Netherlands
The Journal of Medicine

SPECIAL REPORT

Optimisation of the antibiotic guidelines in the Netherlands VII. SWAB guidelines for antimicrobial therapy in adult patients with infectious endocarditis

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ABSTRACT

The Working Party on Antibiotic Policy (Dutch acronym is SWAB) is a Dutch organisation that develops guidelines for in-hospital antimicrobial therapy of bacterial infectious diseases. This present guideline describes the antimicrobial treatment for adult patients with infective endocarditis. The choice and duration of antimicrobial therapy is determined by the infecting micro-organism, sensitivity of this micro-organism for antimicrobial therapy, location of the endocarditis, left-sided or right-sided, and presence of intracardial prosthetic material. In this guideline, the empirical therapy for endocarditis is discussed as well as the therapy for the most frequent causative organisms: streptococci, enterococci, staphylococci and HACEK micro-organisms

The Stichting Werkgroep Antibioticabeleid (the Working Party on Antibiotic Policy) or SWAB develops guidelines for intramural use of antibiotics, the aim being to optimise antibiotic therapy to contribute to preventing resistance and to achieving better management of the costs and the use of antibiotics in the Netherlands. The guidelines apply for adult patients in hospital. For guidelines for children, see 'Blueprint for paediatric antimicrobial therapy'.

The guidelines are based on the following important criteria for the use of antibiotics: the indications for the prescription are correct, therapy is directed against the presumed causative agent or, preferably, the demonstrated causative agent, the drug is administered at the proper time and therapy is not unnecessarily prolonged because a drug with the smallest possible spectrum, which is as safe and inexpensive as possible, is administered via the preferred route.

The guideline for endocarditis has been written according to the principles of 'evidence-based medicine' (M. Offringa, W.J.J. Assendelft, R.J.P.M. Scholten, Inleiding in evidence-based medicine. Bohn Stafleu van Loghum 2000). The various levels of proof are defined in *table 1*. Due to the low incidence of endocarditis, large randomised clinical studies on the effect of the various therapies are scarce. This and other guidelines are, therefore, partly based on the experience of experts obtained with relatively small numbers of patients as well as on experimental animal studies. A shorter report in Dutch will be published in the Nederlands Tijdschrift voor Geneeskunde.

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Table 1

Explanation of the levels of proof according to the principles of evidence-based medicine

A1	Meta-analyses which cover at least several studies on the A2 level, whereby the results of the separate studies were consistent
A2	Randomised comparative clinical study of good quality (randomised, double-blind controlled trials) of sufficient scope and consistency
B	Randomised clinical trials of moderate quality or of insufficient scope or other comparative studies (nonrandomised, cohort studies, case-control studies)
C	Noncomparative studies
D	Expert opinion, for example members of work groups

Classification of literature according to the degree of proof (CBO Handleiding voor werkgroepleden, 2000. www.cbo.nl).

EPIDEMIOLOGY

In the Netherlands, there are at least 250 cases of infective endocarditis (IE) a year.[2,3] The largest proportion of these patients has a community-acquired infection. The number of nosocomial cases of endocarditis is unknown but endocarditis as the result of an intravascular catheter-associated bacteraemia is not uncommon.[4-6] The disease occurs twice as often among men than women and the incidence clearly increases with age. Approximately half of adult patients are previously known to have a cardiac abnormality which predisposes to endocarditis. In decreasing order of frequency, the most common predisposing abnormalities are mitral valve prolapse with mitral insufficiency, degenerative abnormalities of the aorta and mitral valve, congenital abnormalities of the heart and rheumatic valve abnormalities. Before the introduction of antibiotics, mortality for endocarditis was 100%. Even today, endocarditis is a severe condition which is characterised by a high morbidity and mortality: approximately 20% of patients die during hospital admission.

