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REVIEW

Changes and advances in the field of infective endocarditis

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Abstract

Infective endocarditis is a rare but deadly disease, with a highly variable presentation. The clinical manifestations of the condition are often multisystemic, ranging from dermatological to ophthalmic, and cardiovascular to renal. Thus, patients with infective endocarditis may first present to the acute or general physician, who may have a variable knowledge of the condition. The diagnosis of infective endocarditis can be challenging, relying on clinical, imaging and microbiological features. Recent decades have seen a transformation in the epidemiology and microbiology of infective endocarditis and yet, despite advances in diagnostics and therapeutics, mortality rates remain high. This review outlines the emerging studies and guidelines on the assessment and management of infective endocarditis, focusing on the evolving epidemiology of the condition, the role of new imaging modalities, updated diagnostic criteria, the latest on antimicrobial and surgical management, and the role of a multidisciplinary approach in the management of patients with infective endocarditis.

Key words: Echocardiography; Embolism; Heart failure; Infection; Infective endocarditis

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Introduction

Infective endocarditis is inflammation of the endocardial surface of the heart caused by infection. The most commonly affected regions of the heart are the heart valves, followed by intra-cardiac devices and congenital heart defects (Habib et al, 2015). The typical lesion pathognomonic of infective endocarditis, a vegetation, develops as a result of the body's inflammatory response to a microorganism, leading to clumping of platelets, fibrin and inflammatory cells (Cahill and Prendergast, 2016). Other possible lesions include a perivalvular abscess (a cavity with necrosis and purulent material not connecting with the cardiovascular lumen) and a perivalvular pseudoaneurysm (a cavity connecting with the cardiovascular lumen) (Habib et al, 2015).

Rapid diagnosis and early initiation of treatment are paramount in order to prevent the most serious sequelae including heart failure, systemic embolism and death. Despite advances in the diagnosis and management of infective endocarditis over recent decades, the challenges associated with the condition remain significant, and complication and mortality rates are substantial. This is, in part, because of evolving epidemiological risk factors reflecting a sea change in the patient population at risk, as well as the ongoing challenges in the diagnosis and prompt treatment.

Until the late 2000s, guidelines on the management of infective endocarditis were predominantly based on consensus opinion owing to a lack of robust data (Horstkotte et al, 2004; Naber et al, 2007; Wilson et al, 2007). The last decade has seen a relative surge in the accumulation of knowledge on infective endocarditis, with greater evidence on epidemiology, imaging, antibiotic therapy, optimal timing of surgery and antibiotic prophylaxis. Nonetheless, many gaps in the knowledge persist. This review provides an overview of the assessment and management of patients with infective endocarditis for the general and acute physician, highlighting recent research, advances and guidance.

Changes in epidemiology and aetiology

Infective endocarditis is a rare condition, with an estimated incidence between 2.6 and 7 cases per 100 000 people per year, compared with pneumonia with 160 cases per 100 000

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people per year (Almirall et al, 2000; Slipczuk et al, 2013). In spite of the advances in the management of infective endocarditis over recent decades, the incidence of the condition has not significantly altered. Likewise, mortality rates remain high, with 15–30% of patients dying during their index admission (Leone et al, 2012; Olmos et al, 2013). The epidemiology of infective endocarditis has shifted over recent years, from a group of younger patients with rheumatic disease to older, often comorbid patients (Slipczuk et al, 2013), patients with a history of intravenous drug use (Goodman-Meza et al, 2019), and those with a history of a previous valve replacement or an intra-cardiac device, such as a permanent pacemaker (Athan et al, 2012). Among patients with valve replacements, those with bioprosthetic valves are at higher risk of infective endocarditis than those with mechanical valves (Anantha-Narayanan et al, 2020). The authors hypothesise that this may reflect differences between patient populations, rather than inherent differences in the valves themselves, as the vast majority of patients who receive bioprosthetic valves are older adults who have comorbid conditions, making them more vulnerable to infective endocarditis.

