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***Consensus Report** / Uzlaşı Raporu*

Consensus Report on Diagnosis, Treatment and Prevention of Infective Endocarditis by Turkish Society of Cardiovascular Surgery (TSCVS), Turkish Society of Clinical Microbiology and Infectious Diseases (KLIMIK), Turkish Society of Cardiology (TSC), Turkish Society of Nuclear Medicine (TSNM), Turkish Society of Radiology (TSR), Turkish Dental Association (TDA) and Federation of Turkish Pathology Societies (TURKPATH) Cardiovascular System Study Group

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ABSTRACT

Infective endocarditis (IE) is rare, but associated with significant morbidity and mortality rates. Estimates of the incidence of IE in Turkey are compromised by the absence of population-based prospective studies. Due to the frequent presence of predisposing cardiac conditions and higher rates of nosocomial bacteremia in high-risk groups, the incidence of IE is expected to be higher in Turkey. Additionally, while IE generally affects older people in developed countries, it still affects young people in Turkey. In order to reduce the mortality and morbidity, it is critical to diagnose the IE to determine the causative agent and to start treatment rapidly. However, most of the patients cannot be diagnosed in their first visits, about half of them can be diagnosed after three months, and the disease often goes unnoticed. In patients diagnosed with IE, the rate of identification of causative organisms is significantly lower in Turkey than in developed countries. Furthermore, most of the centers do not perform some essential microbiological diagnostic tests as a routine practice. Some antimicrobials that are recommended as the first-line of treatment for IE, particularly antistaphylococcal penicillins, are not available 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. Physicians can follow patients with IE in many specialties. Diagnosis and treatment processes of IE should be standardized at every stage so that management of IE, a setting in which many physicians are involved, can always be in line with current recommendations. Study Group for Infective Endocarditis and Other Cardiovascular Infections of the Turkish Society of Clinical Microbiology and Infectious Diseases has called for collaboration of the relevant specialist organizations to establish a consensus report on the diagnosis, treatment, and prevention of IE in the light of current information and local data in Turkey.

Keywords: Diagnosis, endocarditis, prevention, treatment.

ÖZ

İnfektif endokardit (İE) nadir görülmesine karşın, önemli morbidite ve mortaliteye neden olan bir hastalıktır. Türkiye'de İE insidensi konusunda yapılmış toplum temelli prospektif çalışmalar bulunmadığı için hastalığın insidensi tam olarak bilinmemektedir. Ancak 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. Ek olarak 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 üç aydan sonra konulabilmekte ve hastalık sıklıkla gözden kaçmaktadır. İnfektif endokardit tanısı konulmuş hastalarda, bu infeksiyona neden olan mikroorganizmaların belirlenme oranı gelişmiş ülkelere göre Türkiye'de çok daha düşüktür. İnfektif endokarditli 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. İnfektif endokarditli 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.

Anahtar sözcükler: Tanı, endokardit, önleme, tedavi.

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This is a summary of the original full-text article.

Although infective endocarditis (IE) is rare, it is still essential as an infectious disease due to the resulting morbidity and substantial mortality rates. Epidemiological studies in developed countries have shown that the incidence of IE has been approximately 6/100,000 in recent years, and it is on the fourth rank among the most life-threatening infectious diseases after sepsis, pneumonia, and intraabdominal infections. Although IE is not a mandatory reportable disease in Turkey and an incidence study has not been performed, its incidence may be expected to be higher due to both more frequent presence of predisposing cardiac conditions and higher rates of nosocomial bacteremia which may lead to IE in risk groups. Additionally, IE often affects elderly in developed countries, while it still affects young individuals in Turkey. To reduce mortality and morbidity, it is critical to diagnose IE to determine the causative agent and to start treatment rapidly. However, most of the patients cannot be diagnosed in their first visits, about half of them can be diagnosed after three 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.

Furthermore, some essential microbiological diagnostic tests are not performed in most of the centers. Some antimicrobials 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 with local data. Physicians can follow patients with IE in many specialties. Diagnosis and treatment processes of IE should be standardized at every stage so that management of IE, a setting in which many physicians are involved, can be always in line with current recommendations. From this point of view, the Study Group for Infective Endocarditis and Other Cardiovascular Infections of the Turkish Society of Clinical Microbiology and Infectious Diseases has called for collaboration of the relevant specialist organizations to establish a consensus report on the diagnosis, treatment, and prevention of IE in the light of current information and local data in Turkey. In the periodic meetings of the assigned representatives from all the parties, various questions were identified. Upon reviewing related literature and international guidelines, these questions were provided with consensus answers.

Why was this consensus report written?

Infective endocarditis often affects elderly individuals in developed countries; however, it still affects young individuals in Turkey. It is one of the most life-threatening infectious diseases and is among the infectious disease leading to mortality frequently in the population. Compared to the European countries and the United States, patients with IE are younger, predisposing factors are different, identification rates of IE pathogens are lower, accessing to some essential diagnostic tests are not possible or hardly possible, some of the antimicrobials recommended for treatment are not available in our country. Therefore, European and American diagnostic and treatment guidelines do not meet our requirements, and this causes a need to prepare a national consensus report for IE.[1-18]

EPIDEMIOLOGY OF IE IN TURKEY AND GLOBALLY

What is the incidence of IE in our country and globally?

The incidence of IE is approximately 6/100,000 people worldwide. There are no data about the incidence of IE in Turkey, which 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 between Turkey and USA/Europe is shown in Table 1.

Which patient populations have a higher risk of developing IE in Turkey and globally?

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

Which are the most frequently identified microorganisms that cause IE in Turkey and globally?

The most frequent causative microorganisms in order are *Staphylococcus aureus (S. aureus)*, streptococci, coagulase-negative staphylococci (CoNS), and Enterococci both in Turkey and globally. Additionally, *Brucella spp*. is the fifth most common causative agent of IE in Turkey (Table 1). *Coxiella burnetii*, which is one of the leading causes of blood culture-negative IE globally, has been identified in some case reports from

Table 1. Comparison of Epidemiological and Clinical Features of Patients with Infective Endocarditis in Turkey and USA/Europe

Feature	Turkey	USA/Europe
Age, year (mean)	47	61
Male (%)	60	65
Predisposing conditions		
Acute rheumatic fever (%)	37	1.85
Prosthetic valve (%)	28	10-30
Intravenous drug user (%)	2	24
Cardiac implantable electronic device (%)	7	15
Chronic hemodialysis (%)	9	13
Causative microorganisms		
Staphylococcus aureus (%)	21	32
Viridans group 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

Table 2. The incidence of infective endocarditis among risk groups

Predisposing condition	Incidence (per 100,000 population)
General population	
Mean age (years)	6
>70	12
>75	19
Structural heart valve diseases	
Rheumatic or degenerative heart valve diseases	348
Mitral valve prolapse (regurgitating)	48
Congenital heart diseases	
Ventricular septal defect (small)	480
Bicuspid aortic valve	66
Intracardiac foreign body	
Prosthetic valve	>1,000 (2,800)
Transcatheter aortic valve implantation	>1,000
Permanent pace-maker/intracardiac defibrillator	1,000
Previous infective endocarditis	7,300
Patient with renal failure	
End-stage chronic renal failure	627
Hemodialysis	1,092
Intravenous drug user	1,125
Solid organ transplant recipient	1,350

our country and, therefore, it must be in the differential diagnosis. Although *Bartonella spp.* and *Tropheryma whipplei* are frequently the causes of blood culture-negative IE globally, and there are no available data about these causative agents in Turkey. The research concerning these agents should be performed. Gram-negative bacilli and fungi are often causative agents of healthcare-associated IE. In patients who underwent implantation of intracardiac prosthetic devices such as prosthetic heart valves in the last decade, *Mycobacterium chimaera* should be kept in mind as a possible pathogen for blood culture-negative IE.[4,82,85-127]

PATHOGENESIS OF IE

What is the pathogenesis of IE?