CLASSIFICATION AND CAUSATIVE MICRO-ORGANISMS

For infective endocarditis a distinction is made between an acute and a subacute course and between IE of a native cardiac valve and a prosthetic valve. Acute IE is a fulminating disease which is often accompanied by rapid destruction of the valve and perivalvular and/or metastatic abscesses. It is caused by virulent micro-organisms, such as *Staphylococcus aureus*, and it often develops on what was a normal cardiac valve. Subacute endocarditis usually develops on a previously damaged cardiac valve due to relatively avirulent micro-organisms such as viridans streptococci. The course is slow and metastatic abscesses are rare. Endocarditis on a native cardiac valve in individuals who are not intravenous drug-users is almost always left-sided and is usually caused by Gram-positive cocci, such as viridans streptococci (60%), *S. aureus* (20%) or enterococci (10%).[7] In patients over 60 years of age endocarditis is caused by *S. bovis* in 10% of cases. Endocarditis caused by *S. bovis* is accompanied in about 45% of cases by abnormalities of the digestive tract, in particular colon carcinoma and villous adenoma.[8,9]

In intravenous drug-users endocarditis usually develops on the right side of the heart and is then caused by *S. aureus* in two-thirds of the cases.[10-12] Other causative agents among drug addicts are *Pseudomonas aeruginosa*, enterococci and *Candida* species. Polymicrobial infections occur regularly in drug-users.[13-15]

Prosthetic valve endocarditis (PVE) is classified according to the time since implantation of the valve. When the infection develops within two to three months of surgery, it is called early PVE. The infection is then usually the result of contamination during the operation or a central venous catheter infection. The most important causative agents of early PVE are *S. epidermidis* and to a lesser extent *S. aureus* and Gram-negative aerobic micro-organisms. After the period of two to three months, the condition is called late PVE; in this case the causative agents are similar to those found for endocarditis of a native cardiac valve. Gram-negative micro-organisms can be isolated in about 5% of cases of endocarditis. In the past they were mainly *Salmonella* species; with modern culture techniques, mainly slow-growing bacteria such as *Haemophilus* species, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens* and *Kingella* species (HACEK) are seen.[16]

MICROBIOLOGICAL DIAGNOSTICS

For the specific aetiological diagnosis of IE, the causative micro-organism must be demonstrated. Although in IE the number of bacteria in blood is often low, the bacteraemia is usually continuous so that often all blood cultures will be positive. For differentiation between contamination and endocarditis, it is recommended that separate samples be taken from peripheral vessels at intervals of at least 15 minutes, three blood cultures being obtained in the first 24 hours and eventually again on the second day. If the patient has already received antibiotic therapy beforehand, incubation of the blood cultures should last longer. Also for isolation of HACEK bacteria, longer incubation of the blood culture is needed. In some cases of endocarditis the bacteria can be cultured from septic embolisms or from material sampled during surgery or autopsy.[17] Serological

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and molecular biological studies can help establish the diagnosis of, for example, *Coxiella* species, *Brucella* species, *Chlamydia* species, *Bartonella* species and *Tropheryma whippelii*.[18-24]
As a result of modern microbiological techniques, the percentage of patients with culture-negative endocarditis has decreased to less than 5%. Culture-negative endocarditis is the result of antimicrobial therapy before the blood samples were collected in more than 50% of cases.[17,25] Finally the differential diagnosis for culture-negative endocarditis must also include noninfectious conditions, such as systemic lupus erythematosus, Loeffler's endocarditis and myxoma.[26,27]

THERAPY

In these guidelines, we will limit ourselves to the antimicrobial treatment of IE and we will not consider the indications for surgery. In all patients with IE, the cardiothoracic surgeon must be consulted at an early stage, especially in patients with complications or with a prosthetic valve.
In these guidelines antimicrobial therapy is presented for the most common causative agents of endocarditis: veridans streptococci, *S. bovis*, enterococci, *S. aureus*, *S. epidermidis* and the HACEK group. For the treatment of less common causative agents, there is insufficient data available to provide a basis for guidelines.
The empirical therapy is presented in *table 2*. For acute endocarditis, immediate empirical therapy is always indicated, but never before three blood samples have been collected at 15-minute intervals. For the subacute form, one can wait in most cases for determination of the bacteria, after which specific therapy can be initiated.

