Infective endocarditis

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Infective endocarditis occurs worldwide, and is defined by infection of a native or prosthetic heart valve, the endocardial surface, or an indwelling cardiac device. The causes and epidemiology of the disease have evolved in recent decades with a doubling of the average patient age and an increased prevalence in patients with indwelling cardiac devices. The microbiology of the disease has also changed, and staphylococci, most often associated with health-care contact and invasive procedures, have overtaken streptococci as the most common cause of the disease. Although novel diagnostic and therapeutic strategies have emerged, 1 year mortality has not improved and remains at 30%, which is worse than for many cancers. Logistical barriers and an absence of randomised trials hinder clinical management, and longstanding controversies such as use of antibiotic prophylaxis remain unresolved. In this Seminar, we discuss clinical practice, controversies, and strategies needed to target this potentially devastating disease.

Published Online
September 2, 2015
http://dx.doi.org/10.1016/S0140-6736(15)00067-7

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Introduction

The challenges associated with infective endocarditis are greater than ever. The patients affected are older and sicker than in the past, often with many comorbidities.[1] Virulent staphylococci have eclipsed penicillin-sensitive streptococci as the most common cause in many high-income countries.[2] The population at risk is growing and health-care-associated staphylococcal bacteraemia, a precursor to infective endocarditis, is a challenge worldwide.[3] Resistance to many antibiotics is rising and has become one of the greatest threats to modern health care.[4]

At the bedside, the variability of disease presentation and course presents difficulties for clinicians.[5] The evidence base for clinical practice, although clearly presented by international guidelines, is derived predominantly from observational cohort studies rather than randomised trials.[6,7] Moreover, logistical challenges abound. Patients with infective endocarditis need prompt diagnosis and a rapid response from several specialists including cardiologists, cardiothoracic surgeons, infectious disease specialists, and radiologists. The delivery of high-level coordinated care remains difficult, even in health-care systems of high-income countries, and is frequently impossible in low-income countries. In this context, we provide an update and overview of best clinical practice in infective endocarditis, highlighting controversies and new research findings.

Epidemiology

Infective endocarditis is rare, with a yearly incidence of about 3–10 per 100 000 people.[1,2,8,9] The pattern of disease varies worldwide, with epidemiology in low-income countries similar to that of high-income countries during the early antibiotic era.[10] Rheumatic heart disease remains the key risk factor for infective endocarditis in low-income countries and underlies up to two-thirds of cases.[11,12] Patients are usually young adults and infection is caused predominantly by community-acquired, penicillin-sensitive streptococci entering via the oral cavity. The prevalence of rheumatic heart disease has fallen in high-income countries because of improved living standards and availability of antibiotics for streptococcal pharyngitis.[13] However, degenerative valve disease, diabetes, cancer, intravenous drug use, and congenital heart disease have replaced rheumatic heart disease as the major risk factors for infective endocarditis. Moreover, patients with infective endocarditis are older, with the average age, which was in the mid-40s during the early 1980s, shifting to older than 70 years in 2001–06 (figure 1).[14]

This changing epidemiology of infective endocarditis in high-income countries reflects wide medical advances.[15] Health-care-acquired infective endocarditis (nosocomial or hospital-acquired, and non-nosocomial or outpatient-acquired) accounts for 25–30% of contemporary cohorts.[1,2] Increasing use of long-term intravenous lines and invasive procedures has led to an upsurge in rates of staphylococcal bacteraemia, a precursor to infective endocarditis.[16–18] Prosthetic valves and indwelling cardiac devices (eg, permanent pacemakers) are widely used and can act as a nidus for infection within the heart (figure 1). As indications for complex devices such as cardiac resynchronisation therapy and implantable cardioverter defibrillators expand, rates of cardiac device infection are rising.[19,20]

Infective endocarditis is rare in children, although improved survival in congenital heart disease (the most important risk factor) has resulted in increasing incidence in recent decades.[21] The highest risk arises in children with cyanotic congenital heart disease, endocardial cushion defects, or high velocity jets (eg, in ventricular

Search strategy and selection criteria

We searched MEDLINE, Embase, and the Cochrane Library using the search terms "endocarditis" or "infective endocarditis" together with "epidemiology", "pathogenesis", "manifestations", "imaging", "treatment", "surgery", or "device". We selected publications mostly from the past 10 years, but did not exclude widely referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected articles that we judged relevant. Recommended review articles are cited to provide readers with more details and background references.

