CONSENSUS REPORT

# Diagnosis, treatment and prevention of infective endocarditis: Turkish consensus report-2019*

## İnfektif endokarditin tanısı, tedavisi ve önlenmesi: Ulusal uzlaşı raporu-2019*

Serap Şimşek Yavuz, M.D.,[1] Ahmet Rüçhan Akar, M.D.,[2] Sinan Aydoğdu, M.D.,[3] Denef Berzeg Deniz, M.D.,[1] Hakan Demir, M.D.,[4] Tuncay Hazırolan, M.D.,[5] Mehmet Ali Özatik, M.D.,[2] Necla Özer, M.D.,[3] Murat Sargın, M.D.,[2] Emine Nursen Topcuoğlu, M.D.,[6] Nesrin Turhan, M.D.,[7] Mehmet Birhan Yılmaz, M.D.,[3] Özlem Azap, M.D.,[1] Seniha Başaran, M.D.,[1] Yasemin Çağ, M.D.,[1] Atahan Çağatay, M.D.,[1] Güle Çınar, M.D.,[1] Sibel Doğan Kaya, M.D.,[1] Lokman Hızmalı, M.D.,[1] Mehmet Emirhan Işık, M.D.[1] Nirgül Kılıçaslan, M.D.[1] Şirin Menekşe, M.D.,[1] Meliha Meriç-Koç, M.D.,[1] Serpil Öztürk, M.D.,[1] Ayfer Şensoy, M.D.,[1] Yasemin Tezer-Tekçe, M.D.,[1] Elif Tükenmez-Tigen, M.D.,[1] Yeşim Uygun-Kızmaz, M.D.,[1] Mutlu Şeyda Velioğlu-Öcalmaz, M.D.,[1] Ayşegül Yeşilkaya, M.D.,[1] Emel Yılmaz, M.D.,[1] Neziha Yılmaz, M.D.,[1] Fatma Yılmaz-Karadağ, M.D.[1]

[1]Turkish Society of Clinical Microbiology and Infectious Diseases, Infective Endocarditis and Other Cardiovascular Infections Study Grup (Istanbul University, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Resarch Hospital, Başkent University, İstanbul Medeniyet University, Ankara University, Kartal Koşuyolu High Speciality Training and Research Hospital, Kırşehir Ahi Evran University, Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, Bezmiâlem Vakıf University, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Resarch Hospital, Ankara City Hospital, Marmara University, Uludağ University, Yozgat Bozok University, Göztepe Training and Research Hospital), İstanbul, Turkey; [2]Turkish Society of Cardiovascular Surgery (Ankara University, Ankara City Hospital, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Resarch Hospital), İstanbul, Turkey; [3]Turkish Society of Cardiology (Ankara City Hospital, Hacettepe University, Dokuz Eylül University), İstanbul, Turkey; [4]Turkish Society of Nuclear Medicine (Kocaeli University), Ankara, Turkey; [5]Turkish Society of Radiology (Hacettepe University), Ankara, Turkey; [6]Turkish Dental Association (İstanbul University), Ankara, Turkey; [7]Federation of Turkish Pathology Societies, Cardiovascular System Study Group (Ankara City Hospital), Ankara, Turkey

***Summary–*** Infective endocarditis (IE) is a rare but still important as an infectious disease due to high rate of morbidity and substantial mortality. Although IE is not a notifiable disease in Turkey, and an incidence study has not been performed, the incidence may be higher than that in the developed countries due to frequent predisposing cardiac conditions and higher rates of nosocomial bacteremia, which may lead to IE in risk groups. IE generally affects the elderly in developed countries but it is frequently encountered among young individuals in Turkey. In order to reduce mortality and morbidity, it is critical to diagnose IE, to determine the causative agent, and to start treatment rapidly. Most patients cannot be diagnosed at the first visit, about half can be diagnosed after 3 months, and the disease often goes unnoticed. In patients diagnosed with IE, the rate of the identification of a causative organism is significantly lower in Turkey than that in developed countries. Some im-

***Özet–*** İnfektif endokardit (İE) nadir görülmesine karşın, yol açtığı morbiditeler ve yüksek mortalite hızı nedeniyle halen önemini koruyan bir infeksiyon hastalığıdır. Türkiye'de İE'nin bildirimi zorunlu bir hastalık olmamasına ve yapılmış bir insidans çalışması bulunmamasına karşın, gerek İE yatkınlığını artıran durumların, gerekse riskli hastalarda İE ile sonuçlanabilen nozokomiyal bakteriyemi oranlarının daha fazla olması nedeniyle, ülkemizdeki İE insidansının daha yüksek olması beklenir. Gelişmiş ülkelerde genellikle yaşlı insanları etkileyen İE, ülkemizde halen genç insanları etkileyebilmektedir. Bu hastalığın mortalite ve morbiditesinin azaltılması için, hızlıca tanınması ve etkeninin belirlenerek, etkene yönelik tedavisinin yapılması kritik öneme sahiptir. Ancak hastaların çoğuna ilk başvurularında tanı konulamamakta, yaklaşık yarısında tanı 3 aydan sonra konulabilmekte ve hastalık sıklıkla gözden kaçmaktadır. İE tanısı konulmuş hastalarda, bu infeksiyona neden olan mikroorganizmaların belirlenme

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*Correspondence:* Dr. Serap Şimşek Yavuz. İstanbul Tıp Fakültesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, İstanbul, Turkey.
Tel: +90 505 - 269 64 12 e-mail: serapsimsekyavuz@gmail.com

portant microbiological diagnostic tests are not performed in most centers and several antimicrobials that are recommended as the first option for the treatment particularly antistaphylococcal penicillins, are unavailable in Turkey. These problems necessitate reviewing the epidemiological, laboratory, and clinical characteristics of IE in our country, as well as the current information about its diagnosis, treatment, and prevention together with local data. The diagnosis and treatment processes of IE should be standardized at every stage so that the management can be conducted in a setting in which physicians of various specialties are involved and is consistent with the current recommendations. The Study Group for Infective Endocarditis and Other Cardiovascular Infections of the Turkish Society of Clinical Microbiology and Infectious Diseases called for the collaboration of the relevant specialist organizations to establish a consensus report on the diagnosis, treatment, and prevention of IE in the context of current information and local data in Turkey.

oranı gelişmiş ülkelere göre Türkiye'de çok daha düşüktür. İE'li hastaların tanısının konulmasında kullanılabilecek bazı önemli mikrobiyolojik testler bu hastaları izleyen merkezlerin çoğunda yapılamamaktadır. Tedavide ilk seçenek olarak önerilen, başta antistafilokoksik penisilinler olmak üzere önemli bazı antimikrobik ajanlar ülkemizde piyasada yoktur. Bu sorunlar, ülkemizde hem İE'nin epidemiyolojik, laboratuvar ve klinik özelliklerini, hem de tanısı, tedavisi ve önlenmesiyle ilgili güncel bilgileri, yerel verileri de içerecek şekilde gözden geçirmeyi zorunlu kılmaktadır. İE'li hastalar birçok uzmanlık dalından hekim tarafından izlenebilir. Birçok daldan hekimin rol aldığı İE'li hastaların yönetiminin daima güncel önerilere uygun olarak yapılabilmesi için, İE'nin tanı ve tedavi süreçlerinin her aşamada standardize edilmesi gerekir. Bu bakış açısıyla, Türk Klinik Mikrobiyoloji ve İnfeksiyon Hastalıkları Derneği İnfektif Endokardit ve Diğer Kardiyovasküler İnfeksiyonlar Çalışma Grubu, ülkemizde güncel bilgilerin ve yerel verilerin ışığında İE'nin tanısı, tedavisi ve önlenmesine yönelik bir uzlaşı raporu oluşturabilmek amacıyla ilgili ulusal uzmanlık kuruluşlarına bir işbirliği çağrısında bulunmuştur.

Although infective endocarditis (IE) is rare, it is still important as an infectious disease because of the resulting morbidity and substantial mortality. Epidemiological studies in developed countries have shown that the incidence of IE has been approximately 6/100,000 in recent years and it is ranked fourth among the most life-threatening infectious diseases after sepsis, pneumonia, and intraabdominal infections. Although IE is not a reportable disease in Turkey, and an incidence study has not been performed, the incidence may be expected to be higher than in developed countries due to both the more frequent presence of predisposing cardiac conditions and higher rates of nosocomial bacteremia, which may lead to IE in risk groups. Additionally, while IE generally affects elderly people in developed countries, it develops in young people in Turkey. In order to reduce mortality and morbidity, it is critical to diagnose IE, to determine the causative agent, and to start treatment rapidly. However, most patients cannot be diagnosed at the first visit, about half can be diagnosed after 3 months, and the disease often goes unnoticed. In patients diagnosed with IE, the rate of identification of causative organisms is more than 90% in developed countries, while it is around 60% in Turkey. Some important microbiological diagnostic tests are not performed in most centers. Some antimicrobials that are recommended as the first option for treatment of IE, particularly antistaphylococcal penicillins, are unavailable in Turkey.[1–18] These problems necessitate reviewing the epidemiological, laboratory, and clinical characteristics of IE in our country, as well as the current information about its diagnosis, treatment, and prevention alongside local data. Patients with IE may be patients of physicians in many specialties. Diagnosis and treatment processes for IE should be

**Abbreviations:**

| | |
|---|---|
| *18F-FDG* | *18F-fluorodeoxyglucose* |
| *AHA* | *American Heart Association* |
| *ANA* | *Anti-nuclear antibody* |
| *ANCA* | *Antineutrophil cytoplasmic antibodies* |
| *ARA* | *Acute rheumatic fever* |
| *CIED* | *Cardiac implantable electronic devices* |
| *CRP* | *C-reactive protein* |
| *CT* | *Computed tomography* |
| *cTnI* | *Cardiac troponin I* |
| *ESC* | *European Society of Cardiology* |
| *ESR* | *Erythrocyte sedimentation rate* |
| *HACEK* | *Haemophilus parainfluenzae, Aggregatibacter spp. Cardiobacterium spp. Eikenella corrodens and Kingella spp.* |
| *IFA* | *Immunofluorescence assay* |
| *IVDU* | *Intravenous drug use* |
| *IE* | *Infective endocarditis* |
| *IM* | *Intramuscular* |
| *IV* | *Intravenously* |
| *MDCTA* | *Electrocardiogram-gated multidetector computed tomography angiography* |
| *MIC* | *Minimum inhibitory concentration* |
| *MRI* | *Magnetic resonance imaging* |
| *MRSA* | *Methicillin-resistant Staphylococcus aureus* |
| *MSSA* | *Methicillin-sensitive Staphylococcus aureus* |
| *NBTE* | *Non-bacterial thrombotic endocarditis* |
| *NT-pro-BNP* | *N-terminal pro b-type natriuretic peptide* |
| *NYHA* | *New York Heart Association* |
| *PCR* | *Polymerase chain reaction* |
| *PET* | *Positron emission tomography* |
| *RF* | *Rheumatoid factor* |
| *SPECT* | *Single-photon emission computed tomography* |
| *TEE* | *Transesophageal echocardiogram* |
| *TTE* | *Transthoracic echocardiogram* |

standardized at every stage so that management of IE can always be in line with current recommendations and should be conducted in a setting in which several physicians are involved. With this in mind, the Study Group for Infective Endocarditis and Other Cardiovascular Infections of the Turkish Society of Clinical Microbiology and Infectious Diseases called for the collaboration of relevant specialist organizations to create a consensus report on the diagnosis, treatment, and prevention of IE in the context of current information and local data in Turkey. In periodic meetings of the assigned representatives of all of the parties, various questions were identified and consensus answers were developed based upon a review of the related literature and international guidelines.