Table 2
Empirical therapy for endocarditis

ANTIBIOTIC	DOSE
Native valve	
Subacute onset and long-term course	
Penicillin *and*	2.10^6 IU iv every 4 h
Gentamicin	3 mg/kg iv once daily
Penicillin allergy	
Vancomycin *and*	15 mg/kg iv every 12 h (max. 1 g every 12 h)
Gentamicin	3 mg/kg iv once daily
Acute onset and fulminating course or iv drug-user	
Flucloxacillin *and*	2 g iv every 4 h
Gentamicin	3 mg/kg iv once daily
Penicillin allergy:	
Vancomycin *and*	15 mg/kg iv every 12 h (max. 1 g every 12 h)
Gentamicin	3 mg/kg iv once daily
Prosthetic valve	
Vancomycin *and*	15 mg/kg iv every 12 h (max. 1 g every 12 h)
Gentamicin	3 mg/kg iv once daily

PRINCIPLES OF TREATMENT

Within the vegetation, micro-organisms are often present in high concentrations (109 CFU/gram),[28] in a metabolically inactive growth phase and surrounded by thrombocytes and fibrin. As a result access is difficult for phagocytising cells and the bacteria are relatively insensitive to antimicrobial therapy. Antibiotics must therefore be bactericidal and have to be administered in high doses intravenously for prolonged periods. The choice and duration of antimicrobial therapy are determined by the type and sensitivity of the isolated micro-organism, the presence of a prosthetic valve, localisation of the infection (right-sided or left-sided) and the occurrence of complications such as intracardial abscesses. In practice the sensitivity is given by the minimal inhibitory concentration (MIC), which is the minimum concentration of antibiotic that inhibits growth *in vitro*.
Several studies have described successful oral treatment of endocarditis. These studies involved such small groups of patients with a short follow-up and the selection of patients who were eligible was so specific that we have excluded this form of therapy from our considerations.[29-32]
Another new development is intravenous home treatment; however in this case, too, the conditions for both the patient and the required situation at home were so specific that we will not discuss this form of therapy in this paper.[33-35]
On the basis of theoretical pharmacokinetic principles and the results of experimental animal studies, some physicians prefer continuous over intermittent administration of β-lactam antibiotics for endocarditis.

EVALUATION OF THE THERAPEUTIC EFFECT

Frequent and careful clinical observation is the best way to evaluate the effect of treatment. The patient must be examined at least once a day for signs of cardiac decompensation or metastatic infections. In addition, the initial microbiological response, in particular of *S. aureus* infections, must be monitored by taking a blood culture 72 hours after initiation of treatment. Most patients with IE become free of fever within three to five days, for those with IE due to *S. aureus*, fever can last somewhat longer. If fever persists for more than a week, this can be attributed to perivalvular infection in most cases.[36,37] When the fever initially disappears and later recurs, then this is usually attributable to hypersensitivity to the antibiotics used. Other causes of persisting or recurrent fever are septic embolisms and an infection of the intravenous entry route.

