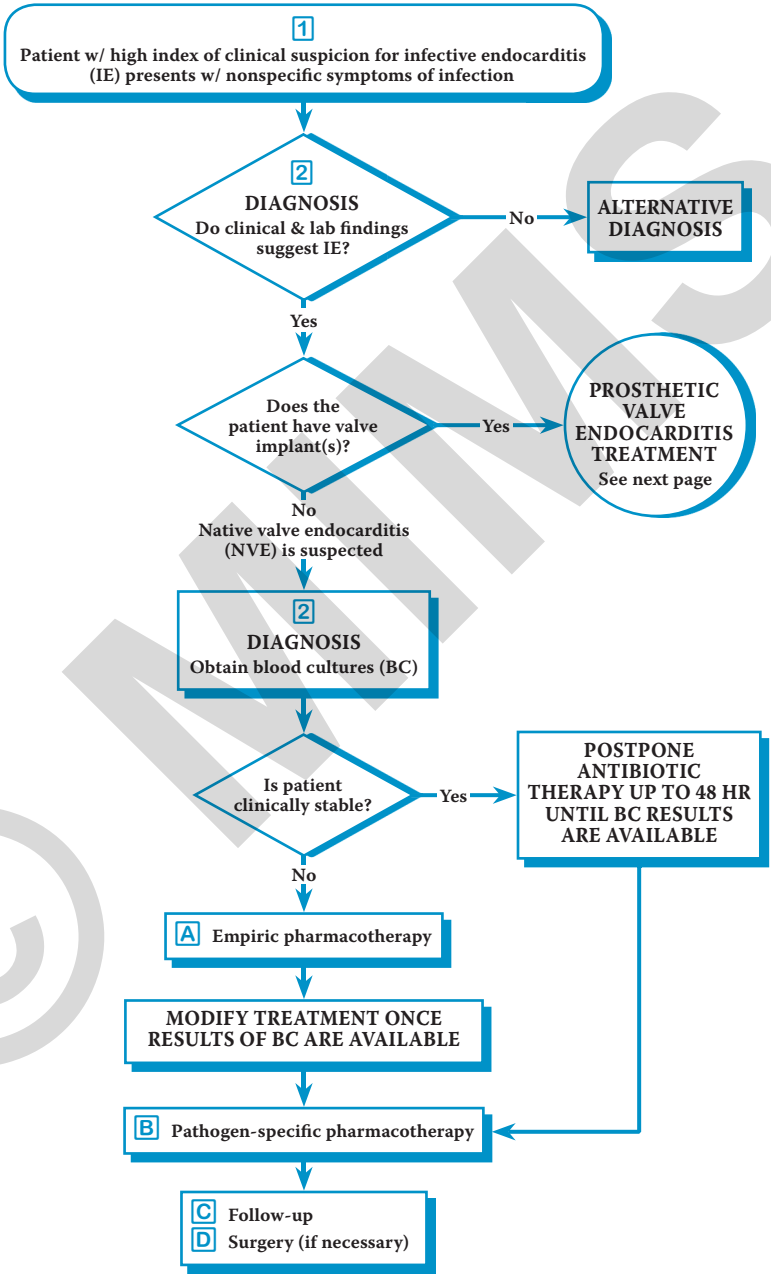
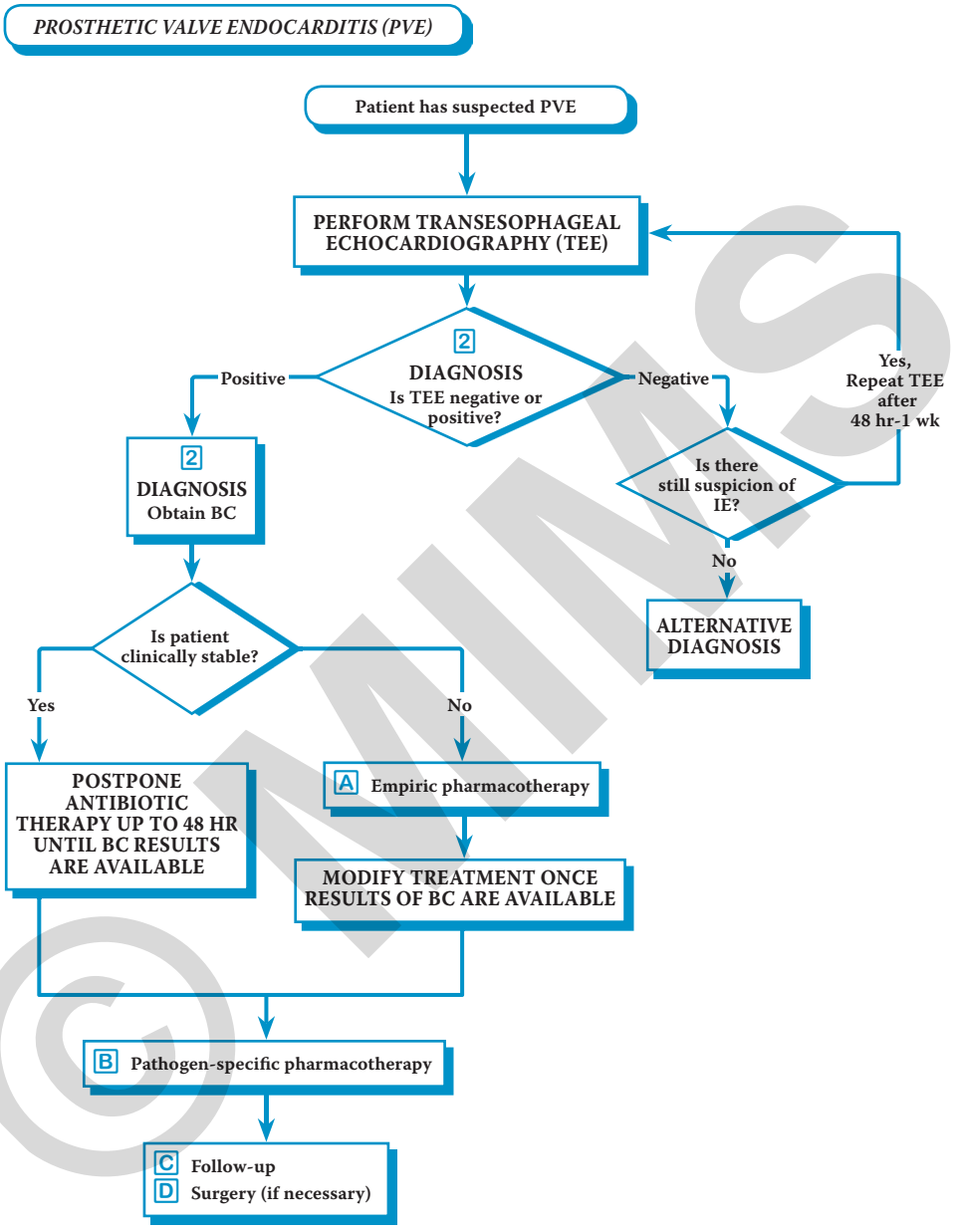
Infective Endocarditis (1 of 20)





1 CRITERIA FOR HIGH CLINICAL SUSPICION OF IE

- **Neonates:** Signs & symptoms are nonspecific; may include fever, thrombocytopenia, peripheral stigmata of blood-borne infection (ie peripheral abscesses-septic arthritis, petechiae, hepatosplenomegaly)
- **Children:** Fever, night sweats, malaise, anorexia, signs & symptoms of heart failure, changing or new cardiac murmur, cutaneous findings (eg Osler's nodes, Janeway lesions), splinter hemorrhages, Roth spots, embolic complications (eg cerebrovascular infarcts or hemorrhages, peripheral arterial embolism, pulmonary infarcts & abscess)