### 1. Why was this consensus report written?

IE generally affects elderly people in developed countries, but it still also affects young people in Turkey. It is one of the most life-threatening infectious diseases and frequently leads to mortality. Compared with European countries and the United States, patients in Turkey with IE are younger, the predisposing factors are different, identification rate of IE pathogens is lower, access to some important diagnostic tests is not possible or hardly possible, and some of the antimicrobials recommended for treatment are not available in our country. Therefore, European and American diagnostic and treatment guidelines do not completely meet our requirements and these conditions led to the preparation of a national consensus report for IE.[1–18]

**Table 1. Comparison of epidemiological and clinical features of patients with infective endocarditis in Turkey and USA/Europe**

| Feature | Turkey | USA/Europe |
|---|---|---|
| Age, years (mean) | 47 | 61 |
| Male (%) | 60 | 65 |
| Predisposing conditions (%) | | |
| Acute rheumatic fever | 37 | 1.85 |
| Prosthetic valve | 28 | 10–30 |
| Intravenous drug use | 2 | 24 |
| Cardiac implantable electronic device | 7 | 15 |
| Chronic hemodialysis | 9 | 13 |
| Causative microorganisms (%) | | |
| *Staphylococcus aureus* | 21 | 32 |
| *Viridans streptococci* | 19 | 18 |
| Coagulase-negative Staphylococci | 10 | 11 |
| *Enterococcus* spp. | 9 | 11 |
| *Brucella* spp. | 7 | – |
| Blood culture-negative (%) | 37 | 8 |
| Nosocomial endocarditis (%) | 25 | 25 |
| Mortality (%) | 24 | 19 |

## Epidemiology of Infective Endocarditis in Turkey and Globally

### 2. What is the incidence of infective endocarditis in our country and globally?

The incidence of IE is approximately 6/100,000 glob-

**Table 2. The incidence of infective endocarditis among risk groups**

| Predisposing condition | Incidence (per 100,000 population) |
|---|---|
| General population | |
| Mean | 6 |
| >70 years old | 12 |
| >75 years old | 19 |
| Structural heart valve diseases | |
| Rheumatic and degenerative heart valve diseases | 348 |
| Mitral valve prolapsus (regurgitating) | 48 |
| Congenital heart diseases | |
| Ventricular septal defect (small) | 480 |
| Bicuspid aortic valve | 66 |
| Intracardiac foreign body | |
| Prosthetic valve | >1000 (2800) |
| Transcatheter aortic valve implantation | >1000 |
| Permanent pacemaker/intracardiac defibrillator | 1000 |
| Previous infective endocarditis | 7300 |
| Patient with renal failure | |
| End-stage chronic renal failure | 627 |
| Hemodialysis | 1092 |
| Intravenous drug use | 1125 |
| Solid organ transplant | 1350 |

ally. There are no data about the incidence of IE in Turkey, though it is predicted to be higher in our country due to higher incidences of both valvular diseases and nosocomial bacteremia.[19–51] A comparison of epidemiological features of IE cases in Turkey and the USA and Europe is shown in Table 1.

### 3. Which patient populations have a greater risk of developing infective endocarditis in our country and globally?

IE is more frequently seen in patients with a previous episode of IE, valvular heart disease, congenital heart disease, any intracardiac prosthetic material, intravenous drug use (IVDU), chronic hemodialysis treatment, and solid organ or hematopoietic stem cell transplantation compared with the normal population. The incidence of IE among risk groups is shown in Table 2.[2,4,5,23,27–31,45,50,52–84]

### 4. Which microorganisms are most frequently identified as the cause of infective endocarditis in our country and globally?

The most frequent causative microorganisms are, in order, *Staphylococcus aureus*, streptococci, coagulase-negative staphylococci, and enterococci, both in Turkey and globally. *Brucella* spp. are the fifth most common causative agent of IE in Turkey (Table 1). *Coxiella burnetii*, which is one of the main causes of blood culture-negative IE globally, has been identified in some case reports from our country and so it must be included in the differential diagnosis. Although *Bartonella* spp. and *Tropheryma whipplei* are frequently the causes of blood culture-negative IE globally, there are no available data about these causative agents in Turkey and research concerning these agents should be performed. Gram-negative bacilli and fungi are generally causative agents of healthcare-associated IE. *Mycobacterium chimaera* should be kept in mind as a possible pathogen for blood culture-negative IE in patients who underwent implantation of an intracardiac prosthetic device, such as a prosthetic heart valve, in the last decade.[4,82,85–127]

## Pathogenesis of Infective Endocarditis

### 5. What is the pathogenesis of infective endocarditis?

Mechanical injury on the endocardial surface leads to the formation of non-bacterial thrombotic endocarditis and bacterial adhesion on the surface occurs during transient bacteremia. The vegetation enlarges and becomes mature through bacterial proliferation, deposition of fibrinogen, and platelet aggregation. *S. aureus* may bind directly to an inflamed but structurally intact endocardial surface and instead being ingested by endothelial cells, causing cellular tissue lysis and damage. These damaged cells induce the release of tissue factor and cytokines, causing blood clotting and promoting the extension of inflammation and vegetation formation.[21,27,86,128–136]

## Diagnosis of Infective Endocarditis

### 6. What are the clinical features in patients with infective endocarditis and which clinical signs should lead to the suspicion of infective endocarditis?

Acute IE must be in the differential diagnosis in patients admitted to the emergency room with a fever who have predisposing factors for IE (valvular heart diseases; intracardiac prosthetic devices, such as a prosthetic valve; IVDU; or chronic hemodialysis, etc.), and in patients who have sepsis of an unknown source, peripheral embolism, multiple infectious foci of sepsis, or a new-onset murmur.

Both subacute and chronic IE must be kept in mind in the differential diagnosis of patients with unexplained fever, fatigue, weight loss, and elevated acute phase reactants; unexplained arterial emboli, including the central nervous system and the pulmonary system; unexplained heart or valvular failure; and unexplained blood culture positivity, especially if there is a predisposing condition for IE.[4,14,23,137–143]

### 7. What are the laboratory findings of infective endocarditis?

Continuous bacteremia in patients with IE causes continuous intravascular stimulation, which consequently leads to acute phase responses to the causative agent and excessive production of both antibodies and immune complexes. Some laboratory test results may be either lower or higher than the normal range due to either sepsis or organ failure caused by the disease itself.[144–172]

### 8. Which echocardiographic methods should be used in the diagnosis of infective endocarditis and what is the appropriate timing?

Transthoracic echocardiography (TTE) must be per-

formed for all patients with suspected IE as soon as possible. Transesophageal echocardiography (TEE) must be performed in case of a negative TTE result when there is a high index of suspicion for IE, particularly when the TTE is of suboptimal quality. TEE should also be performed for patients with a prosthetic valve or other intracardiac prosthetic device.[3,65,66,141,173–183]

### 9. What are the echocardiographic findings leading to a diagnosis of infective endocarditis?

Vegetation, abscess, pseudoaneurysm or intracardiac fistula, valvular aneurysm or perforation, new partial dehiscence of a prosthetic valve, and new or worsening valvular regurgitation are echocardiographic findings and images that raise the suspicion of IE.[3,65,66,141]

### 10. What are the sensitivities and specificities of echocardiographic examinations for diagnosis of infective endocarditis?

The sensitivity of TTE and TEE for the detection of vegetation in IE patients is 70% and 96%, respectively, in native valves, and 50% and 92%, respectively, in prosthetic valves. Both modalities have a specificity of 90% for the detection of vegetation.[173]

### 11. What is the role of echocardiography in the determination of response to treatment and during follow-up of infective endocarditis?

While the size and mobility of the vegetation is expected to decrease with effective antimicrobial treatment, an increase in vegetation size should be taken into account as a risk factor for a new embolic event. It is difficult to interpret persisting and unchanging vegetation size. In this situation, the patient should be evaluated carefully with other clinical and laboratory findings. A well-timed echocardiogram is of vital importance to identify patients with the symptoms and signs (shortness of breath, rhythm-conduction disorders, etc.) of a local cardiac complication (abscess, heart failure, etc.) requiring emergent surgery.[3,173–186]

### 12. When should cardiac computed tomography be performed in patients with suspected infective endocarditis and what are the advantages and disadvantages?

Although cardiac computed tomography (CT) has the advantage of providing more information about cardiac anatomy (anatomy of pseudoaneurysm, abscess, fistula, and perivalvular extension), it is inferior to TEE in the detection of vegetation. Cardiac CT should be performed in the event of high suspicion of either native or prosthetic valve endocarditis following a negative TEE.[65,175,187,188]

### 13. When should magnetic resonance imaging be performed in patients with suspected infective endocarditis and what are the advantages and disadvantages?

The experience using cardiac magnetic resonance imaging (MRI) to define cardiac pathologies in patients with IE is limited. Existing proof suggests that cardiac MRI can be a good option to evaluate the cardiac anatomy, like cardiac CT. Further studies are needed. Currently, MRI is generally used to visualize intracranial complications in patients with neurological symptoms. A cranial MRI should be the diagnostic choice for IE patients with neurological symptoms, as its sensitivity is greater than that of a cranial CT in the detection of cranial lesions.[65,189,190]

### 14. When should 18F-fluorodeoxyglucose positron emission tomography/computed tomography imaging be performed in patients with suspected infective endocarditis and what are the advantages and disadvantages?

Imaging with 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/CT can be used to confirm the diagnosis by identifying both valvular and paravalvular lesions in patients with the suspicion of prosthetic valve endocarditis 3 months after the surgery when the TEE result was negative. 18F-FDG PET/CT can also be used to define septic foci outside the heart in both native and prosthetic valve endocarditis. The most important advantages of this modality are the ability to define infectious foci both inside and outside the heart, to establish functional data, and to monitor response to treatment. False-positivity, especially within the first 3 months after surgery in early prosthetic valve endocarditis and the lower sensitivity to diagnose intracardiac pathologies in native valve endocarditis are disadvantages of 18F-FDG PET/CT.[175,191–197]

### 15. When should radiolabeled leukocyte scintigraphy with single photon emission computed tomography be performed in patients with suspected infective endocarditis and what are the advantages and disadvantages?