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STREPTOCOCCI

Viridans streptococci and *S. bovis* cause 40 to 60% of all cases of community-acquired endocarditis of the native valve.[1] The viridans streptococci are a heterogeneous group of micro-organisms that form the normal flora of the oropharyngeal cavity. The most important clinical representatives are *S. oralis (mitis), S. sanguis, S. mutans, S. milleri* and *S. salivarius. S. bovis* is a group D streptococcus; endocarditis due to this micro-organism is often associated with colorectal growths.[8,9]
The antimicrobial treatment of IE due to viridans streptococci and *S. bovis* is determined by the sensitivity of the micro-organism for penicillin. A distinction is made between 1) MIC ≤0.1 mg/l, 2) MIC >0.1 but <0.5 mg/l and 3) MIC >0.5 mg/l. Most of the viridans streptococci and *S. bovis* have an MIC of <0.1 mg/l. For these micro-organisms there are three different therapeutic regimens, all of which have advantages and disadvantages (*table 3*).[38-44] The oldest therapy is the four-week course of penicillin only, which has the advantage that the use of aminoglycosides with their possible ototoxic and nephrotoxic effects is avoided. The combination of a four-week regimen of penicillin and two weeks of gentamicin is used if the IE has existed for more than three months, if the infection has recurred or if the IE is accompanied by complications. Several studies have demonstrated that in uncomplicated endocarditis a two-week regimen can also be adequate.[42,43] There are, however, a number of prerequisites that must be satisfied: (*table 3*) (level of proof C).[42,44] For the treatment of viridans and bovis strains that exhibit a high resistance against aminoglycosides (MIC >500 mg/l), see the section on enterococci.

Viridans streptococci and *S. bovis* with a relative lack of sensitivity to penicillin (MIC >0.1 but <0.5 mg/l) must be treated with combination therapy consisting of four weeks of penicillin and two weeks of gentamicin (*table 3*) (level of proof D).[38,40,44,45] Strains with an MIC ≥0.5 mg/l must be treated as enterococci (*table 4*).

Table 3
Treatment of endocarditis caused by viridans streptococci and S. bovis with MIC ≤0.1 mg/l of MIC >0.1 and <0.5 mg/l

ANTIBIOTIC	DOSE	DURATION
Native valve MIC <0.1 mg/l		
Penicillin *or*	2.10^6 IU iv every 4 h	4 weeks
Penicillin *and*	2.10^6 IU iv every 4 h	4 weeks
Gentamicin *or*	3 mg/kg iv once daily	2 weeks
Penicillin *and*	2.10^6 IU iv every 4 h	2 weeks*
Gentamicin	3 mg/kg iv once daily	2 weeks*
Penicillin allergy		
Ceftriaxone** *or*	1 dd 2 g iv or IM	4 weeks
Vancomycin	15 mg/kg iv every 12 h (max. 1 g every 12 h)	4 weeks
Native valve MIC ≥0.1 and <0.5 mg/l		
Penicillin *and*	2.10^6 IU iv every 4 h	4 weeks
Gentamicin	3 mg/kg iv once daily	2 weeks
Penicillin allergy	See above but plus two weeks gentamicin 3 mg/kg iv once daily	
Prosthetic valve MIC <0.1 mg/l and MIC ≥0.1 and <0.5 mg/l		
Penicillin *and*	6 dd 2.10^6 IU iv	6 weeks
Gentamicin	3 mg/kg iv once daily	2 weeks

**Requirements for two-week treatment: 1. MIC penicillin <0.1 mg/l, 2. no contraindications or high resistance against aminoglycosides, 3. no cardiovascular risk factors such as heart failure, aortal insufficiency or disturbed conductance, 4. no thromboembolitic complications, 5. native valve, 6. no vegetations >5 mm, 7. clinical response within seven days, 8. duration of clinical phenomena <3 months, 9. no relapse of the endocarditis.*
***Cephalosporins only in the event of a mild (see text) penicillin allergy (cross reactivity).*

Table 4
Treatment of endocarditis due to enterococci or viridans streptococci and S. bovis with an MIC >0.5 mg/l

