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ARTYKUŁ SPECJALNY / *STATE-OF-THE-ART REVIEW*

Infective endocarditis — Cinderella in cardiology

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INTRODUCTION

Infective endocarditis (IE) is uncommon; however, its incidence is on the rise [1]. Despite improvements in its management, IE is associated with significant short- and long-term morbidity and mortality [2]. A definitive diagnosis of IE may be challenging and is often delayed due to the highly variable and non-specific symptoms at patient presentation, alongside limited availability of specialist services [3]. In addition to IE remaining a diagnostic challenge, the decisions about the treatment modality (medical vs. surgical) and the timing of potential valve surgery are demanding, despite established national and international guidelines [4]. Prolonged treatment with antibiotics is required, even following surgical intervention, which incorporates as many as 50% of patients with IE [5]. IE is considered as the 'Cinderella' of heart disease, having a relatively low media profile and limited research funding, like conditions such as acute coronary syndrome. In this article we discuss the recent advances in the diagnostic approach and treatment strategies available for patients with IE.

EPIDEMIOLOGY AND PATHOGENESIS

Infective endocarditis is uncommon in the general population, with an estimated prevalence of 3–9 per 100,000 persons [6] and with a male to female ratio over 2:1. There is an increased incidence of IE in people over 65 years of age. In the past, IE was associated mainly with poor oral hygiene and rheumatic heart disease but many factors such as an ageing population with degenerative valvular disease, injection drug use, and the increasing number of valve replacements and medical interventions have altered the epidemiology. For example, the number of transcatheter aortic valve implantation (TAVI) procedures is on the rise. TAVI procedures with post-procedural leak [7] are associated with a higher risk of prosthetic valve endocarditis (PVE). PVE accounts for 20–30% of all cases. Despite technological advances in cardiovascular medicine, 1-year mortality for IE remains relatively high, with reported rates between 20% and 30%. Furthermore, survivors have increased morbidity and reduced survival compared to the general population [2].

Two of the key factors associated with IE are endothelial/endocardial damage and bacteraemia. Haemodynamic and mechanical stress due to turbulent flow, as witnessed in valvular disease, leads to endocardial injury and subsequent platelet and fibrin deposition. Transient bacteraemia occurs commonly in association with dental procedures. The frequency and intensity of bacteria is related to the nature and severity of the tissue trauma, the density of the microbial flora, and the degree of inflammation or infection. Microorganisms adhere to fibrin and platelets deposits, multiply rapidly, and stimulate further deposition of fibrin and platelets (Fig. 1).

DIAGNOSTIC APPROACH

The diagnostic classification for IE relies on the modified Duke criteria, which are based on clinical features, microbiological results, and echocardiographic findings. Due to the diverse presentation of IE, patients may not present directly to a cardiologist or microbiologist [4]. More frequently, patients with IE present to general physicians with non-specific symptoms, unexplained weakness, signs of infection, or with new onset stroke, leading to delayed diagnosis [8]. Although the diagnosis can be confirmed if blood cultures are positive for IE-specific bacteria and echocardiography demonstrates a clear vegetation, in their absence, IE cannot be excluded. Clinical judgement is therefore key in diagnosing IE in those patients with a high index of clinical suspicion for IE. As a result, a thorough clinical history and examination are pivotal in directing investigations to diagnose IE. A new murmur, fever, stroke with signs of infection, immunological phenomena, and sepsis of unknown origin are important features of IE, which may spark clinical suspicion. Additionally, even if blood cultures are positive for IE-specific bacteria, such as Streptococcus viridans, cardiac imaging is required to exclude IE. Conversely, identifying a valvular mass or lesion may trigger investigations to exclude subclinical infection, including inflammatory markers and blood cultures. In an attempt to address this diagnostic challenge, international guidelines have recommended a multidisciplinary team approach to diagnosing and subsequently managing patients with IE. Several specialists,