Mechanical injury on the endocardial surface consequently leads to non-bacterial thrombotic endocarditis (NBTE) formation on which bacterial adhesion occurs on its surface during transient bacteremia. The vegetation enlarges and becomes mature by bacterial proliferation, deposition of fibrinogen, and platelet aggregation. *S. aureus* may bind directly to an inflamed, but structurally intact endocardial surface and be 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 IE

What are the clinical features in patients with IE, and which clinical signs should lead to the suspicion of IE?

Acute IE must be in the differential diagnosis in patients admitted to the emergency room with fever who have predisposing factors for IE (i.e., valvular heart diseases, intracardiac prosthetic devices including a prosthetic valve or IVDU or chronic hemodialysis). In addition, patients who have sepsis with an unknown source, peripheral embolism, multiple infectious foci of sepsis, and new-onset murmurs should also evaluated for acute endocarditis.

Either subacute and chronic IE must be kept in mind in the differential diagnosis of patients with unexplained fever, fatigue, weight loss, and increased acute phase reactants; unexplained arterial embolism including central nervous system and pulmonary; unexplained heart and valvular failures; unexplained blood culture positivity, particularly if they have a predisposing condition for IE.[4,14,23,137-143]

What are the laboratory findings of IE?

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

Which echocardiographic methods should be used in the diagnosis of IE and what is the appropriate timing to do it?

Transthoracic echocardiography (TTE) must be performed for all patients with suspected IE as soon as possible. Transesophageal echocardiography (TEE) must be performed in case of negative TTE, when there is a high index of suspicion for IE, mainly when TTE is of suboptimal quality. Transthoracic echocardiography should be also performed in patients with prosthetic valves or intracardiac prosthetic devices.[3,65,66,141,173-183]

What are the echocardiographic findings leading to the diagnosis of IE?

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

What are the sensitivities and specificities of the echocardiographic examinations for the diagnosis of IE?

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

What is the role of echocardiography in the determination of response to treatment and during follow-up of IE?

While the size and mobility of the vegetations are 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 challenging to interpret persisting and unchanging vegetation size. In such cases, the patient should be evaluated carefully with other clinical and laboratory findings. Well-timed echocardiography is of vital importance to identify patients with signs and

symptoms (i.e., shortness of breath, rhythm conduction disorders) of a cardiac complication (i.e., heart failure, valvular regurgitation, abscess formation, aneurysm or perforation) requiring an emergent surgery.[3,173-186]

When should cardiac computed tomography (CT) be performed in patients with suspected IE, and what are the advantages and disadvantages of cardiac CT?

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

When should magnetic resonance imaging (MRI) be performed in patients with suspected IE, and what are the advantages and disadvantages of MRI?

The experience with cardiac MRI to define cardiac pathologies in patients with IE is limited. Nevertheless, existing evidence suggests that cardiac MRI can be an excellent option to evaluate cardiac anatomy such as cardiac CT, and further studies are needed. Currently, MRI is often used to visualize intracranial complications in patients with neurological symptoms. Cranial MRI should be the diagnostic choice for IE patients with neurological symptoms as its sensitivity is higher than cranial CT in the detection of cranial lesions.[65,189-190]

When should 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT imaging be performed in patients with suspected IE, and what are the advantages and disadvantages of 18F-FDG PET/CT?

18F-FDG 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 after the first three postoperative months in whom TEE is negative. 18F-FDG PET/CT can be also used to define septic foci outside the heart, both in native and prosthetic valve endocarditis. The most important advantages of this modality are to define infectious foci both inside and outside the heart, to establish useful data, and to monitor response to treatment. The false-positivity, particularly within the first three postoperative

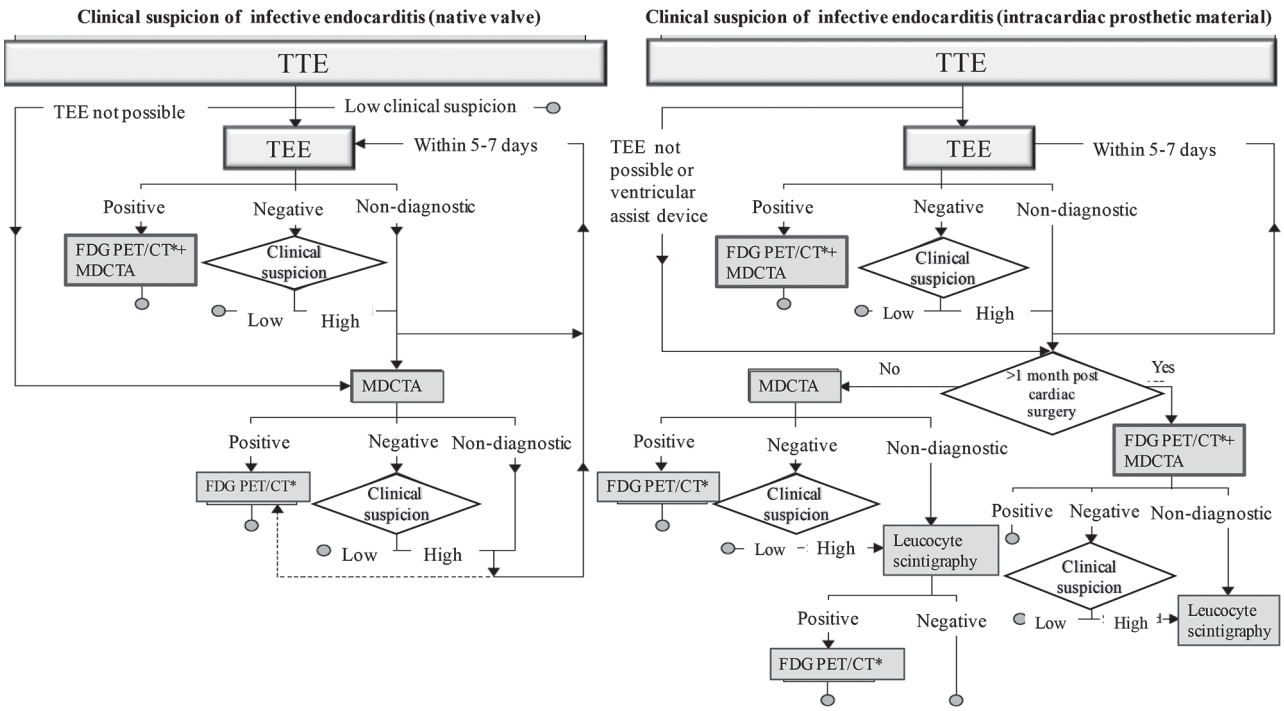

Figure 1. Flowchart for the diagnostic imaging workup of patients suspected of infective endocarditis.[176]

FDG: Fluorodeoxyglucose; PET: Positron emission tomography; MDCTA: Electrocardiogram-gated multidetector CT angiography. TTE: Transthoracic echocardiogram; TEE: Transesophageal echocardiogram. 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.

months in early prosthetic valve endocarditis and its lower sensitivity to diagnose intracardiac pathologies in native valve endocarditis, are the disadvantages of 18F-FDG PET/CT.[175,191-197]

When radiolabeled leukocyte scintigraphy with single-photon emission computed tomography (SPECT)/CT should be done in patients with suspected IE, and what are the advantages and disadvantages of it?

Radiolabeled leukocyte scintigraphy with SPECT/CT can be used as an imaging modality for the diagnosis of prosthetic valve endocarditis within the first three months of prosthesis implantation. Although scintigraphy has a higher specificity, the most significant disadvantage is its lower sensitivity.[65,198,199]

What should be the algorithm for imaging modalities in the diagnosis of IE?