Cardiac Risk Factors for IE

- Use of central venous line
- Congenital heart disease (CHD)
  - **High risk**: Aortic regurgitation, aortic stenosis, coarctation of aorta, cyanotic CHD, patent ductus arteriosus, ventricular septal defect, mitral regurgitation, mitral stenosis w/ regurgitation
  - **Intermediate risk:** Asymmetrical septal hypertrophy, bicuspid aortic valve, mitral stenosis, tricuspid valve disease, pulmonary stenosis
- Previous cardiac surgery w/ or w/o grafts, patches, or prosthesis
- Transcatheter treatment of heart defects
- Post-radiofrequency ablation for arrhythmias

2 DIAGNOSIS

- **Infective endocarditis (IE)**: An infection of the endocardial surface of the heart including infections of the large thoracic vessels & intracardiac foreign bodies characterized by the presence of vegetation which is a nidus for microorganism invasion
- **Native valve endocarditis (NVE):** An endovascular microbial infection of native heart valves that may be local (cardiac) including valvular & perivalvular destruction or distal (noncardiac) due to detachment of septic vegetations w/ embolism,metastatic infection & septicemia. May also be broken down as acute & subacute; the only difference is that subacute endocarditis has a more indolent course than the acute form
- **Prosthetic valve endocarditis (PVE):** An endovascular microbial infection of prosthetic heart valves (intracardiac foreign body) & may be classified as an infection likely to have been acquired perioperatively & thus being nosocomial (early PVE) or likely to have been community-acquired (late PVE). Early PVE occurs w/in 60 days of valve implantation & late PVE occurs ≥60 days after valve implantation

Characteristics of IE

- Often presents in an occult fashion & early diagnosis depends on a high index of clinical suspicion esp in patients w/ congenital heart disease, prosthetic valves or previous IE
- Established diagnosis of IE is demonstrated by a positive blood culture & involvement of the endocardium detected during sepsis or systemic infection
  - IE may also be established if there is involvement of the endocardium detected during sepsis or systemic infection even if BC is negative

Clinical Presentation

Signs & Symptoms

- Moderate & remitting fever is the most common symptom
- Anorexia, wt loss, malaise & night sweats, fatigue, diaphoresis, chills, nausea, vomiting, arthralgia, myalgia
- Feeding difficulties, tachycardia, respiratory distress, & low blood pressure in neonates

Physical Exam

- Heart murmur consistent w/ valvular regurgitation
- Petechiae on the skin, conjunctivae or oral mucosa
- Osler's nodes: Red, painful, indurated lesions, 2-15 mm in diameter seen on the palms or soles & usually in the digital phalanges
- Janeway lesions: Non-tender, erythematous macules that appear on the palms or soles
- "Blue toe syndrome": Embolization of small vegetation fragments
- Roth's spots: Red, retinal hemorrhages w/ a pale center
- Splenomegaly
- Signs of CHF

Lab Tests

Blood Culture (BC)

- Most important laboratory test
- At least 3 BC should be taken at least 1 hr apart & from different venipunctures preferably at the time that body temperature is rising
  - May obtain 2-3 more BCs if no growth by 2nd incubation day
- It is recommended to postpone antimicrobial therapy until BC become positive, unless the patient is septic
- If antimicrobial therapy has been started, wait for at least 3 days after discontinuing short-term antibiotic treatment before taking BC
  - If patient was on long-term antibiotic treatment, positive BC may not appear until after 6-7 days post-therapy
- Identification of causative organism should be up to species level

2 DIAGNOSIS (CONT'D)

Lab Tests (Cont'd)

Other Lab Tests

- CBC w/ differential
  - Many patients have leukocytosis: 15,000-25,000/muL w/ a left shift
  - Anemia is common: Normocytic & normochromic w/ low serum Fe level & TIBC
- Serum electrolytes: Some patients may have elevated serum creatinine
- Urinalysis: May reveal microscopic hematuria, pyuria, RBC casts, bacteriuria, proteinuria
- ESR: Elevated in most cases
- C-reactive protein level: Elevated
- Rheumatoid factor: Elevated in approximately half of the presenting patients

Echocardiogram

- Diagnostic test of choice in detecting vegetations in cardiac valves

Three Echocardiographic Findings Considered to be Major Criteria in the Diagnosis of IE

1. Mobile, echodense mass attached to the valvular or the mural endocardium esp if present on the preferred locations, or attached to implanted prosthetic material w/ no alternative anatomical explanation
2. Demonstration of abscesses or fistulas
3. A new dehiscence of a valvular prosthesis esp when occurring late after implantation

Transthoracic echocardiography (TTE): 2-dimensional transthoracic echocardiography (2-D echo)

- Vegetation appears as a discrete mobile echogenic mass attached to the valvular surface downstream from a high to low pressure chamber
- Vegetations ≥2 mm may be visualized, the larger the size, the more likely a vegetation will be detected
- TTE detection rate is approximately 50% in patients w/ clinically suspected IE
- If the clinical suspicion of IE is low, the TTE is of good quality & the result is negative, endocarditis is unlikely

Transesophageal echocardiography (TEE)

- Has superior resolution, thus carries a greater sensitivity in detecting vegetations as compared w/ TTE although its utility in children is not well established
- If suspicion of IE is high (eg staphylococcal bacteremia), then TEE should be performed in all negative TTE cases
- TEE should be performed in all suspected PVE cases, in cases of aortic location & prior to cardiac surgery during active IE
- If TEE is negative but suspicion of IE remains, then repeat TEE after 48 hr-1 wk; this will allow potential vegetations to become more noticeable

Other Diagnostic Studies

ECG

- May be taken upon admission in patients w/ suspected acute IE
  - Evidence of low septal abscesses w/ involvement of the intraventricular conduction system is detected on ECG
  - Can be used to rule out conduction abnormalities & to establish baseline

Chest Radiograph

- May delineate the presence of CHF
- May show septic pulmonary emboli & infiltrates w/ cavitation that are associated w/ right-sided IE

CT Scan

- Obtain in any patient w/ neurologic signs & symptoms

Etiology

Bacterial

- *Staphylococcus* sp: Causes approximately 8-10% of NVE
  - *S aureus* (coagulase-positive staphylococci): Commonly cause PVE, IE in IV drug abusers (IVDA) & in patients w/ previously normal cardiac valves
  - IVDA often present w/ right-sided cardiac involvement
  - Non-IVDA usually present w/ left-sided cardiac involvement & have skin & soft tissue infections w/ underlying congenital abnormalities
  - *S epidermidis*, *S lugdunensis* (coagulase-negative staphylococci): Most common cause of PVE & has been known to cause NVE
  - Methicillin susceptible *S aureus* (MSSA): May cause right-sided endocarditis in IV drug users
  - Methicillin resistant *S aureus* (MRSA): Occurs particularly in PVE, right-sided endocarditis in IV drug users & nosocomial endocarditis
- *Streptococcus* sp (viridans group of streptococci; *S pneumoniae*; *S pyogenes*; Lancefield group B, C, G streptococci; *S bovis*, *S mitis*, *S mutans*, *S sanguis* & *Abiotrophia* sp): Most common cause of NVE
  - Group B streptococci: Most common β-hemolytic streptococci & cause the most virulent IE among streptococci which is characterized by a fulminant disease w/ large crumbling vegetations w/ the frequency of embolization related to size
  - Group G streptococci: Both native & prosthetic valves can be affected w/ left-sided involvement being more common
  - Viridans streptococci: Most common cause of NVE in patients w/ congenital heart disease or defects & in patients who are not IV drug users
  - *S bovis*: Also causes bacterial endocarditis