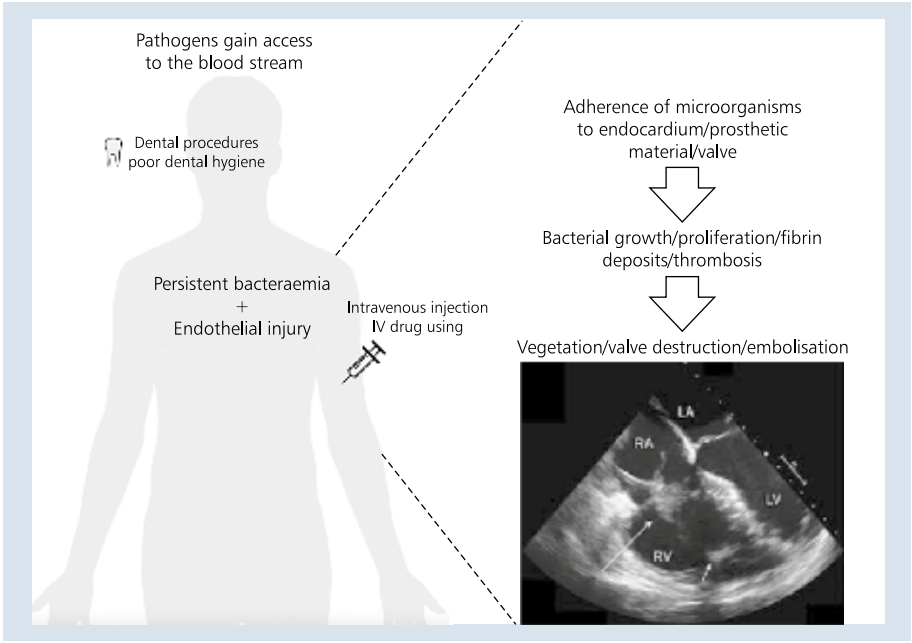

Figure 1. Pathogenesis of infective endocarditis; LA — left atrium; LV — left ventricle; RA — right atrium; RV — right ventricle; arrows — a big vegetation attached to a triacuspid valve and a pacing lead

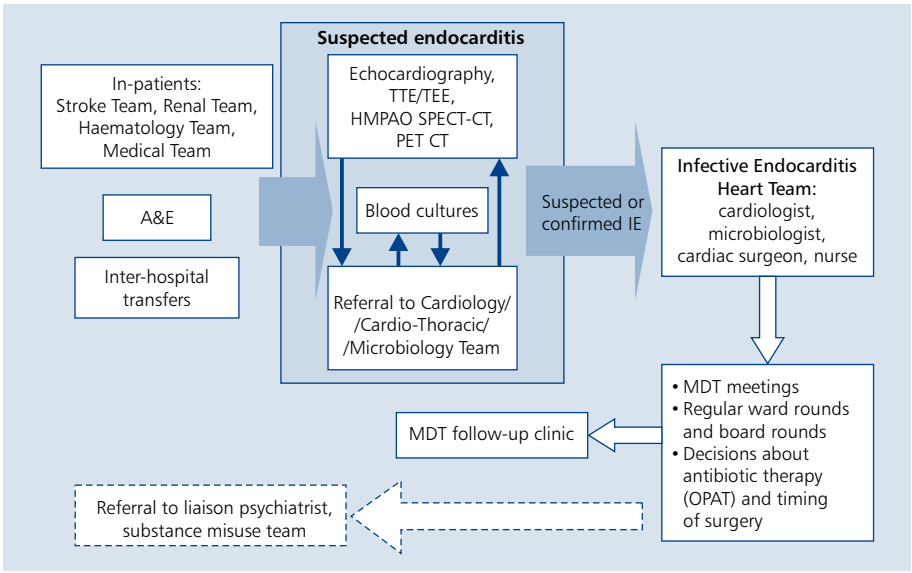

Figure 2. Referral pathway and journey of patients with infective endocarditis (IE); A&E — accident and emergency; MDT — multidisciplinary team; OPAT — outpatient antibiotic therapy; PET — positron emission tomography; SPECT-CT — single-photon emission computed tomography; TEE — transoesophageal echocardiography; TTE — transthoracic echocardiography

including cardiologists, cardiac surgeons, and microbiologists, collectively form the 'Endocarditis Team'. The benefit of this multidisciplinary team approach to patient management is well established for patients with complex conditions such as those undergoing TAVI [9]. Implementation of this collaborative approach for patients with IE may lead to earlier diagnosis, earlier treatment with microorganism-specific antibiotics and earlier surgery, if indicated, which may translate to reduced mortality and morbidity [10].

