Infective endocarditis

Yok-Ai Que and Philippe Moreillon

Abstract | Infective endocarditis (IE) is lethal if not aggressively treated with antibiotics alone or in combination with surgery. The epidemiology of this condition has substantially changed over the past four decades, especially in industrialized countries. Once a disease that predominantly affected young adults with previously well-identified valve disease—mostly chronic rheumatic heart disease—IE now tends to affect older patients and new at-risk groups, including intravenous-drug users, patients with intracardiac devices, and patients exposed to healthcare-associated bacteremia. As a result, skin organisms (for example, *Staphylococcus* spp.) are now reported as the pathogen in these populations more often than oral streptococci, which still prevail in the community and in native-valve IE. Moreover, progress in molecular diagnostics has helped to improve the diagnosis of poorly cultivable pathogens, such as *Bartonella* spp. and *Tropheryma whipplei*, which are responsible for blood-culture-negative IE more often than expected. Epidemiological data indicate that IE mostly occurs independently of medico-surgical procedures, and that circumstantial antibiotic prophylaxis is likely to protect only a minute proportion of individuals at risk. Therefore, new strategies to prevent IE—including improvement of dental hygiene, decontamination of carriers of *Staphylococcus aureus*, vaccination, and, possibly, antiplatelet therapy—must be explored.

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Department of Intensive Care Medicine, Centre Hospitalier Universitaire Vaudois, University of Lausanne, Rue du Bugnon 46, 1011 Lausanne, Switzerland (**Y.-A. Que**). Department of Fundamental Microbiology, University of Lausanne, Biophore 2416.1, 1015 Lausanne, Switzerland (**P. Moreillon**).

Correspondence to: P. Moreillon philippe.moreillon@unil.ch

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Introduction

Over the past 30 years, the overall incidence of infective endocarditis (IE) has remained between 2 and 6 per 100,000 individuals in the general population per year,[1–5] and associated mortality has remained between 10% and 30%, depending on the type of pathogen (for example, oral streptococci are less aggressive than *Staphylococcus aureus*),[6] the underlying condition, and whether the infection occurs on a native or prosthetic heart valve.[7] This stagnation in incidence and mortality is not due to a lack of medical progress, but rather to a continuing evolution of epidemiological features and risk factors for IE. Although chronic rheumatic heart disease was a primary risk factor for IE before the widespread introduction of antibiotics, and is still considered as such in developing countries,[3] this condition is now rare in industrialized countries.[8] New at-risk groups have emerged in the industrial world, including intravenous-drug users, patients with prosthetic valves, individuals undergoing hemodialysis, patients with intravenous catheters, and elderly people with degenerative valve lesions. Whereas oral streptococci are the predominant IE pathogen in the general population,[2,3,9] *Staphylococcus aureus* and coagulase-negative staphylococci (mainly *S. epidermidis*) are more-often found in intravenous-drug users, in patients with prosthetic-valve IE (PVE), and in those with healthcare-related IE,[1,10–12] and group D streptococci (mainly *S. gallolyticus*, previously known as *S. bovis*) are increasingly prevalent in elderly patients and are often associated with colon tumors.[1–3,13,14]

Although the primary focus of the infection is confined to the endocardium, microbial shedding by continuous

bacteremia and embolization of vegetation fragments makes IE a true systemic infection. This disease, therefore, is positioned at the crossroads of multiple medical specialties, including cardiology, cardiac surgery, infectious diseases, internal medicine, neurology, and intensive care. Guidelines for IE prevention and treatment, written by collaborations of multiple clinical societies, have been published in the USA[15] and in Europe.[16] In this Review, we discuss the evolving epidemiology and our current understanding of the pathogenesis of this disease, in addition to providing information and recommendations for IE prevention and therapy on the basis of the guidelines from both sides of the Atlantic Ocean.

Key points

- Infective endocarditis (IE) remains universally lethal if not aggressively treated
- Medical progress has altered the epidemiology of IE
- Healthcare-associated IE has become a major issue in industrialized countries
- Prophylaxis for IE has been questioned and new guidelines have been proposed
- Successful therapy for IE is being challenged by the development of antibiotic resistance

Epidemiology

Once characteristically a disease seen in children and young adults, as a result of chronic rheumatic heart disease,[8] IE is now more-often observed in new at-risk groups in industrialized countries, including intravenous-drug users (mean age 30–40 years)[17] and adults, including elderly individuals (>65 years), with valve prostheses or chronic healthcare-associated conditions. Consequentially, the mean age of patients with IE has increased from 30 years in the 1950s, to 50 years in the 1980s, and to as high as 55-60 years in the 1990s and 2000s.[1,2,4,18–21] In a review of 3,784 cases of IE in the period 1993–2003, the incidence of infection was <5 per 100,000 patients per year in individuals younger than 65 years and >15 per 100,000 patients per year in those older than 65 years.[1,2] This more than threefold higher frequency of IE diagnosis in older individuals probably reflects the clustering of more than one risk factor in the elderly.

Accordingly, the results of epidemiological studies vary depending on the population analyzed.[3,9,12,22] Population-based studies demonstrate this principle, as microbial pathogens tend to differ between the various groups (Table 1).[1–3,9,12,21–24] The type of pathogen has not substantially changed over time—*Streptococcus* spp., *Staphylococcus* spp., and *Enterococcus* spp. still represent more than 80% of all cases—but the repartition of at-risk groups, which tend to be associated with specific types of micro-organism, has.

To help differentiate between these various clinical tendencies, IE can be classified into four categories: left-sided native-valve IE (NVE); left-sided PVE; right-sided IE, including IE in intravenous-drug users and cardiovascular-device-related IE; and healthcare-associated IE, including nosocomial IE (acquired in the hospital) and non-nosocomial IE (associated with healthcare in outpatient settings).

Left-sided NVE

Left-sided NVE is the most frequent form of IE, representing about 70% of all cases.[21,25] In-hospital mortality for patients with community-acquired left-sided NVE is approximately 15%, depending on the type of micro-organism and comorbidities.[23,24] Notably, up to 25–45% of patients with healthcare-associated NVE die in the hospital;[24,26] IE acquired in healthcare settings is discussed in a separate subsection below.

Healthy endothelium is usually resistant to infection, but any pre-existing lesion can favor attachment of circulating bacteria and promote IE (see the section on 'Pathogenesis' below). Congenital heart disease and chronic rheumatic heart disease are often associated with the development of such lesions and are lifelong risk factors that have been extensively reviewed elsewhere.[8,9,12,21,27] Although chronic rheumatic heart disease has decreased to <10 cases per 100,000 individuals in the general population per year in industrialized countries, it has remained the main predisposing factor of IE (up to 50% of cases) in certain developing countries.[9] Therefore, prevention and control of acute rheumatic fever is a critical intervention in such areas.[28]

Mitral-valve prolapse is a relatively common condition that can be inherited—at least three autosomal-dominant loci have been found on chromosomes 11, 13, and 16[29,30]—and affects 2–3% of the general population.[31] Patients with mitral-valve prolapse and valve regurgitation have a 10–100-fold increased risk of IE, and this risk seems particularly high in children and in patients over the age of 50 years.[32]

Degenerative valve lesions are present in up to 25% of patients with IE who are older than 40 years of age, and in 50% of patients with IE who are older than 60 years of age.[33] These lesions involve local inflammation, microulcers, and microthrombi of the endothelium, and are quite similar to those seen in atherosclerosis. A 2004 echocardiographic study identified degenerative valve lesions that might increase the risk of IE in up to 50% of patients older than 60 years of age.[34] The findings of this study might, in part, explain the increased risk of IE in elderly individuals. Moreover, these observations challenge the notion of healthy valve IE—minor valve lesions might not be detected by auscultation and imaging, and numerous predisposing valve conditions might pass undetected until IE is established.

