Chapter

22

Management of Infective Endocarditis

NAVEEN GARG

Infective endocarditis (IE) is an endovascular microbial infection of cardiovascular structures (e.g., native valves, ventricular or atrial endocardium) including endarteritis of the large intrathoracic vessels (e.g., in a patent ductus arteriosus, arteriovenous shunts, coarctation of the aorta) or of intracardiac foreign bodies (e.g., prosthetic valves, pacemaker or ICD leads, surgically created conduits) facing the blood stream.

INCIDENCE

IE continues to remain a serious challenge despite several advances in its diagnosis and treatment. There is considerable uncertainty about the present incidence of the disease; 1.9 to 6.2 annual infections per 100,000 population[1,2]. The estimated incidence of IE in the West has remained unchanged over the past two decades at l.7-6.2 cases per 100,000 patient years[3-5], but such estimates are not available from India. Even assuming the lowest incidence, at least 17,000 episodes of IE must be occurring per year in India[6-9].

DIAGNOSIS

History and Physical Examination

As the clinical history is highly variable depending on the causative microorganism and the presence or absence of predisposing cardiac conditions and other diseases, early suspicion of IE is very important (Table 1). Among the presenting symptoms fever is a non-specific but the most frequent one. It varies from high temperatures with shivers and prostration in acute staphylococcal IE to prolonged febrile states associated with general malaise, weakness, arthralgias and loss of weight in subacute streptococcal infections. Further symptoms often arise as a consequence of complications. Valve destruction leads to increasing shortness of breath, nocturnal dyspnea, orthopnea, or even acute pulmonary edema. In patients with right-sided endocarditis clinical signs of pneumonia and/or right heart failure predominate. Emboli from cardiac vegetations results in CNS symptoms, vascular obstruction in the extremities, pleuritic or abdominal pain.

Table 1: When to suspect infective endocarditis

a.	New valve lesion/ (regurgitant) murmur
b.	Embolic events of unknown origin
c.	Sepsis of unknown origin
d.	Hematuria, glomerulonephritis, and suspected renal infarction
e.	'Fever' plus
	i. Prosthetic material inside the heart
	ii. Other high predisposition for IE
	iii. Newly developed ventricular arrhythmias or conduction disturbances
	iv. First manifestation of CHF
	v. Positive blood cultures (if the organism identified is typical for NVE/PVE)
	vi. Cutaneous (Osler, Janeway) or ophthalmic (Roth) manifestations
	vii. Multifocal rapid changing pulmonic infiltrations (right heart IE)
	viii. Peripheral abscesses (renal, splenic, spine) of unknown origin
	ix. Predisposition and recent diagnostic/therapeutic interventions known to result in significant bacteremia

Among the clinical findings, cardiac murmurs in a febrile patient alert the physician about IE. Newly occurring regurgitant murmurs or growing intensity of preexisting regurgitant murmurs are of particular

importance. However, murmurs are not obligatory and may not occur before perforation or valve disruption. Embolic or immunological complications from vascular occlusion in the systemic circulation present as cerebral ischemia or hemorrhage, ischemia of the limbs, intestinal infarctions, or small cutaneous lesions mostly located on fingers, toes, or in the eyes. Septic pulmonary infarcts with pleuritic chest pain in drug addicts are the typical manifestations of right-sided endocarditis. It is important to realize that none of the above-mentioned clinical signs are specific enough to allow the diagnosis of IE without additional investigations. The detection of endocarditis will, however, depend on the performance of the decisive diagnostic tests such as repeated blood cultures and transthoracic or transoesophageal echocardiography.

Echocardiography

All patients of suspected IE should be screened by transthoracic echocardiography (TTE). An algorithm for the use of echocardiography is given in Figure 1. When the images are of good quality, TTE alone is sufficient for making the diagnosis. Transoesophageal echocardiography (TEE) should be performed in all TTE-negative cases, in suspected PVE, and in cases of aortic location as well as before cardiac surgery during active IE. If TEE also remains negative and there is still suspicion, TEE should be repeated after 48 h to one week to allow potential vegetations to become more apparent. A repeated negative study should virtually exclude the diagnosis unless TEE images are of poor quality[10]. Three echocardiographic findings are considered to be major criteria in the diagnosis of IE:

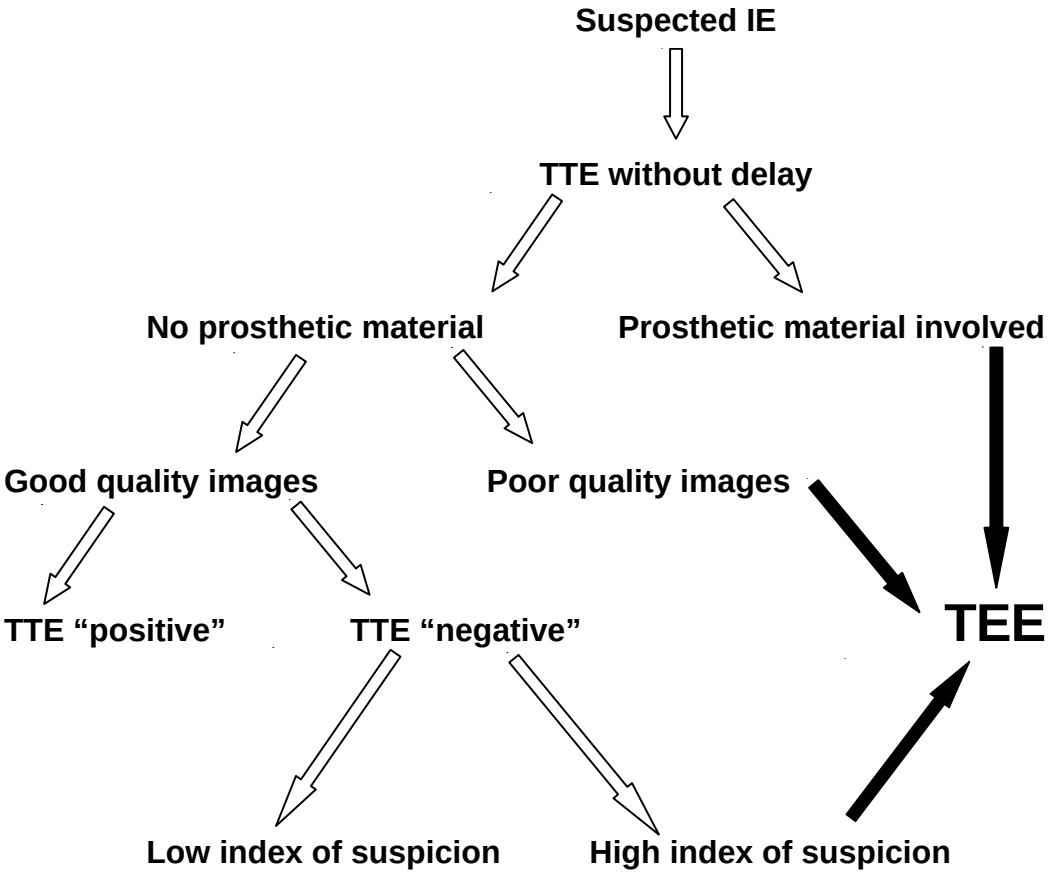

Fig. 1: Algorithm for the use of transthoracic and transesophageal echocardiogram in suspected IE

1. Vegetation
2. Abscesses or fistulas
3. A new dehiscence of a valvular prosthesis, especially when occurring late after implantation.

Vegetations are detected by TTE in about 50% of patients in whom IE is clinically suspected[11]. While only 25% of vegetations less than 5 mm in size are identified[11], the percentage increases to 70% in vegetations larger than 6 mm[11]. On prosthetic valves TTE as a rule is nondiagnostic. Owing to its better resolution, these limitations have been overcome by TEE, especially omniplane TEE. Sensitivity of TEE has been reported to be 88-100% and specificity, 91-100%[11,12]. Echocardiography is not immune to errors. Both false positive and false negative diagnoses do occur. The common differential diagnosis of vegetations in our patients includes—

1. Nodules due to acute rheumatic fever
2. Ruptured chordae
3. Myxomatous degeneration
4. Thrombus or sutures in postoperative patients
5. Other causes of vegetation-like structures include intracardiac neoplasia, autoimmune diseases (systemic lupus erythematosus, Wegener's granulomatosis, and eosinophilic heart disease)
6. Normal structures like Chiari malformation, and Lambl's excrescences.

On the other hand, vegetations may be missed because of poor echo window, small size of vegetations or after embolization. Uncommonly, IE may cause ulcers, pseudo aneurysms etc, but no vegetations.

Blood Cultures

At least three blood cultures should be taken at least 1 hour apart[13]. These should not be taken through intravenous lines because they may be contaminated. If initiation of antimicrobial therapy is urgent (e.g. in septic patients), empiric antibiotic treatment can be started thereafter. In all other cases it is recommended to postpone antimicrobial therapy until blood cultures become positive. If the patient has been on short-term antibiotics, one should wait, if possible, for at least 3 days after discontinuing antibiotic treatment before taking new blood cultures. Blood cultures after long-term antibiotic treatment may not become positive until treatment has been discontinued for 6-7 days. Blood cultures should not be stored in a refrigerator. Cultures drawn from arterial blood have occasionally been advocated as being more yielding than venous blood cultures. But, there are higher chances of contamination as well as of complications. So therefore, they are no longer recommended. Blood cultures are often drawn when the body temperature is rising. In one study, a negative correlation between body temperature and the percentage of positive blood cultures has been documented[14]. Constant bacteremia typical for IE allows the drawing of blood cultures at any time.

