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EPIDEMIOLOGY AND ANTIBIOTIC TREATMENT OF INFECTIVE ENDOCARDITIS: AN UPDATE

Bruno Hoen

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The epidemiological profile of infective endocarditis (IE) has changed dramatically over the last few years.¹ Once a disease affecting young adults with previously well-identified valve disease—mostly rheumatic disease—IE is now affecting older patients, a significant proportion of whom has no previously known valve disease and develop IE as the result of healthcare associated procedures.²

A CHANGING EPIDEMIOLOGY

Until the end of the 1970s, rheumatic valvulopathies and congenital cyanotic cardiopathies were the two most frequent predisposing factors for IE. Then, a few years after the effective eradication of rheumatic fever, post-rheumatic valvulopathies gradually disappeared. However, other predisposing factors emerged, such as intravenous drug use, valve prostheses, degenerative valve sclerosis, and invasive procedures at risk for bacteraemia, which resulted in nosocomial and health care-associated endocarditis.³ These changes had at least two consequences: (1) the absence of a reduction in the incidence of IE; and (2) major changes in the microbiological profile of IE. In a meta-analysis of 26 articles published between 1993 and 2003, including a total of 3784 episodes of IE, Moreillon and Que showed that oral streptococci (also known as viridans streptococci) are now only second to staphylococci as the leading cause of IE.¹ As a result, it is now critical to regard the epidemiology of IE as a set of various clinical situations sometimes differing greatly from one another. Thus, at least five categories of IE have been identified: native valve endocarditis; prosthetic valve endocarditis; endocarditis in intravenous drug users (IVDUs); nosocomial endocarditis; and healthcare-related endocarditis resulting from invasive procedures such as endovascular investigations, haemodialysis, and implanted endovascular or intracardiac devices. Significant geographical variations have also been shown, with the highest increases in the rate of staphylococcal endocarditis being reported in the United States.⁴ In a prospective study of 1779 cases of IE collected in 16 countries, *Staphylococcus aureus* was the primary cause.⁵ In this study, *S aureus* IE was more frequent in the United States, and also in Australia/New Zealand and South America, than in Europe. In the USA, chronic haemodialysis, diabetes mellitus, and intravascular devices are the three main factors associated with the development of *S aureus* endocarditis.^{4,5} In other countries, the main predisposing factor for *S aureus* endocarditis is intravenous drug use.⁶

INCIDENCE OF INFECTIVE ENDOCARDITIS

The incidence of IE varies from country to country, which may reflect more methodological differences in surveys than true incidence variations. In an epidemiologic study conducted in Sweden from 1984 to 1988 the incidence of IE was 5.9 episodes/100 000 person-years after adjusting for both age and sex.⁷ During a similar time period, the total incidence of IE was 9.29 episodes/100 000 person-years in the Philadelphia metropolitan area, which fell to 5.02 episodes/100 000 person-years when cases involving intravenous drug users were excluded.⁸ In the 1990s, French investigators performed two epidemiologic surveys in three regions of France that represented about 25% of the whole French population. In 1991 their survey found the crude incidence to be 2.24 episodes/100 000 person-years, which increased to 2.43 episodes/100 000 person-years after adjustment for age and sex.⁹ When this study was repeated in 1999 the crude and adjusted incidence rates were 3.0 and 3.1 episodes/100 000 person-years.² Of note, in these two surveys, as in others, the incidence of IE was very low in young patients whereas it increased dramatically with age. In France, the peak incidence was 14.5 episodes/100 000 person-years in patients aged between 70–80 years.

MICROBIOLOGY

According to the contribution of blood cultures to the diagnosis of IE, the following classification can be proposed.

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IE with positive blood cultures

This is the most important category, representing about 85% of all episodes of IE. Causative microorganisms are most often streptococci, enterococci, and staphylococci.