Echocardiography is the first imaging modality of choice to define cardiac lesions in patients with suspected IE. Both TTE and TEE are usually necessary for almost all patients. Both are inconclusive in about 15% of all IE cases, whereas this rate increases up to 30% in patients with intracardiac prosthetic devices such as a prosthetic valve or cardiac implantable electronic devices (CIEDs). In these patients, cardiac CT should be the technique of imaging modality in patients with native valve endocarditis. In contrast, cardiac CT or SPECT/CT should be chosen for patients who have prosthetic valve endocarditis within the first one to three months of valve surgery and cardiac CT and PET/CT should be chosen for patients with

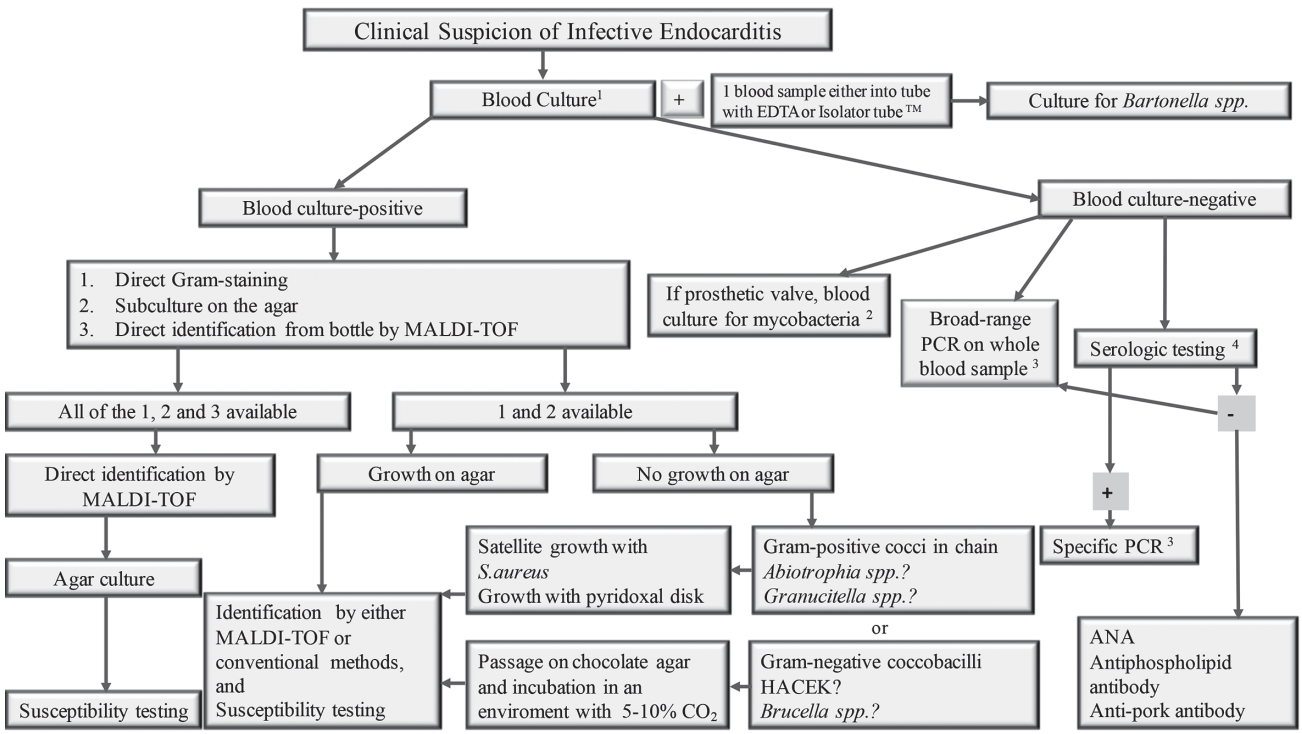

Figure 2. Diagnostic testing algorithm for the identification of the microbiological etiology of IE.

EDTA: Ethylene-diamine-tetra acetic acid; MALDI-TOF: Matrix assisted laser desorption ionization - time of flight; PCR: Polymerase chain reaction; HACEK: *Haemophilus parainfluenzae, Aggregatibacter spp., Cardiobacterium spp., Eikenella corrodens and Kingella spp.,* ANA: Antinuclear antibody; IFA: Indirect immunofluorescence assay; MIC: Minimum inhibitory concentration.

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 h between the first and last draw.

2 In patients who are suspected of having prosthetic valve endocarditis, three additional blood culture bottles specified for mycobacterial growth (BD BACTEC™ Myco/F Lytic, etc.) should be inoculated, unless there is microbial growth in usual blood culture bottles.

3 PCR assays: Multiplex PCR tests targeting streptococci and staphylococci (LightCycler®, SeptiFast, etc.) or broad-range bacterial (16S rRNA) or fungal (18S rRNA) PCR followed by sequencing (SepsiTest®, etc.) should be done for patients with blood culture negative endocarditis and who had taken antibiotics before admission. For patients with a positive serological test results, organism-specific PCR targeting that specific organism should be done

4 Serologic testing: Wright agglutination test with Coombs serum or Brucellacapt® test, Coxiella burnetii phase I IgG, *Bartonella quintana* IgG and B. *henselae* IgG should be ordered first. If those test results were found to be 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: C. *burnetii phase* I IgG antibodies >1/800, *Bartonella spp*. IgG antibodies >1/800, C. pneumoniae IgG antibodies >1/512 and Legionella spp. IgG antibodies >1/256, *Wright agglutination test* >1/160 or Brucellacapt® IgG antibodies >1/320 and a galactomannan optical density index of ≥0.5 should be considered positive.

prosthetic valve endocarditis after three months of valve surgery.[65,66,173-176] Flowchart for the diagnostic imaging work-up of patients suspected of IE is shown in Figure 1.[175]

How should blood culture sampling be performed in patients with suspected IE?

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

How to culture valvular tissues or embolic specimens resected during surgery for the diagnosis of IE?

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

When and which serological tests should be done for the diagnosis of IE?

In patients with negative blood cultures, the Wright agglutination test (with Coomb's serum) and Coxiella phase 1 IgG test (IFA) should be performed initially. If the results of these two tests are negative, IgG antibodies for *Bartonella spp., Legionella spp., Chlamydia spp*., and *Mycoplasma spp*. should be tested, preferably by the IFA method.[4,111,112,210-216]

What are the molecular tests that could be done in either blood or tissue samples of patients with suspected IE, and when should they be on the agenda?

Multiplex polymerase chain reaction (PCR) tests (SeptiFast®, SeptiTest®) should be used to identify

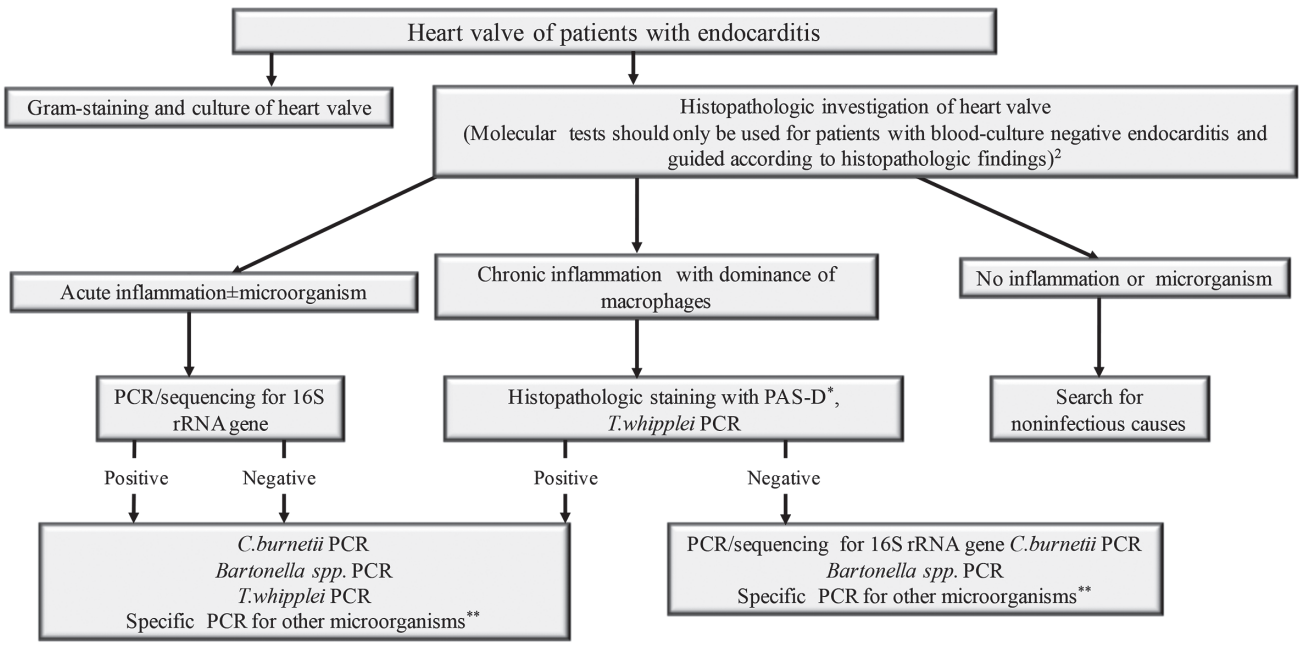

Figure 3. Microbiological and histopathological evaluation of heart valves removed from patient with endocarditis.