One blood cultures consists of one aerobic and one anaerobic bottle, each containing approx. 50 ml of medium. Minimally 5 ml (better 10 ml) of venous blood should be added to each bottle. 10 ml should suffice to detect even low numbers of organisms[13]. In the laboratory, incubation of the blood cultures for 5-6 days is routine. Bottles that give a growth signal are Gram-stained and subcultured to media that support growth of fastidious organisms (e.g. *Abiotrophia spp.*), which are incubated at 37°C for 2-3 days. Identification should be to species level. All organisms should be stored for at least one year for comparison if IE should be recurring or relapsing. Susceptibility testing by disk diffusion helps only to rule out drugs for therapy that are ineffective *in vitro*. Routine determination of minimum bactericidal concentrations or serum bactericidal levels is not recommended any more.

Negative Blood Cultures

A higher percentage of negative blood cultures in our patients are the result of prior antibiotic use. A structured delay in the initiation of antibiotics for 3-5 days can increase the diagnostic yield and improve the outcomes. However, such practices are rarely followed. A negative blood culture not only delays the diagnosis, but also misclassifies the patient precluding appropriate antibiotics. The management approach to a patient with negative blood culture resulting from poor microbiological techniques should be quite different from that of a patient having culture negativity due to atypical organisms. In negative blood culture cases, IE due to atypical organisms should specially be considered in patients with indwelling venous lines, prosthetic valves, pacemakers, renal failure, immunocompromised states and during postpartum period. While IE with unusual organisms must be kept in the mind, one should also avoid wasting resources and time in getting anaerobic and fungal cultures routinely without a clinical background.

False-Positive Blood Cultures

A false-positive blood culture is also not uncommon and leads to difficulties in diagnosis. Bacteremia in the

hospitalized patients should be viewed with suspicion, but *per se* does not diagnose IE in the absence of evidence for endocardial involvement. Enterococcal and Staphylococcal bacteremia can occur in hospitalized patients in the absence of IE, but bacteremia in the absence of an identifiable focus is more likely to result from IE.

DIAGNOSTIC CRITERIA

Duke criteria is currently the most sensitive and specific diagnostic criteria available (Tables 2 and 3)[15]. The Duke criteria use echocardiography as major criteria for diagnosis. Cases are classified as definite in the Duke schema using major and minor criteria in a manner analogous to the Jones criteria for rheumatic fever. The recent ACC guidelines recommend the use of modified Dukes criteria as the primary scheme for the diagnosis of IE[16, 17]. The sensitivity of these criteria has never been tested in the Indian population. In the absence of positive blood cultures and limited echo availability (two of the major criteria), the utility of modified Duke's criteria for the diagnosis of IE in Indian setting is likely to be diminished.

Table 2: Duke criteria for the diagnosis of infective endocarditis

A. Definite Endocarditis

1. Pathologic criteria

Microorganism: demonstrated by culture, in a vegetation at surgery, from an embolized vegetation, or from an intracardiac abscess

Pathologic lesions: vegetations or intracardiac abscess present and confirmed by histology showing active endocarditis

2. Clinical criteria (using specific definitions listed in Table 3)
Two major criteria, or

One major and three minor criteria, or

Five minor criteria

B. Possible Endocarditis

Findings consistent with infective endocarditis that fall short of definite, but not rejected

C. Rejected

-Firm alternate diagnosis for manifestations of endocarditis, or

-Resolution of manifestations of endocarditis, with antibiotic therapy for 4 days or less, or

-No pathologic evidence of infective endocarditis at surgery or autopsy, after antibiotic therapy for 4 days or less

Table 3. Definitions of terminology used in the Duke criteria for infective endocarditis

MAJOR CRITERIA

A. Positive blood culture for infective endocarditis

1. Typical microorganism for infective endocarditis from two separate blood cultures: *Streptococcus viridans, Streptococcus bovis*, HACEK group, or community acquired *Staphylococcus aureus* or *Enterococci*, in the absence of a primary focus, or
2. Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from:
   (i) Blood cultures drawn more than 12 h apart, or
   (ii) All of three or a majority of four or more separate blood cultures, with first and last drawn at least 1 h apart

B. Evidence of endocardial involvement

a. Positive echocardiogram for infective endocarditis

1. Oscillating intracardiac mass on valve or supporting structures, or in the path of regurgitant jets, or on implanted material, in the absence of an alternative anatomic explanation, or
2. Abscess, or
3. New partial dehiscence of prosthetic valve

b. New valvular regurgitation

(Increase or changes in preexisting murmur not sufficient)

MINOR CRITERIA

1. Predisposition: predisposing heart condition or intravenous drug use
2. Fever 38.0°C (100.4°F)
3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
4. Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor
5. Microbiologic evidence: positive blood culture result but not meeting major criterion as noted previously or serologic evidence of active infection with organism consistent with infective endocarditis
6. Echocardiogram: consistent with infective endocarditis but not meeting major criterion noted previously

Management

Initial treatment should be directed by clinical findings and microbiology. In uncomplicated cases, postponement for up to 48 hours, e.g. until the results of initial blood cultures are obtained, may be advisable and should generally be pursued if the patient has been treated with antibiotics within the last 8 days (Fig. 2). In severely ill patients (cases complicated by sepsis, severe valvular dysfunction, conduction disturbances or