Despite the potential benefits of adopting an 'Endocarditis Team' approach in this cohort of patients, there are restrictions to its widespread implementation due to limited local resources. Since 2014, we have implemented a functional 'Endocarditis Team' at Kings College Hospital, London, United Kingdom (UK). All patients with confirmed IE, possible IE, and cases with high clinical suspicion of IE are reviewed by the 'Endocarditis Team' on a twice-weekly basis (Fig. 2). A before/after analysis has demonstrated an associated reduction

in the duration of inpatient stay from 30 days to 25 days, a reduction in cost from £33,000 to £24,000, and a reduction in in-hospital mortality from 20 to 13% (unpublished data).

IMAGING MODALITIES

According to the modified Duke criteria, definite IE can be diagnosed if microbiological and pathological criteria are satisfied. Transthoracic and transoesophageal echocardiography may allow visualisation of valvular vegetations, abscesses, or pseudoaneurysms and new dehiscence in prosthetic valves (Fig. 3). All patients with a clinical suspicion of IE should undergo a transthoracic echocardiography (TTE) as soon as possible. If the TTE appears negative for a vegetation or abscess, or is non-diagnostic, transoesophageal echocardiography (TEE) should be considered in those with heart valve prosthesis or intra-cardiac devices. Repeat TTE and/or TEE is also indicated in those cases deemed to have a high clinical suspicion of IE with a negative initial TTE. There is recent evidence to show that TEE, in addition to TTE, helps in the location of bacterial vegetations and secondary lesions [11]. Echocardiography should also be performed during and after medical treatment, especially when complications are suspected.

Although the sensitivity for identifying vegetations is 50–70% in TTE and 92–96% in TEE, with a specificity of 90%, identification of vegetations may be difficult when pre-existing valvular lesions are present. Given this diagnostic challenge, the latest guidelines on IE encourage the use of additional imaging techniques as an adjunct to echocardiography, including multi-slice computed tomography (MSCT), magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT/CT), and positron emission tomography (PET/CT), to evaluate of patients with suspected IE. MSCT can be used to detect or exclude abscesses or pseudoaneurysms with an accuracy similar to that achieved by TEE. In cases of paravalvular extension of IE or inflammation involving the aorta, MSCT may provide superior imaging to TEE, providing information on the extent of disease in the latter.

Nuclear imaging provides a new possibility for patients with diagnostic difficulties, especially for those with suspected PVE (Fig. 4). It uses autologous radiolabelled leukocytes (SPECT/CT) or radiolabelled glucose (PET/CT) to detect tissues with increased uptake. As discussed later in this article, abnormal activity around a prosthetic valve forms one of the major Duke criteria when diagnosing IE. On the other hand, a negative nuclear scan in the context of an inconclusive echocardiogram may lead to a reduction in the rate of inappropriate antibiotic use due to IE misdiagnosis [12].

While 30% of patients with IE have clinical signs of embolisation, this value is even higher when accounting for asymptomatic lesions. Cerebral MRI scans performed during acute IE have consistently reported lesions in as many as 60–80% of patients [13]. Patients with cerebral lesions without any neurological symptoms score an additional single minor Duke criterion. In a previous study, this additional criterion upgraded 25% of patients to a definite diagnosis [14]. A CT head can be very useful to exclude or confirm a cerebral haemorrhage in addition to being able to diagnose embolic lesions (Fig. 5). A CT scan of the abdomen also has a role in diagnosing embolic lesions in the spleen or kidneys (Fig. 5).

MICROBIOLOGICAL DIAGNOSIS

Obtaining urgent blood cultures is crucial when establishing a diagnosis of IE. At least three separate blood cultures should be taken in 30-min intervals. It is not necessary to wait for pyrexia before taking a set of blood cultures. As bacteraemia in IE is relatively constant, all blood cultures are likely to be positive. A single positive blood culture result should therefore be interpreted with caution because it may represent a contaminant. While it is important to obtain blood samples before administration of antibiotics, this is often not achieved in practice because patients with IE are often pre-treated in primary healthcare or treated for other potential causes of infection, such as for a chest infection or urinary tract infection. To speed up bacterial identification, matrix-assisted laser desorption ionisation time-of-flight spectrometry has recently emerged as a new technique with the potential to reduce identification time by 1 day [15].

