

Seminar

Infective endocarditis

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Despite improvements in health care, the incidence of infective endocarditis has not decreased over the past decades. This apparent paradox is explained by a progressive evolution in risk factors; while classic predisposing conditions such as rheumatic heart disease have been all but eradicated, new risk factors for infective endocarditis have emerged. These include intravenous drug use, sclerotic valve disease in elderly patients, use of prosthetic valves, and nosocomial disease. Newly identified pathogens, which are difficult to cultivate—eg, *Bartonella* spp and *Tropheryma whippelii*—are present in selected individuals, and resistant organisms are challenging conventional antimicrobial therapy. Keeping up with these changes depends on a comprehensive approach, allying understanding of the pathogenesis of disease with the development of new drugs for infective endocarditis. Infection by staphylococci and streptococci is being dissected at the molecular level. New ideas for antimicrobial agents are being developed. These novel insights should help redefine preventive and therapeutic strategies against infective endocarditis.

Infective endocarditis is lethal if not aggressively treated with antibiotics, combined or not with surgery. Developments in antibacterial therapy, clinical microbiology, cardiac imaging, and cardiac surgery have revolutionised its diagnosis and prognosis. Studies of the epidemiology of infective endocarditis have been hampered in the past by several factors—the rarity of the disease, the fact that it is not officially reportable, and the absence of a precise case definition. Therefore, many studies have been based on autopsy series.¹ An improved assessment of infective endocarditis in live patients is now possible, however, because of the introduction of new diagnostic criteria.^{2,3}

In a review (unpublished; raw data available from authors) of 26 publications (for references, see webappendix at <http://image.thelancet.com/extras/02art12165webappendix.pdf>) published between 1993 and 2003 and describing 3784 episodes of infective endocarditis (median number of patients per study 156, range 30–415), the mean age of patients varied between 36 years and 69 years. The median incidence of disease was 3.6 per 100 000 per year (range 0.3–22.4) and increased with age, ranging from five or less to 15 or more per 100 000 per year in individuals aged younger than 50 years and older than 65 years, respectively. The male-to-female ratio was about two-to-one, and the median in-hospital mortality rate was 16% (range 11–26).

Despite improvements in health care, the incidence of disease has not changed over the past two decades.^{4–7} This apparent paradox results from a progressive change in risk factors for infective endocarditis. Chronic rheumatic heart disease, which was a prime risk factor in the pre-antibiotic era,⁸ is now rare in industrialised countries.⁹ This group of at-risk patients has, however, been replaced by new at-risk groups, including intravenous drug users, elderly people with valve sclerosis, patients with intravascular prostheses,

those exposed to nosocomial disease, and haemodialysis patients.^{2,4–6,10–12} Although there were variations between the studies we reviewed (webappendix), staphylococci and oral streptococci accounted for most cases of disease (figure 1 and table 1). Staphylococci tended to prevail, identifying the skin flora as a major infection source. Known associations were confirmed, such as *Staphylococcus aureus*-associated infective endocarditis in intravenous drug users. We also noticed other associations, such as *Streptococcus bovis*-associated infective endocarditis (mostly *Streptococcus gallolyticus*) in elderly populations.⁷ Since disease associated with *Strep bovis* is often connected to digestive neoplasia, the association could mirror the increased frequency of tumours in elderly people. Previously undetected pathogens are also being identified in patients,¹³ and new multidrug-resistant bacteria are challenging conventional therapy.

We review some of these issues, focusing on pathogenesis and management. Clinical features of infective endocarditis are not covered, since they have been extensively reviewed.^{4,5,14,15}

Risk factors

Infective endocarditis is often classified in four categories: native-valve infective endocarditis, prosthetic-valve infective endocarditis, infective endocarditis in intravenous drug users, and nosocomial infective endocarditis. These categories delineate clinical conditions and distributions in microbial pathogens (figure 1 and table 1).

Search strategy

We searched PubMed for articles on infective endocarditis with the key phrase infective endocarditis associated with epidemiology, pathogenesis, experimental, clinics, or therapy. The search was limited to English articles involving people. We also reviewed books written in English on the subject. To generate the epidemiological data presented in figure 1, we searched the PubMed database from 1993 to 2003, using the key phrase infective endocarditis, with English and Review as limits. Only articles that described more than 30 cases and provided appropriate information on the nature of the responsible pathogens were included (see webappendix for references).

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Additionally, the increasing frequency of disease in haemodialysis patients¹² suggests new categories could arise in the future.

Risk of native-valve disease is classically associated with congenital heart disease and chronic rheumatic heart disease. These conditions have been well reviewed,^{9,16} but mitral valve prolapse is a more controversial issue. It is a fairly common inheritable condition (2–4% of the population), which is linked to a dominant marker on chromosome 16.¹⁷ Only patients with valve regurgitation have an increased risk of infective endocarditis.^{18,19} Mitral valve prolapse is associated with a low body-mass index, low blood pressure, and low prevalence of diabetes in American Indians. Thus, the inherited valve anomaly seems to be linked to a cardiovascular protective variable, a darwinian paradox.²⁰

Degenerative valve lesions are a primary cause of senile aortic stenosis or mitral regurgitation, which are risk factors for infective endocarditis. Degenerative valve lesions are present in up to 50% of patients with infective endocarditis who are older than age 60 years.²¹ Therefore, elderly people should be carefully examined for clinical evidence of valve dysfunction.