A shift in the microbiological organisms causing infective endocarditis has also been documented over the last half century. In North America, the percentage of *Staphylococcus aureus* infective endocarditis has increased from 25% of total cases in the 1960s to 52% in the 2000s (Slipczuk et al, 2013), with a similar increase observed in Europe (Duval et al, 2012). These findings are important as *S. aureus* infections are associated with an increased length of hospital stay and risk of mortality (Noskin et al, 2005; Khan et al, 2021). Conversely, the proportion of *Streptococcus viridans* and culture-negative infective endocarditis has reduced over a similar time period (Slipczuk et al, 2013). A recent study from the USA between 2002 and 2017 confirmed these observations, with Staphylococcus-related infective endocarditis being the most common (50.6%), followed by Streptococcus (25.1%), Enterococcus (9.7%) and Gram-negative related infective endocarditis (6.1%) (Khan et al, 2021).

A novel cause of infective endocarditis was identified in 2017 when Public Health England issued guidance on infection caused by *Mycobacterium chimaera*. This infection, generally occurring following cardiac surgery, is likely a consequence of contaminated heater cooler units that are used during cardiopulmonary bypass (Dalvi and Das, 2018). *M. chimaera* can cause severe infection, particularly prosthetic valve endocarditis, and should be considered in all unwell patients with a recent history of cardiac surgery.

Diagnosis

Microbiology

A microbiological diagnosis via a positive blood culture is key to the treatment of infective endocarditis, enabling identification and susceptibility testing of the causative bacterium. The importance of this cannot be overstated. At least three sets of blood cultures (aerobic and anaerobic) should be taken from a peripheral vein at 30-minute intervals before antibiotic administration. A single positive blood culture is often not useful in the diagnosis, whereas multiple positive blood cultures for the same organism form a major Duke criterion. A standard blood culture incubation period of 5 days is adequate for most causes of infective endocarditis. Although less common, blood culture-negative infective endocarditis can occur, most commonly because of recent or concomitant antimicrobial therapy, but can also occur in the presence of an organism that does not grow in routine blood cultures, such as Mycoplasma spp., *Coxiella burnetii*, Brucella spp. or fungi. In such cases, prolonged cultures (for example when fungal or mycobacterial infections are suspected) and directed serological testing (for example Bartonella serology and Q fever serology) can prove useful, while histopathological and molecular diagnostics (16S rRNA gene sequencing) may be used to examine resected valves (Liesman et al, 2017).

Imaging

Imaging plays a central role in the diagnosis and management of infective endocarditis. While echocardiography remains the cornerstone, newer techniques such as computed tomography, magnetic resonance imaging and nuclear imaging are now increasingly important in the diagnosis of infective endocarditis and its complications. Figure 1 presents examples of these different imaging modalities.