Left-sided PVE

Left-sided PVE is the most-severe form of IE, and is associated with high mortality that ranges from 20% to >40%.[7,23,35] This disease occurs in 1–5% of patients with prosthetic valves, or 0.3–0.6% per patient-year,[36,37] and accounts for up to 20% of all cases of IE in some studies.[21,25] The rates of infection associated with mechanical and bioprosthetic valves are similar.[35,36]

PVE is classified as 'early' or 'late' infection on the basis of the time period between surgery and the onset of IE. Early and late PVE were originally defined, somewhat

Table 1 | Microbiology of IE in specific patient groups

Pathogen	Native valve				Prosthetic valve[23]	
	% In those with community-acquired IE (n = 1,065)[24]	% In those with healthcare-associated IE (n = 557)[24]		% In intravenous-drug users with IE (n = 237)[21]	% In those with early IE* (n = 53)	% In those with late IE* (n = 331)
		Nosocomial (n = 303)	Non-nosocomial (n = 254)			
Staphylococcus aureus	20	47	42	68	36	18
Coagulase-negative staphylococci	6	12	15	3	17	20
Enterococcus	9	14	17	5	8	13
Viridans streptococci	28	11	6	10	2	10
Streptococcus bovis	10	3	3	1	2	7
HACEK	3	0	0	0	0	2
Fungi	0	2	2	1	9	3
Other	14.6	7.5	10	3	6	14
Negative blood culture	11	5	6	5	17	12

Data summarized from Murdoch *et al.*,[21] Wang *et al.*,[23] and Benito *et al.*[24] *The definitions used for early and late prosthetic-valve IE were within and more than 60 days after valve implantation, respectively, as defined by Wang *et al.*[23] on the basis of studies from the 1970s. A different group of researchers has suggested that the early and late prosthetic-valve IE be defined as within and more than 1 year after valve implantation, respectively, on the basis of when the major shift from the predominance of one organism to that of another occurs.[41] Abbreviations: HACEK, *Hemophilus parainfluenzae, H. aphrophilus, H. paraphrophilus, H. influenzae, Actinobacillus actinomyctemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae* and *K. denitrificans*; IE, infective endocarditis.

empirically, as occurring either within or more than 2 months after surgery, respectively.[38–40] However, in 2007, investigators demonstrated that a major shift from the predominance of one type of pathogen to that of another occurs approximately 12 months after surgery,[41] and European guidelines now use this time period to classify the condition.[16] Early PVE is often caused by surgery-related and drug-resistant microbes (Table 1), such as methicillin-resistant staphylococci, whereas oral streptococci and, sometimes, Gram-negative bacteria of the so-called HACEK group (*Hemophilus parainfluenzae, H. aphrophilus, H. paraphrophilus, H. influenzae, Actinobacillus actinomyctemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae* and *K. denitrificans*) are more-often responsible for late PVE.[23] This difference is thought to result from the progressive endothelialization of the prosthetic material, which makes it react more like a native valve.

Right-sided IE

Right-sided IE mostly occurs in intravenous-drug users, including those with HIV, but may also occur in patients with congenital heart disease, pacemakers, implantable defibrillators, or central venous catheters. Although highly population-specific, right-sided IE has represented up to 5–10% of cases in general surveys.[2,17] This form of IE has a better prognosis than left-sided IE; in-hospital mortality is <10%,[2,42] although mortality of up to 50% has been observed in patients with AIDS, especially in advanced cases.[43,44]

Intravenous-drug users, including those with HIV, are a group that primarily consists of relatively young adults.[17] Immune deficiency related to HIV, and behaviors associated to this particular at-risk group (for example, alcohol intake and intravenous injections), are risk factors for right-sided IE.[17] In one study, the risk of IE was unaffected in patients with >500 CD4 cells per mm^3, but increased by approximately four to five times in those with <200 cells per mm^3.[43] Although left-sided NVE is not uncommon in intravenous-drug users, the tricuspid valve is usually affected in these patients.[42,45] The causative bacteria often originate from the skin, which explains the predominance of *S. aureus* infections in these patients (Table 1). However, right-sided IE in intravenous-drug users and patients with HIV can also result from streptococci and other micro-organisms, including *Pseudomonas aeruginosa* and, on rare occasions, fungal infections, which are particularly severe.

The frequency of IE in the context of cardiovascular implantable electronic devices increases in parallel with the number of patients equipped with these devices.[46,47] Although most infections associated with cardiovascular implantable electronic devices are limited to the subcutaneous pocket of the apparatus, 10% of such infections are reported to extend to the endocardium.[47] The rate of such IE is estimated at 0.55 cases per 1,000 pacemakers recipients per year.[48] Of such patients, 70% are aged >65 years, and most have more than one coexisting illness.[46] *Staphylococcus* spp. (mostly coagulase-negative species) are the micro-organisms most-frequently responsible for right-sided IE associated with cardiac devices.[48,49] These infections always require ablation of the material in addition to antibiotic therapy.[50]

Healthcare-associated IE

Healthcare-associated IE is an increasingly frequent pathology that accounts for up to 30% of IE cases in industrialized countries,[24] and is a severe complication of healthcare-associated bloodstream infections, which have increased more than threefold in the past three decades.[51,52] Healthcare-associated IE comprises nosocomial IE

and non-nosocomial IE.[16] The two entities share most epidemiological, microbiological, and prognostic characteristics, including high mortality ranging from 25% to 45%.[24,26]

Patients undergoing hemodialysis are the largest subgroup of patients with healthcare-associated IE.[11,53] Chronic hemodialysis has been recognized as an independent risk factor for this type of IE.[11,24] Moreover, hemodialysis is a very strong predictor of *S. aureus* being the causative agent.[24,53,54] Of the patients with healthcare-associated IE who are not undergoing hemodialysis, most have additional debilitating conditions, such as diabetes mellitus, cancer, and disease requiring immunosuppressive therapy. Less than 50% of all patients with healthcare-associated IE have obvious cardiac predisposing factors, such as chronic rheumatic heart disease or mitral valve prolapse.

Staphylococci and enterococci are the most-common pathogens in patients with healthcare-associated IE. Pathogens usually originate from the skin or urinary tract, and a potential source of bacteremia, such as the presence of intravenous lines or invasive procedures, is typically identified.[24] In cases of catheter-induced *S. aureus* bacteremia, the risk of IE is as high as 10%.[25,55,56]

Pathogenesis

The first step in the pathogenesis of IE is the colonization of damaged valves by bacteria circulating in the blood. Physical lesions of the valve endothelium result in exposure of the underlying extracellular matrix proteins, production of tissue factor, and the deposition of fibrin and platelets, as a part of the normal healing process. Such nonbacterial thrombotic endocarditis is an ideal environment for bacterial adherence and infection (reviewed elsewhere[57]).

Endothelial damage can be caused by physical means—by turbulent blood flow associated with congenital heart disease or prosthetic valves, by electrodes or catheters, or, in intravenous-drug users, from repeated intravenous injection of particulate material. Alternatively, endothelial damage can result from inflammation, for example in patients with rheumatic carditis or in elderly individuals with degenerative valve lesions.[33,34] Some researchers have suggested that the presence of *Chlamydia pneumoniae* or cytomegalovirus in endovascular locations might also be linked to arteriosclerosis;[58] whether these organisms also promote valve lesions that result in IE remains to be demonstrated.

Micro-organisms

The most frequent IE pathogens are Gram-positive bacteria—*S. aureus*, *Streptococcus* spp., and enterococci are responsible for more than 80% of all IE cases (Table 1). These bacteria also have the greatest ability to adhere to and colonize damaged valves;[57] they are equipped with several surface adhesins that mediate attachment to extracellular host matrix proteins. Adhesins include both proteins and polysaccharides, and are collectively referred to as MSCRAMMs (for Microbial Surface Component Reacting with Adhesive Matrix Molecules).[59]

Box 1 | Recommendations for IE prophylaxis

Underlying cardiac conditions where antibiotic prophylaxis is recommended for the procedures listed below:

- Prosthetic cardiac valve
- Previous IE
- Nonrepaired cyanotic congenital heart disease, including palliative shunts and conduits
- Repaired congenital heart defect with prosthetic material or device, either by surgically or by catheter intervention, during the first 6 months after the procedure (when endothelialization occurs)
- Repaired congenital heart disease with residual defects at the side or adjacent to the site of a prosthetic patch or device (a situation that inhibits endothelialization)
- Cardiac transplantation recipients who develop cardiac valvulopathy

Procedures for which antibiotic prophylaxis is recommended for the above conditions:

- All dental procedures that involve manipulation of gingival tissues or periapical region of teeth, or perforation of oral mucosa
- Procedures on respiratory tract or infected skin, skin structures, or musculoskeletal tissues only if they imply overt incision of the skin or mucosa*

Note that antibiotic prophylaxis is not recommended for procedures on the genitourinary or gastrointestinal tracts, if indication for prophylaxis implicates only endocarditis prevention

Recommendations are made on the basis of guidelines from the European Society of Cardiology[16] and the American Heart Association.[90] *IE prophylaxis for procedures concerning respiratory tract or skin structure is only recommended in the US guidelines. Abbreviation: IE, infective endocarditis.