1–5% of individuals with infective endocarditis have prosthetic-valve endocarditis (PVE), or 0.3–0.6% per patient-year.^{22,23} Whether mechanical valves or bioprostheses are more prone to infection remains unresolved.²²

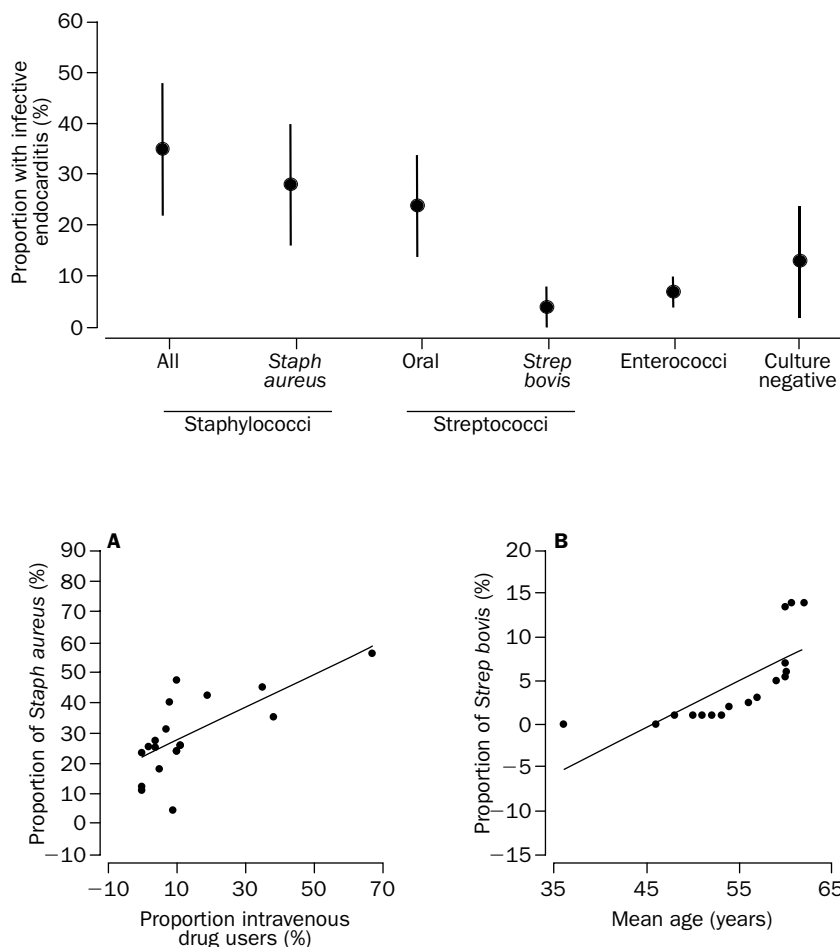


Figure 1: Microbial epidemiology of infective endocarditis

Upper graphs indicate proportion (mean [SD]) of specific pathogens responsible for infective endocarditis in 3784 episodes (webappendix references 1–26). Lower two graphs present linear regressions between proportion of *Staph aureus* endocarditis and proportion of intravenous drug users (A; webappendix references 1, 2, 6–8, 10, 11, 13, 16, 17, 19–24, 26), and proportion of *Strep bovis* disease and mean age (B; webappendix references 1–3, 8, 10–20, 22, 23).

PVE is classified as either early or late infection, depending on whether the infection arises within 60 days of surgery or later. The condition peaks during the first 2 months after valve implantation and is often due to *Staphylococcus epidermidis* or *Staph aureus* (table 1). Progressive endothelialisation of the prosthetic material over 2–6 months reduces the susceptibility of the valve to infection. Late PVE is often due to other organisms—eg, streptococci and gram-negative bacteria of the HACEK group, *Haemophilus* spp, *Actinobacillus actinomycetem-comitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*.²⁴

Intravenous drug users represent a risk group of fairly young people (median age 30–40 years).^{6,25} The tricuspid valve is infected in more than 50% of cases, followed by the aortic valve in 25% and the mitral valve in 20%, with mixed right-sided and left-sided infective endocarditis in a few instances.⁶ 60–80% of patients have no known pre-existing valve lesions. The pathogens usually originate from the skin, explaining the predominance of *Staph aureus* (figure 1 and table 1). *Pseudomonas aeruginosa* and fungi are also encountered and produce severe forms of infective endocarditis.²⁶ In HIV-1-positive intravenous drug users, both the risk of and mortality from infective endocarditis rise inversely to the CD4 count; risk is unaffected in patients with CD4 counts of more than 500 cells per μL , but increases four-fold in those with

CD4 counts of less than 200 cells per μL .²⁷ HIV-1-positive patients sometimes present with infective endocarditis caused by unusual organisms, including bartonella, salmonella, and listeria.

Nosocomial endocarditis is a growing category. In one study¹⁰ it accounted for 22% of 109 patients. Less than 50% of patients had cardiac predisposing factors. Predominant pathogens were staphylococci and enterococci, and were frequently associated with catheters or medico-surgical procedures.^{10,28} The authors of one study²⁹ estimated that up to 13% of nosocomial *Staph aureus* bacteraemia were responsible for subsequent infective endocarditis. Moreover, possible right-sided nosocomial endocarditis was reported in 5% of bone-marrow transplant recipients who had central venous catheters.³⁰ Nosocomial endocarditis is important because its case fatality rate is greater than 50%.^{10,28}

Another iatrogenic risk for infective endocarditis is haemodialysis. The disease is two to three times more frequent in haemodialysis patients than in peritoneal dialysis patients or in the general population. More than 50% of cases are due to *Staph aureus*.^{12,31}

Pathogenesis

The primary event is bacterial adherence to damaged valves. This event is completed within minutes during transient bacteraemia, and involves valve tissue and bacterial factors. The second step involves

Pathogen	Native-valve IE (n=280)	IE in intravenous drug users (n=87)	Prosthetic-valve IE	
			Early (n=15)	Late (n=72)
Staphylococci	124 (44%)	60 (69%)	10 (67%)	33 (46%)
<i>Staph aureus</i>	106 (38%)	60 (69%)	3 (20%)	15 (21%)
Coagulase negative	18 (6%)	0	7 (47%)	18 (25%)
Streptococci	86 (31%)	7 (8%)	0 (0%)	25 (35%)
Oral streptococci	59 (21%)	3 (3%)	0	19 (26%)
Others (non-enterococcal)	27 (10%)*	4 (5%)	0	6 (8%)
<i>Enterococcus</i> spp†	21 (8%)	2 (2%)	1 (7%)	5 (7%)
HACEK group	12 (4%)‡	0	0	1 (1%)
Polymicrobial	6 (2%)	8 (9%)	0	1 (1%)
Other bacteria	12 (4%)§	4 (5%)	0	2 (3%)
Fungi	3 (1%)	2 (2%)	0	0
Negative blood culture	16 (6%)	4 (5%)	4 (27%)	5 (7%)

