

# *Journal of Clinical and Basic Cardiology*

*An Independent International Scientific Journal*



*Journal of Clinical and Basic Cardiology 2001; 4 (1), 25-30*

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# Current Treatment Options of Infective Endocarditis

M. Petzsch, R. Krause<sup>1</sup>, E. C. Reisinger<sup>2</sup>

Grampositive cocci (*Streptococcus viridans* and *bovis*, Enterococci, *Staphylococcus aureus*, coagulase-negative staphylococci) and the so-called HACEK-micro-organisms are the most common causative agents of infectious endocarditis (IE). Although gramnegative Enterobacteriaceae often cause bacteraemia, they rarely cause IE. About 30 % of IE are based on intravenous drug abuse or invasive medical procedures. Treatment strategies for streptococcal endocarditis differentiate between sensitive streptococci (MIC < 0.1 µg/ml), intermediate penicillin-resistant streptococci (MIC between 0.1 and 0.5 µg/ml), and penicillin-resistant streptococci (MIC > 0.5 µg/ml) or enterococci. Treatment strategies for staphylococcal endocarditis distinguish between *Staphylococcus aureus* and coagulase-negative staphylococci on the one hand and infection of native and prosthetic valves on the other hand. Members of the HACEK group make up about 5 % of native valve IE in non-drug addicts and are treated with ampicillin (plus/minus gentamicin) for β-lactamase negative strains and with third generation cephalosporins in case of known or unknown β-lactamase production. *J Clin Basic Cardiol* 2001; 4: 25–30.

**Key words:** endocarditis, treatment, infection, heart

Nearly all infectious agents can cause infective endocarditis (IE). Grampositive cocci (*Streptococcus viridans* and *bovis*, enterococci, *Staphylococcus aureus*, coagulase-negative staphylococci) and the so-called HACEK-microorganisms (*Haemophilus parainfluenzae*, *Haemophilus aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae* and *Sutonella*) are the most common causative agents of IE. The main portals of entry for bacteria to the bloodstream are the oral mucosa (streptococci) and the skin (staphylococci). The bacterial adherence to damaged heart valves is based on their ability to produce dextran (streptococci) or to bind to fibronectin (fibronectin receptors are present on the surface of *Staphylococcus aureus*, *viridans* streptococci, streptococci group A, C and G, enterococci, *Streptococcus pneumoniae* and *Candida albicans*). Protected by thrombotic material (fibrin, collagen, thrombocytes) and bacterial biofilm (teichoic acid, N-acetylglucosamin) bacteria resist the immune system and antibiotics. One third of patients with IE has underlying heart disease, mostly rheumatic and hereditary cardiac lesions (bicuspid aortic valve, mitral valve prolapse, patent ductus arteriosus, ventricular septal defect, coarctation of the aorta, tetralogy of Fallot, pulmonary stenosis, hypertrophic obstructive cardiomyopathy). Degenerative lesions (arteriosclerosis, calcified mitral valve ring) contribute to the development of IE in another third of patients. The frequency of rheumatic heart disease decreases while degenerative lesions are increasing. 13 % to 47 % of IE are based on intravenous drug abuse in urban regions [1]. 13 % to 21 % of IE are nosocomially acquired [2, 3] due to invasive medical procedures like central venous lines, parenteral alimentation and long-term intravascular catheters. Mortality rates in these seriously ill patients can exceed 50 per cent by far [2, 4]. 10 % to 20 % of all IE cases occur in patients with cardiovascular prosthetic material [2], 1 % to 4 % in the first year after surgery, thereafter 1 % each year [1]. The incidence of IE varies between 1/1000 hospitalisations [5], 3.8/100,000 person-years [2] and 5.5 to 7.4/100,000 person-years [6].