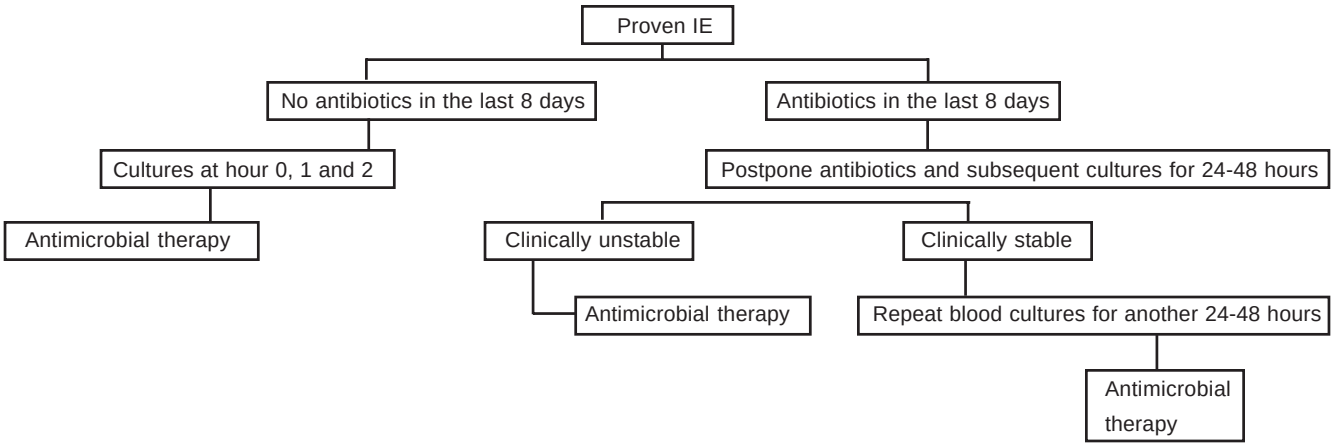

Fig. 2: Empiric antibiotic treatment before identification of causative organism

embolic events) antimicrobial treatment should be started just after taking three blood cultures. Thus, treatment will initially be empirical and later adjusted to the microbiological test results. The therapeutic goal is to produce bactericidal levels of drugs at the infected site for a maximum period of time. The *in vitro* susceptibility to antibiotics may significantly differ from *in vivo* susceptibility at the site of the infection.

STREPTOCOCCAL ENDOCARDITIS

Penicillin

Antibiotic treatment for streptococcal IE is dependent on the species as there are significant differences in antibiotic resistance, tolerance and synergistic activity among different groups of streptococci. Patients with IE caused by streptococci susceptible to penicillin G should be treated with 12-20 million units of penicillin G per 24 h IV divided into 4-6 doses. Frequent dosing is necessary as the initial high peak concentration rapidly decreases due to glomerular filtration, tubular excretion in the kidneys, and inactivation of penicillin (half life 20-30 min) in the circulating blood. Single doses higher than 5 million units are not recommended in order to avoid side effects. Continuous IV administration should be reserved for special circumstances and 'difficult-to-treat' microorganisms. In patients with severe renal failure, the half-life of penicillin may be considerably prolonged. Therefore, adjustment of doses according to creatinine clearance is required. A higher dose of penicillin G should be given in younger patients with higher glomerular filtration rates and in IE due to enterococci, because these bacteria are tolerant to the killing effect of penicillin.

Ceftriaxone

Ceftriaxone has an excellent pharmacokinetic profile to treat streptococcal IE. It is generally accepted to be used as a single daily dose of 2 g ceftriaxone IV. The 2 g dose can be administered as a rapid intravenous infusion. Intramuscular injection should be avoided if possible in IE patients. If intramuscular infections are unavoidable, it is recommended that no more than 1 g should be injected at one site.

Vancomycin and Teicoplanin

Vancomycin in the doses of 30 mg/kg/day can be administered IV divided into two doses. The infusion time should not be less than 45 min in order to avoid side effects. Teicoplanin is an alternative drug that can also be used once daily. However, treatment has been associated with significant failure rates when the dosage was inadequate, as the steady state serum concentration may be achieved only after one week of teicoplanin administration. To overcome these shortcomings, it is recommended to give 10 mg/kg IV twice daily for the first nine doses followed by 10 mg/kg/day IV as a single daily dose.

Aminoglycosides

Synergism of penicillin and aminoglycosides is well documented *in vitro* and *in vivo*, with gentamicin having shown the largest synergistic potential[18]. Penicillin, ceftriaxone, vancomycin or teicoplanin may be used for monotherapy of streptococcal IE but these drugs have been used traditionally in combination with aminoglycoside antibiotics. This synergistic effect allows for a two-week treatment with penicillin or ceftriaxone in combination with gentamicin. Efficacy and safety of this treatment have been documented in clinical studies[19].