*Including nine *Streptococcus agalactiae*, six *Strep bovis*, three *Streptococcus pneumoniae*, two *Streptococcus pyogenes*, one group G *Streptococcus*, and one *Abiotrophia* spp. †>80% *Enterococcus faecalis*. ‡ Includes *Haemophilus* spp, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *E. corrodens*, and *K. kingae*. §Includes four *Escherichia coli*, two *Corynebacterium* spp, two *Proteus mirabilis*, one *Mycobacterium tuberculosis*, and one *Bacteroides fragilis*. Data from studies providing comparable microbiological details.^{4,5,10}

Table 1: Microbiology of infective endocarditis (IE) in general population and in specific at-risk groups

persistence and growth of bacteria within the cardiac lesions, usually associated with local extension and tissue damage. Dissemination of septic emboli to distant organs—eg, kidney, spleen, and brain—then takes place.

Adherence to damaged valves

Mechanical and inflammatory lesions can promote valve seeding during transient bacteraemia (figure 2 A and B, respectively).

Mechanical lesions

Any excoriation of the endothelium results in direct contact between the blood and subendothelial host components, including proteins of the extracellular matrix, thromboplastin, and tissue factor, which trigger blood coagulation. The coagulum that forms on damaged endothelia contains large quantities of fibrinogen—fibrin, fibronectin, plasma proteins, and platelet proteins. Pathogens associated with infective endocarditis avidly bind to these structures and colonise them during transient bacteraemia.³² In turn, adherent bacteria attract and activate blood monocytes to produce more tissue factor as well as cytokines.³⁵ Cytokines and procoagulant factors contribute to further enlargement of the infected coagulum, formally named the vegetation. This process provides a niche for the infecting microbes.

Monocytes that adhere to the early vegetation do not engulf the attached bacteria,³⁴ which hijack the monocytes' coagulation and proinflammatory function to get embedded in the vegetation. Mechanical valve lesions promote infection by all pathogens classically associated with infective endocarditis, including staphylococci, streptococci, and enterococci.³⁵

Inflammatory lesions

Endothelial cells respond to local inflammation by expressing various molecules, including integrins of the β 1 family (very late antigen or VLA).³⁶ Integrins are transmembrane proteins that can connect extracellular factors to the cytoskeleton. Integrins of the β 1 family bind fibronectin to the endothelial surface. *Staph aureus* and a few other infective endocarditis-associated pathogens carry fibronectin-binding proteins on their surface. Thus, binding fibronectin on the endothelium provides an adhesive surface to circulating staphylococci. Once

adhered, *Staph aureus* can trigger their active internalisation by the host cells,³⁷ where they can either persist, escaping host defences and antibacterial agents, or multiply and spread to distant organs. This behaviour is orchestrated by global regulators, such as *agr* (accessory gene regulator) and *sar* (staphylococcal accessory regulator), which sense bacterial density and trigger or not the secretion of haemolysins and toxins for the purpose of invasion.^{38,39}

Staph aureus is associated with infective endocarditis in patients without previously known valve disease, and is frequently responsible for disease in intravenous drug users. Valve inflammation can arise in several clinically silent situations, which are likely to promote local deposition of fibronectin. For instance, up to 25% of patients older than age 40 years have degenerative valve lesions²¹ that harbour microulcerations and local inflammation, resembling arteriosclerosis.⁴⁰ Similarly, repeated injections of impure material by drug users could encourage cytokine production and promote inflammatory lesions, especially on right-sided valves.

Characteristics of microorganisms

The organisms most frequently responsible for infective endocarditis are those that have the greatest ability to adhere to damaged valves.³² Together, *Staph aureus*, *Streptococcus* spp, and enterococci are responsible for more than 80% of all instances of disease (figure 1 and table 1). These organisms have surface adhesins that mediate attachment to the vegetation. These adhesins are referred to as MSCRAMMs or microbial surface component reacting with adhesive matrix molecules.⁴¹

In the instance of *Staph aureus*, fibrinogen-binding proteins—also called clumping factor—and fibronectin-binding proteins are involved in valve colonisation and infection.⁴² The importance of these adhesins was shown by expressing them separately in a surrogate bacterium—ie, *Lactococcus lactis*—which does not have the many other staphylococcal MSCRAMMs. Recombinant lactococci, expressing the staphylococcal adhesins, increased their infectivity by more than 100-fold in experimental endocarditis.⁴² Other *Staph aureus* MSCRAMMs, such as clumping factor B and coagulase, were less likely to play a part.^{43,44} In streptococci, surface adhesins, platelet-activating factors, and exopolysaccharides are involved.³²

In-situ bacterial persistence

After valve colonisation, the infecting microorganisms must survive and avoid host defences. A key event in this process is maturation of the vegetation, within which the microorganisms become fully enveloped. Both staphylococci and streptococci can trigger tissue-factor production from local monocytes⁴⁵ and induce platelet aggregation (figure 2).^{46,47} Bacterial-induced platelet activation is a double-edged sword though; activated platelets release platelet-microbicidal-proteins,⁴⁸ which kill bacteria by altering their plasma membrane.⁴⁹ Microorganisms recovered from patients with infective endocarditis were consistently resistant to platelet-induced killing, whereas similar bacteria recovered from patients with other types of infection were susceptible to platelet-microbicidal proteins.⁵⁰ Therefore, pathogens associated with infective endocarditis must resist platelet-induced killing to take advantage of the platelet procoagulant effect.

