

Área Enfermedades Infecciosas

Atención farmacoterapéutica al paciente con endocarditis infecciosa

Autor: Margarita Beltran García

Servicio de Farmacia Hospitalaria

Hospital Universitario Virgen Macarena

Basada en el capítulo 120 de Dipiro JT et al. Pharmacotherapy:
A Pathophysiologic Approach, 8e

Endocarditis infecciosa (EI): introducción

- Inflamación del endocardio, membrana mucosa que recubre las cavidades de corazón y las válvulas cardíacas .
- Afecta: válvulas nativas, y zonas no valvulares y dispositivos mecánicos implantados: endocarditis de válvula protésica (EVP).
- Incremento de incidencia de factores de riesgo: prolapso y regurgitación de la válvula mitral y por atención sanitaria.
- Clasificación, según presentación clínica y severidad:
 - Aguda, fulminante, fiebre alta y toxicidad sistémica.
Staphylococcus aureus.
 - Subaguda, más indolente. En enfermedad cardíaca valvular preexistente. *Streptococci viridans*

Endocarditis Infecciosa:Etiología

- Factores de riesgo para Endocarditis infecciosa:
 - Presencia de válvula protésica (alto riesgo)
 - Endocarditis previa (alto riesgo)
 - Enfermedad cardíaca congénita
 - Acceso intravenoso permanente
 - Diabetes mellitus
 - Hemodiálisis
 - Disfunción valvular adquirida (p.e., enfermedad cardíaca reumática)
 - Cardiomiopatía reumática
 - Prolapso válvula mitral con regurgitación
 - Adicto a drogas por vía parenteral (ADVP)

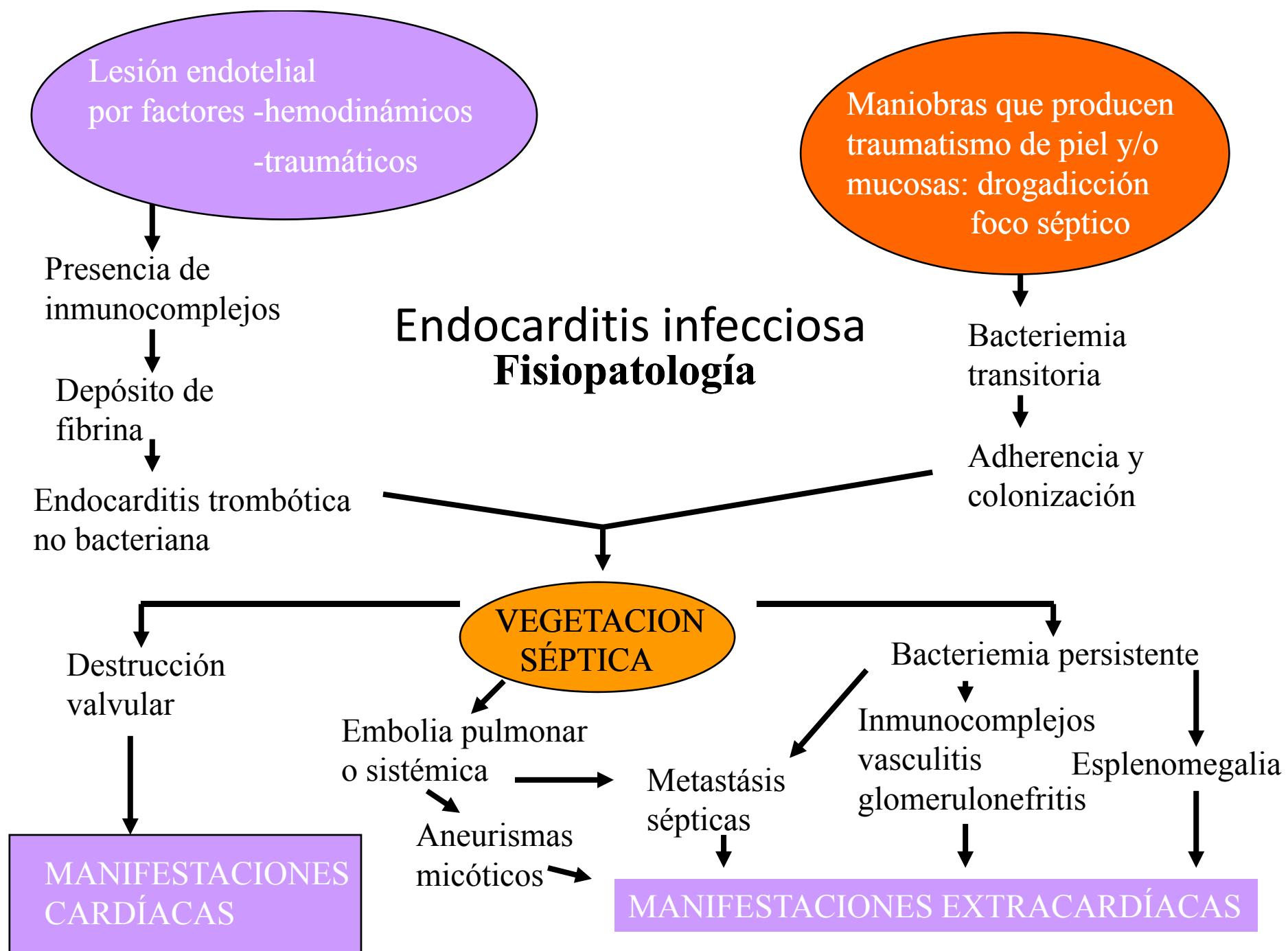
Endocarditis Infecciosa:Etiología

TABLE 120-1 Etiologic Organisms in Infective Endocarditis

Agent	Percentage of Cases (%)
Streptococci	25–35
Viridans streptococci	10–20
Other streptococci	5–10
Staphylococci	45–70
Coagulase positive	30–60
Coagulase negative	3–25
Enterococci	5–18
Gram-negative aerobic bacilli	1.5–13
Fungi	1–4
Miscellaneous bacteria	<5
Mixed infections	1–2
“Culture negative”	<5–24

Adapted from references 2 and 12.

