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Infective endocarditis

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Abstract

Infective endocarditis (IE) is a rare, life-threatening disease that has long-lasting effects even among patients who survive and are cured. IE disproportionately affects those with underlying structural heart disease and is increasingly associated with healthcare contact, particularly in patients who have intravascular prosthetic material. In the setting of bacteraemia with a pathogenic organism, an infected vegetation may form as the end result of complex interactions between invading microorganisms and the host immune system. Once established, IE can involve almost any organ system in the body. The diagnosis of IE may be difficult to establish and a strategy that

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combines clinical, microbiological and echocardiography results has been codified in the modified Duke criteria. In cases of blood culture-negative IE, the diagnosis may be especially challenging and novel microbiological and imaging techniques have been developed to establish its presence. Once diagnosed, IE is best managed by a multidisciplinary team with expertise in infectious diseases, cardiology and cardiac surgery. Antibiotic prophylaxis for the prevention of IE remains controversial. Efforts to develop a vaccine targeting common bacterial causes of IE are ongoing, but have not yet yielded a commercially available product.

ToC blurb

Infective endocarditis (IE) is caused by damage to the endocardium of the heart followed by microbial, usually bacterial, colonization. IE is a multisystem disease that can be fatal if left untreated and antimicrobial prophylaxis strategies for IE remain controversial.

Introduction

Infective endocarditis (IE) is a multisystem disease that results from infection, usually bacterial, of the endocardial surface of the heart. It has been recognized as a pathological entity for hundreds of years and as an infectious process since the 19th century[1]. In his landmark 1885 Gulstonian Lectures on malignant endocarditis, Sir William Osler presented a unifying theory in which susceptible patients developed ‘mycotic’ growths on their valves followed by “transference to distant parts of microbes”[2]. The intervening 130 years have witnessed dramatic growth in our understanding of IE as well as fundamental changes in the disease itself. Medical progress, novel at-risk populations and the emergence of antimicrobial resistance have led to new clinical manifestations of IE. In this Primer, we review our current understanding of IE epidemiology, pathophysiology, aspects of diagnosis and clinical care, and speculate upon future developments in IE and its management.

Epidemiology

IE is a relatively rare but life-threatening disease. In a systematic review of the global burden of IE, crude incidence ranged from 1.5 to 11.6 cases per 100,000 person-years, with high quality data available from only 10 — mostly high-income — countries[3]. Untreated, mortality from IE is uniform. Even with best available therapy, contemporary mortality rates from IE are approximately 25%[4].

Demography

The mean age of patients with IE has increased significantly in the past several decades. For example, the median age of IE patients presenting to Johns Hopkins Hospital was <30 years in 1926[5]. By contrast, more than half of contemporary patients with IE are >50 years old, and approximately two-thirds of cases occur in men[4,6]. Multiple factors have contributed to this changing age distribution in high-income countries. First, the cardiac risk factors predisposing patients to IE have shifted in many high-income countries from rheumatic heart disease, which is primarily seen in young adults, to degenerative valvular disease, which is principally encountered in the elderly. Second, the age of the population has increased steadily. Third, the relatively new entity of healthcare-associated IE, which

disproportionately affects older adults, has emerged secondary to the introduction of new therapeutic modalities such as intravascular catheters, hyperalimentation lines, cardiac devices and dialysis shunts.

Risk factors

Almost any type of structural heart disease can predispose to IE. Rheumatic heart disease was the most frequent underlying lesion in the past, and the mitral valve was most commonly involved site[7]. In developed countries, the proportion of cases related to rheumatic heart disease has declined to 5% or less in the past 2 decades[4]. In developing countries, however, rheumatic heart disease remains the most common predisposing cardiac condition for IE[8].

Prosthetic valves and cardiac devices (permanent pacemakers and cardioverter defibrillators) are significant risk factors for IE. Rates of implantation of these devices have increased dramatically in the past several decades. Consequently, prosthetic valves and devices are involved in a growing proportion of IE cases[9]. For example, in a recent cohort of 2,781 adults in 25 countries with definite IE, one-fifth had a prosthetic valve and 7% had a cardiac device[4].

Congenital heart disease also confers increased risk of IE. In the same study mentioned above, 12% of the 2,781 patients with definite IE had underlying congenital heart disease[4]. Because this cohort was assembled largely from referral centres with cardiac surgery programmes, however, this rate probably overestimates the association between congenital heart disease and IE in the general population. Mitral valve prolapse has been reported as the predominant predisposing structural abnormality in 7–30% of native valve IE in developing countries[10]. In one case-control study, mitral prolapse was associated with IE with an odds ratio of 8.2 (95% confidence interval, 2.4–28.4)[11]. In developed countries, degenerative cardiac lesions assume greatest importance in the 30%–40% of patients with IE who do not have known valvular disease[12]. For example, in an autopsy series, mitral valve annular calcification was noted in 14% of patients with IE who were >65 years old, which is a higher rate than that of the general population[12,13].

Other factors predisposing to IE include injection drug use (IDU), human immunodeficiency virus (HIV) infection and extensive healthcare system contact[4,6]. Health care-associated IE in particular has been rising in the past several decades, especially in developed countries[6]. For example, one-third of a recent prospective, multinational cohort of 1,622 patients with native valve IE and no history of IDU had health-care associated IE[14].

Microbiology

As patient risk factors change, the microbiology of IE shifts as well. Although streptococci and staphylococci have collectively accounted for approximately 80% of IE cases, the proportion of these two organisms varies by region (Figure 1) and has changed over time. The emergence of healthcare-associated IE has been accompanied by an increase in the prevalence of *Staphylococcus aureus*[15] and coagulase-negative staphylococci[14,16], whereas the proportion of IE due to viridans-group streptococci (VGS) has declined[16]. Enterococci are the third leading cause of IE and are increasingly linked to health care contact[17].

Infections involving Gram-negative and fungal pathogens in IE are rare and are primarily health care-associated when they do occur[18,19].

In approximately 10% of cases of IE, blood cultures are negative, most commonly due to patient receipt of antibiotics prior to the diagnostic work-up. 'True' culture-negative IE is caused by fastidious microorganisms that are difficult to isolate with conventional microbiological techniques. Highly specialized assays such as serologic testing and polymerase-chain-reaction (PCR) using blood or valve biopsies can ultimately suggest a causative pathogen in up to 60% of such cases[20]. Although the aetiology of true culture-negative IE varies with geographic and epidemiologic factors, important causes include *Coxiella burnetii* (the causative agent of Q fever), *Bartonella* species, *Brucella* species, and *Tropheryma whipplei*[4,20]. Specific risk factors such as contact with livestock or abattoirs (for *Brucella* and *Coxiella*), homelessness or alcoholism (for *Bartonella quintana*), travel to the Middle East or Mediterranean or consumption of unpasteurized dairy products (for *Brucella*), contact with cats (for *Bartonella henselae*) or extensive healthcare contact in a patient with a prosthetic valve and negative blood cultures (for *Aspergillus*) may be useful clues when evaluating potential IE cases.

Mechanisms/pathophysiology

Experimentally, the normal valvular endothelium is resistant to bacterial colonization upon intravascular challenge[21]. Thus, the development of IE requires the simultaneous occurrence of several independent factors: alteration of the cardiac valve surface to produce a suitable site for bacterial attachment and colonization; bacteraemia with an organism capable of attaching to and colonizing valve tissue; and creation of the infected mass or 'vegetation' by 'burying' of the proliferating organism within a protective matrix of serum molecules (for example, fibrin) and platelets (Figure 2).

Nonbacterial thrombotic endocarditis

As noted above, IE rarely results from intravenous injections of bacteria unless the valvular surface is first perturbed[21]. In humans, equivalent damage to the valvular surface may result from a variety of factors, including turbulent blood flow related to primary valvular damage from specific systemic disease states (such as rheumatic carditis), mechanical injury by catheters or electrodes, or injury arising from repeated injections of solid particles in IDU. This endothelial damage prompts the formation of fibrin-platelet deposits overlying interstitial oedema[21], a pathophysiological entity first termed "nonbacterial thrombotic endocarditis" (NBTE) by Gross and Friedberg in 1936[22]. Serial scanning electron micrographs of such damaged valves of animals experimentally challenged with intravenous boluses of bacteria demonstrate bacterial adhesion to the NBTE surface within 24 hours following infection. This adhesion is followed by the generation of the fully-developed infected vegetation upon further coverage of the bacteria with matrix molecules[23].

Transient bacteraemia

Bloodstream infection is a prerequisite for development of native valve IE and likely the bulk of prosthetic valve IE cases; in the latter setting, intraoperative contamination could

account for valve infection. However, the minimum magnitude of bacteraemia (as measured by colony-forming units (CFU) per mL) required to cause IE is not known. Experimental models have typically used inocula of 10^5–10^8 CFU per ml either as a bolus dose or by continuous infusion over an extended period[24]. Low-grade bacteraemia (≥10 and $<10^4$ CFU per ml) seems to be common after mild mucosal trauma such as with dental, gastrointestinal, urological or gynaecological procedures[25]. Bacteraemia is readily detectible in a majority of patients after dental procedures[26] and after common daily activities such as teeth brushing and chewing[25]. It is thus likely that low levels of bacteraemia, while commonplace, are usually insufficient to cause IE. Additionally, many of the bacterial species present in the blood after mild mucosal trauma are not commonly implicated in cases of IE. For example, complement-mediated bactericidal activity eliminates most gram-negative pathogens[27]. In contrast, organisms traditionally associated with IE (that is, *S. aureus*, *S. epidermidis*, VGS, enterococci and *P. aeruginosa*) adhere more readily to canine aortic leaflets *in vitro* than pathogens that are less common causes of IE[28]. Even within the same species, there may be differences in the propensity to cause IE. Specific clonal complexes of *S. aureus*, for example, are associated with an increased risk of IE[29]. Similarly, members of the *S. mitis-oralis* group predominate as a cause of IE among the many members of VGS[30].

Microorganism-NBTE interaction

Once bacteraemia has been established with a typical IE-inducing pathogen, the next step is adherence of the organism to the fibrin-platelet matrices of NBTE. The importance of this step was demonstrated in a study of dental extraction in rats with periodontitis. In this study, group G streptococci were responsible for 83% of IE episodes despite causing a minority of episodes of bacteraemia. In an *in vitro* model, these organisms were associated with increased adhesion to fibrin-platelet matrices as compared to other species[31]. Adhesion to NBTE is also an important step in fungal IE. Whereas *Candida krusei* adheres poorly and is a rare cause of IE in humans, *Candida albicans* adheres to NBTE *in vitro*, readily produces experimental IE[32] and is the most common cause of IE among candidal species[19].

Mechanisms of bacterial adherence to the endocardium—Although binding of the pathogen to NBTE appears to be a common step in establishing IE, the mechanism by which this occurs may vary considerably. Some organisms appear to bind to components of damaged endothelium or NBTE, such as fibronectin, laminin and collagen[33,34]. Other organisms may bind directly to, or be internalized by, endothelial cells. This appears to be an important mechanism by which *S. aureus* infects cardiac valves (Figure 3)[35,36]. In this model, adhesion is mediated by *S. aureus*–specific surface proteins that bind fibrinogen, such as clumping factor and coagulase[37,38]. It seems that a ‘cooperativity’ exists between fibrinogen- and fibronectin-binding in the induction of *S. aureus* IE, in which both adhesins mediate initial attachment to vegetations, but fibronectin binding is critical for the persistence of organisms at the valvular endothelial site[39]. Additional virulence factors, such as α-toxin, then mediate persistence and proliferation within maturing vegetations[40].

In addition, it seems that a key factor in adherence of oral streptococci to NBTE is dextran, which is a complex bacterial-derived extracellular polysaccharide[41,42]. Other proposed virulence factors that mediate streptococcal adhesion include FimA, which is a surface

protein that functions as an adhesin in the oral cavity[43,44], the sialic acid-binding adhesin Hsa[45] and a phage-encoded bacterial adhesin that mediates a complex interaction between bacteria, fibrinogen and platelets[46–48].