PCR: Polymerase chain reaction; rRNA: Ribosomal RNA; * Periodic-acid Schiff (PAS)-positive staining reaction is seen in the macrophages infected with *Tropheryma whipplei*; ** For example, *Mycoplasma hominis*, *Legionella* spp., *Chlamydia spp*., *Cutibacterium* (formerly *Propionibacterium*) *acnes*, etc.

the pathogen in a whole blood specimen of patients with suspected endocarditis and whose blood cultures are negative and who has received previous antibiotic therapy. If the blood cultures are negative in patients not receiving received previous antibiotic therapy, the 16S rRNA gene and *Tropheryma whipplei* PCR should be, then, performed on the resected heart valve obtained during surgery.[140,217-225]

What is the contribution of histopathological examination of valvular tissue excised from patients with suspected IE?

Histopathological examination of resected valvular tissue gives valuable information about the activation and degree of the inflammation in patients with blood culture-positive endocarditis. In contrast, in blood culture-negative IE patients, it allows identifying pathogens, mainly intracellular ones like *Coxiella burnetii, Bartonella spp.*, and *Tropheryma whipplei* with proper staining and immunohistochemical examinations.[119,138,225-232] Diagnostic testing algorithms for the identification of the microbiological etiology of IE is shown in Figure 2 and Figure 3.

What are the sensitivity and specificity of modified Duke Criteria in the diagnosis of IE?

The modified Duke criteria have a sensitivity of 80% in native valve endocarditis, whereas they are insufficient in patients with prosthetic heart valves, intracardiac prosthetic devices, and blood culture-negative endocarditis. Additional imaging techniques and serological and molecular tests should be added to the diagnostic work-up of these patients.[65,141,233] The modified Duke Criteria, including also modification of the European Society of Cardiology (ESC), is shown in Table 3 and Table 4.[3,65]

How is NBTE differentiated from IE?

Non-bacterial thrombotic endocarditis can be seen with numerous clinical entities such as malignancy, hypercoagulable states, connective tissue, and autoimmune disorders. It can be documented in approximately 1% of patients with malignancy, most frequently with pancreatic adenocarcinoma (10%). The main clinical presentation of NBTE is thromboembolism. It is essential to differentiate NBTE from IE. The same diagnostic work-up recommended for IE should be performed. The diagnosis of NBTE is challenging. It can be diagnosed in patients with the presence of a disease process known to be associated with NBTE with high suspicion, if there is the presence of multiple systemic embolism, fixed vegetation size despite antibiotic therapy, and a new heart murmur. In patients with underlying comorbidities which predispose to NBTE, the presence of heart murmur, the persistence of vegetation despite appropriate antibiotic therapy, multiple systemic embolism should lead to suspicion of the NBTE. Although the vegetations in NBTE are often small, their roots are wide and in an irregular shape. The vegetations in

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

Definite IE
Pathological criteria • Microorganisms demonstrated by culture or on histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or • Pathological lesions; vegetation or intracardiac abscess by histological examination showing active endocarditis
Clinical criteria • 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, as above.

IE: Infective endocarditis

Table 4. Definitions of the Terms 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 two 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 by 18F-FDG PET/CT (only if the prosthesis was implanted for >3 months) or radiolabelled leukocytes SPECT/CT. c. Definite paravalvular lesions by cardiac CT.
Minor criteria
1. Predisposition such as predisposing heart condition, or injection drug use. 2. Fever defined as 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 Modified Duke Criteria (3).

NBTE show minimal inflammation where they are attached.[131,234-236]

PROGNOSTIC ASSESSMENT OF PATIENTS WITH IE AT ADMISSION AND DURING FOLLOW-UP

When should the prognostic assessment be done in IE patients, and what is the benefit of this assessment?

A prognostic risk assessment should be done in patients with suspected IE using the Simplified Risk Scoring System during their first evaluation (Table 5 and Table 6). The patients with a higher mortality risk (risk score >8) should be carefully evaluated on time for urgent surgery and transfer possibility to a reference center and intensive care unit (ICU). Prognostic assessment of a patient with IE should be performed thrice: at admission, within the first week of the start of antibiotic therapy, and before discharge. Predicting the prognosis of IE helps clinicians to make an effort to prevent possible complications and to be prepared to overcome these complications.[65,66,237-240]

THE IE TEAM IN THE MANAGEMENT OF PATIENTS

What is the IE Team, and why is there a necessity for making up such a team?

The IE team is a multidisciplinary team including representatives of relevant specialties who manage the diagnosis and treatment of all IE patients, decide collaboratively on all aspects of the disease, particularly on antimicrobial and surgical treatment and meet once a week or, when needed more frequently, to regularly follow-up and evaluate patients. Patients with IE can be followed by physicians from several specialties, as the disease has a wide range of clinical presentations. Since it is a rare disease, it is also unlikely that each

Table 5. Simplified Risk Score Calculation for 6-Month Mortality in Infective Endocarditis (IE)[237]

Prognostic variable	Weight
Age (year)	
≤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 3 or 4 heart failure caused by IE	+3
Stroke	+2
Paravalvular complications	+2
Persistent bacteremia	+2
Surgical treatment for IE	-2

physician has sufficient experience. All these features drive to the delayed diagnosis and treatment of the disease. Consequently, the delay is associated with increased morbidity and mortality rates.

Therefore the IE teams should be established to diagnose IE, give a standardized therapy following the current guidelines, increase practitioners' knowledge and experience, and follow-up the patients with IE.

A cardiologist, a cardiovascular surgeon, and infectious diseases and clinical microbiology specialists should be present in the IE team, at least. When needed, a neurologist, a radiologist, a nuclear medicine specialist, a pathologist, and a neurosurgeon should join the IE team in referral centers. It has been shown that a multidisciplinary approach decreases morbidity and mortality of IE patients. These patients complicated with heart failure, abscess, neurological complications should be followed in referral centers where there are neurosurgery and cardiac surgery facilities. Uncomplicated cases can be followed in non-reference centers provided that there is close communication with the reference centers, and patients are evaluated by the IE team regularly and should be referred to these centers, when necessary (Table 7 and Table 8).[65,241-245]

Table 6. Probability of 6-Month Mortality in Patients with Infective Endocarditis According to Simplified Risk Score[237]

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

ANTIMICROBIAL TREATMENT OF IE

What are the general principles of antimicrobial treatment of in IE, and how should the duration of treatment be determined?

The bactericidal agents given parenterally for long duration is the general principle of antimicrobial treatment of IE. The duration of the antimicrobial treatment is determined by several factors, including the pathogen, the presence of prosthetic material, and the duration of symptoms. The therapy duration is often four to six weeks for native valve endocarditis and longer than six weeks for prosthetic valve endocarditis.[3,86,140,246,247]

Is oral antibiotic therapy feasible to use in the treatment of left-sided endocarditis?