IE caused by streptococci and enterococci

Oral streptococci form a mixed group of microorganisms, which includes species such as *Streptococcus sanguis*, *S mitis*, *S salivarius*, and *S mutans*, to which one usually adds *Gemella morbillorum* (formerly *S morbillorum*). Microorganisms of this group are almost always susceptible to penicillin G. Members of the “*S milleri*” or “*S anginosus*” group (*S anginosus*, *S intermedius*, and *S constellatus*) must be distinguished from the former group because they tend to form abscesses and cause haematogenously disseminated infection, which often requires a longer duration of antibiotic treatment. Likewise, nutritionally-variant “defective” streptococci, which were recently reclassified into other species (*Abiotrophia* and *Granulicatella*), should also be distinguished because they are often tolerant to penicillin (minimal bactericidal concentration (MBC) much higher than the minimal inhibiting concentration (MIC)). Group D streptococci form the “*Streptococcus bovis*/*Streptococcus equinus*” complex, which includes several commensal species of the human intestinal tract and were until recently grouped under the name of *Streptococcus bovis*. They are generally quite sensitive to penicillin G, like oral streptococci.

Among enterococci, *Enterococcus faecalis*, *E faecium*, and to a lesser extent *E durans*, are the three species that can cause IE.

Staphylococcal IE

Traditionally, episodes of native valve staphylococcal IE are caused by *S aureus*, which are most often susceptible to oxacillin, at least when the strains are community-acquired. By contrast, in prosthetic valve IE, staphylococci are more frequently coagulase-negative staphylococci and are often oxacillin-resistant. However, in a recent study of 1779 cases of IE collected prospectively in 16 countries, *S aureus* was not only the principal cause of IE but also the main cause of prosthetic valve IE.⁵ Conversely, coagulase-negative staphylococci can also cause native valve IE.¹⁰

IE with negative blood cultures because of prior antibiotic treatment

This is the usual situation in a patient in whom the diagnosis of IE was not considered and who received antibiotics for an unexplained fever before any blood culture was performed; the diagnosis is eventually considered in the face of relapsing febrile episodes following antibiotic discontinuation. Blood cultures may remain negative for many days after antibiotic discontinuation and causative organisms are most often oral streptococci or coagulase-negative staphylococci.

IE with often negative blood cultures

These cases of IE are usually caused by fastidious organisms such as nutritionally-variant streptococci, fastidious Gram-negative bacilli of the HACEK group (*Haemophilus parainfluenzae*, *H aphrophilus*, *H paraphrophilus*, *H influenzae*, *Actinobacillus actinomycescomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae* and *K denitrificans*), *Brucella*, and fungi.

IE with always negative blood cultures

These cases are caused by intracellular bacteria such as *Coxiella burnetii*, *Bartonella*, *Chlamydia*, and, as recently

demonstrated, *Tropheryma whipplei*, the bacterium causing Whipple's disease.¹¹ Altogether, they may account for up to 5% of all cases of IE. The diagnosis of such cases of IE relies on specific samples for cell culture or gene amplification.

ANTIBIOTIC TREATMENT

Theoretical considerations

The vegetation that characterises IE is composed of a mixture of fibrin and platelets, contains a large inoculum of bacteria, and is often enclosed in a layer of exopolysaccharides that hampers antibiotic penetration. Thus antibiotic treatment should be bactericidal, and the bactericidal activity should ideally be obtained rapidly and maintained until cure is obtained. However, cure may be difficult to achieve for several reasons:

- ▶ pharmacokinetic: the penetration of some antibiotics inside the vegetation may be very heterogeneous, which may explain why some antibiotics cannot eradicate the microorganism in large vegetations;
- ▶ pharmacodynamic: the concentrations of antibiotics within the vegetation must be sufficiently high and sustained; the absence of post-antibiotic effect of β -lactams on Gram-positive cocci makes it mandatory to maintain short intervals between doses of antibiotics in order to achieve permanent high serum concentrations, several-fold higher than the MIC of the causative microorganism; furthermore, the high bacterial density and the slow metabolic activity of the bacteria inside the vegetation may result in an in vivo sensitivity lower than that predicted by standard in vitro tests; finally antibiotics active against actively growing bacteria (β -lactams, glycopeptides) have a reduced activity against bacteria whose metabolic activity is reduced.