Table 2 | Recommended prophylaxis for patients undergoing dental procedures*

Type of patient	Antibiotic	Dose administered 30–60 min before procedure	
		Adults	Children
Those who can take oral antibiotics	Amoxicillin	2 g	50 mg/kg
Those who are unable to take oral antibiotics	Ampicillin or cefazolin or ceftriaxone	2 g IV or IM 1 g IV or IM 1 g IV or IM	50 mg/kg IV or IM 50 mg/kg IV or IM 50 mg/kg IV or IM
Those who are allergic to penicillin, but who can take oral antibiotics	Cephalexin‡ or clindamycin or clarithromycin	2 g 600 mg 500 mg	50 mg/kg 20 mg/kg 15 mg/kg
Those who are allergic to penicillin and are unable to take oral antibiotics	Cefazolin or ceftriaxone or clindamycin	1 g IV or IM 1 g IV or IM 600 mg IV or IM	50 mg/kg IV or IM 50 mg/kg IV or IM 20 mg/kg IV or IM

Regimens for other procedures should be targeted at the most probable pathogen implicated. For streptococci, antibiotics are the same as above. For staphylococci, anti-staphylococcal β-lactams or vancomycin should be considered. For enterococci, amoxicillin or ampicillin (as above) or vancomycin should be considered. The risk of methicillin-resistant staphylococci (vancomycin recommended) and vancomycin-resistant enterococci (amoxicillin or ampicillin recommended) should be taken into account. *Only for dental procedures listed in Box 1 and in patients with risk factors also listed in Box 1. ‡Or other first-generation or second-generation cephalosporins; note that cephalosporins should not be used patients with a type I allergy to β-lactams. Abbreviations: IM, intramuscular; IV, intravenous. Adapted from Wilson *et al.*[90] (original source: American Heart Association, Inc.).

In *S. aureus*, clumping factor A (ClfA; also known as fibrinogen-binding protein A) and fibronectin-binding protein A (FnBPA) are involved in valve colonization and invasion, whereas other MSCRAMMs seem less implicated.[60,61] Fibrinogen-binding mediates the primary attachment of the bacteria to nonbacterial thrombotic endocarditis, and subsequent binding of fibronectin triggers endothelial cell internalization, followed by local proinflammatory and procoagulant responses.[61–64] Experiments with heterologous gene expression and

Box 2 | Modified Duke criteria for diagnosis of IE

Definition of the major criteria used in the diagnosis

Blood cultures

- At least two separate blood cultures deemed as infected with typical IE micro-organisms (viridans streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus*, or community-acquired enterococci in the absence of primary focus)
- Persistently positive blood cultures (defined as two culture sets drawn >12 h apart, or three or the majority of ≥4 culture sets with the first and last separated by ≥1 h)
- Single positive culture for *Coxiella burnetii* or anti-phase I antibody titer >1:800

Imaging showing endocardial involvement

- New valve regurgitation
- Echocardiogram* showing oscillating intracardiac mass on the valve or supporting structure, in the path of regurgitant jets, or on implanted material, in the absence of an alternative anatomic explanation
- Echocardiogram* showing abscess
- Echocardiogram* showing new partial dehiscence of prosthetic valve

Definition of the minor criteria used in the diagnosis

- Predisposing cardiac condition or intravenous drug use
- Fever (≥38 °C or 100.4 °F)
- Positive blood cultures, but not meeting major criteria; serologic evidence of active infection with plausible micro-organisms
- Vascular phenomena: arterial emboli, mycotic aneurysms, petechiae, and/or Janeway lesions
- Immunologic phenomena: glomerulonephritis, Osler nodes. Roth spots, and/or rheumatoid factor

Diagnosis

Definite

- Pathology or bacteriology of vegetations, or
- Two major criteria, or
- One major and three minor criteria, or
- Five minor criteria

Possible

- One major and one minor criterion, or
- Three minor criteria

Rejected

- Firm alternative diagnosis, or
- Resolution of IE syndrome after ≤4 days of antibiotherapy, or
- No pathologic evidence at surgery or autopsy after ≤4 days of antibiotherapy
- Does not meet criteria mentioned above

*Transesophageal echocardiogaphy recommended in patients with prosthetic valves and patients rated as 'possible' IE by clinical criteria (see Figure 1). Abbreviations: HACEK, *Hemophilus* spp., *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella kingae*; IE, infective endocarditis. Reproduced from Li, J. S. *et al.* Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin. Infect. Dis.* **30**, 633–638 (2000),[92] by permission of Oxford University Press.

truncated proteins have shown that fibrinogen-binding is essential and sufficient for early valve colonization, but not sufficient for invasion, whereas fibronectin-binding does not mediate valve colonization, but triggers endothelial invasion and inflammation after the bacterium is in proximity of the fibronectin (by primary fibrinogen-binding).[61,62] Thus, both binding domains cooperate for productive infection.

FnBPA-mediated endothelial invasion and inflammation have been demonstrated *in vitro* and *in vivo*.[61–64] Inflamed endothelia express a variety of molecules, including integrins of the β1 family, which bind fibronectin. Fibronectin, in turn, is a ligand for circulating bacteria expressing fibronectin-binding proteins, including *S. aureus*, thus promoting further bacterial adherence, inflammation, tissue destruction, and vegetation growth. Therefore, local inflammation resulting from degenerative lesions (for example, in arteriosclerosis) or from as yet undetermined conditions might promote direct endothelial infection. This mechanism might be important in the pathogenesis of IE associated with intracellular pathogens such as *Coxiella burnetii* (the agent of Q fever), *Chlamydia* spp., *Legionella* spp., and *Bartonella* spp.,[65] although experimental evidence for this hypothesis is not available yet.

Several surface proteins, platelet-activating factors, and exopolysaccharides, have been implicated in the adherence of viridans group streptococci to nonbacterial thrombotic endocarditis.[66,67] Likewise, *Enterococcus faecalis* (*E. faecium* and other enterococci species are rarely the cause of IE[68,69]) is equipped with several pathogenic factors, including aggregation substance,[70] endocarditis-associated and biofilm-associated pilus (Ebp),[71] and collagen adhesins Acm and Ace.[72,73] Importantly, studies have shown that Ebp and collagen adhesin Ace are poorly expressed in standard laboratory growth media unless the media are supplemented with serum, collagen, or bicarbonate.[71,73] This finding underlines the importance of gene regulation in the context of specific anatomical niches. A similar observation was made with collections of *S. aureus* from the nostrils of healthy carriers and patients with IE:[74] wide interstrain variation was noted for *in vitro* adherence to fibrinogen and fibronectin, which did not correlate with *in vivo* infectivity. Staphylococcal adhesins, therefore, might also be expressed differentially in laboratory conditions and *in vivo*.

Transient bacteremia

In animals with catheter-induced vegetations of the aortic valve, the importance of transient bacteremia was demonstrated experimentally with dental manipulation.[75] Both the magnitude of bacteremia during dental procedures and the ability of the pathogens to attach to damaged valves were important. Of a great variety of gingival micro-organisms circulating in the blood after dental manipulation, only those able to attach to damaged valves (streptococci and *S. aureus*) produced IE.[75]

Bouts of transient bacteremia also occur during normal activities such as chewing and tooth-brushing. These instances of bacteremia are usually of low grade and short duration (1–100 colony-forming units [CFU]/ml of blood for less than 10 min),[76] but they are recurrent. The cumulative exposure to circulating bacteria (in CFU/ml of blood per year) has been calculated to be more than 100,000 times greater during physiological activities than after a single tooth extraction,[77,78] which could explain why most cases of IE occur independently of prior medico-surgical procedures.[19,79]

The plausibility of this hypothesis has been demonstrated in the laboratory.[80] Experimental IE is inoculum-dependent and is usually induced by inoculating animals with bolus injections of large bacterial numbers (between 10^5 and 10^7 CFU).[81] Veloso *et al.*[80] tested whether the same absolute number of bacteria would also induce experimental IE if injected at a very low pace, resulting in undetectable levels of bacteremia. Low-grade continuous infusion (over at least 10 h) was as infective as high-grade bolus infusion, which confirms the premise that, in terms of bacteremia, the most critical factor for IE induction is the area under the curve for circulating bacteria over time, rather than transient peak concentrations of bacteria. This new understanding of IE induction has important implications for IE antibiotic prophylaxis (discussed below), as well as for healthcare-associated IE, which results from recurrent healthcare-related bacteremia.[11,82]

Role of host defenses

IE usually results from infection by Gram-positive micro-organisms, and rarely from Gram-negative bacteria (Table 1). The reason is probably multifactorial. One explanation could be differences in bacterial adherence to damaged valves. Alternatively, differences in the susceptibility of Gram-positive and Gram-negative bacteria to serum-induced killing might also be responsible—the C5b–C9 membrane-attack complex of complement kills Gram-negative bacteria by perforating their outer membrane, but Gram-positive bacteria are resistant to the membrane-attack complex because they lack an outer membrane and their plasma membrane is protected from it by the thick surrounding peptidoglycan. This notion was demonstrated in experimental IE induced by serum-susceptible *Escherichia coli*.[83] However, some Gram-negative bacteria might have thick capsules or other modifications of their surface that help them resist complement-induced killing. Gram-negative bacteria that provoke IE include complement-resistant bacteria, such as *Pseudomonas aeruginosa*.