The classic signs of IE are fever, chills, new heart murmurs, splenomegaly, vascular phenomena like conjunctival haemorrhages, Janeway lesions, intracranial haemorrhage,

pulmonary or systemic embolization often leading to serious complications and immunologic phenomena like Osler's nodes, Roth's spots, rheumatoid factor. The highly variable and non-specific symptoms like weakness, night-sweats, weight loss, anorexia, dyspnoea, myalgia and arthralgia make the clinical diagnosis of IE often difficult. Heart murmurs are present in 80 % of IE, however most heart murmurs preexisted due to the underlying heart disease. Changing or new heart murmurs are indicative of acute IE or prosthetic valve endocarditis. The rate of heart murmurs in patients with IE varies between 8 % and 85 % [2, 7]. Congestive heart failure resulting from valve destruction has the greatest impact on prognosis. With severe valve destruction mortality is higher than 50 % in patients who are only medically treated, but less than 20 % with antibiotics and cardiac surgery [8, 9]. Up to 39 % of patients exhibit neurological symptoms, in 17 % due to cerebral embolism [10]. In 1 % to 5 % of cases the situation is complicated by intracranial mycotic aneurysms (streptococci 50 %, staphylococci 10 %). The overall mortality rate in affected patients with intracranial mycotic aneurysms exceeds 50 % [6]. Occasionally mononeuritis, seizure, brain abscess, meningitis and cerebral bleeding may occur. Arterial embolism also involves other organs like mesenteric, splenic, renal and coronary arteries in left-sided and pulmonary arteries in right-sided IE. Alterations of laboratory parameters are non-specific and variable: elevated erythrocyte sedimentation rate and C-reactive protein, normochromic anaemia, leucocytosis, thrombocytopenia, elevated rheumatoid factor, microscopic haematuria and proteinuria. The definitive diagnosis is based on a high grade of clinical suspicion, positive blood cultures and a positive echocardiogram (see Table 1, [11]).

Recent reports and recommendations have focused only on some of the pathogens causing IE.

The guidelines of the American Heart Association have focused on grampositive and HACEK-microorganisms [12, 13], other reports have focused on fungi [14] or culture negative IE [15]. In this report we discuss treatment regimens for the whole spectrum of pathogens that commonly cause IE. Guidelines for the antibiotic prophylaxis of IE have been reported elsewhere [16, 17].

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## Treatment of Infective Endocarditis

### Streptococcus viridans and Streptococcus bovis

*Streptococcus viridans* and *Streptococcus bovis* frequently cause subacute IE in patients with rheumatic or hereditary heart diseases. In patients with an uncomplicated course, penicillin sensitive streptococci and a low risk of renal or auditory impairment penicillin G (4 million IU tid or qid i.v.) plus gentamicin (5 mg/kg qd single dose iv) both for two weeks are as effective as a four week course of penicillin G (4 million IU tid or qid i.v.) or ceftriaxon (2 g qd i.v. or i.m.) (see Table 2) [18]. Outpatient therapy with i.m. ceftriaxon (2 g qd i.m.) is the most economic modality in patients suffering from streptococcus (not enterococcus) IE. Patients with prosthetic-valves receive penicillin G (4 million IU tid or qid i.v.) for 6 weeks plus gentamicin (5 mg/kg qd single dose i.v.) for the first two weeks.

Patients with IE due to *Streptococcus viridans* or *bovis* with low *in vitro* penicillin sensitivity (MIC between 0.1 and 0.5 µg/ml) receive penicillin G (4 million IU tid or qid i.v.) for 4 weeks plus gentamicin (5 mg/kg qd single dose i.v.) for the first two weeks (Table 3).

*Streptococcus viridans* or *bovis* resistant to penicillin (MIC > 0.5 µg/ml) require a treatment regimen with penicillin G plus gentamicin, both for 4–6 weeks as reported for enterococci (see enterococci and Table 4). Although the

strains are resistant to penicillin *in vitro*, the combination of penicillin plus gentamicin is considered synergistic.

Patients with severe β-lactam-allergy (anaphylaxis) receive i.v. vancomycin (15 mg/kg bid; not to exceed 2 g/day) for four weeks. To prevent adverse events of vancomycin (red man syndrome, anaphylactoid reactions with a drop of blood pressure, shortness of breath, thrombophlebitis) infusion time should take at least one hour.

### Streptococcus pneumoniae, Streptococcus pyogenes and Streptococcus Group B, C, G and F

These grampositive cocci rarely cause IE. Penicillin-susceptible pneumococci and streptococcus pyogenes (*Streptococcus* group A) are treated with penicillin G (4 million IU tid or qid i.v.) for four weeks. IE caused by pneumococci, that are intermediately or highly resistant to penicillin (MIC > 0.1 or > 1 µg/ml, respectively) should be treated with vancomycin for 4 weeks. For IE due to *Streptococcus* group B, C, F and G, penicillin G (4 million IU tid or qid i.v.) for four to six weeks plus gentamicin (5 mg/kg qd single dose i.v.) for the first two weeks is indicated.

