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Infective Endocarditis – Diagnosis, Treatment and Specific Situations Management – Current Knowledge, Review of the Literature

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ABSTRACT

Introduction

Infective endocarditis (IE) is a severe condition of endocardium, which can manifest through a wide spectrum of unspecific symptoms related to various organ systems. The diagnosis is made on the basis of the presence of bacteraemia and imaging findings confirming IE visualized in echocardiography, computer tomography and nuclear imaging. Anatomical changes or foci of altered metabolism can be located on the valves, in the perivalvular area or in the area of foreign material (e. g. valves prosthesis or implantable device). Not only the diagnostic process can be challenging, but also the treatment, which consists of antibiotic therapy and cardiac surgery. The indications for surgical treatment depend on patients' clinical condition, which can change dynamically. Multidisciplinary approach is required to the proper care of the patients.

Aim of the study

The aim of the study is to review the current knowledge of infective endocarditis and the timing indications of cardiac surgery treatment.

Material and methods

This article presents the current knowledge of the diagnosis and treatment in infective endocarditis, especially on the basis of the guidelines of European Society of Cardiology. Literature analysis, especially papers, which contain recent report in infective endocarditis treatment were analysed using the PubMed platform. The search included the keywords: "infective endocarditis", ,,surgery treatment of infective endocarditis", "endocarditis team", "CIED- related infective endocarditis".

Keywords: infective endocarditis, cardiac surgery treatment, endocarditis team, CIED- related infective endocarditis

Introduction

Etiology and epidemiology

Infective endocarditis (IE) is a disease of an endocardial surface of the heart, described for the first time in 1674. [1] It may affect mural endocardium, native and prosthetic valves, as well as cardiovascular implantable electronic device (CIED). IE occurs at a frequency of 13,8 per 100 000 population. In last decades the incidence increased from about 0.03- 0.1 per 100 person- years. [2, 3] The incidence is higher among men, but women present higher mortality and worse outcomes. [4] IE affects elderly people mostly, with high mortality of two- thirds. Congenital heart diseases, intravenous drugs administration and immunosuppression predispose to IE in younger population. [5] Moreover, IE risk factors remain not only native valves diseases, especially, rheumatic heart disease, but also implanted cardiac devices and central venous or arterial catheters. Iatrogenic risk factors remain undergoing of dental or surgical procedures, haemodialysis and recent hospitalization. [6]

The results of EURO- ENDO registry showed that the most frequent pathogens of IE are *S. aureus*, which are responsible for nearly 31% cases, oral *Streptococci* (17% cases) and coagulase- negative *Staphylococci* (CoNS). Other etiological factors are: *Enterococci (E. faecalis, E. faecium*), Gram- negative bacteria HACEK (*Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella,* and *Kingella)* and non- HACEK (*Brucella* spp, C. *burnetii, Bartonella spp, Legionella spp, Mycoplasma spp.)* and funghi. [7, 8]

Symptoms

Symptoms are unspecific, such as high fever with chills or prolonged subfebrile state accompanied by excessive sweating, malaise, weakness, joint and muscle pain, lack of appetite and weight loss, headache, nausea. Additionally, on examination murmurs of regurgitation of the damaged valve and symptoms of heart failure may be noticed. IE can manifest by neurological symptoms and ischemic disorders. Peripheral vascular manifestations may include petechiae in the skin, under the nail plate, Osler's nodules (painful, red, located mainly on the fingers and toes), Roth's spots (petechiae in the retina with a pale center), Janeway's sign (non-painful hemorrhagic spots on the palms and soles). [2]

Diagnostic tests

The diagnostic process should take a careful insight in patients' condition and combine recommended methods. 2023 European Society of Cardiology (ESC) guidelines for the management of infective endocarditis emphasize microbiology tests and imaging.

Microbiology

Blood cultures need to be detected in samples taken before antibiotic administration; at least three samples in at least 30 minutes intervals. The samples should be taken from a peripheral veins to avoid the risk of contamination. What is important, taking blood samples should not be delayed to the peak of the fever, because bacteremia in IE is almost constant. The most common factors of blood culture- positive IE are: *S. aureus,* oral *Streptococci* and CoNS. [6, 9]

Blood culture- negative IE is characterized by higher incidence of long- term mortality in comparison to blood culture- positive IE with pharmacotherapy alone. [10]

Serological testing should be carried out if *Bartonella, Brucella, Legionella, Chlamydia, Mycoplasma, Tropheryma whipplei, Coxiella burnetii, Mycobacteria* or fungal infection is suspected. PCR testing of ribosomal RNA may also be helpful.