Gram-positive bacteria might be the targets of other nonspecific immune factors, including platelet microbicidal proteins, which are peptides produced by activated thrombocytes that kill bacteria by damaging their plasma membrane. The protective role of platelet microbicidal proteins was suggested by studies of experimental endocarditis,[84] as well as by investigations of IE in humans, in which micro-organisms from patients with IE were consistently resistant to killing induced by platelet microbicidal proteins, whereas similar bacteria from patients with other types of infection were susceptible to platelet microbicidal proteins.[85] Therefore, platelets, which are a major component of the vegetations in IE, are key players in the nonspecific defense against this condition.

The role of humoral defense against IE is controversial. Immunization of rats against the streptococcal MSCRAMM FimA conferred cross-protection against IE resulting from infection by several viridans group streptococci.[86] Likewise, human immunoglobulins against fibrinogen-binding proteins afforded some protection against experimental IE associated with *S. aureus*

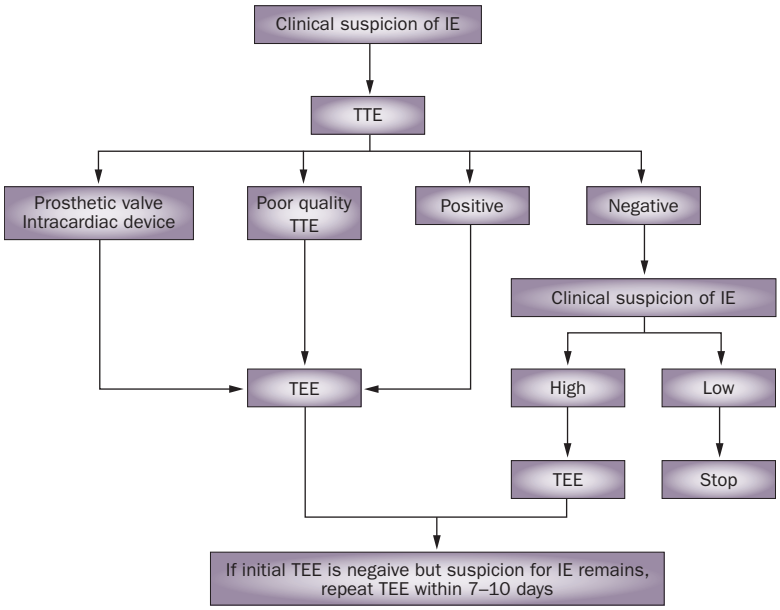

Figure 1 | Indications for echocardiography in cases of suspected IE. Abbreviations: IE, infective endocarditis; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography. Reproduced from Habib, G. *et al.* Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). *Eur. Heart J.* **30**, 2369–2413 (2009),[16] by permission of the European Society of Cardiology.

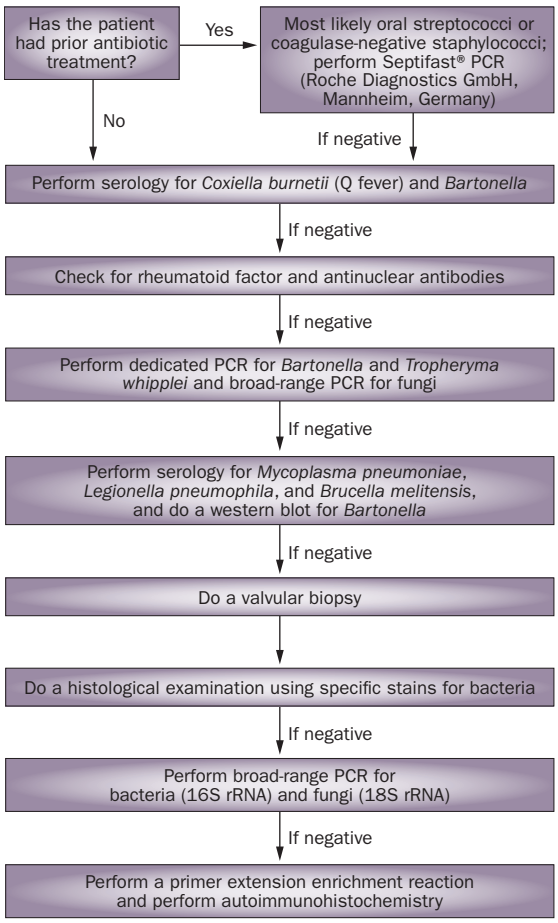

Figure 2 | Diagnostic strategies in blood-culture-negative infective endocarditis, as recommended by Fournier *et al.*[98]

Table 3 | Rare causes of IE associated with negative blood cultures

Pathogens	Diagnostic procedures	Proposed therapy*
Brucella spp.	Blood cultures (fastidious organism‡), serology, and culture, immunohistology and PCR of surgical material	Doxycycline 200 mg/24 h + rifampin 900–1,200 mg/24 h + cotrimoxazole 960 mg/12 h orally Treatment duration >3 months (cure is considered when antibody titers are <1:160) Addition of streptomycin 15 mg/kg/24 h in 2 doses for the first week is optional
Coxiella burneti (agent of Q fever)	Serology (IgG phase I >1:800) and tissue culture, immunohistology and PCR of surgical material	Doxycycline 200 mg/24 h + hydroxychloroquine (200–600 mg/24 h) orally or doxycycline 200 mg/24 h + quinolone (for example, ofloxacin 400 mg/24 h) orally Treatment duration >18 months (cure is considered when IgG phase I titers are <1:200, and IgA and IgM titers are <1:50)
Bartonella spp.	Blood cultures (fastidious organism‡), serology, and culture, immunohistology and PCR of surgical material	Ceftriaxone 2 g/24 h (in 1 dose) IV, amoxicillin 12 g/24 h (in 4–6 doses) IV, or doxycycline 200 mg/24 h orally for 6 weeks, and (with any of the above choices) aminoglycoside§ (for example gentamicin 3 mg/24 h) for 3 weeks Surgery is required in up to 90% of cases
Chlamydia spp.	Serology‖ and culture, immunohistology and PCR of surgical material	Doxycycline 200 mg/24 h or a newer fluoroquinolone (moxifloxacin 400 mg/24 h)¶ For the long term (optimal duration unknown)
Mycoplasma spp.	Serology and culture, immunohistology and PCR of surgical material	Doxycycline 200 mg/24 h or a newer fluoroquinolone (moxifloxacin 400 mg/24 h)¶ Treatment duration >6 months
Legionella spp.	Blood cultures (fastidious organism‡), serology, and culture, immunohistology and PCR of surgical material	Macrolides (for example erythromycin 3 g/24 h IV for 2 weeks and then orally) + rifampin 300–1,200 mg/24 h or ciprofloxacin 1.5 g/24 h orally¶ Treatment duration 6 months
Tropheryma whipplei (agent of Whipple disease)	Histology and PCR of surgical material	Cotrimoxazole 960 mg/12 h alone, or penicillin G 1.2 MU/24 h + streptomycin 1 g/24 h IV for 2 weeks and then cotrimoxazole 960 mg/12 h orally for 1 year, or doxycycline 200 mg/24 h + hydroxychloroquine 200–600 mg/24 h orally for >18 months For the long term (optimal duration unknown)#

Data summarized from Habib *et al.*,[16] Brouqui & Raoult,[65] Brouqui & Raoult,[99] and Moreillon.[127] *Owing to the lack of large series on IE resulting from these pathogens, optimal treatment duration is mostly unknown; treatment durations in the table are indicative, and on the basis of selected case reports. ‡The laboratory must be made aware of this possibility. §Several therapeutic regimens have been reported, including amino-penicillins and cephalosporins combined with aminoglycosides, doxycycline, vancomycin and quinolones. ‖Beware of serologic crossreaction with the more-common IE pathogen *Bartonella* spp.. ¶Newer fluoroquinolones are more potent than ciprofloxacin against intracellular pathogens such as *Mycoplasma* spp., *Legionella* spp., and *Chlamydia* spp.. #Treatment of patients with Whipple IE remains highly empirical; successes were reported with long-term (>1 year) cotrimoxazole therapy. Abbreviation: IE, infective endocarditis.

or coagulase-negative staphylococci,[87] and anti-Ace antibodies protected animals against experimental IE caused by *E. faecalis*.[73] However, immunization of rabbits againstthe enterococcal aggregation substance failed to protect the animals in one study,[88] and worsened valve infection in a more-recent observation, in which passive protection with Fabs was shown to improve disease outcome.[89] These observations indicate that certain types of antibody could be detrimental as a result of their agglutinating or proinflammatory activity. The role of vaccination clearly remains to be elucidated.