STAPHYLOCOCCAL ENDOCARDITIS

Staphylococcal IE is a particularly severe, life-threatening infection, responsible for about one-third of all IE cases. Early start of adequate antibiotic treatment is the key to improve the overall prognosis. About 90% of cases are due to *S. aureus*, the remaining 10% are due to coagulase-negative staphylococcal species (CONS), of which *S. lugdunensis* is particularly serious. Management of staphylococcal endocarditis differs significantly depending upon the presence or absence of intracardiac prosthetic material.

Staphylococcal Endocarditis not Associated with Prosthetic Material

Methicillin-Sensitive Staphylococcus Aureus (MSSA)

At the present time, less than 10% of *S. aureus* strains that cause IE are susceptible to penicillin. *S. aureus* strains causing community-acquired IE are usually penicillin-resistant but susceptible to methicillin. Treatment of choice is a penicillinase-resistant penicillin (oxacillin or its congeners) at a dosage of 2 g IV as a bolus every 6 h for at least 4 weeks. In patients with the immediate type hypersensitivity to penicillin, all beta-lactam antibiotic should be avoided. In these cases, the antibiotic of choice is vancomycin. *In vitro* and clinical studies have shown that the bactericidal activity of vancomycin against *S. aureus* is less than that of penicillinase-resistant penicillins. Therefore, the use of vancomycin should be restricted to MSSA-IE with immediate type allergy. In obese patients, vancomycin dosage should be adjusted according to body weight. The use of vancomycin requires monitoring of plasma levels to adjust the dosage. In clinical studies it has been shown that combinations with gentamicin are associated with faster clearing of bacteremia, which may reduce valve damage and prevent abscess formation. There is thus consensus to combine oxacillin (or vancomycin if appropriate) with gentamicin for the first 3-5 days of treatment. Gentamicin at a dosage of 3 mg / kg every 8 h (maximum 240 mg / day) should be administered as intravenous bolus injection after oxacillin (or vancomycin) has been given.

Methicillin-Resistant Staphylococcus Aureus (MRSA)

Treatment of IE caused by MRSA is a therapeutic challenge as the number of effective antibiotics is small. Vancomycin and Teicoplanin are the most commonly used antibiotics. As most MRSA strains are also resistant to most aminoglycosides, the addition of gentamicin is not likely to change the course or the prognosis of the infection. Rifampicin is not indicated in uncomplicated NVE. If the clinical course is complicated (e.g. by intracardiac abscesses or uncontrolled local infection) treatment should be as for PVE.

Coagulase-Negative Staphylococcal Species (CONS)

NVE caused by CONS can be treated following the same therapeutic algorithm given for *S. aureus* infections. In community-acquired infections, most strains are susceptible to methicillin, while hospital-acquired strains are often resistant to methicillin and to all beta-lactam antibiotics in more than 50% of cases. In any case, it is extremely important to detect hetero-resistance of CONS strains to beta-lactam antibiotics.

Staphylococcal Endocarditis in Patients with Intracardiac Prosthetic Material

MSSA

Prosthetic valve endocarditis (PVE) and infections involving other prosthetic material that are caused by *S. aureus* have a high mortality. Although there are no convincing *in vitro* or clinical studies, penicillinase-resistant penicillin is used for 6-8 weeks, combined with rifampicin throughout the treatment period and with gentamicin during the first 2 weeks. Due to the poor prognosis even with combined antimicrobial therapy, surgery should be considered early.

MRSA and CONS

Patients with PVE caused by MRSA should be treated for 6-8 weeks with a combination of vancomycin, rifampicin and gentamicin, as long as susceptibility has been demonstrated *in vitro*. CONS species causing PVE within the first year after valve replacement are usually methicillin-resistant. Up to 30% of such strains may also be resistant to aminoglycosides while all strains so far have been susceptible to vancomycin. The optimal therapy is a combination of vancomycin and rifampicin for at least 6 weeks with the addition of gentamicin for the initial 2 weeks. If the causative organism is resistant to all aminoglycosides, they can be replaced by a fluoroquinolone. Early PVE caused by CONS is usually associated with perivalvular and myocardial abscesses and often with valve ring dehiscence so that valve re-operation is usually mandatory during the first week. In cases where the infection is due to CONS strains susceptible to methicillin, it is recommended to use oxacillin or one of its congeners instead of vancomycin.

ENTEROCOCCI AND PENICILLIN-RESISTANT STREPTOCOCCI

Unlike streptococci, enterococci are generally resistant to a wide range of antimicrobial agents including most cephalosporins, antistaphylococcal penicillins, clindamycin, and macrolides. Enterococci are also relatively resistant to aminoglycosides, however, when combined with beta-lactam antibiotics, there is a synergistic killing effect. The classical combinations of penicillin and streptomycin, later penicillin and gentamicin have therefore been successfully used for the treatment of enterococcal IE caused by strains susceptible to these antibiotics. However, strains that are resistant to penicillin or ampicillin or highly resistant to aminoglycosides are no longer susceptible to synergistic killing by these combinations. Although the bactericidal activity of ampicillin is two- fold greater than that of penicillin against *E. faecalis*, penicillin is recommended to be part of the treatment because higher serum concentrations of penicillin will compensate for this difference and it is also important to avoid ampicillin rash during long-term treatment. Enterococci with a high-level resistance to gentamicin are also resistant to all other aminoglycosides, except perhaps streptomycin, for which independent testing has to be done. On the other hand, gentamicin susceptibility does not imply susceptibility to other aminoglycosides. Glycopeptides antibiotics are usually not bactericidal against enterococci; therefore, a combination therapy with aminoglycosides is mandatory. Resistance to vancomycin has been recognized with increasing frequency. Strains highly resistant to vancomycin are also resistant to teicoplanin. Both are then useless for treatment.