Platelet aggregation and evolution of the vegetation—Following bacterial colonization of the valve, the vegetation enlarges by further cycles of platelet-fibrin deposition and bacterial proliferation (Figure 2). Some strains of bacteria are potent stimulators of platelet aggregation and the platelet release reaction (that is, degranulation)[49]. In general, IE-producing strains of staphylococci and streptococci more actively aggregate platelets than do other bacteria that less frequently produce IE. *Streptococcus sanguinis* promotes platelet aggregation via two bacterial cell surface antigens[50]. *S. aureus* appears able to bind platelets via platelet-derived von Willebrand factor or directly to the von Willebrand factor receptor[51,52].

Although platelets are key components in the pathogenesis of IE, they also play a pivotal role in host defence against organism proliferation within the cardiac vegetation. For example, platelets phagocytose circulating staphylococci into engulfment vacuoles that fuse with α-granules. These α-granules contain antimicrobial peptides called platelet microbicidal proteins (PMPs). Depending on the intrinsic susceptibility of the specific strain of staphylococci to these bactericidal peptides, the organism is either killed within platelets or survives and disseminates using a 'Trojan Horse' mechanism[53]. Platelets also thwart bacterial proliferation within the vegetation by releasing antibacterial PMPs into the local vegetation environment[54]. Thus, resistance to PMPs (such as in *S. aureus*) contributes to virulence in IE. Finally, bacteria buried deep within the vegetation may exhibit a state of reduced metabolic activity based on inability to uptake critical nutrients[55]. This altered metabolic state promotes organism survival against selected antibiotics.

The invading microbe, the endothelium and the monocyte interact in a complex manner in the pathogenesis of IE. After internalization by endothelial cells *in vitro*, microbes such as *S. aureus* evoke a potent proinflammatory chemokine response, including increased expression of IL-6, IL-8 and monocyte chemotactic peptide[56]. Monocytes are drawn into the endothelial cell microenvironment, where circulating bacteria may then bind directly to their surface, inducing the release of tissue thromboplastin (tissue factor)[57]. This release amplifies the procoagulant cascade leading to progressive evolution of the vegetation. As noted above, this same cascade also induces the antibacterial effect of PMP release by platelets within the vegetation matrix.

Biofilm formation—There is considerable debate concerning the role of 'biofilm' formation and the pathogenesis and/or outcomes of IE. It is clear that IE related to implantable cardiac devices can evoke peri-device biofilms. In these scenarios, biofilm formation contributes directly to the evolution of device-associated vegetation propagation. However, the contribution of biofilm formation to native valve IE is not established. The most convincing data on the effect of biofilm formation in native valve IE comes from experimental studies in *S. aureus* IE. A series of studies over the past decade have linked the ability of *S. aureus* strains to produce biofilms *in vitro* and their ability to cause clinically 'persistent' methicillin-resistant *S. aureus* (MRSA) bacteraemia in humans (defined as >7

days of positive blood cultures despite presence of vancomycin-susceptible isolates and adequate vancomycin treatment regimens)[58,59]. Of interest, clinically-persistent MRSA bacteraemia strains produce significantly more biofilm *in vitro* when exposed to sub-inhibitory concentrations of vancomycin as compared to clinically-resolving MRSA isolates[58].

Quorum-sensing—Since IE vegetations contain large densities of organisms, the role of quorum-sensing genetic regulation (that is, the regulation of gene expression on the basis of bacterial cell density) of virulence factors has been raised. Again, most data in this regard emanate from *S. aureus*, in this case in the context of the quorum-sensing regulon *agr* (accessory gene regulator). Of interest, in experimental IE, the ability of MRSA strains to evoke activation of *agr* early in the growth cycle correlates with the ability to cause vancomycin-persistent IE both clinically and in experimental IE. However, based on *agr* gene knockout studies, the 'early activation' profile of *agr* is, at most, a biomarker for persistent IE strains rather than being directly linked to this outcome pathogenetically[58,60].

Immunopathological factors

IE results in stimulation of both humoral and cellular immunity, as manifested by hypergammaglobulinaemia, splenomegaly and the presence of macrophages in the peripheral blood. Several classes of circulating antibodies are produced in response to the continuous bacteraemia that typically characterizes IE. Opsonic antibodies, agglutinating antibodies, complement-fixing antibodies, cryoglobulins and antibodies directed against bacterial heat-shock proteins and macroglobulins are produced by the host in an effort to control the ongoing infection[61,62].

Effectiveness of antibody responses in IE—Animal studies suggest variable effectiveness of the antibody response to prevent IE. For example, rabbits immunized with heat-killed *S. sanguis* plus Freud's adjuvant had a higher ID_{50} (that is, the *S. sanguis* dose required to produce an infection in 50% of rabbits) than nonimmunized controls after aortic valve trauma[63]. Antibodies against cell-surface components reduce adhesion of *C. albicans* to fibrin and platelets *in vitro* and reduce incidence of IE *in vivo*[64]. By contrast, whole cell-induced antibodies to *S. epidermis* and *S. aureus* did not prevent IE in immunized animals[65]. In addition, when administered in conjunction with antibiotic therapy, antibodies specific for the fibrinogen-binding protein clumping factor A (ClfA) increased bacterial clearance from vegetations[66]. Moreover, recent data suggest a possible role for vaccination against ClfA for the prevention of IE[67], although human studies have not yielded an effective vaccine (see Outlook section).

Pathological antibodies—Rheumatoid factor (which is an anti-IgG IgM antibody) develops in about half of patients with IE of longer than 6 week's duration[68] and decreases with antimicrobial therapy[69]. Although rheumatoid factor might contribute to pathogenesis by blocking IgG opsonising activity, stimulating phagocytosis or accelerating microvascular damage, it does not appear to significantly contribute to immune complex glomerulonephritis associated with IE[70]. Antinuclear antibodies also occur in IE and may contribute to the musculoskeletal manifestations, fever or pleuritic pain[71].

Immune complexes—Circulating immune complexes have been found in high titres in almost all patients with IE[72]. Deposition of immune complexes is implicated in IE-associated glomerulonephritis and may also cause some of the peripheral manifestations of IE, such as Osler's nodes (a skin manifestation of IE) and Roth spots (retinal haemorrhages). Pathologically, these lesions resemble an acute Arthus reaction, in which antigen-antibody complexes are deposited and lead to a local vasculitis, although the finding of positive culture aspirates from Osler's nodes in one series suggests that these may be septic embolic phenomena[73]. Effective treatment leads to a prompt decrease in circulating immune complexes[74] whereas therapeutic failures are characterized by rising titres of circulating immune complexes[75].

Fastidious bacteria

Some organisms, such as the obligate intracellular pathogens *C. burnetii* and *Bartonella* spp., may cause IE by different pathophysiologic mechanisms than those outlined above. In the case of *C. burnetii*, patients display a lack of macrophage activation, promoting intracellular survival of the organism and leading to the histopathologic findings of empty or foamy macrophages that are suggestive of IE associated with Q fever[76]. Specific antibodies are produced, leading to immune complex formation. Affected valves exhibit subendothelial infection with smooth, nodular vegetations that microscopically demonstrate a mixture of fibrin deposits, necrosis and fibrosis without granulomas[77].

Organ-specific pathology

As a systemic disease, IE results in characteristic pathological changes in multiple target organs (Figure 4)[78]. Portions of the platelet-fibrin matrix of the vegetation may dislodge from the infected heart valve and travel with arterial blood until lodging in a vascular bed downstream from the heart. Such septic emboli can involve almost any organ system in the body and can manifest clinically in several ways. First, if the embolus is large enough to deprive adjacent tissue of oxygen where it lodges, infarction of the dependent tissues can result. This is the pathogenetic process for embolic strokes, myocardial infarctions and infarctions of the kidney, spleen, mesentery and skin. Second, bacteria embedded within the embolus can invade local tissues and create a visceral abscess. Finally, extracardiac manifestations may also arise from immune complex deposition or from direct seeding of other tissues as a result of bacteraemia.

Cardiac manifestations—In the heart, the classic vegetation is usually in the line of closure of a valve leaflet on the atrial surface of atrioventricular valves (the mitral and tricuspid valves) or on the ventricular surface of semilunar valves (the aortic and pulmonary valves). Vegetations vary in size and can reach several centimetres in diameter. The infection may lead to perforation of a valve leaflet or rupture of the chordae tendineae, interventricular septum or papillary muscle. Valve ring abscesses with fistula formation in the myocardium or pericardial sac may result, especially with *S. aureus*. Finally, myocardial infarctions may occur as an embolic complication of IE, particularly in patients with aortic valve IE[79].

Renal manifestations—In patients with IE, the kidney may develop infarction due to emboli, abscess due to direct seeding by an embolus or an immune complex

glomerulonephritis. Renal biopsies performed during active IE are uniformly abnormal even in the absence of clinically overt renal disease[80].

Neurovascular manifestations—Mycotic aneurysms are localized enlargements of arteries caused by infection of the artery wall and may be a feature of acute IE or may be detected months to years after successful treatment[81]. These aneurysms can arise via one of several mechanisms: direct bacterial invasion of the arterial wall with subsequent abscess formation; embolic occlusion of the *vasa vasorum* (which are small vessels that supply the walls of larger vessels); or immune complex deposition with resultant injury to the arterial wall[81]. Mycotic aneurysms tend to arise at bifurcation points, most commonly in the cerebral vessels, although almost any vascular bed can be affected. Cerebral aneurysms may be symptomatic, particularly if bleeding complications arise, but they may also be discovered in patients without neurological symptoms. For example, in one prospective series, 10 of 130 consecutive patients with IE who underwent screening by cerebral MRI with angiography (a technique called magnetic resonance angiography) had clinically silent cerebral aneurysms[82]. Approximately 80% of all patients interrogated with magnetic resonance angiography in this latter study showed asymptomatic ‘microbleeds’ in small peripheral cerebral vessels; whether these microbleeds predict future risk of symptomatic intracerebral haemorrhage is unknown[83].

Neurological manifestations of IE most frequently arise from cerebral emboli. These are clinically apparent in approximately 20–30% of patients with IE. However, if MRI imaging of asymptomatic IE patients is routinely undertaken, a majority will have evidence of cerebrovascular complications[82,84]. The incidence of stroke in IE is 4.82 cases per 1,000 patient-days in the first week of IE and drops rapidly after starting antibiotics[85].

Splenic manifestations—Splenic infarcts are frequently found during autopsy of patients who died as a result of IE[86] but may also be clinically occult. Splenic abscesses tend to be clinically apparent, with pain, fever and leukocytosis. Splenomegaly is found in about 10% of contemporary IE patients in the industrialized world[4] and is more common in chronic IE (such as that caused by Q fever or VGS) than in acute cases, possibly as a consequence of prolonged immunological response.

Pulmonary manifestations—Thromboembolic showering — in which ‘showers’ of tiny emboli lodge within and occlude small vessels — can lead to the formation of septic pulmonary emboli, either with or without infarction. This phenomenon is a common complication of tricuspid valve IE or other sources of microemboli, such as central venous catheters, that are located immediately ‘upstream’ of the lungs. Pneumonia, pleural effusions or empyema often accompany septic pulmonary emboli. Although septic pulmonary emboli most commonly appear as peripheral wedge-shaped densities on chest radiographs, rounded ‘cannonball’ lesions mimicking tumours may sometimes develop[87].

Skin manifestations—Skin findings in IE include petechiae, cutaneous infarcts, Osler’s nodes and Janeway lesions. At the microscopic level, Osler’s nodes consist of arteriolar intimal proliferation with extension to venules and capillaries and may be accompanied by thrombosis and necrosis. A diffuse perivascular infiltrate composed of neutrophils and

monocytes surrounds the dermal vessels. Immune complexes may be found within the lesions. Janeway lesions are caused by septic emboli and are characterized by the presence of bacteria, neutrophils, necrosis and subcutaneous haemorrhage[88].

Ocular manifestations—Patients with IE may have Roth's spots in their eyes. These immunologic phenomena appear on funduscopic examination as retinal haemorrhages with a pale centre (Figure 4). Microscopically, they consist of fibrin-platelet plugs or lymphocytes surrounded by oedema and haemorrhage in the nerve fibre layer of the retina[89]. In addition, direct bacteraemic seeding of the eye may occur, causing endophthalmitis (that is, inflammation) involving the vitreous and/or aqueous humours[90]. Endophthalmitis is especially prevalent with *S. aureus* IE. For instance, in a prospective cohort of patients with *S. aureus* bacteraemia, 10 out of 23 (43%) patients who had IE also had ocular infection[91].