Blood culture-negative endocarditis (BCNE) is defined as a negative result using usual blood culture methods. It represents up to 40% of all cases of IE, more frequently in developing countries [16]. It is usually related to previous antimicrobial therapy or infection with fastidious bacteria or fungi. These microorganisms require special media and their growth is slow. When attempting to identify atypical causes of IE, serological or polymerase chain reaction testing should be performed. An experienced microbiologist with an interest in IE should guide targeted therapy. For patients treated surgically, culturing the explanted valve(s) may provide additional information about causality.

DIAGNOSTIC CRITERIA

To summarise, the diagnosis of IE is based on clinical, microbiological, and echocardiographic findings. Histological and microbiological examination of excised valves is a gold standard for diagnosing IE in those managed surgically. The modified Duke criteria have 80% sensitivity in epidemiological studies, and a lower diagnostic accuracy in clinical practice with a sensitivity of 63.2% [17]. The sensitivity is even lower in diagnosing BCNE [18]. As newer imaging techniques (MSCT, PET/CT, SPECT/CT) can improve the sensitivity for diagnosing IE, recent European Society of Cardiology (ESC) guidelines have proposed three new diagnostic criteria (Tables 1 and 2) [4]:

- paravalvular lesions in cardiac MSCT (major criterion);
- abnormal activity around prosthetic valve in PET/CT or SPECT/CT (major criterion);
- embolic events or infectious aneurysm identified by imaging only (minor criterion).

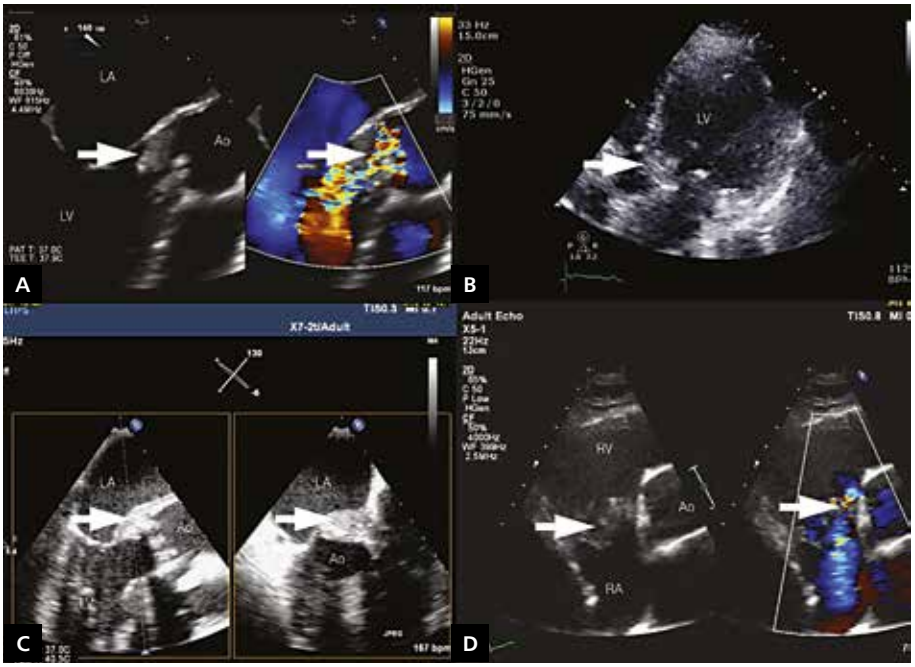

Figure 3. **A.** Transoesophageal echocardiography (TEE): large vegetation on aortic valve with leaflet destruction resulting in severe aortic regurgitation (arrows); **B.** Transthoracic echocardiography (TTE): arrows shows large vegetation on aortic valve; **C.** TEE: aortic root abscess (arrows) with vegetation on aortic valve; **D.** TTE; large vegetation on tricuspid valve with leaflet perforation and moderate-severe tricuspid regurgitation (arrows); Ao — aorta; LA — left artrium; LV — left ventricle; RA — right atrium; RV — right ventricle

