 15$  mm, and surgical treatment, but not surgical timing.<sup>54</sup> There is increased long-term mortality in patients with culture-negative endocarditis when compared with those with culture-positive endocarditis, and this can be alleviated by surgery.<sup>55</sup> It is estimated that the average long-term survival rates after the completion of treatment for IE is 80–90% at 1 year, 70–80% at 2 years and 60–70% at 5 years.<sup>34</sup> Thus, infective endocarditis survivors have an increased morbidity and mortality after successful therapy and long-term surveillance is recommended.

## Pregnancy

The incidence of IE during pregnancy has been reported to be 0.006%,<sup>3</sup> and is either a complication of a pre-existing cardiac lesion or the result of intravenous drug abuse. Maternal and foetal mortality are approximately 30%, with most deaths relating to heart failure or an embolic event. Close attention should be paid to any pregnant woman with unexplained fever and a cardiac murmur, since rapid detection and appropriate treatment is important in reducing the risk of both maternal and foetal mortality.

## Prophylaxis

Turbulent blood flow produced by congenital or valve disease may traumatize the endocardium and endothelial surfaces. Invasion of the bloodstream by microbes that can colonize this damaged site may result in clinical infection. Transient bacteremia may occur after invasive procedures such as gastrointestinal and genitourinary, particularly at a site of preexisting infection. It is also very common during dental procedures and during daily activities such as tooth brushing or defecation. Oral mucosal surfaces and particularly the gingival crevice around teeth are populated by a dense endogenous microflora including species such as streptococci, and at least 126 individual bacteria have been isolated in blood cultures after extractions or toothbrushing.<sup>56, 57</sup> The rationale for endocarditis prophylaxis, therefore, was that antibiotics by limiting bacteremia should be effective in preventing infective endocarditis following invasive procedures. However, there has been no consistent association between interventional procedures, dental or non-dental, and the development of IE, and no controlled, randomized study has proven the efficacy of prophylaxis.<sup>58</sup> There has been evidence that most cases of infective endocarditis are not attributable to an invasive procedure, and that the protective efficacy of antibiotic prophylaxis is not significant.<sup>59, 60</sup> Bacteremia resulting from daily activities such as chewing food, brushing teeth, flossing, use of water irrigation devices and other activities, is much more likely to cause infective endocarditis than bacteremia associated with a dental procedure.<sup>57</sup> The presence of dental disease may increase the risk of bacteremia associated with these routine activities. Maintenance of optimal oral health and hygiene may reduce the incidence of bacteremia from daily activities and is more important than prophylactic antibiotics for a dental procedure in reducing the risk of infective endocarditis (Figure 14, and Table 17). Finally, the risk of a serious allergic reaction to amoxicillin may be greater than the risk of contracting infective endocarditis. In high-risk patients subjected invasive dental procedures (particularly extractions and oral surgical procedures) antibiotic prophylaxis is indeed associated with a lower incidence of postprocedural endocarditis.<sup>61</sup> Both the ACC/AHA, and, especially, the ESC accept that prophylaxis is recommended in high-risk patients as indicated in Tables 18-20. In a 2021 AHA Statement on viridans group streptococcal endocarditis, it is emphasized that if antibiotic prophylaxis is effective in preventing a very small number of cases of viridans group streptococcal endocarditis, it should be recommended only for those patients with an underlying condition.<sup>13</sup> Regarding nondental procedures, recent evidence have prompted an AHA Scientific Advisory to accept that high-risk patients are at increased risk of developing IE after several nondental invasive procedures, including CIED implantation, gastrointestinal endoscopy, and bronchoscopy.<sup>62</sup> Recommended antibiotics are presented in Table 21.

There has also been evidence that invasive dental procedures such as manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa (excluding local anaesthetic injection), indeed contribute a very small number of cases of bacterial endocarditis in patients with

