Complete Summary

GUIDELINE TITLE

Guidelines on prevention, diagnosis and treatment of infective endocarditis. The task force on infective endocarditis of the European Society of Cardiology.

BIBLIOGRAPHIC SOURCE(S)

Horstkotte D, Follath F, Gutschik E, Lengyel M, Oto A, Pavie A, Soler-Soler J, Thiene G, von Graevenitz A. Guidelines on prevention, diagnosis and treatment of infective endocarditis. The Task Force on Infective Endocarditis of the European Society of Cardiology. France: European Society of Cardiology; 2004. 37 p. [390 references]

GUIDELINE STATUS

This is the current release of the guideline.

**** REGULATORY ALERT ****

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse (NGC): This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- July 08, 2008, Fluoroquinolones (ciprofloxacin, norfloxacin, ofloxacin, levofloxacin, moxifloxacin, gemifloxacin): A BOXED WARNING and Medication Guide are to be added to the prescribing information to strengthen existing warnings about the increased risk of developing tendinitis and tendon rupture in patients taking fluoroquinolones for systemic use.
- February 28, 2008, Heparin Sodium Injection: The U.S. Food and Drug Administration (FDA) informed the public that Baxter Healthcare Corporation has voluntarily recalled all of their multi-dose and single-use vials of heparin sodium for injection and their heparin lock flush solutions. Alternate heparin manufacturers are expected to be able to increase heparin production sufficiently to supply the U.S. market. There have been reports of serious adverse events including allergic or hypersensitivity-type reactions, with symptoms of oral swelling, nausea, vomiting, sweating, shortness of breath, and cases of severe hypotension.
- September 11, 2007, Rocephin (ceftriaxone sodium): Roche informed healthcare professionals about revisions made to the prescribing information for Rocephin to clarify the potential risk associated with concomitant use of Rocephin with calcium or calcium-containing solutions or products.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Infective endocarditis (IE)

GUIDELINE CATEGORY

Diagnosis
Management
Prevention
Treatment

CLINICAL SPECIALTY

Cardiology
Dentistry
Family Practice
Infectious Diseases
Internal Medicine
Surgery

INTENDED USERS

Hospitals
Physicians

GUIDELINE OBJECTIVE(S)

To provide recommendations regarding adequate diagnosis, treatment, and prevention of infective endocarditis (IE)

TARGET POPULATION

Patients with and patients at risk for infective endocarditis (IE)

INTERVENTIONS AND PRACTICES CONSIDERED

Prevention

1. Identification of patients at risk
2. Antibiotic prophylaxis, including amoxicillin, ampicillin, clindamycin, azithromycin, gentamicin, and vancomycin
3. Patient education

Diagnosis

1. History, symptoms, signs, and laboratory tests
2. Echocardiography, including transthoracic (TTE) and transoesophageal echocardiography (TEE)
3. Standard blood culture (BC) techniques, including susceptibility testing by disk diffusion and the determination of minimum inhibitory concentration (MIC) for drugs of choice
4. Culture-negative endocarditis (CNE): BC, serology, immunofluorescence, polymerase chain reaction (PCR)

Treatment/Management

1. Antibiotic treatment
    - Penicillin G
    - Gentamicin
    - Ceftriaxone
    - Vancomycin
    - Netilmicin
    - Teicoplanin
    - Oxacillin
    - Rifampicin
    - Amphotericin B or ambisome
    - 5-fluorocytosine
2. Drug level monitoring
3. Surgery for native valve endocarditis
4. Surgery for prosthetic valve endocarditis
5. Management of complications, including embolic events, pulmonary complications of right-sided endocarditis, cardiac failure, myocarditis, renal failure, arrhythmias and conduction disturbances, and relapsing endocarditis

MAJOR OUTCOMES CONSIDERED

- Incidence of bacteraemia
- Predictive value of diagnostic tests
- Sensitivity and specificity of diagnostic tests
- Clinical effectiveness and safety of antibiotic drug regimens
- Antibiotic susceptibility and resistance of microorganisms
- Incidence of complications of infective endocarditis

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

A: Data derived from multiple randomised clinical trials or meta-analyses

B: Data derived from a single randomised trial or nonrandomised studies

C: Consensus opinion of the experts and/or small studies

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The European Society of Cardiology Task Force on Infective Endocarditis (IE) was formed to prepare recommendations regarding adequate diagnosis, treatment and prevention of IE. The advice of additional experts (see appendix 2 of the original guideline document) was obtained whenever the core group felt that additional specific knowledge was mandatory. The document was read by all members of the

Task Force twice, redrafted and approved by the Board of the European Society of Cardiology in 2003.