### Enterococci

Treatment of enterococcal IE usually is difficult. Penicillin, gentamicin and vancomycin are bacteriostatic, but not bactericidal to enterococci [19]. Penicillin, ampicillin or vanco-

**Table 1.** The diagnosis of IE is definitive when two major criteria or one major and three minor criteria or five minor criteria are present

#### Major criteria

Microbiology: persistent positive blood culture  
with typical pathogens like viridans streptococci,  
*Streptococcus bovis*, HACEK group, community acquired  
*Staphylococcus aureus* or enterococci

Positive echocardiogramm:

- oscillating mass
- abscess
- new dehiscence of a prosthetic valve

#### Minor criteria

- Microbiology: neither typical nor persistent bacteraemia
- Echocardiographic abnormalities consistent with IE which do not meet definitions for a major criterion
- Vascular phenomenon (eg, arterial emboli, mycotic aneurysm, Janeway lesion)
- Immunologic phenomenon (eg, Osler's nodes, Roth spots, glomerulonephritis)
- Fever ≥ 38 °C (axillary)
- Predisposing heart condition or intravenous drug abuse

**Table 2.** Treatment for endocarditis due to highly penicillin-susceptible viridans streptococci and *Streptococcus bovis* (MIC < 0.1 µg/ml)\*

Antibiotic	Dosage and route	Duration	Comments
Penicillin G	12 to 16 million U/day in 4 doses i.v.	4 weeks	In patients > 65 years or with renal dysfunction or auditory impairment
Ceftriaxone	2 g qd i.v. or i.m.	4 weeks	
Penicillin G	12 to 18 million U/day in 4 doses i.v.	2 weeks	
plus			
Gentamicin	5 mg/kg qd i.v. or i.m.	2 weeks	
Vancomycin	30 mg/kg (max. 2 g) daily in 2 doses i.v.	4 weeks	In case of β-lactam allergy

\* Dosages given for patients with normal renal function

**Table 3.** Treatment for endocarditis due to strains of viridans streptococci and *Streptococcus bovis* intermediate resistant to penicillin G (MIC > 0.1 and < 0.5 µg/ml)\*

Antibiotic	Dosage and route	Duration	Comments
Penicillin G	16–20 million U/day in 4 doses i.v.	4 weeks	First generation cephalosporin in case of mild penicillin allergy (rash)
plus			
Gentamicin	5 mg/kg qd i.v. or i.m.	4 weeks	
Vancomycin	30mg/kg (max. 2g) daily in 2 doses i.v.	4 weeks	β-lactam allergy (anaphylaxis)

\* Dosages given for patients with normal renal function

**Table 4.** Treatment for endocarditis due to Enterococci\*

Antibiotic	Dosage and route	Duration**	Comments
Penicillin G	20 to 28 million U/day in 4 doses i.v.	4 to 6 weeks	
plus			
Gentamicin	5 mk/kg qd i.v. or i.m.	4 to 6 weeks	
Ampicillin	12 g daily in 4 doses i.v.	4 to 6 weeks	Aminopenicillin plus β-lactamase inhibitor in case of β-lactamase producing bacteria
plus			
Gentamicin	5 mg/kg qd i.v. or i.m.	4 to 6 weeks	
Vancomycin	30 mg/kg (max. 2g) daily in 2 doses i.v.	4 to 6 weeks	In case of severe β-lactam allergy (anaphylaxis)
optionally plus			
Gentamicin	5 mg/kg qd i. v. or i. m.	4 to 6 weeks	

\* Enterococci must be tested for antimicrobial susceptibility

\*\* In patients symptomatic < 3 months: 4 weeks; in patients symptomatic > 3 months: 6 weeks

mycin combined with an aminoglycoside (streptomycin or gentamicin) shows synergism resulting in bactericidal effect. Cephalosporins are not effective against enterococci at all. Sensitivity testing should be performed in every case. Since resistance to gentamicin and streptomycin is mediated by different genes, the aminoglycoside with the lower MIC (lower *in vitro* resistance) should be used. Because of increasing resistance to streptomycin in the last years gentamicin is currently preferred [12]. Other aminoglycosides are less effective than gentamicin and streptomycin. Table 4 shows the recommended treatment regimens in enterococcal endocarditis.