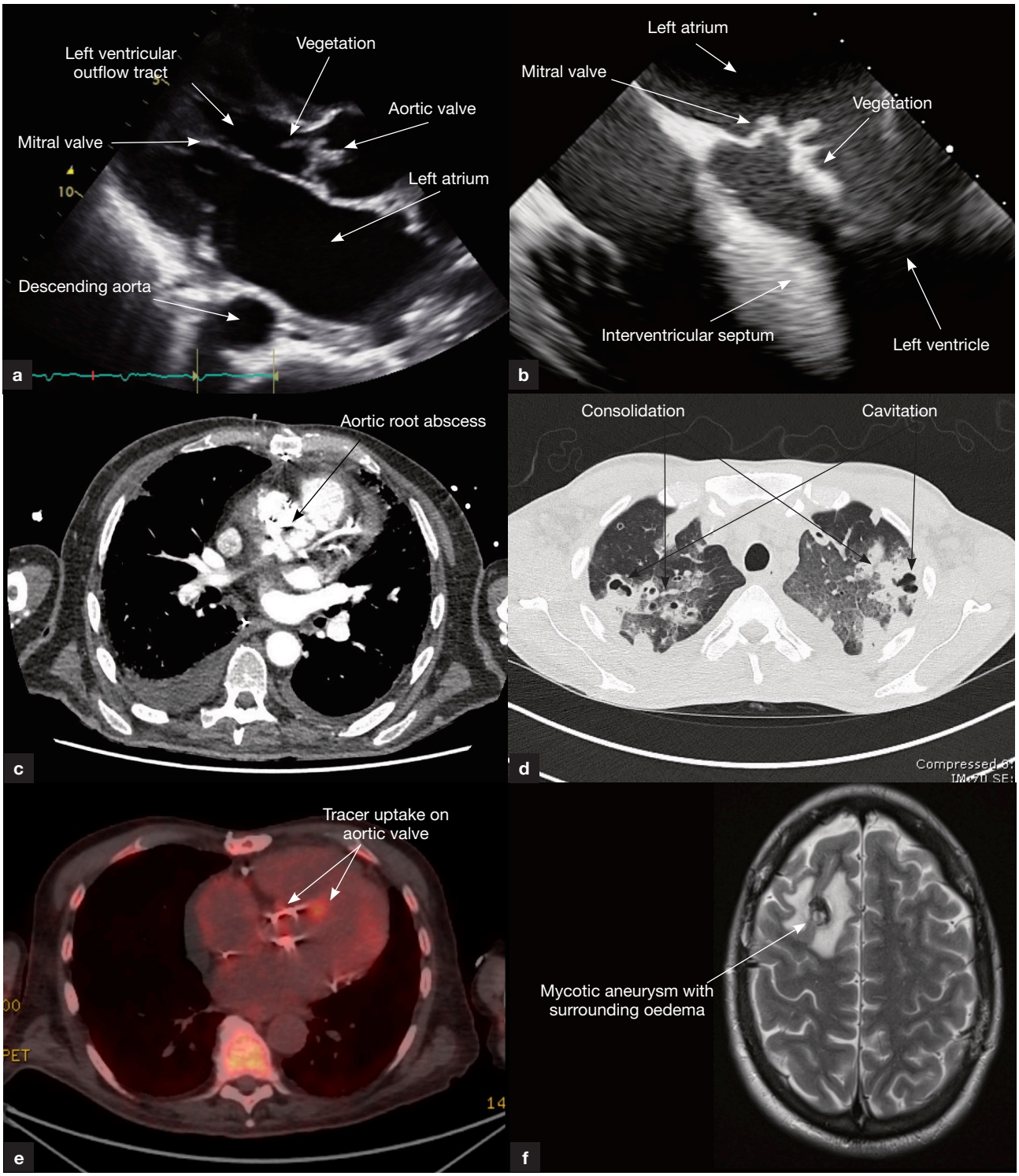

Figure 1. Imaging modalities used in the assessment of infective endocarditis. a. Transthoracic echocardiogram (parasternal short axis) demonstrating an aortic valve vegetation, seen within the left ventricular outflow tract, from the right coronary cusp. b. Transoesophageal echocardiogram (mid-oesophageal four-chamber) demonstrating a vegetation on the anterior leaflet (A2 scallop) of the mitral valve with additional valvular perforation. c. Computed tomography scan, with contrast, of the aorta demonstrating an aortic root abscess (large contrast-filled cavity in the left ventricular outflow tract) seen in the axial plane. d. Computed tomography scan, without contrast, of the thorax demonstrating extensive bilateral pulmonary consolidation and cavitation in a patient with endocarditis, seen in the axial plane. e. Positron emission tomography-computed tomography scan demonstrating moderate tracer uptake within a prosthetic aortic valve replacement, suggestive of prosthetic valve endocarditis, seen in the axial plane. f. T2-weighted magnetic resonance imaging of the brain demonstrating a right frontal mycotic aneurysm with surrounding oedema in a patient with endocarditis.

Echocardiography

Transthoracic echocardiography is the first-line imaging modality in the assessment of infective endocarditis. The Greaves criteria can be used to guide the appropriate use of transthoracic echocardiography in infective endocarditis (Greaves et al, 2003). In a study of 500 patients, the absence of all five of the following criteria – vasculitic or embolic phenomena, the presence of a central venous access, a recent history of injected drug use, the presence of a prosthetic heart valve and a positive blood culture – was associated with the absence of evidence of infective endocarditis on transthoracic echocardiography in all cases. In infective endocarditis, the sensitivity of transthoracic echocardiography is 70% for native and 50% for prosthetic valves, vs 96% and 92% respectively for transoesophageal echocardiography (Mügge et al, 1989; Habib et al, 2010; Bonzi et al, 2018). Transoesophageal echocardiography should be performed if transthoracic echocardiography is negative for infective endocarditis but clinical suspicion remains high, or in cases confirmed on transthoracic imaging but where the anatomy or complications cannot be fully assessed, as a normal transthoracic echocardiography does not necessarily exclude infective endocarditis (Habib et al, 2015). It must be noted that small vegetations do not always represent infective endocarditis and can simply be the result of valve degradation, highlighting the need for expert review of all imaging. Another differential diagnosis to consider for vegetations is non-bacterial thrombotic endocarditis (also referred to as marantic endocarditis), characterised by sterile vegetations which are not associated with bacteraemia or valve destruction, and associated with conditions such as cancer, systemic lupus erythematosus and autoimmune disorders (Habib et al, 2015).