Endocarditis infecciosa Fisiopatología



Complicaciones

- Vegetaciones: permiten crecimiento lento de microorganismos y las protegen (antibióticos y defensas del huésped).
- Complicaciones de EI:
 - Daño perivalvular (destrucción de válvula y dehiscencia en EVP)
 - Embolización de fragmentos sépticos por desprendimiento de la estructura a lugares remotos (abcesos o infartos).
 - Formación de complejos inmunes, depositados en órganos: glomerulonefritis, infartos (cerebral y esplénicos) abcesos y manifestaciones cutáneas (petequias, nodos Osler y lesiones Janeway)

Presentación clínica

TABLE 120-2 Clinical Presentation of Infective Endocarditis

General

The clinical presentation of infective endocarditis is highly variable and nonspecific.

Symptoms

The patient may complain of fever, chills, weakness, dyspnea, night sweats, weight loss, and/or malaise.

Signs

Fever is common, as is a heart murmur (sometimes new or changing). The patient may have embolic phenomenon, splenomegaly, or skin manifestations (e.g., Osler nodes, Janeway lesions).

Laboratory tests

The patient's white blood cell count may be normal or only slightly elevated.

Nonspecific findings include anemia (normocytic, normochromic), thrombocytopenia, an elevated erythrocyte sedimentation rate or C-reactive protein, and altered urinary analysis (proteinuria/microscopic hematuria).

The hallmark laboratory finding is continuous bacteremia; three sets of blood cultures should be collected over 24 hours.

Other diagnostic tests

An electrocardiogram, chest radiograph, and echocardiogram are commonly performed. Echocardiography to determine the presence of valvular vegetations plays a key role in the diagnosis of infective endocarditis; it should be performed in all suspected cases.

Diagnóstico

- La piedra angular de diagnóstico: hemocultivos y ecocardiografía
- Signos clínicos de enfermedad subaguda: nódulos Osler, lesiones Janeway, hemorragias en astilla, petequias, manchas Roth y eventos embólicos.
- El aguda (ADVP y por *S. aureus*) se manifiestan con frecuencia con sepsis.
- Esplenomegalia, frecuente en EI prolongada
- Hemocultivo en EI, bacteriemia continua (90-95% casos): 3 hemocultivos, extraídos de sitios diferentes en 24 horas previo al inicio del tratamiento antibiótico.
- Causas de hemocultivo negativo en paciente con diagnóstico clínico de EI:
 - tratamiento antibiótico previo,
 - toma inapropiada de cultivo o
 - microorganismos exigentes (requiere cultivo durante 1 mes)
- Otras pruebas:
 - Ecocardiografía (el test más importante) .
 - Electrocardiografía (bloqueo cardíaco),
 - radiografía de tórax (importante en EI derecha, embolia séptica pulmonar) y

DIAGNÓSTICO

- Ecocardiografía: transtorácica (ETT) y transesofágica (ETE). Detecta vegetaciones en EI.
- ETE, útil en alto riesgo de EI (válvula prostática, enfermedad cardíaca congénita, fallo cardíaco, nuevo murmullo cardíaco)
- Evalúa estabilidad hemodinámica y necesidad de intervención quirúrgica urgente (riesgo de embolismo)

Diagnóstico

- El diagnóstico de EI requiere la integración de manifestaciones clínicas, de laboratorio y resultados ecocardiográficos.
- Los 2 criterios diagnósticos mayores son: bacteriemia y cambios ecocardiográficos (ej vegetación valvular).

TABLE 120-3 Diagnosis of Infective Endocarditis According to the Modified Duke Criteria

Major Criteria

Blood culture positive for infective endocarditis

Typical microorganisms consistent with infective endocarditis from two separate blood cultures:

Viridans streptococci, Streptococcus bovis, HACEK group, Staphylococcus aureus; or

Community-acquired enterococci, in the absence of a primary focus; or

Microorganisms consistent with infective endocarditis from persistently positive blood cultures, defined as follows:

At least two positive cultures of blood samples drawn greater than 12 hours apart; or

All of three or a majority of four or more separate cultures of blood (with first and last sample drawn at least 1 hour apart)

Single positive blood culture for *Coxiella burnetii* or antiphase I immunoglobulin G antibody titer $>1:800$.

Evidence of endocardial involvement

Echocardiogram positive for infective endocarditis (transesophageal echocardiography recommended for patients with prosthetic valves, rated at least “possible infective endocarditis” by clinical criteria, or complicated infective endocarditis [paravalvular abscess]; transthoracic echocardiography as first test for other patients), defined as follows:

Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets or on implanted material in the absence of an alternative anatomic explanation; or

Abscess; or

New partial dehiscence of prosthetic valve

New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)

Minor Criteria

Predisposition, predisposing heart condition, or injection drug use

Fever, temperature $>38^{\circ}\text{C}$ (100.4°F)

Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions

Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor

Microbiologic evidence: Positive blood culture but does not meet a major criterion as noted above or serologic evidence of active infection with organism consistent with infective endocarditis

Echocardiographic minor criteria eliminated

HACEK, *Haemophilus* species (*H. parainfluenzae*, *H. aphrophilus*, *H. paraphrophilus*), *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*.

Note: Cases are defined clinically as *definite* if they fulfill two major criteria, one major criterion plus three minor criteria, or five minor criteria; cases are defined as *possible* if they fulfill one major and one minor criterion or three minor criteria. Cases are rejected if there is a firm alternate diagnosis explaining evidence of infective endocarditis; resolution of infective endocarditis syndrome with antibiotic therapy for <4 days; no pathologic evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for <4 days; or does not meet criteria for possible infective endocarditis, as above.