Penicillin plus gentamicin is indicated if both drugs are active or low level resistant *in vitro*. In case of  $\beta$ -lactamase-production an aminopenicillin (ampicillin or amoxycillin) plus a  $\beta$ -lactamase inhibitor (sulbactam or clavulanic acid) is preferred. With intrinsic penicillin resistance vancomycin is indicated. In case of resistance to penicillin and vancomycin teicoplanin might be used after *in vitro* testing, since vancomycin and teicoplanin do not exhibit cross resistance in every case.

The combination of ciprofloxacin plus ampicillin reduced vegetations in rabbits with enterococcal endocarditis (ampicillin-, vancomycin- and high level aminoglycosid-resistant), however clinical experience is lacking [20].

In uncomplicated cases the above mentioned regimens should be given for at least four weeks, in patients with prosthetic valves or symptoms lasting longer than three months treatment should be given for at least six weeks [21]. In case of high level aminoglycoside-resistance the duration of penicillin G or ampicillin therapy (without aminoglycosid) is extended up to eight to twelve weeks. In patients not responding to this antibiotic regimen surgery is indicated. Aminoglycosides exhibit ototoxicity and nephrotoxicity, vancomycin and teicoplanin exhibit ototoxicity. Combinations of aminoglycosides with vancomycin or teicoplanin could increase the nephrotoxic and ototoxic potential, therefore these combinations are justified only in special circumstances and aminoglycosid and vancomycin serum levels should be monitored. Clinical experience is more common with penicillin and ampicillin than with vancomycin. With mild penicillin-allergy (eg, rash in the case history, but not after anaphylactic reactions) therapy with penicillin or ampicillin is preferred particularly in life threatening IE.

### Staphylococci

*Staphylococcus aureus* and coagulase-negative staphylococci (eg, *Staphylococcus epidermidis*) cause IE of native or prosthetic valves. Staphylococcal endocarditis is increasingly diagnosed in intravenous drug addicts and in nosocomial infections. Coagulase-negative staphylococci are frequently recovered in prosthetic-valve endocarditis. IE of prosthetic valves is often associated with perivalvular invasion requiring early surgical intervention.

### Staphylococcus-endocarditis without prosthetic valves

A minority of staphylococci is susceptible to penicillin (10–20 %), in this case IE is best treated with intravenous penicillin G (4 million IU qid) for four weeks. Most staphylococci are penicillin resistant ( $\beta$ -lactamase producers), therefore penicillinase-resistant semisynthetic penicillins (methicillin, oxacillin, flucloxacillin, nafcillin) are indicated. Co-administration of gentamicin in the first two weeks of a six-week nafcillin course did not result in improved clinical outcome, but the frequency of renal dysfunction was higher in the gentamicin group [22]. Because of the rapid clearance of bacteraemia with the combination, the co-administration of gentamicin in the first three to five days of therapy is considered to prevent heart damage and abscess formation [12].

The probability of adverse renal effects is considerably lower with short duration of aminoglycoside therapy. Penicillinase-resistant semisynthetic penicillins should then be continued for a total of four to six weeks. Drug abusers with uncomplicated right heart IE due to *Staphylococcus aureus* are treated with oxacillin (or flucloxacillin) plus gentamicin for two weeks [23]. In these patients the combination of oral ciprofloxacin plus oral rifampin for four weeks has been used with success, although the number of cases was small [24]. In penicillin-allergy a first generation cephalosporin (eg, cefazolin) or vancomycin is indicated (Table 5). For the treatment of penicillin-susceptible and methicillin-susceptible staphylococci, vancomycin is inferior to penicillin G and penicillinase-resistant semisynthetic penicillins, respectively [25].