To end up with a readable paper, including a maximum of information and covering the majority of issues frequently associated with IE, the text has been condensed to essential information accompanied by key references to allow for the information. The text is thus not a substitute for textbooks.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Strength of Recommendation

Class I: Conditions for which there is evidence or general agreement that a given procedure or treatment is useful and effective

Class II: Conditions for which there is conflicting evidence or a divergence of opinion about the usefulness/efficacy of a procedure or treatment

- **Class IIa**: Weight of evidence/efficacy is in favor or usefulness/efficacy
- **Class IIb**: Usefulness/efficacy is less well established by evidence/opinion

Class III: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

A review coordinator is appointed with the Committee for Practice Guidelines (CPG). The document is reviewed by the members of the CPG, the European Society of Cardiology Board Members, and other experts in the field chosen from joint societies, working groups, and other sources.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The class of recommendations (I-III) and level of evidence (A-C) are defined at the end of the "Major Recommendations" field.

The following is the Executive Summary of the Guidelines on Prevention, Diagnosis, and Treatment of Infective Endocarditis (IE) (See "Companion

Documents" field). Please refer to the Full Text of the guidelines for the complete set of recommendations and supporting evidence.

Prevention of infective endocarditis

For prophylactic reasons, antibiotics should be given before a bacteraemia is expected. If antibiotic prophylaxis is not given prior to this event, antibiotics may help a late clearance if administered intravenously within 2 to 3 h.

Cardiac conditions/Patients at risk

A previous history of IE, the presence of prosthetic heart valves or other foreign material, surgically created conduits, and complex cyanotic congenital abnormalities are considered high-risk situations. Only patients with high or moderate risk (See below and refer to table 2 in the "Executive Summary" [See "Companion Documents" field]) should receive prophylaxis. This is a **class I recommendation based on level C evidence**.

Cardiac conditions in which antimicrobial prophylaxis is indicated

- Prosthetic heart valves (high-risk group)
- Complex congenital cyanotic heart diseases (high-risk group)
- Previous IE (high-risk group)
- Surgically constructed systemic or pulmonary conduits (high-risk group)
- Acquired valvular heart diseases
- Mitral valve prolapse with valvular regurgitation or severe valve thickening
- Non-cyanotic congenital heart diseases (except for secundum type atrial septal defect) including bicuspid aortic valves
- Hypertrophic obstructive cardiomyopathy

Patient-related noncardiac conditions

Older age, conditions (a) promoting nonbacterial thrombotic vegetation; (b) compromising host defense; (c) compromising local nonimmune defense mechanisms; and (d) increased risk/frequency/amount of bacteraemia are considered patient related, noncardiac risk conditions.

Predisposing diagnostic and therapeutic interventions

Procedures which may cause bacteraemia and for which antimicrobial prophylaxis is recommended are given below (Also refer to Table 3 in the "Executive Summary" [See "Companion Documents" field]). Prophylaxis is not recommended for cardiac catheterization.

Dental hygiene is of major importance for the prevention of IE.

Diagnostic and therapeutic interventions likely to produce bacteraemia

- Bronchoscopy (rigid instrument)
- Cystoscopy during urinary tract infection
- Biopsy of urinary tract/prostate

- Dental procedures with the risk of gingival/mucosal trauma
- Tonsillectomy and adenoidectomy
- Oesophageal dilation/sclerotherapy
- Instrumentation of obstructed biliary tracts
- Transurethral resection of prostate
- Urethral instrumentation/dilation
- Lithotripsy
- Gynecologic procedures in the presence of infection

Prophylactic antibiotic regimens

Prophylaxis aims primarily at viridans streptococci and a group of bacteria consistent of *Haemophilus* spp., *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae* (HACEK) organisms before dental, oral, respiratory, and oesophageal procedures, and at enterococci and *Streptococcus bovis* before gastrointestinal and genitourinary procedures. Despite a lack of convincing evidence, antibiotic prophylaxis (See below and refer to table 4 in the "Executive Summary" [See the "Companion Documents" field]) is a **class I recommendation based on level C evidence**.