Adapted from references 19 and 20.

PRONÓSTICO

- Factores asociados con mortalidad:
 - IC (peor pronóstico a corto plazo)
 - Edad avanzada
 - El por microorganismos resistentes (hongos, gram negativos). Pseudomonas (>50%)
 - El lado izquierdo: Estafilococo spp (25-47%), enterococo (15-25%).
 - Complicaciones paravalvulares
 - Infección asociada a cuidados de salud.
 - EVP
- Riesgo recaída (<2 semanas tras suspender antimicrobiano):
 - Estreptococo viridans (2%)
 - Enterococo spp (8-20%)
 - EPV (10-15%)

TRATAMIENTO

- Aislamiento y sensibilidad del microorganismo.
- Inicio administración parenteral (intrahospitalario) y puede completarlo en domicilio siempre que:
 - Defervescencia de EI
 - Hemocultivo negativo
- Duración prolongada y altas dosis debido a :
 - Ubicación del microorganismo (vegetación y depósitos fibrina)
 - Microorganismos protegidos de defensas huésped (acción fagocítica)
 - Efecto inóculo en vegetación, se reduce actividad bactericida.

Tratamiento no farmacológico

- Cirugía (valvectomía y/o reemplazo de válvula)
- Objetivo: eliminar tejido infectado y restaurar la función hemodinámica.
- Indicación de intervención quirúrgica:
 - Vegetación persistente o aumento de su tamaño tras tratamiento antibacteriano prolongado
 - Extensión paravalvula (abscesos)
 - Bacteriemia persistente o fracaso del tratamiento antimicrobiano apropiado o microorganismos resistentes (p.e., hongos y bacterias Gram negativas)
 - Insuficiencia cardíaca, Disfunción valvular

Guías de tratamiento

- Betalactámicos, Penicilina G (o Ceftriaxona), Cloxacilina y ampicilina, fármacos de elección para endocarditis por estreptococo, estafilococo y enterococo respectivamente.
- *Enterococo spp* necesita terapia de combinación con aminoglucósidos para efecto bactericida.
- Asociar aminoglucósidos a betalactámicos en tratamiento de EI puede:
 - Disminuir la emergencia de microorganismos resistentes (ej EVP por Estafilococos coagulasa negativo)
 - Acelerar el ritmo de respuesta clínica y microbiológica (p.e., algunas infecciones estreptocócicas y estafilocócicas).
 - Acortar la duración del tratamiento ocasionalmente.

Endocarditis estreptocócica

- Estreptococos es la causa más común de EI.
 - Estreptococos bovis no es del grupo viridans pero el manejo terapéutico es similar.
- Determinar la sensibilidad de la cepa nos guiará el tratamiento
 - La mayoría sensibles a Penicilina G (CMI<0,12mcg/mL)
 - 10-20% moderadamente sensibles (CMI: 0,12-0,5mcg/mL)
- Cumplimiento de requisitos para considerar 2 semanas de tratamiento (según British Society for Antimicrobial Chemotherapy)
 - Estreptococos viridans o *S. bovis* penicilin sensible (CMI<0,1mcg/ml).
 - No factores de riesgo cardiovascular (IC, insuficiencia aórtica, alteraciones en conducción).
 - No enfermedad tromboembólica.
 - Infección de válvula nativa.
 - No vegetación >5mm diámetro en Ecocardiograma.
 - Respuesta clínica a los 7 días (temperatura normal, sin síntomas, apetito del paciente normal)

Recomendaciones para endocarditis por *Estreptococo viridans*:

- Infecciones complicadas (ej foco extracardíaco) o CMI (0,12-0,5mcg/mL) a Estreptococo: combinar con aminoglucósidos las dos 1^a semanas seguido de Penicilina G o Ceftriaxona sola durante 2 semanas adicionales.
- La endocarditis de válvula protésica u otro material protésico por Estreptococo viridans y *S bovis*: tratar igual que válvula nativa pero durante 6 semanas. Si patógeno es relativamente resistente, se asocia a gentamicina las 6 semanas.
- En endocarditis estreptocócica la administración de aminoglucósidos con ampliación del intervalo igual de eficaz que la administración convencional.
- Algunos Estreptococos viridans con exigencias nutricionales o Estreptococos con CMI>0,5mcg/ml, el tratamiento es similar a Endocarditis enterocócica (Vancomicina).
- Historia de hipersensibilidad tipo-inmediata a Penicilina: tratamiento alternativo, Vancomicina. No se recomienda asociar Gentamicina.

Tratamiento de E.I. válvula nativa por *Streptococos grupo viridans* y *S bovis* muy sensible a Penicilina

TABLE 120-4 Therapy of Native Valve Endocarditis Caused by Highly Penicillin-Susceptible Viridans Group Streptococci and *Streptococcus bovis*