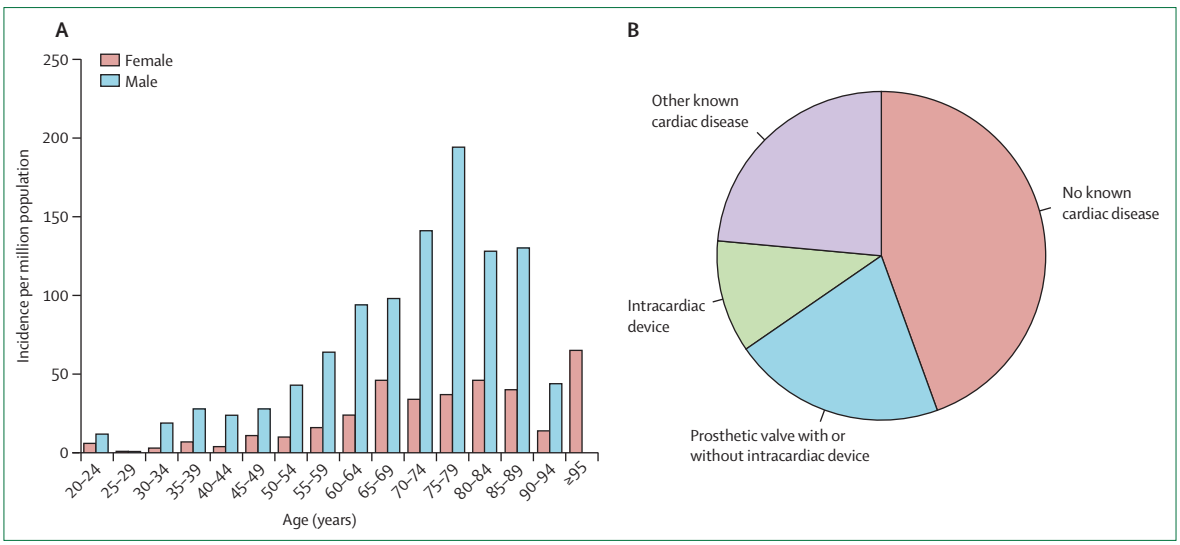

Figure 1: **Epidemiology**
Incidence of infective endocarditis according to (A) age and sex, and (B) previous cardiac history, in a French population study of 497 adults. The incidence peaks at 194 cases per million in men aged 75–79 years. Adapted from Selton-Suty and colleagues.[2]

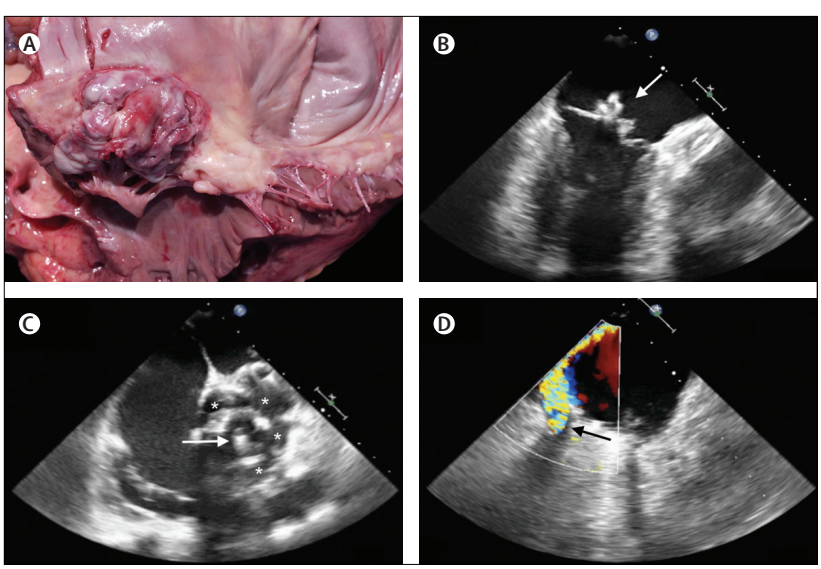

Figure 2: **Diagnosis of infective endocarditis**
(A) Vegetation in staphylococcal endocarditis. A vegetation is a dense aggregate of microorganisms, platelet-rich thrombus, and inflammatory leucocytes, and is the cardinal feature of infective endocarditis. (B) Transoesophageal echocardiogram (TOE) with a mitral valve vegetation (arrow). (C) TOE with the aortic valve en face (arrow) surrounded by many abscesses (*). (D) Jet of mitral regurgitation (arrow) arising at the site of new prosthetic mitral valve dehiscence. Vegetation, abscess, and prosthetic valve dehiscence are the major echocardiographic criteria for diagnosis of infective endocarditis with the modified Duke score.

septal defect).[22] The risk of infective endocarditis is reduced after repair with no residual shunt or prosthetic material, but the cumulative risk can be high in patients with repaired complex congenital heart disease, abnormal valves, residual shunts, or prostheses—up to 21% over 30 years in valvular aortic stenosis.[23] In the absence of congenital heart disease, paediatric infective endocarditis is often a complication of indwelling vascular catheters, for example in premature infants.[24]

In view of the changing nature of infective endocarditis, historical classification by rate of clinical onset (ie, acute, subacute, chronic) is now outdated. Instead, description of the valve involved, whether native or prosthetic, and the source of infection (community or health-care-acquired) has implications for clinical work-up and empirical antibiotic choice.[25] As results become available, the description can be further refined to include the causative organism and the presence or absence of complications.

Pathophysiology

The healthy cardiac endothelium is resistant to frequent bacteraemia caused by daily activities such as chewing and tooth brushing.[26] After endothelial injury, however, release of inflammatory cytokines and tissue factors with associated fibronectin expression leads to formation of a platelet-fibrin thrombus that eases bacterial adherence.[27] Damage to the endothelium is caused by valve sclerosis, rheumatic valvulitis, or by direct bacterial activity (particularly from *Staphylococcus aureus*).[28] Adhesin proteins such as fibronectin binding protein and staphylococcal clumping factors A and B are the bacterial mediators of adherence and key determinants of pathogenicity.[29–34] Bacterial colonisation triggers additional cycles of endothelial injury and thrombus deposition, eventually forming an infected vegetation (figure 2A). Production of a biofilm (a multilayered bacterial aggregate containing a polysaccharide and proteinaceous matrix) assists bacterial persistence and contributes to antibiotic tolerance.[35]

Microbiology

The Gram-positive cocci of the staphylococcus, streptococcus, and enterococcus species account for 80–90% of infective endocarditis (panel 1). *S aureus* is the

most frequently isolated microorganism associated with infective endocarditis in high-income countries and is reported in up to 30% of cases.[1,2] Staphylococcal infective endocarditis extends beyond traditional at-risk groups such as patients on haemodialysis and intravenous drug users, and can affect both native and prosthetic valves.[36] Moreover, it has notorious propensity to acquire antibiotic resistance, and meticillin-resistant strains have emerged worldwide.[37]

Coagulase-negative staphylococci (eg, *Staphylococcus epidermidis*, *Staphylococcus lugdunensis*, and *Staphylococcus capitis*) are ubiquitous skin commensals. They colonise indwelling lines and devices and are the most common isolate in early prosthetic valve endocarditis.[38–40] Coagulase-negative staphylococci also frequently cause hospital-acquired native valve endocarditis.[2,41,42] Biofilm production, high rates of abscess formation, and multi-antibiotic resistance are characteristic features of these commensals.[43]