2 DIAGNOSIS (CONT'D)

MODIFIED DUKE CLINICAL CRITERIA FOR DIAGNOSIS OF IE

Definite IE

Pathologic Criteria

- Microorganisms demonstrated by culture or histologic exam of a vegetation, a vegetation that has embolized, or an intracardiac abscess; ***or***
- Pathological lesions: vegetation or intracardiac abscess are present & confirmed by histology showing active endocarditis

Clinical Criteria: Using specific definitions found below

- 2 major criteria; ***or***
- 1 major criterion + 3 minor criteria; ***or***
- 5 minor criteria

Possible IE

- Findings consistent w/ IE but lacks points to be considered as "definite" but not "rejected"

Rejected IE

- Firm alternate diagnosis for manifestations of endocarditis; ***or***
- Resolution of manifestations of endocarditis w/ antibiotic therapy for ≤4 days; **or**
- No pathological evidence of IE at surgery or autopsy, after antibiotic therapy for ≤4 days

DEFINITIONS OF TERMS USED IN THE DUKE CRITERIA FOR THE DIAGNOSIS OF IE

Major Criteria

1. Positive BC for IE

- Typical microorganism consistent w/ IE from ≥2 separate BC: Viridans streptococci, *Streptococcus bovis*, or HACEK group, community-acquired *Staphylococcus aureus* or enterococci, in the absence of a primary focus; or

b. Microorganisms consistent w/ IE from persistently positive BC defined as:

- ≥2 positive cultures of blood samples drawn >12 hr apart; ***or***
- All of 3 or a majority of ≥4 separate BC (regardless of time obtained)

3. Single positive BC for *Coxiella burnetii* or antiphase 1 IgG antibody titer >1:800

2. Evidence of endocardial involvement

a. Positive echocardiogram for IE [TEE recommended in patients w/ prosthetic valves, rated at least "possible IE" by clinical criteria, or complicated IE (paravalvular abscess); TTE as 1st test in other patients] defined as:

1. 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***
2. Abscess; ***or***
3. New partial dehiscence of prosthetic valve, ***or***

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

Minor Criteria

1. Predisposition: predisposing heart condition or IV drug use
2. Fever: Temp ≥38°C
3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, & Janeway lesions
4. Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots & rheumatoid factor
5. Microbiological evidence: Positive BC but does not meet a major criterion as noted above or serological evidence of active infection w/ organism consistent w/ IE

Modified from: Baltimore RS, Gewitz M, Baddour LM, et al. Infective endocarditis in childhood: 2015 update: a scientific statement from the American Heart Association. Circulation. 2015 Sep 15:8-9.

2 DIAGNOSIS (CONT'D)

Etiology (Cont'd)
- Enterococci
- Culture negative organisms: Common causative organisms of endocarditis producing negative BCs
  - HACEK (***H**aemophilus parainfluenzae, aphrophilus*, & *paraphrophilus*; ***A**ctinobacillus actinomycetemcomitans*; ***C**ardiobacterium hominis*, ***E**ikenella corrodens*; & ***K**ingella* sp): Can cause NVE & PVE
  - *Bartonella henselae*: Exposure to infected cats may predispose patient to IE
  - *Brucella*
  - *Chlamydia psittaci*: Exposure to infected birds may predispose patient to IE
  - *Coxiella burnetii*: Exposure to infected sheep, cattle & wild rabbits may predispose patient to IE
  - *Legionella*
    - Characterized by a febrile course that extends up to mth w/ cardiac signs of newly developed murmurs & extremely high anti-*Legionella* titers
  - *Mycobacterium*
  - *Pseudomonas aeruginosa*: Most commonly occur in IVDA & is an important pathogen in early PVE
    - Commonly involves the tricuspid valve & may present as subacute infection w/ septic pulmonary emboli & right-sided HF

Fungal
- An increasing cause of PVE: *Candida* sp, *Aspergillus* sp, *Nocardia* sp

Alternative Diagnosis
- Diagnose & treat patient appropriately for other disease states (eg atrial myxoma, SLE w/ marantic endocarditis, acute rheumatic fever & cardiac syndrome) presenting w/ similar signs & symptoms

A EMPIRIC PHARMACOTHERAPY

- In uncomplicated cases, antibiotics should be postponed up to 48 hr until results of initial BC are known
- Empiric antibiotic treatment should be initiated immediately after 3 BC have been taken in cases complicated by:
  - Sepsis, severe valvular dysfunction, conduction disturbances or embolic events
- Empiric therapy should include use of agents that are effective against streptococci, staphylococci & enterococci
  - Community-acquired NVE/late PVE: Ampicillin IV *plus* antistaphylococcal Penicillins IV *plus* Gentamicin IV/IM *or* Vancomycin IV *plus* Gentamicin IV/IM
  - Early PVE: Vancomycin IV *plus* Gentamicin IV/IM *plus* Rifampin IV/PO
- Subsequent changes in the antibiotic regimen should be based on the results of culture & sensitivity testing

Initial Antibiotic Regimen
- Combining an antistaphylococcal penicillin w/ an aminoglycoside covers against *S viridans*, *S aureus* & Gram negative organisms
- Vancomycin can be substituted for a semisynthetic penicillin if MRSA infection or Penicillin allergy is suspected

B PATHOGEN-SPECIFIC PHARMACOTHERAPY

General Therapeutic Principles
- Counting days of duration of therapy should start on the 1st day on which blood cultures become negative in cases in which initial BC were positive
- At least 2 sets of BCs should be obtained every 24-48 hr until blood stream infection is cleared
- Prolonged therapy of at least 4 wk or 6-8 wk is recommended
- For patients w/ NVE who undergo valve resection w/ prosthetic valve replacement, the post-op treatment should be the one recommended for PVE
  - If the resected tissue is culture positive then the entire course of therapy is recommended after valve resection
  - If the resected tissue is culture negative, then treatment should be given less the number of days of treatment administered for NVE before valve replacement
- Determination of the minimum inhibitory concentration (MIC) of an antibiotic may be used in choosing the best treatment against the causative agent especially against atypical organisms, agents resistant to 1st-line treatments, & uncontrolled bacteremia
- Bactericidal agents should be used rather than bacteriostatic antimicrobials based on reported high incidence of treatment failures & relapses w/ bacteriostatic agents
- If combination antimicrobial therapy is used, then the agents should be administered close together to improve synergistic killing effect

The therapeutic goal is to produce bactericidal levels of drugs at the infected site for a max period of time

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B PATHOGEN-SPECIFIC PHARMACOTHERAPY (CONT'D)

Streptococcal IE

Penicillin-Susceptible Viridans Group Streptococci (MIC ≤0.1 mcg/L)

- Ceftriaxone or Penicillin G
  - Both agents when used alone x 4 wk obtain high bacteriologic cure rates
  - 4 wk of monotherapy has the advantage of avoiding the potential ototoxic or nephrotoxic effects of Gentamicin
  - Ceftriaxone has the advantage of once-daily dosing
- (Ampicillin, Ceftriaxone or Penicillin) *plus* Gentamicin
  - When given in selected patients, gives similar cure rates to 4 wk of monotherapy
  - (Ampicillin, Ceftriaxone or Penicillin) x 6 wk *plus* Gentamicin x 2 wk is recommended for those w/ PVE
  - Should be used w/ caution in children especially those at increased risk for aminoglycoside-related adverse events
  - Once daily dosing of Gentamicin may be used

Relatively Resistant Viridans Group Streptococci (MIC >0.1 to 0.5 mcg/L)