Computed tomography

Multi-slice computed tomography can be useful for detecting abscesses and pseudoaneurysms caused by infective endocarditis, with a similar diagnostic accuracy to transoesophageal echocardiography (Feuchtner et al, 2009; Fagman et al, 2012). In aortic valve infective endocarditis, computed tomographic angiography of the aorta can help define aortic anatomy in order to guide surgical intervention, while computed tomographic coronary angiography can be used as an alternative to invasive coronary angiography, reducing the theoretical risk of vegetation embolisation (Hekimian et al, 2010). Computed tomography is also helpful for detecting the presence of pulmonary, renal and cerebral emboli, infarcts or haemorrhages.

Magnetic resonance imaging

Magnetic resonance imaging is primarily used for the detection of any cerebral consequences of infective endocarditis, with a higher sensitivity than computed tomography. In studies examining the systematic use of cerebral magnetic resonance imaging in infective endocarditis, the prevalence of cerebral complications is as high as 60–80%, with most being small ischaemic lesions (Snygg-Martin et al, 2008; Cooper et al, 2009).

Nuclear imaging

Nuclear imaging, including whole body 18F-fluorodeoxyglucose positron emission tomography or 18F-fluorodeoxyglucose computed tomography single-photon emission computed tomography, is increasingly used in the assessment of suspected or challenging cases of infective endocarditis (Erba et al, 2012). A meta-analysis found that the sensitivity of 18F-fluorodeoxyglucose positron-emission tomography-computed tomography was 76%, with a specificity of 78.5% (Mahmood et al, 2019). Notably, the sensitivity was higher (80.5%) in patients suspected of having prosthetic valve endocarditis. This is of particular interest as it is difficult to differentiate chronic postoperative changes from acute active pathology on both transthoracic and transoesophageal imaging. An additional benefit of 18F-fluorodeoxyglucose positron emission tomography-computed tomography is that it enables the assessment of extracardiac sequalae such as root abscess, mycotic aneurysm or splenic infarcts, as well as incidental but potential alternate diagnoses (for example aortitis or pneumonia). In one study, the use of 18F-fluorodeoxyglucose positron emission tomography-computed tomography resulted in a change in management in 35%

of patients, including the prevention of eight unnecessary device extractions, prolongation of antimicrobial therapy and referral for surgical intervention (Orvin et al, 2015).

Diagnostic criteria

Adapted from the original Durack et al (1994) and modified Li at al (2000) Duke criteria, the 2015 European Society of Cardiology infective endocarditis guidelines further updates these diagnostic criteria (Table 1) (Habib et al, 2015). In brief, a definite diagnosis of infective endocarditis requires the presence of either two major criteria, one major criterion and three minor criteria, or five minor criteria. Possible infective endocarditis is defined as one major criterion and one minor criterion, or three minor criteria. A notable change in these updated guidelines is the inclusion of newer imaging techniques within the diagnostic criteria, with abnormal activity around the site of a prosthetic valve on nuclear imaging and

Table 1. Major and minor criteria for the diagnosis of infective endocarditis

Major criteria	Blood cultures positive for infective endocarditis	Typical microorganisms consistent with infective endocarditis from two separate blood cultures:	1. *Viridans streptococci*, *Streptococcus gallolyticus* (*Streptococcus bovis*), HACEK group, *Staphylococcus aureus*; or 2. Community-acquired enterococci, in the absence of a primary focus
		Microorganisms consistent with infective endocarditis from persistently positive blood cultures:	1. ≥2 positive blood cultures of blood samples drawn >12 hours apart 2. All of three or a majority of ≥4 separate cultures of blood (with first and last samples drawn ≥1 hour apart)
		Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titre >1:800	
	Imaging positive for infective endocarditis	Echocardiogram positive for infective endocarditis	1. Vegetation 2. Abscess, pseudoaneurysm or intracardiac fistula 3. Valvular perforation or aneurysm 4. New partial dehiscence of prosthetic valve
		Abnormal activity around the site of a prosthetic valve implantation detected by 18F-fluorodeoxyglucose positron-emission tomography-computed tomography (only if the prosthesis was implanted for >3 months) or radiolabeled leukocytes single-photon emission computed tomography or computed tomography	
		Definite paravalvular lesions by cardiac computed tomography	
Minor criteria	Predisposition such as predisposing heart condition or injection drug use		
	Fever defined as a temperature >38°C		
	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		
	Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots and rheumatoid factor		
	Microbiological evidence: a positive blood culture but it does not meet a major criterion as noted above, or serological evidence of an active infection with an organism consistent with infective endocarditis		

Reproduced from the European Society of Cardiology guidelines (Habib et al, 2015).

paravalvular lesions on cardiac computed tomography now qualifying as major criteria, and embolic events identified on imaging (for example cerebral magnetic resonance imaging or whole-body computed tomography) now classed as a minor criterion.