Methicillin-resistant staphylococci (*Staph. aureus* and coagulase negative staphylococci) are resistant to all  $\beta$ -lactam antibiotics (also carbapenems). IE due to methicillin-resistant staphylococci is treated with i.v. vancomycin. Alternatively teicoplanin (400 mg qd i.v. or i.m., first dose 800 mg), fusidic acid (500 mg tid i.v. or p.o.), fosfomycin (3–5 g tid i.v.) or clindamycin (600 mg tid i.v.) might be used. When rifampin (3 mg/kg tid) is used alone, resistance may develop quickly. Rifampin plus vancomycin is a well accepted combination which may shorten the duration of bacteraemia. The combination of vancomycin plus aminoglycosides may potentiate nephrotoxic and ototoxic side effects of either drug and should therefore be administered only in special situations like prosthetic valve endocarditis.

### Staphylococcal prosthetic valve endocarditis

Coagulase-negative staphylococci (CNS) are methicillin-resistant more frequently than *Staphylococcus aureus*. This is an emerging problem in foreign body infections like prosthetic heart valve endocarditis [26]. Initial treatment of IE due to CNS consists of the combination of vancomycin plus rifampin plus gentamicin until susceptibility tests are available (Table 6). Vancomycin and rifampin are administered for six weeks, gentamicin is added for the first two weeks. Fluoroquinolones (ofloxacin, ciprofloxacin) can be used instead of aminoglycosides to reduce the adverse effects of aminoglycosides [26].

Methicillin-sensitive CNS are best treated with oxacillin (2 g qid to 4 g tid) or flucloxacillin (2 g qid to 4 g tid) plus rifampin plus gentamicin (Table 6). In penicillin-allergic patients oxacillin can be exchanged by first generation cephalosporins (cefazolin 2 g tid).

**Table 5.** Treatment for staphylococcal endocarditis in the absence of prosthetic material

Antibiotic	Dosage and route	Duration
<b>Methicillin- (oxacillin-) susceptible staphylococci</b>		
Oxacillin*	2 g every 4 hours i.v.	4 to 6 weeks
plus		
Gentamicin	5 mg/kg qd i.v. or i.m.	First 3 to 5 days of treatment
<b>Mild penicillin allergy (delayed skin rash)</b>		
Cefazolin	2 g tid i.v.	4 to 6 weeks
plus		
Gentamicin	5 mg/kg qd i.v. or i.m.	First 3 to 5 days of treatment
<b>Methicillin- (oxacillin-) resistant staphylococci or severe penicillin allergy (urticarial or anaphylactic reactions)</b>		
Vancomycin	30 mg/kg (max. 2 g) daily in 2 doses i.v.	4 to 6 weeks

\* For penicillin G susceptible staphylococci penicillin G can be used instead of oxacillin for 4 to 6 weeks (see Table 1)

IE due to methicillin-sensitive *Staphylococcus aureus* is treated with oxacillin (or flucloxacillin) for six weeks plus gentamicin (5 mg/kg qd i.v.) in the first two weeks. In case of methicillin-resistant strains and/or penicillin allergy vancomycin is used instead of oxacillin.

### HACEK-microorganisms

HACEK-microorganisms are fastidious gramnegative rods and part of the human oral flora. These organisms cause 5–10 % of IE in non-drug addicted persons [27]. IE due to HACEK-microorganisms is treated with ampicillin (2–4 g tid i.v.) plus

**Table 6.** Treatment for staphylococcal endocarditis in the presence of a prosthetic valve or other prosthetic material

Antibiotic	Dosage and route	Duration	Comments
<b>Methicillin- (oxacillin-) resistant staphylococci</b>			
Vancomycin	30 mg/kg (max. 2 g) daily in 2 doses i.v.	At least 6 weeks	
plus			
Rifampin	300 mg tid p.o.		
plus			
Gentamicin	5 mg/kg qd i.v. or i.m.	First 2 weeks of treatment	
<b>Methicillin- (oxacillin-) susceptible staphylococci</b>			
Oxacillin*	2 g tid i.v.	At least 6 weeks	
plus			
Rifampin	300 mg tid p.o.	At least 6 weeks	
plus			
Gentamicin	5 mg/kg qd i.v. or i.m.	First 2 weeks of treatment	

\* Cefazolin may be used in mild penicillin allergy instead of oxacillin (delayed skin rash); vancomycin may be used in severe penicillin allergy instead of oxacillin (urticarial or anaphylactic reactions)