Practical aspects of antibiotic treatment of IE

The intravenous route for antibiotic administration is the best since it provides maximal bioavailability. Most antibiotics are administered as short infusions (30 minutes). There are some exceptions, however. Penicillin G is usually administered continuously because of the risk of seizures secondary to the high serum concentrations achieved with intermittent infusion. One- to two-hour infusions of vancomycin improve the tolerability of the drug. For antibiotics with time-dependent effects (β -lactams), the interval between infusions must be adjusted to take the elimination half-life into account. For antibiotics with concentration-dependent effects (aminoglycosides), twice- or thrice-daily administration is recommended. However, there are experimental and clinical data in favour of once-daily administration of gentamicin or netilmicin in IE caused by penicillin-sensitive streptococci.^{12–14}

Both the efficacy and the tolerance of the treatment need to be carefully monitored. In terms of efficacy, apart from the absence of relapse at the end of the treatment, there is no totally reliable clinical or biological criterion. This emphasises the importance of clinical and biological surveillance (disappearance of fever, sterilisation of blood cultures, and normalisation of inflammation markers) during treatment and in the subsequent four weeks (period of maximal risk of relapse of IE). The determination of blood concentrations of antibiotics, especially aminoglycosides, is useful to verify both that the peak concentrations are high enough (efficacy objective) and that the trough concentrations are not excessively high (tolerance objective).

Table 1 Antibiotic treatment for infective endocarditis caused by penicillin susceptible (MIC <0.1 mg/l) or penicillin relatively resistant ($0.1 < \text{MIC} \leq 0.5$ mg/l) streptococcal endocarditis

	No allergy to penicillin		Allergy to penicillin		
	Drug	Dosage	Drug	Dosage	Duration
Penicillin-susceptible streptococci (MIC <0.1 mg/l)					
Non-complicated native valve IE	Penicillin G or amoxicillin or ceftriaxone $\pm$ gentamicin*	200–300 000 U/kg/d 100 mg/kg/d 2 g/d 3 mg/kg/d	Vancomycin or teicoplanin $\pm$ gentamicin*	30 mg/kg/d 6–10 mg/kg/d 3 mg/kg/d	2 weeks combination or 4 weeks β -lactam
Complicated and/or prosthetic valve IE	Penicillin G or amoxicillin $\pm$ gentamicin*	200–300 000 U/kg/d 100 mg/kg/d 3 mg/kg/d	Vancomycin or teicoplanin $\pm$ gentamicin*	30 mg/kg/d 6–10 mg/kg/d 3 mg/kg/d	2 weeks combination + 2–4 weeks β -lactam
Penicillin-relatively resistant streptococci G† ($0.1 < \text{MIC} \leq 0.5$ mg/l)					
Non-complicated native valve IE	Penicillin G or amoxicillin $\pm$ gentamicin*	300–400 000 U/kg/d 200 mg/kg/d 3 mg/kg/d	Vancomycin or teicoplanin $\pm$ gentamicin*	30 mg/kg/d 6–10 mg/kg/d 3 mg/kg/d	2 weeks combination + 2 weeks β -lactam
Complicated and/or prosthetic valve IE	Penicillin G or amoxicillin $\pm$ gentamicin*	300–400 000 U/kg/d 200 mg/kg/d 3 mg/kg/d	Vancomycin or teicoplanin $\pm$ gentamicin*	30 mg/kg/d 6–10 mg/kg/d 3 mg/kg/d	2 weeks combination + 2–4 weeks β -lactam

*Other choice: netilmicin (5–6 mg/kg/d); for both drugs, once daily administration.

†Including tolerant streptococci (MBC/MIC >32) for which amoxicillin is to be preferred to penicillin.

IE, infective endocarditis; MBC, minimal bactericidal concentration; MIC, minimal inhibitory concentration.