Certain bacteria can hide inside endothelial cells; bridging *Staph aureus* and endothelial cells via fibronectin triggers bacterial internalisation both in vitro³⁷ and in experimental endocarditis.⁵¹ Endothelial invasion can also

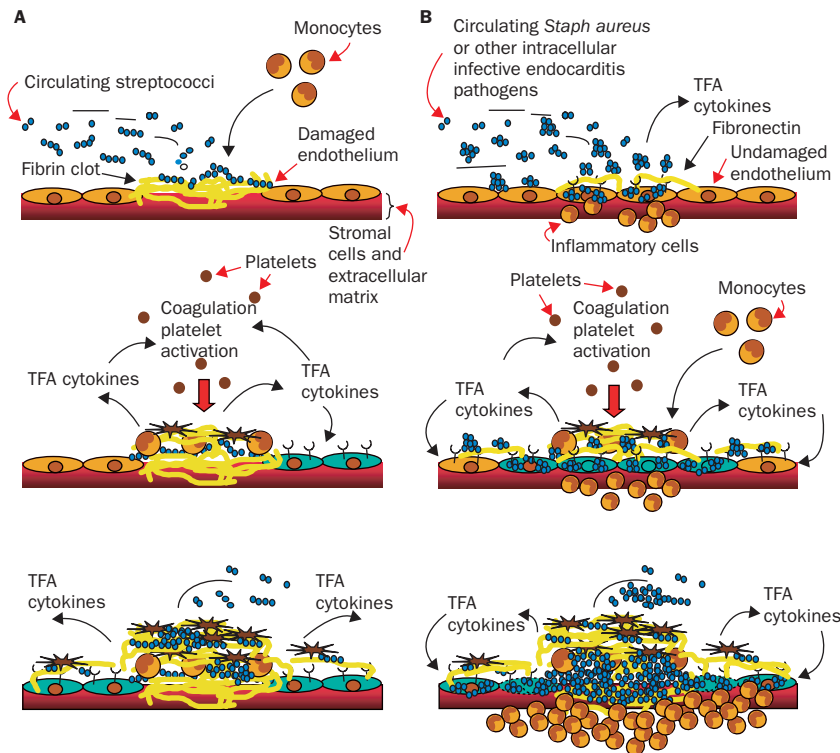


Figure 2: **Early steps in bacterial valve colonisation**³²

(A) *Colonisation of damaged epithelium:* exposed stromal cells and extracellular matrix proteins trigger deposition of fibrin-platelet clots to which streptococci bind (upper panel); fibrin-adherent streptococci attract monocytes and induce them to produce tissue-factor activity (TFA) and cytokines (middle panel); these mediators activate coagulation cascade, attract and activate blood platelets, and induce cytokine, integrin, and TFA production from neighbouring endothelial cells (lower panel), encouraging vegetation growth.

(B) *Colonisation of inflamed valve tissues:* in response to local inflammation, endothelial cells express integrins that bind plasma fibronectin, which microorganisms adhere to via wall-attached fibronectin-binding proteins, resulting in endothelial internalisation of bacteria (upper panel); in response to invasion, endothelial cells produce TFA and cytokines, triggering blood clotting and extension of inflammation, and promoting formation of the vegetation (middle panel); internalised bacteria eventually lyse endothelial cells (green cells) by secreting membrane-active proteins—eg, haemolysins (lower panel). Adapted from reference 32 with permission from Elsevier.

arise with rare intracellular infective endocarditis pathogens, such as *Coxiella burnetii* (the agent of Q fever), *Chlamydia* spp, *Legionella* spp, and *Bartonella* spp.¹³ The exact mechanism of action of these infections is unknown.

Invasion and dissemination

Tissue invasion and abscess formation are primary features of infective endocarditis. Besides surface-bound adhesins, *Staph aureus* produce a wealth of exoenzymes that convert local host tissues into nutrients for bacterial growth, and exotoxins that are detrimental to the host. The expression of these factors is controlled by the global regulators *agr* and *sar* and maybe *sigB* (sigma B).^{38,39,52} *sar* is activated in infected vegetations.⁵³ Moreover, inactivation of *agr* by mutation or by blocking agents greatly decreases the formation of subcutaneous abscesses in mice.⁵⁴ Invasion and dissemination of other pathogens associated with infective endocarditis probably follow similar scenarios. However, since they are less destructive than *Staph aureus* they have been less well studied.³²

Role of transient bacteraemia

Medicosurgical procedures in non-sterile sites can provoke bacteraemia. Such bacteraemias are usually low grade and of short duration (1–100 colony forming units per mL of blood for less than 10 min in the case of dental extraction). However, they can promote infective endocarditis in

patients with pre-existing valve lesions, as simulated in rats with catheter-induced aortic vegetations; animals with experimental gingivitis were at a greater risk of postextraction endocarditis than those with healthy gingivae.⁵⁵

Transient bacteraemia arises spontaneously during chewing, tooth-brushing, and other normal activities, which probably explains why most instances of infective endocarditis are not preceded by medicosurgical procedures.^{56–58} Spontaneous bacteraemias that arise during chewing could explain why oral streptococci are a predominant cause of disease. Hence, even if antibiotic prophylaxis during dental procedures were effective, it would only prevent a limited number of cases.⁵⁹ Good dental hygiene is the best preventive measure.

Role of host defences

Infective endocarditis is more often due to gram-positive than gram-negative bacteria (figure 1 and table 1), possibly because of differences in adherence to damaged valves or because of differences in their susceptibility to serum-induced killing.⁶⁰ The C5b–C9 membrane-attack complex of the complement system kills gram-negative bacteria by perforating their outer membrane; gram-positive bacteria, however, have no outer membrane and are resistant to such attack. Some gram-negative bacteria have thick capsules or other properties that help them resist complement-induced killing. An important subgroup of gram-negative

pathogens associated with infective endocarditis includes microorganisms of the HACEK group, as well as *Paeruginosa* in intravenous drug users.^{24,26}

Gram-positive pathogens might also resist other humoral and cellular host defences. They can resist platelet-induced killing⁵⁰ and inconsistently respond to antibodies. Immunisation of rats against the streptococcal MSCRAMM FimA conferred cross-protection against infective endocarditis due to other oral streptococci.⁶¹ By contrast, immunisation of rabbits against the enterococcal aggregation-substance did not protect them against disease.⁶² In this case, the antibodies that arose from vaccination could not penetrate inside the vegetation. Administration of granulocyte colony-stimulating factor did not affect the course of disease either.⁶³ Infective endocarditis is not noticeably more frequent in immunocompromised patients than in those without immune defects. This fact explains why successful treatment of disease relies primarily on the ability of antibiotics to kill bacteria in situ rather than on host defences.