Since there are questions about the feasibility and efficacy of oral antimicrobial treatment of left-sided endocarditis in our country and since left-sided endocarditis is related to a substantially higher mortality rate, the parenteral route should be preferred for the complete duration of antimicrobial treatment of left-sided endocarditis in Turkey. In case of unavailability of IV access or outpatient parenteral antibiotic therapy, oral therapy may be feasible to complete the therapy duration in stable patients with uncomplicated native valve endocarditis as a result of drug-susceptible viridans group Streptococci. Probability of compliance and follow-up is not going to be a problem, provided that initial two weeks of antibiotic therapy completed parenterally, the patient is informed about all the possible risks and give informed consent. Switching to oral therapy should be a joint decision of the IE team.[248-251]

Is empirical treatment necessary for IE?

Antibiotic therapy should be initiated without any delay, as it reduces not only the risk of an embolic event in patients with either acute or subacute IE, but

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
	Infectious Disease and Clinical Microbiology
Patients with indication for emergent surgery	Cardiovascular surgery
Patients with an indication for urgent/elective surgery	Cardiology
	Infectious Disease and Clinical Microbiology
Patients without any surgical indications	Cardiology
	Infectious Disease and Clinical Microbiology

Table 8. Approach to the patient with suspected endocarditis	
Recommendations	Timing
Determination of patient's hemodynamic status and decision for place of hospitalization accordingly	Immediately
Prediction of prognosis according to simplified risk score and referral of the patients with a score of ≥8 to the reference centre	In the first 24 hours or after getting the results of blood cultures and weekly
TTE	Immediately
TEE When TTE is of suboptimal quality or complications are suspected Other conditions	 Immediately 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., 30th and 60th minutes)
Collection of blood samples in to three plain tubes and 1 EDTA tube • Sending of the first plain tube of blood to the laboratory for RF, ANA and Wright agglutination testing • Sending of the second plain tube of blood to the laboratory for Coxiella burnetii phase I IgG testing • Sending of third plain tube and first EDTA tube of blood to the laboratory for multiplex and specific PCR testing and other serological antibody testing	 In the first 24 hours In the case of blood cultures negativity In the case of blood cultures negativity
ECG	Immediately
Repeating 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 USG	In the case of persistent fever and searching for a minor Duke criterion In the first 7 days
Cardiac CT, MRI, 18F-FDG PET/CT, SPECT/CT with scintigraphy with labelled leukocyte	In patients with inconclusive echocardiographic results and suspected IE In the first 7 days

TTE: Transesophageal echocardiography; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; BUN: Blood urea nitrogen; ALT: Alanine aminotransferease; AST: Aspartate aminotransferase; NT-pro-BNP: NT-pro B-type natriuretic peptide; cTnI: Cardiac troponin I; EDTA: Ethylene-diamine-tetra acetic acid; ANA: Antinuclear antibody; PCR: Polymerase chain reaction; ECG: Electrocardiogram; USG: Ultrasonography; CT: Computed tomography; MRI: Magnetic resonance imaging; 18F-FDG: 18F-Fluorodeoxyglucose; PET: Positron emission tomography; SPECT: Single-photon emission computed tomography.

also decreases mortality associated with sepsis in patients with acute IE. Therefore, empirical antibiotics should be promptly initiated after blood cultures are taken.[3,65,140,205,246,252]

What are the empirical drugs of choice for native, early and late prosthetic valve IE in adults in our country?

Ampicillin-sulbactam±gentamicin can be initiated empirically in the treatment of community-acquired, with both subacute and chronic courses of native and late prosthetic valve endocarditis, whereas vancomycin+ampicillin-sulbactam (or ceftriaxone)±gentamicin can be the choice for the acute course. 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 be also added to the empirical treatment of early prosthetic valve endocarditis. Daptomycin alone is not a drug of choice for the initial empirical treatment of IE due to its suboptimal efficacy for Streptococci and Enterococci and the ease development of resistance in these strains during treatment (Table 7).[3,65,137,205,253-258]

What are the drugs of choice in the treatment of streptococcal native and prosthetic valve endocarditis Turkey?

The decision of treatment in streptococcal IE is made according to penicillin G minimum inhibitory concentration (MIC) values of the pathogen. The first treatment of choice is penicillin G in strains that are sufficiently 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, which are sensitive to penicillin and vancomycin, due to the possibility of development of resistance during treatment.[4,86,205,259-268]

What are the drugs of choice in the treatment of enterococcal endocarditis in Turkey?

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. Daptomycin+ampicillin+gentamicin combination is recommended if it is resistant to ampicillin, vancomycin, and teicoplanin. Gentamicin should take part in the treatment unless there is a high level of gentamicin resistance.[1-4,65 205,269-282]

What are the drugs of choice in the treatment of staphylococcal endocarditis in Turkey?

Cefazolin is the drug of choice in methicillin-sensitive *Staphylococcus aureus* (MSSA) IE in Turkey since anti-staphylococcal penicillins are not available in the domestic market. In patients with CNS septic embolism, vancomycin+cefazolin or cefotaxime should be preferred. Daptomycin should be chosen in patients who have hypersensitivity reactions 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 *Staphylococcus aureus* (MRSA) until antimicrobial susceptibility test results are achieved. Following test results indicating MSSA, treatment should be continued with cefazolin. Adding rifampicin and gentamicin is not recommended in native valve IE. In the prosthetic valve IE, cefazolin+gentamicin and rifampicin combination is recommended.

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

THE COMPLICATIONS OF IE AND THEIR MANAGEMENT

What are the clinical and laboratory signs of heart failure developing in patients with IE, and how can they be managed?

Nearly half of the left-sided IE cases, particularly those with aortic valve involvement, develop heart failure in which the mortality risk is higher compared to the right side. Dyspnea, pulmonary edema, hypotension, and other organs' dysfunction in patients with IE can be alarming for heart failure. In IE patients with heart failure, urgent surgery drops mortality rates significantly.[81,169,173,180,356-364]

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

			Duration (weeks)		
Type of infective endocarditis	Antimicrobial agent	Dosage and route	Native	Prosthetic valve	Comment
Native valve and late prosthetic valve (>1 year), community acquired endocarditis, subacute course	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	Vancomycin +	30-60 mg/kg/day i.v. in 2-3 doses	4-6	≥6	Duration of treatment should be 6 and ≥6 weeks for native and prosthetic valve endocarditis, respectively, especially in the case 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 gr/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 gr/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 gr/day, i.v. in 3 doses	6		
	Rifampin	900 mg/day, i.v. or orally in 3 doses	6		
Cardiac Implantable Electronic Device (CIED) related lead or valve endocarditis	Vancomycin ±	30-60 mg/kg/day i.v. in 2-3 doses	Antimicrobial therapy should be continued for 2-4 and 4-6 weeks for the lead and valve endocarditis, respectively, after the removal of the device.		Addition of either gentamicin, or cefepime, or meropenem to vancomycin should be considered especially for septic patients with unstable hemodynamic status.
	Gentamicin, or	3 mg/kg/day i.v. in 1 dose			
	Cefepime, or	6 gr/day, i.v. in 3 doses			
	Meropenem	3 gr/day, i.v. in 3 doses			

* Same regimens could be used for patients with negative blood cultures and serological test results.

In IE patients, what are the clinical and laboratory signs showing uncontrolled infection, and how should they be managed?

In IE patients who develop persistent infections characterized by fever and culture positivity exceeding five to 10 days or infection spreading around valve annulus forming an abscess, pseudoaneurysm, fistula, atrioventricular block despite antibiotic treatment, shows that infection is not under control. In persistent infections, repeated blood cultures, and echocardiographic examinations, imaging for different foci of infection and changing of intravascular catheters should be performed. Despite all of these, patients with persistent fever, particularly persistent blood culture positivity with no other infection source, should be

evaluated for early valve surgery. Since recent studies have shown that blood culture positivity lasting for >48 to 72 hours increases mortality, early surgery for these patients may be also beneficial.[3,65,86,110,173,271,365-367]

What are the incidence and risk factors of embolic events in patients with IE? How should embolic events be managed?