Recommendations for the antibiotic treatment of IE

The most recent recommendations for the antibiotic treatment of IE were issued by the European Society of Cardiology¹⁵ and the American Heart Association.¹⁶

Antibiotic treatment of streptococcal and enterococcal IE

We will only discuss in this section IE caused by oral streptococci, group D streptococci, and enterococci, for which there is a clear consensus in the literature (tables 1 and 2).

1. Native valve streptococcal endocarditis

In the absence of allergy to penicillin, the treatment of IE caused by highly penicillin-susceptible streptococci (MIC ≤ 0.1 mg/l)—most oral and group D streptococci—should combine penicillin G, 10–20 million units per day, with an aminoglycoside (gentamicin, 3 mg/kg/day, or netilmicin, 5–6 mg/kg/day, in one daily dose). The combination is administered for two weeks, provided that all the following conditions for short-course therapy are fulfilled: highly penicillin-susceptible streptococcal strain; native valve endocarditis; no heart failure, aortic insufficiency or conduction

Table 2 Antibiotic treatment for enterococcal, nutritionally-variant and penicillin-resistant (MIC >0.5 mg/l) streptococcal endocarditis

Condition	No allergy to penicillin		Allergy to penicillin		
	Drug	Dosage	Drug	Dosage	Duration
Enterococcal strain susceptible to penicillin, aminoglycosides, and vancomycin	Amoxicillin or penicillin G $\pm$ gentamicin*	200 mg/kg/d 300–400 000 U/kg/d 3 mg/kg/d	Vancomycin or teicoplanin $\pm$ gentamicin*	30 mg/kg/d 6–10 mg/kg/d 3 mg/kg/d	4–6 weeks†
Enterococcal strain susceptible to penicillin, streptomycin, vancomycin, and resistant to gentamicin	Amoxicillin or penicillin G $\pm$ streptomycin‡	200 mg/kg/d 300–400 000 U/kg/d 15 mg/kg/d	Vancomycin or teicoplanin $\pm$ streptomycin‡	30 mg/kg/d 6–10 mg/kg/d 15 mg/kg/d	4–6 weeks†
Enterococcal strain resistant to penicillin (intrinsic resistance), susceptible to gentamicin and vancomycin	Vancomycin or teicoplanin $\pm$ gentamicin*	30 mg/kg/d 6–10 mg/kg/d 3 mg/kg/d	Vancomycin or teicoplanin $\pm$ gentamicin*	30 mg/kg/d 6–10 mg/kg/d 3 mg/kg/d	6 weeks
Enterococcal strain resistant to penicillin (β -lactam producing), susceptible to gentamicin and vancomycin	Co-amoxycylav $\pm$ gentamicin*	175 mg/kg/d amoxicillin 3 mg/kg/d	Vancomycin or teicoplanin $\pm$ gentamicin*	30 mg/kg/d 6–10 mg/kg/d 3 mg/kg/d	6 weeks
Streptococcal and enterococcal strains with high-level resistance to all aminoglycosides	Amoxicillin	>200 mg/kg/d	Vancomycin	30 mg/kg/d	≥ 8 weeks
<i>E faecalis</i> resistant to penicillin, aminoglycosides and vancomycin	Amoxicillin $\pm$ ceftriaxone or imipenem	200 mg/kg/d 2 g/d 2 g/d	—	—	≥ 8 weeks
<i>E faecium</i> resistant to penicillin, aminoglycosides and vancomycin	Linezolid, or quinupristin-dalfopristin	1200 mg/d 22.5 mg/kg/d	Linezolid, or quinupristin-dalfopristin	1200 mg/d 22.5 mg/kg/d	≥ 8 weeks

*Two or three daily doses.

†Duration of aminoglycoside administration could be shortened to 2–3 weeks; the total duration of treatment should be 6 weeks when vancomycin or teicoplanin are used.