ANTIBIOTIC	DOSE	DURATION
Native valve		
Penicillin *and*	2.10^6 IU iv every 4 h	4-6 weeks*
Gentamicin *or*	3 mg/kg iv once daily	4-6 weeks**
Amoxicillin (1st choice with enterococci) *and*	2 g iv every 4 h	4-6 weeks*
Gentamicin	3 mg/kg iv once daily	4-6 weeks**
Penicillin allergy		
Vancomycin *and*	15 mg/kg iv every 12 h (max. 1 g every 12 h)	4-6 weeks*
Gentamicin	3 mg/kg iv once daily	4-6 weeks**
High gentamicin resistance (MIC >500 mg/l)		
Amoxicillin *or*	2 g iv every 4 h	8-12 weeks
Vancomycin	15 mg/kg iv every 12 h (max. 1 g every 12 h)	8-12 weeks
Prosthetic valve		
Amoxicillin	2 g iv every 4 h 6 dd 2 g iv	6-8 weeks
Gentamicin	3 mg/kg iv once daily	6 weeks**
β-*lactamase formation*		
Amoxicillin-clavulanate acid *and*	2000/200 mg iv every 4 h	6-8 weeks
Gentamicin	3 mg/kg iv once daily	6 weeks**
High gentamicin resistance (MIC >500 mg/l)		
Amoxicillin	2 g iv every 4 h	8-12 weeks

**Six weeks of treatment when the infection exists for more than three months, in the event of complications (e.g. septic embolisms) and relapse of infection.*
***There are indications that the period of administration of aminoglycosides can be shortened.[54]*

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For the treatment of patients with endocarditis due to streptococci with a prosthetic valve or a known allergy to penicillin, see *table 3*.
Less common streptococci that also cause endocarditis are *S. pneumoniae, S. pyogenes* and group B, C, and G streptococci. *S. pneumoniae* has become a rare cause of endocarditis since the introduction of penicillin (less than 2%).[2,46] The course is highly fulminating and is accompanied by meningitis in 60% of cases. Most of the pneumococci in the Netherlands are sensitive to penicillin.[47] Endocarditis due to β-haemolytic streptococci is not very common but is an acute disease with a high morbidity and mortality. Group A streptococci (*S. pyogenes*) are quite sensitive to penicillin and the preferred treatment therefore consists of penicillin (6 million U/4 hours iv) for four to six weeks. Alternatives to penicillin are first-generation cephalosporins, vancomycin or teicoplanin. No data are available on the value of including clindamycin in the treatment of endocarditis, in contrast to the streptococcal toxic shock syndrome. Group B, C and G streptococci are in general not as sensitive to penicillin as group A streptococci. Some experts recommend, therefore, that gentamicin should also be administered during the first two weeks of treatment of these causative agents (level of proof D).

ENTEROCOCCI

Enterococci were formerly included in the genus *Streptococcus* but are now classified separately under the genus *Enterococcus*. There are at least 12 species, *E. faecalis* being the most important clinically followed by *E. faecium*. In a Dutch study, 35 of 40 (87.5%) patients with endocarditis caused by enterococci had *E. faecalis* and three had *E. faecium*.[7] This is in agreement with the findings of an American study of enterococcal endocarditis[48] and is approximately equal to the species distribution in nosocomial enterococcal bacteraemias.[49] Enterococci are part of the normal flora of the digestive tract and the proximal part of the urethra. They cause about 10% of cases of IE, especially among men over 60 and women who have recently delivered a child or undergone abortion.[49] Both normal and damaged cardiac valves can be affected by this group of bacteria.[48,50] The mortality for endocarditis due to enterococci is 25%, which is much higher than that for endocarditis due to viridans streptococci (6%).[7] Intrinsically, enterococci are relatively resistant to penicillin with a median MIC of 2 mg/l, sensitive to amoxicillin and totally resistant to cephalosporins. The β-lactam antibiotics only have a bacteriostatic effect on enterococci so that treatment in the form of monotherapy usually fails (*table 4*). All enterococci are resistant to the standard dose of aminoglycosides.[50] However, gentamicin and streptomycin do have a clear synergistic effect when added to a treatment regimen with penicillin, amoxicillin or vancomycin so that *in vitro* the combination has a bactericidal effect.[40,50,52-57] Streptomycin and gentamicin cannot simply be replaced by other aminoglycosides. Tobramycin, for example, does not have a synergistic effect when administered in combination with penicillin.[53]

In general, it is recommended that the aminoglycosides are added to the antimicrobial regimen during the entire period of treatment. Because enterococcal endocarditis occurs more frequently among elderly patients, prolonged administration of aminoglycosides can sometimes lead to problems related to nephrotoxic and ototoxic complications.