Radiolabeled leukocyte scintigraphy with single-photon emission computed tomography (SPECT)/CT can

be used as an imaging modality for the diagnosis of prosthetic valve endocarditis within the first 3 months of prosthesis implantation. Although scintigraphy has a higher specificity, the most important disadvantage is a lower sensitivity.[65,198,199]

## 16. What should the algorithm be for imaging modalities in the diagnosis of infective endocarditis?

Echocardiography is the first imaging modality of choice to define cardiac lesions in patients with suspected IE. Both TTE and TEE are necessary in almost all patients. TTE and TEE are inconclusive in approximately 15% of all IE cases, whereas the percentage is up to 30% in patients with intracardiac prosthetic devices, such as a prosthetic valve or a cardiac implantable electronic device (CIED). In these patients, cardiac CT should be the imaging technique in patients with native valve endocarditis, while cardiac CT or SPECT/CT should be applied for patients who have prosthetic valve endocarditis within the first 1–3 months of valve surgery, and cardiac CT and PET/CT should be selected for patients with prosthetic valve endocarditis 3 months after valve surgery.[65,66,173–176] A flowchart for the diagnostic imaging work-up of patients suspected of IE is presented in Figure 1.[175]

## 17. How should blood culture sampling be performed in patients with suspected infective endocarditis?

In patients with suspected IE, 3 sets of blood cultures (3 pairs of aerobic and anaerobic bottles, 6 bottles in total) should be drawn at 30-minute intervals without waiting for a febrile period. Each blood culture set, comprising 1 aerobic and 1 anaerobic bottle, should be inoculated with 18–20 mL of blood (9–10 mL blood per bottle). A total of 60 mL of blood should be drawn from a patient with suspected IE. In patients who had cardiac surgery in the previous decade and there is a suspicion of prosthetic valve endocarditis, 3 additional blood culture bottles specified for mycobacterial growth should be inoculated, unless there is microbial growth in the initial blood culture bottles. Two sets of control blood cultures should be repeated every 48 hours after the initiation of therapy until the blood cultures are sterile.[3,65,86,119,200–207]

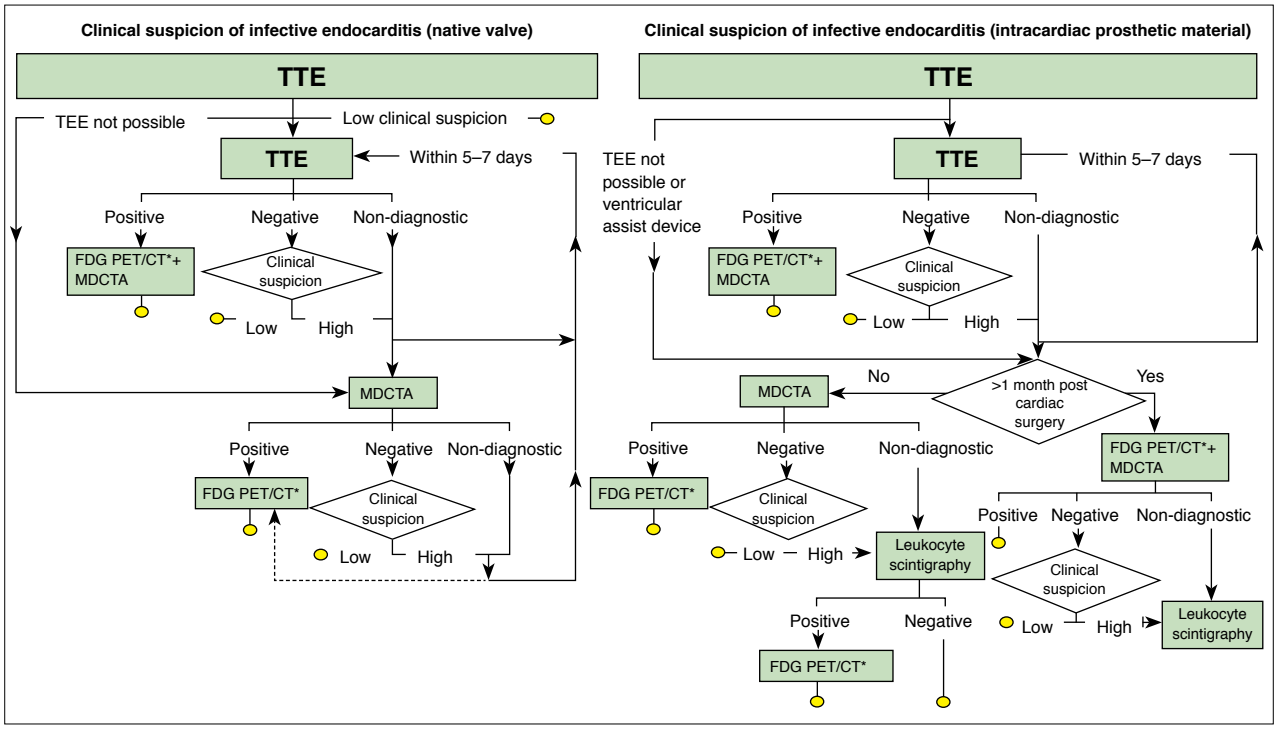


**Figure 1.** Flowchart for the diagnostic imaging work-up of patients suspected of infective endocarditis.[175] Yellow circles indicate the end of a diagnostic pathway when efforts to diagnose (extracardiac complications of) infective endocarditis can be ceased. *Allocation specifically for the detection of extracardiac foci. FDG PET: Fluorodeoxyglucose positron emission tomography; MDCTA: Electrocardiogram-gated multidetector computed tomography angiography; TEE: Transesophageal echocardiogram; TTE: Transthoracic echocardiogram.

## 18. How should valvular tissue or embolic specimens resected during surgery be cultured for the diagnosis of infective endocarditis?

Excised valvular tissue from patients with suspected IE should be evaluated both microbiologically (stains, culture, molecular techniques) and histopathologically.[208–210]

## 19. Which serological tests should be performed for the diagnosis of infective endocarditis and when?

In patients with negative blood cultures, a Wright agglutination test (with Coomb's serum) and a Coxiella phase 1 immunoglobulin G (IgG) test with the reference immunofluorescence assay (IFA) should be performed first. If the results of these 2 tests are negative, IgG antibodies for *Bartonella* spp., *Legionella* spp., *Chlamydia* spp., and *Mycoplasma* spp. should be tested, preferably using an IFA.[4,111,112,210–216]

## 20. What molecular tests can be used in either blood or tissue samples of patients with suspected infective endocarditis and when should they be considered?

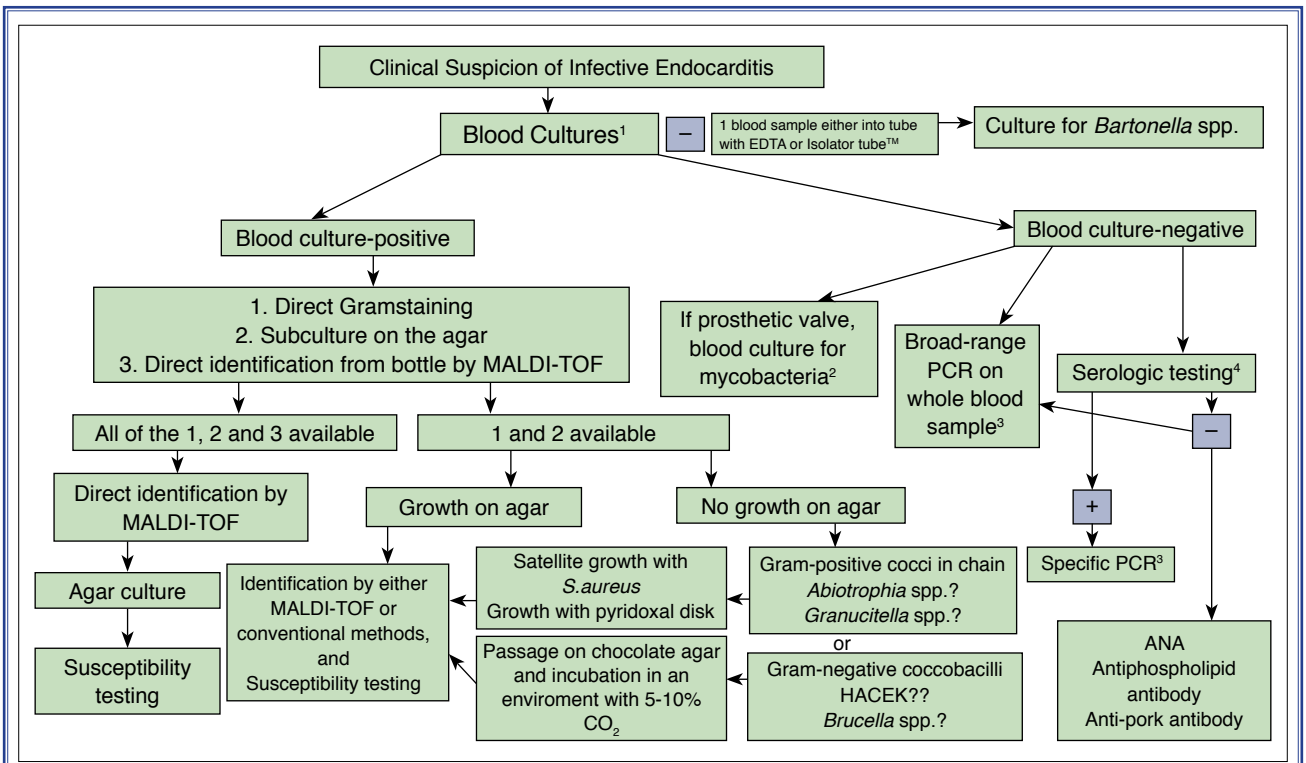


**Figure 2.** Diagnostic testing algorithm for the identification of the microbiological etiology of infective endocarditis. [1]Blood cultures: Three sets of blood cultures (a total of 6 bottles each inoculated with 10 mL of blood) collected from different venipuncture sites with at least 1 hour between the first and last draw. [2]In patients who are suspected of having prosthetic valve endocarditis, 3 additional blood culture bottles specified for mycobacterial growth (BD BACTEC Myco/F Lytic [Becton, Dickinson and Company, Franklin Lakes, NJ, USA], etc.) should be inoculated, unless there is microbial growth in the usual blood culture bottles. [3]PCR assays: Multiplex PCR tests targeting streptococci and staphylococci (LightCycler, SeptiFast, [F. Hoffmann-La Roche Ltd., Basel, Switzerland], etc.) or broad-range bacterial (16S rRNA) or fungal (18S rRNA) PCR followed by sequencing (SepsiTest; Molzym, Bremen, Germany, etc.) should be done for patients with blood culture-negative endocarditis who had taken antibiotics before admission. For patients with positive serological test results, organism-specific PCR should be conducted. [4]Serologic testing: Wright agglutination test with Coombs serum or Brucellacapt test (Vircell S.L., Granada, Spain), *Coxiella burnetii* phase I IgG, *Bartonella quintana* IgG, and *Bartonella henselae* IgG should be ordered first. If those test results are negative, then Legionella spp. IgG, Mycoplasma spp. IgG, *Chlamydophila pneumoniae* IgG and galactomannan antigen for *Aspergillus* spp. should be investigated in the serum. Interpretation of serological test results: *Coxiella burnetii* phase I IgG antibodies >1/800, *Bartonella* spp. IgG antibodies >1/800, *Chlamydia pneumoniae* IgG antibodies >1/512, *Legionella* spp. IgG antibodies >1/256, Wright agglutination test >1/160 Brucellacapt IgG antibodies >1/320, and a galactomannan optic density index of ≥0.5 should be considered positive. ANA: antinuclear antibody; EDTA: Ethylenediaminetetraacetic acid; HACEK: *Haemophilus parainfluenzae*, *Aggregatibacter* spp., *Cardiobacterium* spp., *Eikenella corrodens*, and *Kingella* spp.; IFA: Indirect immunofluorescence assay; IgG: Immunoglobulin G; MALDI-TOF: Matrix-assisted laser desorption ionization-time of flight; MIC: Minimum inhibitory concentration; PCR: Polymerase chain reaction.