- Dental, oral, respiratory, and esophageal procedures (P)
    - Not allergic to penicillin
        - Amoxicillin 2.0 g (children 50 mg/kg) orally (p.o.) 1 h before P
        - Unable to take oral medication: amoxicillin or ampicillin 2.0 g (children 50 mg/kg) intravenously (i.v.) 1/2 to 1 h before P
    - Allergic to penicillin: clindamycin 600 mg (children 20 mg/kg) or azithromycin/clarithromycin 500 mg (children 15 mg/kg) 1 h before P
- Genitourinary and gastrointestinal procedures (P)
    - Not allergic to penicillin
        - High-risk group: ampicillin or amoxicillin 2.0 g i.v. plus gentamicin 1.5 mg/kg i.v. 1/2 to 1 h before P; 6 h later, ampicillin or amoxicillin 1.0 g p.o.
        - Moderate-risk group: ampicillin or amoxicillin 2.0 g i.v. (children 50 mg/kg) ½ to 1 h before P; or amoxicillin 2.0 g (children 50 mg/kg) p.o. 1 h before P
    - Allergic to penicillin
        - High-risk group: vancomycin 1.0 g (children 20 mg/kg) over 1 to 2 h before P plus gentamicin 1.5 mg/kg i.v. or intramuscularly (i.m.)
        - Moderate-risk group: vancomycin (see above) without gentamicin

Diagnosis

History, symptoms, signs and laboratory tests

The diagnosis of IE is established (definite IE) if, during a systemic infection, involvement of the endocardium is demonstrated. If, in addition, bacteraemia (positive blood cultures) or bacterial deoxyribonucleic acid (DNA) are found, IE is definite and culture/microbiologically positive; otherwise IE is definite but culture/microbiologically negative (Please refer to table 5 of the "Executive Summary" [See the "Companion Documents" field] for information on criteria that

should raise suspicion of IE). Duke or modified Duke criteria may be used to make the diagnosis in otherwise unclear cases.

Echocardiography

Any patient suspected of having native valve endocarditis (NVE) by clinical criteria should be screened by transthoracic echocardiography (TTE). When images are of good quality and prove to be negative and there is only a low clinical suspicion of IE, endocarditis is unlikely and other diagnoses are to be considered. If suspicion of IE is high, transoesophageal echocardiography (TEE) should be performed in all TTE-negative cases, in suspected prosthetic valve endocarditis (PVE), and if TTE is positive but complications are suspected or likely and before cardiac surgery during active IE. If TEE remains negative and there is still suspicion, it should be repeated within one week. A repeatedly negative study should virtually exclude the diagnosis (Please refer to figure 1 of the original guideline document for an algorithm for the use of TTE and TEE in suspected IE). These **class I recommendations are based on level B evidence**.

Three echocardiographic findings are considered to be major criteria in the diagnosis of IE: (a) a mobile, echodense mass attached to the valvular or the mural endocardium or to implanted prosthetic material; (b) demonstration of abscesses or fistulas; and (c) a new dehiscence of a valve prosthesis, especially when occurring late after implantation.

Standard blood culture (BC) techniques

Three or more BCs should be taken irrespective of body temperature at least 1 h apart. If the patient has been on short-term antibiotics, one should wait, if possible, at least for three days after discontinuing antibiotic treatment before new BCs are taken. Blood cultures after long-term antibiotic treatment may not become positive after treatment has been discontinued for 6 to 7 days.

One BC consists of one aerobic and one anaerobic bottle, each containing approx. 50 mL of medium (less in pediatric BC bottles). Venous blood, minimally 5 mL and better 10 mL in adults and 1 to 5 mL in children, should be added to each bottle. Minimum inhibitory concentrations should be determined for the drugs of choice.