About 20 to 50% of patients with IE have embolic complications in which the most critical risk factor is the size (>10 mm) and mobility of vegetations. This risk dramatically declines with the start of antibiotic treatment. The decision of early surgery to prevent embolism is always challenging, and each patient should be separately evaluated. The factors which influence this decision are the size and mobility of the vegetation, the existence of recurrent embolism under treatment, the type of the microorganism, and the duration of the antibiotic treatment.[3,65,181,183,368-375]

SURGICAL TREATMENT OF IE

What are the indications and appropriate timing of valvular surgery in the management of IE?

Urgent surgery is recommended in IE patients with heart failure. Early surgery is recommended in uncontrolled local (abscess, fistula, aneurysm) or systemic (ongoing blood culture positivity or fever with no other source) infection, recurrent embolism, large vegetations, and severe left heart valve regurgitation or stenosis without clinical signs of heart failure. If urgent surgery is indicated, starting antimicrobial treatment would be enough. There is no need to wait for the clearance of growth in blood cultures.

The decision of heart valve surgery in IE patients should be made by the IE team (or by cardiologist, cardiovascular surgeon and infectious diseases, and clinical microbiologist) by evaluating all aspects of the disease. In patients with neurological complications, surgical decision should be made by the IE team including a neurologist and a neurosurgeon according to the presence/absence of silent embolism/transient ischemic attack (TIA), 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 TIA, cardiac surgery, if indicated, is recommended without delay (Table 10 and Table 11).[65]

MONITORING TREATMENT RESPONSE IN PATIENTS WITH IE AND FOLLOW- UP AFTER DISCHARGE

How should treatment response be monitored in IE patients?

In IE patients receiving appropriate antibiotic treatment and undergoing surgical repair (when needed), fever and serum C-reactive protein (CRP) levels should decrease, blood cultures are negative,

Table 10. Class I Indications and Timing for Surgery in Left-Sided Valve Infective Endocarditis (Recommendations from the European Society of Cardiology 2015 Infective Endocarditis Guideline)[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 vegetations >10 mm after one or more embolic episode despite appropriate antibiotic therapy	Urgent	I	B

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 (AATS) 2016 Consensus Guideline)[377]

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

IE: Infective endocarditis.

valve functions be stabilized, vegetation size in echocardiography should not be enlarged, instead, be reduced, foci of abscess should vanish. Therefore, after starting antimicrobial treatment, two sets of blood cultures should be taken every 48 hours, until positivity in blood cultures be cleared, serial CRP measurements should be done, and gradual decrease of CRP level during treatment and reaching normal levels by the end of the treatment should be expected. The echocardiographic examination should also be performed during hospitalization and immediately before discharge.[65,102,400-404]

What recommendations should be made to IE patients at discharge?

Since the history of IE is a significant risk factor for recurrent endocarditis, patients should be informed about the probability of recurrence of the disease and 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 be also informed about prophylaxis of endocarditis, and to avoid procedures (piercing, tattoo) that may cause bacteremia and endocarditis.[65]

How should operated/non-operated IE patients be followed in outpatient clinics?

In follow-up for detection of possible secondary heart failure, patients should be monitored with periodic TTE: on discharge as a baseline and serially in the first year. The patients should be evaluated for the late side effects of the antibiotics, particularly of aminoglycosides, used for endocarditis treatment at the hospital. Periodic follow-up should be scheduled on the first, third, sixth, and 12th months after hospital discharge. In these outpatient follow-up visits, clinical examination, leukocyte count, CRP, and erythrocyte sedimentation rate (ESR) measurements, and TTE should be performed to detect a possible heart failure.[65]

SPECIFIC CONDITIONS

What are the critical topics in the management of patients with prosthetic valve endocarditis?

The diagnosis of prosthetic valve endocarditis is more complicated than native valve endocarditis, since both blood culture and echocardiographic examination are frequently negative. The sensitivities of TTE and TEE in the diagnosis of prosthetic valve endocarditis are 30% and 80%, respectively. Infective endocarditis should be carefully investigated using novel imaging modalities such as multidetector computed tomographic angiography (MDCTA), PET/CT in patients with suspected prosthetic valve endocarditis with normal echocardiography. Surgery is frequently needed besides antibiotic treatment in patients who have heart failure or paravalvular abscess and with endocarditis caused by *S. aureus* or fungi.[4,65,187,405-411]

What are the critical topics in the management of IE associated with CIEDs?

A CIED-associated IE represents almost 10% of all episodes of IE and is expected to increase proportionately to the increased number of devices implanted. Infective endocarditis should be kept in the differential diagnosis either when there is one or combination of any of the clinical presentations (fever of unknown origin, pocket infection, bacteremia with an unknown source, complications of multiple pulmonary embolisms) in patients with CIED. Blood cultures should be taken promptly; if not, TTE and TEE should investigate any findings of IE. Radiolabeled leukocyte scintigraphy or PET/CT modalities can be additive in case of a routine echocardiographic examination in the diagnosis of CIED-associated endocarditis. The specific treatment of CIED-associated endocarditis should be done with the combination of antimicrobials covering most prominent Staphylococci and complete hardware removal. Percutaneous removal of hardware must be preferred in all cases and particularly in patients with vegetation <20 mm in diameter. The duration of antimicrobial therapy should be two to four weeks in patients with vegetation diagnosed at the extracted lead tip after complete hardware removal, whereas four to six weeks in patients with endocardial lesions. Blood cultures should be negative for at least 14 days to implant a new device in patients with valvular endocarditis who indicate CIED. In cases of other situations, 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 cefazolin prophylaxis just before the implantation of CIED is recommended, additional doses are not required.[69,70,412-432] Management of suspected CIED infections, management of bacteremia without evidence of CIED infection, and management of suspected pocket infection are shown in Figures 4, 5, and 6, respectively.

What are the critical topics in the management of patients with non-CIED related right-sided endocarditis (IVDU)?

Right-sided endocarditis is most common among intravenous drug users (IVDUs). The incidence of IE related to IVDU is going to be increased in parallel with the increasing prevalence of IVDU in Turkey and globally. It is not necessary to make TEE as TTE