- (Ampicillin, Ceftriaxone or Penicillin) x 4 wk *plus* Gentamicin x 2 wk should be given
- (Ampicillin, Ceftriaxone or Penicillin) *plus* Gentamicin x 6 wk is recommended for those w/ PVE

Highly Resistant Viridans Group Streptococci (MIC >0.5 mcg/L)

- Should be treated w/ regimens recommended for enterococcal endocarditis

Nutritionally variant Viridans Streptococci

- Should be treated w/ regimens recommended for enterococcal endocarditis

Special cases

- Vancomycin *plus* Gentamicin x 4 wk is recommended for those unable to tolerate β-lactam antibiotic agents
  - Given for 6 wk for those w/ PVE
- Patients w/ NVE caused by *S pneumoniae* may be given Penicillin w/ or w/o aminoglycosides

Enterococcal IE

- All enterococci causing IE should be tested for antimicrobial susceptibility to determine optimal therapy
  - *In vitro* susceptibility to Penicillin & Vancomycin along w/ high-level resistance to Gentamicin & Streptomycin should be tested
- Successful treatment requires the synergistic action of Penicillin, Ampicillin or Vancomycin w/ either Gentamicin or Streptomycin
- Multi-daily dosing should be used for the aminoglycosides
- Cephalosporins should not be used to treat enterococcal IE regardless of *in vitro* susceptibility

Ampicillin or Penicillin G + Aminoglycoside

- For enterococcal strains susceptible to Penicillin:
  - Bactericidal activity of Ampicillin is 2x that of Penicillin against *E faecalis*
  - Penicillin may be preferred because higher serum concentrations of Penicillin will compensate for the difference & because it is important to avoid Ampicillin rash during long-term treatment
  - Recommended treatment duration is 4-6 wk for NVE & prolonged to 6 wk for those w/ PVE

Enterococci w/ High-level Resistance to Gentamicin

- These enterococci are usually resistant to all other aminoglycosides except Streptomycin (test independently for Streptomycin sensitivity)

Glycopeptides (Vancomycin, Teicoplanin) + Aminoglycoside

- Should be reserved for patients allergic to Penicillin or in penicillin-resistant strains
- Glycopeptides need to be combined w/ aminoglycosides since they are not usually bactericidal against enterococci

Vancomycin Resistant Strains & Strains Resistant to Both Gentamicin & Streptomycin

- Consultation w/ microbiologist/infectious disease specialist is recommended

Staphylococcal IE

- Appropriate antibiotic therapy should be started promptly to improve overall prognosis
- *S aureus* in non-IVDA usually involves the left-sided cardiac valves
- Factor in determining antibiotic treatment is whether the organism is sensitive to Methicillin
- Gentamicin in the following regimens should be administered in multiple daily-dosing at 3 mg/kg/day

NVE-MSSA

- Antistaphylococcal Penicillin (Nafcillin or Oxacillin) w/ or w/o Gentamicin
  - Antistaphylococcal Penicillin is the treatment of choice
  - Adding Gentamicin for the 1st 3-5 days may protect the infected valve from further damage & may decrease the duration of bacteremia which may result in faster defervescence
- Antistaphylococcal penicillin + Fusidic Acid
  - This combination may be an option for Fusidic acid sensitive strains

B PATHOGEN-SPECIFIC PHARMACOTHERAPY (CONT'D)

Staphylococcal IE (Cont'd)

NVE-MSSA (Cont'd)

- Cephalosporin (1st Generation) w/ or w/o Gentamicin
  - May be used for the treatment of MSSA endocarditis when patient has non-anaphylactoid Penicillin allergy
- 4 wk therapy w/ antistaphylococcal penicillin or cephalosporin may be used for uncomplicated infection
  - Complicated IE eg abscess formation or septic metastatic complications should be treated x 6 wk
- Vancomycin + Gentamicin
  - Reserved for patients allergic to beta-lactams; there are recent reports of suboptimal outcomes w/ Vancomycin therapy for serious *S aureus* infections
  - Vancomycin + Gentamicin x 3-5 days in MSSA is associated w/ faster clearing of bacteremia

NVE-MRSA

- Vancomycin
  - Treatment of choice in MRSA
  - Most MRSA are also resistant to aminoglycosides therefore addition of Gentamicin is not likely to change the course of infection; if the strain is susceptible may use x 3-5 days
  - Rifampicin is not necessary in uncomplicated cases
- Linezolid or (Co-trimoxazole, Doxycycline or Minocycline w/ or w/o Rifampicin)
  - These agents may be an option in patients who are intolerant of Vancomycin or fail therapy
  - Data on clinical efficacy is limited compared to other agents

PVE-MSSA

- Antistaphylococcal Penicillin + Rifampicin + Gentamicin
  - *S aureus* IE in PVE patients has a high mortality rate & surgery should be combined w/ antimicrobial therapy
  - Though *in vitro* & clinical studies are lacking, it is accepted that this 3 drug combination is used to treat MSSA in PVE
  - Cefazolin may be substituted for those w/ non-anaphylactoid-type Penicillin allergy
- Vancomycin + Rifampicin + Gentamicin
  - Used for MRSA & coagulase negative staphylococci

IE Caused by HACEK

- HACEK group may not be identified in BC for a wk or longer & empiric antibiotics may be necessary while awaiting culture results
- β-lactamase producing strains of HACEK are appearing w/ increased frequency
  - Difficult to perform antimicrobial susceptibility tests on HACEK organisms therefore these should now be considered Ampicillin resistant & Ampicillin should not be used for treatment
- Ceftriaxone
  - Single agent use is justified by its excellent pharmacokinetic profile
  - Effective against both β-lactamase producing & non-β-lactamase producing strains of the HACEK group
  - May be administered alone x 4 wk in NVE & x 6 wk in PVE
  - Alternative: Another 3rd or 4th generation cephalosporin or Ampicillin *plus* Gentamicin

Other Causes of IE

- Treatment of these less common causes of IE are still not adequately defined
- May consider giving an extended-spectrum penicillin (Piperacillin/Tazobactam) or cephalosporin (Ceftazidime, Ceftriaxone, Cefotaxime) plus an aminoglycoside x ≥6 wk
  - There are limited data on the pediatric use of quinolones for IE

***Bartonella* sp**

- Most cases of *Bartonella* sp IE have required antibiotic therapy & valve replacement surgery for cure

***Brucella* sp**

- Few patients have been cured w/ antimicrobial agents alone; most require valve replacement in combination w/ antibiotics

Coxiella burnetii

- Clinical response only persists as long as antimicrobial therapy continues; eradication is unlikely & reinfection of prosthetic material occurs after surgical replacement of infected valves

Pseudomonas aeruginosa

- Most cases occur in IVDA & right-sided pseudomonal IE can usually be treated w/ antibiotic therapy w/ or w/o surgery
- Valve replacement is usually considered mandatory in left-sided pseudomonal IE since medical therapy is rarely effective alone

***Enterobacteriaceae* sp**

- Susceptibility of these organisms can be unpredictable therefore treatment should be based on susceptibility testing

Fungi

- Amphotericin B w/ or w/o Flucytosine remains the 1st-line therapy for fungal IE
- Surgery combined w/ antifungal agents is necessary for most patients

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B PATHOGEN-SPECIFIC PHARMACOTHERAPY (CONT'D)

RECOMMENDED ANTIMICROBIAL THERAPY

Choice of therapy will depend on results of culture & sensitivity, patient's allergy profile, patient status & CV risk factors. If possible, reserve Vancomycin for patients w/ severe Penicillin allergy.