Multiplex polymerase chain reaction (PCR) tests, such as SeptiFast (F. Hoffmann-La Roche Ltd., Basel, Switzerland) and SeptiTest (Molzym, Bremen, Germany), etc. should be used to identify the pathogen in a whole blood specimen of patients with suspected IE whose blood cultures are negative and the patient previously received antibiotic therapy. If the blood cultures are negative in a patient who has not received antibiotic therapy, then 16S rRNA gene and *Tropheryma whipplei* PCR testing should be performed on the resected heart valve obtained during surgery.[140,217–225]

## 21. What is the contribution of a histopathological examination of valvular tissue excised from patients with suspected infective endocarditis?

Histopathological examination of resected valvular tissue provides valuable information about the activation and degree of the inflammation in patients with blood culture-positive IE, whereas in blood culture-negative IE patients, it provides a means to identify pathogens, particularly intracellular pathogens, such as *Coxiella burnetii*, *Bartonella* spp. and *Tropheryma whipplei* with proper staining and immunohistochemical examinations. Figure 2 and Figure 3 are diagnostic testing algorithms for the identification of the microbiological etiology of IE.[119,138,225–232]

## 22. What is the sensitivity and specificity of the modified Duke criteria in the diagnosis of infective endocarditis?

The modified Duke criteria have a sensitivity of 80% in native valve endocarditis and are insufficient in patients with prosthetic heart valves, intracardiac prosthetic devices, or blood culture-negative endocarditis. Additional imaging techniques and serological-molecular tests should be added the diagnostic work-up of these patients.[65,141,233] The modified Duke criteria are presented in Table 3 and the modified European Society of Cardiology criteria are provided in Table 4.[3,65]

## 23. How is non-bacterial thrombotic endocarditis differentiated from infective endocarditis?

Non-bacterial thrombotic endocarditis (NBTE) can be seen with numerous clinical entities such as malignancy, connective tissue and autoimmune disorders, and hypercoagulable states. NBTE can be documented in approximately 1% of patients with

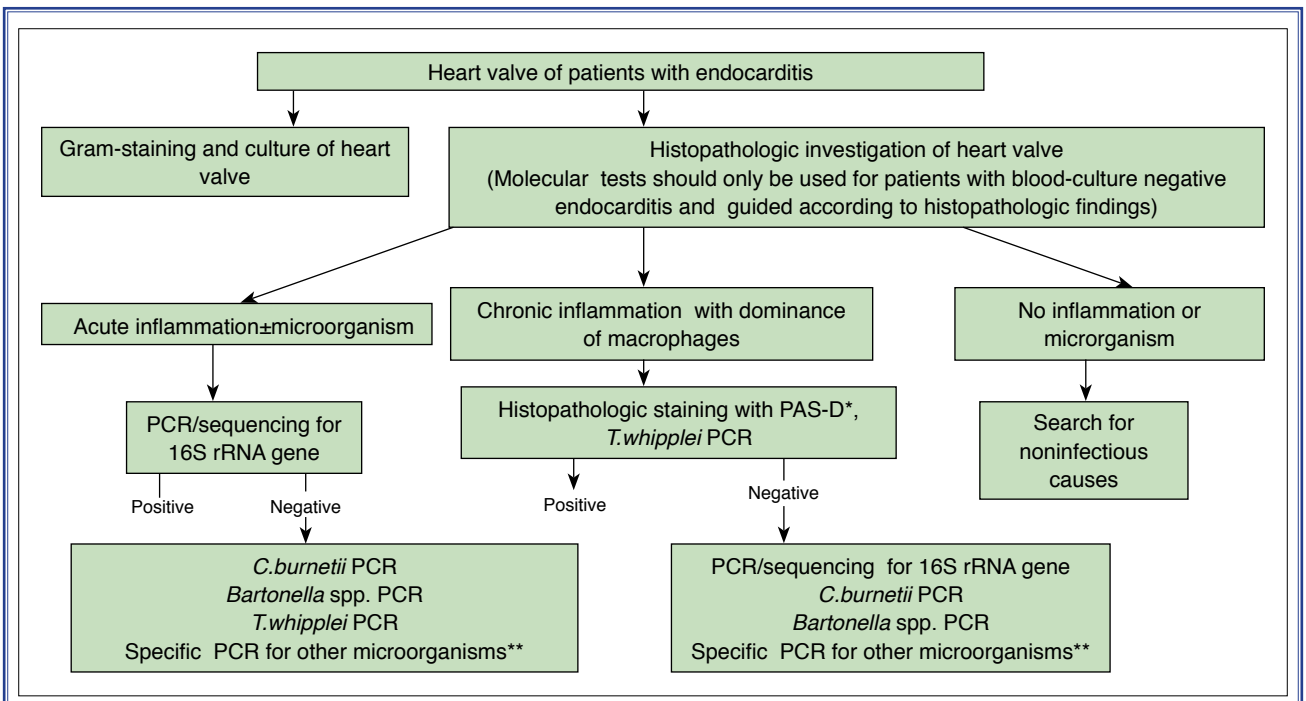


**Figure 3.** Microbiological and histopathological evaluation of heart valves removed from patient with endocarditis. *PAS-positive staining reaction is seen in macrophages infected with *Tropheryma whipplei*. **For example, *Mycoplasma hominis, Legionella* spp., *Chlamydia* spp., *Cutibacterium* (formerly Propionibacterium), acne, etc. PAS: Periodic-acid Schiff; PCR: Polymerase chain reaction.

**Table 3. Definition of infective endocarditis according to the modified Duke criteria[3,65]**

| Definite IE |
|---|
| Pathological criteria |
| • Microorganisms: demonstrated by culture or histology in a vegetation, or in a vegetation that has embolized, or in an intracardiac abscess specimen, or |
| • Pathological lesions: vegetation or intracardiac abscess confirmed by histology showing active endocarditis |
| Clinical criteria |
| • 2 major criteria, or |
| • 1 major criterion and 3 minor criteria, or |
| • 5 minor criteria |
| Possible IE |
| • 1 major criterion and 1 minor criterion, or |
| • 3 minor criteria |
| Rejected IE |
| • Firm alternate diagnosis, or |
| • Resolution of symptoms suggesting IE with antibiotic therapy for ≤4 days, or |
| • No pathological evidence of IE at surgery or autopsy, with antibiotic therapy for ≤4 days, or |
| • Does not meet criteria for possible IE above |

IE: Infective endocarditis.

malignancy, most frequently with pancreatic adenocarcinoma (10%). The primary clinical presentation of NBTE is a thromboembolism. It is essential to differentiate NBTE from IE. The same diagnostic work-up that is recommended for IE should be completed. The diagnosis of NBTE is challenging. NBTE can be diagnosed in a patient with the presence of a disease process known to be associated with NBTE with high suspicion in the presence of multiple systemic emboli, unchanged vegetation size despite antibiotic therapy, or a new heart murmur. In patients with underlying comorbidities that predispose to NBTE, the presence of a heart murmur, persistence of vegetation despite appropriate antibiotic therapy, or multiple systemic emboli should lead to suspicion of NBTE. Although the vegetations in NBTE are generally small, their roots are wide and irregular in shape. The vegetations in NBTE show minimal inflammation where they are attached.[131,234–236]

**Table 4. Definitions used in the European Society of Cardiology 2015 Modified Criteria for the Diagnosis of Infective Endocarditis[3,65]**

| Major criteria |
|---|
| 1. Blood cultures positive for IE |
| a. Typical microorganisms consistent with IE from 2 separate blood cultures: |
| • Viridans streptococci, *Streptococcus gallolyticus (Streptococcus bovis)*, HACEK group, *Staphylococcus aureus*; or |
| • Community-acquired enterococci, in the absence of a primary focus; or |
| b. Microorganisms consistent with IE from persistently positive blood cultures: |
| • ≥2 positive blood cultures of blood samples drawn >12 h apart; or |
| • All of 3 or a majority of ≥4 separate cultures of blood (with first and last samples drawn ≥1 h apart); or |
| c. Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titre >1:800. |
| 2. Imaging positive for IE |
| a. Echocardiogram positive for IE;* |
| • Vegetation; |
| • Abscess, pseudoaneurysm, intracardiac fistula; |
| • Valvular perforation or aneurysm; |
| • New partial dehiscence of prosthetic valve. |
| b. Abnormal activity around the site of prosthetic valve implantation detected with 18F-FDG PET/CT (only if the prosthesis was implanted >3 months prior) or leukocyte SPECT/CT. |
| c. Definite paravalvular lesions observed with cardiac CT. |
| Minor criteria |
| 1. Predisposition, such as predisposing heart condition, or injection drug use. |
| 2. Fever, defined as a temperature >38°C. |
| 3. Vascular phenomena (including those detected by imaging only): major arterial emboli, septic pulmonary infarcts, infectious (mycotic) aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions. |
| 4. Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor. |
| 5. Microbiological evidence: positive blood culture, but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE. |

*Although it is was not included in the ESC 2015 modified Duke criteria, "new valvular regurgitation (worsening or changing or pre-existing murmur not sufficient)" was included as a major echocardiographic criterion in the original Duke criteria.[3] $^{18}$F-FDG PET/CT: $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography; HACEK: *Haemophilus parainfluenzae, Aggregatibacter* spp., *Cardiobacterium* spp., *Eikenella corrodens* and *Kingella* spp.; IE: Infective endocarditis; IgG: Immunoglobulin G; SPECT/CT: Single-photon emission computed tomography.

**Table 5. Simplified risk score calculation for 6-month mortality in infective endocarditis[237]**

| Prognostic variable | Weight |
|---|---|
| Age (years) | |
| ≤45 | 0 |
| 46–60 | +2 |
| 61–70 | +3 |
| >70 | +4 |
| History of dialysis | +3 |
| Nosocomial IE | +2 |
| Prosthetic valve IE | +1 |
| Symptoms >1 month before admission | -1 |
| *Staphylococcus aureus* as causative agent | +1 |
| Viridans group streptococci as causative agent | -2 |
| Aortic vegetation | +1 |
| Mitral vegetation | +1 |
| NYHA class III or IV heart failure caused by IE | +3 |
| Stroke | +2 |
| Paravalvular complications | +2 |
| Persistent bacteremia | +2 |
| Surgical treatment for IE | -2 |
| Probability of 6-month mortality = 2.4169 x score + 0.1099 score$^2$–4.849. | |

IE: Infective endocarditis; NYHA: New York Heart Association.