‡Two daily doses.

abnormalities; no evidence of extracardiac septic complications; vegetation diameter ≤ 10 mm; clinical response within seven days (temperature returns to normal); and no surgical treatment of endocarditis. In patients with contraindications to aminoglycosides, penicillin alone for four weeks is as effective as the previous regimens. In patients with complicated IE, the combination is administered for two weeks followed by two weeks of penicillin alone. In all these regimens, penicillin G may be conveniently replaced by ceftriaxone (2 g once daily).^{13 14 17}

For streptococci with reduced susceptibility to penicillin ($0.1 < \text{MIC} \leq 0.5$ mg/l), the same combination of penicillin and aminoglycoside is given, with higher doses of penicillin (30 million units per day in adults). Ampicillin and amoxicillin are alternatives to penicillin, 200 mg/kg/day in six infusions. This regimen should also be given for IE caused by tolerant streptococci. The combination should be given for two weeks and followed by β -lactam monotherapy, with a total duration of treatment of at least four weeks, and up to six weeks in complicated IE.

IE caused by streptococci with $\text{MIC} > 0.5$ mg/l as well as IE due to nutritionally variant streptococci (*Abiotrophia* and *Granulicatella*) should be treated in the same way as enterococcal IE.

2. Native valve enterococcal endocarditis

Enterococci are now classified as an individual genus. *E. faecalis*, *E. faecium* and, to a lesser extent, *E. durans* are most commonly responsible for IE. They are far less sensitive to penicillins than streptococci. MICs to β -lactams are 10- to 100-fold higher for enterococci than for streptococci. This is even more pronounced for *E. faecium* than for *E. faecalis*, with MIC_{50} to penicillin of 8 and 1 mg/l and to amoxicillin of 4 and 0.5 mg/l, respectively. In addition, *E. faecium* strains are almost always penicillin-tolerant. β -lactamase producing strains of *E. faecalis* have been described in the United States, but not yet in Europe.

High-level resistance to aminoglycosides is found in about 10% of endocarditis strains of *E. faecalis*. For management of endocarditis, enterococcal isolates must be routinely checked for high-level resistance in order to avoid the use of aminoglycosides when no synergy with either β -lactams or glycopeptides can be expected. In addition, netilmicin should not be used in *E. faecium* IE because this species possesses a constitutive AAC6' enzyme that inactivates netilmicin.

Glycopeptide-resistant enterococci were first described in the late 1980s. Most often these strains exhibit high-level resistance to both vancomycin ($\text{MIC} > 64$ mg/l) and teicoplanin ($\text{MIC} > 16$ mg/l). This resistance profile (van-A phenotype) is plasmid-mediated—that is, potentially transferable from one strain to another. Occasionally (mostly in Europe) teicoplanin sensitivity is preserved despite presence of high-level resistance to vancomycin (van-B phenotype).

Optimal antibiotic prescribing for enterococcal IE requires that MICs of penicillin, amoxicillin, aminoglycosides, and glycopeptides be determined. When the strain exhibits only low-level resistance to aminoglycoside, recommended therapy is a combination of high-dose β -lactam (30–40 million units/day penicillin or 200 mg/kg/day amoxicillin) plus gentamicin for 4–6 weeks. The aminoglycoside component should be administered in two or three equally divided doses; this recommendation is based on results of experimental studies.¹⁸

In the case of high-level resistance to gentamicin, cross-resistance may be expected with all other aminoglycosides,

except sometimes streptomycin. If the strain shows low-level resistance to streptomycin, the latter can be used in combination with high doses of a cell-wall active agent, either a β -lactam or a glycopeptide. If the strain shows high-level resistance to streptomycin as well, the best treatment option is monotherapy with amoxicillin or a glycopeptide given at high dose for at least eight weeks. Even with such prolonged treatment, antibiotic therapy often fails, and surgery is likely to be required.