Imaging

Echocardiography is the main diagnostic tool in IE and the most accessible one. Transthoracic echocardiography (TTE) is recommended as the first imaging modality in suspected IE. [4] It shows high specificity (>90%) and sensitivity (75%) in detecting vegetations. [11] Transesophageal echocardiography (TEE) is considered to be more sensitive diagnostic test to detect vegetations than TTE. [12] TTE's lower sensitivity in detecting prosthetic valves IE is due to the possible shadowing from their components. [13] TEE is required in patients with prosthetic valves or implantable device, in case of non- diagnostic or negative TTE and specific complications, e. g. abscesses. Echocardiographic IE findings include: vegetations, leaflet perforation or thickening, perivalvular complications (abscesses, pseudoaneurysms, fistula, prosthetic valve dehiscence, infected collection). Repeated imaging should be performed if new complications are suspected. Three- dimensional echocardiography supplements information on vegetation morphology and size, which provides more accurate embolic risk evaluation and treatment planning. [14, 15]

Alternative diagnostic tool is computer tomography (CT) performed for detecting perivalvular and periprosthetic complications. CT is superior to TEE in imaging abscesses and pseudoaneurysms. [16] Pre- operative assessment of coronary artery disease (CAD) in patients at high risk, with aortic valve vegetations is highly recommended instead of coronary angiography. CT is used also for detecting distant lesions and sources of bacteremia including septic pulmonary embolism, mycotic arterial aneurysms and central nervous system complications. [6]

Despite the low spatial resolution and lower sensitivity in detecting lesions, especially on prosthetic valves, than in CT, cardiac magnetic resonance (CMR) can also help in differentiating thrombus and vegetations. [17] The main role of CMR is detecting neurological complications, such as cerebral embolic events, cerebral microbleeds and spine lesions. Due to this fact, CMR may also lead to earlier confirmation of the diagnosis of IE and adding the minor criterion in neurologically asymptomatic patients with non- definite diagnosis. Ischemic lesions occur in 50-80% of patients with IE, but most of them do not influence the decision- making. Cerebral microbleeds are present in 50-60% of IE patients, but they should not be taken as a minor criterion. [6, 18, 19]

Finally, nuclear imaging- [^{18}F]fluorodeoxyglucose ([^{18}F]FDG)- positron emission tomography (PET) -CT and white blood cell (WBC) single photon emission computed tomography (SPECT)/CT are used for prosthetic valve endocarditis, detection distant lesions and sources of bacteremia and evaluation of cardiac devices infection. [^{18}F]FDG- PET- CT showed high sensitivity (86%) and specificity (84%) for detecting prosthetic valve endocarditis. [20] Another role of [^{18}F]FDG- PET- CT includes monitoring of antimicrobial response in patients qualified to surgery, delayed due to the high risk. [21] However, some cases as recent surgery, vasculitis or another inflammatory process may cause false positive result. WBC SPECT/CT is useful when [^{18}F]FDG- PET- CT is unavailable, especially its sensitivity increases in the periprosthetic abscesses presence. [22]

Ultimately, presented imaging methods provide supplementary information in the diagnostic process and management of patients with IE.

Diagnosis

The diagnosis is being made on the basis of modified ESC criteria from 2023. (Table 1) [6] IE classification is based on number of fulfilled criteria. The definite IE is stated when: 2 major criteria or 1 major criterion and at least 3 minor criteria or 5 minor criteria are completed, while for possible IE- 1 major criterion and 1 or 2 minor criteria or 3–4 minor criteria have to be met. IE is rejected when the patient does not meet criteria for definite or possible at admission with or without a firm alternative diagnosis.

MAJOR CRITERIA

1. Blood cultures positive for IE

(a) Typical microorganisms consistent with IE from two separate blood cultures: *Oral streptococci, Streptococcus gallolyticus* (formerly *S. bovis*), HACEK group, *S. aureus, E. Faecalis*
(b) Microorganisms consistent with IE from continuously positive blood cultures:
   - ≥2 positive blood cultures of blood samples drawn >12 h apart,
   - All of 3 or a majority of ≥4 separate cultures of blood (with first and last samples drawn ≥1 h apart).
(c) Single positive blood culture for C. burnetii or phase I IgG antibody titre >1:800.