Prophylaxis

Because of its severity, infective endocarditis should be prevented whenever possible. Determination of adequate prophylaxis implies establishing the patients at risk, the procedures that might provoke bacteraemia, the most

Modified Duke criteria for diagnosis of infective endocarditis (IE)*

Major criteria

Blood culture

Positive blood cultures ($\geq 2/2$) with typical IE microorganisms (viridans streptococci, *Strep bovis*, HACEK group, ***Staph 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 most of four culture sets with the first and last separated by ≥ 1 h
Single positive culture for *C burnetti* or antibody titre against phase I >1 in 800

Endocardial involvement

Positive echocardiogram for IE (**transoesophageal echo recommended in patients with prosthetic valves, patients rated as possible IE by clinical criteria, or complicated IE (paravalvular abscess); transthoracic echo as first option in other patients**):
(i) oscillating intracardiac mass on valve or supporting structure, or in the path of regurgitant jets, or on implanted material, in the absence of an alternative anatomical explanation, or
(ii) abscess, or
(iii) new partial dehiscence of prosthetic valve.
New valvular regurgitation (worsening of changing or pre-existing murmur not sufficient)

Minor criteria

Predisposing cardiac condition or intravenous drug use
Fever (temperature $\geq 38^\circ\text{C}$)
Vascular factors—major arterial emboli, septic pulmonary infarct, mycotic aneurysms, intracranial haemorrhage, conjunctival haemorrhage, Janeway's lesions
Immunological factors: glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor
Microbiology—positive blood cultures, but not meeting major criteria, serological evidence of active infection with plausible microorganisms‡
Echocardiogram consistent with disease but not meeting major criteria§

Diagnosis

Definite

Pathology or bacteriology of vegetations, major emboli, or intracardiac abscess specimen, 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 syndrome after ≤ 4 days of antibiotherapy, or
No pathological evidence at surgery or autopsy after ≤ 4 days of antibiotherapy
Does not meet criteria mentioned above

*Modifications of criteria proposed by Li and colleagues³ in bold.

†Original Duke criteria state: "or community-acquired *S aureus* or enterococci in the absence of primary focus".² ‡Excludes single positive cultures of coagulase-negative staphylococci and organisms that do not cause endocarditis. §In original Duke criteria,² but abandoned in revised criteria.³ ¶Original Duke criteria state: "findings consistent with IE that fall short of "Definite", but not "Rejected".² Adapted from references 2 and 3 with permission from Mosby.

effective prophylactic regimen, and a balance between the risks of side-effects of prophylaxis and of developing the disease. Patients at risk and procedures that induce bacteraemia have been identified by clinical studies, and recommendations for prophylaxis have been proposed in several countries.⁶⁴⁻⁶⁶ However, the efficacy of prophylactic antibiotics is based on experiments done in animals. Randomised, placebo-controlled studies have not been undertaken, since the number of patients needed to treat is too large and would raise ethical issues because of the severity of the disease.⁶⁷ Results of case-control studies^{56,59,68} indicate that prophylaxis is effective, but prevents only a limited number of cases. Indeed, most instances of infective endocarditis are not preceded by medicosurgical procedures.⁵⁶⁻⁵⁸ Therefore, the primary prevention of disease should target infected foci responsible for spontaneous bacteraemia—eg, poor dental hygiene.⁶⁴⁻⁶⁶

Diagnosis: Duke criteria

Precise diagnosis is mandatory to guide therapy. In theory, infective endocarditis combines both persistent bacteraemia and anatomical lesions of the valves. However, blood cultures remain negative in about 10% of cases (figure 1 and table 1). Diagnosis is difficult in culture-negative cases, or when the valve status is unclear.^{2,3}

In 1994, new diagnostic criteria based on both microbiological data and echocardiographic imaging were proposed.² These so-called Duke criteria were validated

	Diagnostic procedure	Proposed therapy*
Pathogen		
<i>Brucella</i> spp	Blood cultures; serology; culture, immunohistology, and PCR of surgical material	Doxycycline plus rifampin or cotrimoxazole (treatment for >3 months) ¹⁰⁵
<i>C burnetti</i>	Serology (IgG phase I >1 in 800); tissue culture, immunohistology, and PCR of surgical material	Doxycycline 100 mg orally twice daily plus hydroxychloroquine 200 mg orally three times daily, ¹⁰⁶ or doxycycline plus quinolone (>18 months' treatment)
<i>Bartonella</i> spp	Blood cultures; serology; culture, immunohistology, and PCR of surgical material	β lactams or doxycycline plus aminoglycoside (>6 weeks' treatment)†
<i>Chlamydia</i> spp	Serology‡; culture, immunohistology, and PCR of surgical material	Doxycycline or newer fluoroquinolones§ (long-term treatment, optimum duration unknown)
<i>Mycoplasma</i> spp	Serology; culture, immunohistology, and PCR of surgical material	Doxycycline; newer fluoroquinolones§ (>12 weeks' treatment)
<i>Legionella</i> spp	Blood cultures; serology; culture, immunohistology, and PCR of surgical material	Macrolides plus rifampin or new fluoroquinolones§ (>6 months' treatment)
<i>T whipplei</i>	Histology and PCR of surgical material	Cotrimoxazole¶ or β lactam plus aminoglycoside (long-term treatment, optimum duration unknown)

*Due to lack of large series on infective endocarditis caused by these pathogens, optimum treatment duration is mostly unknown; durations in table are indicative and based on selected case reports. †Several therapeutic regimens reported, including aminopenicillins and cephalosporins combined with aminoglycosides, doxycycline, vancomycin, and quinolones.¹³ ‡Beware of serological cross-reaction with more common pathogen associated with infective endocarditis—*Bartonella* spp. §Newer fluoroquinolones more potent than ciprofloxacin against intracellular pathogens such as *Mycoplasma* spp, *Legionella* spp, and *Chlamydia* spp. ¶Treatment highly empirical. Successes reported with long-term (>1 year) cotrimoxazole therapy. γ interferon plays protective part in intracellular infections, and was proposed as adjuvant therapy in Whipple's disease.⁷⁸ Adapted from reference 13 with permission from Mosby.