Streptococcal infective endocarditis caused by the oral viridans group remains most common in low-income countries.[10] From the Latin term viridis, which means green (referring to the characteristic discoloration of blood agar medium), this group includes *Streptococcus mutans*, *Streptococcus salivarius*, *Streptococcus anginosus*, *Streptococcus mitis*, and *Streptococcus sanguinis*. These organisms are commensals of the oral, gastrointestinal, and urogenital tract. Group D streptococci (eg, *Streptococcus gallolyticus*, *Streptococcus bovis*) are notable for causing infective endocarditis associated with an underlying colonic tumour, which provides the portal of entry. Enterococci account for 10% of cases overall.[1,2] Most isolates are *Enterococcus faecalis*, causing both native valve endocarditis and prosthetic valve endocarditis in elderly or chronically ill patients. *Enterococcus faecium* carries increasing resistance to vancomycin, aminoglycosides, and ampicillin.[44]

The remaining microbes that can cause infective endocarditis are a mixture of fastidious bacteria, zoonotic bacteria, and fungi. The HACEK bacteria (haemophilus, aggregatibacter, cardiobacterium, *Eikenella corrodens*, kingella), which cause about 3% of cases, are slow-growing organisms that colonise the oropharynx.[45] Zoonotic endocarditis is caused by *Coxiella burnetii* and *Brucella* (from livestock), *Bartonella henselae* (from cats), and *Chlamydia psittaci* (from parrots, pigeons). Other rare causes include Gram-negative bacteria (eg, *Acinetobacter* spp, *Pseudomonas aeruginosa*), and *Legionella* spp, *Mycoplasma* spp, and *Tropheryma whippelii*.[46] Fungal endocarditis, usually *Candida* or *Aspergillus*, is rare but often fatal, arising in patients who are immunosuppressed or after cardiac surgery, mostly on prosthetic valves.[47]

Panel 1: **Proportion of cases of infective endocarditis caused by different microorganisms from a French population-based cohort of 497 patients[2]**

Staphylococci
Staphylococcus aureus: 26·6%
Coagulase-negative staphylococci: 9·7%

Streptococci and enterococci
Oral streptococci: 18·7%
Non-oral streptococci: 17·5%
Enterococci: 10·5%
Other: 1·6%

HACEK (haemophilus, aggregatibacter, cardiobacterium, *Eikenella corrodens*, kingella) microorganisms
1·2%

***Candida* species**
1·2%

Other*
6·0%

Polymicrobial (≥2 microorganisms)
1·8%

No microorganism identified
5·2%

*Includes small numbers of Enterobacteriaceae, *Propionibacterium acnes*, *Pseudomonas aeruginosa*, *Lactobacillus* spp, *Corynebacterium* spp, *Coxiella burnetii*, *Bartonella quintana*, *Tropheryma whipplei*, *Gordonia bronchialis*, *Bacillus* spp, *Erysipelothrix rhusiopathiae*, *Neisseria elongata*, *Moraxella catarrhalis*, *Veillonella* spp, *Listeria monocytogenes*, *Acinetobacter ursingii*, *Campylobacter fetus*, *Francisella tularensis*, and *Catabacter hongkongensi*.

Clinical features

The clinical presentation of infective endocarditis is particularly diverse and non-specific. In his seminal 1885 Gulstonian lectures, William Osler remarked, "Few diseases present greater difficulties in the way of diagnosis than malignant endocarditis, difficulties which in many cases are practically insurmountable."[48] More than 100 years later, the diagnosis is still frequently missed or uncertain, delaying definitive management and contributing to mortality.

Infective endocarditis should be considered in anyone with sepsis of unknown origin, or fever in the presence of risk factors. The manifestations of sepsis can range from general malaise to shock, influenced by microbial virulence and the host immune response.[28,49] Infective endocarditis can also present with a complication, particularly stroke or systemic embolism. Irrespective of presentation, patients with a persistent unexplained bacteraemia should be investigated for infective endocarditis. In particular, *S aureus* bacteraemia is associated with infective endocarditis in 25–30% of cases, and all patients should be examined with echocardiography.[50,51]

Initial clinical assessment of a patient with suspected infective endocarditis involves evaluation of risk factors and a search for a supportive history and examination findings. Core cardiac risk factors are previous infective endocarditis, a prosthetic valve or cardiac device, and valvular or congenital heart disease. Non-cardiac risk

Panel 2: **Modified Duke criteria for diagnosis of infective endocarditis**

Pathological criteria

Microorganisms on histology or culture of a vegetation or intracardiac abscess

Evidence of lesions: vegetation or intracardiac abscess showing active endocarditis on histology

Major clinical criteria

1) Blood cultures positive for infective endocarditis

Typical microorganisms consistent with infective endocarditis from two separate blood cultures:

- *Staphylococcus aureus*, viridans streptococci, *Streptococcus bovis*, HACEK (haemophilus, aggregatibacter, cardiobacterium, *Eikenella corrodens*, kingella) group, or community-acquired enterococci, in the absence of a primary focus

or

Microorganisms consistent with infective endocarditis from persistently positive blood cultures:

- At least two positive blood cultures from blood samples drawn >12 h apart, or
- All of three, or most of ≥4 separate cultures of blood (with first and last sample >1 h apart)

or

Single positive blood culture for *Coxiella burnetii*, or phase 1 IgG antibody titre >1:800

2) Evidence of endocardial involvement

Echocardiography positive for infective endocarditis

- Defined by presence of a vegetation, abscess, or new partial dehiscence of prosthetic valve

New valvular regurgitation

- Note—increase or change in pre-existing murmur is not sufficient

Minor clinical criteria

1) Predisposition: predisposing heart condition, intravenous drug use

2) Fever: temperature >38°C

3) Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhages, conjunctival haemorrhages, Janeway lesions

4) Immunological phenomena: glomerulonephritis, Osler's nodes, Roth spots, rheumatoid factor

5) Microbiological evidence: positive blood culture that does not meet a major criterion or serological evidence of active infection with organism consistent with infective endocarditis

Diagnosis of infective endocarditis is definite in the presence of one pathological criterion, or two major criteria, or one major and three minor criteria, or five minor criteria

Diagnosis of infective endocarditis is possible in the presence of one major and one minor criteria, or three minor criteria

Modified Duke criteria were originally published by Li and colleagues.[55]

factors are intravenous drug use, indwelling intravenous lines, immunosuppression, or a recent dental or surgical procedure.