Management

The 'endocarditis team'

In the last decade, growing emphasis has been placed on the role of the 'endocarditis team' (Chambers et al, 2014). Infective endocarditis is a condition that inherently benefits from a collaborative management approach, because of its variable presenting features and multisystem involvement. Input from a number of specialties is often required, including cardiologists, cardiothoracic surgeons, radiologists, microbiologists, infectious disease specialists, neurologists, and, when appropriate, congenital heart disease specialists. With approximately half of the patients with infective endocarditis undergoing surgical intervention during their hospital admission, the early involvement of cardiac surgeons is paramount (Tornos et al, 2005).

Studies assessing the impact of multidisciplinary teams that regularly meet during treatment and organise close follow-up appointments after the completion of treatment have shown a dramatic reduction in mortality rates (Botelho-Nevers et al, 2009; Chirillo et al, 2013). As a consequence, the latest European guidelines stress the importance of the endocarditis team, usually conducted by a multidisciplinary team (Habib et al, 2015) and based in large reference (tertiary) centres with access to advanced imaging and surgical facilities, although smaller hospitals should remain in regular consultation with these centres. Patients with complicated infective endocarditis (for example patients with associated heart failure, an abscess, embolic or neurological complications) should be referred early to the reference centre. Patients who survive to hospital discharge should be followed up regularly, ideally at 1, 3, 6 and 12 months. This should include an assessment for symptoms and signs of heart failure, regular echocardiographic assessment, monitoring of white cell count, C-reactive protein level and blood cultures, and adequate dental surveillance where appropriate (Habib et al, 2015).

Antimicrobial therapy

To eradicate infection, antimicrobial therapy with bactericidal agents is required for at least 4 weeks, but frequently longer (Hubers et al, 2020). Initially, empirical treatment based on patient-specific and epidemiological factors can be initiated after taking three sets of blood cultures while waiting for microbiological confirmation and sensitivities, particularly in severely ill patients. The European Society of Cardiology provides advice on empirical treatment regimens (Table 2)(Habib et al, 2015). In clinical practice, local

Table 2. Recommended empirical treatment regimens for the treatment of infective endocarditis

Aetiology	Antibiotic regimen
Native valve infective endocarditis or Late prosthetic valve infective endocarditis (>12 months following surgery)	Ampicillin 12 g/day intravenously in 4–6 doses with Flucloxacillin 12 g/day intravenously in 4–6 doses with Gentamicin 3 mg/kg/day intravenously or intramuscular in 1 dose
Early prosthetic valve infective endocarditis (<12 months following surgery) or Healthcare-associated infective endocarditis	Vancomycin 30 mg/kg/day intravenously in 2 doses with Gentamicin 3 mg/kg/day intravenously or intramuscular in 1 dose with Rifampicin 900–1200 mg intravenously or orally in 2–3 doses

Based on European Society of Cardiology guidelines (Habib et al, 2015).

microbiological guidelines and advice should be followed. Empirical treatment for native valve endocarditis should cover staphylococci, streptococci and enterococci, whereas early treatment for prosthetic valve endocarditis should cover methicillin-resistant staphylococci, enterococci and non-HACEK Gram-negative pathogens (Habib et al, 2015). The choice of ongoing antibiotic therapy depends on the isolated bacteria and its sensitivities, the severity of illness, allergy status, weight and renal function. Commonly, streptococcal infective endocarditis is treated with amoxicillin 2 g intravenously 6 times a day and staphylococcal infective endocarditis (methicillin-sensitive *S. aureus*) is treated with flucloxacillin 2g intravenously 4–6 times a day, with vancomycin and gentamicin used as substitutes in those with a penicillin allergy (Habib et al, 2015). Standard antibiotic treatment is for at least 4 weeks, although complicated infective endocarditis often requires 6 weeks of antibiotic therapy, alongside other treatments such as surgical intervention. Of note, a Cochrane review examining the comparative effectiveness of different antibiotic regimens in infective endocarditis was not able to support or reject any specific antibiotic regimen, owing to the limited and low-quality evidence (Martí-Carvajal et al, 2020).