A recently published observational Swedish study indicated that a proportion of the patients can also be cured with a short-term supplementary course of aminoglycosides.[54] Resistance against aminoglycosides is variable, an MIC of 500 mg/l is usually taken as the cut-off point between low and high resistance. In a Dutch investigation, approximately 10% (4/40) of enterococci isolated from patients with endocarditis exhibited high resistance against gentamicin and amikacin, whereas only one of the 40 isolates showed high resistance against streptomycin.[7] For these high-resistant bacteria it is not worthwhile to add an aminoglycoside because the synergetic effect no longer occurs.

STAPHYLOCOCCI

Endocarditis can be caused by coagulase-positive (*S. aureus*) and by coagulase-negative (including *S. epidermidis*) staphylococci. Endocarditis caused by coagulase-negative staphylococci (CNS) occurs particularly in patients with a prosthetic valve and to a much lesser extent in patients with a native valve. The treatment of staphylococcal endocarditis differs according to the location of the infection (right-sided or left-sided) and the presence or absence of artificial material. Endocarditis caused by *Staphylococcus aureus* differs in the negative sense from endocarditis due to other causative agents in the high mortality and the frequent occurrence of complications in and outside the heart.[59,60] The treatment of staphylococcal endocarditis of the native valve is given in *table 5*. As a result of β-lactam formation, approximately 90% of the *S. aureus* strains isolated in the Netherlands are not susceptible to penicillin but they are sensitive to the semisynthetic penicillinase-resistant penicillins such as floxacillin. Combination of a β-lactam antibiotic with aminoglycosides is controversial because it does not decrease the morbidity and mortality of *S. aureus* infections, yet there is more nephrotoxicity (level of proof A2).[61-63] By adding an aminoglycoside the patient becomes free of fever much sooner and the blood

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Table 5
Treatment of native valve endocarditis caused by staphylococci (coagulase-positive and coagulase-negative)

ANTIBIOTIC	DOSE	DURATION
Left-sided		
PSSA[*] of PS coagulase-negative staphylococci		
Penicillin *and*	2.10^6 IU iv every 4 h	4-6 weeks[$]
Gentamicin	3 mg/kg iv once daily	3-5 days
MSSA[#] of MS coagulase-negative staphylococci		
Flucloxacillin *and*	2 g iv every 4 h	4-6 weeks[$]
Gentamicin	3 mg/kg iv once daily	3-5 days
MRSA[‡] of MR coagulase-negative staphylococci or penicillin hypersensitivity		
Vancomycin *and*	15 mg/kg iv every 12 h (max. 1 g every 12 h)	4-6 weeks[$]
Gentamicin	3 mg/kg iv once daily	3-5 days
Right-sided		
PSSA[*]		
Penicillin *and*	2.10^6 IU iv every 4 h	2-4 weeks[&]
(possibly with gentamicin)	3 mg/kg iv once daily	2 weeks
MSSA[#]		
Flucloxacillin	2 g iv every 4 h	2-4 weeks[&]
(possibly with gentamicin)	3 mg/kg iv once daily	2 weeks[&]
MRSA[‡] or penicillin hypersensitivity		
Vancomycin *and*	15 mg/kg iv every 12 h (max. 1 g every 12 h)	4 weeks
Gentamicin	3 mg/kg iv once daily	3-5 days

