# Guidelines
# for The Management of
# Infective Endocarditis


**By**

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Infective endocarditis IE is an infection of the endocardial surface of the heart, which may include one or more heart valves, the mural endocardium, or a septal defect.
Its intracardiac effects include severe valvular insufficiency, which may lead to intractable congestive heart failure, myocardial abscesses & death.
The Duke diagnostic criteria are used to make a definitive diagnosis which combines the clinical, microbiologic, pathologic, and echocardiographic characteristics of a specific case.

**Definitive pathological diagnosis** is established by demonstrating microorganisms, by culture or histology, in vegetations removed by surgery, embolectomy or drainage of an intracardiac abscess.
*Alternatively*, a **definitive clinical diagnosis** is made based on the presence of:
• 2 major criteria or
• 1 major criterion and 3 minor criteria or
• 5 minor criteria
**Possible endocarditis**:
• 1 major and 1 minor criteria or
• 3 minor criteria
**Rejection criteria** for the diagnosis of IE are as follows:
• The presence of a firm alternative diagnosis of the manifestations of endocarditis
• Resolution of manifestations of endocarditis 4 or fewer days of antimicrobial therapy
• No pathologic evidence of IE at surgery or autopsy after 4 or fewer days of antimicrobial therapy

**Blood Culture**
▪ The criterion standard test for diagnosing IE is the documentation of a continuous bacteremia (>30 min in duration) based on blood culture results.
▪ Three sets should be obtained by separate venepuncture sites on the first day.
*Never rely on one set of blood cultures; as one is worse than none.*
▪ If there is no growth by the second day of incubation, two more may be taken.
▪Antibiotics maybe withheld for 48 hours or longer in clinically stable patients with negative blood cultures. However; in the case of acute IE; three sets may be drawn over 30 minutes (with separate venipunctures) to help document a continuous bacteremia within 60-90 minutes, followed by the infusion of the appropriate empirical antibiotic regimen**.**

**Other Investigations**
CXR, ECG, urinalysis, CBC, ESR, liver function tests, rheumatoid factor which has high specificity (94%) and CRP which has high sensitivity (97%) for IE.

## The Modified Duke Criteria

| | |
|---|---|
| **Definite endocarditis:** | 2 major criteria *or*<br>1 major plus 3 minor criteria *or*<br>5 minor criteria |
| **Possible endocarditis:** | 1 major and 1 minor criteria *or*<br>3 minor criteria |

| **Major Criteria** | **Comments** |
|---|---|
| 1. Microbiologic | Typical microorganisms isolated from ≥2 blood cultures:<br>Viridans strep, HACEK organisms, Staph aureus,<br>community acquired enterococci *or*<br>- Coxiella burnetii detected in ≥1 blood culture. |
| | Microorganisms consistent with IE from persistently positive blood cultures:<br>- ≥2 positive cultures of samples drawn >12 hours apart *or*<br>- All of 3 or majority of ≥4 separate cultures of blood<br>(with first and last sample drawn 1 hour apart). |
| 2 .Endocardial | New regurgitant murmur *or*<br>Findings on echocardiogram including:<br>- Echogenic, oscillating intracardiac mass.<br>- Periannular abscess.<br>- New dehiscence of prosthetic valve. |
| **Minor criteria** | |
| 1.Predisposing risk factors | **High risk:**<br>Previous endocarditis, aortic valve disease, rheumatic heart disease, prosthetic valve, coarctation, complex cyanotic heart disease.<br>**Moderate risk:**<br>Mitral valve prolapse (regurgitation/valve thickening), mitral stenosis, tricuspid disease, pulmonary stenosis, Cardiomyopathy.<br>**Low risk:**<br>ASD, IHD, mitral valve prolapse without regurgitation. |
| 2. Clinical | - Fever (Temperature ≥ 38ºC).<br>- Vascular phenomenon (emboli, Janeway lesions).<br>Immunologic phenomenon (glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor) |
| 3. Microbiologic | Single positive blood culture (except coagulase negative Staph. or gram negative bacilli) or serologic evidence of active infection with organism associated with endocarditis. |
| 4. Echocardiogram | Results consistent with IE but not meeting major echocardiographic criteria |

HACEK organisms *:*

*Haemophilus*, *Aggregatibacter* , *Cardiobacterium*, *Eikenella*, *Kingella*

**Four primary reasons form the rationale for revising the guidelines**:
• IE is more likely to result from frequent exposure to random bacteremias associated with daily activities than from bacteremia caused by a dental, gastrointestinal GI or genitourinary GU procedure.
• Maintenance of optimal oral health and hygiene may reduce the incidence of bacteremia from daily activities and thus the risk of IE, and is more important than the use of prophylactic antibiotics for dental procedures
• Prophylaxis prevents an exceedingly small number of cases of IE, if any, in individuals who undergo a dental, GI tract or GU tract procedure.
• The risk of antibiotic-associated adverse events exceeds the benefit, if any, from prophylactic antibiotic therapy except in very high-risk situations.