The development of outpatient parenteral antibiotic therapy services has facilitated the administration of intravenous antibiotics and monitoring of infective endocarditis in the outpatient setting, once the patient is medically stable (Cervera et al, 2011; Duncan et al, 2013). In patients with mitral or aortic infective endocarditis, caused by either streptococcus, *Enterococcus faecalis*, *S. aureus* or coagulase-negative staphylococci, who are stable after treatment with intravenous antibiotics for at least 10 days, randomised controlled trial evidence now supports switching from intravenous to oral antibiotic therapy, with outpatient follow up two to three times per week (Iversen et al, 2019). Indeed, follow up at 6 months showed no difference in mortality rates, unplanned cardiac surgery, embolic events or recurrent bacteraemia. At present, extrapolation of these results to the wider cohort of patients with infective endocarditis (for example patients with organisms other than those stated above, patients with valvular abscesses and patients who have not stabilised on intravenous therapy) is not possible.

Surgery

Approximately half of the patients with infective endocarditis require inpatient cardiac surgery (Chambers et al, 2014). The three main indications for surgical intervention in infective endocarditis are heart failure, failure to control infection and the prevention of embolism. In patients with severe acute regurgitation, valvular obstruction or fistula causing refractory cardiogenic shock or pulmonary oedema, surgery should be performed on an emergency basis (within 24 hours) (Habib et al, 2015). In other circumstances, guidelines suggest that surgery may be performed urgently (within less than 7 days) or electively within 1–2 weeks, depending on the individual circumstances. In a meta-analysis, early surgical intervention (within 7 days or less) was associated with a lower mortality rate when compared with delayed surgery or medical therapy (Anantha-Narayanan et al, 2016). While the most common surgical approach is via a sternotomy, newer minimally-invasive techniques are gaining traction (Shih et al, 2021). The prognostic markers of mortality after surgery include increasing age, female sex, prosthetic valve endocarditis, presence of cardiogenic shock, previous cardiac surgery, renal failure and *S. aureus* infection (Varela Barca et al, 2019). Perioperative mortality is no higher in infective endocarditis associated with intravenous drug use than in patients with infective endocarditis which is not associated with drug use, although studies suffer from selection bias as they only included patients accepted for surgical intervention (Hall et al, 2019).

Antibiotic prophylaxis

In the past, patients at risk of infective endocarditis were prescribed antibiotic prophylaxis before dental and certain non-dental interventional procedures (upper and lower respiratory tract procedures, upper and lower gastrointestinal procedures and genitourinary procedures). In 2008, after reviewing the evidence, the National Institute for Health and Care Excellence published guidance advising against antibiotic prophylaxis before these procedures, citing a lack of effectiveness. A subsequent analysis published in 2015 observed that, while the

prescription of antibiotic prophylaxis had reduced following publication of the NICE guidelines, the incidence of infective endocarditis had increased (Dayer et al, 2015). Although a causal association could not be established, the National Institute for Health and Care Excellence reviewed the evidence and updated its guidance in 2016, stating that 'antibiotic prophylaxis against infective endocarditis is not routinely recommended' (National Institute for Health and Care Excellence, 2016), meaning that prophylaxis should be considered in certain groups, specifically those at high risk of infective endocarditis. The European Society of Cardiology and the Scottish Dental Clinical Effectiveness Programme have developed helpful guides for clinicians, summarising these key issues (Figure 2) (Habib et al, 2015; Scottish Dental Clinical Effectiveness Programme, 2018). Briefly, patients at high risk of infective endocarditis include those with previous infective endocarditis, those with previous valvular repair or replacement involving prosthetic material and those with structural congenital heart disease. Dental procedures requiring antibiotic prophylaxis include procedures involving manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa (a full list can be found in the Scottish Dental Clinical Effectiveness Programme guidance). In high-risk patients undergoing these procedures, antibiotic prophylaxis is still recommended. Suggested antibiotic regimens include amoxicillin 3 g orally 1 hour before the procedure, or clindamycin 600 mg orally in those allergic to penicillin (Scottish Dental Clinical Effectiveness Programme, 2018). In patients not meeting these criteria, routine antibiotic prophylaxis is not recommended.