**Table 7.** Treatment for endocarditis due to HACEK-microorganisms

Antibiotic	Dosage and route	Duration	Comments
Ampicillin	12 g daily in 4 doses i.v.	4 weeks	
optionally plus			
Gentamicin	5 mg/kg qd i.v. or i.m.	4 weeks	
Ceftriaxone*	2 g qd i.v. or i.m.	4 weeks	If $\beta$ -lactamase production is considered

\* Alternative: other third-generation cephalosporins

**Table 8.** Treatment of fungal endocarditis

Antibiotic	Dosage and route	Duration	Comments
Liposomal amphotericin B	3 to 5 mg/kg qd i.v.	At least 8 weeks	Dosage of liposomal amphotericin B may be reduced in case of combination with flucytosin
alternatively			
Non-liposomal amphotericin B	0.4 to 0.6 mg/kg qd i.v.	At least 8 weeks	
plus			
Flucytosin	40–50 mg/kg qid i.v.	At least 8 weeks	
Fluconazole*	200 to 400 mg qd p.o.	6 months to lifelong	optimal duration is unknown

\* Infective endocarditis due to *Candida albicans* or *Cryptococcus neoformans*

gentamicin. Because of increasing  $\beta$ -lactamase- (penicillinase-)production and difficult *in vitro* testing third generation cephalosporins (cefotaxim, ceftriaxone) should be used in case of uncertainty about the  $\beta$ -lactamase status of the individual HACEK strain (Table 7) [28]. Therapy should be given for three to four weeks, in prosthetic heart valves for six weeks. Fluorochinolones, trimethoprim-sulfamethoxazole and aztreonam may also be effective, but since clinical data are rare, these antibiotics are regarded as alternatives in case of inadequacy of cephalosporins.

### Endocarditis in HIV-Patients

IE in HIV-patients mostly results from intravenous drug abuse or central-venous catheters. *Staphylococcus aureus* is the most frequent strain. In intravenous drug addicts IE is often found at the tricuspid valve, in non drug-addicted patients right- and left-sided IE occur with the same frequency. Treatment is the same as for *Staphylococcus aureus* endocarditis mentioned before but with a prolonged course of 6 weeks in cases with decreased CD4 counts (Tables 5 and 6). After 4 weeks of intravenous therapy oral treatment may be considered, however, drug-interaction with antiretrovirals is common.

### Culture-Negative Endocarditis

Blood culture in IE might be negative due to recent antimicrobial therapy or due to organisms that are not able to be or difficult to isolate (5 % of all cases of IE). The recommended initial treatment for culture-negative endocarditis is ampicillin plus gentamicin as indicated above. For patients with a prosthetic heart valve and culture-negative endocarditis vancomycin is added initially. Among the more common fastidious or non-culturable organisms are the HACEK-microorganisms, *Coxiella burnetii*, and fungi [15]. Rarely *Brucella*, *Legionella*, *Neisseria gonorrhoea*, *Bartonella*, *Corynebacteria*, *Listeria*, *Mycobacteria*, *Chlamydia* spp. and others have been described causing IE [29].

### Fungal Endocarditis

A large number of fungal organisms has been identified as a cause of IE, the most common being *Candida albicans* (32 %) and *Aspergillus* spp. (27 %) [14]. Open heart surgery with valve replacement, i.v. drug abuse, immunocompromised hosts (eg, HIV, organ or bone marrow transplantation) are the major predisposing factors.

Fungal IE is characterized by fever, changing heart murmurs and peripheral emboli in more than 50 % of cases. The echocardiographical detection of bulky vegetations in view of frequent negative blood cultures induces a high level of clinical suspicion for fungal IE. Ocular manifestations (especially with *candida*) should be excluded by eye-ground examination. The clinical outcome of fungal endocarditis is poor because embolic events and metastatic abscesses to other organs limit survival or leave the patient with considerable sequelae.