Table 2: Rare causes of infective endocarditis associated with negative blood cultures

	Dose and route	Duration (weeks)	Comments
Penicillin-susceptible viridans streptococci and <i>Strep bovis</i>			
Procain benzylpenicillin	6×2–3 million U daily IV	4	Preferred in patients older than age 65 years or with impaired renal function
Ceftriaxone*	1×2 g daily IV or IM	4	
Procain benzylpenicillin with gentamicin	6×2–8 million U daily IV 3×1 mg/kg daily IV or IM	2	Gentamicin once daily might be adequate
Ceftriaxone* with netilmicin	1×2 g daily IV or IM 1×4 mg/kg daily IV	2	
Vancomycin	2×15 mg/kg daily IV	4	Recommended for patients allergic to β lactam
Intermediate penicillin-resistant (MIC 0.1–1 mg/L) viridans streptococci and <i>Strep bovis</i>			
Procain benzylpenicillin with gentamicin	6×3 million U daily IV 3×1 mg/kg daily IV or IM	4	Gentamicin once daily might be adequate
Vancomycin	2×15 mg/kg daily IV	4	Recommended against highly resistant strains or for patients allergic to β lactam
<i>Enterococcus spp</i>†			
Procain benzylpenicillin with gentamicin	6×3–5 million U/daily IV 3×1 mg/kg daily IV or IM	4–6	6-weeks' therapy recommended for patients with >3 months symptoms
Ampicillin with gentamicin	6×2 g/daily IV 3×1 mg/kg daily IV or IM	4–6	Gentamicin once daily might be adequate
Vancomycin with gentamicin	2×15 mg/kg daily IV 3×1 mg/kg daily IV or IM	4–6	Monitor drug serum concentrations and renal function
Microorganisms of the HACEK group‡			
Ceftriaxone*	1×2 g daily IV or IM	4	
Ampicillin with gentamicin	6×2 g daily IV 3×1 mg/kg daily IV or IM	4	Gentamicin once daily might be adequate

Table 3: Suggested treatment for native-valve endocarditis due to streptococci, enterococci, and HACEK microorganisms

worldwide,^{69–75} and were refined in 2000 to more accurately detect infective endocarditis in the case of negative blood cultures and *Staph aureus*-associated bacteraemia (panel).³ All patients suspected of having infective endocarditis should undergo at least one echocardiographic assessment, including transoesophageal echo in selected individuals. However, a negative echo does not rule out the disease if other criteria are positive.

The importance of blood culture cannot be overemphasised. It remains the best identification method and provides live bacteria for susceptibility testing. For the main causative agents, the first two blood cultures (drawn 30 min or more apart) will be positive in more than 90% of cases. Culture-negative disease is often associated with antibiotic consumption within the previous 2 weeks. Disease might also be due to fastidious or intracellular pathogens that are not easily detected by standard culture conditions.

Identification of the pathogen in culture-negative disease depends on special procedures, which comprise inactivating antibiotics in the culture media, prolonging incubation

(≥ 2 weeks), serology, agglutination, indirect fluorescence, ELISA, complement fixation, and PCR amplification of the 16S ribosomal RNA gene—ie, genes that are specific for bacteria.^{13,76} PCR is useful since it identifies bacterial DNA in tissue samples, including valves and peripheral emboli.⁷⁷ The procedure is invaluable in the detection of poorly or non-cultivable bacteria such as *T whipplei*.⁷⁸ Nevertheless, PCR results can remain positive even after long-term treatment with antibiotics. Thus, specific knowledge and careful interpretation is needed to avoid erroneous conclusions.

Undiagnosed culture-negative infective endocarditis is a problem because unusual pathogens might not respond to empirical treatment with β lactams or aminoglycosides. Table 2 lists the main organisms in this group, and the proposed diagnostic procedures and therapy options.¹³

Management

Treatment of infective endocarditis depends on a multidisciplinary approach, involving at least specialists in infectious disease, cardiologists, and cardiac surgeons. The

	Dose and route	Duration (weeks)	Comments
Native valves			
Meticillin-susceptible staphylococci			
Flucloxacillin, or oxacillin, or nafcillin with gentamicin (optional)	6×2 g daily IV 3×1 mg/kg daily IV or IM	4–6	Benefit of gentamicin addition not known
Cefazolin (or other first generation cephalosporins) with gentamicin (optional)	3×2 g daily IV 3×1 mg/kg daily IV or IM	4–6	Alternative for patients allergic to penicillins (not in case of immediate-type penicillin hypersensitivity)
Vancomycin	2×15 mg/kg daily IV	4–6	Recommended for patients allergic to β lactam
Meticillin-resistant staphylococci			
Vancomycin	2×15 mg/kg daily IV	4–6	Recommended for patients allergic to β lactam
Prosthetic valves			
Meticillin-susceptible staphylococci*			
Flucloxacillin, or oxacillin, or nafcillin with rifampicin	6×2 g daily IV 3×300 mg daily orally	≥ 6	Rifampin increases hepatic metabolism of numerous drugs, including warfarin
and gentamicin	3×1 mg/kg daily IV or IM	2	
Vancomycin	2×15 mg/kg daily IV	≥ 6	Recommended for patients allergic to β lactam
with rifampicin	3×300 mg daily orally	≥ 6	
and gentamicin	3×1 mg/kg daily IV or IM	2	
Meticillin-resistant staphylococci			
Vancomycin	2×15 mg/kg daily IV	≥ 6	
with rifampicin	3×300 mg daily orally	≥ 6	
and gentamicin	3×1 mg/kg daily IV or IM	2	

IV=intravenous. IM=intramuscular. *Rifampicin plays a special part in prosthetic device infection, because it helps kill bacteria attached to foreign material. Rifampicin should never be used alone, because it selects for resistance at a high frequency (about 10^{-6}). Adapted from references 79–81 with permission from Mosby.