IE is not noticeably more frequent in immunocompromised patients than in those without an immune defect, with the exception of patients with HIV who might have additional risk factors and behaviors.[17] In established infection, bacteria are clustered in amorphous platelet–fibrin clots (the vegetations), permitting little access to phagocytes for removal of the bacteria. Such a 'therapeutic sanctuary' explains why successful treatment of IE relies primarily on antibiotic-induced death of bacteria, rather on host defenses.

Prophylaxis

IE should be prevented whenever possible. The choice of appropriate prophylactic measures requires identification of patients at risk, determination of the procedures or circumstances that may result in bacteremia, choice of an appropriate antimicrobial regimen, and balancing of the known risks against the possible benefits of intervention.

In the past few years, working groups of the American Heart Association[90] and the European Society of Cardiology[16] successively revised their guidelines for prophylaxis, the content of which is summarized in Box 1 and Table 2. The American[90] and European[16] guidelines greatly simplify the choice of prophylactic drugs and, therefore, might improve compliance. Notably, however, the lack of controlled prospective studies means that the level of evidence for these guidelines still relies on expert opinion, except for the case of prophylaxis before cardiac surgery. Because prospective studies of IE prophylaxis in humans raise ethical issues and would require too many patients, the practice of IE prophylaxis is still based on its proven efficacy in experimental animal models.

The guideline working groups reviewed the English-language literature on the subject and found that there were practically no epidemiological correlations between dental or other medico-surgical procedures and ensuing IE. They concluded that only an extremely small number of cases of IE might be prevented by antibiotic prophylaxis

Table 4 | Suggested empirical antibiotic treatment for patients with IE*

Antibiotic used	Adult daily dose	Pediatric daily dose‡	Treatment duration (weeks)	Comments
Ampicillin-sulbactam (or amoxicillin-clavulanate) + gentamicin§	4×3–4 g IV (for either) + 3 mg/kg IV or IM in 2–3 equally divided doses, respectively.	300 mg/kg IV in 4–6 equally divided doses + 3 mg/kg IV or IM in 2–3 equally divided doses, respectively.	4–6	For patients with NVE or late (≥12 months after surgery) PVE. Patients with blood-culture-negative IE should be treated in consultation with an infectious disease specialist.
Vancomycin‖ + gentamicin§ + ciprofloxacin	2×15 mg/kg IV + 3 mg/kg IV or IM in 2–3 equally divided doses + 2×500 mg orally or 2×400 mg IV, respectively.	Fluoroquinolones are contraindicated in children. Consult an infectious disease specialist.	4–6	For patients with NVE or late (≥12 months after surgery) PVE who are unable to tolerate β-lactams; ciprofloxacin is not uniformly active on *Bartonella* spp and so addition of doxycycline 200 mg/24 h is an option if *Bartonella* spp. is highly plausible.
Vancomycin‖ + gentamicin§ + rifampin	2×15 mg/kg IV + 3 mg/kg IV or IM in 2–3 equally divided doses + 3×300 mg orally, respectively.	40 mg/kg IV in 2–3 equally divided doses + 3 mg/kg per day IV or IM in 2–3 equally divided doses + 20 mg/kg IV or orally in 3 equally divided doses respectively.	6, 2, and 6, respectively	For patients who have early (<12 months after surgery) PVE. If no clinical response, surgery and, possibly, extension of the antibiotic spectrum to gram-negative pathogens must be considered.

*Empirical regimens described in this table are based on consensus opinion of experts and on most likely infective pathogen and antibiotic susceptibility. ‡Pediatric doses should not exceed adult doses. §Renal function and serum concentrations of gentamicin should be monitored once a week (twice in case of renal failure); when given in three divided doses, pre-dose (trough) serum concentrations of gentamicin should be <1 mg/l and postdose (peak; 1 h after injection) serum concentrations should be 3–4 mg/l. ‖Serum concentrations of vancomycin should be 10–15 mg/l before treatment (trough level) and 30–45 mg/l 1 h after infusion is completed (peak level). Abbreviations: IE, infective endocarditis; IM, intramuscular; IV, intravenous; NVE, native-valve infective endocarditis; PVE, prosthetic-valve infective endocarditis. Reproduced from Habib, G. *et al.* Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). *Eur. Heart J.* **30**, 2369–2413 (2009),[16] by permission of the European Society of Cardiology.

for dental procedures, even if such prophylactic therapy were 100% effective; IE prophylaxis for dental procedures is only appropriate for patients with underlying cardiac conditions associated with the highest risk of adverse outcome from IE; for patients with these underlying cardiac conditions, prophylaxis is appropriate for all dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa; prophylaxis is not recommended solely on the basis of an increased lifetime risk of acquisition of IE; and administration of antibiotics solely to prevent IE is not recommended for patients who undergo a genitourinary or gastrointestinal tract procedure.[16,90]

The recurrent bouts of bacteremia during physiological activity[76–78] and the demonstration that continuous low-grade bacteremia induces experimental IE in animals[80] described above, indicate that prescription of antibiotic prophylaxis should be limited. As a result, most at-risk populations are left without any suggestions for how to prevent IE. Although this guidance might be difficult to accept by patients who have tediously learned to comply with previous guidelines, new avenues for prevention should open up as a result of this conclusion. One measure is to promote dental hygiene, since inflamed gums are more likely to release bacteria into the blood than healthy gums.[78] Another is to revisit the ideas of vaccination[69,82,83] and antiaggregant therapy,[91] which could be more effective in the setting of low-grade bacteremia than when patients are overwhelmed by high concentrations of circulating bacteria, as recapitulated in current IE experimental models.

Diagnosis

Blood cultures and cardiac imaging with echocardiography are the cornerstones of IE diagnosis and cannot be bypassed. This point is emphasized in the modified Duke criteria for diagnosis of IE (Box 2), which were developed to more-accurately detect IE in the cases of negative blood cultures and *S. aureus* bacteremia.[92] Identification of the infecting organisms is of primary importance because this knowledge guides antibiotic therapy. Culture-positive IE represents approximately 85% of all cases. Two sets of blood cultures taken 30 min apart will reveal the causative organism in approximately 90% of cases and three sets will provide this information in up to 98% of cases.[93]

Ideally, all patients with suspected IE should undergo early echocardiography to assess valve status and cardiac function, and evaluate the risk of embolic events (Figure 1).[16,94] For the detection of vegetations, transesophageal echocardiography has a sensitivity of 90–100%, whereas that of transthoracic echocardiography ranges from 40% to 63%.[95]

Blood-culture-negative IE is an important consideration in the diagnosis of this disease, and falls in three categories: IE in patients who received antibiotherapy before blood cultures were drawn (~50% of cases);[96] IE resulting from infection by fastidious organisms such as nutritionally-variant streptococci, fastidious Gram-negative bacilli of the HACEK group, *Brucella* spp. (in endemic areas), and fungi;[96] and IE caused by intracellular bacteria such as the zoonotic agents *Coxiella burnetii* and *Bartonella,* and *Tropheryma whipplei*, which is the bacterium that causes Whipple disease.[97] Bacteria in patients who have received previous antibiotics, and bacteria of the HACEK group, might be detected after prolonged (more than 1 week) incubation of the blood cultures—the laboratory must be made aware of these possibilities. Additionally, diagnosis of intracellular bacteria relies on serologies and gene amplification, and might require valve material. Figure 2 depicts an algorithm proposed by Fournier and colleagues in 2010 to address the issue of culture-negative IE.[98] Table 3 lists the principal organisms responsible for blood-culture-negative IE, and the proposed diagnostic procedures and therapies.[65,99]