Combined medical (Table 8) and surgical treatment increased the survival rate from 20 % to 50 % [14]. Valves should be replaced shortly after the initiation of amphotericin B (0.5–1.0 mg/kg/qd i.v.). The recommended duration of therapy is at least eight weeks. Adverse events with amphotericin B (nephrotoxicity, fever, chills, thrombophlebitis, abdominal pain and electrolyte disturbances) can be considerably reduced by the application of liposomal amphotericin B (3 to 5 mg/kg qd i.v.). Amphotericin B plus 5-fluorocytosin (150 mg/kg/qid i.v.) shows antifungal synergism in case of in-

fective endocarditis due to *Candida*, *Aspergillus* or *Cryptococcus* and helps reduce the dosage of amphotericin B (reduced dosage of non-liposomal amphotericin B: 0.4–0.6 mg/kg/qd i.v.). However, leucopenia is a major adverse effect of 5-fluorocytosin. Prolonged treatment with amphotericin B plus fluconazole (5 mg/kg/qd i.v.) is considered to increase the cure rate of fungal endocarditis caused by *Candida albicans* or *Cryptococcus neoformans*. In some cases prophylaxis with fluconazole (200–400 mg/qd p.o.) is given from six months to several years [30] or lifelong in some cases [31].

### Q-Fever Endocarditis

Q-fever is caused by *Coxiella burnetii* which is a strict intracellular pathogen. In 5 % Q-fever is a chronic disease with endocarditis. The patients present with fever, cardiac failure, hepatosplenomegaly or arterial embolism. The predominant laboratory findings are increased erythrocyte sedimentation rate, increased gamma-globulins, increased serum creatinine, anaemia and thrombocytopenia. Echocardiography is not very helpful because vegetations are seen in only 25 % of cases. Diagnosis is confirmed by a rise in specific serum antibody titers or by detection of *Coxiella burnetii* in excised heart valves.

Tetracycline is the mainstay [32] in therapy of Q-fever endocarditis (doxycycline 100 mg bid). A mortality rate of 44 % with tetracycline alone, relapses and the culture of *Coxiella burnetii* from heart valves up to four years after therapy, makes a combined antibiotic treatment regimen reasonable. In a recent study with 35 patients relapses of Q-fever endocarditis were less frequent in patients with doxycycline plus chloroquine (9 %) compared to doxycycline plus ofloxacin (48 %). Mortality was below 5 % with both regimens [33, 34]. Other potentially active compounds are rifampin and trimethoprim-sulfamethoxazole. Combined antibiotic treatment has to be continued for 18 months to 4 years, infectious disease consultant is advised. Surgical intervention is required in case of valve destruction with haemodynamic deterioration and in prosthetic valve endocarditis.

### Discussion

Relapses of IE are common during the first eight weeks and can early be recognized when blood cultures remain positive. Persistent detection of *Staphylococcus aureus* or CNS in blood cultures should lead to the suspicion of valve abscess or metastases to other organs.

Valve surgery is required in uncontrollable congestive heart failure resulting from valvular destruction (mainly *Staph. aureus*, *Staph. lugdunensis*, pneumococci, salmonellae), uncontrolled infection (mainly enterococci, staphylococci, candida) [35, 36], arterial embolism and extravalvular extension of the infective process [37].

Death is mostly attributed to congestive heart failure (valve dysfunction) and embolic complications.

Recommendations concerning anticoagulation emphasise the risk of intracerebral haemorrhage and consider anticoagulation as contraindicated [6]. Meanwhile the administration of antithrombotic agents is still in discussion. Recently published animal studies reveal an advantage of antithrombotic therapy, ahead ASS and fibrinolytic therapy with rtPA [38, 39]. Administration of ASS before and during antibiotic therapy leads to reduction of vegetation size and to accelerated aseptis of the valves [38]. In an IE rabbit model with *Staphylococcus aureus* the administration of ASS and salicylic acid reduced the vegetation size, the bacterial density in vegetations and the incidence of embolisation [40]. The

combination of ASS plus ticlopidine also reduced the weight of aortic valve vegetations in *Staphylococcus aureus* endocarditis [41]. In another rabbit-model the combination of rtPA and penicillin showed significant reduction of vegetations and ischaemia of the heart [39].

In the 1960s therapy of IE made its greatest strides by the introduction of antibiotics, followed by surgical valve replacement one decade later. In future years reduction of vegetation size by antithrombotic or fibrinolytic agents might create more effectiveness of antibiotics in a smaller nidus, preventing valve destruction and spread of infection.

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