prosthetic valves.<sup>63</sup> In an analysis of extensive insurance databases in the US between 2003 to 2015, more restrictive prescribing of antibiotic prophylaxis was accompanied by an increased incidence in cases of infective endocarditis.<sup>64</sup> In a Canadian Registry, infective endocarditis-related hospitalizations have increased since 2010, 3 years after the guideline revision, among both high- and moderate-risk patients, but were considered unlikely to be related to change in antibiotic prophylaxis due to the observed time lag, the increase in both high- and moderate-risk groups and not just the moderate-risk group, for whom recommendations changed, and the relative decrease of the proportion of streptococcal IE versus staphylococcal IE.<sup>65</sup> Thus, antibiotic infective endocarditis prophylaxis remains a rather empirical practice. It should be given to high-risk patients prior to dental procedures that involve manipulation in gingival tissue or periapical region of the teeth or perforation of the oral mucosa. In these high risk patients prophylaxis is cost-effective.<sup>66</sup> Prophylaxis is no longer needed for routine anesthetic injections through noninfected tissue, dental radiographs, placement of removable prosthodontic or orthodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth or bleeding from trauma to the lips or oral mucosa. Antibiotic infective endocarditis prophylaxis is also no longer indicated in patients with native valve disease such as aortic stenosis, mitral stenosis, or mitral valve prolapse. However, in a report of the GAMES registry, individuals with bicuspid aortic valve and mitral prolapse had a higher risk of developing endocarditis than the general population, and endocarditis in these patients was characterized by an aggressive clinical course, comparable to that of high-risk patients in terms of adverse events, and with a higher surgical need in BAV patients.<sup>67</sup> The changes in recommendations have not resulted in a higher incidence of streptococcal endocarditis in France,<sup>68</sup> but this finding was not verified in a subsequent US study that demonstrated a significant rise in the incidence of *Streptococcus* IE since the 2007 guideline revisions.<sup>69</sup> Furthermore, several invasive nondental medical procedures, especially coronary artery bypass grafting; procedures involving the skin and management of wounds; transfusion; dialysis; bone marrow puncture; and certain endoscopic procedures, particularly bronchoscopy, are associated with an increased risk of developing infective endocarditis.<sup>70</sup>

Thus, in certain cases, especially involving high-risk patients or cardiac conditions about which data are virtually lacking, such as coarctation of the aorta, significant native valve disease, or severe hypertrophic obstructive cardiomyopathy, as well as in patients subjected to dental or other procedures in the presence of active infection, or before vaginal delivery, the situation should be discussed, and patient preferences should be assessed. If doctors and patients feel more comfortable they can continue using prophylaxis with the antibiotic schemes proposed by ACC/AHA and ESC.

## References

1. Hoen B and Duval X. Clinical practice. Infective endocarditis. *N Engl J Med*. 2013;368:1425-33.
2. Moreillon P and Que YA. Infective endocarditis. *Lancet*. 2004;363:139-49.
3. Ahmed O, et al. Non-bacterial thrombotic endocarditis: a clinical and pathophysiological reappraisal. *Eur Heart J*. 2025;46:236-249.
4. Cahill TJ and al. e. Challenges in Infective Endocarditis. *J Am Coll Cardiol*. 2017;69:325 – 4 4.
5. Murdoch DR, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Pro prospective Cohort Study. *Arch Intern Med*. 2009;169:463-73.
6. Lucas MJ, et al. Endocarditis in adults with bacterial meningitis. *Circulation*. 2013;127:2056-62.
7. Habib G, 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;40:3222-3232.
8. Olmos C, et al. The Evolving Nature of Infective Endocarditis in Spain: A Population-Based Study (2003 to 2014). *J Am Coll Cardiol*. 2017;70:2795-2804.