Duration of treatment should be at least 4 weeks for the combination and at least 6 weeks in complicated cases, in patients having symptoms for more than 3 months, and in PVE.

GRAM-NEGATIVE ORGANISMS

Enterobacteriaceae

Enterobacteriaceae species most often associated with IE are Escherichia coli, Klebsiella spp., Enterobacter spp. and Serratia spp. As susceptibility of these microorganisms is unpredictable, treatment must be based on susceptibility testing. Initial treatment is usually with a beta-lactam antibiotic at high doses plus gentamicin, 3 mg / kg / day divided into 2-3 doses for 4-6 weeks.

Pseudomonas Species

Treatment is based on the results of *in vitro* susceptibility studies. The combination of high doses of a beta-lactam antibiotic with antipseudomonas activity and tobramycin (3 mg / kg / day divided into 2-3 doses) for 6 weeks is considered the most adequate initial antibiotic treatment.

HACEK Group Organisms

For empiric treatment decisions, HACEK group organisms causing IE should be considered ampicillin-resistant and the treatment of choice should be a third-generation cephalosporin, such as ceftriaxone 2 g / day IV in a single dose given for 3-4 weeks in NVE and for 6 weeks in PVE. Ceftriaxone has an excellent pharmacokinetic profile with a long half-life, thus a single daily dose is justified. If susceptibility to ampicillin has been demonstrated, ampicillin can be given (up to 12 g / day divided into 3-4 doses) in combination with gentamicin (3 mg / kg / day divided into 2-3 doses). Aminopenicillins and semisynthetic penicillins generally have a longer half-life in blood than penicillin and can thus be administered safely three to four times daily.

Coxiella burnetii

The drug of choice is doxycycline, 100 mg IV every 12 h in combination with rifampicin. The combination of tetracyclines and fluoroquinolones has proven effective in clinical studies. In most patients, valve replacement is required to prevent relapses. As coxiellae are intracellular organisms, antimicrobial therapy should be maintained postoperatively for a period of at least one year, or even life-long.

FUNGAL IE

Due to the high mortality on treatment with antimycotic agents alone and the decreasing perioperative mortality in surgery for active IE, surgery is the primary option. Amphotericin B or the less toxic ambisome preparations are the drugs of choice for the treatment of fungal IE, with a daily dose of 1 mg / kg. A continuous infusion may help to prevent side effects, e.g. therapy associated fever. Combination with 5-flurocytosine has a synergistic effect *in vitro*, although it has not been demonstrated that the combination is more effective *in vivo* than amphotericin alone. To control the infection, surgery is necessary in almost all cases.

CULTURE-NEGATIVE ENDOCARDITIS (CNE)

Before treatment is started in CNE cases, the detailed diagnostic strategy should be employed in order to focus on more likely organisms responsible for a particular type of IE. It should also be noted whether the patient has been on prior antimicrobial treatment. Unless IE due to Bartonella spp., Chlamydia spp., Coxiella spp., Legionella spp., Nocardia spp., or fungi is suspected, the scheme based on clinical experience (Table 4) appears most useful at the present time.

Table 4: Empirical antimicrobial therapy in CNE of native (NVE) or prosthetic cardiac valves (PVE)

NVE		
Vancomycin	15.0 mg/kg IV every 12 h	4-6 weeks
+Gentamicin	1.0 mg/kg IV every 8 h	2 weeks
PVE		
Vancomycin	15.0 mg/kg IV every 12 h	4-6 weeks
+Rifampicin	300-450 PO every 8 h	4-6 weeks
+Gentamicin	1.0 mg/kg IV every 8 h	2 weeks

PROSTHETIC VALVE ENDOCARDITIS (PVE)

Infections of intracardiac prosthesis may occur early or late after implantation, which is the key issue defining etiology, clinical presentation, treatment, and prognosis. Coagulase-negative staphylococci (CONS) are the most frequent infecting organisms in early PVE, followed by *S. aureus* and enterococci. The microbiology of late PVE does not differ much from that of native valve endocarditis. The principles of antimicrobial therapy for PVE are basically the same as those for NVE. However, therapy should be prolonged for up to six weeks. Treatment of PVE may be particularly difficult as the special environment may prevent microorganisms from being cleared by antibiotics. CONS strains may produce extracellular slime, which inhibits host-defense mechanisms and protects bacteria from being killed.