Culture-negative endocarditis (CNE)

The most frequent cause of CNE is previous antimicrobial treatment. If traditional (non-automatic) BC systems are used, longer incubation periods (>6 days) are required when organisms of the HACEK group, *Propionibacterium* spp., *Neisseria* spp., *Brucella*, *Abiotrophia* spp., or *Campylobacter* spp. are suspected. Especially in CNE all material excised during cardiac surgery for active IE should also be cultured and examined.

The value of serology has been proven for IE due to *Bartonella*, *Legionella*, *Chlamydia* (immunofluorescence) and *Coxiella burnetii*.

The use of broad-spectrum polymerase chain reaction (PCR) provides a significant improvement in the capability to detect difficult-to-culture organisms and even dead bacteria.

Treatment and management

Antimicrobial therapy

For treatment strategies refer to the following tables 6-8 from the "Executive Summary" (see the "Companion Documents" field).

Table 6: Decision making for antibiotic treatment of native (NVE) and prosthetic valve endocarditis (PVE) due to streptococci

Regimen A: NVE; full susceptibility to penicillin (Minimal inhibitory concentration [MIC] ≤0.1 mg/L)	
Patients ≤65 years, normal serum creatinine levels	Penicillin G 12–20 million units/24 h IV, divided into 4–6 doses for 4 weeks plus gentamicin 3 mg/kg/24 h IV (maximum 240 mg/day), divided into 2–3 doses for 2 weeks
Same conditions as above with uncomplicated courses and rapid clinical response to therapy	Penicillin G 12–20 million units/24 h IV, divided into 4–6 doses for 2 or 4 weeks with ambulatory treatment after 7 days treatment in hospital[a]
Patients ≥65 years and/or serum creatinine levels elevated or allergy to penicillin	Penicillin G adapted to renal function for 4 weeks or ceftriaxone 2 g/24 h IV[b] as single dose for 4 weeks
Patients allergic to penicillin and cephalosporins	Vancomycin 30 mg/kg/24 h IV divided into 2 doses for 4 weeks
Regimen B: Susceptibility to penicillin (MIC 0.1 mg/L–0.5 mg/L) or PVE	
	• Penicillin G 20–24 million units/24 h IV divided into 4–6 doses or[b] ceftriaxone 2 g/24 h IV as single dose both for 4 weeks plus gentamicin 3 mg/kg/24 h IV, divided into 2–3 doses for 2 weeks[c] followed by ceftriaxone 2 g/24 h IV for additional 2 weeks • Vancomycin as single drug treatment for 4 weeks (dosage see above)

Regimen C: Resistance to penicillin; MIC >0.5 mg/L[d]	
	Treatment like IE due to enterococci (Refer to full version of original guideline document)

Notes:

[a] For 2 weeks regimen see table 5 in the original guideline document

[b] Especially for patients allergic to penicillin

[c] 2–3 mg/kg netilmicin once daily may be an alternative (peak serum level <16 mg/L).

[d] High level resistance (HLR) to penicillin or ceftriaxone (MIC >8 mg/l) and HLR to gentamicin (MIC >500 mg/l) or resistance to vancomycin or teicoplanin (MIC ≥4 mg/L) are rare among strains of streptococci. In such situations, extended susceptibility testing and a close cooperation with the clinical microbiologist are mandatory.

Table 7: Decision-making for antibiotic treatment of IE due to enterococci and penicillin-resistant streptococci

Penicillin (MIC ≤8 mg/L) and gentamicin (MIC <500 mg/L)	Penicillin G, 16–20 million units in 4–6 divided doses plus gentamicin 3 mg/kg, IV, divided in 2 doses for 4-6 weeks
Penicillin-allergic patients and penicillin/gentamicin susceptible enterococcal isolates	Vancomycin 30 mg/kg/day IV in two divided doses plus gentamicin (dosage as above) for 6 weeks
Penicillin-resistant strains (MIC >8 mg/L)[a]	Vancomycin plus gentamicin (dosage as above) for 6 weeks
Vancomycin-resistant strains including strains with low resistance to vancomycin (MIC 4-16 mg/L) or highly resistance to gentamicin[a]	Assistance of an experienced microbiologist is mandatory. If antimicrobial therapy fails, valve replacement should be considered early

Note:

[a] For resistant enterococci, treatment with oxazolidinone may be an option but should be initiated only after advice from a reference centre has been taken.