Clinical examination shows variable signs of disease, with fever (present in about 90% of cases) and a cardiac murmur (in about 85%) being most common. Splenomegaly or cutaneous manifestations, such as petechiae or splinter haemorrhages, are supportive signs.[52,53] Contrary to popular medical teaching, Osler's nodes, Janeway lesions, and Roth spots are rare. Signs of complications such as heart failure, stroke, or metastatic infection (eg, vertebral osteomyelitis, peripheral abscess) are much more common. Overall, the sensitivity and specificity of any one sign is low and the diagnosis of infective endocarditis should not be excluded on the basis of clinical examination alone.

Results of routine laboratory investigation are typically non-specific, showing raised inflammatory markers and a normocytic–normochromic anaemia. Rheumatoid factor might be positive. Urinalysis often shows microscopic haematuria and sometimes red cell casts or pyuria. An admission (and initially daily) electrocardiogram is essential, since new conduction disease (eg, first degree atrioventricular block, bundle branch block, or complete heart block) suggests paravalvular or myocardial extension of infection.[54]

Diagnosis

Diagnosis of infective endocarditis necessitates integration of clinical findings, microbiological analysis, and imaging results. The modified Duke clinical diagnostic criteria incorporate these three domains and weigh findings as either major or minor criteria (panel 2). A definite diagnosis requires two major, one major with three minor, or five minor criteria.[55] Alternatively, if pathology specimens are available (from surgery or autopsy), the diagnosis can be made by histology or positive culture of vegetation or abscess tissue. Clinicians and investigators should note that the Duke criteria were originally developed to help with scientific research classification and not as a clinical instrument. They have reduced sensitivity in patients with suspected prosthetic valve endocarditis, right-sided infective endocarditis, and cardiac device infection, and should be used as a diagnostic guide rather than a replacement for clinical judgment.[56]

Microbiology

Positive blood culture is the cornerstone of microbiological diagnosis. Three sets of blood cultures detect 96–98% of bacteraemia and samples should always be taken for culture before patients start antibiotics.[57,58] Bacteraemia in infective endocarditis is continuous, so cultures do not need to be timed with peaks of fever.

Strict aseptic technique and sample acquisition from separate sites help to distinguish skin contaminants from genuine bacteraemia.[59,60]

About 10% of patients with infective endocarditis show no growth from blood cultures resulting in thwarted diagnosis. Several causes can account for this: antibiotics given before blood cultures, infection with fastidious bacteria or fungi, or alternative diagnoses such as non-bacterial thrombotic endocarditis, which occurs in advanced cancer.[61] A causative organism can be identified in about two-thirds of patients by further microbiological testing.[62] If cultures are negative at 5 days, serological testing for coxiella and bartonella should be done, and if also negative, testing for brucella, mycoplasma, legionella, and chlamydia should be undertaken.[60] Extended blood culture after 7 days provides no further useful yield, even for the HACEK bacteria, which are characteristically slow-growing.[60,63] If excised valve material is available, molecular techniques have a complementary role. Broad-range PCR is a highly sensitive technique that amplifies small quantities of conserved bacterial or fungal DNA, and if combined with sequencing, it can identify the specific organism.[64–66] This is particularly valuable in patients with previous antibiotic exposure, since bacterial DNA frequently persists, and also for non-cultivable pathogens such as *T whipplei*.[65–67] PCR carries the risk of a false-positive result due to sample contamination—it might also remain positive after eradication of viable bacteria and should not be used to guide the duration of therapy. Novel techniques combining PCR with mass spectrometry hold promise for direct characterisation of bacteria in peripheral blood or valve tissue.[68]

Echocardiography

Echocardiography is central to diagnosis and detection of complications, and an abnormal result (defined by valvular vegetation or abscess, or new dehiscence of a prosthetic valve) is a major modified Duke criterion (figure 2).[69] Echocardiography also provides information regarding the mechanism and haemodynamic severity of the valve lesion and assessment of underlying left and right ventricular function.

In suspected native valve endocarditis, transthoracic echocardiography (TTE) is moderately sensitive (75%) and specific (more than 90%) for detection of a vegetation.[69] In patients with an equivocal or negative TTE, but high clinical likelihood of infective endocarditis, transoesophageal echocardiography (TOE) is necessary and has a sensitivity of more than 90%. A normal TOE strongly predicts absence of disease, but if clinical suspicion is high, a repeat examination should be done 7–10 days later (figure 3). If this examination is negative, further echocardiography rarely brings additional value.[70] The specificity of echocardiography is not 100% and false-positive cases can occur with cardiac tumours, thrombi, and fibrous strands on the aortic valve.