Diagnosis, screening and prevention

Diagnosis

The diagnosis of IE typically requires a combination of clinical, microbiological and echocardiography results. Historically, and as is probably still the case in resource-limited settings, IE was diagnosed clinically based on classic findings of active valvulitis (such as cardiac murmur), embolic manifestations and immunological vascular phenomena in conjunction with positive blood cultures. These manifestations were the hallmarks of subacute or chronic infections, most often in young patients with rheumatic heart disease. In the modern era in developed countries, however, IE is usually an acute disease with few of these hallmarks because the epidemiology has shifted towards healthcare-associated IE, often with early presentations due to *S. aureus*. In this context, fever is the most common presenting symptom, but is nonspecific[4]. The presence of other risk factors, such as IDU or the presence of intravascular prosthetic material, should increase the clinical suspicion for IE in a febrile patient. This clinical variability complicates efforts to identify patients with IE who would benefit from early effective antibiotics or cardiac valve surgery. The ability to reliably exclude IE is also important, both to avoid extended courses of unnecessary antibiotics and also to focus diagnostic considerations onto other possibilities.

Diagnostic techniques—Blood culture is the most important initial laboratory test in the workup of IE. Bacteraemia is usually continuous[92] and the majority of patients with IE have positive blood cultures[4]. If antibiotic therapy has been administered prior to the collection of blood cultures, the rate of positive cultures declines[93]. Modern blood culture techniques now enable isolation of most pathogens that cause IE. For this reason, practices that were traditionally used to facilitate isolation of fastidious pathogens, such as the use of specific blood culture bottles or extending incubation beyond 5 days, are no longer generally recommended[94]. In cases of suspected IE that are culture-negative[95], other microbiological testing approaches may be useful (Table 1). For example, serological testing is necessary for the diagnosis of Q fever, murine typhus[96] and psittacosis[97]. In addition, *Bartonella* can be isolated with special culture techniques[98] and serological studies may also be helpful for identifying this pathogen. Culture of valvular tissue may yield a causative organism when blood cultures are negative and microscopy for fastidious or intracellular pathogens may also

be diagnostic[76,99]. Molecular techniques to recover specific DNA or 16S ribosomal RNA from valve tissue[100] and blood or serum samples[20] have been helpful in selected cases. Other investigative techniques have been reported (Table 1) though are not widely available.

Echocardiography is the second cornerstone of diagnostic efforts and should be performed in all patients in whom IE is suspected[101,102]. Transthoracic echocardiography (TTE) may enable visualization of vegetations in many patients (Figure 5). The sensitivity of TTE is variable[103] and is highest in right-sided IE due to the proximity of the tricuspid and pulmonic valves to the chest wall. Transoesophageal echocardiography (TOE) is more sensitive than TTE for the detection of vegetations and other intracardiac manifestations of IE, especially in the setting of prosthetic valves[104]. Therefore, TTE and TOE are best seen as complementary imaging modalities. Both the 2015 European Society of Cardiology (ESC) and 2015 American Heart Association (AHA) guidelines advocate echocardiography for all cases of suspected IE and encourage TOE for cases in which TTE is negative but suspicion for IE remains. These guidelines diverge regarding TOE in patients with positive TTE results. In this setting, ESC guidelines recommend subsequent TOE in almost all cases to detect local valvular complications such as abscess or fistula. By contrast, AHA guidelines only advocate TOE for patients with a positive TTE if they are thought to be at high risk for such complications. Due to its relative convenience, TTE is often performed first, although TOE may be the appropriate initial test in a difficult imaging candidate such as an obese patient or a patient with a prosthetic valve. Additionally, the timing of echocardiography is important. Echocardiography findings may be negative early in the disease course. Thus, repeat echocardiography after several days is recommended in patients in whom initial echocardiography is negative but high suspicion for IE persists[101,102]. Intraoperative TOE can help identify local complications and is recommended in all cases of IE requiring surgery. Patients with *S. aureus* bacteraemia should undergo echocardiography because of the high frequency of IE in this setting. TTE may be adequate in a carefully selected minority of patients who do not have a permanent intracardiac device, have sterile follow-up blood cultures within 4 days after the initial set, are not haemodialysis dependent, have nosocomial acquisition of bacteraemia, do not have secondary foci of infection and do not have clinical signs of IE[105]. To differentiate patients with *S. aureus* bacteraemia who are at high risk of IE from those at low risk, several scoring systems have been proposed[106–110] although none has been prospectively evaluated.

Other imaging modalities have been evaluated for the diagnosis of IE in preliminary fashion. These include 3D TEE, cardiac CT, cardiac MRI (Figure 5 and supplementary movie) and ^{18}F-fluorodeoxyglucose PET-CT (Figure 5)[111–113]. The use of multimodality imaging is likely to increase in the future if additive benefits can be demonstrated, and the 2015 ESC guidelines have incorporated these modalities into the diagnostic algorithm of prosthetic valve IE[102].

Diagnostic criteria—The original[114] and subsequently modified Duke criteria[115] provide the current gold standard diagnostic strategy, which is both sensitive and specific for IE. The original Duke criteria were evaluated in multiple studies[116–120] from geographically and clinically diverse populations, confirming their high sensitivity and specificity.

The modified Duke criteria stratify patients with suspected IE into three categories — ‘definite’, ‘possible’ and ‘rejected’ IE — on the basis of major and/or minor criteria (Box 1). Microbiological criteria form the first major criterion, with diagnostic weight accorded to bacteraemia with pathogens that typically cause IE. For organisms with a weaker association with IE, persistently positive blood cultures are required. The second major criterion is evidence of endocardial involvement, as demonstrated by echocardiography or findings of new valvular regurgitation. Minor criteria include a predisposing heart condition or injection drug use, fever, vascular phenomena, immunological phenomena or microbiological evidence that does not meet a major criterion.

Thus, IE diagnosis cannot be made on the basis of a single symptom, sign or diagnostic test. Rather, the diagnosis requires clinical suspicion, most commonly triggered by systemic illness in a patient with risk factors, followed by evaluation according to the diagnostic schema outlined in the modified Duke criteria. It is worth keeping in mind that the Duke criteria were originally developed to facilitate epidemiological and clinical research efforts and the application of the criteria to the clinical practice setting is more difficult. The heterogeneity of patient presentations necessitates clinical judgment in addition to application of the criteria. Additionally, the criteria may be further modified as evidence accrues for new microbiological and imaging modalities. The 2015 ESC diagnostic algorithm has incorporated additional multimodal imaging (such as cardiac CT, PET-CT or leukocyte-labelled single-photon emission CT) for the challenging situation of ‘possible’ or ‘rejected’ prosthetic valve IE by modified Duke criteria, but with a persisting high level of suspicion for IE[102].

Prevention

The substantial morbidity and mortality of IE has inspired efforts to prevent its occurrence in at-risk individuals. These prevention efforts have historically focused on oral health because VGS are normal oral flora and cause approximately 20% of IE cases[16]. Based upon the assumption that dental procedures may lead to IE in patients with underlying cardiac disease, the AHA and other major society guidelines previously recommended prophylactic antibiotic therapy to prevent IE in patients with underlying cardiac conditions who underwent dental procedures[121]. More recently, however, this recommendation has come into question. There is now substantial evidence that transient bacteraemia is common with normal daily activities including tooth brushing, flossing and chewing food, and the efficacy of antimicrobial prophylaxis is unknown[25]. In a departure from previous guidance, the 2002 French IE prophylaxis guidelines were the first to dramatically reduce dental prophylaxis indications[122]. The 2007 AHA guidelines reduced the recommended scope of cardiac conditions for which dental prophylaxis is reasonable to four clinical settings: patients with prosthetic valves or valve material; patients who had previous IE; patients with a subset of congenital heart disease; and cardiac transplantation recipients who develop cardiac valvulopathy[121]. Prophylaxis is no longer recommended for gastrointestinal or genitourinary procedures. Guidelines from the ESC similarly recommended using dental prophylaxis only for those with highest risk of developing IE[102]. Recommendations of the British National Institute for Health and Clinical Excellence (NICE) were published in 2008 and were even

more restrictive, advising against IE prophylaxis for any dental, gastrointestinal, genitourinary or respiratory tract procedures[123].

Subsequent to the 2008 NICE guidelines, there was a highly significant 78.6% reduction in prescribing of antibiotic prophylaxis before dental procedures in the UK. With two years of follow-up data after guideline publication, there did not appear to be an appreciable increase in IE cases or deaths[124]. Similarly reassuring data were reported following the introduction of the revised AHA and French guidelines[16,125]. Poor adherence to the AHA guidelines, however, complicates interpretation of these results in the United States[126].

Recently, increasing concerns have accompanied the availability of longer durations of follow-up. After extending the follow-up period in England through 2013, the number of IE cases appeared to increase significantly over the projected historical trend, leading to an estimated additional 35 more cases per month than would have been expected if prior prophylaxis rates had continued[127]. The increase was seen in patients in all risk categories as defined in the AHA and ESC guidelines. This study did not contain organism-specific data, however, so it was not possible to tell whether this increase was due to VGS – which might plausibly have been prevented by dental prophylaxis – or to other pathogens such as *S. aureus*. Subsequently, in the United States, a retrospective review of 457,052 IE-related hospitalizations in the Nationwide Inpatient Sample (NIS) database suggested a similar trend, with an increase in IE hospitalization rates, both overall and among due to organisms categorized as ‘streptococcal’, after the release of the new guidelines[128]. It was noted that enterococci were included in the streptococcal category, however, and that the apparent increase in streptococcal IE might thus be due to rising enterococcal IE rates[129].

To date, at least 9 population-based studies have examined IE rates before and after guideline changes (Table 2). Taken together, these data suggest that there may be both efficacy and risk (in the form of antibiotic-related adverse events) associated with antibiotic prophylaxis. Importantly, all of the available evidence derives from observational cohorts, with imprecise microbiological data. Further, even if IE rates did increase following guideline changes, a causal relationship cannot be established. No prospective randomized controlled studies to assess the efficacy of prophylaxis have been performed, despite calls for such a trial for at least the past 25 years[130]. In a 2015 review of the prior 2008 guidelines, NICE elected not to change any of the prior recommendations and reiterated the need for a randomized trial comparing prophylaxis with no prophylaxis, including long-term follow-up for incident IE[131].

In addition to dental prophylaxis, efforts at prevention of intravascular catheter-related bacteraemia may also reduce the incidence of healthcare-associated IE. Bacteraemia rates are reduced by quality improvement interventions such as care bundles or checklists consisting of strict hand hygiene, use of full-barrier precautions during the insertion of central catheters, cleaning the skin with chlorhexidine, avoiding the femoral site if possible, and removing unnecessary catheters.[132] Confirmatory data for the impact of these interventions on IE incidence are not available.

Management

In the modern era, management of IE typically requires a multidisciplinary team including, at a minimum, an infectious disease specialist, a cardiologist and a cardiac surgeon[133]. All patients should receive antimicrobial therapy and a subset may benefit from cardiovascular surgical intervention.

General principles of antimicrobial therapy

The primary purpose of antimicrobial therapy is to eradicate infection. Several characteristics of infected vegetations pose particular challenges in this regard[55], including high bacterial density (also called the 'inoculum effect')[134], slow rates of bacterial growth in biofilms and low microorganism metabolic activity[135]. As a result, extended courses of parenteral therapy with bactericidal (or fungicidal) agents are typically required.

Duration of therapy—The duration of therapy must be sufficient to completely eradicate microorganisms within cardiac vegetations. Due to poor penetration of antibiotics into these vegetations and the slowly bactericidal properties of some of the commonly used drugs (such as vancomycin), extended courses of antibiotics are usually required. When bactericidal activity is rapid, shorter courses may be feasible. For example, combination therapy with penicillin or ceftriaxone and an aminoglycoside is synergistic for VGS-associated IE, enabling effective courses as short as two weeks for susceptible strains[101]. Right-sided vegetations tend to have lower bacterial densities and may also be amenable to shorter course therapy.