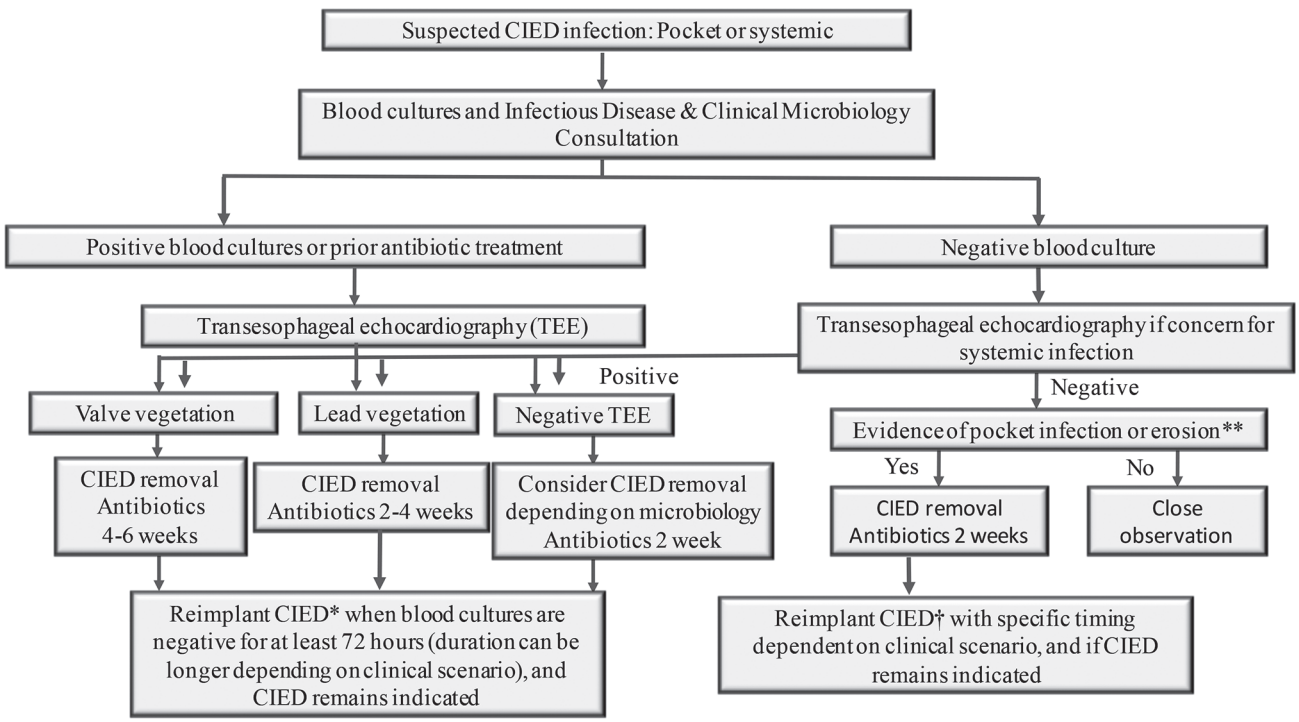

Figure 4. Management of suspected CIED infection.

CIED: Cardiac implantable electronic devices; Antimicrobial therapy should be 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 a valve vegetation, 4 weeks of antibiotics for *Staphylococcus aureus* and 2 weeks for other pathogens is recommended.* Usually the contralateral side; a subcutaneous ICD may also be considered; ** 2010 AHA CIED Infection Update distinguishes between pocket infection and erosion.[70,415]

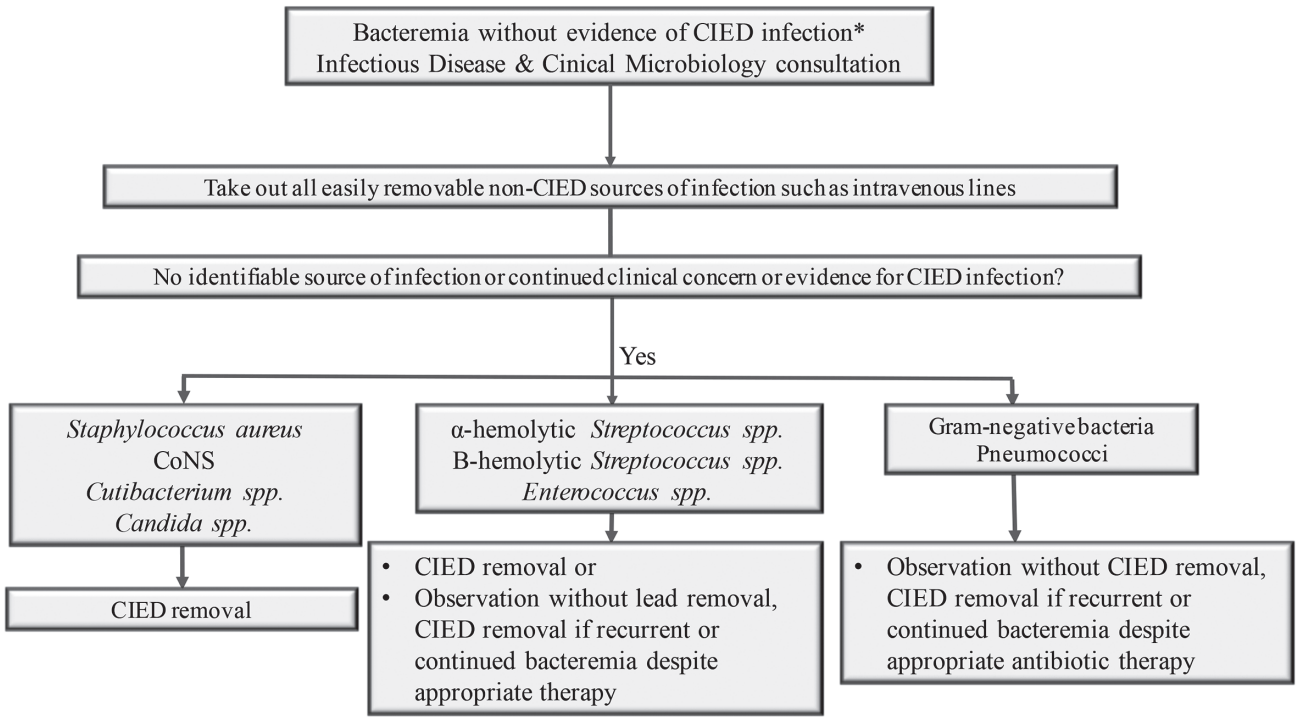

Figure 5. Management of bacteremia without evidence of CIED infection.

CIED: Cardiac implantable electronic devices; * Important to distinguish between blood stream infection and contamination in bacteremia involving skin flora.[70,415]

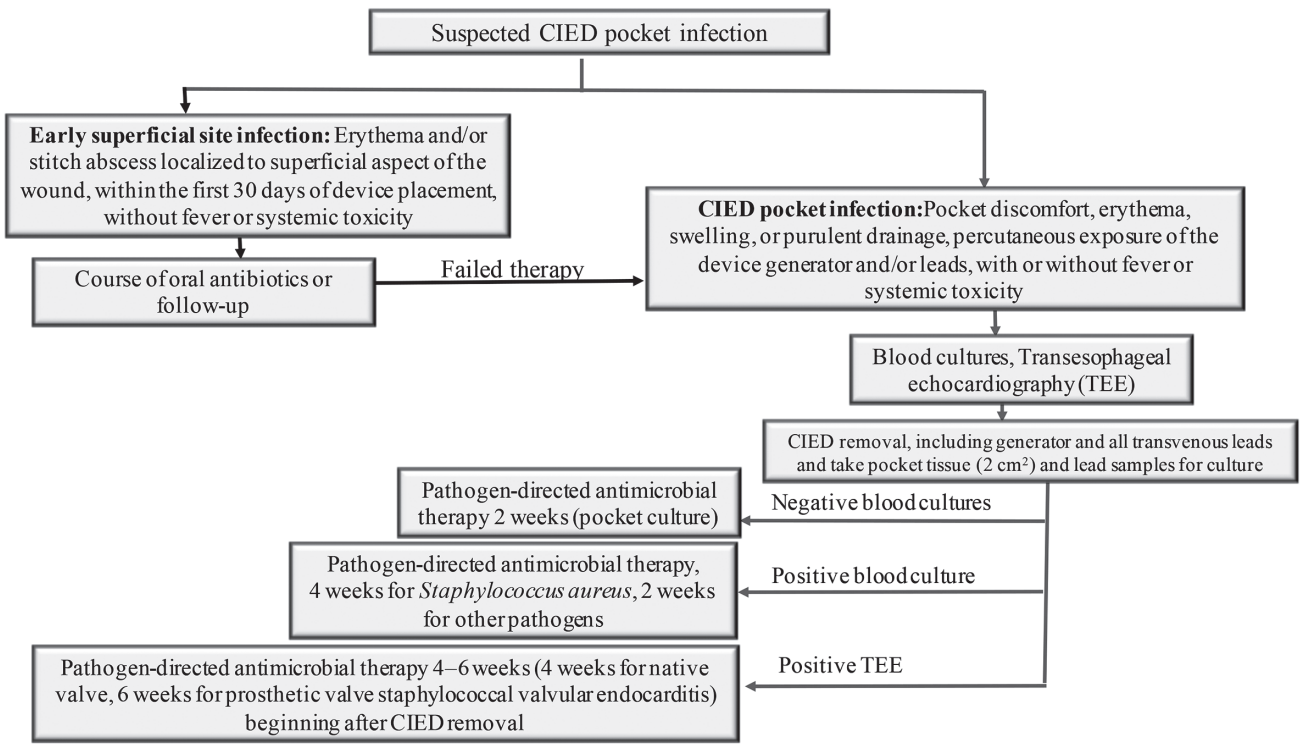

Figure 6. Management of suspected pocket infection.[70,413,415]