Regimen	Dosage ^a and Route	Duration (week)	Strength of Recommendation	Comments
Aqueous crystalline penicillin G sodium <i>or</i> Ceftriaxone sodium	12–18 million units/24 hours IV either continuously or in four or six equally divided doses 2 g/24 hours IV/IM in one dose Pediatric dose ^b : penicillin 200,000 units/kg per 24-hour IV in four to six equally divided doses; ceftriaxone 100 mg/kg per 24 hours IV/IM in 1 dose	4 4	I A I A	Preferred for most patients older than age 65 years or patients with impairment of 8th cranial nerve function or renal function
Aqueous crystalline penicillin G sodium <i>or</i> Ceftriaxone sodium <i>plus</i> Gentamicin sulfate ^c	12–18 million units/24 hours IV either continuously or in six equally divided doses 2 g/24 hours IV/IM in 1 dose 3 mg/kg per 24 hours IV/IM in 1 dose Pediatric dose: penicillin 200,000 units/kg per 24 hours IV in four to six equally divided doses; ceftriaxone 100 mg/kg per 24 hours IV/IM in 1 dose; gentamicin 3 mg/kg per 24 hours IV/IM in one dose or three equally divided doses ^d	2 2 2	I B I B I B	2-week regimen not intended for patients with known cardiac or extracardiac abscess or for those with creatinine clearance of <20 mL/min, impaired 8th cranial nerve function, or <i>Abiotrophia</i> , <i>Granulicatella</i> , or <i>Gemella</i> spp. infection; gentamicin dosage should be adjusted to achieve peak serum concentration of 3–4 mcg/mL and trough serum concentration of <1 mcg/mL when three divided doses are used (second option to single daily dose)
Vancomycin hydrochloride ^e	30 mg/kg per 24 hours IV in two equally divided doses not to exceed 2 g/24 hours unless concentrations are inappropriately low Pediatric dose: 40 mg/kg per 24 hours IV in two to three equally divided doses	4	I B	Vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone; vancomycin dosage should be adjusted to obtain peak (1 hour after infusion completed) serum concentration of 30–45 mcg/mL and a trough concentration range of 10–15 mcg/mL

Minimum inhibitory concentration <0.12 mcg/mL.

^aDosages recommended are for patients with normal renal function.

^bPediatric dose should not exceed that of a normal adult.

^cOther potentially nephrotoxic drugs (e.g., nonsteroidal antiinflammatory drugs) should be used with caution for patients receiving gentamicin therapy.

^dData for once-daily dosing of aminoglycosides for children exist, but no data for treatment of infective endocarditis exist.

^eVancomycin dosages should be infused during course of at least 1 hour to reduce risk of histamine release “red man” syndrome.

From reference 4, with permission. Copyright 2005, American Medical Association.

Tratamiento de E.I. válvula nativa por *Streptococos grupo viridans* y *S bovis* relativamente resistente a Penicilina

TABLE 120-5 Therapy of Native Valve Endocarditis Caused by Strains of Viridans Group Streptococci and *Streptococcus bovis* Relatively Resistant to Penicillin

Regimen	Dosage ^a and Route	Duration (week)	Strength of Recommendation	Comments
Aqueous crystalline penicillin G sodium <i>or</i>	24 million units/24 hours IV either continuously or in four to six equally divided doses	4	I B	Patients with endocarditis caused by penicillin-resistant (MIC >0.5 mcg/mL) strains should be treated with regimen recommended for enterococcal endocarditis (see Table 120-9)
Ceftriaxone sodium <i>plus</i>	2 g/24 hours IV/IM in one dose	4	I B	
Gentamicin sulfate ^b	3 mg/kg per 24 hours IM/IV in one dose Pediatric dose ^c : penicillin 300,000 units/24 hours IV in four to six equally divided doses; ceftriaxone 100 mg/kg per 24 hours IV/IM in one dose; gentamicin 3 mg/kg per 24 hours IV/IM in one dose or three equally divided doses	2		Although it is preferred that gentamicin (3 mg/kg) be given as a single daily dose to adult patients, as a second option, gentamicin can be administered daily in three equally divided doses
Vancomycin hydrochloride ^d	30 mg/kg per 24 hours IV in two equally divided doses not to exceed 2 g/24 hours unless serum concentrations are inappropriately low Pediatric dose: 40 mg/kg per 24 hours in two or three equally divided doses	4	I B	Vancomycin ^d therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy

Minimum inhibitory concentration (MIC) >0.12 mcg/mL to ≥0.5 mcg/mL.

^aDosages recommended are for patients with normal renal function.

^bSee Table 120-4 for appropriate dosage of gentamicin.

^cPediatric dose should not exceed that of a normal adult.

^dSee Table 120-4 for appropriate dosage of vancomycin.

From reference 4, with permission. Copyright 2005, American Medical Association.

Tratamiento de E.I. válvula protésica u otro material protésico por *Streptococos grupo viridans* y *S bovis*.

TABLE 120-6 Therapy for Endocarditis of Prosthetic Valves or Other Prosthetic Material Caused by Viridans Group Streptococci and *Streptococcus bovis*

Regimen	Dosage ^a and Route	Duration (week)	Strength of Recommendation	Comments
Penicillin-susceptible strain (minimum inhibitory concentration ≤0.12 mcg/mL)				
Aqueous crystalline penicillin G sodium or Ceftriaxone sodium with or without Gentamicin sulfate ^b	24 million units/24 hours IV either continuously or in four to six equally divided doses 2 g/24 hours IV/IM in one dose 3 mg/kg per 24 hours IM/IV in one dose Pediatric dose ^c : penicillin 300,000 units/24 hours IV in four to six equally divided doses; ceftriaxone 100 mg/kg per 24 hours IV/IM in one dose; gentamicin 3 mg/kg per 24 hours IV/IM in one dose or three equally divided doses	6 6 2	I B I B I B	Penicillin or ceftriaxone together with gentamicin has not demonstrated superior cure rates compared with monotherapy with penicillin or ceftriaxone for patients with highly susceptible strain; gentamicin therapy should not be administered to patients with creatinine clearance of <30 mL/min
Vancomycin hydrochloride ^d	30 mg/kg per 24 hours IV in two equally divided doses Pediatric dose: 40 mg/kg per 24 hours in two or three equally divided doses	2	I B	Vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy
Penicillin relatively or fully resistant strain (minimum inhibitory concentration >0.12 mcg/mL)				
Aqueous crystalline penicillin sodium or Ceftriaxone plus Gentamicin sulfate	24 million units per 24 hours IV either continuously or in four to six equally divided doses 2 g/24 hours IV/IM in one dose 3 mg/kg per 24 hours IV/IM in one dose Pediatric dose: penicillin 300,000 units/kg per 24 hours IV in four to six equally divided doses	6 6 6	I B I B I B	
Vancomycin hydrochloride	30 mg/kg per 24 hours IV in two equally divided doses Pediatric dose: 40 mg/kg per 24 hours IV in two or three equally divided doses	6	I B	Vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy

^aDosages recommended are for patients with normal renal function.