Duration of antimicrobial therapy is generally calculated from the first day on which blood cultures are negative. Blood cultures should be obtained every 24–72 hours until it is demonstrated that the bloodstream infection has cleared[101,102]. If operative valve tissue cultures are positive, an entire antimicrobial course should be considered following cardiovascular surgery.

Selection of the appropriate antimicrobial agent—Therapy should be targeted to the organism identified in blood cultures or serological studies. While awaiting microbiological results, an empiric regimen may be selected based upon epidemiologic and patient demographic features. Because most IE cases are caused by Gram-positive bacteria, vancomycin is often an appropriate empiric choice. However, other empiric agents may also be appropriate based on local microbiology and susceptibility patterns. Detailed recommendations for antimicrobial treatment of specific pathogens are comprehensively addressed in recent treatment guidelines[101,102,136]. Key points are summarized in Table 3.

Considerations for prosthetic valves and implantable cardiac devices—For native valve infective endocarditis (NVIE), treatment duration ranges from 2 weeks to 6 weeks, whereas a treatment duration of 6 weeks is usually used for prosthetic valve infective endocarditis (PVIE). The antibiotics for NVIE and PVIE are typically the same, with the exception of staphylococcal PVIE, for which the addition of rifampin and gentamicin is recommended.

Infections of cardiac implantable electronic devices (such as pacemakers and defibrillators) may occur with or without associated valvular IE[137]. Regardless of whether infection appears to involve the device lead alone (which is sometimes termed 'lead endocarditis'), the valve alone, or both, complete device and lead removal is recommended[138]. There are limited clinical data to inform the optimal duration of antibiotic therapy for cardiac device infections; at least 4–6 weeks, using the same antibiotics as for valvular IE, are recommended for lead endocarditis[138].

Organism-specific considerations

Staphylococci—The critical distinction in selecting antibiotic therapy for *S. aureus*–associated IE is whether the isolate is methicillin-resistant (MRSA) or methicillin-susceptible (MSSA). Antistaphylococcal β-lactam antibiotics are recommended whenever possible for MSSA–associated IE, as data from observational studies suggest worse outcomes for patients with MSSA bloodstream infections who are treated with vancomycin[105,139]. Whether it is necessary to use a β-lactam antibiotic as empiric therapy is unclear; small retrospective studies have suggested a potential benefit[140]. A more recent cohort study among >5000 patients with MSSA bacteraemia suggested that β-lactams are superior for definitive therapy once MSSA has been identified, but not for empiric treatment[139]. Providers might avoid prescribing β-lactams to patients with reported penicillin allergies. However, among patients with a reported penicillin allergy, most do not have a true allergy when skin testing is performed[141] and skin testing appeared cost-effective in decision analyses for treating MSSA bactaeremia[142] and IE[143].

For MRSA IE, vancomycin has historically been the antibiotic of choice and it remains a first-line therapy in treatment guidelines[101,102,136,144]. Recent reports have raised the concern that after decades of use, the vancomycin minimum inhibitory concentration (MIC) for *S. aureus* might be rising[145]. Increased vancomycin MICs, even among isolates still classified as susceptible, might be associated with worse outcomes in MRSA bacteraemia, although meta-analyses have reached different conclusions[146,147]. In a prospective cohort of 93 patients with left-sided MSSA IE who were treated with cloxacillin, high vancomycin MIC (≥1.5 mg per L) was associated with increased mortality, even though these patients did not receive vancomycin[148]. In light of this finding, it seems that a higher vancomycin MIC may be a surrogate marker for host-specific or pathogen-specific factors that lead to worse outcomes. Clinicians may consider use of an alternative antibiotic for MRSA IE with a vancomycin MIC of ≥1.5 mg per L, but data are lacking to support a mortality benefit for alternative approaches. Ultimately, the patient's clinical response should determine the continued use of vancomycin, independent of the MIC[144].

Daptomycin is FDA-approved for treatment of adults with *S. aureus* bactaeremia and right-sided IE and is an alternative to vancomycin for MRSA IE[101]. The FDA-approved dose for IE is 6 mg per kg per day, but many authorities use higher doses (such as 8–10 mg per kg per day) due to concerns for treatment-emergent resistance, which occurred in approximately 5% (7 of 120 daptomycin-treated patients) in the Phase III clinical trial comparing daptomycin to standard therapy for *S. aureus* bacteraemia and IE[149]. Daptomycin seems to be safe and effective at these higher doses[150–152].

Gentamicin is not recommended for staphylococcal NVIE[101] because it is associated with nephrotoxicity and does not have robust data to support clinical benefit[153]. Similarly, rifampin is also not recommended as an adjunct therapy for NVIE[101] because it has been associated with adverse effects[154] and prolonged bacteraemia[155] and should be avoided in staphylococcal NVIE unless there is another indication for its use, such as concurrent osteoarticular infection. For staphylococcal PVIE, weak evidence supports the use of both gentamicin and rifampin[156]. A large trial examining the role of adjunctive rifampin for *S. aureus* bacteraemia has recently completed enrollment[157].

Observational data have been reported for other antibiotic combinations. For example, ceftaroline is a cephalosporin antibiotic active against MRSA and has been used as salvage therapy for IE alone or in combination with other anti-staphylococcal antibiotics[158,159]. Other combinations have displayed *in vitro* synergy and have limited human data in MRSA bacteraemia, such as vancomycin or daptomycin paired with other β-lactams or with trimethoprim-sulfamethoxazole, daptomycin plus fosfomycin, or fosfomycin combined with β-lactams[160,161].

Recommended treatment regimens for coagulase-negative staphylococci are the same as those for *S. aureus*[101,102].

Streptococci—Standard treatment for streptococcal IE is a β-lactam antibiotic (such as penicillin, amoxicillin or ceftriaxone) for 4 weeks. The addition of an aminoglycoside may enable a shorter 2-week course of therapy when administered once daily in combination with ceftriaxone for streptococcal NVIE[101,162]. For streptococcal isolates with an increased penicillin or ceftriaxone MIC, gentamicin should be added[101].

Enterococci—From the early days of the antibiotic era, clinicians noted that penicillin worked less well for enterococci than for streptococci and combination therapy with an aminoglycoside was therefore recommended[163]. Although this has remained the standard approach, increasing rates of aminoglycoside resistance and the toxicity associated with this class of antibiotics have spurred efforts to find alternative therapeutic options.

Recent data suggest that the combination of ampicillin and ceftriaxone may be effective for IE due to ampicillin-susceptible *E. faecalis*, particularly in patients with aminoglycoside resistance, or in whom there is concern for nephrotoxicity with an aminoglycoside[164,165]. Vancomycin-resistant enterococcal IE is fortunately rare, but has been successfully treated with linezolid[166] and daptomycin[152]; If daptomycin is used, high dose therapy may be considered[101].

Other organisms—HACEK group organisms (*Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species) were historically treated with ampicillin. However, β-lactamase producing strains are increasingly problematic and susceptibility testing may fail to identify these strains[167]. Therefore, HACEK organisms should be considered ampicillin-resistant and ceftriaxone is preferred. A duration of 4 weeks of therapy is generally sufficient for these organisms[101].

IE due to non-HACEK Gram-negative bacilli is rare[18]. Consequently, optimal management strategies are not defined. Cardiac surgery combined with prolonged antibiotic therapy is considered a reasonable strategy in many cases[101].

Fungal IE is also rare but outcomes are poor. Valve surgery is often employed but this approach is not clearly associated with improved outcomes[168]. Following initial parenteral therapy with an amphotericin-based regimen or an echinocandin, indefinite azole therapy is recommended, particularly if valve surgery is not performed[169,170].

Culture-negative IE—Culture-negative IE cases are particularly challenging to manage. Although sterile blood cultures are most commonly due to patient receipt of antibiotics prior to obtaining blood cultures, they may also arise from inadequate microbiological techniques, infection with fastidious organisms or noninfectious causes of valvular vegetations such as marantic or Libman-Sacks IE. Choosing an antibiotic regimen in these cases requires balancing the need for empiric therapy for all the likely pathogens with the potential adverse effects of using multiple antibiotics. Investigation for ‘true’ culture-negative IE (that is, for uncommon pathogens that do not grow in routine blood cultures) may yield an aetiology in these cases.

Surgery

The rate of early valve replacement or repair has increased over time[4] in keeping with the prevailing opinion that surgery is a key component of the management of many complicated IE cases. The evidence base for this practice, however, is decidedly mixed. A single randomized trial demonstrated a significant reduction in the composite outcome of in-hospital deaths and embolic events with early surgery[171]. While clearly transformational, study generalizability was nonetheless questioned. Study subjects were younger, healthier and infected with less virulent pathogens (for example, VGS) than contemporary IE patients encountered in general practice[172]. For most patients with IE, recommendations for surgery are based on observational studies and expert opinion.

The principal consensus indications for valve surgery are heart failure, uncontrolled infection and prevention of embolic events in patients at high risk. Uncontrolled infection may be related to paravalvular complications, such as abscess, an enlarging vegetation or dehiscence of a prosthetic valve. In addition, uncontrolled infection may be manifested by ongoing systemic illness with persistent fevers and positive blood cultures despite appropriate antibiotic therapy. As larger left-sided vegetations are more likely to lead to embolic events, IE with a vegetation of >10 mm in length is a relative indication for surgical intervention.

The timing of cardiac surgery for patients with IE and neurovascular complications remains controversial. A large prospective cohort study of 857 patients with IE complicated by ischemic stroke without haemorrhagic conversion found that no patient benefit was gained from delaying surgery[173]. By contrast, patients with embolic stroke complicated by haemorrhagic conversion sustained higher mortality when surgery was performed within 4 weeks of the haemorrhagic event compared with later surgery (75% versus 40%, respectively)[174]. On the basis of these observational data, the AHA currently recommends

that valve surgery may be considered in patients with IE who also have stroke or subclinical cerebral emboli without delay if intracranial haemorrhage has been excluded by imaging studies and neurological damage is not severe (such as coma). In patients with major ischemic stroke or intracranial haemorrhage, AHA guidelines currently state that delaying valve surgery for at least 4 weeks is reasonable[101].

Valve surgery was traditionally recommended for difficult-to-treat pathogens such as *Pseudomonas aeruginosa*, fungal organisms and β-lactam resistant staphylococci. However, these pathogen-specific recommendations for surgery have been recently called into question in favour of an individualized decision-making approach based upon hemodynamic and structural indications[168,175].

Other adjunctive therapies

Anticoagulation—Patients with PVIE who are receiving oral anticoagulants may be at an increased risk of death from cerebral haemorrhage[176]. Antiplatelet therapies are not currently recommended for IE. A single randomized trial examined the role of 325 mg of aspirin daily for patients with IE. The incidence of embolic events was similar in between aspirin- and placebo-treated patients, and there was a non-significant increase in the rate of cerebral bleeding episodes[177]. There are several limitations to this study, however, that include dose of aspirin used and delayed initiation of aspirin. For patients with another indication for antiplatelet therapy, it may be reasonable to continue the antiplatelet agent unless bleeding complications develop. Similarly, it is not recommended to initiate anticoagulant therapy such as warfarin for the purpose of treating IE. In patients with IE who have another indication for anticoagulation therapy, such as a mechanical valve, data are contradictory on whether to continue anticoagulation during acute therapy[176,178] and bridging therapy with heparin products has not been studied.

Management of metastatic foci—Metastatic foci of infection frequently complicate IE. As with any infection, recognition of these foci of infection is important so that targeted interventions, such as drainage of abscesses or removal of infected prosthetic material, may be undertaken. This is of critical importance in patients who require valve surgery because a persistent source of infection may serve as a source from which a recently placed prosthetic valve or annuloplasty ring becomes infected[101,102]. Some metastatic foci, such as vertebral osteomyelitis, may require additional antibiotic therapy beyond what is typically indicated for IE[179]. There is currently insufficient evidence to recommend specific imaging strategies to look for metastatic foci in all patients with IE.