**The 3 major steps in the pathogenesis of IE that are vulnerable to antibiotic prophylaxis are the following:**
1. Killing of the pathogen in the bloodstream before it can adhere to the valve
2. Preventing adherence to the valve/fibrin-platelet thrombus
3. Eradicating any organisms that have attached to the thrombus
*Successful antibiotic prophylaxis requires identifying those patients who are at risk, prioritizing the procedures that require prophylaxis, and selecting an appropriate antibiotic regimen*

**Antibiotic prophylaxis is indicated for the following *high-risk* cardiac conditions:**
• Acquired valvular heart disease with stenosis or regurgitation
• Prosthetic cardiac valve
• History of infective endocarditis
• Cardiac transplantation recipients with cardiac valvular disease
• Congenital heart disease (CHD) with a *high-pressure gradient lesion* :
(1) unrepaired cyanotic CHD, including palliative shunts and conduits;
(2) completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure;
(3) repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibits endothelialization)

**Antibiotic prophylaxis against infective endocarditis is *not recommended***:
• For dental procedures unless involve the manipulation of gingival tissue, the periapical region of teeth or the perforation of the oral mucosa
• For upper and lower respiratory tract (including ear, nose and throat) procedures and bronchoscopy unless the procedure involves incision of the respiratory tract mucosa like (tonsillectomy, adenoidectomy) or invasive procedures to treat an established infection (drainage of abscess or empyema).
• For upper & lower gastrointestinal tract procedures and endoscopy unless involve incision of the mucosa
• For urological, gynaecological and obstetric procedures including childbirth unless involves incision and drainage of an abscess

• For skin or musculoskeletal tissue procedures unless involves incision and drainage of an abscess
• For prevention of Cardiac Implantable Electronic Device CIED infection in patients with pacemakers or intracardiac defibrillators during invasive procedures not directly related to device manipulation.
• Chlorhexidine mouthwash should not be offered as prophylaxis against infective endocarditis to people at risk of infective endocarditis undergoing dental procedures

**Treatment Regimens**
• The most common cause of endocarditis for dental, oral, respiratory tract, or esophageal procedures is *S viridans* (alpha-hemolytic streptococci).
• Amoxicillin, Ampicillin, and Penicillin V are equally effective against alpha-hemolytic streptococci; however, amoxicillin is preferred because of superior gastrointestinal absorption that provides higher and more sustained serum levels. The antibiotic should be administered *once as a single dose 30-60 min* before the procedure.
• *Standard general prophylaxis*
Amoxicillin Adult dose: 2 g PO
Pediatric dose: 50 mg/kg PO; not to exceed 2 g/dose
*If unable to take oral medication*
Ampicillin Adult dose: 2 g IV/IM
Pediatric dose: 50 mg/kg IV/IM; not to exceed 2 g/dose
*If allergic to penicillin*
Clindamycin Adult dose: 600 mg PO
Pediatric dose: 20 mg/kg PO; not to exceed 600 mg/dose
Cephalexin or Cephazoline or other first- or second-generation oral cephalosporin in equivalent dose (do not use cephalosporins in patients with a history of immediate-type hypersensitivity penicillin allergy, such as urticaria, angioedema, anaphylaxis)
Adult dose: 2 g PO
Pediatric dose: 50 mg/kg PO; not to exceed 2 g/dose
Azithromycin or clarithromycin
Adult dose: 500 mg PO
Pediatric dose: 15 mg/kg PO; not to exceed 500 mg/dose
*If allergic to penicillin and unable to take oral medication*
Clindamycin Adult dose: 600 mg IV
Pediatric dose: 20 mg/kg IV; not to exceed 600 mg/dose
Cefazolin or ceftriaxone (do not use cephalosporins in patients with a history of immediate-type hypersensitivity penicillin allergy, such as urticaria, angioedema, anaphylaxis) .
Adult dose: 1 g IV/IM
Pediatric dose: 50 mg/kg IV/IM; not to exceed 1 g/dose
• For lower abdominal, urogenital procedure (if indicated); add Gentmycin 80 mg IV, IM
• If the causative organism is known or suspected to be Staphylococcus aureus in cases of respiratory, skin structure or musculoskeletal infection; administer an anti-staphylococcal Penicillin, Cephalosporin or Vancomycin (if patient is unable to tolerate beta-lactam antibiotics).