Table 8: Decision-making for antibiotic treatment of IE due to staphylococci

Regimen A: Native valve endocarditis

MSSA[a] no allergy to penicillin	Oxacillin[b] 8–12 g/24 h IV, divided into 4 doses for at least 4 weeks[c] plus gentamicin 3 mg/kg/24 h IV (maximum 240 mg/d), divided into 2-3 doses for the first 3–5 days of treatment
MSSA[a] "allergy" to penicillin[d]	Vancomycin 30 mg/kg/24 h IV divided into 2 doses[e] for 4–6 weeks[f], plus gentamicin 3 mg/kg/24 h IV (maximum 240 mg/d) divided into 2-3 doses for the first 3–5 days of treatment
MRSA[g]	Vancomycin 30 mg/kg/24 h IV divided into 2 doses[e] for 6 weeks
Regimen B: Endocarditis involving prosthetic material/cardiac valve prostheses	
MSSA[a]	Oxacillin[b] 8–12 g/24 h IV, divided into 3–4 doses plus rifampicin 900 mg/24 h IV divided into 3 doses, both for 6–8 weeks, plus gentamicin 3 mg/kg/24 h IV (maximum 240 mg/d) divided into 2–3 doses for the first 2 weeks of treatment
MRSA[g],CONS[h,i]	Vancomycin 30 mg/kg/24 h IV divided into 2 doses[e] for 6 weeks, plus rifampicin 900 mg/24 h IV divided into 3 doses, plus gentamicin[j] 3 mg/kg/24 h IV (maximum 240 mg/d) divided into 2–3 doses, all for 6–8 weeks

Notes:

[a] Methicillin-susceptible *Staphylococcus aureus*

[b] Or its congeners

[c] Except for drug addicts for whom a two-week regimen may be sufficient

[d] For both immediate (immunoglobulin E [IgE]) type and hypersensitivity reaction during treatment

[e] Infusion over at least 60 min

[f] Total treatment duration for patients initially treated with oxacillin should be at least 4 weeks. These patients should not have a second course of gentamicin treatment.

[g] Methicillin-resistant *S. aureus*

[h] Coagulase-negative staphylococci. In oxacillin-susceptible CONS, vancomycin should be replaced by oxacillin.

[i] For resistant staphylococci, treatment with oxazolidinone may be an option but should be initiated only after advice from a reference centre has been taken.

[j] If gentamicin susceptibility has been shown in vitro, gentamicin is added in MRSA for the full course but for CONS only for the first two weeks of treatment. If the organism is resistant to all aminoglycosides, gentamicin may be substituted by a fluoroquinolone.

All patients with streptococcal IE should be treated for at least 2 weeks in hospital and observed for cardiac and non-cardiac complications. Patients may then be candidates for outpatient and home parenteral antibiotic therapy. Treatment recommendations for streptococcal IE are based on consistent results of a large number of studies (**class I recommendation based on level B evidence**).

IE caused by methicillin-resistant *S. aureus* (MRSA) is a therapeutic challenge, as most strains are also resistant to most aminoglycosides. If the clinical course is complicated, treatment should be as for PVE.

Coagulase-negative species (CONS) causing PVE within the first year after valve replacement are usually methicillin-resistant. Therapy of choice is a combination of vancomycin and rifampicin for at least 6 weeks with the addition of gentamicin for the initial 2 weeks.

Despite lacking randomized studies and thus level A evidence, the scientific material available is convincing and allows for a **class I recommendation**.

Enterococci are generally resistant to a wide range of antimicrobial agents including aminoglycosides (minimum inhibitory concentration [MIC] for gentamicin 4 to 64 mg/L). (Refer to the table above for information on decision-making for antibiotic treatment of IE due to enterococci and penicillin-resistant streptococci).