Table 4: Suggested treatment for native-valve and prosthetic-valve endocarditis due to staphylococci

standard therapeutic regimens proposed below are a consensus based on five articles^{79–83} selected in the 1993–2003 PubMed search described above. Regimens for resistant organisms or blood culture negative infective endocarditis are addressed in further sections. Most publications express specialist opinion or detail small case-control studies. No large or blinded studies have been undertaken as far as we are aware.

Bactericidal antibiotics are a cornerstone of therapy. Therapeutic schemes recommended for the most common pathogens are presented in tables 3 and 4.^{79–81} High concentrations of antibiotic in the serum are desirable to ensure diffusion into the vegetations. Long-term treatment is mandatory to kill dormant bacteria clustered in the infected foci. Outpatient and oral therapy is sometimes proposed,^{82,83} but long-term parenteral therapy is usually recommended.

The choice of an optimum regimen is based on antibiotic susceptibility testing. Minimum inhibitory concentrations (MIC) of the principal drugs for the infecting pathogens should be ascertained. Resistant pathogens and culture-negative infective endocarditis might not respond to standard treatments and are discussed below.

Penicillin-resistant streptococci

Streptococci are becoming increasingly resistant to penicillin and other β lactams, owing to a decreased β -lactam affinity of their membrane-bound penicillin-binding proteins. Penicillin-resistant streptococci are classified as having either intermediate (MIC 0.1–1 mg/L) or high resistance (MIC >1 mg/L).

Intermediately resistant streptococci might respond to standard therapy because β -lactam concentrations in the serum are much greater than the MIC for these bacteria. Peak serum concentrations of penicillin, amoxicillin, or ceftriaxone are 100 mg/L or so—ie, 100–1000 times greater than the MIC of intermediately resistant streptococci (MIC 0.1–1 mg/L). Nonetheless, potentiating the activity of β lactams by combining them with an aminoglycoside is recommended in such situations.

Alternative drugs should be considered against highly resistant streptococci—eg, vancomycin, to which streptococci are still widely susceptible. New quinolones with anti-gram-positive activity and quinupristin/dalfopristin could also prove useful.^{84,85} Oxazolidinones are an alternative, but they are poorly bactericidal.^{86,87}

Meticillin-resistant staphylococci

All meticillin-resistant staphylococci carry a low-affinity penicillin-binding protein called PBP2A, which confers cross-resistance to most β lactams. Furthermore, meticillin-resistant staphylococci are usually resistant to most other drugs, leaving only vancomycin with which to treat severe infections.

Vancomycin resistance is, however, beginning to develop. *Staph aureus* and coagulase-negative staphylococci with intermediate resistance to vancomycin have emerged worldwide.^{88,89} The mechanism of intermediate resistance is mediated by chromosomal mutations, affecting the synthesis of the cell wall.^{90,91} High vancomycin resistance emerged 15 years ago in enterococci, and can be transferred experimentally to *Staph aureus*.⁹² A few highly vancomycin-resistant *Staph aureus* organisms have been isolated in clinics; their vancomycin-resistance genes were also acquired from enterococci.^{93,94}

New approaches need to be developed for the treatment of infective endocarditis caused by vancomycin-resistant staphylococci. A few compassionate-use (ie, not formally

licensed for his indication) alternatives are available, including old and new β lactams with fairly good affinity to PBP2A,^{95–97} quinupristin/dalfopristin combined or not to β lactams,^{84,98,99} antibiotic combinations, including co-trimoxazole,¹⁰⁰ and maybe oxazolidinones.¹⁰¹ Meticillin-resistant staphylococci are usually resistant to newer quinolones.

Multidrug-resistant enterococci

These organisms are resistant to most drugs, including vancomycin.^{102,103} Treatment of such bacteria relies on the combination of multiple drugs and the use of experimental antibiotics.¹¹ It depends on precise determination of antibiotic susceptibilities, testing for bactericidal activity, ascertainment of the serum inhibitory and bactericidal titres, and monitoring of drug concentrations in the serum. Although aminoglycoside-resistance is often present, these drugs can still synergise with cell-wall inhibitors provided that the aminoglycoside's MIC is 1000 mg/L or less.¹⁰⁴ Streptomycin is worth testing because it can be active against enterococci that are resistant to other aminoglycosides.¹¹ Salvage regimens suggested against highly aminoglycoside-resistant, but ampicillin-susceptible, enterococci include continuous infusion of high-dose ampicillin alone or combined with ceftriaxone, other β -lactam combinations, or oxazolidinones. Whenever used, such an approach should be based on specialist advice.

Culture-negative endocarditis

Table 2 summarises the treatment options for infective endocarditis due to rare pathogens. Disease caused by *Brucella* spp responds to 3 months or more of treatment with doxycycline (100–200 mg every 12 h) plus co-trimoxazole (960 mg every 12 h) or rifampicin (300–600 mg daily) combined or not with streptomycin (16 mg/kg per day). Surgery might be needed.¹⁰⁵ Cure is defined by an antibody titre returning to less than one in 160.

Disease associated with *C burnetii* is often treated with doxycycline combined with a fluoroquinolone for up to 3 years. Recurrences are common. A combination of doxycycline and hydroxychloroquine has been tested¹⁰⁶ and seemed more effective than the fluoroquinolone combination. Treatment is considered a success when the antigen against phase I IgG titre is less than one in 800, and IgM and IgA titres are less than one in 50.¹⁰⁶

Infective endocarditis caused by *Bartonella* spp responds to β lactams (amoxicillin or ceftriaxone) combined with aminoglycosides (netilmicin or gentamicin) for at least 2 weeks, or β lactams combined with other drugs—eg, doxycycline—for 6 weeks or more.¹⁰⁷ Combination with surgery is reported in at least 90% of cases.

