



ESC Guidelines

Guidelines on Prevention, Diagnosis and Treatment of Infective Endocarditis

Executive Summary

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Preamble

Guidelines and Expert Consensus documents aim to present all the relevant evidence on a particular issue in order to help physicians to weigh the benefits and risks of a particular diagnostic or therapeutic procedure. They should be helpful in everyday clinical decision-making.

A great number of Guidelines and Expert Consensus Documents have been issued in recent years by different organizations, the European Society of Cardiology (ESC) and by other related societies. By means of links to web sites of National Societies several hundred guidelines are available. This profusion can put at stake the authority and validity of guidelines, which can only be guaranteed if they have been developed by an unquestionable

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decision-making process. This is one of the reasons why the ESC and others have issued recommendations for formulating and issuing Guidelines and Expert Consensus Documents.

In spite of the fact that standards for issuing good quality Guidelines and Expert Consensus Documents are well defined, recent surveys of Guidelines and Expert Consensus Documents published in peer-reviewed journals between 1985 and 1998 have shown that methodological standards were not complied within the vast majority of cases. It is therefore of great importance that guidelines and recommendations are presented in formats that are easily interpreted. Subsequently, their implementation programmes must also be well conducted. Attempts have been made to determine whether guidelines improve the quality of clinical practice and the utilisation of health resources.

The *ESC Committee for Practice Guidelines (CPG)* supervises and coordinates the preparation of new *Guidelines* and *Expert Consensus Documents* produced by Task Forces, expert groups or consensus panels. The Committee is also responsible for the endorsement of these Guidelines and Expert Consensus Documents or statements.

Level of recommendations and evidence

Strength of recommendation	Definition
Class I	Evidence and/or general agreement that a given treatment or a diagnostic approach is beneficial, useful and effective
Class II	Conflicting evidence and/or a divergence of opinions about the usefulness/efficacy of a treatment or a diagnostic measure
IIa	Weight of evidence/opinion is in favour of usefulness/efficacy
IIb	Usefulness/efficacy is less well established by evidence/opinion
Class III	Evidence or general agreement that the treatment/diagnostic measure is not useful/effective and in some cases may be harmful

Level of evidence	Available evidence
A	At least two randomized trials supporting the recommendation
B	Single randomized trial and/or a meta-analysis of non-randomized studies supporting the recommendation
C	Consensus opinion of experts based on trials and clinical experience

Introduction

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. In this respect, it is of utmost importance that (a) IE is considered early in every patient with fever or septicaemia and cardiac murmurs; (b) echocardiography is applied without delay in suspected IE; (c), cardiologists, microbiologists and cardiac surgeons cooperate closely if IE is suspected or definite.

Definitions, terminology

IE is an endovascular, microbial infection of intracardiac structures facing the blood including infections of the large intrathoracic vessels and of intracardiac foreign bodies. The early characteristic lesion is a variably sized vegetation, although destruction, ulceration or abscess formation may be seen earlier by echocardiography.

Terminology (Table 1) should give the following information: (a), activity of the disease and recurrence; (b), diagnostic status; (c), pathogenesis; (d), anatomical site; and (e), microbiology.

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 2–3 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 (Table 2) should receive prophylaxis. This is a class I recommendation based on level C evidence.

Patient-related non-cardiac conditions

Older age, conditions (a), promoting non-bacterial thrombotic vegetation; (b), compromising host defense; (c), compromising local non-immune defence mechanisms; and (d), increased risk/frequency/amount of bacteraemia are considered patient related, non-cardiac risk conditions.

Predisposing diagnostic and therapeutic interventions

Procedures which may cause bacteraemia and for which antimicrobial prophylaxis is recommended are given in Table 3. Prophylaxis is not recommended for cardiac catheterization.

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

Table 1 Terminology for infective endocarditis (IE). Examples: active mitral valve IE due to *Enterococcus faecalis*; healed recurrent prosthetic aortic valve endocarditis due to *Staphylococcus epidermidis*; suspected culture-negative late prosthetic mitral valve endocarditis

	Activity	Recurrence	Diagnostic terminology	Pathology	Anatomical site	Microbiology
First episode ^a	Active healed	→ Relapsing → recurrent			Mitral aortic tricuspid mural etc	Microorganism culture-negative, serologically negative, PCR negative, histologically negative
Definite ^a			→ Suspected → Possible			
Native ^a				→ Early prosthetic → Late prosthetic → IVDA ^b		

^aIf the columns 'recurrence', 'diagnostic terminology', and/or 'pathology' are without text, they signify the first episode of IE (not relapsing or recurrent), 'definite' IE (not suspected or possible) and involvement of a native cardiac valve.