can easily visualize the tricuspid valve anatomy and its pathology in those patients. Infective endocarditis is mostly right-sided among IVDU, and *S. aureus* is the most common pathogen. The most prominent symptoms of IE among IVDU are fever and pulmonary symptoms mimicking respiratory tract infections. It is not possible to use short term (two-week duration) treatment modality in the treatment of right-sided endocarditis among IVDU due to MSSA in our country as anti-Staphylococcal penicillins are not currently available. Instead, these patients must be treated with cefazolin for a duration of four to six weeks. Oral combination therapy with ciprofloxacin and rifampin can be used for the treatment of uncomplicated right-side endocarditis in IVDUs caused by strains susceptible to both drugs; however, this approach should be reserved for special situations with the requirement of regular post-discharge follow-up patients in which conventional IV antibiotic therapy is not possible, or it is undesirable due to problems during their hospital stay. The increasing quinolone resistance among *S. aureus* strains may limit the use of this approach.[65,138,433-443]

What are the critical topics in the management of healthcare-associated IE?

At least a quarter of IE cases are healthcare-associated endocarditis at present. It is classified as nosocomial endocarditis, if it develops during the hospital stay or within six months after discharge. It is named as non-nosocomial healthcare-associated endocarditis, when the patient is exposed to health care interventions (i.e., hemodialysis, chemotherapy) outside the hospital within 30 days before the onset of signs or symptoms consistent with IE. Infective endocarditis has to be well-classified as community-acquired, nosocomial, or non-nosocomial healthcare-associated IE on admission, since the choices of empirical therapy are entirely different for healthcare-associated IE and community-acquired IE.[4,22,83,84,444-449]

What are the critical topics in the management of IE in HIV-infected patients?

Infective endocarditis among HIV-infected patients is common, particularly among IVDUs with HIV infection. The risk of developing IE is not increased in HIV-infected patients without IVDU. The IE incidence is higher among HIV-positive than HIV-negative IVDU. The development of IE is more natural compared to immunocompetent patients, and the mortality rate is higher in patients with lower $CD4^+$ T lymphocyte count. The morbidity and mortality rate of cardiovascular surgery is similar in IE of both HIV-positive and HIV-negative IVDU. The decision for valvular replacement has to be individualized in case of a repetitive risk of IE in patients due to the continuing habit of IVDU.[74,450-464]

What are the critical topics of IE in elderly patients?

Infective endocarditis has become more widespread in elderly patients. The clinical presentation is more silent in older patients with smaller vegetations and less embolic events. Healthcare-associated endocarditis is more common among older patients, as they have more prosthetic materials compared to younger patients. The causative pathogens are either Staphylococci acquired by healthcare or *Streptococcus gallolyticus* (*Streptococcus bovis* biotype I) or enterococci related to the intestinal or urinary source. Infective endocarditis in the elderly is more fatal than younger patients. The best explanation for the higher mortality rates among elderly is to have less likely surgery, when needed. Additionally, the antimicrobial treatment is unique in older patients with an increased risk of severe side effects and drug-drug interactions. A team involving a geriatric physician, a cardiologist, a cardiovascular surgeon, and an infectious disease specialist is essential to advocate for deciding diagnostic and therapeutic strategies in older patients with IE to accomplish these difficulties.[4,24,30,143,465-473]

What are the critical topics of IE observed in solid organ transplant (SOT) recipients?

The risk for IE is higher in SOT recipients than the general population, and IE is frequently overlooked. Gram-negative cocci and fungi can be the causative pathogens beside well-known classical pathogens such as taphylococci. If either the source of any bacteremia or fungemia is not known or a new embolic event occurs in SOT recipients, IE should be kept in mind in the differential diagnosis.[4,5,7,8,79,80,474-485]

What are the critical topics in the management of IE in patients with chronic renal failure and among patients receiving chronic hemodialysis?

Although all patients with chronic renal failure are at an increased risk of IE, the risk is highest among hemodialysis patients. The most important two factors to explain this situation are the increased prevalence of bacteremia and cardiac valvular calcifications occurring in hemodialysis patients. Nowadays, chronic hemodialysis patients comprise 10 to 20% of patients with IE, and IE occurs in 1 to 3% of patients with chronic hemodialysis. Left-sided endocarditis, with the involvement of the mitral valve, is common in patients with chronic renal failure. The most common

pathogen is *S. aureus*. The risk of surgery and the risk of developing complications such as embolization is higher in this population. However, valvular surgery can be both feasible and beneficial in appropriately selected patients in whom guideline recommendations can be applied as well. There is no significant difference in the survival rates between the biological valve and the prosthetic valve replaced patients. The bioprosthetic valve is supposed to be more rational due to the increased tendency to hemorrhage and difficulty in long term anticoagulation among elderly with a short life expectancy.[77,78,486-498]

What are the critical topics in the management of the patient with endocarditis in the ICU?

The conditions predisposing to IE should be investigated in patients with ICU admission with acute heart failure, sepsis, and cranial or peripheral embolic events. Infective endocarditis should be in the differential diagnosis in those susceptible patients when a heart murmur is heard during the physical examination, and appropriate empirical treatment should be initiated promptly, if necessary. The echocardiographic examination should be performed to rule out the diagnosis of IE in ICU patients with persistent fever and continuing blood culture positivity, despite appropriate antimicrobial treatment.[65,499-524]

What are the critical topics in the management of IE in pregnant women?

The IE risk is not increased 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 for the first two trimesters. Cardiovascular surgery following an elective cesarean section is preferred after 28 gestation weeks. Emergent surgery must be planned, despite its higher fetal mortality in case of IE leading to acute heart failure. The principles of antimicrobial therapy for severe infections in pregnant women are also valid for pregnant women with IE.[104,525-530]

Should cancer screening be done in patients with IE?

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

ANTITHROMBOTIC THERAPY IN IE

Which antithrombotic agents in which indications should be used in patients with IE and how?

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

PREVENTION OF IE

How and in what situations should antimicrobial prophylaxis be done in patients with IE?

Antimicrobial prophylaxis is only being 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 and cardiac allograft valvulopathy). A single dose of 2 g amoxicillin or 600 mg clindamycin given orally one hour before the procedure is recommended as prophylaxis.

Patients with IE should be examined by the dentist to be sure of the probable dental source of infection, and if a probable source is existing, it must eliminated. An additional dose of prophylactic antimicrobial agent, preferably selecting a different class of antibiotic to cover whole probable pathogens should be given one hour before the procedure to those patients who have already been receiving appropriate antimicrobials for their IE.[3,17,25,58,61,65,66,269,376,539-567]

What is recommended to high-risk patients for IE about their oral and dental hygiene?

High-risk patients to develop IE should seek professional dental care twice a year, whereas intermediate-risk patients should have it annually.[65]

What are the other measures in the prevention of IE?

Central venous catheters should not be placed to patients with the risk of IE, unless required. If catheterization is necessary, the catheter should be, then, 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. Anti-staphylococcal therapy for five and seven days is recommended for patients with a predisposing condition for the acquisition of IE, if *S. aureus* is isolated from their removed intra-venous catheter's tip culture. There has been no vaccine available in clinical use to prevent IE recently. The procedures breaching the skin integrity like tattoos and body piercing should be avoided. Nose picking should be avoided to prevent the nasal carriage of *S. aureus* and transient bacteremia, if *S. aureus* nasal carriage is already present.

The Stöckert 3T heater-cooler system devices manufactured in the years between 2006 and 2014 are known to be contaminated with M. chimera and should not be used at the cardiovascular surgery centers, if particularly either prosthetic valve or vascular graft will be replaced.[65,102,121,568-585]

Infective Endocarditis and Other Cardiovascular Infections Study Group

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