**Approach considerations for management of IE**

General measures include the following:

- Treatment of congestive heart failure
- Oxygen
- Hemodialysis (may be required in patients with renal failure)
- Three sets of blood cultures should be drawn over a few hours, and then empiric antibiotic therapy tailored to the patient's history and circumstances

## For initial empirical treatment (before or without pathogen identification)

***Native valve NVE and Prosthetic valve endocarditis PVE ( > 12 months after surgery)***

- Ampicillin-Sulbactam 12g/day IV or Amoxacillin-Clavulanate 12g/day IV with Gentamaycin 3mg/kg/day IV for 4-6 weeks
- For patient not tolerating ß-lactam or suspected MRSA: Vancomycin 30mg/kg/day IV **with** Gentamycin 3mg/kg/day IV **with** Ciprofloxacin 800 mg/day IV or 1000mg/day oral

***Prosthetic valave endocarditis PVE (<12 months after surgery)***

Vancomycin 30mg/kg/day IV for 6 weeks with Gentamycin 3mg/kg/day IV for 2 weeks with Rifampicin 1200mg/day

*If vancomycin-resistant infection is suspected:*

Linezolid 600 mg IV q12h **or** Daptomycin 6 mg/kg IV q24h

## Antibiotics recommendations for known pathogens

***NVE caused by penicillin-susceptible Streptococci***:

Penicillin G 12-18 million U/d IV in 6 equally divided doses or infusion for 4 weeks **or**
Cefazolin at 6 g/d IV in 3 equally divided doses for 4 weeks **or**
Ceftriaxone at 2 g/d IV for 4 weeks **with**
Gentamicin at 3 mg/kg/d for 2 weeks;
*If allergic to penicillin*;
Vancomycin at 30 mg/kg/d IV in 2 divided doses for 4 weeks (do not exceed 2 g/d)

***NVE caused by non-resistant enterococci, resistant Streptococci***:

Penicillin G 18-30 million U/d IV in 6 equally divided doses or infusion **or**
Ampicillin 12 g/d by IV in 6 equally divided doses or infusion **with**
Gentamicin at 3 mg/kg/d for 4-6 weeks
*If allergic to penicillin*;
Vancomycin at 30 mg/kg/d IV in 2 divided doses for 4 weeks (do not exceed 2 g/d)

***NVE caused by resistant enterococci*** Continuously infused high dose Ampicillin.
Alternative choices: imipenem, ciprofloxacin, or ampicillin with sulbactam.

***PVE caused by Streptococcus***

*Highly penicillin-susceptible S viridans and S* bovis:

Aqueous penicillin G 24 MU IV q24h in 6 equally divided doses or infusion for 6wk **with/out** Gentamicin 3 mg/kg/d IV for 2wk **or**
Ceftriaxone 2 g/d IV for 6wk **with/out** Gentamicin 3 mg/kg/d IV for 2wk
*If allergic to penicillin or cephalosporin intolerant*
Vancomycin at 30 mg/kg/d IV in 2 divided doses for 6 weeks (do not exceed 2 g/d)

***NVE caused by Staphylococcus aureus***

◘ *Methicillin-susceptible*:

Nafcillin12 g/d IV in 4-6 divided doses for 6wk **with/out** Gentamicin 3mg/kg/day IV **or**
Cefazolin 6 g/day IV in 3 divided doses for 6wk **with/out** Gentamicin 3 mg/kg/day IV `

◘ *Methicillin-resistant or penicillin-intolerant:*

Vancomycin 30 mg/kg/day IV in 2 divided doses for 6wk
Patients with unstable renal function: Consider Linezolid 600 mg IV q12h

***PVE caused by Staphylococcus aureus***

Consideration should be given to early surgical intervention.