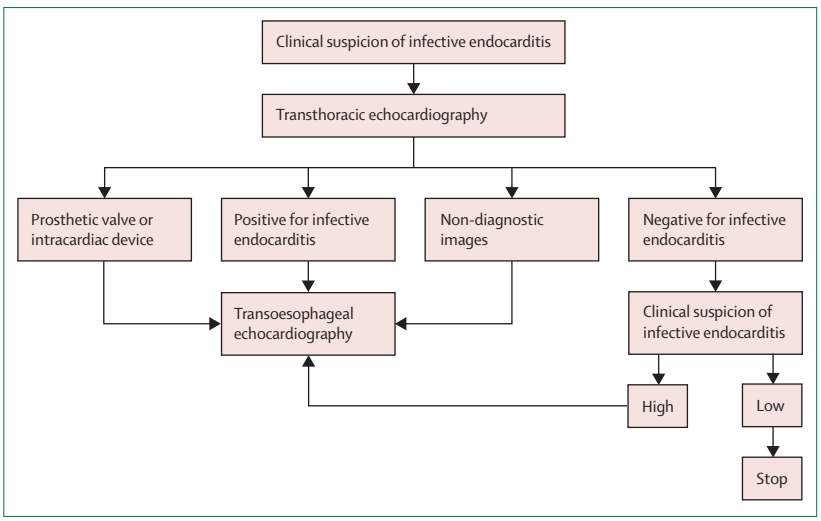

Figure 3: **Use of echocardiography in suspected infective endocarditis**
Transthoracic echocardiography (TTE) is the initial investigation of choice for suspected infective endocarditis because it is accessible, quick, and safe. Patients with a prosthetic valve or cardiac device will usually necessitate additional imaging using transoesophageal echocardiography (TOE). This should be undertaken even if TTE is diagnostic because TOE is better for the detection of complications. In patients with a negative TTE but a high clinical suspicion of infective endocarditis, TOE is suggested and might need to be repeated at 7–10 days to confidently exclude the diagnosis. Adapted from Habib and colleagues.[69]

TOE is better than TTE for detection of the main cardiac complications such as abscess, leaflet perforation, and pseudoaneurysm, and should therefore be undertaken in most cases, even if TTE was sufficient to reach diagnosis.[71,72] In patients with prosthetic valves, the sensitivity of TTE is lower (36–69%), and therefore TOE is usually necessary. TOE is also the method of choice for suspected cardiac device infection.[73,74] TTE should be repeated if a complication is suspected, and at the completion of therapy as a baseline for follow-up.

Management

The management of patients with infective endocarditis necessitates a multidisciplinary approach with input from cardiologists, cardiothoracic surgeons, and infectious disease specialists. Recent guidelines[75] from an international valve working group specifically emphasise the role of a dedicated hospital endocarditis team. Randomised clinical trials to guide management decisions are almost non-existent, and none of the recommendations in international guidelines on infective endocarditis are backed by level A evidence (ie, many randomised controlled trials).[6,7]

Antibiotics

On an empirical basis, antibiotics should be started as soon as blood cultures have been acquired, but clinicians can also await culture results if the patient is clinically stable.[60] Empirical antibiotic regimens for native valve endocarditis and prosthetic valve endocarditis are based on definitive guidelines[60] produced by the British Society for Antimicrobial Chemotherapy (table). Nevertheless,

	Empirical antibiotic regimen and dose	Comment
Native valve endocarditis—indolent presentation	Amoxicillin (2 g, every 4 h, intravenously) + gentamicin* (optional; 1 mg/kg of actual bodyweight)	Better activity than benzylpenicillin against enterococci and many HACEK bacteria; the use of gentamicin before availability of culture results is controversial
Native valve endocarditis— severe sepsis (without risk factors for multiresistant enteric Gram-negative bacilli, pseudomonas)	Vancomycin* (dose as per local guidelines) + gentamicin* (1 mg/kg of ideal bodyweight, every 12 h, intravenously)	Activity against staphylococci (including meticillin-resistant *Staphylococcus aureus*)
Native valve endocarditis—severe sepsis (with risk factors for multiresistant enteric Gram-negative bacilli, pseudomonas)	Vancomycin* (dose as per local guidelines) + meropenem (2 g, every 8 h, intravenously)	..
Prosthetic valve endocarditis—pending blood cultures or with negative blood cultures	Vancomycin* (1 g, every 12 h, intravenously) + gentamicin* (1 mg/kg, every 12 h, intravenously) + rifampicin (300–600 mg, every 12 h, orally or intravenously)	..

Adapted from Gould and colleagues.[60] All antibiotic doses are adjusted according to renal function. HACEK=*Haemophilus* spp, *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*. *Regular measurement of serum concentrations needed to monitor and adjust dosing.

Table: **Empirical treatment for different clinical scenarios in patients with suspected infective endocarditis**

the involvement of local microbiological experts is strongly recommended. The antimicrobial regimen can be modified according to culture results, resistance patterns, severity of infection, and the presence or absence of prosthetic material. In general, combination intravenous therapy is preferred over monotherapy, to reduce emergence of resistance and provide synergistic antimicrobial activity. The exception is meticillin-sensitive *S aureus*, for which flucloxacillin monotherapy is sufficient and addition of gentamicin increases nephrotoxicity.[76] Treatment for at least 4–6 weeks is usually necessary, and for substantially longer in some cases (eg, Q fever infective endocarditis). Patients with uncomplicated native valve endocarditis due to highly sensitive streptococci might be suitable for a short 2-week course of intravenous benzylpenicillin or ceftriaxone in combination with gentamicin.[60] Other selected patients who are responsive to treatment and have suitable domestic living circumstances could be eligible for home or outpatient antibiotic care after the first 2-week period in which the frequency of complications is highest.[60]

Surgery

Surgery is undertaken in 40–50% of patients with infective endocarditis.[77] There are three principal indications: valve dysfunction leading to heart failure, uncontrolled infection, and for prevention of embolism. Valvular, perivalvular, and remote complications of infective endocarditis are shown in figure 4. The aims of surgery are to eradicate infection and reconstruct cardiac anatomy. Both valve repair and replacement are options for reconstruction, and no definitive evidence favours a bioprosthetic valve more than a mechanical replacement.