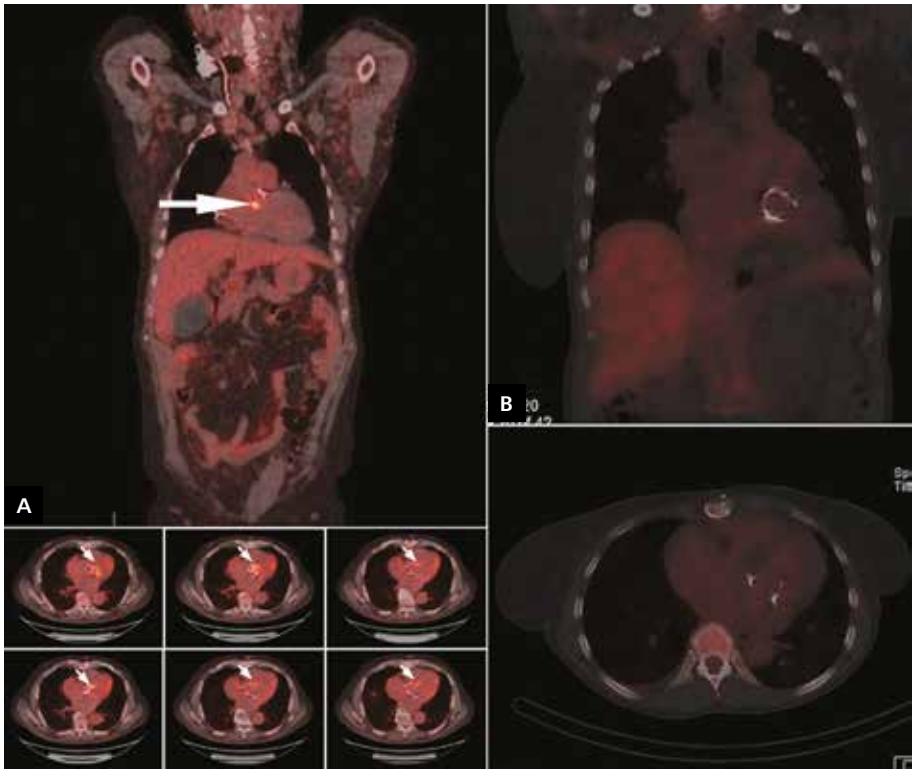

Figure 4. **A.** Positron emission tomography/computed tomography (CT) after injection of 332 MBq 18F-FDG; increased metabolic activity in the aortic valve replacement (arrows) consistent with active endocarditis with no apparent aortic root involvement. The low-dose non-contrast CT data was used for attenuation correction and anatomic localisation. Reconstructed images in the axial and coronal views were interpreted; **B.** 99mTc-HMPAO-labelled leukocyte single-photon emission computed tomography — negative for prosthetic valve endocarditis