Pathogen	NVE	PVE
Viridans group streptococci, *Streptococcus bovis* Penicillin-susceptible	Ceftriaxone IM/IV x 4 wk	Ceftriaxone IM/IV x 6 wk *w/ or w/o* Gentamicin IM/IV x 2 wk
	Penicillin G IV x 4 wk	
	Penicillin G IV or Ceftriaxone IM/IV x 2 wk *plus* Gentamicin IM/IV x 2 wk	Penicillin IV x 6 wk *w/ or w/o* Gentamicin IM/IV x 2 wk
	Vancomycin IV x 4 wk	Vancomycin IV x 6 wk
Viridans group streptococci, *Streptococcus bovis* Penicillin-relatively resistant (Pen MIC >0.1 but ≤0.5 mcg/L)	Ceftriaxone IM/IV x 4 wk *plus* Gentamicin IM/IV x 2 wk	Ceftriaxone IM/IV x 6 wk *plus* Gentamicin IM/IV x 6 wk
	Penicillin G IV x 4 wk *plus* Gentamicin IM/IV x 2 wk	Penicillin IV x 6 wk *plus* Gentamicin IM/IV x 6 wk
	Vancomycin IV x 4 wk	Vancomycin IV x 6 wk
Viridans group streptococci, *Streptococcus bovis* Penicillin-resistant (Pen MIC >0.5 mcg/L) or Enterococci strains susceptible to Vancomycin, Penicillin, Gentamicin	Ampicillin IV x 4-6 wk *plus* Gentamicin IM/IV x 4-6 wk	
	Amoxicillin IV x 4-6 *plus* Ceftriaxone IM/IV x 6 wk	
	Penicillin G IV x 4-6 wk *plus* Gentamicin IM/IV x 4-6 wk	
	Vancomycin IV x 6 wk *plus* Gentamicin IM/IV x 6 wk	
Enterococci strains susceptible to Penicillin, Streptomycin & Vancomycin but resistant to Gentamicin	Ampicillin IV x 4-6 wk *plus* Streptomycin IM/IV x 4-6 wk	
	Penicillin IV x 4-6 wk *plus* Streptomycin IM/IV x 4-6 wk	
	Vancomycin IV x 6 wk *plus* Streptomycin IM/IV x 6 wk	
Enterococci strains resistant to Penicillin & susceptible to aminoglycoside & Vancomycin	**Beta-lactamase - producing strain:** Ampicillin-Sulbactam IV x 6 wk *plus* Gentamicin IM/IV x 6 wk Vancomycin IV x 6 wk *plus* Gentamicin IM/IV x 6 wk	
	Intrinsic Penicillin resistance: Vancomycin IV x 6 wk *plus* Gentamicin IM/IV x 6 wk	
Enterococci strains resistant to Penicillin, aminoglycoside & Vancomycin	***E. faecium*:** Linezolid IV/PO x ≥8 wk Quinupristin-Dalfopristin IV x ≥8 wk	
	***E. faecalis*:** Imipenem/Cilastatin IV x ≥8 wk *plus* Ampicillin IV x ≥8 wk Ceftriaxone IM/IV x ≥8 wk *plus* Ampicillin IV x ≥8 wk	

B PATHOGEN-SPECIFIC PHARMACOTHERAPY (CONT'D)

RECOMMENDED ANTIMICROBIAL THERAPY (CONT'D)

Choice of therapy will depend on results of culture & sensitivity, patient's allergy profile, patient status & CV risk factors.

Pathogen	NVE	PVE
Methicillin-susceptible *S aureus* (MSSA)	Antistaphylococcal penicillin IV x 4-6 wk *w/ optional addition of* Gentamicin IM/IV x 3-5 days	Antistaphylococcal penicillin IV x ≥6 wk *plus* Rifampicin PO/IV x ≥6 wk *plus* Gentamicin IM/IV x 2 wk
	Antistaphylococcal penicillin IV x 4-6 wk *plus* Fusidic acid PO x 4-6 wk	
	For Penicillin-allergic patients: Cephalosporin (1st gen) IV x 6 wk *w/ optional addition of* Gentamicin IM/IV x 3-5 days	
	Co-trimoxazole IV X 1 wk plus PO x 5 wk *plus* Clindamycin IV x 1 wk	
	Vancomycin IV x 4-6 wk	
Methicillin-resistant *S aureus* (MRSA)	**1st-line agent:** Vancomycin IV x 4-6 wk	Vancomycin IV x ≥6 wk *plus* Rifampicin PO/IV x ≥6 wk *plus* Gentamicin IM/IV x 2 wk
	Vancomycin treatment failure/ intolerance may try the following: Daptomycin IV x 4-6 wk *or* Co-trimoxazole IV x 1 wk *plus* Clindamycin IV x 1 wk *or* Linezolid ***or*** Doxycycline or Minocycline w/ or w/o Rifampicin	
Fungi	Amphotericin B IV x 4-6 wk ***or*** Flucytosine PO x 4-6 wk	-
HACEK organisms	Ceftriaxone IM/IV x 4 wk or Cefotaxime IV x 4-6 wk *or* Ampicillin/Sulbactam IV x 4 wk *or* Gentamicin or Tobramycin IV x 4-6 wk *or* Amikacin IV x 4-6 wk	-

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B PATHOGEN-SPECIFIC PHARMACOTHERAPY (CONT'D)

RECOMMENDED ANTIMICROBIAL THERAPY (CONT'D)

Choice of therapy will depend on results of culture & sensitivity, patient's allergy profile, patient status & CV risk factors.

Pathogen	NVE	PVE
Culture negative endocarditis including *Bartonella* sp	Ampicillin/Sulbactam IV x 4-6 wk *plus* Gentamicin IM/IV x 4-6 wk	**Early, PVE (≤1 yr)** Vancomycin IV x 6 wk *plus* Gentamicin IM/IV x 2 wk *plus* Cefepime IV x 6 wk *plus* Rifampicin PO/IV x 6 wk
	Vancomycin IV x 4-6 wk *plus* Gentamicin IV/IM x 4-6 wk *plus* Ciprofloxacin[1] PO/IV x 4-6 wk	**Late, PVE (>1 yr)** Ampicillin/sulbactam IV x 4-6 wk *plus* Gentamicin IM/IV x 4-6 wk ***Or*** Vancomycin IV x 4-6 wk *plus* Gentamicin IV/IM x 4-6 wk *plus* Ciprofloxacin[1] PO/IV x 4-6 wk
		Suspected Bartonella negative culture Ceftriaxone IM/IV x 6 wk plus Gentamicin IM/IV x 2 wk *w/ or w/o* Doxycycline PO/IV x 6 wk
		Bartonella **confirmed** Doxycycline PO/IV x 6 wk *plus* Gentamicin[2] IM/IV x 2 wk
Pseudomonas aeruginosa	Treatment should be based on *in vitro* sensitivity studies Antipseudomonal beta-lactam x 6 wk *plus* Tobramycin x 6 wk	Treatment should be based on *in vitro* sensitivity studies Antipseudomonal beta-lactam *plus* Tobramycin
Enterobacteriaceae sp *(E coli, Klebsiella* sp, *Enterobacter* sp & *Serratia* sp)	Treatment should be based on *in vitro* sensitivity studies Beta-lactam at high doses x 4-6 wk *plus* Gentamicin x 4-6 wk	Treatment should be based on *in vitro* sensitivity studies Beta-lactam at high doses *plus* Gentamicin

[1]Ciprofloxacin is generally not recommended for patients <18 yr of age.
[2]May be replaced w/ Rifampin PO/IV if Gentamicin cannot be given