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 patients with PVE. These **class IIa recommendations are based on level B evidence**.

Drug level monitoring

Gentamicin trough levels should be less than 0.1 mg/L to avoid renal or ototoxic effects.

Optimum vancomycin effects are achieved if serum concentrations are continuously kept at least 2–4 times above the MIC of the causative organism. Trough levels should be at least 10–15 mg/L. In patients with normal renal function, drug levels should be controlled once, but 2–3 times weekly if combined with aminoglycosides.

Empirical therapy

In cases complicated by sepsis, severe valvular dysfunction, conduction disturbances, or embolic events, empirical antimicrobial therapy should be started after three blood cultures have been taken (See standard blood culture techniques section above).

Recommendations for empirical antibiotic treatment (before microbiologic test results are available) and CNE are given below and in table 9 of the "Executive Summary" (See "Companion Documents" field).

Table 9: Antimicrobial treatment in CNE or if therapy is urgent and the causative organism unidentified

NVE		
Vancomycin	15 mg/kg i.v. every 12 hours[a, b]	4-6 weeks
+ Gentamicin	1.0 mg/kg i.v. every 8 h	2 weeks
PVE		
Vancomycin	15 mg/kg i.v. every 12 h	4-6 weeks
+ Rifampicin	300-450 mg p.o. every 8 h	4-6 weeks
+ Gentamicin	1.0 mg/kg i.v. every 8 h	2 weeks

Notes:

[a] Maximum 2 g/day; for drug level monitoring see above and refer to full text in the original guideline document

[b] Aminopenicillin may be added.

Special subsets

Antimicrobial therapy for infections of permanently implanted pacemakers or implantable cardioverter defibrillator (ICD) leads is based on culture and susceptibility results. Duration of therapy should be 4 to 6 weeks in most cases. Removal of the entire system is generally recommended.

In intravenous drug abusers (IVDAs), a methicillin-susceptible *S. aureus* (MSSA) is the causative organism in about 60 to 70% of cases. The tricuspid valve is affected in more than 70%. The most common organism (*S. aureus*) must always be covered by the antibiotic regimen. Treatment will include either penicillinase-resistant penicillins or vancomycin, depending on the local prevalence of MRSA. If the patient is a pentazocine addict, an antipseudomonas agent should be added. If IVDAs use brown heroine dissolved in lemon juice, *Candida* should be considered and antifungal treatment added. In IVDAs with underlying valve lesions and/or left-sided involvement, antibiotic treatment against streptococci and enterococci must be added.

Management of complications

Rapid and effective antimicrobial treatment may help to prevent embolism. If the patient is on long-term oral anticoagulation, coumarin therapy should be

discontinued and replaced by heparin immediately after the diagnosis of IE has been established.

After an embolic complication, the risk for recurrent episodes is high. After manifestation of a cerebral embolism, cardiac surgery to prevent a recurrent episode is not contraindicated if performed early (best within 72 h) and cerebral haemorrhage has been excluded by cranial-computed tomography immediately before the operation. If surgery is not performed early, it is advisable to be postponed for 3 to 4 weeks.

Surgery for active NVE

The following indications for urgent valve surgery are accepted:

- Heart failure due to acute aortic regurgitation
- Heart failure due to acute mitral regurgitation
- Persistent fever and demonstration of bacteremia for more than 8 days despite adequate antimicrobial therapy
- Demonstration of abscesses, pseudoaneurysms, abnormal communications like fistulas or rupture of one or more valves, conduction disturbances, myocarditis or other findings indicating local spread (locally uncontrolled infection)
- Involvement of microorganisms which are frequently not cured by antimicrobial therapy (e.g., fungi; *Brucella* and *Coxiella*) or microorganisms which have a high potential for rapid destruction of cardiac structures (e.g., *S. lugdunensis*)

If vegetations are larger than 10 mm on the mitral valve or if they are increasing in size despite antibiotic therapy or if they represent mitral kissing vegetations, early surgery should be considered.