^bIntravenous drug abuse.

Table 2 Cardiac conditions in which antimicrobial prophylaxis is indicated

- Prosthetic heart valves^a
- Complex congenital cyanotic heart diseases^a
- Previous infective endocarditis^a
- Surgically constructed systemic or pulmonary conduits^a
- Acquired valvular heart diseases
- Mitral valve prolapse with valvular regurgitation or severe valve thickening
- Non-cyanotic congenital heart diseases (except for secundum type ASD) including bicuspid aortic valves
- Hypertrophic cardiomyopathy

^aHigh-risk group (see text).

Table 3 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 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 (Table 4) is a class I recommendation (based on level C evidence).

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 DNA are found, IE is definite and culture/microbiologically positive, otherwise IE is definite but culture/microbiologically negative (Table 5). Duke or modified Duke criteria may be used to make the diagnosis in otherwise unclear cases.

Echocardiography

Any patient suspected of having 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 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 (Fig. 1). 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,

Table 4 Prophylactic antibiotic regimens

- Dental, oral, respiratory, and esophageal procedures (P)
 - not allergic to penicillin
 - amoxicillin 2.0 g (children 50 mg/kg) p.o. 1 h before P
 - **unable to take oral** medication: amoxicillin or ampicillin 2.0 g (children 50 mg/kg) i.v. $\frac{1}{2}$ –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. $\frac{1}{2}$ –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) $\frac{1}{2}$ –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 1–2 h before P plus gentamicin 1.5 mg/kg i.v. or i.m.
 - moderate-risk group: vancomycin (see above) without gentamicin

Table 5 Criteria that should raise suspicion of IE

- High clinical suspicion (urgent indication for echocardiographic screening and possibly hospital admission)
 - new valve lesion/ (regurgitant) murmur
 - embolic event(s) of unknown origin (esp. cerebral and renal infarction)
 - sepsis of unknown origin
 - haematuria, glomerulonephritis, and suspected renal infarction
 - 'fever' plus
 - prosthetic material inside the heart
 - other high predispositions for IE
 - newly developed ventricular arrhythmias or conduction disturbances
 - first manifestation of CHF
 - positive BCs (if the organism identified is typical for NVE/PVE)
 - cutaneous (Osler, Janeway) or ophthalmic (Roth) manifestations
 - multifocal/rapid changing pulmonic infiltrations (right heart IE)
 - peripheral abscesses (renal, splenic, spine) of unknown origin
 - predisposition and recent diagnostic/therapeutic interventions known to result in significant bacteraemia
- Low clinical suspicion
 - fever plus none of the above

echodense mass attached to the valvular or the mural endocardium or to implanted prosthetic material; (b), demonstration of abscesses or fistulas; (c), a new dehiscence of a valve prosthesis, especially when occurring late after implantation.

Standard blood culture techniques

Three or more blood cultures (BC) 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 6–7 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 1–5 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.

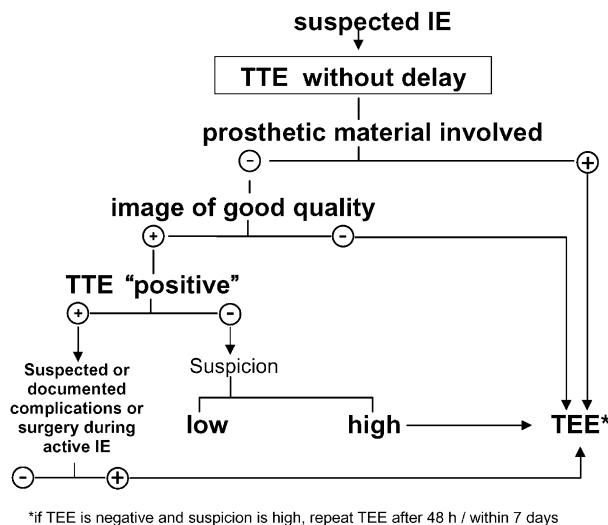


Fig. 1 Algorithm for the use of transthoracic (TTE) and transoesophageal echocardiography (TEE) in suspected IE. N.B. TTE "positive" indicates finding typical of IE (e.g. fresh vegetation or abscess formation)

Treatment and management

Antimicrobial therapy

For treatment strategies refer to Tables 6–9.