C FOLLOW-UP

- Daily exam including temp & periodic blood tests to monitor for signs of infection
  - Temp should normalize w/in 5-10 days w/ uncomplicated IE
- Continue to monitor for cardiac murmurs, BP, signs of HF & embolism in the CNS, lungs, spleen & skin
- Secondary infections in joint & spine may occur
- C-reactive protein (CRP) decreases rapidly during 1st or 2nd wk of therapy but may stay slightly elevated for 4-6 wk or longer
  - Persistently high CRP typically means an inadequately controlled infection
- Normalization of WBC should also occur w/in 1-2 wk
  - Persistently elevated WBC indicates active infection
- Monitor renal function

D SURGERY

Principles of Surgical Treatment

- Combined medical & surgical therapy for IE can decrease mortality among patients who have CHF, perivalvular invasive disease, or uncontrolled infection despite maximal antimicrobial therapy
- The decision to perform surgery & its timing is dependent upon the cardiac & systemic complications caused by the infection, the microorganism's virulence & the response to antimicrobial therapy
  - The optimal time to perform surgery is before severe hemodynamic disability or spread of the infection to perivalvular tissue occurs
- CHF is the strongest indication for surgery in IE
- The main objectives in performing surgery in IE patients are:
  - To remove infected cardiac tissues
  - To replace or repair damaged tissues

Surgery should be considered in the following:

- NVE patients w/ acute aortic or mitral regurgitation w/:
  - Refractory pulmonary edema/cardiogenic shock secondary to severe acute regurgitation/valve obstruction or cardiac chamber/pericardial fistula
  - Severe regurgitation but w/o CHF
  - Severe acute regurgitation/valve obstruction & CHF w/ diagnostic signs of hemodynamic compromise
- Evidence of perivalvular extension (valvular dehiscence/rupture/fistula, new obstructions, large/extensive abscess despite antibiotic therapy)
- Persistent infection after 7-10 days of adequate antimicrobial therapy
- Infection w/ microorganisms that have poor response to antibiotic therapy (eg fungi, *Brucella* sp, *Coxiella* sp, *Staphylococcus lugdunensis*, *Enterococcus* sp w/ high-level resistance to Gentamicin, gram-negative organisms)
- NVE patients w/ large mobile vegetation >10 mm, ≥1 embolic episode during the 1st 2 wk of antibiotic therapy, or ≥2 embolic episode during or after antimicrobial therapy
- NVE patients w/ highly large vegetations >15 mm
- Vegetations increasing in size or recurrent emboli despite adequate antibiotic therapy
- Obstructive vegetations
- Early PVE
- PVE caused by *S aureus*
- Relapsing PVE after prolonged medical therapy
- Hemodynamically significant prosthetic valve

Emergency surgery (w/in 24 hr) is recommended for the following:

- NVE patients w/ refractory pulmonary edema/cardiogenic shock secondary to severe acute regurgitation/valve obstruction
- NVE patients w/ cardiac chamber/pericardial fistula causing refractory pulmonary edema/cardiogenic shock

PREVENTION

- Antibiotic prophylaxis for the 1st 6 mth post-dental procedure is recommended
  - Mainly targets oral *Streptococci* growth
- Recommended regimens 30-60 min prior to dental procedure:
  - Amoxicillin or Ampicillin 50 mg/kg PO/IV single dose
  - Clindamycin 20 mg/kg PO/IV single dose (for those w/ Penicillin/Ampicillin allergy)
- Antibiotic prophylaxis should be started immediately prior to cardiac surgery

Recommendations for antibiotic prophylaxis: (adapted from the 2015 European Society of Cardiology guidelines for the prevention, diagnosis & treatment of IE)

- Patients at highest risk for IE:
  - Patients w/ a prosthetic valve/material post-cardiac valve repair
  - Patients w/ previous IE
  - Patients w/ CHD
    - Cyanotic CHD, w/o surgical repair, or w/ residual defects, palliative shunts or conduits
    - CHD w/ complete repair w/ prosthetic material whether placed by surgery or by percutaneous technique >6 mth post-op
    - Post-operative residual defect at the prosthesis implantation site (after cardiac surgery or percutaneous technique)
- Dental procedures requiring gingival or periapical teeth region manipulation or any procedures involving oral mucosa perforation
- Not recommended for the following procedures:
  - Dental procedures w/ local anesthetic application in non-infected tissue, suture removal, braces/orthodontic appliance manipulation, dental X-rays, deciduous teeth eruption, mouth trauma
  - Respiratory tract procedures (eg bronchoscopy, laryngoscopy, endotracheal intubation)
  - Gastrointestinal procedures (eg gastroscopy, colonoscopy, cystoscopy, transesophageal echocardiography)
  - Any dermatological or musculoskeletal procedures

Dosage Guidelines

AMINOGLYCOSIDES

Drug	Dosage	Remarks
Gentamicin	3-7.5 mg/kg/day IM/IV divided 8 hrly **Max dose:** 240 mg/day	**Adverse Reactions** • Ototoxic effects (can cause irreversible ototoxicity resulting in hearing loss, dizziness, vertigo); Renal effects (reversible nephrotoxicity, acute renal failure has been reported usually when other nephrotoxic drugs have also been administered); Neuromuscular effects (neuromuscular blockade resulting in resp depression & muscular paralysis); Hypersensitivity reactions **Special Instructions** • Ototoxicity & nephrotoxicity are most likely in dehydrated patients, those w/ renal impairment, in patients who are receiving high doses or for long periods or who are also receiving or have received other ototoxic/nephrotoxic drugs - Consider monitoring of serum concentrations &/or peak serum concentrations/MIC ratio in these patients • Use w/ caution in patients w/ conditions associated w/ muscle weakness (eg myasthenia gravis), patients w/ pre-existing renal dysfunction, vestibular or cochlear impairment
Netilmicin	**<1 wk:** 6 mg/kg/day IV divided 12 hrly **>1 wk:** 7.5-9 mg/kg/day IV divided 8 hrly **Older childn:** 6-7.5 mg/kg/day IV divided 8 hrly ***or*** **Neonates <6 wk:** 4-6.5 mg/kg/day IV divided 12 hrly **Older infants & childn:** 5.5-8 mg/kg/day IV divided 8-12 hrly	
Streptomycin	20-30 mg/kg/day IM/IV divided 12 hrly	
Tobramycin	6-7.5 mg/kg/day IM/IV divided 6-8 hrly	

ANTIBACTERIAL COMBINATION

Drug	Dosage	Remarks
Co-trimoxazole [Sulfamethoxazole (SMZ) & Trimethoprim (TM)]	8-12 mg/kg/day PO divided 12 hrly based on TM ***Or*** 8-12 mg/kg/day IV divided 6 hrly based on TM	**Adverse Reactions** • GI effects (N/V, anorexia, diarrhea, rarely antibiotic- associated diarrhea/colitis, glossitis); Dermatologic effects (rash, pruritus, photosensitivity); Hypersensitivity reactions (rash, Stevens-Johnson syndrome); Hematologic effects (more common if given for long periods or w/ high doses); Hepatic effects; Renal effects; Other effects (crystallization in the urine, aseptic meningitis) **Special Instructions** • Maintain adequate fluid intake • Contraindicated in patients allergic to sulfonamides • Use w/ extreme caution or not at all in patients w/ hematological disorders esp megaloblastic anemia due to folic acid deficiency • Use w/ caution in patients w/ renal impairment or severe hepatic dysfunction & w/ caution in patients w/ folate deficiency (may consider administration of folinic acid)