**Table 6. Probability of 6-month mortality in patients with infective endocarditis according to simplified risk score[240]**

| Total risk score | Probability of 6-month mortality (%) |
|---|---|
| 0–6 | 8–12 |
| 7–8 | 16–20 |
| 9–10 | 30–34 |
| 11–16 | 42–50 |
| 17–22 | >60 |

## Prognostic Assessment of Patients with Infective Endocarditis At Admission and During Follow-Up

### 24. When should a prognostic assessment be performed in patients with infective endocarditis and what is the benefit of this assessment?

A prognostic risk assessment should be performed in patients with suspected IE using the simplified risk score calculation during the first evaluation (Table 5 and Table 6). Patients with a higher mortality risk (risk score >8) should be carefully evaluated in a timely manner for urgent surgery and for the possibility of transfer to a reference center and intensive care unit. Prognostic assessment of a patient with IE should be performed 3 times: at admission, within the first week of the start of antibiotic therapy, and before discharge. Making a prediction of the prognosis of IE can help clinicians to prevent probable complications and to be prepared to overcome complications if they occur.[65,66,237–240]

## Infective Endocarditis Team in the Management of Patients with Infective Endocarditis

### 25. What is an infective endocarditis team and why is such a team necessary?

An IE team is a multidisciplinary team including representatives of relevant specialties who manage the diagnosis and treatment of all IE patients at the institution, decide collaboratively on all aspects of the disease, especially on antimicrobial and surgical treatment, and meet once a week, or more frequently when needed, to regularly follow-up and evaluate patients. IE patients may be treated by physicians from several specialties because the disease has a wide range of clinical presentations. Since it is a rare disease, it is unlikely that every physician has sufficient experience. These features drive delayed diagnosis and treatment of the disease, and consequently, increased morbidity and mortality. Therefore, IE teams should be established at institutions in order to promptly diagnose IE, provide standardized therapy following the current guidelines, increase practitioners' knowledge and experience, and provide comprehensive follow-up to patients with IE.

At a minimum, there should be a cardiologist, a cardiovascular surgeon, and an infectious diseases and clinical microbiology specialist on the IE team. When needed, a neurologist, a radiologist, a nuclear medicine specialist, a pathologist, and a neurosurgeon should join the team at reference centers. It has been shown that a multidisciplinary approach leads to a decrease in morbidity and mortality of IE patients. IE cases complicated with heart failure, abscess, neurological complications, etc. should be followed up at reference centers where there are neurosurgery and cardiac surgery facilities. Uncomplicated cases can be followed up at non-reference centers, provided that

**Table 7. Department of hospitalization for patients with infective endocarditis**

| Patient's condition | Department of hospitalization |
|---|---|
| Patients with unstable hemodynamic condition, or severe valve dysfunction, or within the first days of *Staphylococcus aureus* endocarditis | Intensive care unit or coronary intensive care unit |
| Patients with stable hemodynamic status and good valve function | Cardiology<br>Infectious disease and clinical microbiology |
| Patients with indication for emergent surgery | Cardiovascular surgery |
| Patients with an indication for urgent/elective surgery | Cardiology<br>Infectious disease and clinical microbiology |
| Patients without any surgical indications | Cardiology<br>Infectious disease and clinical microbiology |

there is close communication with a reference center and the patient is regularly evaluated by the IE team and referred to a reference center when necessary (Table 7 and Table 8).[65,241–245]

## Antimicrobial Treatment of Infective Endocarditis

### 26. What is the general principle of antimicrobial treatment of infective endocarditis and how should the duration of treatment be determined?

The general principle of antimicrobial treatment of IE is prolonged, parenteral administration of bactericidal agents. The duration of antimicrobial treatment is determined according to the pathogen, the presence of prosthetic material, and the duration of symptoms. The therapy duration is generally 4–6 weeks for native valve endocarditis and >6 weeks for prosthetic valve endocarditis.[3,86,140,246,247]

### 27. Is oral antibiotic therapy feasible in the treatment of left-sided endocarditis?

Since there are questions about the feasibility and efficacy of oral antimicrobial treatment of left-sided endocarditis, and since left-sided endocarditis is associated with substantially higher mortality, the parenteral route should be preferred for the complete duration of antimicrobial treatment of left-sided endocarditis in our country. In the event that IV access is unavailable or outpatient parenteral antibiotic therapy is unavailable, oral therapy may be feasible to complete the treatment in stable patients with uncomplicated native valve endocarditis due to drug-susceptible viridans group streptococci when there is a high probability of compliance and confidence in follow-up, provided that the initial 2 weeks of antibiotic therapy were completed parenterally, the patient is informed about all of the possible risks and provides informed consent. Switching to oral therapy should be a joint decision of the IE team.[248–251]

### 28. Is empirical treatment necessary for infective endocarditis?

Antibiotic therapy should be initiated without delay, as it reduces not only the risk of an embolic event in patients with either acute or subacute IE, but also decreases the mortality associated with sepsis in patients with acute IE. Therefore, treatment with empirical antibiotics should be initiated promptly once blood cultures have been performed.[3,65,140,205,246,252]

### 29. What are the empirical drugs of choice for native, early, and late prosthetic valve infective endocarditis in adults in our country?

Ampicillin/sulbactam±gentamicin can be initiated empirically in the treatment of community-acquired cases with either a subacute or a chronic course of native or late prosthetic valve endocarditis, while vancomycin+ampicillin/sulbactam or ceftriaxone±gentamicin may be the choice for an acute course. A vancomycin+cefepime±gentamicin combination can be initiated empirically in the treatment of nosocomial native, early, and late prosthetic valve endocarditis. Gentamicin should be avoided in patients with initial impaired renal function. Rifampin can also be added to empirical treatment of early prosthetic valve endocarditis. Daptomycin alone is not a drug of choice for initial empirical treatment of IE because of its suboptimal efficacy for streptococci and enterococci and the probability of the easy development of resistance in these strains during therapy (Table 9).[3,65,137,205,253–258]

**Table 8. Approach to a patient with suspected endocarditis**

| Recommendations | Timing |
|---|---|
| Determination of patient's hemodynamic status and appropriate decision for hospitalization placement | Immediately |
| Prediction of prognosis according to simplified risk score and referral of patients with a score of ≥8 to a reference center | In the first 24 hours or following results of blood cultures and then weekly |
| TTE | Immediately |
| TEE | |
| When TTE is of suboptimal quality or complications are suspected | Immediately |
| Other conditions | In the first 48 hours |
| Whole blood count, serum CRP, ESR, procalcitonin, BUN, creatinine, urine analysis, ALT, AST, glucose, NT-pro-BNP and cTnI levels | Immediately |
| Three sets of blood cultures | Within the first hour (at 0, 30$^{th}$, and 60$^{th}$ minutes) |
| Collection of blood samples in 3 plain tubes and 1 EDTA tube | |
| • Send the 1st plain tube of blood to the laboratory for RF, ANA, and Wright agglutination testing | In the first 24 hours |
| • Send the 2$^{nd}$ plain tube of blood to the laboratory for *Coxiella burnetii* phase I IgG testing | In the case of negative blood cultures |
| • Send the 3$^{rd}$ plain tube and 1st EDTA tube of blood to the laboratory for multiplex and specific PCR testing and other serological antibody testing | In the case of negative blood cultures |
| ECG | Immediately |
| Repeat blood cultures in patients with a history of antibiotic usage in the previous 10 days and stable general condition | 72 hours after discontinuation of antibiotics |
| Fundoscopic examination | In the first 48 hours |
| Classification of the diagnosis according to modified Duke criteria | In the first 5 days |
| Abdominal ultrasound | In the case of persistent fever and examination for a minor Duke criterion<br>In the first 7 days |
| Cardiac CT, MRI, 18F-FDG PET/CT, SPECT/CT with scintigraphy with labeled leukocytes | In patients with inconclusive echocardiographic results and suspected IE<br>In the first 7 days |

$^{18}$F-FDG PET/CT: $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography; ALT: Alanine aminotransferase; ANA: Antinuclear antibody; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CRP: C-reactive protein; CT: Computed tomography; cTnI: Cardiac troponin I; ECG: Electrocardiogram; EDTA: Ethylenediaminetetraacetic acid; ESR: Erythrocyte sedimentation rate; IgG: Immunoglobulin G; MRI: Magnetic resonance imaging; NT-pro-BNP: N-terminal pro b-type natriuretic peptide; PCR: Polymerase chain reaction; SPECT/CT: Single-photon emission computed tomography; RF: Rheumatoid factor; TEE: Transesophageal echocardiogram; TTE: Transthoracic echocardiogram.

## 30. What are the drugs of choice in the treatment of streptococcal native and prosthetic valve endocarditis in our country?

The treatment decision in streptococcal IE is made according to the penicillin G minimum inhibitory concentration (MIC) values of the pathogen. The first treatment of choice is penicillin G in strains that are fully sensitive to penicillin G, penicillin+gentamicin in relatively resistant strains, and vancomycin or teicoplanin in resistant strains. Daptomycin is not recommended in endocarditis caused by streptococci that are sensitive to penicillin and vancomycin due to the possibility of the development of resistance during therapy.[4,86,205,259–268]

**Table 9. Empirical antimicrobial treatment of infective endocarditis**[3,65,137,205,368]*

| Type of infective endocarditis | Antimicrobial agent | Dosage and route | Duration (weeks) | | Comment |
|---|---|---|---|---|---|
| | | | Native | Prosthetic valve | |
| Native valve and late prosthetic valve (>1 year), community-acquired endocarditis, subacute course doses | Ampicillin/ sulbactam + | 12 g/day** i.v. in 4–6 doses | 4 | 6 | Gentamicin should be avoided in patients with initial high serum level of creatinine |
| | Gentamicin | 3 mg/kg/day i.v. in 1 dose | 2 | 2 | |
| Native valve and late prosthetic valve (>1 year), community-acquired endocarditis, acute course doses | Vancomycin + | 30–60 mg/kg/day i.v. in 2–3 | 4–6 | ≥6 | Duration of treatment should be 6 weeks in cases of native endocarditis and ≥6 weeks for prosthetic valve endocarditis, especially in the event of complicated IE, such as with metastatic foci, etc. |
| | Ampicillin/ sulbactam, or | 12 g/day** i.v. in 4–6 doses | 4–6 | ≥6 | |
| | Ceftriaxone | 2 g/day, i.v. in 1 dose | 4–6 | ≥6 | |
| Native valve and late prosthetic valve (>1 year), healthcare-associated endocarditis | Vancomycin + | 30–60 mg/kg/day i.v. in 2–3 doses | 4 | 6 | |
| | Cefepime | 6 g/day, i.v. in 3 doses | 4 | 6 | |
| Native valve and late prosthetic valve (>1 year) endocarditis, β-lactam allergy | Vancomycin + | 30–60 mg/kg/day i.v. in 2–3 doses | 4 | 6 | Gentamicin should be avoided in patients with a higher risk of nephrotoxicity |
| | Gentamicin | 3 mg/kg/day i.v. in 1 dose | 2 | 2 | |
| Early prosthetic valve endocarditis (≤1 year) | Vancomycin + | 30–60 mg/kg/day i.v. in 2–3 doses | | 6 | |
| | Gentamicin + | 3 mg/kg/day i.v. in 1 dose | 2 | | |
| | Cefepime + | 6 g/day, i.v. in 3 doses | 6 | | |
| | Rifampin | 900 mg/day, i.v. or orally in 3 doses | 6 | | |
| Cardiac implantable electronic device, lead-related, or valve endocarditis doses | Vancomycin ± | 30–60 mg/kg/day i.v. in 2–3 | Antimicrobial therapy should be continued for 2-4 weeks and 4-6 weeks for lead-related and valve endocarditis, respectively, after the removal of the device | | Addition of either gentamicin, or cefepime, or meropenem to vancomycin should be considered for septic patients with unstable hemodynamic status |
| | Gentamicin, or | 3 mg/kg/day i.v. in 1 dose | | | |
| | Cefepime, or | 6 g/day, i.v. in 3 doses | | | |
| | Meropenem | 3 g/day, i.v. in 3 doses | | | |

*Same regimen may be used for patients with negative blood cultures and serological test results. ** As ampicillin.