[*] *PSSA = penicillin sensitive S. aureus,* [#] *MSSA = meticillin sensitive S. aureus,* [‡] *MRSA = meticillin resistant S. aureus,* [$] *in case of metastatic infections and poor clinical reaction to initial therapy: 6 weeks,* [&] *prerequisite for two-week treatment: no septic embolisms outside of the lungs, no severe pulmonary embolisms, no combination of right-sided and left-sided IE, no high aminoglycoside resistance.*

cultures are negative sooner.[64] For this reason, it is usually recommended that an aminoglycoside be included in the therapeutic regimen for the first three to five days (level of proof D). In the event of contraindications for aminoglycosides or resistance, some authors recommend including fusidic acid in the treatment protocol; data on the effectiveness of this combination are, however, limited.[65,66] In the event of a light or mild penicillin allergy (gastrointestinal complaints or exanthema after use of amoxicillin/ ampicillin), a cephalosporin can be chosen.[67] Cephazolin, for instance, is effective as antistaphylococcal agent. In the event of a severe penicillin allergy (IgE-mediated, type 1 allergy or other types of allergy involving the organs or with fever) vancomycin is to be preferred above teicoplanin because it is more effective.[68-70] Coagulase-negative staphylococci and *S. aureus* are usually quite sensitive to rifampicin but in the case of monotherapy, resistance develops quickly.[68] Rifampicin penetrates well into tissues and abscesses and also penetrates into the biofilm on artificial materials. When administered in combination with other antibiotics, synergism, antagonism and a lack of any extra effect have all been described. In certain cases, especially for patients who react poorly to the therapy instituted, rifampicin is sometimes added to the therapeutic regimen. The duration of treatment for left-sided endocarditis caused by staphylococci on a native valve is four weeks; in the case of metastatic infections or a poor reaction to initial therapy this must be prolonged to six weeks (level of proof D). The choice of the antibiotic is dependent on the sensitivity of the micro-organism (see *table 5*). In principle the same rules apply to the treatment of coagulase-positive and coagulase-negative strains.

Right-sided staphylococcal endocarditis of the native valve, encountered mainly among drug-users, is a milder disease with a much lower mortality (5-10%) than left-sided endocarditis (25-40%). Patients with right-sided endocarditis are often young and usually do not exhibit severe comorbidity; usually there are no metastatic infections outside of the lungs and there is rarely a problem of heart failure so that surgical intervention is, in general, not necessary. Various studies have been carried out to investigate the possibility of shorter and/or oral treatment of right-sided endocarditis.[31,32,63,72-74] Intravenous treatment for 14 days with only a penicillinase-resistant penicillin, such as floxacillin, appears to be an effective therapy for this form of endocarditis (*table 5*) (level of proof B). Prerequisites for this two-week therapeutic course are that there are no septic embolisms outside of the lung, there are no severe pulmonary problems (such as empyema) and the endocarditis is localised only in the right side of the heart. To satisfy the first prerequisite, history-taking and the physical examination of these patients must be directed specifically toward the discovery of eventual signs of metastatic infections and – when necessary – supplementary imaging techniques must be carried out. In the event of allergy to penicillin, vancomycin or teicoplanin can be used as alternative. Both drugs are, however, less effective against *S. aureus* so that in this case treatment must last for four weeks (level of proof B).[68,69,72,75] A study of patients with IE caused by methicillin-resistant *S. aureus* treated with vancomycin showed a clearly delayed response with a longer period of fever (median 7 days) and bacteraemia (median 9 days).[75,76] Addition of rifampicin did not improve the response.

Prosthetic valve endocarditis caused by staphylococci can, as previously mentioned, be subdivided into early and late PVE. In early PVE due to staphylococci, perivalvular abscesses and valve dysfunction often develop and then both antimicrobial and surgical therapy are needed.

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The therapies recommended for PVE are presented in *table 6*.[77-79]

The mortality for prosthetic valve IE due to *S. aureus* is high. For this reason, treatment during the first two weeks is usually combined with gentamicin to be on the safe side. Data on this aspect are lacking.