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Dosage Guidelines

ANTIFUNGAL		
Drug	**Dosage**	**Remarks**
Amphotericin B	**Initial dose:** 15 mg/kg via 60 min IV infusion **Maintenance dose:** **≤7 days:** 10 mg/kg via 60 min IV infusion 12 hrly **8-30 days:** 10 mg/kg via 60 min IV infusion 8 hrly **>30 days:** 10 mg/kg via 60 min IV infusion 6 hrly	**Adverse Reactions** • GI effects (N/V, anorexia, wt loss, epigastric pain, dyspepsia, diarrhea); Renal effects (nephrotoxicity, hypokalemia, azotemia, increased serum creatinine, hyposthenuria, renal tubular acidosis, nephrocalcinosis); Other effects (fever, chills, headache, malaise, generalized muscle & joint pain, inj site pain, anemia) • Rarely CV toxicity, hematologic reactions, neurologic reactions, liver failure **Special Instructions** • Avoid rapid IV infusion • Monitor renal & hepatic function, serum electrolytes & blood counts

ANTIMALARIALS		
Drug	**Dosage**	**Remarks**
Hydroxychloroquine	**Administered w/ Doxycycline for Q-fever:** 6.5 mg/kg/day PO in divided doses	**Adverse Reactions** • Headache, skin eruptions, pruritus & GI effects (N/V, diarrhea); Rarely mental changes • Serious adverse effects: Visual disturbances (eg keratopathy which is reversible & retinopathy that may be irreversible) **Special Instructions** • Use w/ caution in patients w/ liver or renal dysfunction, those w/ severe GI disorders, psoriasis, myasthenia gravis, G6PD deficiency & neurologic disorder esp epilepsy

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Dosage Guidelines

CEPHALOSPORINS

Drug	Dosage	Remarks
First Generation		
Cefazolin	25-100 mg/kg/day IM/IV divided 6-8 hrly	**Adverse Reactions** • Hypersensitivity reactions (urticaria, pruritus, rash, severe reactions eg anaphylaxis can occur); GI effects (diarrhea, N/V, rarely antibiotic-associated diarrhea/colitis); Other effects (Candidal infections, inj site inflammation) • High doses may be associated w/ CNS effects (encephalopathy, convulsions); Rarely hematologic, hepatic & renal effects have occurred • Prolonged prothrombin time (PT), prolonged activated partial thromboplastin time (APTT), &/or hypoprothrombinemia (w/ or w/o bleeding) have been reported & occurs most frequently w/ N-methylthiotetrazole (NMTT) side chain containing cephalosporins **Special Instructions** • May be taken w/ food to decrease gastric distress • Ceftriaxone is contraindicated in hyperbilirubinemic neonates • Avoid simultaneous administration of Ceftriaxone w/ IV Ca-containing soln • Use suspension containing sodium benzoate w/ caution in neonates as this has been associated w/ gasping syndrome • Use w/ caution in patients allergic to Penicillin, there may be 10% chance of cross sensitivity; & patients w/ renal impairment & GI disease esp w/ history of colitis
Second Generation		
Cefoxitin	**≥3 mth:** 80-160 mg/kg/day IM/IV divided 4-6 hrly **Max dose:** 12 g/day	
Third Generation		
Cefotaxime	**0-1 wk:** 50 mg/kg IV 12 hrly **>1-4 wk:** 50 mg/kg IV 8 hrly **1 mth-12 yr; <50 kg:** 510-180 mg/kg IM/IV divided 4-6 hrly	
Ceftazidime	**<40 kg:** 150 mg/kg/day IM/IV divided 8 hrly **Max dose:** 6 g/day	
Ceftizoxime	**≥6 mth:** 50 mg/kg IM/IV 6-8 hrly	
Ceftriaxone	50-75 mg/kg/day IM/IV single dose or divided 12 hrly **Max dose:** 2 g/day **PVE Viridans Group *Streptococci* & *S bovis*; IE caused by HACEK; Suspected *Bartonella* sp culture negative:** 100 mg/kg IM/IV 24 hrly **Enterococcal IE Resistant to Penicillin, aminoglycosides & Vancomycin:** 100 mg/kg/day IM/IV divided 12 hrly **Max dose:** 4 g/day	
Fourth Generation		
Cefepime	30-150 mg/kg/day IM/IV divided 8-12 hrly	
Cefoperazone	50-200 mg/kg/day IM/IV divided 12 hrly **Max dose:** 400 mg/kg/day	

OTHER ANTIBIOTICS

Drug	Dosage	Remarks
Fusidate		
Fusidic acid (Na fusidate)	20 mg/kg/day slow IV divided 8 hrly ***or*** **<1 yr:** 15 mg/kg PO 8 hrly **1-5 yr:** 250 mg PO 8 hrly **5-12 yr:** 500 mg PO 8 hrly	**Adverse Reactions** • GI effects (mild GI upset); Hepatic effects (jaundice & changes in liver function which returns to normal once drug is discontinued) **Special Instructions** • Use w/ caution in patients w/ liver dysfunction & monitoring of hepatic function in these patients is recommended if on high or prolonged doses

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Dosage Guidelines

OTHER ANTIBIOTICS (CONT'D)		
Drug	**Dosage**	**Remarks**
Glycopeptides		
Teicoplanin	**Neonates:** **Initial dose:** 16 mg/kg IV on the 1st day **Maintenance dose:** 8 mg/kg/day IV infusion **Childn:** 10 mg/kg IV 12 hrly x 3 doses followed by 6-10 mg/kg IM/IV 24 hrly	**Adverse Reactions** • Fever, chills, skin rash, pruritus, occasionally anaphylaxis or bronchospasm have been reported; generally better tolerated than Vancomycin • Other hypersensitivity reactions can occur (eg Stevens Johnson syndrome); GI effects (GI disturbances); CNS effects (dizziness, headache); Hematologic effects; Hepatic effects; Renal effects (renal impairment, but less often than w/ Vancomycin); Ototoxic effects have occurred but less frequently than w/ Vancomycin **Special Instructions** • Use w/ caution in patients w/ pre-existing renal dysfunction & monitor renal & auditory function if on prolonged therapy • Periodic monitoring of CBC & LFTs are advised
Vancomycin	40 mg/kg/day IV divided 6-12 hrly **Max dose:** 2 g/day	**Adverse Reactions** • "Red neck syndrome" which is usually related to too rapid infusion: Flushing, erythema, rash over face & upper torso, sometimes hypotension & shock-like symptoms also occur • Hypersensitivity reactions (can range from mild to severe eg anaphylactoid reactions, Stevens Johnson syndrome); Hematologic effects; Renal effects (nephrotoxicity may occur esp at high doses or in patients w/ predisposing factors); Ototoxic effects (ototoxicity which is more likely w/ high plasma concentrations or in renal impairment, may be irreversible, tinnitus may precede hearing loss & can be used as a sign to discontinue treatment) **Special Instructions** • Avoid in patients w/ a history of impaired hearing • Use w/ caution in patients w/ impaired renal function • Monitoring of serum concentrations may be done to help avoid renal & otic toxicity, monitoring of CBC & renal function during treatment is suggested along w/ monitoring of auditory function
Lincosamide		
Clindamycin	**<1 mth:** 15-20 mg/kg/day IM/IV divided 6-8 hrly **>1 mth:** 20-40 mg/kg/day IM/IV divided 6-8 hrly	**Adverse Reactions** • GI effects (diarrhea, severe antibiotic-related pseudomembranous colitis, N/V, abdominal pain, metallic taste); Hypersensitivity reactions (rash, urticaria, rarely anaphylaxis); Severe dermatologic effects have occurred (erythema multiforme, exfoliative & vesiculobullous dermatitis); cardiac, hematologic & hepatic effects have occurred; Other effect (polyarthritis) **Special Instructions** • Use w/ caution in patients w/ GI disease esp w/ history of colitis, in atopic patients & in patients w/ renal or hepatic impairment • Discontinue if diarrhea occurs