Care at completion of therapy

Most patients with IE in the modern era are cured and attention can eventually turn to a follow-up plan. Elements of follow-up may include an echocardiogram at the completion of antimicrobial therapy to establish a new baseline for subsequent comparison, referral to a drug cessation program for patients who are IDUs and a thorough dental evaluation. A comprehensive search for the initial portal of pathogen entry may be undertaken so that this can be addressed to minimize repeat episodes of IE. In a prospective single centre experience, a systematic search revealed the likely source in 74% of 318 patients[180]. Routine

blood cultures at completion of antibiotic therapy are not recommended given a very low rate of positivity in patients with no signs of active infection. Patients should also be monitored for complications of IE, including relapse, incident heart failure and complications of antibiotic therapy, such as audiologic toxicity from aminoglycosides or incident *Clostridium difficile* infection.

Quality of Life

In addition to the stress associated with being diagnosed with a potentially lethal infection, patients with IE routinely experience prolonged hospitalizations and adverse reactions to treatment, and undergo multiple invasive procedures. For instance, treatment for left-sided IE requires extended courses of intravenous antibiotics, which involves long-term venous access and probably erodes patient quality of life (QOL). To what extent these factors may impair patients' QOL after they are discharged from the hospital is not well known, as only a few studies have addressed these issues[181–183]. In addition, life-threatening illness may cause posttraumatic stress disorder (PTSD), which has been shown to impair patient well-being in survivors of various life-threatening infectious diseases.

In one study of QOL in survivors of left-sided native valve IE, 55 of 86 eligible adults completed questionnaires 3 and 12 months after discharge from hospital and 12 more patients completed the 12-month questionnaires only. The health-related QOL was measured using the SF-36 and the PTSD questionnaires. In this study, 41 of 55 patients (75%) and 36 of 67 patients (54%) still had physical symptoms 3 and 12 months after the end of antimicrobial treatment, respectively. The most prevalent symptoms were weakness of the limbs (51%), fatigue (47%) and concentration disorders (35%). One year after discharge, 7 of 64 patients (11%) were still suffering from PTSD. The 37 patients who were ≤60 years old at the time of IE were questioned about their employment status. Before IE, 30 (81%) patients were employed and working. At 3 and 12 months, 16 of 31(52%) and 24 of 37 (65%) patients were working again, respectively[182]. Given the low number of patients evaluated, the effect of factors such as causative microorganisms or valve surgery on QOL and on the rate of PTSD could not be assessed. In one study conducted in patients without IE who had undergone mitral valve surgery, the type of surgery (replacement versus repair) had no impact on patients' QOL[184].

Whether a comprehensive cardiac rehabilitation programme (which typically involves exercise and information sessions) may improve QOL of patients surviving IE is currently being explored through a randomized clinical trial, the CopenHeart$_{IE}$ study[185] in which 150 patients treated for left-sided (native or prosthetic valve) or cardiac device IE will be randomized to either cardiac rehabilitation or usual care[186].

In a qualitative evaluation of 11 patients recovering from IE, Rasmussen *et al.* described the innovative concept of 'insufficient living'[187]. Some patients described an 'altered life' period as a phase of adaptation to a new life situation, which some perceived as manageable and temporary, whereas others found extremely distressing and prolonged. Patients also described a 'shocking weakness' feeling that was experienced physically, cognitively and emotionally. These feelings subsided quickly for a few, whereas most patients experienced a

persisting weakness and felt frustrated about the prolonged recovery phase. Finally, patients expressed that support from relatives and healthcare professionals, as well as one's own actions, were important in facilitating recovery. This original study emphasized the need for research in follow-up care to support patients' ability to cope with potential physical and psycho-emotional consequences of IE[187].

Given the scarcity of data on the subject, future studies are needed to define the effect of IE on patient QOL. Potential priorities for future research in IE QOL are listed in Box 2.

Outlook

Treatment

Future treatments for IE will emphasize pragmatism. For example, an effective treatment strategy for left-sided IE that avoids long-term venous access would be an important advance. At least two randomized clinical trials are testing the effectiveness and safety of replacing part of the standard intravenous antibiotic course with a 'step-down' strategy to oral antibiotics[188]. In addition, two newly approved antistaphylococcal antibiotics — dalbavancin and oritavancin — might eventually represent alternatives to the current standard intravenous treatment strategies for IE.

Along these lines, the Partial Oral Treatment of Endocarditis (POET) study uses a noninferiority, multicentre, prospective, randomized, open-label study design to test the hypothesis that partial oral antibiotic treatment is as safe and effective as parenteral therapy in left-sided IE[188,189]. A total of 400 stable patients with streptococcal, staphylococcal or enterococcal aortic or mitral IE will be randomized to receive a full 4–6 weeks of intravenous antibiotics or to receive oral antibiotics after a minimum of 10 days of parenteral therapy. Patients will be followed up for 6 months after completion of antibiotic therapy. The primary end point is a composite of all-cause mortality, unplanned cardiac surgery, embolic events and relapse of positive blood cultures with the primary pathogen. A non-inferiority margin of 10% is proposed.

The RODEO study, using the same primary end point, will also evaluate the impact of switching to oral therapy for left-sided IE[189]. In this study, 324 subjects with IE due to MSSA will receive at least 10 days of intravenous antibiotic therapy, then will be randomised to complete a full 4–6 weeks of intravenous therapy or to receive oral levofloxacin and rifampin for at least 14 additional days.

Dalbavancin and oritavancin, lipoglycopeptide-class antibiotics that were approved in 2014 by the Food and Drug Agency for the treatment of acute bacterial skin and skin structure infections (ABSSSI), represent potential improvements to our current options of intravenous therapy for IE. An important property is their extremely long half-life, estimated to be from 10–14 days[190,191], which allows infrequent administration. Dalbavancin is FDA approved for the treatment of ABSSSI using a single 1500 mg dose or with a two dose strategy: a 1 gm loading dose on day 1 followed by a 500 mg infusion one week later[192,193]. Oritavancin is approved for the treatment of ABSSSI as a single 3 hour infusion of 1200 mg[194]. These dosing strategies might ultimately avoid the need for home health or skilled nursing facility

care for outpatient intravenous antibiotics. Although no data are currently available for the efficacy of such treatment strategies in IE, the pharmacokinetics of dalbavancin dosed 1,000 mg of dalbavancin on day 1 followed by 500 mg weekly for seven additional weeks appeared favourable in one Phase I study[190]. In addition, dalbavancin was studied in catheter-associated blood stream infection[195]. Therapies not requiring extended intravenous access, such as dalbavancin or oritavancin, could be especially advantageous in treating IE in patients with IDU or who have limited options for intravascular line placement.

Vaccines to prevent common bacterial causes of IE

The best way to treat IE is to prevent it. Although most efforts to date on IE prevention have focused on infection control and dental prophylaxis, considerable resources have also been invested in vaccine development targeting common bacterial causes of IE. Success has been mixed and none of these agents is currently commercially available. Nonetheless, future prevention strategies for some causes of IE are likely to include vaccines. Although vaccine candidates for pathogens such as VGS[196] and *C. albicans*[197] have been evaluated in animal models, human studies in vaccines targeting causes of IE have been primarily limited to *P. aeruginosa*, Group B streptococcus and *S. aureus*.

Passive immunization strategies for staphylococcal infections—At least 10 studies have tested vaccines or immunotherapeutics for the prevention or treatment of *S. aureus* infections, including bacteraemia (Table 6). Efforts to date have pursued two approaches: passive immunization with existing antibodies or active immunization by stimulating a host antibody response in a classical vaccine design. Two passive immunization strategies have been attempted: treatment of active staphylococcal infections as an adjunct in addition to standard treatment; and prevention of staphylococcal infections in patients deemed to be at high risk of developing infection. Each approach has strengths and limitations. Treatment strategies provide the design advantage of a relatively small sample size and relative ease of enrolment due to provision of standard of care treatment in both arms, but will require demonstrating superiority over standard of care therapy for FDA approval. Although three immunotherapeutic compounds to date have been evaluated as treatment adjuncts in patients with *S. aureus* infection, none has demonstrated efficacy. A fourth compound, 514G3, is currently undergoing evaluation in a Phase II safety and efficacy study in hospitalized patients with *S. aureus* bacteraemia[198].

Three passive immunotherapeutic compounds have undergone clinical trials to prevent staphylococcal infections (aimed at both *S. aureus* and *Staphylococcus epidermidis*) in neonates. None exhibited significant protection. Pagibaximab, a humanized murine chimeric monoclonal antibody that targets lipoteichoic acid in the cell wall of *S. aureus*, showed an encouraging trend in outcomes in the Phase II study but no significant protective effect in the registrational trial.

Active immunization strategies for staphylococcal infections—Two *S. aureus* vaccine candidates have been evaluated in Phase III clinical trials as active immunizations for *S. aureus*. A third registrational trial is underway[199]. All three trials focus on specific adult populations at high risk for *S. aureus* infection, including those undergoing

haemodialysis (in the Staphvax vaccine trial), cardiac surgery (in the V710 vaccine trial) and spinal surgery (the SA4Ag vaccine trial).

Staphvax is a bivalent vaccine of capsular proteins 5 and 8 that was tested in 1804 haemodialysis patients with a primary fistula or synthetic graft vascular access. Although receipt of Staphvax was associated with a statistically significant reduction in rates of *S. aureus* bacteraemia at 40 weeks post vaccination (efficacy 57%; p = 0.02), the study failed to demonstrate significantly reduced rates of *S. aureus* bacteraemia at the prespecified endpoint of 54 weeks post-vaccination[200]. Therefore, a second trial of Staphvax in 3600 haemodialysis patients was undertaken. In this second study, the primary efficacy endpoint was set at 6 months. Unfortunately, this unpublished trial also failed to demonstrate protection against development of *S. aureus* bacteraemia.

V710 is a vaccine targeting the cell wall-constitutive iron regulatory protein IsdB that tested in patients undergoing median sternotomy. The study was terminated after approximately 8000 patients were enrolled due to lack of efficacy and also a higher rate of multiorgan system failure–related deaths among patients who received V710. In *post hoc* analyses, patients that received V710 and subsequently became infected with *S. aureus* were approximately 5 times more likely to die than patients that received control and then became infected with *S. aureus* (23.0 vs 4.2 per 100 person-years)[150]. The reason for this increased mortality is unknown.

A Phase IIb study of the SA4Ag vaccine has been initiated. This study seeks to test the efficacy and safety of a vaccine targeting *S. aureus* infection in patients undergoing elective posterior instrumented lumbar spinal fusion surgery[199]. Unlike previous *S. aureus* vaccine approaches, this candidate vaccine includes four epitopes: ClfA, MntC and capsular polysaccharides 5 and 8.

At least two other *S. aureus* vaccine candidates are in late pre-clinical development. Candidate vaccine NDV-3 contains the N-terminal portion of the *C. albicans* agglutinin-like sequence 3 protein (Als3p) formulated with an aluminium hydroxide adjuvant. Preclinical studies demonstrated that the Als3p vaccine antigen protects mice from both mucocutaneous and intravenous challenge with both *C. albicans*[197] and *S. aureus*[201]. The vaccine has been shown to be safe and immunogenic in healthy adults[202] Most recently, a multi-subunit vaccine that targets five known *S. aureus* virulence determinants — α-haemolysin (Hla), ess extracellular A (EsxA), ess extracellular B (EsxB), and surface proteins ferric hydroxamate uptake D2 and conserved staphylococcal antigen 1A — was described. When formulated with a novel Toll-like receptor 7-dependent agonist, the five antigens provided high levels of Th1-driven protection against *S. aureus* in animal models[203].