Table 6
Treatment of prosthetic valve endocarditis caused by staphylococci

ANTIBIOTIC	DOSE	DURATION
S. aureus		
Flucloxacillin *and*	2 g iv every 4 h	6 weeks
Gentamicin *and*	3 mg/kg iv once daily	2 weeks
Rifampicin	600 mg orally every 12 h	6 weeks
Coagulase-negative staphylococci		
Vancomycin *and*	15 mg/kg iv every 12 h (max. 1 g every 12 h)	6 weeks
Gentamicin *and*	3 mg/kg iv once daily	2 weeks
Rifampicin	600 mg orally every 12 h	6 weeks
MRSA		
Vancomycin *and*	15 mg/kg iv every 12 h (max. 1 g every 12 h)	6-8 weeks
Gentamicin *and*	3 mg/kg iv once daily	2 weeks
Rifampicin	600 mg orally every 12 h	6-8 weeks

HACEK MICRO-ORGANISMS

HACEK micro-organisms (*Haemophilus* species, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens* and *Kingella* species) are slow-growing Gram-negative bacteria. As a result it often takes a long time for the blood culture to become positive. When the primary source is unknown, the growth of these bacteria from blood is highly suggestive of the diagnosis of endocarditis, even when clinical signs of endocarditis are absent.[16] Because β-lactam-producing strains have recently been identified and it is sometimes difficult to determine the resistance of these micro-organisms, some authors recommend empirical treatment with third-generation cephalosporins (such as cefotaxime or ceftriaxone) with adjustment of the therapy based on the antibiogram (level of proof D).[40] When amoxicillin is used, gentamicin must be added for the same reason (see *table 7*). In the event of hypersensitivity to penicillin, the choice of antibiotic is difficult since only a few case reports on alternative therapies have been published. *In vitro* the HACEK micro-organisms are susceptible to cotrimoxazole and fluorchinolone.

Table 7
Treatment of endocarditis caused by HACEK micro-organisms

ANTIBIOTIC	DOSE	DURATION
Native valve		
Ceftriaxone *or*	2 g iv once daily	4 weeks
Cefotaxine *or*	2 g iv every 8 h	4 weeks
Amoxicillin *and*	2 g iv every 4 h	4 weeks
Gentamicin*	3 mg/kg iv once daily	4 weeks
Artificial valve		
Ceftriaxone *or*	2 g iv once daily	6 weeks
Cefotaxine	2 g iv every 8 h	6 weeks

**Gentamicin need not be administered if it is known that the strain does not produce β-lactamase.*

NOTE

A brief Dutch version of this paper will appear in Nederlands Tijdschrift voor Geneeskunde.

ACKNOWLEDGEMENT

The committee wishes to thank Prof. P.J. van den Broek, Leiden; Dr. F.J. ten Cate, Rotterdam; Dr. J.M. Dantzig, Eindhoven; Dr. I.C. Gijssens, Rotterdam; Prof. Y. Hekster, Rotterdam; Prof. I.M. Hoepelman, Utrecht; Dr. W.N.M. Hustinx, Utrecht, Dr. R. Janknecht, Sittard; Dr. B.J. Kullberg, Nijmegen; Dr. E.J. Kuijper, Leiden; Prof. S. Lauwers, Brussel, Belgium; Drs. A.W. Lenderink, Tilburg; Prof. J.W.M. van der Meer, Nijmegen; Dr. F.J. Meijboom, Rotterdam; Dr. J. W. Mouton, Nijmegen; Prof. W. Peetermans, Leuven, Belgium; Dr. J.M. Prins, Amsterdam; Dr. P.J.G.M. Rietra, Amsterdam, Dr. E.E. Stobberingh, Maastricht; Prof. C.M.J.J. Vandenbrouke, Amsterdam; Dr. A. van der Ven, Nijmegen; Prof. G. Verschraegen, Gent, Belgium for their assistance in the preparation of this report.

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