^bSee Table 120-4 for appropriate dosage of gentamicin.

^cPediatric dose should not exceed that of a normal adult.

^dSee text and Table 120-4 for appropriate dosage of vancomycin.

From reference 4, with permission. Copyright 2005, American Medical Association.

Endocarditis estafilocócica

- Incremento prevalencia: por ADVP y catéter venoso (*S aureus*); y cirugía de reemplazo de válvula (*S . coagulasa negativo, S epidermidis*).
- Factores predictores de alto riesgo de EI en pacientes con bacteriemia por *S aureus* :
 - Ausencia de foco primario
 - Signos metastásicos de infección
 - Vegataciones valvulares detectadas por ecocardiografía.
- Endocarditis por Estafilococo spp lado izquierdo (mortalidad 25-47%) meticilin sensible:
 - Infecciones no complicadas, suficiente 4 semanas con cloxacilina
 - Resto, 6 semanas con cloxacilina más curso corto de gentamicina.
 - En alergia retardada a Penicilina, alternativa: Cefazolina.
 - Alergia inmediata a Penicilina y fracaso a vancomicina: desensibilización.
 - Vancomicina es tratamiento elección en MRSA y *S coagulasa negativo*.
 - En resistencia a Meticilina y Vancomicina: Linezolid y Daptomicina.

Tratamiento de E.I. por *Stafilococo spp* en ausencia de material protésico.

TABLE 120-7 Therapy for Endocarditis Caused by Staphylococci in the Absence of Prosthetic Materials

Regimen	Dosage ^a and Route	Duration	Strength of Recommendation	Comments
Oxacillin-susceptible strains with	Nafticillin or oxacillin ^b 12 g/24 hours IV in four to six equally divided doses	6 weeks	I A	For complicated right-sided infective endocarditis and for left-sided infective endocarditis; for uncomplicated right-sided infective endocarditis, 2 weeks (see text)
Optional addition of gentamicin sulfate ^c	3 mg/kg per 24 hours IV/IM in two or three equally divided doses	3–5 days		Clinical benefit of aminoglycosides has not been established
For penicillin-allergic (nonanaphylactoid type) patients: with	Cefazolin 6 g/24 hours IV in three equally divided doses	6 weeks	I B	Consider skin testing for oxacillin-susceptible staphylococci and questionable history of immediate-type hypersensitivity to penicillin
Optional addition of gentamicin sulfate	3 mg/kg per 24 hours IV/IM in two or three equally divided doses Pediatric dose: cefazolin 100 mg/kg per 24 hours IV in three equally divided doses; gentamicin 3 mg/kg per 24 hours IV/IM in three equally divided doses	3–5 days		Cephalosporins should be avoided in patients with anaphylactoid-type hypersensitivity to β -lactams; vancomycin should be used in these cases ^d Clinical benefit of aminoglycosides has not been established
Oxacillin-resistant strains				
Vancomycin ^e	30 mg/kg per 24 IV in two equally divided doses Pediatric dose: 40 mg/kg per 24 hours IV in two or three equally divided doses	6 weeks	I B	Adjust vancomycin dosage to achieve 1-hour serum concentration of 30–45 mcg/mL and trough concentration of 10–15 mcg/mL

^aDosages recommended are for patients with normal renal function.

^bPenicillin G 24 million units/24 hours IV in four to six equally divided doses may be used in place of nafticillin or oxacillin if strain is penicillin susceptible (minimum inhibitory concentration \leq 0.1 mcg/mL) and does not produce β -lactamase.

^cGentamicin should be administered in close temporal proximity to vancomycin, nafticillin, or oxacillin dosing. See Table 120-4 for appropriate dosage of gentamicin.

^dPediatric dose should not exceed that of a normal adult.

^eFor specific dosing adjustment and issues concerning vancomycin, see Table 120-4 footnotes.

From reference 4, with permission. Copyright 2005, American Medical Association.

Endocarditis estafilocócica: ADVP

- E.I. en ADVP es causada por *S aureus* (0-70%)
- La afectación más frecuente es lado derecho (válvula tricúspide).
- Buena respuesta al tratamiento (lado derecho), aunque puede requerir cirugía.
- Endocarditis por MSSA lado derecho (curación clínica y microbiológica >85%), se puede tratar con curso corto (2 semanas) de oxacilina + aminoglucósidos.
- Curso corto (2 semanas) cloxa + aminoglucósidos, no debería usarse en:
 - Endocarditis lado izquierdo
 - Inapropiado en: VIH, IR, meningitis, complicaciones pulmonares (abcesos en EI lado derecho)

Endocarditis estafilocócica: válvula protésica (EVP)

- 15% de todas los casos.
- Aparición en 2 meses tras cirugía, nosocomial: frecuente MARSA, elección Vancomicina
- Riesgo elevado hasta 12 meses tras cirugía.
- Alta morbi-mortalidad y refractariedad: Frecuente combinación antimicrobianos.
- Rifampicina (combinado con Vancomicina o Cloxacilina):
 - Mayor tasa curación microbiológica
 - Se asocia a Vancomicina durante 6 semanas o más.
- Aminoglucósidos, se combinan durante las 2 primeras semanas
- Recomendación en anticoagulados: Mantener anticoagulación durante 2 semanas en EVP (*S. aureus*) si ocurrió evento embólico del SNC