2. Single positive blood culture for *C. brunetii* or phase I IgG antibody titre > 1:800.

3. Imaging positive for IE

Valvuar, perivalvuar/periprosthetic and foreign material anatomic and metabolic lesions characteristic of IE detected by any of the following imaging techniques:

- Echocardiography (TTE and TOE).
- Cardiac CT.
- [18F]-FDG-PET/CT(A).
- WBC SPECT/CT.

MINOR CRITERIA

1. Predisposing conditions (i.e. predisposing heart condition at high or intermediate risk of IE or people who injected drugs)

2. Fever defined as temperature >38°C

3. Embolic vascular dissemination (including those asymptomatic detected by imaging only):

- Major systemic and pulmonary emboli/infarcts and abscesses.
- Haematogenous osteoarticular septic complications (i.e. spondylodiscitis).
- Mycotic aneurysms.
- Intracranial ischaemic/haemorrhagic lesions.
- Conjunctival haemorrhages.
- Janeway's lesions.

4. Immunological phenomena: • Glomerulonephritis. • Osler nodes and Roth spots. • Rheumatoid factor.
5. Microbiological evidence: • Positive blood culture but does not meet a major criterion as noted above. • Serological evidence of active infection with organism consistent with IE.

Table 1. The diagnostic criteria of infective endocarditis, the table from 2023 European Society of Cardiology Guidelines for endocarditis management;
IE- infective endocarditis, HACEK- *Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella,* and *Kingella,* TTE- transthoracic echocardiography, TOE- transesophageal echocardiography

Treatment

The ESC 2023 guidelines emphasize complexity of the problem and a need for the multidimensional approach, using endocarditis team, early diagnosis and treatment. Endocarditis team consists of cardiologists, cardiovascular surgeons, infectious disease specialists and microbiologists. Their crucial role is to optimize proper treatment and manage complications. Endocarditis team evaluation is required in complicated and uncomplicated IE.

Complex management include pharmacotherapy and surgical treatment. Definite IE should be treated with empirical antibiotic at the beginning and, additionally, after receiving the blood culture results according to it.

Antimicrobial therapy

The choice of intravenous antibiotic treatment depends on many factors, such as: presence of native or prosthetic valve (time from the operation- less or more than 12 months- early vs late prosthetic valve endocarditis [PVE]) or implantable devices, localization of the infection, epidemiology and antibiotic resistance and the patients' immunological status.

Antibiotic empirical treatment should be started immediately after blood cultures samples taking. Treatment should cover *Staphylococci, Streptococci*, and *Enterococci* in case of native valve or late PVE. In early PVE, nosocomial and non- nosocomial healthcare-associated IE, methicillin-resistant *Staphylococci, Enterococci* and non-HACEK Gram-negative pathogens should be covered. After receiving blood culture tests results, the treatment should be verified and switched according to the guidelines in 24- 48 h period. The first line

treatment include one of the following antibiotics: ampicillin, cloxacillin, ceftriaxone, or vancomycin + gentamycin. [6]

Optimal pharmacotherapy has to be continued for at least 4 weeks. In the critical phase (up to 2 weeks) intravenous treatment supplements surgical treatment, removing implantable devices if needed, or, draining abscesses. It is continued up to 6 weeks. In the continuation phase oral administration or intravenous- at home treatment should be considered in stable cases, who do not need surgical procedure anymore or did not undergo embolic events. [23]

The details of antibiotic choice according to blood culture results following the 2023 ESC IE guidelines are listed in the Table 2.