Conclusions

Although much has changed since Osler elucidated its fundamental disease mechanisms in the late 1800s, IE remains a disease of high morbidity and mortality with far-reaching effects on the QOL of survivors. In the near term, the epidemiology will continue to reflect the epidemiological and microbiological effect of healthcare contact. Improved algorithms for diagnosis of IE will incorporate new microbiological techniques, especially for blood-

culture negative cases. We can safely assume that imaging technology will continue to advance and further research is needed to define which patients with suspected IE should undergo TOE and which patients may benefit from newer imaging modalities. Novel Gram-positive antibiotics are promising but as yet untested in IE. If proven to be effective, they might enable simpler and more patient-friendly treatment regimens. It is likely that the debate around IE prophylaxis will continue until prophylaxis strategies are compared prospectively. Vaccine development has not yet yielded an effective and commercially available product, but numerous candidates are in the pipeline.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1

Modified Duke Criteria for the diagnosis of infective endocarditis

Major clinical criteria

Blood culture positivity for either of the following:

- Typical microorganism (viridans group streptococci, *S. gallolyticus*, HACEK organisms, *S. aureus*, community-acquired enterococci in the absence of a primary focus) from 2 separate blood cultures
- Persistent bactaeremia (two positive cultures >12 hours apart or three positive cultures or a majority of ≥4 culture positive results >1 hour apart)

Either of the following forms of evidence for endocardial involvement:

- Echocardiographic findings of mobile mass attached to valve or valve apparatus, abscess, or new partial dehiscence of prosthetic valve*
- New valvular regurgitation

Serology:

- Single positive blood culture for *C. burnetii* or antiphase 1 IgG antibody titre of ≥1:800

Minor clinical criteria

Predisposing condition:

- Intravenous drug use
- Predisposing cardiac condition

Vascular phenomena:

- Arterial embolism
- Septic pulmonary emboli
- Mycotic aneurysm
- Intracranial haemorrhage
- Conjunctival haemorrhages
- Janeway’s lesions

Application of criteria

Definite IE is defined by either:

- Pathologically proven IE

- Fulfilment of clinical criteria: either two major criteria, one major and three minor criteria or five minor criteria

Possible IE is defined by either:

- One major and one minor clinical criterion
- Three minor clinical criteria

Rejected IE is defined by any of the following:

- Firm alternative diagnosis
- Resolution of IE syndrome with antibiotic therapy for ≤4 days
- No pathologic evidence of IE at surgery or autopsy with antibiotic therapy ≤4 days
- Does not meet criteria for possible IE

*The 2015 ESC diagnostic algorithm has incorporated additional multimodal imaging (such as cardiac CT, PET-CT or leucocytes labeled single photon emission CT) for the evaluation of ‘possible’ or ‘rejected’ prosthetic IE by modified Duke criteria, but with a persisting high level of suspicion for IE[102]

Adapted from Li et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis.* 2000;30:633–638.[115]

HACEK, *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species; IE, infective endocarditis

Box 2

Priorities for quality of life research in endocarditis

- Engage patient networks and advocacy groups for input on priorities in infective endocarditis (IE) research
- Develop a validated quality of life (QOL) score for IE
- Add QOL measures to data that is routinely collected in prospective cohorts of patients with IE
- Test interventions aimed at improving QOL in IE, such as cardiac rehabilitation[186]

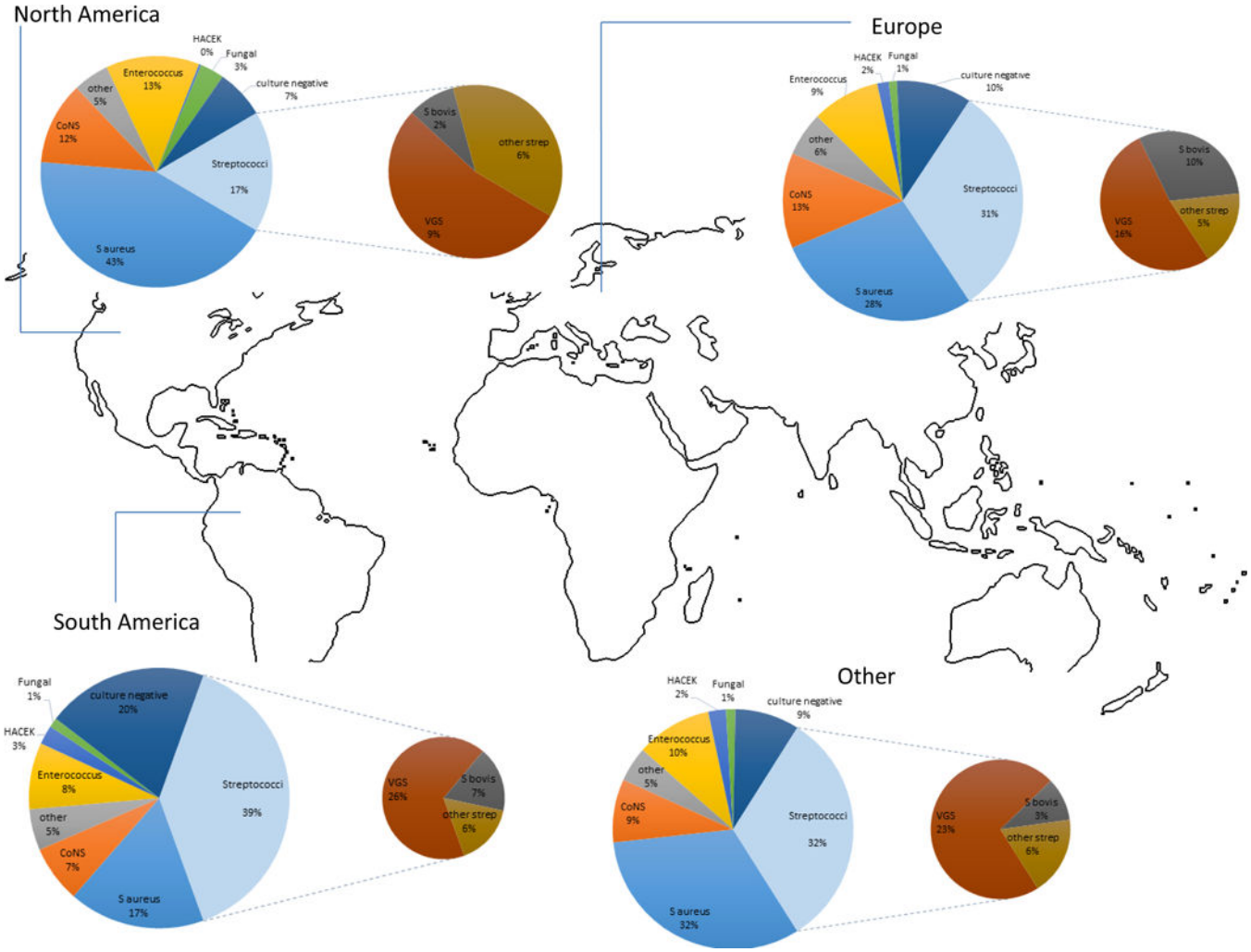

Figure 1. Global epidemiology of causative pathogens involved in endocarditis

The causative agents of infective endocarditis differ geographically. Data derived from Murdoch et al[4]. CoNS, Coagulase-negative staphylococci; HACEK, *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species; Strep, streptococcal species; VGS, viridans group streptococci.

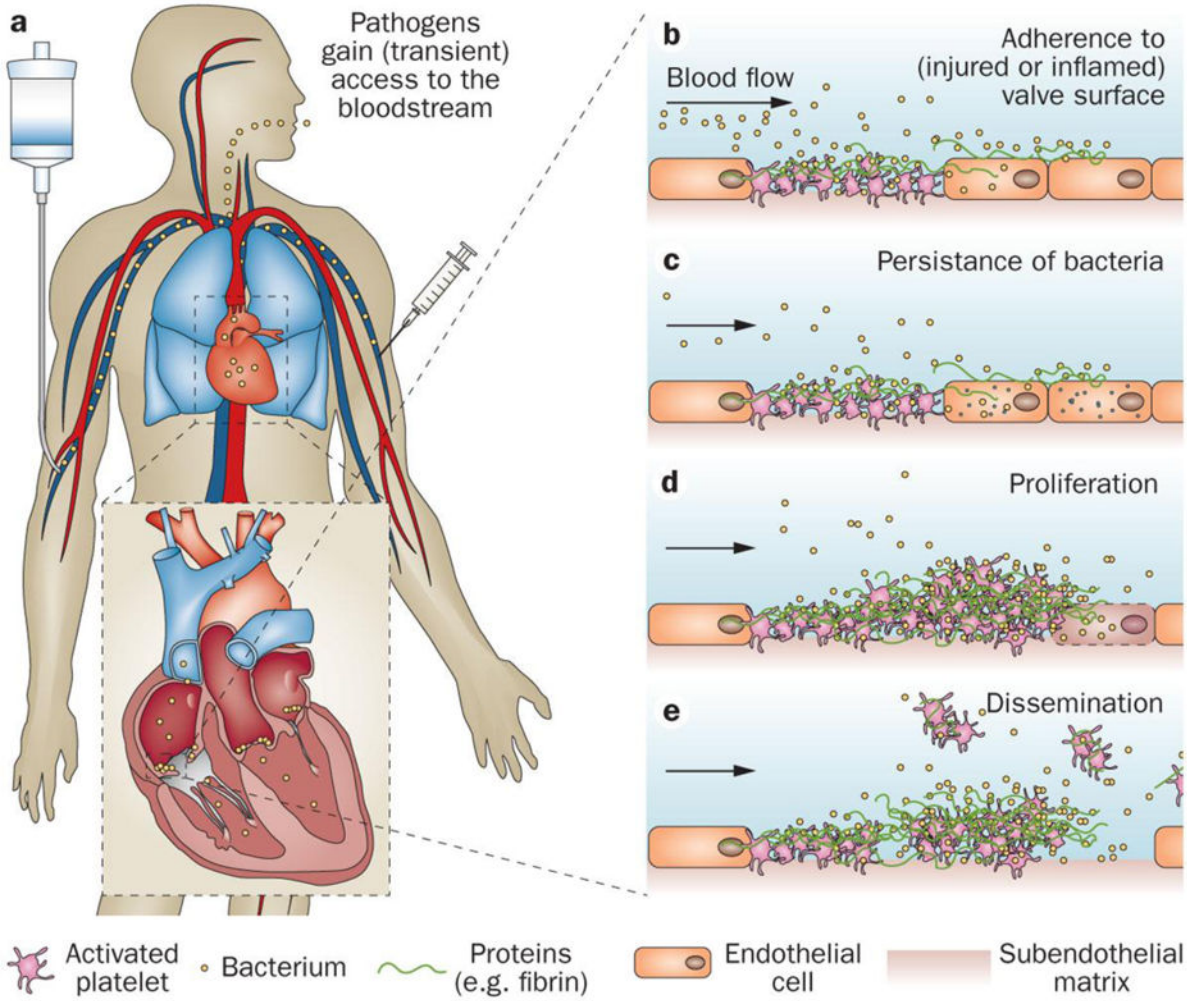

Figure 2. Pathogenesis of endocarditis

a. Pathogens gain access to the bloodstream, for example via an intravenous catheter, injection drug use or from a dental source. b Pathogens adhere to an area of abnormal cardiac valve surface. c Some pathogens, such as *S. aureus*, obtain intracellular access to the valve endothelium. d The infected vegetation is created by burying of the proliferating organism within a protective matrix of serum molecules. e –Vegetation particles can detach and disseminate to form emboli. These may lead to complications such as ischemic stroke, mycotic aneurysms and infarcts or abscesses at remote sites. Figure adapted from Werdan et al. Mechanisms of infective endocarditis: pathogen-host interaction and risk states. *Nat Rev Cardiol*. 2014;11:35–50[204].