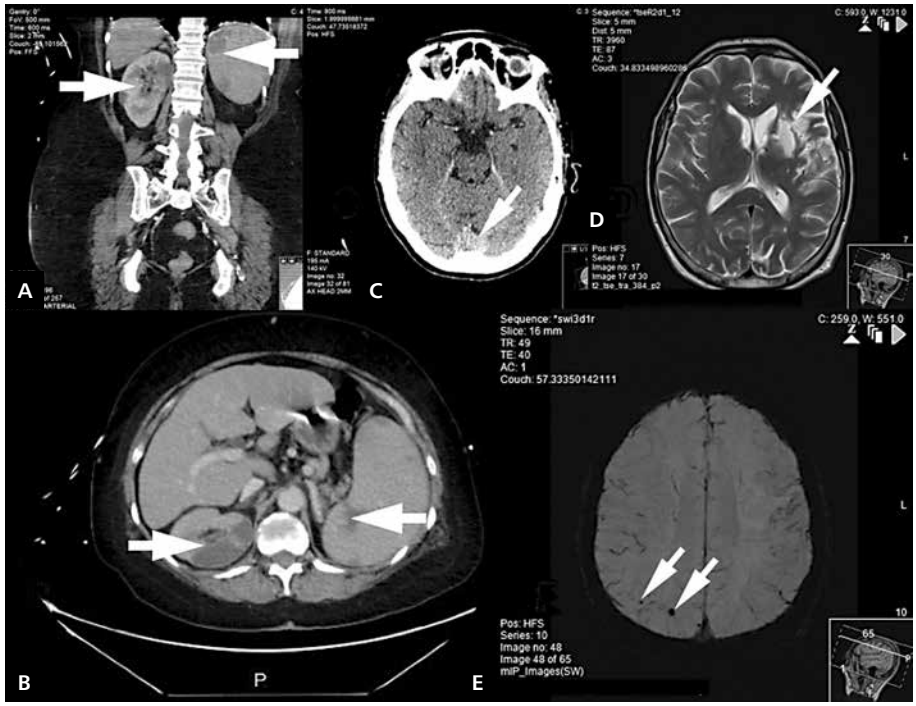

Figure 5. A, B. Computed tomography (CT) abdomen: spleen and kidney emboli secondary to infective endocarditis (arrows); C. CT head: occipital cerebral emboli with brain haemorrhage (arrows); D. Head magnetic resonance imaging (MRI): acute ischaemic lesion (arrows); E. Head MRI: multiple cortical and subcortical microbleeds (arrows)

Table 1. Definition of infective endocarditis (IE) according to the modified Duke criteria (adapted from Li et al. [19])

DEFINITE IE
Pathological criteria
— Microorganisms demonstrated by culture or on histological examination of a vegetation, a vegetation that has embolised, or an intracardiac abscess specimen; or
— Pathological lesions; vegetation or intracardiac abscess by histological examination showing active endocarditis
Clinical criteria
— Two major criteria; or
— One major criterion and three minor criteria; or
— Five minor criteria
POSSIBLE IE
— One major criterion and one minor criterion; or
— Three 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

MANAGEMENT

Rapid implementation of appropriate antibiotics is crucial in the management of IE. As alluded to above, it is important to take three blood cultures prior to antibiotic administration. Current guidelines offer details on antibiotic recommendations for the key bacteria responsible for most cases of IE. Most antibiotic regimens include combined antibiotic therapy to improve treatment effectiveness and decrease the probability of selection-resistant bacteria. Treatment should continue for 2–6 weeks with native valve endocarditis (NVE) and at least 6 weeks in cases of PVE. In both scenarios, the antibiotics used are similar, except for staphylococcal PVE, where the addition of rifampicin is recommended. The duration of treatment should be based on the first day of effective antibiotic therapy (negative blood culture). If surgery is performed, preoperative treatment duration is included in the total treatment time. Following surgery, foregoing antibiotics should be continued, unless valve cultures are positive and alternative antibiotics are recommended following sensitivity analysis. A new full course of antibiotics should be started in this situation. The first 2 weeks of antibiotic treatment should be administered in hospital, during which most complications occur, including perivalvular abscesses, septic emboli, stroke, and acute heart failure. The remainder of antibiotic treatment can be continued in the outpatient setting for selected clinically stable patients with regular post-discharge evaluation (Fig. 6).

Table 2. Definitions of the terms used in the European Society of Cardiology 2015 [4] modified criteria for the diagnosis of infective endocarditis (IE)

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:
   - ≥ two positive blood cultures of blood samples drawn > 12 h apart; or
   - All of three or a majority of ≥ four 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
   - 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 haemorrhage, conjunctival haemorrhages, and Janeway's lesions
4. Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor.
5. Microbiological evidence: positive blood culture but not meeting a major criterion as noted above or serological evidence of active infection with organism consistent with IE

CT — computed tomography; SPECT — single-photon emission computed tomography; PET — positron emission tomography