Glycopeptide-resistant enterococci are often multidrug resistant, also exhibiting high MICs to β -lactams and high levels of resistance to aminoglycosides. In vitro studies showed that combinations of cell-wall active antibiotics may be synergistic in such strains without an added aminoglycoside. This was demonstrated for combinations such as teicoplanin–imipenem,¹⁹ ampicillin–ceftriaxone,^{20 21} and ampicillin–imipenem²² on *E. faecalis* strains. Ampicillin (12 g daily)–ceftriaxone (2 g daily) and ampicillin (12 g daily)–imipenem–ceftriaxone (2 g daily) are now recommended for the treatment of multidrug resistant *E. faecalis* IE.¹⁶

Combinations of cell-wall active agents are, however, insufficient for the treatment of *E. faecium* IE. Newer agents such as quinupristin–dalbavancin and linezolid appear to be preferable options in this setting. Quinupristin–dalbavancin (Q/D) (Synercid) is a new parenteral streptogramin combination which is potent against most Gram-positive pathogens, including multidrug resistant *E. faecium*, with the notable exception of *E. faecalis*. In multidrug resistant *E. faecium* endocarditis, Q/D was effective in an animal model and in anecdotal case reports.²³ Linezolid is the first licensed representative of the oxazolidinones, a new class of antibiotics that acts by inhibiting protein synthesis. Linezolid has significant activity against mutiresistant Gram-positive pathogens, including vancomycin-resistant enterococci. Only a few studies have evaluated this compound in the treatment of IE. Further studies are needed to confirm the potential value of these two new drugs as well as newer glycopeptides (dalbavancin, telavancin) and lipopeptides (daptomycin) for the treatment of enterococcal endocarditis.

3. Prosthetic valve endocarditis caused by streptococci and enterococci

The same regimens as for native valve IE are recommended. The minimal duration of treatment is four weeks for highly susceptible streptococci and six weeks for enterococci, with at least two weeks and four weeks of β -lactam–aminoglycoside combination, respectively. If the prosthetic valve is replaced during the course of antibiotic treatment, the duration of antibiotic treatment should be 4–6 weeks if valve culture is found to be positive. Otherwise, the total duration of treatment should not be prolonged.²⁴

4. Streptococcal and enterococcal endocarditis in patients allergic to penicillin

In patients allergic to penicillin, vancomycin is the best alternative. Teicoplanin, another glycopeptide, can also be used (loading dose 6 mg/kg every 12 hours for 48–72 hours, followed by a once-daily dose of 6–10 mg/kg).

Antibiotic treatment of staphylococcal IE (table 3)

1. Native valve staphylococcal endocarditis

In the absence of allergy to penicillin, if the staphylococcal strain is oxacillin-susceptible, oxacillin or cloxacillin (150 mg/kg/day in six intravenous infusions, maximal daily

Table 3 Antibiotic treatment for staphylococcal infective endocarditis (IE)

	No allergy to penicillin		Allergy to penicillin		
	Drug	Dosage	Drug	Dosage	Duration
Native valve IE					
Oxa-S strain	Oxacillin† + gentamicin‡	150–200 mg/kg/d 3 mg/kg/d	Vancomycin§ or cefamandole** + gentamicin‡	30 mg/kg/d 75–100 mg/kg/d 3 mg/kg/d	4–6 weeks (5 days combination)
Oxa-R strain	Vancomycin§ ± gentamicin‡	30 mg/kg/d 3 mg/kg/d	Vancomycin§ ± gentamicin‡	30 mg/kg/d 3 mg/kg/d	4–6 weeks (5 days combination)
Prosthetic valve IE*					
Oxa-S strain	Oxacillin† + gentamicin‡ + rifampicin	150–200 mg/kg/d 3 mg/kg/d 20–30 mg/kg/d	Vancomycin§ + gentamicin‡ + rifampicin	30 mg/kg/d 3 mg/kg/d 20–30 mg/kg/d	≥6 weeks combination (aminoglycoside no longer than 15 days)
Oxa-R, genta-S strain	Vancomycin§ + rifampicin + gentamicin‡	30 mg/kg/d 20–30 mg/kg/d 3 mg/kg/d	Vancomycin§ + rifampicin + gentamicin‡	30 mg/kg/d 20–30 mg/kg/d 3 mg/kg/d	≥6 weeks combination (aminoglycoside no longer than 15 days)
Oxa-R, genta-R strain	Vancomycin§ + rifampicin¶ + other antistaphylococcal drug, if available	30 mg/kg/d 20–30 mg/kg/d	Vancomycin§ + rifampicin¶ + other antistaphylococcal drug, if available	30 mg/kg/d 20–30 mg/kg/d	≥6 weeks combination

*Valve replacement should be considered, inasmuch as IE develops early after valve implantation.