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Dosage Guidelines

OTHER ANTIBIOTICS (CONT'D)		
Drug	**Dosage**	**Remarks**
Oxazolidinone		
Linezolid	30 mg/kg/day PO/ IV divided 8 hrly	**Adverse Reactions** • GI effects (diarrhea, N/V, metallic taste, constipation, antibiotic associated diarrhea/colitis can occur); CNS effects (headache, insomnia, dizziness); Hepatic effects (abnormal LFT); Hematologic effects (reversible myelosuppression including leucopenia, anemia, pancytopenia, thrombocytopenia have occurred); Other effect (moniliasis infection) **Special Instructions** • Use w/ caution in patients w/ pre-existing myelosuppression & in patients w/ severe renal dysfunction • Recommend monitoring of blood counts wkly
Rifamycin		
Rifampicin	20 mg/kg/day PO/ IV divided 8-12 hrly **Max dose**: 900 mg/day	**Adverse Reactions** • Generally well tolerated; GI effects (N/V, anorexia, diarrhea, GI distress, antibiotic associated diarrhea/colitis has occurred); Discoloration of urine & body fluids • Rarely hepatic effects (transient abnormalities in liver function, hepatitis rarely occurs); Hematologic effects have occurred; Renal effects have been reported w/ intermittent therapy; CNS effects can occur (headache, drowsiness, ataxia, etc) **Special Instructions** • Rifampicin accelerates the metabolism of drugs metabolized by the CYP450 • Use w/ caution in patients w/ pre-existing liver dysfunction, monitor liver function during therapy in these patients
Streptogramin		
Quinupristin/ Dalfopristin	22.5 mg/kg/day IV divided 8 hrly	**Adverse Reactions** • GI effects (N/V, diarrhea, antibiotic-associated diarrhea/ colitis); CNS effect (headache); Hypersensitivity reactions (pruritus, rash, rarely anaphylaxis); Hematologic effects (anemia, eosinophilia, leukopenia, neutropenia); Musculoskeletal effects (myalgia, arthralgia have occurred & may improve w/ decreasing dose frequency); Hepatic effects have occurred **Special Instructions** • Contraindicated in severe hepatic impairment • Use w/ caution in patients w/ hepatic dysfunction • May cause prolongation of QT interval, use w/ caution in patients w/ cardiac arrhythmia

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Dosage Guidelines

OTHER BETA-LACTAM		
Drug	**Dosage**	**Remarks**
Imipenem/Cilastatin	60-100 mg/kg/day IV divided 6 hrly **Max dose:** 2 g/day	**Adverse Reactions** • GI effects (diarrhea, N/V, antibiotic-associated diarrhea/colitis, tongue/tooth discoloration, altered taste); Hypersensitivity reactions (rash, anaphylaxis); Other effects (Candidal infections) • CNS effects (mental disturbances, confusion, seizures & convulsions esp in patients w/ a history of CNS lesions &/or renal dysfunction); Rarely severe dermatologic reactions (eg exfoliative dermatitis, Stevens-Johnson syndrome, etc); Rarely hepatic effects **Special Instructions** • Use w/ caution in patients allergic to penicillins, cephalosporins or other beta-lactams, patients w/ renal impairment • Use w/ caution in patients w/ CNS disorders (eg epilepsy)

PENICILLINS		
Drug	**Dosage**	**Remarks**
Benzylpenicillin (Penicillin G, Penicillin G Na, Penicillin G K)	**Penicillin-susceptible *Streptococci* (Pen MIC ≤0.1 mcg/L):** 200,000 IU//kg/day IV in 4-6 divided doses **Penicillin-relatively resistant *Streptococci* (Pen MIC >0.1 mg/L & <0.5 mcg/L):** 300,000 IU//kg/day IV in 4-6 divided doses **Enterococci strains susceptible to Penicillin, Gentamicin & Vancomycin:** 300,000 IU/kg/day IV in 4-6 divided doses **Max dose:** 18,000,000 IU/day	**Adverse Reactions** • Hypersensitivity reactions (rash, urticaria, pruritus, severe reactions eg anaphylaxis can occur); GI effects (diarrhea, N/V, rarely antibiotic-associated diarrhea/colitis); Other effect (Candidal infections) • Rarely hematologic, renal & hepatic effects; High doses may be associated w/ CNS effects (encephalopathy, convulsions) **Special Instructions** • Avoid in patients w/ Penicillin allergy • Use w/ caution in patients w/ renal impairment
Aminopenicillins w/ or w/o Beta-lactamase Inhibitor		
Amoxicillin (Amoxycillin)	**<40 kg:** 40-90 mg/kg/day IM/slow IV divided 8-12 hrly **Max dose:** 3 g/day **Oral prophylaxis:** 50 mg/kg PO single dose To be taken 1 hr before procedure	
Ampicillin	100-400 mg/kg/day IM/IV in 4-6 divided doses **Max dose:** 12 g/day	
Ampicillin/Sulbactam (Sultamicillin: Pro-drug of Ampicillin/Sulbactam)	300 mg/kg/day IM/IV in 4-6 divided doses **Max dose:** 4 g sulbactam/day	

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Dosage Guidelines

PENICILLINS (CONT'D)

Drug	Dosage	Remarks
Antistaphylococcal Penicillins		
Cloxacillin	**<7 days & <2 kg:** 25 mg/kg/day PO/IV divided 12 hrly **7-28 days & <2 kg or ≤7 days & ≥2 kg:** 25 mg/kg/day PO/IV divided 8 hrly **7-28 days & ≥2 kg:** 25 mg/kg/day PO/IV divided 6 hrly **≥1 mth & <20 kg:** 50-100 mg/kg/day PO/IV divided 6 hrly **Max dose:** 4 g/day For severe infection, up to 200 mg/kg/day PO/IV in divided doses **Max dose:** 12 g/day	**Adverse Reactions** • Hypersensitivity reactions (rash, urticaria, pruritus, severe reactions eg anaphylaxis can occur); GI effects (diarrhea, N/V, rarely antibiotic-associated diarrhea/colitis); Other effect (Candidal infections) • Rarely hematologic, renal & hepatic effects; High doses may be associated w/ CNS effects (encephalopathy, convulsions) **Special Instructions** • Avoid in patients w/ Penicillin allergy • Use w/ caution in patients w/ renal impairment • Cloxacillin to be taken 1 hr before or 2 hr after meals
Nafcillin	150-200 mg/kg/day IV divided 4-6 hrly	
Oxacillin	150-200 mg/kg/day IV divided 4-6 hrly	

TETRACYCLINE

Drug	Dosage	Remarks
Doxycycline	2-4 mg/kg/day PO/IV divided 12 hrly	**Adverse Reactions** • GI effects (N/V, diarrhea, antibiotic-associated diarrhea/colitis has occurred, dysphagia, esophageal ulceration has occurred when taken w/ an insufficient amount of liqd); Dermatologic effects (photosensitivity); Other effects (Candidal infections, discoloration of teeth, interference w/ skeletal development & bone growth, photosensitivity) • Rarely renal dysfunction, hepatotoxicity, hematologic effects, intracranial pressure w/ headache & visual disturbances; hypersensitivity reactions have occurred **Special Instructions** • Avoid prolonged exposure to sunlight or tanning beds - Take w/ plenty of fluid while sitting or standing & before retiring to bed • Avoid in patients ≤8 yr; avoid in patients w/ SLE • Use w/ caution in renal or hepatic impairment

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