There is no treatment for disease caused by *Chlamydia* spp, *Mycoplasma* spp, and *Legionella* spp. However, since these organisms are highly susceptible to newer fluoroquinolones in vitro, this drug type should probably be part of the treatment.

Infective endocarditis associated with *T whipplei* is rare. In Whipple's disease not associated with infective endocarditis, co-trimoxazole (960 mg every 12 h) given for at least 1 year is recommended.⁷⁸ Some authors recommend sequential treatment, starting with penicillin plus streptomycin, or ceftriaxone plus gentamicin, for 2–6 weeks, followed by long-term co-trimoxazole. A review¹⁰⁸ of 35 cases of Whipple-associated disease lends support to this approach and suggests that surgical valve-replacement might be a prerequisite for successful therapy.

Surgery

Surgery is important in the treatment of infective endocarditis.¹⁰⁹ This highly specialised area is, however, beyond the scope of our review. It encompasses both radical valve replacement and more conservative vegetectomy and valve repairs.¹¹⁰ Surgery is necessary in 25–30% of cases during acute infection, and in 20–40% in later phases.^{111,112} The final outcome has little relation to the duration of previous antibiotic therapy.^{113–115} The main indications for surgery comprise refractory cardiac failure caused by valvular insufficiency, persistent sepsis caused by a surgically removable focus or a valvular ring or myocardial abscess, and persistent life-threatening embolisation. The decision to operate should be made by a team, though the delay associated with such a multidisciplinary approach can be difficult to justify in the case of embolic stroke, in which a delay to surgery can be detrimental. Results of studies on surgery for active infective endocarditis indicate mortality rates of 8–16%, with actuarial survival at 5 years of 75–76% and at 10 years of 61%.^{113,116–120}

New developments

Developments on ways to prevent and treat infective endocarditis reflect modification of both the bacterium and the host. Vaccines or artificial peptides directed against specific bacterial adhesins could interfere with valve colonisation. Some experimental successes have been achieved with a vaccination against the streptococcal FimA protein¹²¹ and the staphylococcal fibronectin-binding and collagen-binding proteins.^{122–125} Encouraging clinical successes were reported in haemodialysis patients.¹²⁶ However, limits to vaccination are the multiplicity of bacterial adhesins and the quality of the host immune response.

Blocking the anchoring of adhesins at the bacterial surface could alter adherence. Sortase is an enzyme that covalently attaches surface proteins to the wall of gram-positive bacteria.^{127,128} Inhibition of the action of sortase impedes the surface-attachment of numerous MSCRAMMs, and decreases infectivity in some animals.^{129–132} However, the strategy is limited because bacteria do not only use sortase to attach proteins at their surface.¹³³

Decreasing formation of the vegetation by treatment with platelet antiaggregants—eg, acetylsalicylate and ticlopidine—has seen some experimental success.^{134–137} However, antiaggregants simultaneously decrease platelet-induced bacterial killing.¹³⁸ Moreover, like anticoagulants,¹³⁹ antiaggregants increase the risk of secondary bleeding in the case of cerebral emboli. Antiaggregants are not, therefore, recommended in the management of infective endocarditis.

For *Staph aureus*, bacterial invasion could be decreased by shutting off *agr*-mediated secretion of haemolysins and toxins, as has been achieved by inhibiting molecules that mimic the *agr* autoinducing peptides.⁵⁴ Although not curative, such strategies could decrease tissue inflammation and destruction, thus improving the symptoms of the patient, receiving concomitant antibiotic therapy.

Modified biomaterials with antiadherence properties are being researched as a means of preventing disease associated with prosthetic valves. Prevention of infection of biomaterials by impregnation with antiseptics has been tested in clinical trials. However, whether the technology works remains inconclusive.¹⁴⁰

Finally, new drugs are being investigated, which have novel mechanisms of action. Academic research has resulted in the development of a novel compound that

takes advantage of bacteriophage-encoded bacteriolytic enzymes. Such purified molecules digest the essential gram-positive peptidoglycan within minutes, and have unique antibacterial effects against both pneumococci and *Bacillus anthracis*.^{141,142} Likewise, direct targeting of *Staph aureus* with their own bacteriophage is an ancient notion that has been attempted as a last resort therapy for burn patients in Georgia.¹⁴³ Although developmental, these examples indicate the multiple facets that arise from the increasing comprehension of the pathogenesis of disease.

Conclusion

Improvements in health care have almost eradicated classical forms of infective endocarditis. Increased life expectancy and new medical and social behaviours have, however, generated a new group of at-risk patients. Prosthetic-valve endocarditis, nosocomial endocarditis, and endocarditis in intravenous drug users and in haemodialysis patients are not due to classic pneumococci, gonococci, or streptococci, but rather to staphylococci, gram-negative bacteria, and fungi. The apparent increase in infective endocarditis associated with *Bartonella* spp and *Strep bovis* in homeless and elderly patients could reflect further epidemiological drifts.⁷ Numerous questions remain unanswered. Why is the disease so rare compared with the frequency of valve disease? Can bacterial decolonisation or vaccination prevent *Staph aureus*-associated disease in haemodialysis patients and maybe in intravenous drug users? Could vegetectomy prevent major embolisation? Results of experiments indicate that the magnitude of bacteraemia is positively correlated with the risk of infection,⁴² and that decreasing bacteraemia or bacterial adherence is protective. Hence, bacterial decolonisation or antiadhesin vaccines should be helpful.¹²⁶ Whether embolisation can be prevented by vegetectomy is uncertain. Most patients are diagnosed after embolisation, and predictors of such events are controversial.^{144,145} Solving all of these issues will depend on continuing clinical and laboratory research, particularly into the decrypting of the bacterial-host interplay.

Conflict of interest statement

None declared.

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