Tratamiento de E.I. en válvula protésica por *Estafilococo spp.*

TABLE 120-8 Therapy for Prosthetic Valve Endocarditis Caused by Staphylococci

Regimen	Dosage ^a and Route	Duration (week)	Strength of Recommendation	Comments
Oxacillin-susceptible strains				
Nafcillin or oxacillin <i>plus</i>	12 g/24 hours IV in four to six equally divided doses	≥6	1B	Penicillin G 24 million units per 24 hours IV in four to six equally divided doses may be used in place of nafcillin or oxacillin if strain is penicillin susceptible (minimum inhibitory concentration ≤0.1 mcg/mL) and does not produce β-lactamase; vancomycin should be used in patients with immediate-type hypersensitivity reactions to β-lactam antibiotics (see Table 120-4 for dosing guidelines); cefazolin may be substituted for nafcillin or oxacillin for patients with nonimmediate-type hypersensitivity reactions to penicillins
Rifampin <i>plus</i>	900 mg per 24 hours IV/orally in three equally divided doses	≥6		
Gentamicin ^b	3 mg/kg per 24 hours IV/IM in two or three equally divided doses Pediatric dose: nafcillin or oxacillin 200 mg/kg per 24 hours IV in four to six equally divided doses; rifampin 20 mg/kg per 24 hours IV/orally in three equally divided doses; gentamicin 3 mg/kg per 24 hours IV/IM in three equally divided doses	2		
Oxacillin-resistant strains				
Vancomycin <i>plus</i>	30 mg/kg per 24 hours in two equally divided doses	≥6	1B	Adjust vancomycin to achieve 1-hour serum concentration of 30–45 mcg/mL and trough concentration of 10–15 mcg/mL
Rifampin <i>plus</i>	900 mg/24 hours IV/orally in three equally divided doses	≥6		
Gentamicin	3 mg/kg per 24 hours IV/IM in two or three equally divided doses Pediatric dose: vancomycin 40 mg/kg per 24 hours IV in two or three equally divided doses; rifampin 20 mg/kg per 24 hours IV/orally in three equally divided doses (up to adult dose); gentamicin 3 mg/kg per 24 hours IV or IM in three equally divided doses	2		

^aDosages recommended are for patients with normal renal function.

^bGentamicin should be administered in close proximity to vancomycin, nafcillin, or oxacillin dosing. See Table 120-4 for appropriate dosage of gentamicin.

^cPediatric dose should not exceed that of a normal adult.

From reference 4, with permission. Copyright 2005, American Medical Association.

Endocarditis enterocócica

- *Enterococos Faecium y faecalis.* *E. faecalis* es la más frecuente (90%).
- Enterococo causa 5-18% de las endocarditis, pero más resistentes al tratamiento que Estafilococo y Estreptococo.
- Endocarditis por Enterococo:
 - Antibióticos solos no son bactericidas (recaída del 50-80% con Penicilina)
 - CMI a penicilina relativamente altas (1-25mcg/mL)
 - Resistencia intrínseca a todas las cefalosporinas y relativa a aminoglucósidos (R de bajo nivel)
 - Acción bactericida (sinergia) al combinar aminoglucósido a Vancomicina o Penicilina (recaída 15%)
- Requiere tratamiento de 4-6 semanas de Ampicilina o Penicilina G (altas dosis) más aminoglucósido. Para éxito terapéutico se necesitan niveles séricos relativamente bajos de gentamicina, pico: 3-4 mcg/mL.
- Terapia para Enterococos multirresistentes: *E faecium* (Linezolid o quinopristina-dalfopristina) y *E. faecalis* (Ampicilina + imipenem-cilastatina o Ceftriaxona).
- Cirugía y reemplazamiento de válvula puede ser la única opción.

Tratamiento de E.I. en válvula nativa o protésica por *Enterococo spp.* sensible a Penicilina, Gentamicina y Vancomicina.

TABLE 120-9 Therapy for Native Valve or Prosthetic Valve Enterococcal Endocarditis Caused by Strains Susceptible to Penicillin, Gentamicin, and Vancomycin

Regimen	Dosage ^a and Route	Duration (week)	Strength of Recommendation	Comments
Ampicillin sodium or	12 g/24 hours IV in six equally divided doses	4–6	I A	Native valve: 4-week therapy recommended for patients with symptoms of illness less than 3 months; 6-week therapy recommended for patients with symptoms greater than 3 months
Aqueous crystalline penicillin G sodium plus	18–30 million units per 24 hours IV either continuously or in six equally divided doses	4–6	I A	Prosthetic valve or other prosthetic cardiac material: minimum of 6 weeks of therapy recommended
Gentamicin sulfate ^b	3 mg/kg per 24 hours IV/IM in three equally divided doses	4–6		
Vancomycin hydrochloride ^c	30 mg/kg per 24 hours IV in 2 equally divided doses	6	I B	Vancomycin therapy recommended only for patients unable to tolerate penicillin or ampicillin
Gentamicin sulfate	3 mg/kg per 24 hours IV/IM in three equally divided doses Pediatric dose ^c : vancomycin 40 mg/kg per 24 hours IV in two or three equally divided doses; gentamicin 3 mg/kg per 24 hours IV/IM in three equally divided doses	6		6 weeks of vancomycin therapy recommended because of decreased activity against enterococci

^aDosages recommended are for patients with normal renal function.

^bDosage of gentamicin should be adjusted to achieve peak serum concentration of 3–4 mcg/mL and a trough concentration of less than 1 mcg/mL. See Table 120-4 for appropriate dosage of gentamicin.

^cPediatric dose should not exceed that of a normal adult.

^dSee text and Table 120-4 for appropriate dosing of vancomycin.

From reference 4, with permission. Copyright 2005, American Medical Association.