Pathogen	**NVE/PVE**	**Treatment**	**Treatment duration**
Streptococci	NVE	Ceftriaxone + gentamycin	4 weeks
Streptococci	PVE	Ceftriaxone + gentamycin	6 weeks
Staphylococci	NVE	Flucloxacillin or cefazolin or vancomycin	4-6 weeks
Staphylococci	PVE	Flucloxacillin, vancomycin, or cefazolin + gentamycin and rifampicin	6 weeks
Enterococci	NVE	Ampicillin + gentamycin, vancomycin + gentamycin, or ampicillin + ceftriaxone	6 weeks
Enterococci	PVE	Ampicillin + gentamycin, vancomycin + gentamycin, or ampicillin + ceftriaxone	6 weeks
Brucella spp.	NVE/PVE	Doxycycline + cotrimoxazole + rifampin p.o	≥ 3 – 6 months
C. burnetii	NVE/PVE	Doxycycline + hydroxychloroquine p. o.	> 18 months
Bartonella spp.	NVE/PVE	Doxycycline p. o. for 4 weeks + gentamicin i.v. for 2 weeks	4 weeks
Legionella spp.	NVE/PVE	Levofloxacin i.v. or p. o. for ≥6 weeks or clarithromycin i.v. for 2 weeks, then orally for 4 weeks + rifampin	>6 weeks
Mycoplasma spp.	NVE/PVE	Levofloxacin i.v. or p. o.	≥6 weeks

T. whipplei	NVE/PVE	Doxycycline + hydroxychloroquine p. o.	≥18 months

Table 2. Antibiotic choice and time of the treatment according to detecting the pathogen by blood cultures or serological tests results, depending on NVE or PVE.

NVE- native valve endocarditis, PVE- prosthetic valve endocarditis

Surgical treatment

2023 ESC guidelines for management of IE highlight three main reasons for surgical treatment: heart failure, uncontrolled infection and prevention of septic embolism.

Heart failure is the most frequent surgical indication. It occurs as a consequence of leaflet perforation or rupture, mitral chordae rupture or fistulae. The mode of surgery depends on clinical manifestation- emergency in pulmonary oedema and cardiogenic shock and urgent in dyspnoea and echocardiographic signs of poor heamodynamic tolerance. [6]

Uncontrolled infection is defined as persistent infection (7 days of positive blood cultures after adequate antibiotic therapy) despite proper treatment, resistant or very virulent pathogens or local complications which do not respond to pharmacotherapy. Septic shock is one of the most lethal IE complications, which occurs at a frequency of 5- 10% of patients. Locally uncontrolled infection include abscess, false aneurysm, fistula, enlarging vegetation, prosthetic dehiscence, new atrioventricular block and is an indication for urgent operation. Particular attention while considering surgery should be given to infection caused by fungi and multiresistant pathogens and, in PVE, ethiology of *S. aureus* and non-HACEK Gram-negative bacteria. [6, 24, 25, 26]

Embolic prevention include cardiac surgery in case of aortic or mitral valve vegetation with a size of 10 mm or more after at least one embolic episode despite appropriate antibiotic therapy (I class). However, lack of severe valve dysfunction and previous embolic events gives lower recommendation class- II b- for surgery. [6]

The mode of surgical treatment depends on many factors. Immediate mode (on the same day) is carried out in patients with pulmonary edema and cardiogenic shock. Urgent mode, i.e. 3-5 days, is recommended for local complications (abscesses, fistulas, pseudoaneurysms), persistently positive blood cultures, PVE (caused by *S.aureus* or most G (-), presence of embolism or high risk of occurrence large vegetations ≥10 mm and hemodynamic intolerance of heart failure. Deferred mode, during the same hospitalization, is recommended in a case of well-tolerated heart failure symptoms and “controlled” course of infection (no local

complications, bacterial etiology- multidrug-resistant strains or fungal- depending on the patient's condition). [6, 27]

Specific situations management

CIED- related endocarditis

A specific type of IE is CIED- related IE. The number of this serious complication of implantable devices therapy is increasing. The cause of this condition may be more complex procedures, increasing age of patients undergoing the implantation. [28] CIED- related IE may be localized in the pocket or involve parts of the device- generator and leads, or superficially, without pocket and hardware involvement. The diagnosis should be based on blood cultures and imaging. Especially useful diagnostic tool is [18F]FDG- PET- CT (in suspected CIED-associated IE without signs of lodge infection) or WBC SPECT. The definition includes clinical signs of the pocket infection and/ or imaging findings typical for valvular infection. Indications for extraction of the entire system are definite CIED- related IE. Complex removal should be considered in valvular IE even without certain CIED involvement, for probable CIED-associated IE with G(+) bacteremia or fungemia persisting despite antimicrobial treatment. For probable CIED-associated IE with G(-) bacteremia persisting/recurring despite antimicrobial treatment system removal may be considered. [6] CIED removal is not recommended after 1 positive blood culture without other clinical features of infection. Empirical antibiotic therapy should cover methicillin-resistant *S aureus* (MRSA) and Gram-negative bacteria. [29] Decision- making process should take many factors into account, especially, procedural risk, patients' condition and peacemaker dependency.