The prognosis of right-sided IE is favourable. Surgery is necessary if tricuspid vegetations are larger than 20 mm after recurrent pulmonary emboli.

Surgery for active PVE

The following indications are accepted:

- Early PVE (less than 12 months after surgery)
- Late PVE complicated by prosthesis dysfunction including significant perivalvular leaks or obstruction, persistent positive blood cultures, abscess formation, conduction abnormalities, and large vegetations, particularly if staphylococci are the infecting agents

Postoperative antibiotic treatment

A full course of antimicrobial treatment should be completed regardless of the duration of treatment prior to surgery, but at least 7 to 15 days postoperatively.

Definitions

Class Strength of Recommendations

Class I: Conditions for which there is evidence or general agreement that a given procedure or treatment is useful and effective

Class II: Conditions for which there is conflicting evidence or a divergence of opinion about the usefulness/efficacy of a procedure or treatment

- **Class IIa**: Weight of evidence/efficacy is in favor or usefulness/efficacy
- **Class IIb**: Usefulness/efficacy is less well established by evidence/opinion

Class III: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful

Levels of Evidence

A: Data derived from multiple randomised clinical trials or meta-analyses

B: Data derived from a single randomised trial or nonrandomised studies

C: Consensus opinion of the experts and/or small studies

CLINICAL ALGORITHM(S)

Clinical algorithms are provided in the original guideline document for the use of transthoracic (TTE) and transoesophageal echocardiography (TEE) in suspected infective endocarditis (IE) and for empiric antibiotic treatment before identification of causative microorganism(s).

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

If untreated, infective endocarditis (IE) is a fatal disease. Major diagnostic (first of all echocardiography) and therapeutic progress (mainly surgery during active IE) have contributed to some prognostic improvement during the last decades. If the diagnosis is delayed or appropriate therapeutic measures postponed, mortality is still high. Differences in morbidity and mortality recently reported point to the importance of an early and proper diagnosis and adequate treatment.

POTENTIAL HARMS

- Vancomycin, gentamicin, and other aminoglycosides may cause renal dysfunction.
- Gentamicin trough levels should be less than 0.1 mg/L to avoid renal or ototoxic effects.
- Aminoglycosides should be used in special indications only during pregnancy because of the potential of eighth cranial nerve toxicity in the fetus.
- Amphotericin may cause drug-associated fever.
- Fluconazole use during pregnancy has produced dose-dependent teratogenic effects (grossly dysmorphic infants).
- Cardiac surgery during pregnancy poses the risk of fetal distress, growth retardation, and fetal death.
- Prolonged high-dose beta-lactam antibiotics may inhibit granulopoiesis and result in neutropenia.

CONTRAINDICATIONS

CONTRAINDICATIONS

- Quinolones are contraindicated during pregnancy.
- In patients with the antecedent of immediate type (immunoglobulin E [IgE]-type) hypersensitivity to penicillin, any beta-lactam antibiotic should be avoided.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

The term "bacterial endocarditis" has been replaced by "infective endocarditis" (IE) since fungi are also involved as causative pathogens.

Classification and terminology

In contrast to older classifications distinguishing between acute, subacute, and chronic IE, the present classification refers to (a) activity of the disease and recurrence; (b) diagnostic status; (c) pathogenesis; (d) anatomical site; and (e) microbiology.

- **A**: With respect to activity, differentiation between active and healed IE is especially important for patients undergoing surgery. Active IE is present if positive blood cultures and fever are present at the time of surgery, or positive cultures are obtained at surgery, or active inflammatory morphology is found intraoperatively, or surgery has been performed before completion of a full course of antibiotic therapy. More recently, it has been recommended to call IE active if the diagnosis has been established two months or less before surgery.

  IE is recurrent if it develops after eradication of a previous IE, while in persistent IE, the infection has never been truly eradicated. It can be difficult or even impossible to differentiate between the two unless another episode of IE is caused by a different organism. Endocarditis developing more than one

year after operation is usually considered recurrent. Recurrent IE is a dreaded complication with high mortality.