Table 5 | Suggested treatment for NVE caused by oral streptococci and group D streptococci*

Antibiotic used	Adult daily dose	Pediatric daily dose‡	Treatment duration (weeks)	Comments
Penicillin-susceptible (MIC <0.125 mg/l) infection				
Penicillin G§	6×2–3 million U IV	200,000 U/kg in 4–6 divided doses	4	Standard treatment. Preferred choice in patients aged >65 years or with impaired renal function
Penicillin G§ + gentamicin‖	6×2–3 million U IV + 1×3 mg/kg IV or IM, respectively	200,000 U/kg in 4–6 divided doses + 3 mg/kg IV or IM in 1 dose or in 3 equally divided doses, respectively	2	Short-term treatment (combination with an aminoglycoside allows a shorter duration of treatment)
Ceftriaxone	1×2 g IV or IM	1×100 mg/kg IV or IM	4	Standard treatment. Preferred choice for outpatient therapy, which should be considered in the absence of complications and in patient who are medically stable. Education of patient and staff is essential, as are regular evaluations after discharge (that is, nurse every day and physician in charge once or twice per week)
Ceftriaxone + netilmicin (or gentamicin if netilmicin is not available)	1×2 g IV or IM + 1×4 mg/kg IV (or 1×3 mg/kg IV or IM for gentamicin), respectively	1×100 mg/kg IV or IM + (as netilmicin has not been studied in children) gentamicin 3 mg/kg IV or IM in 1 dose or in 3 equally divided doses, respectively	2	Short-term treatment (combination with an aminoglycoside allows a shorter duration of treatment). Preferred choice for outpatient therapy as above
Vancomycin¶	2×15 mg/kg IV	40 mg/kg IV in 2–3 equally divided doses	4	For patients allergic to β-lactam
Penicilin resistant (MIC >1 mg/l)# infection				
Penicillin G§ + gentamicin‖	6×2–3 million U IV + 1×3 mg/kg IV or IM, respectively	200,000 U/kg in 4–6 divided doses + 3 mg/kg IV or IM in 1 dose or in 3 equally divided doses, respectively	4	Gentamicin should be used for only the first 2 weeks of treatment
Vancomycin¶ + gentamicin‖	2×15 mg/kg IV + 1×3 mg/kg IV or IM, respectively	40 mg/kg IV in 2–3 equally divided doses	4	For patients allergic to β-lactam. Gentamicin should be used for only the first 2 weeks of treatment

Recommendations are made on the basis of guidelines from the American Heart Association[15] and the European Society of Cardiology.[16] *Notes for other streptococcal species: short-term (2 weeks) therapy should not be used for other streptococcal species, owing to a lack of experience; IE caused by *S. pneumoniae* is often accompanied by meningitis—ceftriaxone (not penicillin) and, possibly, vancomycin should be used in this case; treatment for IE associated with a nutritionally variant streptococci (for example, *Abiotrophia*) should include aminoglycosides for at least 4 weeks. ‡Pediatric doses should not exceed adult doses. §Amoxicillin or ampicillin (100–200 mg/kg/24 h in 4–6 equally divided doses is proposed as alternative to penicillin G in European guidelines.[16] ‖Renal function and serum concentrations of gentamicin should be monitored once every week; when given in a single daily dose, as recommended here, serum concentrations of gentamicin should be <1 mg/l before treatment (trough level) and ~10–12 mg/l 1 h after injection (peak level). ¶Serum concentrations of vancomycin should be 10–15 mg/l before treatment (trough level) and 30–45 mg/l 1 h after infusion is completed (peak level). #Some guidelines consider MIC >0.5 mg/l to be full resistance. Abbreviations: IE, infective endocarditis; IM, intramuscular; IV, intravenous; NVE, native-valve infective endocarditis.

Management

Successful treatment of patients with IE relies on microbial eradication by antimicrobial drugs alone or in combination with surgery. Therapeutic schemes recommended for patients who have not yet received a firm diagnosis, and for IE associated with the most common pathogens —streptococci, staphylococci, *Enterococcus* spp., and fastidious Gram-negative bacteria of the HACEK group —are presented in Tables 4–8, respectively. High concentrations of antibiotics in the serum are desirable to ensure drug penetration into vegetations. Prolonged (4–6 weeks) treatment is necessary to kill dormant bacteria clustered in infected foci. Antibiotic choice is based on the minimal inhibitory concentration (MIC) of the drug for the pathogen. More sophisticated tests, such as inhibitory or bactericidal concentrations of the serum have been proposed, but their therapeutic utility has not been validated. Synergistic bactericidal drug combinations should be considered in many cases.

Drug treatment for patients with PVE is longer (at least 6 weeks) than that for patients with NVE (2–6 weeks), but is qualitatively similar except in the case of staphylococcal PVE, where treatment should include rifampin whenever the strain is susceptible to this agent. Treatment failure can result from inadequate antibiotic administration, the presence of a focus that must be removed surgically, or antibiotic resistance. The three most-problematic microbes with respect to antibiotic resistance are penicillin-resistant streptococci, methicillin-resistant and vancomycin-resistant staphylococci, and multiple-drug-resistant enterococci. Culture-negative IE resulting from intracellular pathogens can also fail to respond to standard therapy (Table 3).

Surgery is necessary in up to 50% of IE cases.[21] The main indications for surgery (Box 3) are heart failure (usually related to valve dysfunction), uncontrolled infection (often associated with perivalvular extension and atrioventricular conduction defects), and prevention of systemic embolism. The question of whether surgery should be performed early (within the initial hospitalization, as defined by Lalani and colleages[100]) or later in the course of therapy has been debated, as the latest published observational studies have provided conflicting findings.[101–105] However, when using appropriate statistical models, early valve surgery is shown to be beneficial in terms of long-term survival and improved prognosis, despite being associated with a slight increase in early postoperative mortality.[106] As a result, a propensity to recommend early surgery during the active phase of IE now exists, to avoid progression to heart failure and irreversible structural damage, and to prevent

Table 6 | Suggested treatment for left-sided IE* caused by staphylococci infection

Antibiotic used	Adult daily dose	Pediatric daily dose‡	Treatment duration	Comments
Native-valve IE				
Oxacillin (or [flu]cloxacillin) + gentamicin‡	6×2 g IV (for either) + 3 mg/kg IV or IM in 2–3 equally divided in doses, respectively	200 mg /kg IV in 4–6 equally divided doses (for either) + 3 mg/kg IV or IM in 3 equally divided doses, respectively	4–6 weeks and 3–5 days, respectively	For methicillin-susceptible staphylococci. The clinical benefit of gentamicin addition is not formally demonstrated; its use is optional.
Cefazolin (or other first generation cephalosporins) + gentamicin§	3×2 g IV + 3 mg/kg IV or IM in 2–3 equally divided in doses, respectively	100 mg/kg IV in three equally divided doses + 3 mg/kg IV or IM in 3 equally divided doses, respectively	4–6 weeks and 3–5 days, respectively	For methicillin-susceptible staphylococci. Alternative to above treatment strategy for patients allergic to penicillins, except for immediate-type penicillin hypersensitivity and only in absence of allergic reaction to cephalosporins. The clinical benefit of gentamicin addition is not formally demonstrated; its use is optional.
Vancomycin‖	2×15 mg/kg IV	40 mg/kg IV in 2–3 equally divided doses	4–6 weeks	For methicillin-resistant staphylococci and for patients allergic to β-lactams.
Prosthetic-valve IE				
Oxacillin (or [flu]cloxacillin) + gentamicin‡ + rifampin¶	6×2 g IV + 3 mg/kg/day IV or IM in 2–3 equally divided doses + 3×300 mg orally, respectively	200 mg/kg IV in 4–6 equally divided doses (for either) + 3 mg/kg IV or IM in 2–3 equally divided doses + 20 mg/kg IV or orally in 3 equally divided doses, respectively	>6 weeks, 2 weeks, and >6 weeks, respectively	For methicillin-susceptible staphylococci. Although the clinical benefit of gentamicin has not been demonstrated, it is recommended for patients with PVE.
Vancomycin‖ + gentamicin§ + rifampin¶	2×15 mg/kg IV + 3 mg/kg IV or IM in 2–3 equally divided doses + 3×300 mg orally, respectively	40 mg/kg IV in 2–3 equally divided doses + 3 mg/kg IV or IM in 2–3 equally divided doses + 20 mg/kg iv or orally in 3 equally divided doses, respectively	>6 weeks, 2 weeks, and >6 weeks, respectively	For methicillin-resistant staphylococci and for patients allergic to β-lactams.