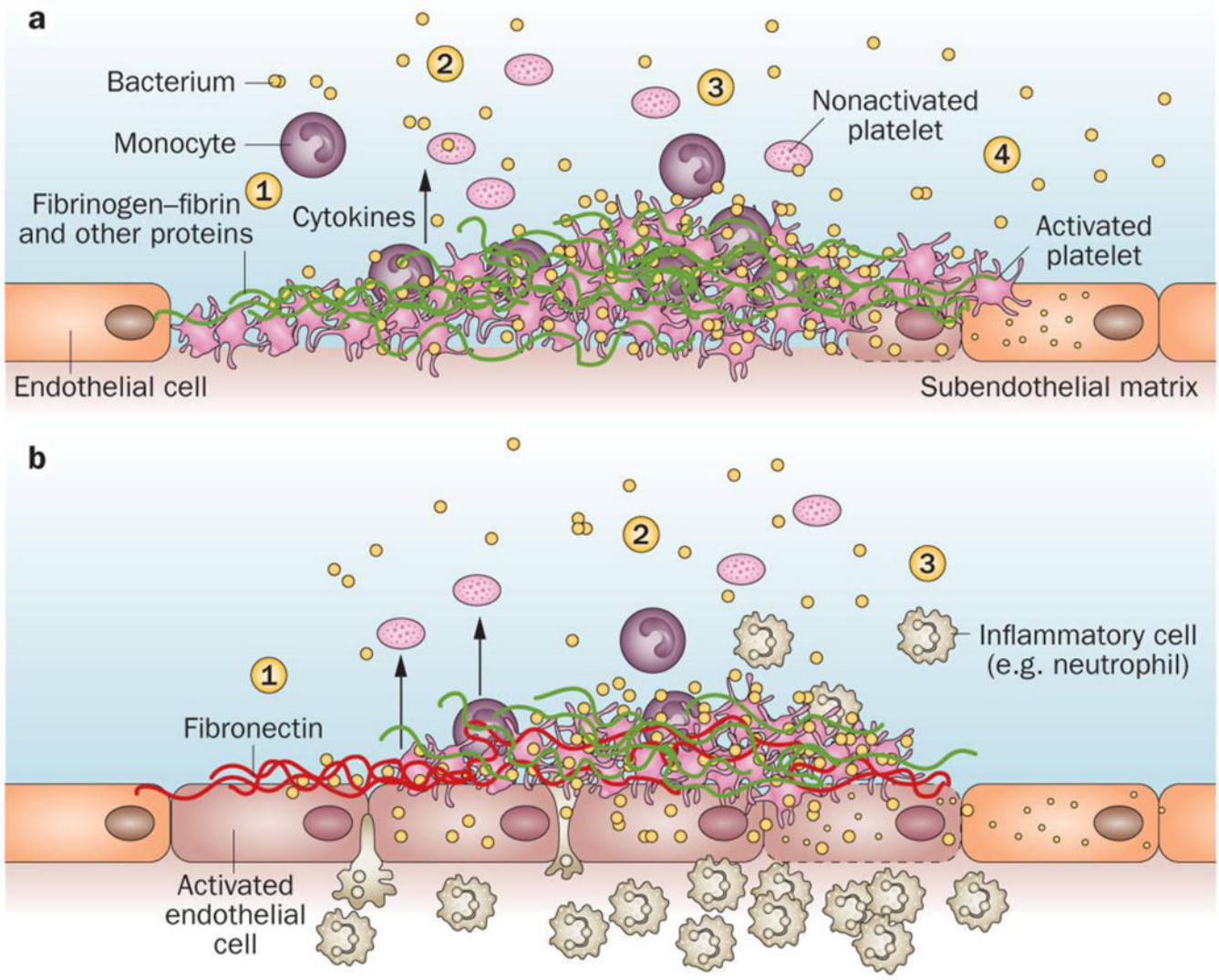

Figure 3. Mechanisms of infective endocarditis

a Valve colonization as a consequence of mechanical injury. 1) Nonbacterial thrombotic endocarditis. 2) Bacteria bind to coagulum and colonize it during transient bacteraemia. Adhered monocytes release tissue factor and cytokines. 3) More platelets are attracted and become activated and the vegetation grows. 4) Endothelial cells are infected and can be lysed by bacterial products, or bacteria can persist inside the cells. b Valve colonization as a consequence of an inflammatory endothelial lesion. 1) Activated endothelial cells express integrins that promote the local deposition of fibronectin; bacteria such as *S. aureus* adhere to this protein. 2) Bacteria are internalized and endothelial cells release tissue factor and cytokines, causing blood clotting and promoting the extension of inflammation and vegetation formation. 3) Infected endothelial cells can be lysed by bacterial products or bacteria can persist inside the cells. Figure adapted from Werdan et al. Mechanisms of infective endocarditis: pathogen-host interaction and risk states. *Nat Rev Cardiol.* 2014;11:35–50.[204]

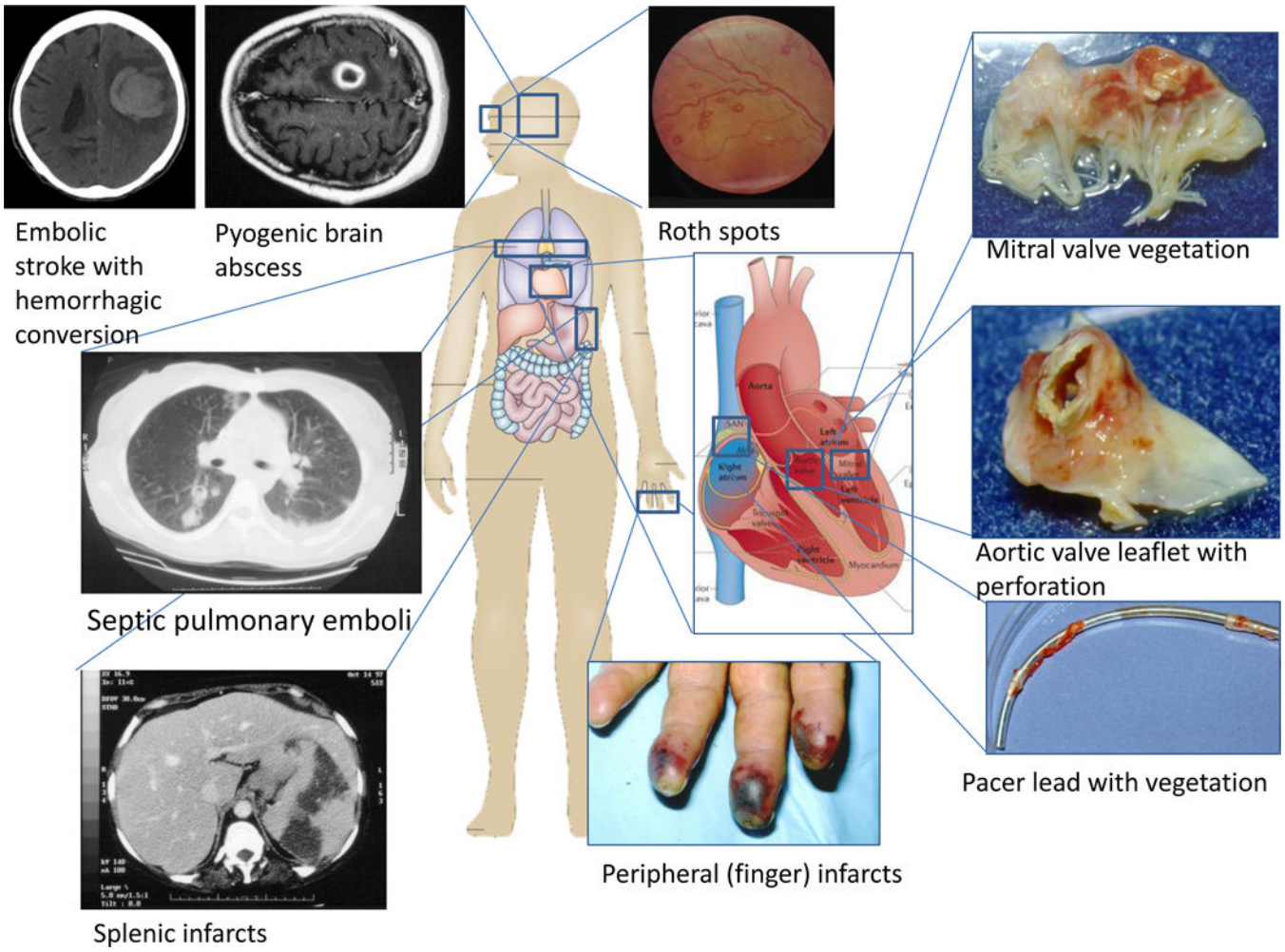

Figure 4. End-organ manifestations of endocarditis

A) CT scans of pyogenic brain abscess and embolic stroke with haemorrhagic conversion. B) CT scan demonstrating multiple septic pulmonary emboli. C) CT scan demonstrating peripheral wedge-shaped splenic infarcts. D) Roth spots on funduscopic exam. E) Infarcts affecting multiple fingers. F) Explanted mitral valve with vegetation. G) Explanted aortic valve leaflet with vegetation and perforation. H) Pacemaker lead with vegetation. Roth spots photo courtesy of Walter B. Holland, MD.

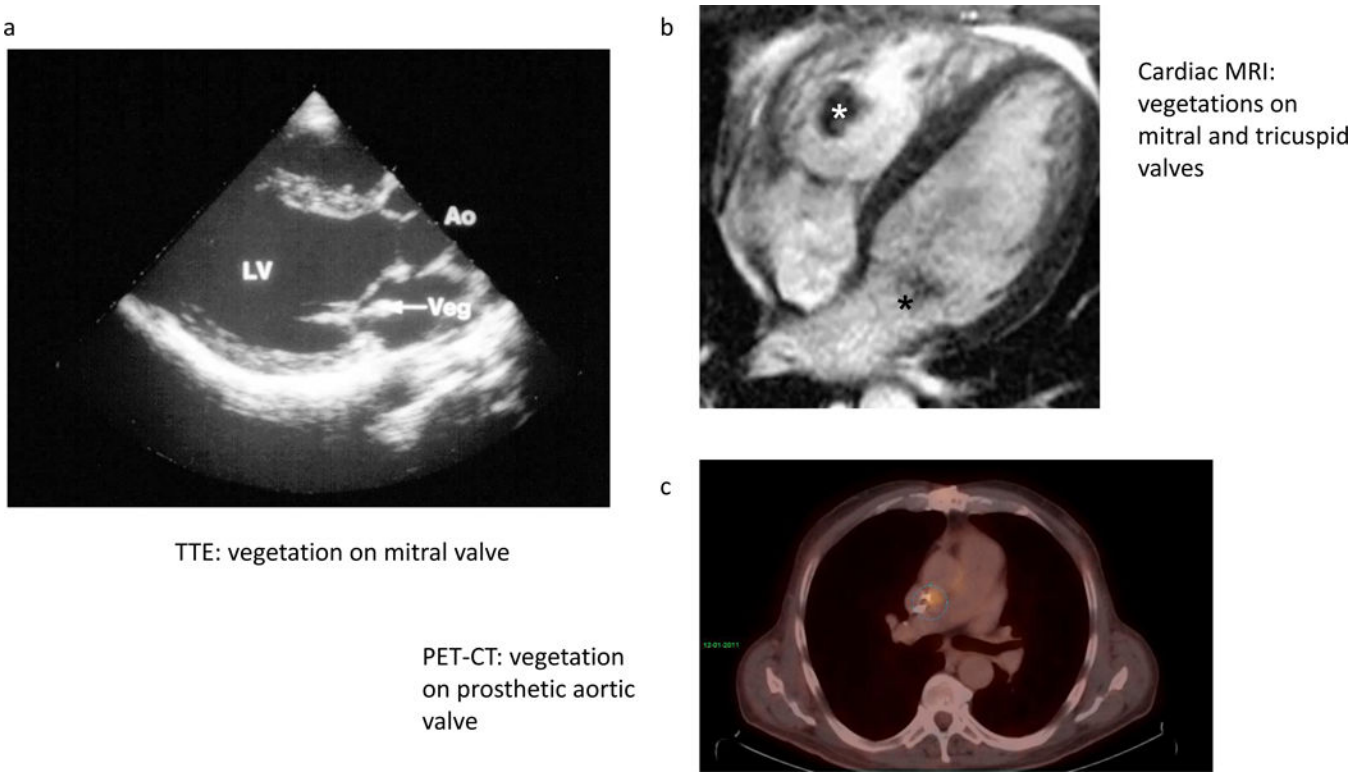

Figure 5. Imaging modalities for diagnosis of endocarditis

a Transthoracic echocardiography demonstrating native mitral valve vegetation. b Cardiac MRI, systolic frame demonstrating vegetations in the sub-tricuspid valve chordal apparatus with adherent thrombus (white asterisk) and posterior mitral valve leaflet (black asterisk). c PET-CT – In this patient, infection of a prosthetic aortic valve was suspected but echocardiography was inconclusive. Using PET-CT, inflammatory leukocytes are visualized after taking up radiolabeled glucose, demonstrating an area of active infection on the aortic valve. Ao, aorta; LV, left ventricle; Veg, vegetation. Pacemaker lead images courtesy of Gail Peterson, MD.