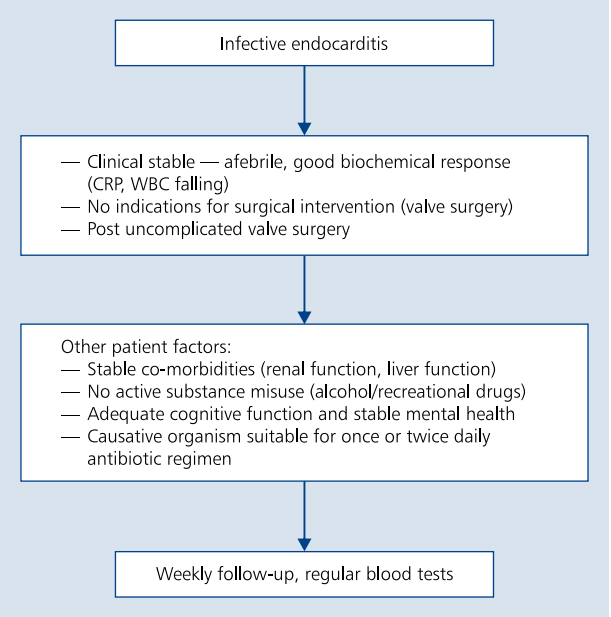

Figure 6. Selection process to determine patient suitability for outpatient parenteral antibiotic therapy for infective endocarditis

SURGERY

The two primary objectives of surgery are to remove infected tissue and to reconstruct cardiac morphology [20]. There are three main indications for surgery in IE: heart failure, uncontrolled infection, and emboli prevention. Although the theoretical indications for surgery are clear, their practical application depends on a range of factors, including the patient's clinical status, co-morbidities, and operative risk. A recent French study revealed that up to 73% of patients had at least one class I or IIa indication for surgery, according to ESC guidance, in left-sided NVE [21], but only 60% of patients underwent surgery. It is unsurprising that the cohort of patients who did not undergo surgery had a significantly worse outcome compared to those operated on. These findings emphasise the importance of surgery, when indicated. With regards to timing of surgery, a recent meta-analysis showed that early surgery (during initial hospitalisation or before 30 days of treatment) was associated with lower in-hospital and long-term mortality [22].

Coronary angiography is recommended in men over 40 years old, in postmenopausal women, and in patients with at least one cardiovascular risk factor or a history of coronary artery disease [23]. In the presence of mobile aortic valve vegetations with a high risk of embolisation, MSCT may be used to rule out significant coronary artery disease. It is important that extracardiac foci of infection are eradicated prior to surgery. Valve repair is favoured whenever possible, particularly when IE affects the mitral or tricuspid valve without significant destruction [24]. When valve replacement is indicated (technique of choice in aortic valve IE), mechanical and biological prostheses have similar operative mortality [25]. Postoperative mortality following acute or emergency surgery ranges from 10% to 20% [26]. The most frequent post-operative complications include severe coagulopathy,

bleeding, tamponade, acute renal failure, stroke, low cardiac output syndrome, pneumonia, and atrioventricular block [27].

FOLLOW-UP AND PROGNOSIS

Infective endocarditis recurrence is estimated in as many as 2–6% of patients following their initial infection [28–35]. There are two types of recurrences: relapses (the same microorganism as the initial) and reinfections (new microorganism). Early recurrence with the same microorganism can be considered as both. In such a situation, a cut-off of 6 months distinguishes relapse (before 6 months) and reinfection (after 6 months) [36]. Factors associated with an increased risk of relapse are: inadequate antibiotic treatment, resistant microorganisms, polymicrobial infection in intravenous drug abusers (IVDA), periannular extension, PVE, persistent foci of infection, resistance to conventional antibiotic regimens, positive valve cultures, persistence of fever at the seventh postoperative day, and chronic dialysis. Reinfection rates are higher in IVDA [35], PVE [37], dialysed patients [35], and patients with multiple risk factors for IE [4]. Patients with reinfection have a worse prognosis and are more likely to need valve replacement surgery [35].

All patients with IE should undergo a prognostic assessment on admission. The in-hospital mortality rate ranges from 15% to 30% [38, 39] and is determined by four main factors: patient characteristics, cardiac and non-cardiac complications, the infecting microorganism, and the echocardiographic findings. These factors are summarised in Table 3 [40, 41]. An additional independent risk factor is positive blood cultures after 48–72 h of antibiotic treatment [42]. Early identification of these factors and referring patients for early surgery can positively influence outcome [43]. These patients should be carefully assessed by the 'Endocarditis Team'.

Long-term survival after completion of treatment is estimated to be 80–90% at 1 year, 70–80% at 2 years, and 60–70% at 5 years [28–35]. Survival has been shown to be predicted by patient age, the presence of co-morbidities, and heart failure recurrence. These findings justify the importance of close monitoring of patients after discharge. Patients should be educated on the symptoms associated with IE recurrence and about oral and skin hygiene maintenance.