Recommendations are made on the basis of guidelines from the American Heart Association[15] and the European Society of Cardiology.[16] *For right-sided IE, uncomplicated disease (that is, with fully susceptible organisms and no cardiac failure or peripheral complications) has been successfully treated with short-course (2 weeks) treatment with cloxacillin alone or in combination with gentamicin,[128] and with 4 weeks oral therapy combining either ciprofloxacin (2×750 mg/day) or, preferentially, a newer quinolone (moxifloxacin 400 mg/day), with rifampin (2×300 mg/day); daptomycin (at least 6 mg/kg/day for 4 weeks) can be used against methicillin-susceptible and methicillin-resistant *S. aureus* right-sided IE. ‡Pediatric doses should not exceed adult doses. §Renal function and serum concentrations of gentamicin should be monitored once a week (twice in case of renal failure); when given in three divided doses, pre-dose (trough) serum concentrations of gentamicin should be <1 mg/l and post-dose (peak; 1 h after injection) serum concentrations should be 3–4 mg/l. ‖Serum concentrations of vancomycin should be 10–15 mg/l before treatment (trough level) and 30–45 mg/l 1 h after infusion is completed (peak level). ¶Rifampin is thought to be particularly useful in infection of a prosthetic device, because it helps eradicate bacteria attached to foreign material; however, this drug should never be used alone, because it selects for resistance at a high frequency (~10^{-6}) and physicians should note that it increases the hepatic metabolism of warfarin and other drugs. Abbreviations: IE, infective endocarditis; IM, intramuscular; IV, intravenous.

systemic embolism.[16,107,108] Neurological events can be considered as contraindications for cardiac surgery, owing to the risk of anticoagulation-related cerebral hemorrhage. Nevertheless, studies published in the past 5 years indicate that surgery can be performed with a minimum risk of neurological complications, particularly in patients with transient ischemic attack or silent stroke.[109,110] Pathological findings on routine cerebral imaging should not, therefore, prevent surgery in asymptomatic patients. In the case of coma or cerebral hemorrhage, however, surgery should be postponed.[16]

Empirical treatment

Treatment of IE should be started promptly after a minimum of three sets of blood cultures at 30 min interval are drawn.[93] The choice of empirical therapy (Table 4) depends on whether the patient has received prior antibiotherapy, on whether the infection is an NVE or a PVE, on whether PVE infection is early (<12 months after surgery) or late (>12 months after surgery), and on knowledge of the local epidemiology, including antibiotic resistance and specific blood-culture-negative pathogens.[111,112] NVE and late PVE regimens should account for the possibility of staphylococci, streptococci, HACEK species and *Bartonella* spp. Treatment must be adjusted immediately after diagnosis of the pathogen.

Penicillin-resistant streptococci

All streptococci that cause IE can demonstrate intermediate penicillin-resistance (MIC of 0.1–1 mg/l) or full penicillin-resistance (MIC >1 mg/l), with the exception of *S. gallolyticus* and group A streptococci, which are still uniformly susceptible to penicillin. Treatment of patients with IE caused by penicillin-susceptible and penicillin-resistant streptococci is qualitatively similar, except that short-course (2 weeks) therapy should not be used in case of resistance, and synergistic bactericidal combinations of β-lactams with aminoglycosides are preferred in these cases (Table 5).[113] Little experience exists with highly resistant isolates (MIC ≥4 mg/l); vancomycin might be preferred in such circumstances.

MRSA and vancomycin-resistant staphylococci

Methicillin-resistant *S. aureus* (MRSA) are usually resistant to multiple antibiotics, and vancomycin is currently the only therapeutic option for severe infections (Table 6). However, vancomycin-intermediate *S. aureus* (MIC 4–16 mg/l) and heterovancomycin-intermediate *S. aureus* (MIC ≤2 mg/l, but with subpopulations growing at higher concentrations) have become prevalent, and have been associated with failure of IE therapy.[114] In addition, a few highly vancomycin-resistant *S. aureus* (MIC ≥32 mg/l) with a vancomycin-resistance cassette

Table 7 | Suggested treatment for IE caused by *Enterococcus* spp.

Antibiotic used	Adult daily dose	Pediatric daily dose*	Treatment duration (weeks)	Comments
Penicillin G + gentamicin‡	6×3–5 million U IV + 3 mg/kg IV or IM in 2–3 equally divided doses, respectively	200,000 U/kg IV in 4–6 equally divided doses + 3 mg/kg IV or IM in 3 equally divided doses, respectively	4–6	6-weeks therapy recommended for patients with >3 months symptoms
Ampicillin (or amoxicillin)§ + gentamicin‡‖	6×2 g IV (for either) + 3 mg/kg IV or IM in 2–3 equally divided doses, respectively	300 mg/kg IV in 4–6 equally divided doses (for either) + 3 mg/kg IV or IM in 3 equally divided doses, respectively	4–6	Alternative to above treatment strategy
Vancomycin¶ + gentamicin‡	2×15 mg/kg IV + 3 mg/kg IV or IM in 2–3 equally divided doses, respectively	40 mg/kg IV in 2–3 equally divided doses + 3 mg/kg IV or IM in 3 equally divided doses, respectively	6	For patients allergic to β-lactams

Recommendations are made on the basis of guidelines from the American Heart Association[15] and the European Society of Cardiology.[16] Aminoglycosides toxicity remains a problem. One study reported success with a shorter course (2–3 weeks) of aminoglycoside combined with β-lactams.[129] On the other hand, a link between aminoglycoside nephrotoxicity and mortality in patients with IE has not been demonstrated.[130] In cases of multiresistance to aminoglycosides, β-lactams, and vancomycin: some suggested alternatives are linezolid 2×600 mg/day IV or orally for >8 weeks (control hematological toxicity), quinupristin-dalfopristin 3×7.5 mg/kg per day for >8 weeks, β-lactam combinations including imipenem + ampicillin or ceftriaxone + ampicillin for >8 weeks. *Pediatric doses should not exceed adult doses. ‡Renal function and serum concentrations of gentamicin should be monitored once a week (twice in case of renal failure); when given in three divided doses, pre-dose (trough) serum concentrations of gentamicin should be <1 mg/l and post-dose (peak; 1 h after injection) serum concentrations should be 3–4 mg/l. In cases of high-level resistance to gentamicin (MIC >1,000 mg/l), replace gentamicin with streptomycin 15 mg/kg per day in two equally divided doses, if the infection is susceptible to streptomycin, or use a more-prolonged course of β-lactam therapy. §In case of β-lactam resistance, replace ampicillin with ampicillin-sulbactam or amoxicillin with amoxicillin-clavulanate, if resulting from β-lactamase production, or use vancomycin-based regimens, if resulting from stuctural alteration and overexpression of penicillin-binding protein 5. ‖Ampicillin can be combined with ceftriaxone 2×2 g/24 h in the case of gentamicin-resistant *E. faecalis*.[120] ¶Serum concentrations of vancomycin should be 10–15 mg/l before treatment (trough level) and 30–45 mg/l 1 h after infusion is completed (peak level). Abbreviations: IE, infective endocarditis; IM, intramuscular; IV, intravenous; MIC, minimal inhibitory concentration.