Conclusions

This review demonstrates the ongoing challenges associated with infective endocarditis, both in terms of the prompt and precise diagnosis, and early involvement of specialists, particularly cardiac surgeons for refractory and critical cases. As cardiac care becomes more complex, with increasing reliance on novel and percutaneous techniques, the landscape of infective endocarditis has evolved, with increasing numbers of older and frail patients presenting with the condition. While rare, physicians should maintain a high index of suspicion for infective endocarditis, particularly in patients with a recent cardiac procedure, while ensuring that appropriate blood cultures are taken before antibiotics are given, not after. In clinical practice, infective endocarditis is often complex, and may not neatly fit within the evidence base and guidance summarised in this article. As such, management

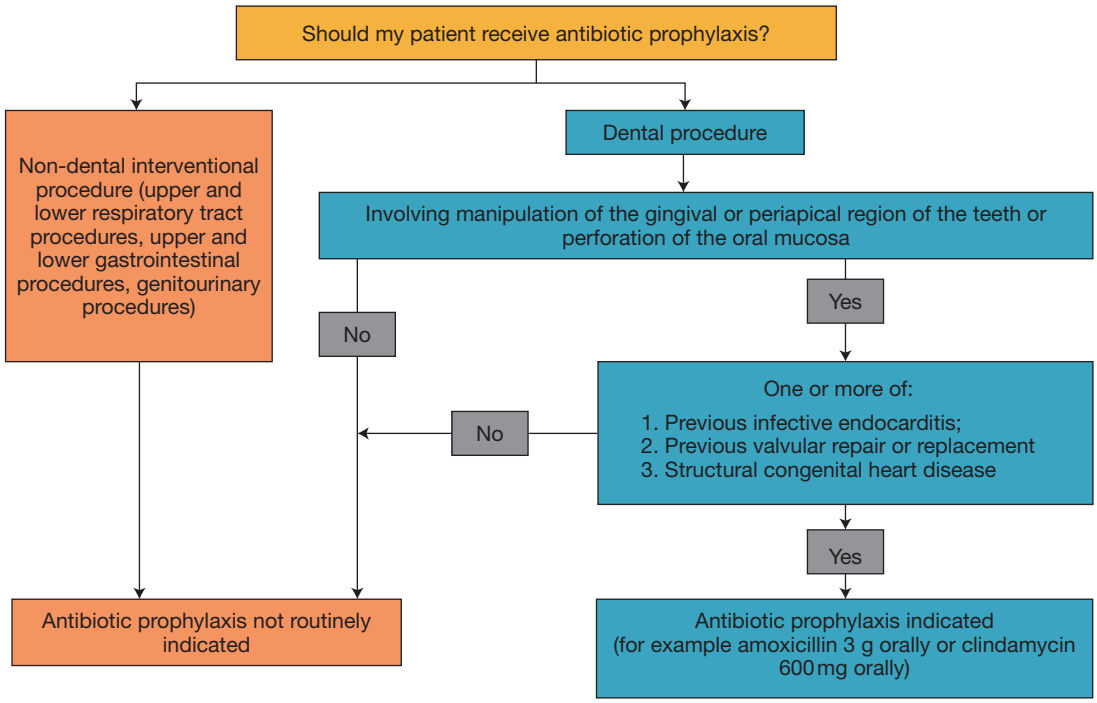

Figure 2. Antibiotic prophylaxis of infective endocarditis.

Key points

- The mortality rate of infective endocarditis remains high and has not changed significantly over recent decades.
- The proportion of *Staphylococcus aureus* infective endocarditis, the most aggressive form of endocarditis, is increasing.
- The sensitivity of transthoracic echocardiography for detecting vegetations on a native heart valve is approximately 70% vs >96% for transoesophageal echocardiography.
- Newer imaging techniques, such as computed tomography and nuclear imaging, are assuming greater roles in the assessment of infective endocarditis.
- Management should be coordinated by an endocarditis team, comprising cardiologists, surgeons and infectious disease or microbiology specialists.
- Antibiotic prophylaxis before dental procedures is no longer routinely recommended, although it is still advised in patients at high risk of infective endocarditis.

decisions are often the result of the consensus opinion of an expert multidisciplinary team. Further studies into the diagnosis and management of infective endocarditis would benefit from the establishment of a local endocarditis team, and from a mandatory national database for infective endocarditis.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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