### 31. What are the drugs of choice in the treatment of enterococcal endocarditis in our country?

In the treatment of enterococcal endocarditis, if the strain is sensitive to ampicillin (or penicillin G), the recommended regimen is ampicillin+gentamicin or ampicillin+ceftriaxone (if the strain is *Enterococcus faecalis*). The recommended regimen is vancomycin or teicoplanin+gentamicin if the strain is resistant to ampicillin. A daptomycin+ampicillin+gentamicin combination is recommended if it is resistant to ampicillin, vancomycin, and teicoplanin. Gentamicin should be included in the treatment unless there is high-level gentamicin resistance.[1–4,65,205,269–282]

### 32. What are the drugs of choice in the treatment of staphylococcal endocarditis in our country?

Cefazolin is the drug of choice in methicillin-sensitive *S. aureus* (MSSA) IE in our country, since anti-staphylococcal penicillins are not available in the domestic market. In patients with central nervous system-septic emboli, vancomycin+cefazolin or cefotaxime should be preferred. Daptomycin should be used in patients who have a hypersensitivity reaction, such as anaphylaxis, to β-lactam agents. Vancomycin in combination with cefazolin may be given to patients who are in risk groups for methicillin-resistant *S. aureus* (MRSA) until antimicrobial susceptibility test results are completed. Following test results indicating MSSA, treatment with cefazolin should be continued. Adding rifampicin and gentamicin is not recommended in native valve IE. In prosthetic valve IE, the cefazolin+ gentamicin and rifampicin combination is recommended.

In MRSA IE, if the MIC is ≤2 μg/mL, vancomycin is recommended. Loading doses of vancomycin should be used, especially for septic patients, followed by daily doses modified according to serum levels, the patient's weight, and renal function. If the vancomycin MIC is >2 μg/mL, daptomycin is recommended in doses of 8–12 mg/kg/day, which is determined according to the MIC values, in combination with cefazolin or trimethoprim/sulfamethoxazole. In patients with MRSA IE, especially if there is persistent bacteremia (>3–7 days), a combined vancomycin-cefazolin regimen can be used. In cases of MRSA prosthetic valve IE, if the strain is sensitive, rifampicin and gentamicin should be added to vancomycin. When there is resistance to these agents, ciprofloxacin can be used as an alternative, if there is sensitivity.[3,4,65,86,104,205,259,269,283–355]

## Complications of Infective Endocarditis and Their Management

### 33. What are the clinical and laboratory signs of heart failure development in patients with infective endocarditis and how it can be managed?

Nearly half of left-sided IE cases, especially those with aortic valve involvement, develop heart failure, which has a higher risk of mortality. Dyspnea, pulmonary edema, hypotension, and other organ dysfunction in patients with IE can be alarms signaling possible heart failure. In IE patients with heart failure, urgent surgery reduces the mortality rate significantly.[81,169,173,180,356–364]

### 34. What are the clinical and laboratory signs of uncontrolled infection in infective endocarditis patients and how should they be managed?

Persistent infection in IE patients is characterized by fever and culture positivity, a duration of 5–10 days, or infection spreading around the valve annulus forming an abscess, pseudoaneurysm, fistula, or atrioventricular block etc. despite antibiotic treatment, demonstrating that the infection is not under control. In cases of persistent infection, repeated blood cultures and echocardiographic examination imaging for different foci of infection and changing intravascular catheters should be performed. Patients with continuing fever despite all of these measures, especially continuing blood culture positivity with no other infection source, should be evaluated for early valve surgery. Recent studies have indicated that blood culture positivity lasting >48–72 hours increases mortality. Early surgery for these patients may be beneficial.[3,65,86,110,173,271,365–367]

### 35. What is the incidence of embolic events in patients with infective endocarditis and what are the risk factors? How should embolic events be managed?

Some 20–50% of patients with IE have embolic complications. The most important risk factor is the size (>10 mm) and mobility of the vegetation. The risk declines substantially with the start of antibiotic treatment. The decision to perform early surgery to prevent embolism is always challenging and there should be a unique evaluation for each patient. The factors that influence this decision are the size and mobility of the vegetation, recurrent embolism under treatment, the type of microorganism, and the duration of antibiotic treatment.[3,65,181,183,368–375]

## Surgical Treatment in Infective Endocarditis

### 36. What are the indications and appropriate timing for valvular surgery in the management of infective endocarditis?

Urgent surgery is recommended in IE patients with heart failure. Early surgery is recommended in uncontrolled local (abscess, fistula, aneurysm, etc.) or systemic infection (ongoing blood culture positivity or fever with no other source), recurrent emboli, large vegetation, and severe left heart valve regurgitation or stenosis without clinical heart failure. If urgent surgery

**Table 10. Class I indications and timing of surgery in left-sided valve infective endocarditis (Recommendations from the European Society of Cardiology 2015 infective endocarditis guidelines)[65]**

| Indications | Timing | Class of recommendation | Level of evidence |
|---|---|---|---|
| Heart failure | | | |
| Aortic or mitral NVE or PVE with severe acute regurgitation, obstruction, or fistula causing refractory pulmonary edema or cardiogenic shock | Emergency | I | B |
| Aortic or mitral NVE or PVE with severe regurgitation or obstruction causing symptoms of HF or echocardiographic signs of poor hemodynamic performance | Urgent | I | B |
| Uncontrolled infection | | | |
| Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation) | Urgent | I | B |
| Infection caused by fungi or multiresistant organisms | Urgent/elective | I | C |
| Prevention of embolism | | | |
| Aortic or mitral NVE or PVE with persistent vegetation >10 mm after 1 or more embolic episodes despite appropriate antibiotic therapy | Urgent | I | B |

HF: Heart failure; NVE: Native valve endocarditis; PVE: Prosthetic valve endocarditis.

**Table 11. Class I indications for surgery in left-sided valve infective endocarditis (Recommendations from the American Association for Thoracic Surgery 2016 consensus guidelines)[377]**

| Indications | Class of recommendation | Level of evidence |
|---|---|---|
| Surgery during initial hospitalization is indicated in patients with IE who present with valve dysfunction resulting in symptoms of heart failure, independent of the completion of a full therapeutic course of antibiotics. | I | B |
| Surgery during initial hospitalization is indicated in patients with left-sided IE caused by *S. aureus*, fungal, or other highly resistant microorganisms, independent of the completion of a full therapeutic course of antibiotics. | I | B |
| Surgery during initial hospitalization is indicated in patients with IE complicated by heart block, annular or aortic abscess, or destructive penetrating lesions, independent of the completion of a full therapeutic course of antibiotics. | I | B |
| Surgery during initial hospitalization is indicated in patients with evidence of persistent infection manifested by persistent bacteremia or fever lasting longer than 5–7 days after initiation of appropriate antimicrobial therapy, independent of the completion of a full therapeutic course of antibiotics. | I | B |
| Once an indication for surgery is established, the patient should be operated on within days. | I | B |

is indicated, antimicrobial treatment can be initiated before there is evidence of growth in blood cultures.

A decision to perform heart valve surgery in IE patients should be made by the IE team (or by a cardiologist, cardiovascular surgeon, and infectious diseases and clinical microbiology specialist) after evaluating all aspects of the disease. In patients with neurological complications, a surgical decision should be made by the IE team with the addition of a neurologist and a neurosurgeon, according to the presence/absence of silent emboli/transient ischemic attack, ischemic stroke or hemorrhagic stroke, severity of the neurological situation, and urgency of cardiovascular surgery.[2,3,27,65,181,376–399] After a silent embolism or transient ischemic attack, if indicated, cardiac surgery is recommended without delay (Table 10 and Table 11).[65]

## Monitoring Treatment Response in Patients with Infective Endocarditis and Follow-Up After Discharge

### 37. How should treatment response be monitored in patients with infective endocarditis?

In IE patients who have been given the appropriate antibiotic treatment and undergone surgical repair (when needed), fever and serum C-reactive protein (CRP) level should decrease, blood cultures should be negative, valve functions should be stabilized, vegetation size on echocardiography should not be enlarged, but rather reduced, and the foci of an abscess should vanish. Therefore, after starting antimicrobial treatment, 2 sets of blood cultures should be taken every 48 hours until there is clear positivity, serial CRP measurements should be taken, and a gradual decrease in the CRP level during treatment reaching a normal level should be expected by the end of treatment. An echocardiographic examination should also be performed during hospitalization and just prior to discharge.[65,102,400–404]

### 38. What recommendations should be made to infective endocarditis patients at discharge?

Since a history of IE is an important risk factor for recurrent endocarditis, patients should be informed about the probability of recurrence of the disease and the signs and symptoms of the condition. They should be informed about avoiding the use of empirical antibiotics before blood cultures are collected in case of fever, chills, and other symptoms of infection. They should also be informed about prophylaxis for endocarditis, and to avoid procedures (piercing, tattoo, etc.) that may cause bacteremia and endocarditis.[65]

### 39. How should operated/non-operated infective endocarditis patients be followed-up in outpatient clinics?

A TTE should be performed on discharge to provide a baseline, and as part of the follow-up, patients should be monitored with additional, periodic TTE examinations in the first year to detect possible secondary heart failure. Periodic follow-up visits should be scheduled at 1, 3, 6, and 12 months after hospital discharge. Patients should be evaluated for late side effects of the antibiotics, especially aminoglycosides used for the endocarditis treatment. A clinical examination should be accompanied by measurements of leukocyte count, CRP, and erythrocyte sedimentation rate in addition to the TTE.[65]

## Specific Conditions

### 40. What are important concerns in the management of patients with prosthetic valve endocarditis?

It is more difficult to diagnose prosthetic valve endocarditis than native valve endocarditis because both blood culture and echocardiographic examination results are frequently negative. The sensitivity of TTE and TEE in diagnosis of prosthetic valve endocarditis is 30% and 80%, respectively. IE should be carefully investigated using newer imaging modalities like multidetector computed tomographic angiography (MDCTA) and PET/CT in patients with suspected prosthetic valve endocarditis with a normal echocardiogram. Surgery is frequently required in addition to antibiotic treatment in patients who have heart failure or a paravalvular abscess or endocarditis caused by *S. aureus* or fungi.[4,65,187,405–411]

### 41. What are important concerns in the management of infective endocarditis associated with cardiac implantable electronic devices?