9. Chamat-Hedemand S, et al. Prevalence of Infective Endocarditis in Streptococcal Bloodstream Infections Is Dependent on Streptococcal Species. *Circulation*. 2020;142:720-730.
10. Pericàs JM and al. e. Prospective Cohort Study of Infective Endocarditis in People Who Inject Drugs. 2021.
11. Ostergaard L, et al. Incidence and factors associated with infective endocarditis in patients undergoing left-sided heart valve replacement. *Eur Heart J*. 2018.
12. Corban MT and al. e. Antiphospholipid Syndrome Role of Vascular Endothelial Cells and Implications for Risk Stratification and Targeted Therapeutics. *J Am Coll Cardiol*. 2017;69:2317-30.
13. Wilson WR, et al. Prevention of Viridans Group Streptococcal Infective Endocarditis: A Scientific Statement From the American Heart Association. *Circulation*. 2021:CIR0000000000000969.
14. Foster E. Clinical practice. Mitral regurgitation due to degenerative mitral-valve disease. *N Engl J Med*. 2010;363:156-65.
15. Mylonakis E and Calderwood SB. Infective endocarditis in adults. *N Engl J Med*. 2001;345:1318-30.
16. Cuervo G and al. e. The Clinical Challenge of Prosthetic Valve Endocarditis. *JACC*. 2024.
17. Greenspon AJ, et al. Timing of the most recent device procedure influences the clinical outcome of lead-associated endocarditis results of the MEDIC (Multicenter Electrophysiologic Device Infection Cohort). *J Am Coll Cardiol*. 2012;59:681-7.
18. Baddour LM, et al. Update on Cardiovascular Implantable Electronic Device Infections and Their Prevention, Diagnosis, and Management: A Scientific Statement From the American Heart Association: Endorsed by the International Society for Cardiovascular Infectious Diseases. *Circulation*. 2024;149:e201-e216.
19. Baddour LM, 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;132:1435-86.
20. Wilson LE, et al. Prospective study of infective endocarditis among injection drug users. *J Infect Dis*. 2002;185:1761-6.
21. Bruun NE, et al. Cardiac imaging in infectious endocarditis. *Eur Heart J*. 2014;35:624-32.
22. Pizzi MN, et al. Improving the Diagnosis of Infective Endocarditis in Prosthetic Valves and Intracardiac Devices With 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Angiography: Initial Results at an Infective Endocarditis Referral Center. *Circulation*. 2015;132:1113-26.
23. Swart LE, et al. Improving the Diagnostic Performance of (18)F-FDG PET/CT in Prosthetic Heart Valve Endocarditis. *Circulation*. 2018.
24. Swart LE, et al. 18F-fluorodeoxyglucose positron emission/computed tomography and computed tomography angiography in prosthetic heart valve endocarditis: from guidelines to clinical practice. *Eur Heart J*. 2018;39:3739-3749.
25. Caobelli F, et al. Simultaneous dual-isotope solid-state detector SPECT for improved tracking of white blood cells in suspected endocarditis. *Eur Heart J*. 2016.
26. Erba PA, et al. Multimodality Imaging in Infective Endocarditis: An Imaging Team Within the Endocarditis Team. *Circulation*. 2019;140:1753-1765.
27. Ostergaard L, et al. Prevalence of infective endocarditis in patients with positive blood cultures: a Danish nationwide study. *Eur Heart J*. 2019;40:3237-3244.
28. Shah ASV, et al. Incidence, Microbiology, and Outcomes in Patients Hospitalized With Infective Endocarditis. *Circulation*. 2020;141:2067-2077.
29. Tattevin P, et al. Update on blood culture-negative endocarditis. *Med Mal Infect*. 2015;45:1-8.
30. Houpi kian P and Raoult D. Diagnostic methods current best practices and guidelines for identification of difficult-to-culture pathogens in infective endocarditis. *Infect Dis Clin North Am*. 2002;16:377-92, x.
31. Kohler P, et al. Healthcare-associated prosthetic heart valve, aortic vascular graft, and disseminated Mycobacterium chimaera infections subsequent to open heart surgery. *Eur Heart J*. 2015;36:2745-53.
32. Blumer V and al. e. Hemophagocytic Lymphohistiocytosis Associated With Endocarditis: A Case Years in the Making. *Circulation*. 2022.
33. Delgado V, et al. 2023 ESC Guidelines for the management of endocarditis. *Eur Heart J*. 2023.
34. Habib G, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for

- Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J*. 2015;36:3075-128.
35. Iversen K, et al. Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis. *N Engl J Med*. 2019;380:415-424.
  36. Pries-Heje MM, et al. Clinical implementation of partial oral treatment in infective endocarditis: the Danish POETry study. *Eur Heart J*. 2023;44:5095-5106.
  37. El Sabbagh A, et al. Outcomes of Percutaneous Mechanical Aspiration in Right-Sided Infective Endocarditis: A Multicenter Registry. *J Am Coll Cardiol*. 2025.
  38. Pericas JM, et al. A Contemporary Picture of Enterococcal Endocarditis. *J Am Coll Cardiol*. 2020;75:482-494.
  39. Wilson WR, et al. Vascular Graft Infections, Mycotic Aneurysms, and Endovascular Infections: A Scientific Statement From the American Heart Association. *Circulation*. 2016;134:e412-e460.
  40. Thuny F, et al. The timing of surgery influences mortality and morbidity in adults with severe complicated infective endocarditis: a propensity analysis. *Eur Heart J*. 2011;32:2027-33.
  41. Kang DH, et al. Early surgery versus conventional treatment for infective endocarditis. *N Engl J Med*. 2012;366:2466-73.
  42. Garcia-Cabrera E, et al. Neurological complications of infective endocarditis: risk factors, outcome, and impact of cardiac surgery: a multicenter observational study. *Circulation*. 2013;127:2272-84.
  43. Chu VH, et al. Association between surgical indications, operative risk, and clinical outcome in infective endocarditis: a prospective study from the International Collaboration on Endocarditis. *Circulation*. 2015;131:131-40.
  44. Diab M, et al. Cytokine Hemoadsorption During Cardiac Surgery Versus Standard Surgical Care for Infective Endocarditis (REMOVE): Results From a Multicenter Randomized Controlled Trial. *Circulation*. 2022;145:959-968.
  45. Sambola A, et al. Predictors of embolism and death in left-sided infective endocarditis: the European Society of Cardiology EURObservational Research Programme European Infective Endocarditis registry. *Eur Heart J*. 2023;44:4566-4575.
  46. Hubert S, et al. Prediction of symptomatic embolism in infective endocarditis: construction and validation of a risk calculator in a multicenter cohort. *J Am Coll Cardiol*. 2013;62:1384-92.
  47. Chan KL, et al. A randomized trial of aspirin on the risk of embolic events in patients with infective endocarditis. *J Am Coll Cardiol*. 2003;42:775-80.
  48. Yanagawa B, et al. Surgical Management of Infective Endocarditis Complicated by Embolic Stroke: Practical Recommendations for Clinicians. *Circulation*. 2016;134:1280-1292.
  49. Habib G. How do we reduce embolic risk and mortality in infective endocarditis? Measure the size of the vegetation and operate early in patients with large vegetations. *Eur Heart J*. 2019.
  50. Hahn RT. Tricuspid Regurgitation. *N Engl J Med*. 2023;388:1876-1891.
  51. Lopez J, et al. Prognostic role of persistent positive blood cultures after initiation of antibiotic therapy in left-sided infective endocarditis. *Eur Heart J*. 2013;34:1749-54.
  52. Thornhill MH, et al. Quantifying infective endocarditis risk in patients with predisposing cardiac conditions. *Eur Heart J*. 2017.
  53. Shih CJ, et al. Long-term clinical outcome of major adverse cardiac events in survivors of infective endocarditis: a nationwide population-based study. *Circulation*. 2014;130:1684-91.
  54. Mirabel M, et al. Long-term outcomes and cardiac surgery in critically ill patients with infective endocarditis. *Eur Heart J*. 2014;35:1195-204.
  55. Kong WKF, et al. Outcomes of culture-negative vs. culture-positive infective endocarditis: the ESC-EORP EURO-ENDO registry. *Eur Heart J*. 2022;43:2770-2780.
  56. Hill EE, et al. Infective endocarditis: changing epidemiology and predictors of 6-month mortality: a prospective cohort study. *Eur Heart J*. 2007;28:196-203.
  57. Lockhart PB, et al. Bacteremia associated with toothbrushing and dental extraction. *Circulation*. 2008;117:3118-25.
  58. Chen TT and al. e. Risk of Infective Endocarditis After Invasive Dental Treatments. Case-Only Study. *Circulation* 2018.
  59. Lacassin F, et al. Procedures associated with infective endocarditis in adults. A case control study. *Eur Heart J*. 1995;16:1968-74.
  60. Van der Meer JT, et al. Efficacy of antibiotic prophylaxis for prevention of native-valve endocarditis. *Lancet*. 1992;339:135-9.
  61. Thornhill MH, et al. Antibiotic Prophylaxis Against Infective Endocarditis Before Invasive Dental Procedures. *J Am Coll Cardiol*. 2022;80:1029-1041.
  62. Baddour LM, et al. Nondental Invasive Procedures and Risk of Infective Endocarditis: Time for a Revisit: A Science Advisory From the American Heart Association. *Circulation*. 2023;148:1529-1541.
  63. Tubiana S, et al. Dental procedures, antibiotic prophylaxis, and endocarditis among people with prosthetic heart valves: nationwide population based cohort and a case crossover study. *BMJ*. 2017;358:j3776.
  64. Thornhill MH and al. e. Antibiotic Prophylaxis and Incidence of Endocarditis Before and After the 2007 AHA Recommendations. *JACC*. 2018.
  65. Garg P, et al. Infective Endocarditis Hospitalizations and Antibiotic Prophylaxis Rates Before and After the 2007 American Heart Association Guideline Revision. *Circulation*. 2019;140:170-180.
  66. Franklin M, et al. The Cost-Effectiveness of Antibiotic Prophylaxis for Patients at Risk of Infective Endocarditis. *Circulation*. 2016;134:1568-1578.
  67. Zegri-Reiriz I, et al. Infective Endocarditis in Patients With Bicuspid Aortic Valve or Mitral Valve Prolapse. *J Am Coll Cardiol*. 2018;71:2731-2740.

68. Duval X, et al. Temporal trends in infective endocarditis in the context of prophylaxis guideline modifications: three successive population-based surveys. *J Am Coll Cardiol*. 2012;59:1968-76.
69. Pant S, et al. Trends in infective endocarditis incidence, microbiology, and valve replacement in the United States from 2000 to 2011. *J Am Coll Cardiol*. 2015;65:2070-6.
70. Janszky I and al. e. Invasive Procedures Associated With the Development of Infective Endocarditis. *JACC*. 2018.