Table 8 | Suggested treatment of IE caused by fastidious Gram-negative bacteria of the HACEK group

Antibiotic used	Adult daily dose	Pediatric daily dose*	Treatment duration (weeks)	Comments
Ceftriaxone	1x2 g IV or IM	1x100 mg/kg IV or IM	4	Preferred for outpatient treatment, since it is a once-a-day treatment
Ampicillin‡ + gentamicin§	6x2 g IV+3x1 mg/kg IV or IM,‖ respectively	300 mg/kg IV in 4–6 equally divided doses + 3 mg/kg IV or IM in 1 dose or in 3 equally divided doses, respectively	4	Alternative to above treatment strategy

Recommendations are made on the basis of guidelines from the American Heart Association[15] and the European Society of Cardiology.[16] *Pediatric doses should not exceed adult doses. ‡Ampicillin should not be used if microbes produce β-lactamases. §Renal function and serum concentrations of gentamicin should be monitored once a week (twice in case of renal failure); when given in three equally divided doses, pre-dose (trough) serum concentrations of gentamicin should be <1 mg/l and postdose (peak; 1 h after injection) serum concentrations should be 3–4 mg/l. ‖Studies suggest that gentamicin 3 mg/kg once daily might be adequate. Abbreviations: HACEK, *Hemophilus parainfluenzae, H. aphrophilus, H. paraphrophilus, H. influenzae, Actinobacillus actinomyctemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae* and *K. denitrificans*; IE, infective endocarditis; IM, intramuscular; IV, intravenous.

acquired from enterococci have been isolated from infected patients in the past 10 years.[115,116]

Treating patients with IE caused by vancomycin-resistant staphylococci requires new approaches. The lipopeptide daptomycin (6 mg/kg per day intravenously) was approved in 2006 by the FDA and the EMA for *S. aureus* bacteremia and right-sided IE.[117] 'Compassionate studies' suggest that daptomycin might also overcome methicillin resistance and vancomycin resistance in left-sided IE, but definitive studies are missing. Appropriate daptomycin dosing is an important consideration to avoid resistance selection.[117] Other alternative therapies include newer β-lactams with relatively good affinity for penicillin-binding protein 2A,[118] tigecycline, quinupristin–dalfopristin alone or in combination with β-lactams, β-lactams plus oxazolidinones, or β-lactams plus vancomycin. Such cases warrant consultation with an infectious disease specialist.

Multiple drug-resistant enterococci

Bactericidal synergism between cell-wall inhibitors and aminoglycosides is mandatory for therapeutic success in the case of enterococcal IE. However, *E. faecalis* (responsible for >80% of entercococcal IE) and *E. faecium* are frequently resistant to gentamicin[119]—an aminoglycoside MIC >500 mg/l is synonymous with loss of bactericidal synergism. Streptomycin can remain active and, therefore, be used instead of gentamicin. Another alternative therapy for gentamicin-resistant *E. faecalis* is the combination of ampicillin with ceftriaxone,[120] which synergize by inhibiting complementary penicillin-binding proteins. Otherwise, more prolonged courses of β-lactams or vancomycin must be undertaken (Table 7).

Resistance to either β-lactam or vancomycin is mainly observed in *E. faecium*. Nevertheless, dual resistance is rare and so β-lactam can usually be used against vancomycin-resistant strains and *vice versa*. Various results, including treatment failure, were reported with quinupristin-dalfopristin, linezolid, daptomycin, and tigecycline.[121] IE associated with such organisms requires consultation with an infectious-disease specialist.

Gram-negative bacteria

HACEK-related species are fastidious organisms responsible for less than 5% of all IE cases (Table 1). Because these micro-organisms grow slowly, MIC tests can be difficult to interpret. Some HACEK bacilli produce β-lactamases; therefore, ampicillin is not the first-line option in patients with this type of infection. HACEK-related species are susceptible to ceftriaxone, other third-generation and fourth-generation cephalosporins, and quinolones. Table 8 lists β-lactam-based treatments. Ciprofloxacin (2 × 400 mg per day intravenously, or 1,000 mg per day orally) is an alternative to these

therapies, though success with this treatment is not as well-demonstrated.

Non-HACEK Gram-negative species

In one large survey, IE caused by non-HACEK Gram-negative bacteria were present in 49 of 2,761 (1.8%) cases.[122] Most (59%) were PVE, and only 4% occurred in intravenous-drug users. *Escherichia coli* (29%) and *Pseudomonas aeruginosa* (14%) were most-frequently reported, followed by *Salmonella* spp., *Klebsiella* spp., *Serratia marcescens*, and *Neisseria gonorrhea*. Early surgery was frequent (51%) and in-hospital mortality was 24%. The treatment paradigm of such cases is early surgery plus long-term (≥6 weeks) antibiotics with bactericidal combinations of β-lactams with aminoglycosides, and sometimes with quinolones or cotrimoxazole.

Fungi

Fungal IE is very rare, representing only 2% of reported IE cases,[21,123] and is particularly difficult to treat. In the late 1990s, mortality among patients with fungal IE was reported to exceed 50%.[123,124] No breakthroughs have occurred in the past two decades; therefore, the death rate associated with this particular type of IE probably remains at a similar level. Fungal IE is primarily caused by *Candida* spp. or *Aspergillus* spp., the latter of which is blood-culture-negative, and is most-often diagnosed in cases of PVE, in intravenous-drug users, and in patients who are immunocompromised. Management of patients with fungal IE requires a multidisciplinary approach, as treatment must involve both antifungal administration and valve replacement.[123,124] Most patients are treated intravenously before, during, and after surgery with various forms of amphotericin (the lipid preparation is preferred to reduce adverse effects and allow uninterrupted administration), alone or in combination with azoles. Optimal duration of treatment with amphothericin B is unknown. A few reports describe success with intravenous capsofungin therapy administered over several weeks or months.[125,126] Suppressive treatment with oral azoles is often maintained for very long periods, and is sometimes even recommended for life,[123–126] which raises obvious concerns about compliance and possibly toxicity.

Conclusions

Although the epidemiology of IE has followed a constant evolution in industrialized countries, the types of initial valve lesions that promote bacterial colonization, and the panel of microbial pathogens, have remained qualitatively the same. The changes in epidemiology have resulted from changes in other sociocultural factors, such as increased use of intravenous recreational drugs, aging of the population, increases in the number of patients equipped with intracardiac implants, and increases of bacteremia associated with healthcare-related invasive manipulations. Such conditions favor IE caused by skin pathogens (for example, *Staphylococcus* spp.) and enteral streptococci (for example, in elderly patients with colon tumors) rather than more-classical oral streptococci.

Box 3 | Timing of surgery in the course of infective endocarditis

Emergency surgery (within 24 h)

- NVE (aortic or mitral) or PVE associated with severe or refractory congestive heart failure or cardiogenic shock caused by acute valvular regurgitation or severe prosthetic dysfunction (dehiscence or obstruction)
- Fistula into a cardiac chamber or the pericardial space

Urgent surgery (within days)

- NVE or PVE with persisting congestive heart failure, signs of poor hemodynamic tolerance, or abscess
- PVE caused by staphylococci or Gram-negative micro-organisms
- Large vegetation (>10 mm) with an embolic event despite antimicrobial treatment or other predictors of a complicated course
- Very large vegetation (>15 mm), especially if conservative surgery is available
- Large abscess and/or periannular involvement with uncontrolled infection

Early elective surgery (during the in-hospital stay)

- Severe aortic or mitral regurgitation with congestive heart failure and good response to medical therapy
- PVE with valvular dehiscence or congestive heart failure and good response to medical therapy
- Presence of abscess or periannular extension
- Persisting infection when extracardiac focus has been excluded
- Fungal or other infections resistant to medical cure

Abbreviations: NVE, native valve infective endocarditis; PVE, prosthetic valve infective endocarditis. Permission obtained from Wolters Kluwer Health © Prendergast, B. D. & Tornos, P. Surgery for infective endocarditis: who and when? *Circulation* **121**, 1141–1152 (2010).

Once established, IE remains a severe condition that requires aggressive antibiotic and, often, surgical therapy. Therefore, every effort should be made to prevent this disease. Key issues to be considered in future prevention strategies include the valve lesion —which might be unavoidable in numerous circumstances (for example, in elderly patients with valve sclerosis)—and bacteremia. Intuitively, simple measures to prevent bacteremia could be to promote dental hygiene and decontaminate nasal carriers of *S. aureus* who have prosthetic devices or are undergoing chronic hemodialysis. Simple measures to impede bacteremia could include vaccination, since antibodies might be more efficacious in the setting of recurrent low-grade bacteremia than in overwhelming high-grade bacterial inoculation (the condition usually tested in IE experimental models). Low-dose antiaggregant therapy, which is commonly used to prevent coronary heart disease, might be useful in reducing valve colonization and inhibiting vegetation development.

Review criteria

We searched the PubMed database for articles with the key phrase 'infective endocarditis' associated with 'epidemiology', 'pathogenesis', 'experimental', 'clinics', or 'therapy'. The search was limited to English-language articles and reviews published between 1970 and 2011. We also reviewed books written in English on the subject. We checked particularly for newly published guidelines and for publications form the International Collaboration on Endocarditis (ICE).

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Both authors contributed to discussion of content for the article, researched data to include in the manuscript, wrote, reviewed and edited the manuscript before submission, and revised the manuscript in response to the peer-reviewers' comments.