◘ *Methicillin-susceptible:*

Nafcillin 12 g/day IV in 6 divided doses for ≥ 6wk **plus**
Gentamicin 3 mg/kg/day IV in 2-3 divided doses for 2wk **plus**
Rifampin 900-1200 mg/day IV or PO in 3 divided doses for ≥ 6wk

▪ If the organism is gentamicin resistant, then other aminoglycosides may be used depending on susceptibility
▪ If the organism is resistant to all aminoglycosides, then substitute a fluoroquinolone with other 2 drugs for the entire course of therapy
▪ If the organism is both aminoglycoside and fluoroquinolone resistant, then linezolid, cefatrizine or trimethoprim-sulfamethoxazole can be used for the first 2 weeks of treatment

◘ *Methicillin-resistant*:

▪ Vancomycin 30 mg/kg/day IV in 2 divided doses for 6wk **plus**
Rifampin 900-1200 mg/day IV or PO in 3 divided doses for ≥ 6wk **plus**
Gentamicin 3 mg/kg/day IV in 2-3 divided doses for 2wk
▪ For patients with fluctuating renal function, consider linezolid 600 mg q12h **or** cefatrizine 600 mg q12h;
▪ Patients failing therapy on vancomycin (fever or symptoms persist, or for breakthrough bacteremia), vancomycin in such cases should be substituted by:
Linezolid 600 mg IV every 12 hours especially in patients who are seriously ill, it does not need adjusted in patients with renal failure but complete blood profile should be monitored **or** Daptomycin (6-12 mg/kg/24 h) has been approved for the treatment of *S. aureus* blood stream infection and right-sided IE.

***NVE or PVE caused by Gram-negative bacilli***

▪ Pseudomonas aeruginosa endocarditis, especially if prosthetic valves or left-sided requires consideration for surgical excision
▪ Pseudomonas aeruginosa endocarditis can be medically treated, especially native valve, with tobramycin 8 mg/kg daily IV once daily; **plus**
ticarcillin, piperacillin, cefepime, or ceftazidime

***NVE or PVE caused by HACEK organisms***

▪ Ceftriaxone 2 g/day IV or IM in 1 dose for 4wk **or**
▪ Ampicillin-sulbactam 12 g/day IV in 4 divided doses for 4wk
▪ *If patient is penicillin or cephalosporin intolerant*: Ciprofloxacin 1000 mg/day IV or IM in 2 divided doses for 4wk

***NVE caused by Fungi***

▪ Amphotericin B 0.7-1 mg/kg/d for at least 6wk
▪ For *Aspergillus* or *Mucor*, increase amphotericin B dose to 1-1.5 mg/kg **plus** flucytosine (5-FC) 150 mg/kg divided in 4 doses and renally adjusted for at least 6wk
▪ Lipid formulation of amphotericin B may be used for renal failure,

***PVE caused by Fungi***

▪ Surgical excision of prosthetic valve
▪ Relapse is high in *Candida* endocarditis, even with surgical excision, and fluconazole 200-400 mg recommended for prolonged period after surgery
▪ Fluconazole, caspofungin or fluconazole, and amphotericin B have been used for Candida PVE without surgery in a few cases

***NVE caused by Culture-negative organisms***

▪ Ampicillin: 12 g/day IV in 4 divided doses for 4-6wk **plus**
Gentamicin 3 mg/kg/day IV or IM in 2-3 divided doses for 4-6wk
▪ *If patient is penicillin intolerant*: Vancomycin 30 mg/kg/day IV in for 4-6wk **plus**
Gentamicin 3 mg/kg/day IV or IM in 2-3 divided doses for 4-6wk **plus**
Ciprofloxacin 1000 mg/day IV or IM in 2 divided doses for 4-6wk

***PVE caused by Culture-negative organisms (≤ 1y after implantation)***

Vancomycin 30 mg/kg/day IV for 6wk **plus**
Gentamicin 3 mg/kg/day IV or IM in 2-3 divided doses 2wk **plus**
Cefepime 6 g/day IV in 3 divided doses for 6wk **plus**
Rifampin 900-1200 mg/day PO or IV in 3 divided doses for 6wk

***PVE caused by Culture-negative organisms ( > 1y after implantation):***

Same regimen as for patients with culture-negative native valve endocarditis, with the addition of Rifampin 900-1200 mg/day PO or IV in 3 divided doses for 6wk

◘ Drug treatment of prosthetic valve endocarditis (PVE) should last longer (at least 6 weeks) than that of native valve endocarditis (NVE) (2–6 weeks), but is otherwise similar, except for staphylococcal PVE where the regimen should include Rifampin whenever the strain is susceptible.
◘ In NVE needing valve replacement by prosthesis during antibiotic therapy, the post-operative antibiotic regimen should be that recommended for NVE, not for PVE.
◘ In both NVE and PVE, the duration of treatment is based on the first day of effective antibiotic therapy, not on the day of surgery. After surgery, a new full course of treatment should only start if valve cultures are positive, the choice of antibiotic being based on the susceptibility of the latest recovered bacterial isolate.