Endocarditis: Grupo HACEK

- Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella.
- Representa el 5-10% de válvula nativa (infección adquirida de la comunidad).
- Gram negativos, flora orofaríngea.
- Se presenta como enfermedad subaguda grandes vegetaciones y riesgo embólico
- Crecimiento lento y causa de “cultivo negativo”.
- Duración 4 semanas, se extiende a 6 semanas en EVP por grupo HACEK.
- Regímenes posibles, en combinación con aminoglucósidos:
 - Ceftriaxona
 - Ampicilina-Sulbactam
 - Ciprofloxacino oral (sólo si: intolerancia al resto de tratamientos y >18 años)

Tratamiento de E.I. en válvula nativa o protésica por microorganismos HACEK.

TABLE 120-10 Therapy for Both Native and Prosthetic Valve Endocarditis Caused by HACEK^a Microorganisms

Regimen	Dosage and Route	Duration (week)	Strength of Recommendation	Comments
Ceftriaxone ^b sodium	2 g/24 hours IV/IM in one dose	4	I B	Cefotaxime or another third- or fourth-generation cephalosporin may be substituted
or				
Ampicillin-sulbactam ^c	12 g/24 hours IV in four equally divided doses	4	IIa B	
or				
Ciprofloxacin ^{c,d}	1,000 mg/24 hours orally or 800 mg/24 hours IV in two equally divided doses Pediatric dose ^e : Ceftriaxone 100 mg/kg per 24 hours IV/IM once daily; ampicillin-sulbactam 300 mg/kg per 24 hours IV divided into four or six equally divided doses; ciprofloxacin 20–30 mg/kg per 24 hours IV/orally in two equally divided doses	4	IIb C	Fluoroquinolone therapy recommended only for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin, gatifloxacin, or moxifloxacin may be substituted; fluoroquinolones generally not recommended for patients younger than 18 years old Prosthetic valve: Patients with endocarditis involving prosthetic cardiac valve or other prosthetic cardiac material should be treated for 6 weeks.

^a*Haemophilus parainfluenzae*, *H. aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*.

^bPatients should be informed that IM injection of ceftriaxone is painful.

^cDosage recommended for patients with normal renal function.

^dFluoroquinolones are highly active in vitro against HACEK microorganisms. Published data on use of fluoroquinolone therapy for endocarditis caused by HACEK are minimal.

^ePediatric dose should not exceed that of a normal adult.

From reference 4, with permission. Copyright 2005, American Medical Association.

Endocarditis por microorganismos atípicos

- *Bartonella, Coxiella burnetii, Brucella, Candida, Aspergillus spp, Legionella* y Gram negativos (*Pseudomonas spp*) es infrecuente.
- Endocarditis por Gram negativo: Poco éxito, mal pronóstico y tasas mortalidad 60-80%. Se recomienda cirugía cardiaca junto con tratamiento antimicrobiano prolongado.
- Endocarditis por hongos: 2-4% de casos. Se recomienda cirugía cardíaca junto con tratamiento antimicrobiano prolongado. *Candida spp o Aspergillus spp*. Alta tasa mortalidad (>80%).
- Endocarditis por *C. burnetii* (fiebre Q), se identifica por test serológicos. La terapia es combinación Doxicilina con (trimetroprim-sulfametoxazol, rifampicina o fluorquinolonas)
- Endocarditis por *Brucella spp*. Curación requiere reemplazamiento valvular y terapia con: doxicilina + (aminoglucósido o trimetroprim-sulfametoxazol o Rifampicina) durante 8 semanas hasta meses.

Endocarditis: cultivo negativo

- E.I. con cultivos negativos, 5-20%.
- Causas:
 - Endocarditis derecha subaguda no identificada
 - Tratamiento antibiótico previo
 - Crecimiento lento de microorganismos exigentes.
 - Etiología no bacteriana
 - Incorrecta recogida de muestras
- En sospecha de EI, si no hay crecimiento tras 48-72 horas: avisar al laboratorio y mantener crecimiento durante 1 mes para detectar crecimiento de microorganismos exigentes

Tratamiento de E.I. con cultivo negativo incluyendo *Bartonella spp.*

TABLE 120-11 Therapy for Culture-Negative Endocarditis Including *Bartonella* Endocarditis

Regimen	Dosage ^a and Route	Duration (week)	Strength of Recommendation	Comments
Native valve				
Ampicillin-sulbactam				
plus	12 g/24 hours IV in four equally divided doses	4–6	IIb C	Patients with culture-negative endocarditis should be treated with consultation with an infectious diseases specialist
Gentamicin sulfate ^b	3 mg/kg per 24 hours IV/IM in three equally divided doses	4–6		
Vancomycin ^c	30 mg/kg per 24 hours IV in 2 equally divided doses	4–6	IIb C	Vancomycin recommended only for patients unable to tolerate penicillins
plus				
Gentamicin sulfate	3 mg/kg per 24 hours IV/IM in three equally divided doses	4–6		
plus				
Ciprofloxacin	1,000 mg/24 hours orally or 800 mg/24 hours IV in two equally divided doses	4–6		
Pediatric dose ^e : ampicillin-sulbactam 300 mg/kg per 24 hours IV in four to six equally divided doses; gentamicin 3 mg/kg per 24 hours IV/IM in three equally divided doses; vancomycin 40 mg/kg per 24 hours in two or three equally divided doses; ciprofloxacin 20–30 mg/kg per 24 hours IV/orally in two equally divided doses				
Prosthetic valve (early, <1 year)				
Vancomycin	30 mg/kg per 24 hours IV in two equally divided doses	6	IIb C	
plus				
Gentamicin sulfate	3 mg/kg per 24 hours IV/IM in three equally divided doses	2		
plus				
Cefepime	6 g/24 hours IV in three equally divided doses	6		
plus				
Rifampin	900 mg/24 hours orally/IV in three equally divided doses Pediatric dose: vancomycin 40 mg/kg per 24 hours IV in two or three equally divided doses; gentamicin 3 mg/kg per 24 hours IV/IM in three equally divided doses; cefepime 150 mg/kg per 24 hours IV in three equally divided doses; rifampin 20 mg/kg per 24 hours orally/IV in three equally divided doses	6		
Prosthetic valve (late, >1 year)		6	IIb C	Same regimens as listed above for native valve endocarditis with the addition of rifampin
Suspected <i>Bartonella</i>, culture negative				
Ceftriaxone sodium	2 g/24 hours IV/IM in one dose	6	IIa B	
plus				
Gentamicin sulfate	3 mg/kg per 24 hours IV/IM in three equally divided doses	2		
with/without				
Doxycycline	200 mg per 24 hours IV/orally in two equally divided doses	6		
Documented <i>Bartonella</i>, culture positive				
Doxycycline	200 mg/24 hours IV or orally in two equally divided doses	6	IIa B	If gentamicin cannot be given, then replace with rifampin, 600 mg/24 hours orally/IV in two equally divided doses
plus				
Gentamicin sulfate	3 mg/kg per 24 hours IV/IM in three equally divided doses Pediatric dose: ceftriaxone 100 mg/kg per 24 hours IV/IM once daily; gentamicin 3 mg/kg per 24 hours IV/IM in three equally divided doses; doxycycline 2–4 mg/kg per 24 hours IV/orally in two equally divided doses; rifampin 20 mg/kg per 24 hours orally/IV in two equally divided doses	2		