Table 3. Predictors of poor outcome in patients with infective endocarditis (IE) [40, 41]

Patient characteristics
Older age
Prosthetic valve IE
Diabetes mellitus
Comorbidity (e.g. frailty, immunosuppression, renal or pulmonary disease)
Clinical complications of IE
Heart failure
Renal failure
> Moderate area of ischaemic stroke
Brain haemorrhage
Septic shock
Microorganism
Staphylococcus aureus
Fungi
Non-HACEK Gram-negative bacilli
Echocardiographic findings
Periannular complications
Severe left-sided valve regurgitation
Low left ventricular ejection fraction
Pulmonary hypertension
Large vegetations
Severe prosthetic valve dysfunction
Premature mitral valve closure and other signs of elevated diastolic pressures

HACEK — Haemophilus parainfluenzae, H. aphrophilus, H. paraphrophilus, H. influenzae, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae, and K. denitrificans

PROPHYLAXIS OF IE

The role of antibiotic prophylaxis prior to invasive procedures was emphasised following a series of studies that described post-procedural transient bacteraemia with attachment of bacteria to the endocardium in patients with predisposing cardiac conditions. In recent years, controversially, the indications for antibiotic prophylaxis were relaxed. For example, the National Institute for Health and Care Excellence (NICE) guidelines published in the UK in 2008 recommend the cessation of antibiotic prophylaxis for all patients at risk of IE, who are undergoing a range of invasive procedures, including dental work [44]. Since the introduction of these guidelines, the incidence of IE has been rising; however, a causal relationship between the lack of antibiotic prophylaxis and new cases of IE is still debated [1]. Although there is criticism towards the restrictive use of antibiotic prophylaxis, there are some conceptions that support such a statement. The estimated risk of IE related to dental procedures is very low, so antibiotic prophylaxis may avoid only a small number of new cases of IE, while the risk of resistant bacteria due to inappropriate antibiotic use increases. Everyday oral routines, including brushing, carry more cumulative risk of bacteraemia than sporadic dental procedures. Most case-control studies did not report an association between dental procedures and increased risk of IE, and there are no prospective randomised controlled trials that have investigated this hypothesis.

Current European guidelines recommend antibiotic prophylaxis only for high-risk patients: patients with prosthetic valves (including transcatheter valves) or with prosthetic material used for cardiac valve repair, patients with a previous episode of IE, and patients with cyanotic congenital heart

disease or those with congenital heart disease who have post-operative palliative shunts, conduits, or other prostheses [4]. These patients are advised to take amoxicillin, ampicillin, or clindamycin (if there is an allergy to the aforementioned antibiotics) prior to dental procedures requiring manipulation of the gingival or periapical regions of the teeth or perforation of the oral mucosa. Scaling consists of the elimination of tartar by ultrasonic or manual instruments. The goal of root canal therapy is to completely clean the inflamed or infected tissue from the affected root, and then totally seal the emptied pulp canal to the tip of the root. Debris left in the end of the pulp canal can harbour bacteria that may cause an infection.

Patients undergoing other procedures, including respiratory, gastrointestinal, genitourinary, dermatological, or musculoskeletal procedures, do not require any antibiotic prophylaxis, even in high-risk patients. It should be emphasised that in these situations, antibiotic use is justified in the context of infection, such as drainage of an abscess. All patients at high risk of developing IE should be sensitised to oral and cutaneous hygiene.

CONCLUSIONS

Despite improvements in its management, IE remains a life-threatening condition with a high mortality. With the increasing use of intracardiac devices and prostheses, strategies for IE prevention are necessary. Reducing the time to diagnosis and commencing definitive management may help reduce the morbidity and mortality rate. As reflected in the 2015 ESC guidelines on IE, this requires the implementation of an IE multidisciplinary team and the full use of multimodality imaging alongside echocardiography [4]. With much of the evidence derived from observational studies, a move towards research networks focusing on multicentre trials is necessary, for example, addressing uncertainties in the role of antibiotic prophylaxis in IE and the timing of surgery.

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