CIED-associated IE represents almost 10% of all episodes of IE and the percentage is expected to increase with the growing number of devices implanted. IE should be kept in the differential diagnosis when there is 1 or more of any of the clinical presentations (fever of unknown origin, pocket infection, bacteremia with unknown source, complications of multiple pul-

monary embolisms) in patients with a CIED. Blood cultures should be performed promptly and any findings of IE should be investigated with TTE and TEE. Radiolabeled leukocyte scintigraphy or PET/CT modalities can be additive to a diagnosis of CIED-associated endocarditis in the case of a normal echocardiographic examination. The exact treatment of CIED-associated endocarditis should be the combination of antimicrobials covering the most prominent staphylococci and complete hardware removal. Percutaneous removal of hardware must be preferred in all cases, and especially in patients with vegetation <20 mm in diameter. The duration of antimicrobial therapy should be 2–4 weeks in patients with a vegetation diagnosed at the extracted lead tip after complete hardware removal, while 4–6 weeks of treatment is necessary in patients with endocardial lesions. Blood cultures should be negative for at least 14 days before implanting a new device in patients with valvular endocarditis who have an indication for CIED. In other cases, blood cultures should be negative for at least 72 hours before the placement of a new device. To prevent CIED-related infections, a single dose of prophylaxis cefazolin just before the implantation of a CIED is recommended; additional doses are not required.[69,70,412–432] The management of suspected CIED infection, bacteremia without evidence of CIED infection, and management of suspected pocket infection is detailed in Figures 4, 5, and 6, respectively.

## 42. What are important concerns in the management of patients with non-CIED-related right-sided endocarditis (IVDU, etc.)?

In cases of IVDU, right-sided endocarditis is most common. The incidence of IE related to IVDU is likely to increase with the increasing prevalence of IVDU in Turkey and globally. It is not necessary to use TEE, as the tricuspid valve anatomy and its pathology can easily be visualized with TTE. *S. aureus* is the most common pathogen. The most prominent symptoms of IE in cases of IVDU are fever and pulmonary symptoms mimicking respiratory tract infections. It is not possible to use a short term (2-week

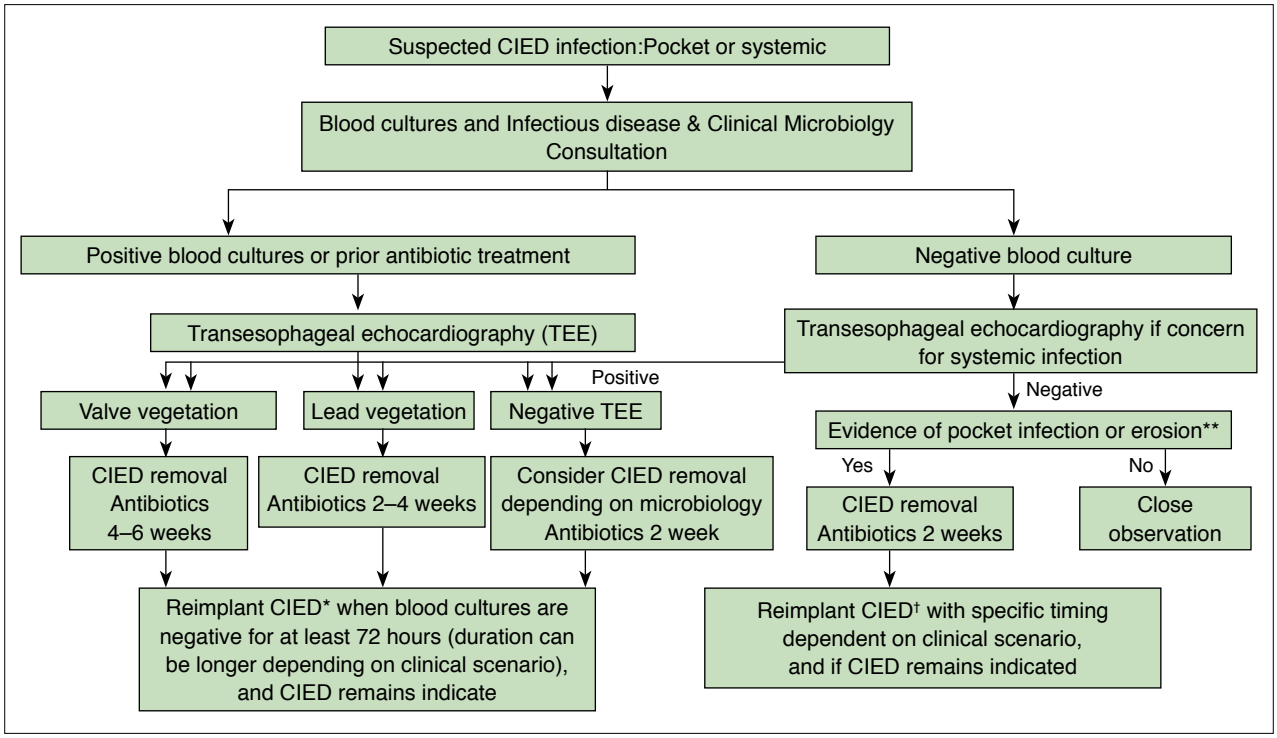


**Figure 4.** Management of suspected CIED infection. Antimicrobial therapy should be maintained for at least 4–6 weeks for endocarditis (4 weeks for native valve, 6 weeks for prosthetic valve or staphylococcal valvular endocarditis). If lead vegetation is present in the absence of valve vegetation, 4 weeks of antibiotics for *Staphylococcus aureus* and 2 weeks for other pathogens is recommended. *Usually the contralateral side; a subcutaneous implantable cardioverter-defibrillator may also be considered. **2010 American Heart Association CIED Infection Update distinguishes between pocket infection and erosion.[70,415] CIED: Cardiovascular implantable electronic device; TEE: Transesophageal echocardiography.

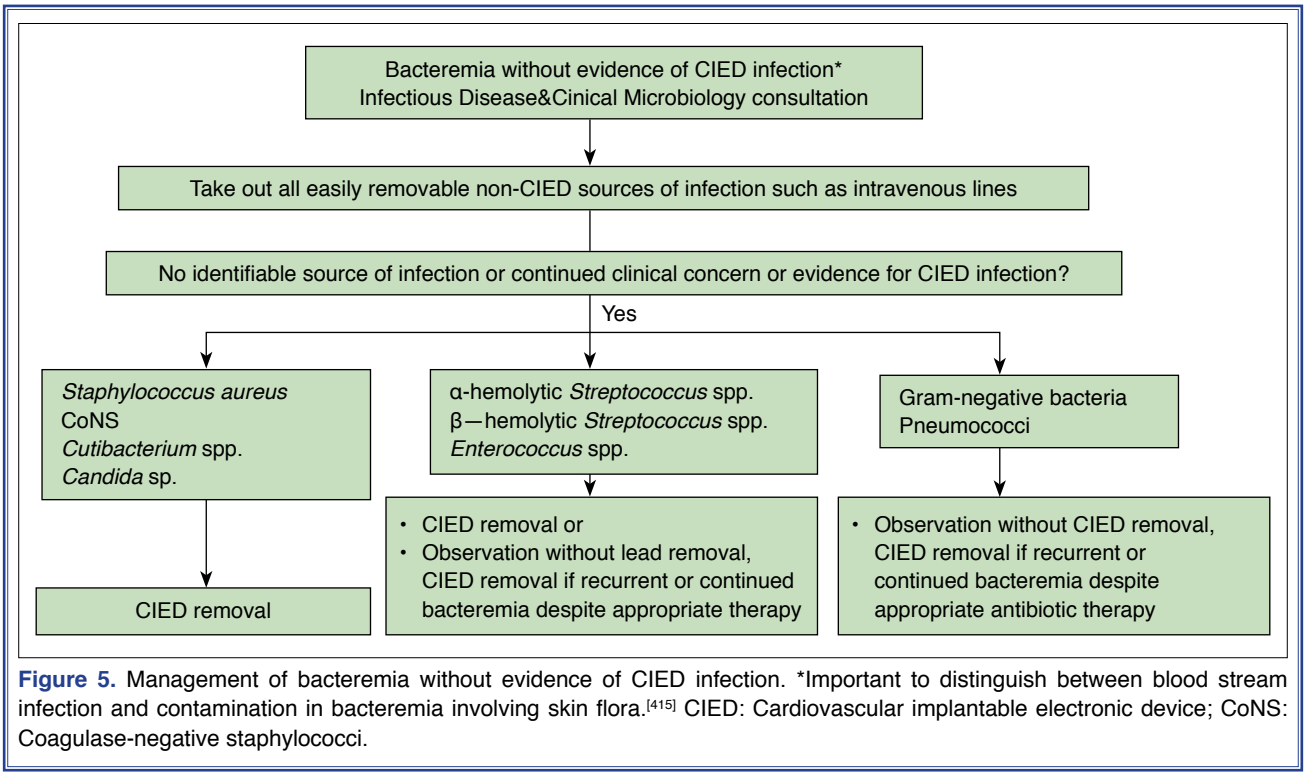


**Figure 5.** Management of bacteremia without evidence of CIED infection. *Important to distinguish between blood stream infection and contamination in bacteremia involving skin flora.[415] CIED: Cardiovascular implantable electronic device; CoNS: Coagulase-negative staphylococci.

duration) treatment modality to treat right-sided endocarditis with IVDU due to MSSA, as anti-staphylococcal penicillins are not currently available in our country. Instead, these patients must be treated with cefazolin for a duration of 4-6 weeks. Oral combination therapy with ciprofloxacin and rifampin can be used to treat uncomplicated right-side endocarditis with IVDU caused by strains susceptible to both drugs, but this approach should be reserved for special situations in which conventional intravenous antibiotic therapy is not possible or is undesirable because of problems during the hospital stay, and there should be a requirement of regular post-discharge follow-up. The increasing resistance to quinolones among *S. aureus* strains may limit the use of this approach.[65,138,433–443]

## 43. What are important concerns in the management of healthcare-associated infective endocarditis?

Currently, at least a quarter of IE cases are healthcare-associated endocarditis. It is classified as nosocomial endocarditis if development arises during a hospital stay or within 6 months of discharge. It is considered non-nosocomial healthcare-associated endocarditis when the patient was exposed to healthcare interventions (hemodialysis, chemotherapy, etc.) outside the hospital within 30 days prior to the onset of signs or symptoms consistent with IE. The classification of community-acquired, nosocomial, or non-nosocomial healthcare-associated IE at admission is important because the choice of empirical therapy is completely different for healthcare-associated IE and community-acquired IE.[4,22,83,84,444–449]