^aDosages recommended are for patients with normal renal function.

^bSee text and Table 120-4 for appropriate dosing of gentamicin.

^cSee Table 120-4 for appropriate dosing of vancomycin.

^dPediatric dose should not exceed that of a normal adult.

^eFrom reference 4, with permission. Copyright 2005, American Medical Association.

Consideraciones farmacoeconómicas

- Regímenes curso corto:
 - Endocarditis estreptocócicas ($CMI < 0,12 \text{ mcg/mL}$) 2 semanas de Ceftriaxona (o Penicilina G altas dosis) + gentamicina es tan efectivo como 4 semanas de Penicilina sola.
 - Endocarditis MSSA lado derecho no complicada en ADVP, se puede tratar con 2 semanas de combinación cloxacilina + aminoglucósidos, en lugar de 4 semanas con Cloxacilina sola.
- Inicio precoz de terapia domiciliaria, cuando se dan estas circunstancias:
 - Hemodinámicamente estable
 - Respuesta favorable del tratamiento
 - Monitorización estrecha de la medicación
 - Comprensión de complicaciones potenciales de la enfermedad.
 - Acceso inmediato al cuidado médico
- Ej, Endocarditis estreptocócica (Ceftriaxona)
- Problema: descompensación cardíaca súbita en medio extrahospitalario.

Evaluación objetivo terapéutico

- **Signos y síntomas**
 - Fiebre, persistir >7 días indica ineffectividad tratamiento, embolismo, infección cateter o reacciones a fármaco.
 - Defervescencia de infección, inicio de mejoría de síntomas y disminución de letargia o debilidad.
 - Ecocardiografía (ETT): hacerla tras finalizar el tratamiento antibiótico, para determinar función cardíaca basal (función y tamaño ventricular).
- **Hemocultivos ,**
 - Tras varios días deben negativizarse. Si son positivos: fracaso al tratamiento.
 - Realizar hemocultivos hasta negativizarse, luego y durante el tratamiento no hacer más.
 - Tras éxito y fin del tratamiento, hacer 1-2 hemocultivos tras 8 semanas.
- **CMI para los antimicrobianos**
- **Niveles plasmáticos de aminoglucósidos (excepto estreptomicina) y Vancomicina.**
 - Endocarditis por cocos Gram positivos con régimen 3 veces al día. Pico sérico: 3-4 mcg/mL Gentamicina.
 - Endocarditis por Streptococo , se usa administración intervalo extendido.
 - Vancomicina, concentración valle objetivo es: 15-20mcg/mL.

PREVENCIÓN

TABLE 120-12

Cardiac Conditions Associated with the Highest Risk of Adverse Outcome from Endocarditis for Which Prophylaxis with Dental Procedures is Recommended

Prosthetic cardiac valves

Previous infective endocarditis

Congenital heart disease (CHD)^a

Unrepaired cyanotic CHD, including palliative shunts and conduits

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^b

Repaired CHD with residual defects (that inhibit endothelialization) at the site or adjacent to the site of a prosthetic patch or prosthetic device

Cardiac transplantation recipients who develop cardiac valvulopathy

^aExcept for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD.

^bProphylaxis is recommended because endothelialization of prosthetic material occurs within 6 months after the procedure.

From reference 4, with permission. Copyright 2005, American Medical Association.

TABLE 120-13 Dental Procedures for Which Endocarditis Prophylaxis Is Recommended for Patients Described in Table 120-12

All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa^a

^aThe following procedures and events do not need prophylaxis: routine anesthetic injections through noninfected tissue, taking dental radiographs, placement of removable prosthodontic or orthodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth, and bleeding from trauma to the lips or oral mucosa.

From reference 4, with permission. Copyright 2005, American Medical Association.

TABLE 120-14 Antibiotic Regimens for a Dental Procedure

Regimen: Single Dose 30 to 60 Minutes Before Procedure			
Situation	Agent	Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin	2 g IM or IV	50 mg/kg IM or IV
	or		
	Cefazolin or ceftriazone	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin (oral)	Cephalexin ^{a,b}	2 g	50 mg/kg
	or		
	Clindamycin	600 mg	20 mg/kg
	or		
	Azithromycin or clarithromycin	500 mg	15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone ^b	1 g IM or IV	50 mg/kg IM or IV
	or		
	Clindamycin	600 mg IM or IV	20 mg/kg IM or IV

^aOr other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.

^bCephalosporins should not be used for an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.

From reference 4, with permission. Copyright 2005, American Medical Association.