Heart failure caused by valvular regurgitation or obstruction is the most common indication for surgery. Historical cohorts show that the outcome is dire without emergency surgery once the patient has developed refractory pulmonary oedema or cardiogenic shock.[78,79] Patients with well-tolerated severe valve regurgitation might be appropriate candidates for deferred surgery (after a period of stabilisation on antibiotic therapy), but there is limited evidence to guide clinical practice in this area.

Uncontrolled or complex infection is the second indication for surgery. Spread of infection beyond the valve annulus might cause abscess, pseudoaneurysm, fistula, or atrioventricular block. A pseudoaneurysm is a perivalvular cavity that communicates with the cardiovascular lumen, as shown by colour Doppler flow with echocardiography, whereas an abscess is a thickened, pus-filled perivalvular cavity that has no such communication.[69] Progressive perivalvular infection can lead to fistula formation (usually aorto-cavitary) and carries a mortality of more than 40% even with surgery.[80] Persistent or relapsing infection, or infection caused by aggressive or antibiotic-resistant microorganisms (eg, *S aureus*, *S lugdunensis*, pseudomonas, fungi) are also indications for surgery.[81]

The third indication for surgery is to prevent embolism, a devastating complication that affects 25–50% of patients.[82] Stroke is most common, but embolism to any vascular bed is possible with resulting end-organ infarction (kidneys, spleen, limbs, mesenteric, and coronary arteries). Additionally, vegetation embolism can cause secondary infection in the vascular wall, leading to formation of a mycotic aneurysm. These aneurysms are most often seen in the cerebral vessels and are noted on brain imaging in 3–5% of patients with infective endocarditis, although most such aneurysms remain clinically silent.[83–85] Patients with right-sided infective endocarditis are at risk of emboli to the lungs, or to the systemic circulation through a patent foramen ovale. Most emboli occur in the first 2 weeks after diagnosis and the risk decreases rapidly after antibiotics are given.[86,87] Embolism is more likely when vegetations are large (more than 10 mm in length), highly mobile, and located on the mitral valve.[88] Surgery is suggested in patients with recurrent emboli and patients with

persistent threatening vegetations shown with echocardiography. Surgery is not contraindicated after an ischaemic stroke, but should be delayed for at least 1 month if cerebral haemorrhage has taken place.

Prognosis and ongoing care

The in-hospital mortality of infective endocarditis is estimated at around 20%, increasing to 25–30% at 6 months, although this mortality varies substantially according to the infecting organism and clinical circumstances.[1,2,89,90] The most important adverse prognostic factors are old age, prosthetic valve endocarditis, heart failure, paravalvular complication, stroke, and infection with *S aureus*. Improved patient-specific risk stratification is necessary—and might be achievable by integration of clinical indices, biomarker results, and imaging findings in an admission risk scoring system—which could be used to prioritise the timing of intervention.[91,92] Long-term survival ranges between 60% and 90% at 10 years, affected mainly by age, heart failure, and comorbidities.[93–95]

Ongoing monitoring is recommended after hospital discharge, mainly for recurrent infection (either relapse or reinfection) and progressive valve dysfunction. Patients should be informed that they remain at risk of recurrent infective endocarditis, estimated to occur at a rate of 1·3% per patient-year.[96] Preventive measures such as good oral hygiene and consideration of antibiotic prophylaxis at the time of dental and other invasive procedures are relevant for this high-risk group (see section on Prevention of infective endocarditis). After completion of treatment, the European Society of Cardiology advises follow-up with TTE and blood testing for inflammatory markers at 1, 3, 6, and 12 months.[6] Anyone who has previously suffered from infective endocarditis should be advised to seek urgent medical attention in the event of developing a systemic infection.