MONITORING AND ASSESSMENT OF THERAPEUTIC EFFICACY

Careful observation of the patient with clinical and laboratory controls is essential to assess the efficacy of the antibiotic regimen. Follow-up consists of daily bedside examination, measurements of body temperature, and periodic blood tests to monitor signs of infection and to survey the renal function. In case of suspected infectious complications new blood cultures, ECG, Holter and echocardiography are also essential.

Fever

Fever is a very useful and important criterion to follow the evolution of IE. In patients with an uncomplicated clinical course the temperature should normalize within 5-10 days. In general, infections due to viridans streptococci respond faster to antibiotics than those caused by *S. aureus* or enterococci. Persistent fever beyond the first week often indicates the development of complications such as progressive valve destruction, extension of infection to the valve annulus, or the occurrence of a perivalvular abscess. Septic emboli with localized infection can also be the reason for persisting fever. Recurrent fever in patients with stable clinical and hemodynamic conditions following an afebrile period is most frequently observed during the third and fourth weeks of treatment and is often due to adverse reactions to beta-lactam antibiotics. It may occur with or without accompanying skin rash. However, cardiac complications, arthritis and septic systemic emboli may sometimes occur at a later stage.

Clinical Examination

Repeated clinical examinations are performed to look for changes in cardiac murmurs, blood pressure, signs of cardiac failure, and embolic phenomena. Secondary metastatic infections in joints and spine may also occur. It is important to remember that cardiac and systemic complications often arise during the first few days after the beginning of adequate antibiotic treatment. In patients with pleural rub or effusion and flank pain, splenic abscesses should be suspected. Patients at special risk should have regular abdominal ultrasound examinations and eventually CT/MRI scans. Ophthalmic follow-up examinations to detect Roth spots should especially be considered in IE due to staphylococci and fungi.

Investigations

Among the laboratory measures, CRP is the best criterion to judge therapeutic response. CRP values usually decrease rapidly during the first or second week, but may remain slightly elevated up to 4-6 weeks or longer. A persistently high CRP should be interpreted as a sign of an inadequately controlled infection with cardiac or other septic complications. In contrast to CRP the ESR is not suitable for disease evaluation since high values may persist over several weeks despite a good therapeutic response.

The normalization of elevated WBC count can also be expected during the first 1-2 weeks. Persistently high WBC counts also indicate active infection. It is important

to recognize that prolonged high dose treatment with beta-lactam antibiotics may inhibit granulopoiesis and result in neutropienia. Platelet and erythrocyte count should also be monitored regularly.

Monitoring of renal function by repeated serum creatinine measurements is essential for early detection of renal dysfunction, which is a frequent complication of IE or an adverse effect of the antibiotic therapy, especially with aminoglycosides and vancomycin.

Echocardiography is the most relevant examination if cardiac complications are suspected. Despite the use of potent antibiotics the incidence of valve destruction and/or perivalvular abscesses remains high. Echocardiography is also necessary at the end of antibiotic therapy to document the site and extent of valvular damage. The final echocardiogram is invaluable for comparison during long-term follow-up and facilitates the recognition of a late relapse or reinfection.

DOMICILIARY TREATMENT OF IE

'Ambulatory treatment' refers to situation in which the patient attends a hospital where antibiotics are injected (outpatient treatment) and then returns home. The term **'non-inpatient'** refers to a patient who receives his injection at home, e.g. by a visiting nurse, at the practitioner's clinic, or by self-administration. The term **'outpatient and home parenteral antibiotic therapy' (OHPAT)** has been suggested to cover all these aforementioned settings. There is no prospective study comparing inpatient treatment to partial or total OHPAT for IE, but several studies have shown that selected patients may be safely treated at home[20]. All patients with IE should be admitted and treated for at least 1-2 weeks in hospital and observed for cardiac and non-cardiac complications, especially embolic events, after that a significant proportion of patients could be the candidates for OHPAT. But, this approach needs to be carefully assessed by proper clinical studies.

ROLE OF SURGERY

Surgery is mandatory in at least 30% of cases with active IE and in another 20-40% after healing[21]. Since surgery may be required at any time during its course, IE should be managed in consultation with the cardiac surgery team. Definite indications for surgery are:

1. Refractory CHF due to valvular dysfunction
2. Myocardial or valve ring abscess requiring drainage
3. Uncontrolled infection (Persistent fever and demonstration of bacteremia for more than 7-10 days despite adequate antimicrobial therapy)
4. Prosthetic valve dysfunction or dehiscence with unstable prosthesis or valve obstruction
5. If microorganisms are involved are such which are frequently not cured by antimicrobial therapy, e.g. Fungi, Brucella spp. and Coxiella spp, or those that have a potential for rapid destruction of cardiac structures, e.g. Staphylococcus lugdunensis.
6. Two or more relapses.

Relative indications for surgery include:

1. Multiple embolic episodes
2. Vegetation of >10 mm size
3. Aneurysm of sinus of Valsalva
4. Persistence of complete heart block after I week of treatment.