◘ Consider outpatient parenteral antibiotic OPAT after 2 weeks of starting treatment if the patient is stable clinically and has no complications

**Indications for surgical intervention in patients with NVE are:**
▪ Congestive heart failure refractory to standard medical therapy
▪ Fungal IE (except that caused by *Histoplasma capsulatum*)
▪ Persistent sepsis after 72 hours of appropriate antibiotic treatment
▪ Recurrent septic emboli, especially after 2 weeks of antibiotic treatment
▪ Rupture of an aneurysm of the sinus of Valsalva
▪ Conduction disturbances caused by a septal abscess
▪ Kissing infection of the anterior mitral leaflet in patients with IE of the aortic valve
▪ Mobile & large (≥ 1cm) vegetations to decrease risk of embolization

**Prosthetic valve replacement surgery should be performed promptly if there is:**
▪ No response to antimicrobial therapy and blood cultures results remain positive
▪ Relapse of bacteremia occurs after infection
▪ Fungal endocarditis (combined with amphotericin-B therapy)
▪ Moderate-to-severe congestive heart failure,
▪ Valve dysfunction,
▪ Perivalvular or myocardial abscess formation,
▪ Presence of vegetations larger than 1 cm in diameter
▪ Unstable valve that is becoming detached from the valve ring,
▪ More than one embolic episode with persistent vegetations observed on transtracheal echocardiogram,

**Infected Cardiovascular Implantable Electronic Device CIED are removed in:**
▪ All patients with definite CIED infection, as shown by valvular and/or lead endocarditis or sepsis
▪ All patients with CIED pocket infection, as shown by abscess formation, device erosion, skin adherence, or chronic draining sinus without involvement of the transvenous section of the lead system
▪ All patients with valvular endocarditis without definite involvement of the lead(s), device, or both
▪ Patients with occult staphylococcal bacteremia & those with persistent occult gram-negative bacteremia despite appropriate antibiotic therapy

**Monitoring for posttreatment bacteremia**
▪ Patients should have blood cultures taken after 3-4 days of treatment to document eradication of the bacteremia as persistent fever or other signs develop that suggest failing treatment
▪ Fever lasting longer than 10 days into therapy or failure to sterilize the blood stream should prompt a search for metastatic infection or suppurative complications (abscesses, especially splenic, or mycotic aneurysm)
▪ Return of fever after the initial response is caused by an intracardiac abscess or metastatic infection. Causes of unresponsive fever include myocardial or septal abscesses, large vegetations that resist sterilization, and metastatic infection

▪ Relapse of IE usually occurs within 2 months of finishing clinically effective therapy. Infection with *S. aureus*, enterococci, gram-negative organisms (especially *P aeruginosa*) are associated with a high rate of relapse.
Enterococcal infection of the mitral valve has the greatest potential for relapse
▪ Recurrent IE occurs most often in individuals who abuse IV drugs. Those with pretreatment symptoms of IE of more than 3 months' duration are at greater risk for relapse. Other significant risk factors for recurrence include a previous episode of IE, the presence of a prosthetic valve, and congenital heart disease.
▪ Infected vascular catheters should be removed.

**Antithrombotic Therapy**
▪ In ischaemic stroke without cerebral haemorrhage, replacement of oral anticoagulant therapy by unfractionated heparin for 2 weeks is indicated with a close monitoring of activated partial thromboplastin or the activated cephalin clotting time
▪ In the absence of stroke, replacement of oral anticoagulant therapy by unfractionated heparin during 2 weeks may be considered in case of *Staphylococcus aureus* IE with a close monitoring of activated thromboplastin or the activated cephalin clotting time
▪ Interruption of all antiplatelet & anticoagulation therapy are only recommended in the presence of major bleeding or intracranial haemorrhage
▪ In patients with intracranial haemorrhage and a mechanical valve, unfractionated heparin should be reinitiated as soon as possible (with close monitoring of activated partial thromboplastin or activated cephalin clotting time) following multidisciplinary discussion

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