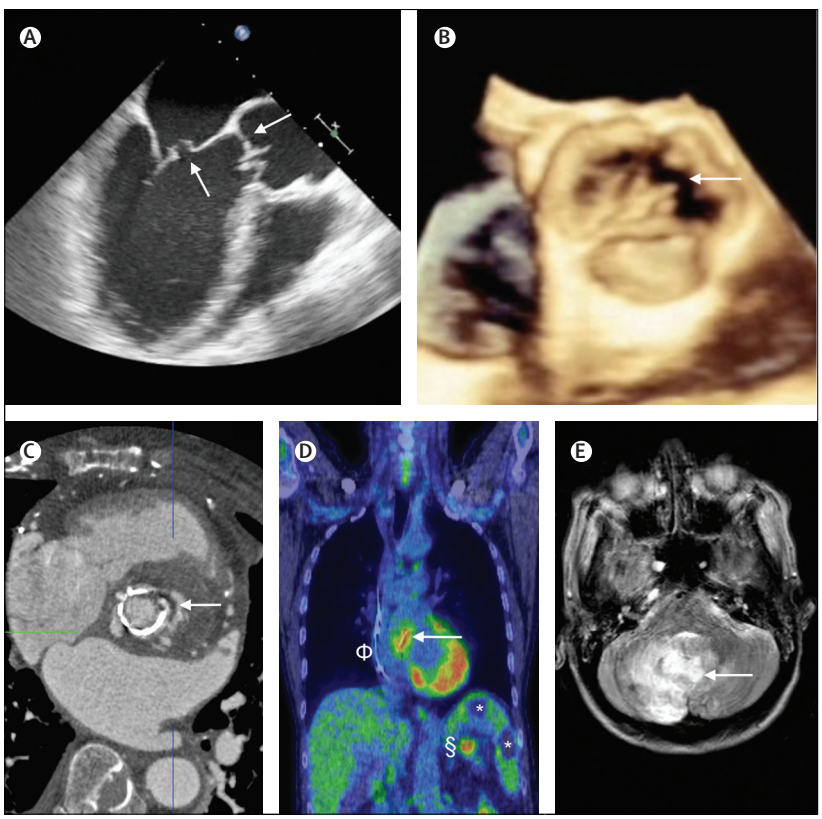

Figure 4: **Complications of infective endocarditis**
(A) Two-dimensional transoesophageal echocardiogram (TOE) showing perforations in both the aortic and mitral valves (arrow) in a case of double valve infective endocarditis. (B) The aortic valve perforation is seen more clearly using three-dimensional TOE. (C) Gated multislice cardiac CT image with paravalvular extension of infection and root abscess formation (arrow) in prosthetic valve endocarditis. (D) ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT imaging is shown in a case of prosthetic valve endocarditis. High abnormal ^{18}F-FDG signal from the prosthetic valve (arrow) is consistent with infection and distinct from the healthy signal from the left ventricle. An implantable cardioverter defibrillator lead (ϕ) can be seen in the right ventricle, which is ^{18}F-FDG negative. Filling defects are present in the spleen (*) consistent with embolic infarction. High localised signal can be seen in the splenic artery (§) and was subsequently confirmed on CT angiography as a mycotic thrombus. (E) MRI of the brain with widespread haemorrhage (arrow) complicating a cerebral abscess.

Special circumstances

Infective endocarditis is a highly heterogeneous disease and there are a number of special circumstances with different clinical presentations, microbiology, and necessary management.

Prosthetic valve endocarditis

Prosthetic valve endocarditis occurs in 3–4% of patients within 5 years of index surgery and affects mechanical and bioprosthetic valves equally.[97,98] More than a third of cases are health-care-acquired.[99] Early prosthetic valve endocarditis (less than 1 year after initial surgery) predominantly occurs in the first 2 months after surgery and is most often due to coagulase-negative staphylococci or *S aureus*.[100] Beyond 1 year, the range of organisms causing prosthetic valve endocarditis is the same as in native valve endocarditis. Clinical presentation is often atypical and negative imaging findings are more common, leading to lower sensitivity of the Duke criteria.[101] Root abscess formation and valve dehiscence occur in up to 60% of patients—surgery is usually necessary and is often technically demanding and high risk, with rates of recurrent prosthetic valve endocarditis ranging from 6% to 15%.[77] The mortality of prosthetic valve endocarditis is very high, particularly with *S aureus* infection, for which the 1-year mortality is almost 50%.[99,102]

Cardiac device infection

Cardiac devices include permanent pacemakers, cardiac resynchronisation therapy, and implantable cardioverter defibrillators. As the use of cardiac devices has expanded, the rate of cardiac device infection has increased in parallel.[19,20] Infection affects up to 2% of cardiac devices during the first 5 years after implantation, and might involve the generator pocket, the device leads, or the surrounding endocardial surface.[103] Risk factors for cardiac device infection include haematoma formation

at the incision site, renal failure, complex device implantation (compared with permanent pacemakers), revision procedures, and an absence of antibiotic prophylaxis. Signs of generator pocket infection include local cellulitis, discharge, dehiscence, or pain. Infection involving the leads or endocardium can cause fever, malaise, and sepsis. With the exception of cases involving simple superficial skin wound infections, complete removal of the device is usually needed, which reduces mortality at 1 year after infection.[104,105] Accurate diagnosis is crucial because device removal (usually achieved using percutaneous techniques) carries a small risk of life-threatening complications. Controversies, including diagnostic criteria, timing of device re-implantation, and the duration of antibiotic therapy, are comprehensively reviewed in recent UK guidelines[106] for cardiac device infection.

Right-sided endocarditis

Right-sided infective endocarditis is less common, accounting for only 5–10% of cases. It is usually associated with intravenous drug use, cardiac device infection, central venous catheters, HIV, and congenital heart disease. The tricuspid valve is most often affected. In addition to features of sepsis, patients often have respiratory symptoms resulting from pulmonary emboli, pneumonia, and pulmonary abscess formation. Most patients can be managed medically and the outcome is good.[107] Treatment of infective endocarditis in active intravenous drug users (involving the tricuspid valve in more than 70% of cases) is challenging because of low compliance with treatment—5-year survival is about 50% in patients needing surgery.[108] A short course of parenteral antibiotic therapy preceding an oral antibiotic regimen might be justified in highly selected intravenous drug users to achieve the requisite 4–6 weeks of treatment.[109]

Controversies and challenges

Given the absence of high-level evidence in the field of infective endocarditis, controversies abound. The debate spans across strategies for disease prevention, use of diagnostic techniques, and patient selection and timing of surgical intervention.

Novel imaging strategies

Several adjunctive cardiac imaging modalities are being assessed for diagnosis and detection of complications (figure 3).[110] High-resolution multislice gated cardiac CT provides cross-sectional and three-dimensional reconstructed images of the valves and heart. CT is particularly good—possibly better than TOE—at defining the anatomy of paravalvular complications such as abscess.[111,112] CT can also be used to define the coronary anatomy and exclude atherosclerosis in patients with infective endocarditis who need surgery, if conventional invasive angiography carries the risk of dislodging a vegetation. Three-dimensional TOE, which allows visualisation of the affected valve in several planes, has additive value over two-dimensional echocardiography for diagnosis of leaflet perforation and is particularly useful to guide surgical strategy.[113] Intracardiac echocardiography, undertaken invasively with a probe in the right heart, might have a place in suspected cardiac device infection when TOE is negative.[114] Cardiac MRI can also be useful to help to distinguish a vegetation from a tumour if clinical uncertainty exists.[115]

Beyond the heart, systematic cerebral (or even whole body) imaging is recommended in challenging groups of patients with possible infective endocarditis according to Duke criteria. In a cohort with definite or possible infective endocarditis, brain MRI was abnormal in 106 of 130 (82%) of cases, showing acute (mostly subclinical) ischaemic lesions, microabscesses, microhaemorrhages, mycotic aneurysms, and cortical haemorrhages.[84,85] These findings upgraded 14 of 53 (26%) patients with possible infective endocarditis to definite status and altered the management plan in 24 of 130 (18%) patients.