It is surprising that even during active infection less than 5% of newly implanted valves get infected. Even when an abscess is present, the rate of infection of a newly implanted valve is low. However, an abscess makes a valve replacement technically difficult and the overall prognosis worse. It is reasonable to pretreat the patient with antibiotics for at least 2-3 days in an attempt to sterilize the blood, but an undue delay in surgery especially with CHF may simply convert an elective procedure to an emergency procedure with high mortality. Valvuloplasty with resection of vegetation (vegetectomy) may be the preferred approach in patients with relatively preserved valve tissue especially in young women. Valve resection may he done in IE involving tricuspid valve and very rarely pulmonary valve. Resection without replacement may be especially useful in intravenous drug abusers (to prevent recurrent IE) provided pulmonary arterial hypertension is not there in which event valve has to be replaced.

REFERENCES

1. Van Der Meer JT, Thompson J, Valkenburgh HA, et al. Epidemiology of bacterial endocarditis in the Netherlands. I. Patients characteristics. Arch Inter Med 1992;152:1863-8.
2. Young SE. Etiology and epidemiology of infective endocarditis in England and Wales. J Antimicrob Chemother 1987; 20 (Suppl A):7-14.
3. Berlin JA, Abrutyn E, Strom BL, Kinman JL, Levison ME, et al. Incidence of infective endocarditis in the Delaware Valley, 1988-1990. Am J Cardiol 1995; 76:933-6.
4. Hogevik H, Olaison L, Andersson R, Lindberg J, Alestig K. Epidemiological aspects of infective endocarditis in an urban population. A 5-year prospective study. Medicine (Baltimore) 1995;74:324-39.

5. Kothari SS, Ramakrishnan S, Bahl VK. Infective endocarditis-an Indian perspective. Indian Heart J 2005;57:289-94.
6. Garg N, Kandpal B, Garg N, Tewari S, et al. Characteristics of infective endocarditis in a developing country—clinical profile and outcome in 192 Indian patients, 1992-2001. Int J Cardiol 2005;98:253-60.
7. Chaudhary R, Grover A, Varma J, et al. Active infective endocarditis observed in an Indian hospital 1981- 1991. Am J Cardiol 1992;70:1453-58.
8. Jalal S, Khan KA, Alai MS, et al. Clinical spectrum of infective endocarditis: 15 years experience. Indian Heart J 1998;50:516-9.
9. Agarwal R, Bahl VK, Malviya AN. Changing spectrum of clinical and laboratory profile of infective endocarditis. J Assoc Physicians Ind 1992;40:721-3.
10. Sochowski RA, Chan KL. Implication of negative results on a monoplane transoesophageal echocardiographic study in patients with suspected infective endocarditis. J Am Coll Cardiol 1993;21:216-21.
11. Erbel R, Rohmann S, Drexler M, et al. Improved diagnostic value of echocardiography in patients with infective endocarditis by transoesophageal approach. A prospective study. Eur Heart J 1988;9:43-53.
12. Birmingham GD, Rakho PS, Ballantyne F. Improved detection of infective endocarditis with transoesophageal endocarditis. Am Heart J 1992;123:774-81.
13. The task force on infective endocarditis of the European Society of Cardiology. Horstkotte D, Follath F, Gutschik E, et al. Guidelines on prevention, diagnosis and treatment of infective endocarditis. European Heart Journal 2004;00:1-37.
14. Horstkotte D. Mikrobiell verursachte Endokarditis. Darmstadt: Steinkopff, 1995.
15. Dodds GA, Sexton DJ, Durack DT. Negative predictive value of Duke Criteria for infective endocarditis. Am J Cardiol 1996;77:403-7.
16. Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, et al. Committee on Rheumatic fever, Endocarditis, and Kawasaki disease. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals. Council on cardiovascular disease in the young, and the council on clinical cardiology, stroke and cardiovascular surgery and anesthesia, American Heart Association: endorsed by infectious disease society of America. Circulation 2005;111:e394-434.
17. Lamas CC, Eykyn SJ. Suggested modification to the Duke criteria for the clinical diagnosis of native valve and prosthetic valve endocarditis: analysis of 118 pathologically proven cases. Clin Infect Dis 1997;25:713-9.
18. Mollering RCJ. Antimicrobial susceptibility of enterococci: in vitro studies of the action of antibiotics alone and in combination. In: Bisno AL, (Editor): Treatment of Infective Endocarditis. New York: Grune & Stratton; 198181-86.
19. Roberts SA, Lang SDR, Ellis- Pegler SB. Short course treatment of penicillin susceptible viridans streptococcal endocarditis with penicillin and gentamicin. Infect Dis Clin Pract 1993;2:191-4.
20. Francioli PB, Stamboulian D. The endocarditis working group of the international society for chemotherapy. Outpatient treatment of infective endocarditis. Clin Microbiol Infect 1998;4(Suppl 3):s47-55.
21. Jault F, Gandjbakhch I, Rama A, et al. Active native valve endocarditis; determinants of operative death and late mortality. Ann Thorac Surg 1997;63:1737-41.