†Other choices: cloxacillin 100–150 mg/kg/d; cefamandole 75–100 mg/kg/d.

‡Other choice: netilmicin (5–6 mg/kg/d).

§Other choice: teicoplanin, target serum trough concentrations 25–30 mg/l.

¶If strain resistant to rifampicin, combine vancomycin with one or two other antistaphylococcal drugs, according to susceptibility pattern.

**The use of a cephalosporin is not recommended in patients with a history of anaphylactic reaction to penicillin.

dose 6–8 g) should be used in combination with an aminoglycoside (gentamicin or netilmicin) for the first 3–5 days and then continued alone for a total of 4–6 weeks. In the case of allergy to penicillin, a combination of cefamandole and an aminoglycoside may be considered in non-anaphylactic allergy. Otherwise, vancomycin is recommended. However, based on in vitro experiments, as well as on small clinical trials, vancomycin is less effective than β -lactams where staphylococci are oxacillin-sensitive,²⁵ and therefore oxacillin or cloxacillin should be preferred.

The treatment of IE caused by oxacillin-resistant staphylococci requires the use of vancomycin. Teicoplanin may be an alternative, provided that an adequate dosage is given. The goal is to obtain a residual serum concentration of 20–30 mg/l, which is usually obtained with a single daily dose of 10 mg/kg/day, after an induction phase at 6 mg/kg every 12 hours for 3–4 days.²⁶ The combination with an aminoglycoside should be reserved for the treatment of IE caused by staphylococci sensitive to aminoglycosides, for no more than 5–7 days.

In non-complicated oxacillin-susceptible native valve endocarditis in IVDUs, a two week course of intravenous cloxacillin, with or without an aminoglycoside, proved to be effective.^{25–27} When it is difficult to prolong in-hospital and/or intravenous antibiotic treatment, the combination of oral ciprofloxacin (750 mg twice daily) and rifampicin (300 mg twice daily) after a short period of intravenous treatment is efficacious,^{28–29} provided that the strain is susceptible to both drugs and compliance with treatment is high.

2. Prosthetic valve staphylococcal endocarditis

Such infections are often caused by coagulase-negative staphylococci, which are often resistant to oxacillin. Vancomycin in combination with rifampicin and an aminoglycoside is the most effective combination, provided that rifampicin and the aminoglycoside are active in vitro. If not, an alternative triple association still seems warranted. According to the strain susceptibility, fusidic acid, a

fluoroquinolone or fosfomycin may be used. The latter can be used only in the absence of heart failure since it contains a large amount of sodium (1 g of fosfomycin contains 14.4 mmol of sodium and the dose of fosfomycin is 8–12 g/day).

If the staphylococcal strain is oxacillin-susceptible, the triple combination of oxacillin or vancomycin (in patients allergic to penicillin) plus an aminoglycoside and rifampicin is recommended. The duration of treatment should be six weeks, with at least two weeks of treatment with the aminoglycoside. Valve surgery is most often required.

Antibiotic treatment of IE with negative blood cultures

This is a challenging condition to treat and the diagnostic procedures used should be rigorous, based on close collaboration with the bacteriology laboratory^{30–31} (table 4).

In patients with native valve endocarditis, potential causative microorganisms include nutritionally variant streptococci, Gram-negative HACEK coccobacilli, *Brucella*, and intracellular bacteria that do not grow on conventional media, including *Coxiella burnetii*, *Bartonella*, and *Tropheryma whippelii*. When blood cultures are negative because of prior antibiotic treatment, any other microorganism has to be considered, including staphylococci. While waiting for the results of special blood cultures and serology, treatment should consist of amoxicillin and an aminoglycoside.