## 44. What are important concerns in the management of infective endocarditis in HIV-infected patients?

IE among HIV-infected patients is common, especially among cases of IVDU with HIV infection. The risk for developing IE is not increased in an HIV-infected patient without IVDU. The incidence of IE is higher among HIV-positive IVDU individuals than HIV-negative IVDU individuals. The development of IE is easier and the mortality rate is higher in patients with a low CD4+ T lymphocyte count. The morbidity and mortality rate of cardiovascular surgery is similar in IE in HIV-positive and HIV-negative IVDU. The decision to perform a valvular replacement must be individualized according to the risk of recurrence of IE in patients who continue IVDU.[74,450–464]

## 45. What are important concerns related to infective endocarditis in elderly patients?

IE is seen with increasing frequency in elderly patients. The clinical presentation is more silent in

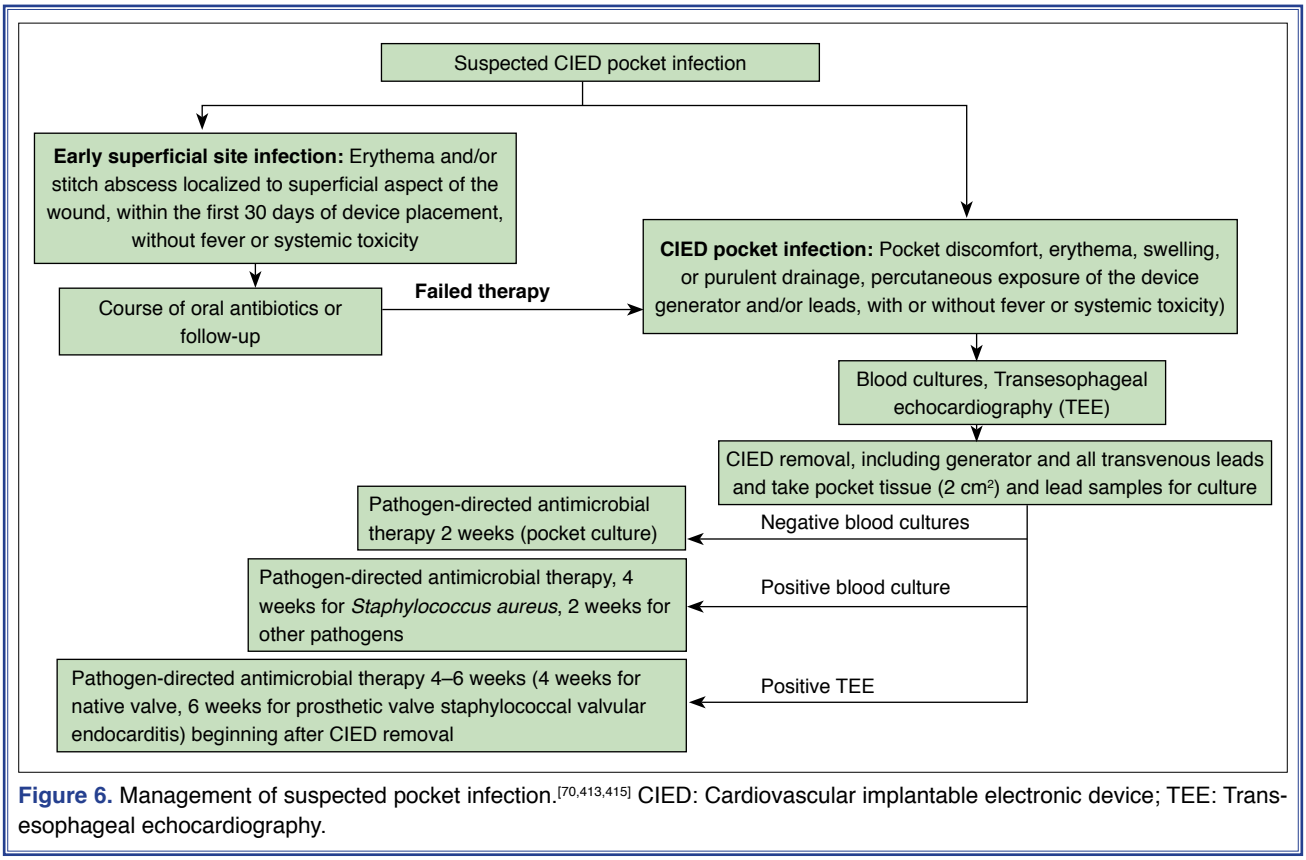


**Figure 6.** Management of suspected pocket infection.[70,413,415] CIED: Cardiovascular implantable electronic device; TEE: Transesophageal echocardiography.

these patients, with smaller vegetations, and fewer embolic events. Healthcare-associated endocarditis is more common among older patients, in part because the group has more prosthetic materials. The causative pathogens are typically either staphylococci acquired through healthcare or *Streptococcus gallolyticus* (*Streptococcus* bovis biotype I) or *Enterococci* related to an intestinal or urinary source. IE in the elderly has greater mortality. The best explanation for the mortality rate among older patients is the reduced likelihood of surgery when needed. In addition, the antimicrobial treatment is unique in older patients, with the increased risk of severe side effects and drug-drug interactions. A team involving a geriatrist, a cardiologist, a cardiovascular surgeon, and an infectious disease specialist is essential to decide on the appropriate diagnostic and therapeutic strategy in older patients with IE in order to overcome these difficulties.[4,24,30,143,465–473]

## 46. What are important concerns related to infective endocarditis in solid organ transplant recipients?

The risk for IE is greater in solid organ transplant recipients than in the normal population and IE is often overlooked. Gram-negative bacilli and fungi may be causative pathogens in addition to classic pathogens, such as staphylococci. If the source of any bacteremia or fungemia is not known or a new embolic event occurs in solid organ recipients, IE should be kept in mind in the differential diagnosis.[4,5,7,8,79,80,474–485]

## 47. What are important concerns in the management of infective endocarditis in patients with chronic renal failure and patients receiving chronic hemodialysis?

Although all patients with chronic renal failure are at increased risk of IE, the risk is greatest among hemodialysis patients. The 2 most important factors to explain this are the increased prevalence of bacteremia and cardiac valvular calcifications in hemodialysis patients. Currently, chronic hemodialysis patients comprise 10–20% of patients with IE and IE occurs in 1–3% of patients with chronic hemodialysis. Left-sided endocarditis with the involvement of mitral valve is common in patients with chronic renal failure. The most common pathogen is *S. aureus*. The risk of surgery and risk of developing complications, such as an embolization,

is higher. However, valvular surgery can be both feasible and beneficial in appropriately selected patients for whom general guideline recommendations can be applied. There was no significant difference in the survival rate of biological valve and prosthetic valve replacement patients. A bioprosthetic valve is thought to be a more rational choice because of the increased tendency to hemorrhage and difficulty in long-term anticoagulation among older patients with a short life expectancy.[77,78,486–498]

### 48. What are important concerns in the management of a patient with infective endocarditis in the intensive care unit?

Conditions predisposing to IE should be investigated in patients with an intensive care unit admission with acute heart failure, sepsis, and cranial or peripheral embolic events. IE should be in the differential diagnosis in susceptible patients when a heart murmur is heard during the physical examination and appropriate empirical treatment should be initiated promptly, if necessary. An echocardiographic examination should be performed to rule out the diagnosis of IE in intensive care unit patients with persistent fever and continued blood culture positivity despite appropriate antimicrobial treatment.[65,499–524]

### 49. What are important concerns in the management of infective endocarditis in pregnant women?

The IE risk is not greater in pregnant women. However, if IE develops in a pregnant woman with a predisposing condition, the timing of both cardiovascular surgery and delivery should be decided by a multidisciplinary team composed of a cardiologist, a cardiovascular surgeon, an obstetrician, and a neonatologist. Cardiovascular surgery is not recommended in the first 2 trimesters. Cardiovascular surgery following an elective caesarean section is preferred after 28 gestational weeks. Emergent surgery has to be planned in the case of IE leading to acute heart failure, despite a higher risk of fetal mortality. The principles of antimicrobial therapy for severe infections in pregnant women are also valid for pregnant women with IE.[104,525–530]

### 50. Should cancer screening be performed in patients with infective endocarditis?

As the risk of the presence of colon cancer has been found to be greater in patients with *Streptococcus gallolyticus* (*Streptococcus bovis* biotype I) endocarditis, a colonoscopy is recommended for these patients. A colonoscopy should also be considered in patients with enterococcal endocarditis if the source of infection has not been identified. Cancer patients are in a higher risk group for the acquisition of healthcare-associated endocarditis as they are more exposed to invasive procedures and they need more healthcare. The probability of IE should be kept in mind and a diagnostic work-up should be performed when cancer patients have a fever of unknown origin or a persistent blood culture positivity.[531–536]

## Antithrombotictherapy in Infective Endocarditis

### 51. Which antithrombotic agents should be used and for which indications in patients with infective endocarditis and how?

All antithrombotic therapy should be ceased in the case of a severe intracranial hemorrhage in patients with IE who are already on oral anticoagulants for a prosthetic valve. However, it is recommended to initiate parenteral anticoagulation as soon as possible for these patients. Ongoing oral anticoagulants have to be shifted to a parenteral route in the case of an ischemic neurological event without hemorrhage in patients with IE. It is very important to make all decisions following a multidisciplinary discussion.[181,537,538]

## Prevention of Infective Endocarditis

### 52. How and in what situations should antimicrobial prophylaxis be administered in patients with infective endocarditis?

Antimicrobial prophylaxis is only recommended before invasive dental procedures in patients at the highest risk for the acquisition of IE (previous IE, presence of prosthetic heart valve or ring annuloplasty, cyanotic congenital heart disease, cardiac allograft valvulopathy). A single dose of 2 g amoxicillin or 600 mg clindamycin given orally 1 hour before the procedure is recommended as prophylaxis. Patients with IE should be examined by a dentist to determine any dental source of infection and eliminate it as necessary. An additional dose of prophylactic antimicrobial agent, preferably selecting a different class of antibiotic to cover all probable pathogens, should be administered 1 hour before the procedure to patients who have already been receiving appropriate antimicrobials for IE.[3,17,25,58,61,65,66,269,376,539–567]

### 53. What is recommended for patients at high risk for infective endocarditis about their oral and dental hygiene?

Patients at high risk to develop IE should obtain professional dental care twice a year, whereas a yearly exam is recommended for intermediate-risk patients.[65]

### 54. What are other measures for the prevention of infective endocarditis?

A central venous catheter should not be placed in patients at risk of developing IE unless required. If catheterization is necessary, then the catheter should be inserted using an aseptic technique and maximal sterile barrier precautions, including the use of a cap, mask, sterile gown, sterile gloves, and a sterile full body drape. Antistaphylococcal therapy for 5–7 days is recommended for patients with a predisposing condition for the acquisition of IE if *S. aureus* is isolated from the removed intra-venous catheter's tip culture. There is no vaccine available in clinical use to prevent IE. Procedures breaching the skin integrity, such as tattoos and body piercing, should be avoided. The potential for nasal carriage of *S. aureus* through habits such as rhinotillexis should also be avoided. Stöckert 3T heater-cooler system devices (LivaNova PLC, London, England) manufactured between 2006 and 2014 were found to have been contaminated with *Mycobacterium chimaera* and should not be used in cardiovascular surgery centers, particularly if either a prosthetic valve or a vascular graft will be replaced.[65,102,121,568–585]

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