Prosthetic valve endocarditis

Not only the incidence of CIED- related IE increase is being noted, but also for prosthetic valve IE. Nowadays it accounts for 20- 30%, more commonly in patients with biological than mechanical prosthetic valve (2.2% vs 1.5%). [30] Etiology differs dependently on the time from the surgery. In early PVE the most common factors are *S. aureus, Staphylococcus epidermidis*, Gram-negative pathogens or fungi. In late PVE pattern of the infection factor imitates NVE- Streptococci and Staphylococci. [31] The diagnosis may be challenging due to atypical symptoms and negative imaging results, especially, in early post-operative period. Echocardiography is obliged in PVE suspicion, although it's specificity of 60% may postpone the diagnosis. The most accurate diagnostic tool is [18F]FDG-PET/CT. [4] On account of the relatively high hospital mortality (20-40%), early diagnosis and treatment is

recommended. Operation is required in early PVE in valve replacement and debridement. Another surgery indications remain as in NVE. [4]

Transcatheter prosthetic valve endocarditis

The most frequently used percutaneous procedures for managing valvular heart disease include transcatheter aortic valve implantation (TAVI). The incidence of transcatheter prosthetic valve IE fluctuates from 0.3 to 1.9 per 100 person-years and is comparable to surgical treatment. [4, 32] Echocardiography is also necessary to be perform, but it is nuclear imaging which showed the ability to change the diagnosis status to certain in 33% of cases. [33] *Enterococci* and *S. aureus* are the most frequent pathogens in infective endocarditis after TAVI, followed by *streptococci* and coagulase-negative staphylococci (CoNS). [34] Antimicrobial therapy for infective endocarditis following TAVI is essentially the same as that used for PVE. [4] The rate of infective endocarditis linked to TAVI has reduced in recent years, largely thanks to enhancements in procedural techniques and the continuous development and refinement of the devices used.

Congenital heart diseases endocarditis

Patients with congenital heart disease (CHD) are at a higher risk of developing IE. Especially predisposed are those with residual cardiac shunts and turbulent blood flow, patients, who underwent cardiac procedures and had foreign material implanted, those with uncorrected cyanotic heart disease and previous IE. [35] In recent years the number of adults living with CHD has increased. Although the incidence of IE in pediatric population is low (0.041 per 100 person-years), among adults is noted 0.13 per 100 person-years, which is 30- fold higher than in general population. [36, 37] The more complex heart defect is, the higher risk of IE it brings. [38]

Summary

IE, as a life-threatening condition affecting the heart's endocardial surface, often constitutes diagnostic and therapeutic challenge. Its complexity stems from a broad spectrum of symptoms, demanding a multidisciplinary approach for effective management. The integration of essential diagnostic tools is crucial for confirming IE and guiding treatment decisions. Treatment of IE combines pharmacological and surgical strategies. Empirical antibiotic therapy, based on pathogen identification, forms the cornerstone of medical management. However, surgical intervention becomes indispensable in severe cases, particularly those involving heart failure, persistent infection, or high embolic risk. Surgical treatment addresses complications like valve

dysfunction, abscesses, and large vegetations. Timely intervention—emergency, urgent, or deferred—depends on the patient's clinical condition and the nature of the complications. The decision-making process underscores the necessity of individualized care to improve prognosis. The 2023 European Society of Cardiology (ESC) guidelines emphasize the importance of an "endocarditis team" comprising cardiologists, surgeons, microbiologists, and infectious disease specialists to ensure optimal care.

In conclusion, infective endocarditis demands early and precise evaluation. Multidimensional management, combining targeted pharmacotherapy and timely surgical intervention, is pivotal for reducing mortality and improving patient outcomes. As medical advancements continue, the comprehensive approach outlined in the ESC guidelines serves as a cornerstone for managing this formidable condition.

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