Another imaging strategy uses ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET-CT to visualise the vegetations of infective endocarditis. Infectious foci are metabolically active and avidly take up the glucose tracer ^{18}F-FDG. PET has shown particular promise in cases of suspected prosthetic valve endocarditis or cardiac device infection with equivocal or negative TOE. It can help with diagnosis and characterisation of metastatic and embolic spread, and with difficult cases of pyrexia of unknown origin.[116] The addition of valve uptake of ^{18}F-FDG as a major Duke criterion increases the sensitivity of the modified Duke score from 70% to 97%.[117]

Patient selection and timing for surgery

In a landmark randomised controlled trial in 2012,[118] early surgery (within 48 h) was compared with conventional treatment (including surgery if necessary) in 76 stable, relatively young (mean age of 47 years) patients with native valve endocarditis who had large vegetations and few comorbidities. The early surgery group showed significant reduction in the composite primary endpoint of in-hospital death or embolism within 6 weeks, driven entirely by a reduction in the rate of embolism. These results have led to a focus on early surgical intervention and consideration of prophylactic surgery as a strategy for patients at high risk of (first) embolism—although this remains contentious. In an unselected, real-world setting, however, challenges to the notion of early surgery exist and the applicability of the study findings to most patients with infective endocarditis in high-income countries has been questioned. In the International Collaboration on Endocarditis-Prospective Cohort Study report from 2015,[119] 202 of 863 (24%) of patients with an indication for surgery were not operated on due to a combination of poor prognosis, instability, comorbidity or recent stroke, or death before intended operation. Additionally, overcoming the logistical barriers

facing early surgery will necessitate substantial reconfiguration of clinical services. One promising strategy to achieve this might be provision of a dedicated hospital infective endocarditis team, which has been shown in one study to reduce the time to surgery and both operative and long-term mortality.[120]

The optimum timing of surgery remains unclear in prosthetic valve endocarditis. In view of the high rate of complications such as abscess and fistula, early and definitive surgical intervention to eradicate infection and replace the valve is empirically attractive. Although no randomised trials have been done, the role of early surgery was studied in a large cohort of 1045 patients with prosthetic valve endocarditis.[121] Unexpectedly, the outcome after early surgery—defined here as surgery undertaken at a median of 8 days during the index hospital admission—was not noted to be better than medical therapy. This finding has since been confirmed in a smaller cohort focusing on prosthetic valve endocarditis caused by *S aureus*.[102] Despite the stringent adjustments for bias in patient selection and survival, definitive conclusions are difficult to draw from these observational studies. A randomised trial of early surgery in prosthetic valve endocarditis is urgently needed, but might prove impossible because of the necessity for multicentre international collaboration and a long period of recruitment arising from the low incidence at each centre.

Prevention of infective endocarditis

Reduction of bacteraemia is the intuitive upstream approach to prevention of infective endocarditis. The optimisation of use and care of central venous catheters, including aseptic techniques, early line removal, and avoidance of femoral access, reduces the rates of catheter-associated bacteraemia.[122] Poor oral hygiene is associated with bacteraemia after tooth brushing and has long been recognised as an easily modifiable risk factor for infective endocarditis.[123] For patients undergoing cardiac device implantation, antibiotic prophylaxis reduces the risk of subsequent infection.[124,125]

For more than 50 years, oral antibiotic prophylaxis was given to reduce bacteraemia in patients at risk of infective endocarditis undergoing an invasive (especially dental) procedure. In 2008, the UK National Institute for Health and Clinical Excellence advised cessation of this practice, citing the absence of a strong evidence base, the overall low risk of infective endocarditis arising from dental procedures, and the potential hazards of indiscriminate antibiotic use.[126] By contrast, the European Society of Cardiology, American College of Cardiology, and American Heart Association have recommended ongoing use of antibiotic prophylaxis for patients at highest risk: those with history of infective endocarditis, prosthetic valves, and cyanotic congenital heart disease. Since 2008, several observational studies have examined the effect of total (in the UK) or partial (in the USA and rest of Europe) cessation of antibiotic prophylaxis.[8,127–129] Although earlier studies showed no change in infective endocarditis incidence, Dayer and colleagues reported in 2015 a small but statistically significant increase in infective endocarditis cases in the UK since 2008.[129] The temporal correlation between decreased use of antibiotic prophylaxis and increased incidence of infective endocarditis clearly raises concerns about current UK prophylaxis policy, although causation has not been established. The apparent link might be confounded by increased rates of bacteraemia or numbers of at-risk individuals, or factors related to diagnostic coding. In view of this ongoing uncertainty, many UK cardiologists are deferring to the European and American society guidelines and continue to prescribe prophylactic antibiotics to patients at highest risk.[128,130]

Conclusions

Action on many fronts is needed to tackle infective endocarditis. A reduction in incidence depends on strategies to minimise health-care-associated bacteraemia, and clarity on the issue of oral antibiotic prophylaxis. Insights into pathophysiology need to be translated into infection-resistant materials for prosthetic valves and cardiac devices. Functional integration of multidisciplinary infective endocarditis teams, multimodality imaging, and microbiological services will drive earlier decision making and intervention. Beyond individual hospitals, national and international collaborations are needed to initiate and maintain multicentre clinical trials. Coordinated and sustained action will be necessary to keep pace with this constantly evolving and deadly disease.

Contributors

TJC and BDP jointly drafted and revised the manuscript.

Declaration of interests

We declare no competing interests.

Acknowledgments

The work of BDP has been supported by the Oxford Partnership Comprehensive Biomedical Research Centre with funding from the UK Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme. The views expressed in this Seminar are his and not necessarily those of the Department of Health. The authors are grateful to Dr Andrew Kelion, Dr Jim Newton, and Dr Nik Sabharwal for assistance with images.

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