Table 1

Diagnostic options for blood culture-negative infective endocarditis

Technique	Description	Pathogens identified	Limitations
Serology[20,94]	Detection of serum antibodies to specific pathogens may identify causative agents	*C. burnetii*[*], *Bartonella* spp, *Chlamydophila* spp, *Brucella* spp, *Mycoplasma* spp and *Legionella pneumophila*	Cross-reactions limit interpretability of *Bartonella* and *Chlamydia* species; IE due to *Mycoplasma* and *Legionella* are very rare
Histopathology[77,205]	Enhanced examination of resected valves, such as by using special stains (for example, Warthin-Starry stain for *Bartonella* spp. or Periodic acid-Schiff stain for *T. whipplei*)	Streptococci, staphylococci, *Bartonella* spp, *T. whipplei, C. burnetii* and fungi	Requires an experienced microbiologist
Polymerase chain reaction (PCR)[20,205,206]	Amplification of 16S ribosomal DNA for bacteria or 18S ribosomal DNA for fungi, which can then be sequenced for pathogen identification	Streptococci, staphylococci, *Bartonella* spp, *T. whipplei* and *C. burnetii*	Low sensitivity on blood samples; requires cardiac valve tissue
Immunohistology[205]	Specific monoclonal or polyclonal antibodies may enable antigen detection in valve tissue	*Bartonella* spp, *T. whipplei* and *C. burnetii*	Unknown sensitivity and specificity; use is limited to specialized laboratories
Autoimmunohistochemistry[207]	Uses a peroxidase-based method with patient's own serum as source of antibodies against specific pathogens in valve-tissue specimens	*Bartonella* spp, *T. whipplei* and *C. burnetii*	Reported in single publication from a specialized laboratory
Metagenomic analysis[208]	DNA is extracted from resected valve and then 'next-generation' sequencing is used to identify bacterial genome fragments	Case reports for *E. faecalis, S. mutans, S. sanguinis*; in theory could identify broad range of bacteria, fungi, and viruses	Reported in very limited fashion thus far; should be considered exploratory only
Host gene signatures[209,210]	Analysis of host inflammatory response, which may be unique for specific pathogens	*S. aureus*	Technique in development; has not been used to make a clinical infective endocarditis diagnosis

[*] Serology for *C. burnetii* is included in the modified Duke criteria

Table 2

Population-based studies of infective endocarditis before and after guideline changes

Author	Study Years	Country	Population	Results
Dayer *et al.*[127]	2000–2103	England	English hospital discharge records	Increased incidence of IE within 3 months since 2008 NICE IE prevention guidelines
DeSimone *et al.*[211]	1999–2010	United States	Adults, Olmsted County, Minnesota, NIS database	No increase in VGS-associated IE incidence before and after 2007 AHA IE prevention guidelines
Thornhill *et al.*[124]	2000–2010	England	English hospital discharge records	No significant change in the upward trend in IE cases due to oral streptococci; 78.6% reduction in antibiotic prophylaxis prescriptions
Duval *et al.*[16]	1991, 1999, 2008	France	11 million patients aged ≥20	No increase in VGS-IE incidence since 2002 French IE prophylaxis guidelines
Bikdeli *et al.*[212]	1999–2010	United States	US Medicare beneficiaries aged ≥65	No increase in rates of hospitalization after 2007 AHA IE prevention guidelines
Pasquali *et al.*[125]	2003–2010	United States	Paediatric Health Information Systems Database	No increase in IE admission in US children's hospitals (n=37) following 2007 AHA IE prevention guidelines
DeSimone *et al.*[213]	1999–2013	United States	Adults, Olmsted County, Minnesota, NIS database	No increase in streptococcal IE incidence
Pant *et al.*[128]	2000–2011	United States	NIS database	Increase in streptococcal IE incidence, however enterococci and streptococci other than VGS included in the streptococcal category, and may reflect a rise in these entities, rather than VGS
Mackie *et al.*[214]	2002–2013	Canada	Canadian Institute for Health Information Discharge database	The streptococcal IE hospitalization rate was not affected after the 2007 AHA guidelines

AHA, American Heart Association; IE, infective endocarditis; NICE, National Institute for Health and Care Excellence; NIS, Nationwide Inpatient Sample; VGS, viridans group streptococci.

Adapted from DeSimone et al..[213]

Table 3

Pathogen-specific therapy of infective endocarditis

Pathogen	Regimen(s)	Comments
Penicillin-susceptible (MIC ≤0.12 mcg per ml) viridans streptococci and *S. bovis*	Penicillin	Adverse effects include hypersensitivity and seizures
	Ceftriaxone	Generally well tolerated, once daily administration may enable outpatient therapy
	Penicillin (or ceftriaxone) + gentamicin	Addition of an aminoglycoside enables a shorter treatment duration (2 weeks vs 4 weeks) at the expense of potential aminoglycoside adverse effects (renal, vestibular and cochlear toxicity)
	Vancomycin	Use should be limited to those with true penicillin allergy
Penicillin-intermediate (MIC >0.12 and ≤0.5 mcg per ml) viridans streptococci	Penicillin (or ceftriaxone) + gentamicin	4 weeks of therapy recommended
	Vancomycin	For penicillin-allergic patients or to avoid gentamicin
Enterococci and penicillin-resistant (MIC >0.5 mcg per ml) viridans streptococci	Penicillin (or ampicillin) + gentamicin	Extended therapy (6 weeks) recommended for prosthetic valves and prolonged duration of symptoms prior to diagnosis
	Ampicillin + ceftriaxone	Favoured in patients with renal insufficiency or high-level aminoglycoside resistance
	Vancomycin + gentamicin	Nephrotoxic regimen; role of gentamicin is uncertain
	Daptomycin	For vancomycin-resistant and penicillin-resistant enterococci; may combine with β-lactam
	Linezolid	May be used for vancomycin- and penicillin-resistant enterococci, although adverse events including bone marrow suppression and neuropathy are of concern with extended treatment courses
Staphylococci	Nafcillin	For MSSA; adverse effects include rash, interstitial nephritis
	Cefazolin	For MSSA; better tolerated than nafcillin
	Vancomycin	For MRSA
	Nafcillin + gentamicin	2 week regimen for IV drug users with uncomplicated right-sided IE*
	Nafcillin + gentamicin + rifampin	For prosthetic valve IE; substitute vancomycin for nafcillin in patients with MRSA
	Daptomycin	FDA-approved for right-sided *S. aureus* IE; observational data supports use in left-sided IE as well; may combine with β-lactam
HACEK strains	Ceftriaxone	Effective for β-lactamase producing strains
	Ampicillin/sulbactam	For β-lactamase producing strains
	Ciprofloxacin	For patients intolerant of β-lactam therapy
Enterobacteriaceae	Extended-spectrum penicillin or cephalosporin + aminoglycoside (or fluoroquinolone)	Rare cause of IE and may require a tailored approach depending on the pathogen
Pseudomonas aeruginosa	An anti-pseudomonal β-lactam (such as ticarcillin, piperacillin, ceftazidime, cefepime or imipenem) + tobramycin (or fluoroquinolone)	Typically requires prolonged therapy and valve surgery
Fungi	Parenteral antifungal agent (most commonly an amphotericin product)	Long-term suppressive therapy with an oral antifungal agent is often required

*defined as IE involving only the tricuspid valve, with no renal insufficiency and no extrapulmonary infection.

FDA, Food and Drug Administration; HACEK, *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella* species; IE, infective endocarditis; IV, intravenous; MIC, Minimum inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus.*

Table 4

Candidate vaccines for prevention of invasive *S. aureus* infections

Compound	Product	Phase (status)	Study design	Results
Passive immunization (treatment of *S. aureus* bacteremia)				
Tefibazumab[215]	Humanized monoclonal anti-clumping factor A antibodies	Phase II (completed)	Randomized, double-blind, placebo-controlled trial of standard treatment plus either tefibazumab or placebo (n=63)	No differences in adverse events or rate of death, relapse or complications
Altastaph[216]	Pooled human anti-capsular polysaccharide (CP) types 5 and 8 antibodies	Phase II (completed)	Randomized, double-blind, placebo-controlled trial of standard treatment plus Altastaph or placebo for *S. aureus* bacteraemia in adults (n=40)	No significant mortality difference; shorter length of stay in Altastaph vs placebo (9d vs. 14d; p=0.03)
Aurograb (not published in a peer-reviewed journal)	Single-chain antibody variable fragment against ABC transporter component GrfA	Phase II (completed)	Unpublished by sponsor	Addition of Aurograb to standard therapy for life-threatening staphylococcal infections failed to show efficacy
514G3[198]	Human monoclonal antibody (target antigen not disclosed)	Phase I–II (currently enrolling)	Study of the safety and efficacy of a true human antibody (derived from a natural human immune response), 514G3, in patients hospitalized with bacteraemia due to *S. aureus*	Phase I of the study will include a single dose of 514G3 at three different dose levels. The Phase II study will use a single dose of 514G3 at the highest dose level. Standard antibiotic therapies will be used in both phases.
Passive immunization (prevention)				
Altastaph[217]	Polyclonal human IgG to capsular polysaccharides 5 and 8	Phase II (completed)	Randomized, double-blind, placebo-controlled trial of Altastaph or placebo for prevention of nosocomial *S. aureus* infections in very low birth weight babies (n=206)	High levels of antibodies; No difference in the rate of invasive *S. aureus* infection (3 cases of *S. aureus* bacteremia in each group)
Veronate[218]	Pooled human IgG to clumping factor A (ClfA) (*S. aureus*) and serine-aspartate dipeptide G (SdrG) (*S. epidermidis*)	Phase III (completed)	Double-blind, placebo-controlled trial of INH-21 (Veronate) vs placebo for prevention of staphylococcal late-onset sepsis in infants with birth weights 500 to 1250g (n=1983)	No difference in staphylococcal late-onset sepsis (5% INH-21 vs 6% placebo; p=0.34)
Pagibaximab[219]	Humanized mouse chimeric monoclonal antibody against lipoteichoic acid	Phase II (completed)	Randomized, double-blind, placebo-controlled dose ranging study for prevention of staphylococcal infection in patients with birth weight between 700–1300 g (n=88)	Definite staphylococcal sepsis occurred in 0% (90 mg per kg), 20% (60 mg per kg) and 13% (placebo) (P=0.11). Findings not confirmed in Phase III trial[220] (not published)
Active Immunization				
StaphVax[200]	Bivalent vaccine of capsular polyasaccharides 5 and 8 conjugated individually to recombinant exoprotein A	Phase III (completed)	Randomized, double-blind, placebo controlled trial of StaphVax in prevention of *S. aureus* bacteraemia in hemodialysis dependent adults (n=1804)	Efficacy in reduction of *S. aureus* bacteraemia at 54 weeks was non-significant (p=0.23); post-hoc efficacy estimate at 40 weeks was 57% (p=0.02)
V710[221]	Vaccine containing a recombinant iron-regulated surface determinant B (IsdB), a *S. aureus* surface protein	Phase III (stopped prematurely)	Randomized, double-blind, placebo controlled event trial of efficacy of V710 to prevent major *S. aureus* infection in adults undergoing median sternotomy (n=8031)	Study was stopped prematurely by data monitoring committee. No significant efficacy. Vaccine recipients who developed *S. aureus* infection

Compound	Product	Phase (status)	Study design	Results
				were 5 times more likely to die than control recipients who developed *S. aureus* infection (23.0 vs 4.2 per 100 person-years, difference, 18.8 (95% CI, 8.0–34.1))
SA4Ag[199]	Multi-subunit vaccine consisting of ClfA, MntC and capsular polysaccharides 5 and 8	Phase IIb/III (currently enrolling)	Randomized, double-blind, placebo-controlled study of safety and efficacy of SA4Ag in adults undergoing lumbar spinal fusion procedures (target enrolment n=2600)	Primary outcome will be the number of patients in each treatment group with postoperative *S. aureus* blood stream infections and/or deep incisional or organ/space surgical site infections occurring within 90 days of elective posterior instrumented lumbar spinal fusion

Adapted from Fowler et al.[222]