Treatment depends on the time elapsed since the implantation of the prosthetic valve. In early-onset IE (onset less than one year after insertion), staphylococci (especially oxacillin-resistant coagulase-negative staphylococci) are most likely to be responsible. A combination of vancomycin, rifampicin, and an aminoglycoside is recommended. Valve replacement should be considered rapidly if the clinical course is unfavourable. In late-onset IE (more than one year after insertion), staphylococci are still potentially responsible but other microorganisms such as streptococci and the

Table 4 Causes of infective endocarditis with apparently negative blood cultures and suggestions for improving the diagnosis

Causes	Diagnostic
▶ Previous antibiotic treatment	Discontinuation of antibiotics whenever possible Blood cultures on specific media with adsorbent resins Specific blood culture techniques
▶ Fastidious bacteria Nutritionally variant streptococci HACEK* bacteria <i>Brucella</i> species <i>Legionella</i> species <i>Neisseria</i> species <i>Nocardia</i> species, mycobacteria	
▶ Intracellular growing bacteria <i>Chlamydia</i> species <i>Coxiella burnetii</i> <i>Bartonella</i> species <i>Mycoplasma pneumoniae</i> <i>Tropheryma whippelii</i> (Whipple disease)	Serology Serology and PCR techniques Serology and PCR techniques Serology Gene amplification
▶ Fungi <i>Candida</i> species <i>Aspergillus</i> species	Specific blood culture techniques + serology

*HACEK: *Haemophilus parainfluenzae*, *H aphrophilus*, *H paraphrophilus*, *H influenzae*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*, *K denitrificans*.

HACEK group of bacteria should also be considered. As first line therapy, a combination of vancomycin and an aminoglycoside is recommended. The addition of a third-generation cephalosporin (cefotaxime, 100–200 mg/kg/day in six infusions) is recommended when the first line combination is unsuccessful.

Within “culture-negative” endocarditis, some situations deserve special consideration because specific therapeutic regimens are to be used.

- ▶ *Coxiella burnetii* is probably the most frequent cause of IE with negative blood cultures,^{32, 33} although its incidence varies substantially from one geographical area to another. Doxycycline, rifampicin and fluoroquinolones are efficacious in vitro but none of these is bactericidal. The duration of treatment is very long, often several years. Serology appears to be the most reliable criterion of cure, when phase I IgG titres are < 200 and phase I IgA titres are undetectable. Doxycycline is the cornerstone antibiotic, and its efficacy is improved when combined with hydroxychloroquine, which acts as a lysosomotropic alkalinising agent.³⁴ This combination helps decrease the duration of antibiotic treatment and the failure and relapse rates.
- ▶ *Bartonella*, mainly *B henselae* and *B quintana*, and occasionally *B elizabethae*, are second to *Coxiella burnetii* as agents responsible for culture-negative endocarditis.³³ While *B henselae* is most commonly encountered in patients with previous valve disease and in subjects who have been in contact with cats, IE caused by *B quintana* occurs in homeless alcoholics with no previously known heart disease.³⁵ Treatment consists of a combination of an aminoglycoside and a β -lactam—for example, amoxicillin for at least two weeks.³⁶
- ▶ IE caused by *Legionella* is rare and occurs mainly in patients with prosthetic valves. The usual treatment regimen consists of a combination of a fluoroquinolone and rifampicin. The duration of treatment should be at least two months, and valve surgery is almost always required.

Epidemiology and treatment of infective endocarditis: key points

- ▶ Overall, *Staphylococcus aureus* has become the major pathogen responsible for infective endocarditis
- ▶ This epidemiological shift results mainly from improved dental care and hygiene and from the growing incidence of nosocomial and healthcare-related endocarditis
- ▶ Antibiotic treatment of streptococcal, enterococcal, and staphylococcal endocarditis should strictly comply with updated experts' guidelines
- ▶ Short-course (14 days) β -lactam + aminoglycoside treatment is a validated option for uncomplicated penicillin-susceptible native valve endocarditis
- ▶ A rifampicin-containing triple combination is warranted for the treatment of staphylococcal prosthetic valve endocarditis

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