- **B**: The diagnosis of IE is established (definite IE) if during septicaemia or systemic infection involvement of the endocardium can be demonstrated, preferably by multiplane transoesophageal echocardiography (TEE). If IE is strongly suspected clinically (see Section 4.4 of the original guideline document) but involvement of the endocardium has not been proven so far, endocarditis should be classified as "suspected" to express a more or less high suspicion of IE. If IE is only a potential differential diagnosis in febrile patients, a situation which is of special importance when applying the Duke criteria, one should describe this as "possible" IE.
- **C**: Native (NVE), prosthetic valve endocarditis (PVE) and IE in intravenous drug abuse (IE in IVDA) differ with respect to pathology. PVE should be classified as an infection more likely to have been acquired perioperatively and thus being nosocomial (early PVE), or more likely to have been community-acquired (late PVE). Because of significant differences in the microbiology of PVE observed within one year of operation and later, the cut-off between early and late PVE should be at one year.
- **D**: Due to the differences in clinical manifestation and prognosis, IE involving structures of the left and the right heart should be distinguished and referred to as right heart or left heart IE, respectively. If the anatomical site of the infection has been identified properly (e.g., by transoesophageal echocardiography), it should be part of the definition (e.g., mitral, aortic, mural).
- **E**: When the causative organism has been identified, it should be included in the terminology, as it provides crucial information regarding clinical presentation, treatment and prognosis. As long as cultures, serological tests, histological and/or molecular biological methods (e.g., broad-spectrum polymerase chain reaction [PCR]) have remained negative, this information should also be included in the terminology (e.g., culture, serology, histologically, PCR-negative or -positive IE). If all techniques have been applied and were negative, the term "microbiologically negative" is considered appropriate.
- **F**: Classification referring to the population involved (e.g. IE in addicts, in patients with congenital heart disease, neonates, children, in the elderly; nosocomial NVE) is helpful for epidemiological purposes and clinical management.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Clinical Algorithm
Personal Digital Assistant (PDA) Downloads
Pocket Guide/Reference Cards
Slide Presentation

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Horstkotte D, Follath F, Gutschik E, Lengyel M, Oto A, Pavie A, Soler-Soler J, Thiene G, von Graevenitz A. Guidelines on prevention, diagnosis and treatment of infective endocarditis. The Task Force on Infective Endocarditis of the European Society of Cardiology. France: European Society of Cardiology; 2004. 37 p. [390 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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GUIDELINE DEVELOPER(S)

European Society of Cardiology - Medical Specialty Society

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GUIDELINE COMMITTEE

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European Society of Cardiology (ESC) Committee for Practice Guidelines

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The Task Force makes every effort to avoid any actual or potential conflicts of interest that might arise as a result of an outside relationship or personal interest of a member of the writing panel. Specifically, all members of the writing panel, before final approval by the Committee for Practice Guidelines (CPG), are asked to provide disclosure statements of all such relationships that might be perceived as real or potential conflicts of interest. Once they have verbally accepted to become members of the Task Force, a written consent form is signed as well as this "Disclosure form" and this for all Guidelines. The disclosure form must be updated if any changes occur during the elaboration to the document.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the European Society of Cardiology (ESC) Web site.

Print copies: Available from Elsevier Science Ltd. European Heart Journal, ESC Guidelines - Reprints, 32 Jamestown Road, London, NW1 7BY, United Kingdom. Tel: +44.207.424.4422; Fax: +44 207 424 4515; Web site: http://www.eurheartj.org

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Guidelines on prevention, diagnosis and treatment of infective endocarditis. Executive summary. 2004. Electronic copies: Available in Portable Document Format (PDF) from the European Society of Cardiology (ESC) Web site.
- Prevention, diagnosis and treatment of infective endocarditis. Pocket guidelines. Available from the ESC Web site. Also available for PDA download from the ESC Web site.
- Prevention, diagnosis and treatment of infective endocarditis. Slide set. Available from the ESC Web site.

Print copies: Available from Elsevier Science Ltd., 32 Jamestown Road, London, NW1 7BY, United Kingdom. Tel: +44.207.424.4422; Fax: +44 207 424 4433; Web site: http://www.eurheartj.org

PATIENT RESOURCES

None available

NGC STATUS

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