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 (MIC for gentamicin 4–64 mg/l). (Table 7)

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).

Recommendations for empirical antibiotic treatment (before microbiologic test results are available) and CNE are given in Table 9.

Special subsets

Antimicrobial therapy for infections of permanently implanted pacemakers or ICD leads are based on culture and susceptibility results. Duration of therapy should be 4–6 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 60–70% 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 3–4 weeks.

Surgery for active NVE

The following indications for urgent valve surgery are accepted:

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 (MIC \leq 0.1 mg/l)	
<ul style="list-style-type: none"> patients \leq65 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> patients \geq65 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
<ul style="list-style-type: none"> patients allergic to penicillin and cephalosporins 	vancomycin 30 mg/kg/24 h IV divided into two 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	

^aFor 2 weeks regimen see table 5.1.2 of the full version of these guidelines.

^bEspecially for patients allergic to penicillin

^c2–3 mg/kg netilmicin once daily may be an alternative (peak serum level $<$ 16 mg/l).

^dHigh 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 \geq 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 \leq 8 mg/l and for gentamicin MIC $<$ 500 mg/l	Penicillin G, 16–20 million units in 4–6 divided doses plus gentamicin 3 mg/kg, IV, divided in two doses for 4 weeks
Penicillin-allergic patients with 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 high resistance to gentamicin ^a	Assistance of an experienced microbiologist is mandatory. If antimicrobial therapy fails, valve replacement should be considered early

^aFor resistant enterococci treatment with oxazolidinone may be an option but should be initiated only after advice from a reference centre has been taken.

- 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 also 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)

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 3–4 doses for at least 4 weeks ^c plus gentamicin 3 mg/kg/24 h IV (maximum 240 mg/day), 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 two doses ^e for 4–6 weeks ^f , plus gentamicin 3 mg/kg/24 h IV (maximum 240 mg/day) divided into 2–3 doses for the first 3–5 days of treatment
MRSA ^g	vancomycin 30 mg/kg/24 h IV divided into two 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 three doses, both for 6–8 weeks, plus gentamicin 3 mg/kg/24 h IV (maximum 240 mg/day) 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 two doses ^e for 6 weeks, plus rifampicin 900 mg/24 h IV divided into three doses, plus gentamicin ^j 3 mg/kg/24 h IV (maximum 240 mg/day) divided into 2–3 doses, all for 6–8 weeks

^aMethicillin-susceptible *S. aureus*.

^bOr its congeners.

^cExcept for drug addicts for whom a 2-week regimen may be sufficient (see chapters 5.6.3 of the full version of this guideline).

^dFor both, immediate (IgE) type and hypersensitivity reaction during treatment.

^eInfusion over at least 60 min.

^fTotal 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.

^gMethicillin-resistant *S. aureus*.

^hCoagulase-negative staphylococci. In oxacillin-susceptible CONS vancomycin should be replaced by oxacillin.

ⁱFor resistant staphylococci treatment with oxazolidinone may be an option but should be initiated only after advice from a reference centre has been taken.

^jIf gentamicin susceptibility has been shown in vitro, gentamicin is added in MRSA for the full course but for CONS only for the first 2 weeks of treatment. If the organism is resistant to all aminoglycosides, gentamicin may be substituted by a fluoroquinolone.

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

^aMaximum 2 g/day; for drug level monitoring see below and full guideline text.

^bAminopenicillin may be added.

- 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 7–15 days postoperatively.

List of Abbreviations

ASD	Atrial septal defect
BC	Blood culture
CNE	Culture-negative endocarditis
CONS	Coagulase-negative staphylococci
HACEK	Group of bacteria consistent of <i>Haemophilus</i> spp., <i>Actinobacillus actinomycetemcomitans</i> , <i>Cardiobacterium hominis</i> , <i>Eikenella corrodens</i> , <i>Kingella kingae</i>
HLR	High level resistance
ICD	Implantable cardioverter defibrillator
IE	Infective endocarditis
IVDA	Intravenous drug abuser
MIC	Minimal inhibitory concentration
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
MSSA	Methicillin-sensitive <i>Staphylococcus aureus</i>
NVE	Native valve endocarditis
PCR	Polymerase chain reaction
PVE	Prosthetic valve endocarditis
spp	Plural of ‘species’
TEE	Transoesophageal echocardiography
TTE	Transthoracic echocardiography

Further Reading

Refer to full guidelines for complete reference list at www.esccardio.org

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