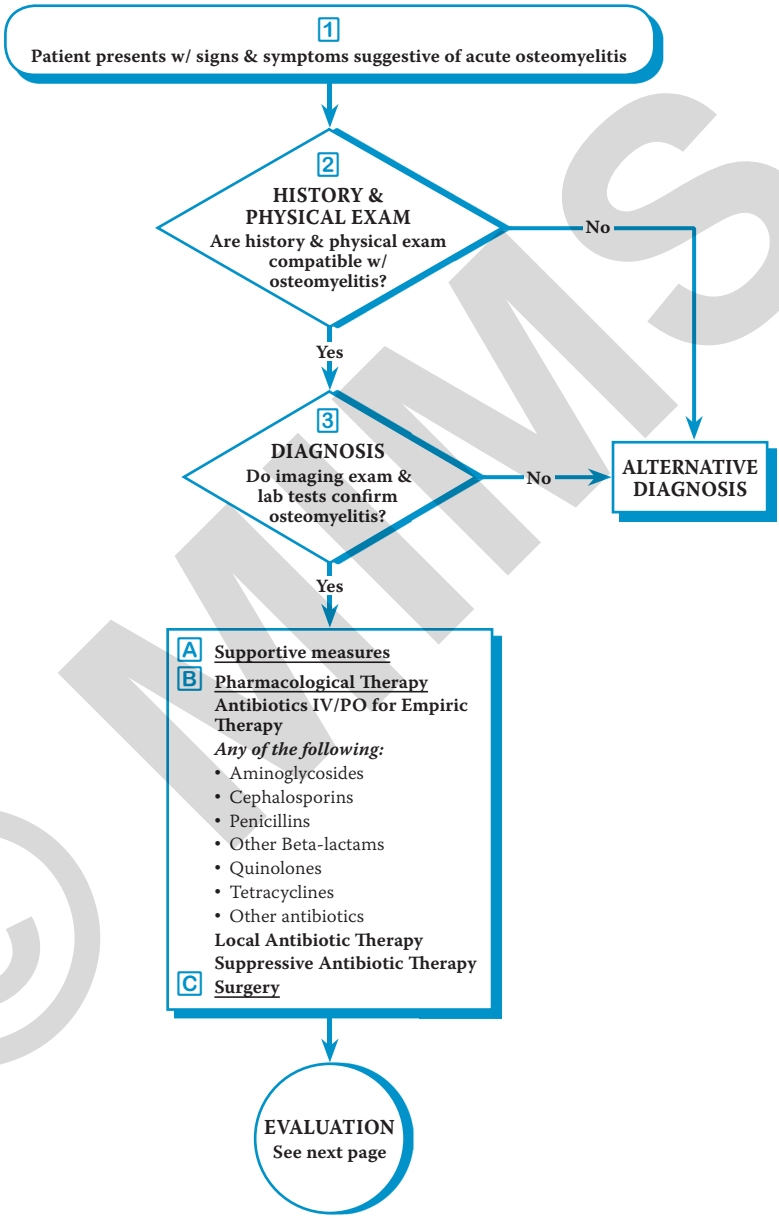
Osteomyelitis (1 of 15)



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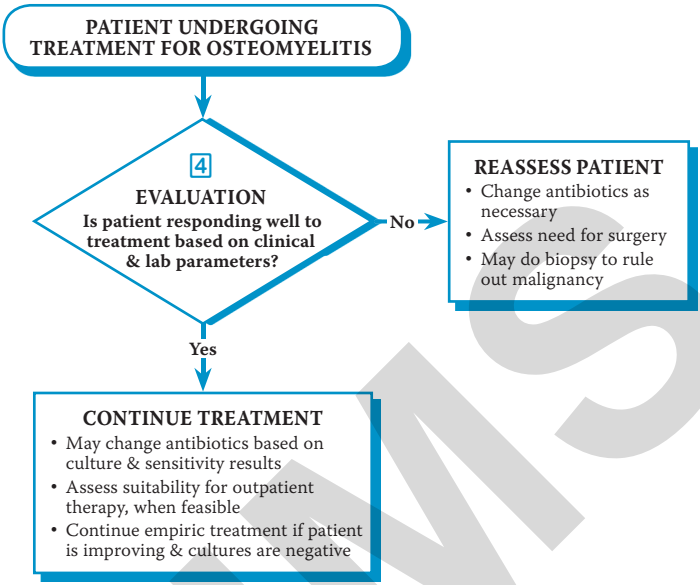

1 CLINICAL PRESENTATION

- Osteomyelitis is an acute or chronic inflammation of the bone due to an infection resulting from hematogenous spread, contiguous spread from soft tissues & joints to bone, or direct inoculation into bone from surgery or trauma
  - Infection is generally due to a single microorganism but polymicrobial infections may also occur
  - *Staphylococcus aureus* is the most common cause of acute or chronic hematogenous osteomyelitis in children & adults

Signs & Symptoms

- Fever
- Inflammatory findings of erythema, warmth, pain, & swelling over the involved area
- Draining sinus tracts over affected bone
- Limited movement of affected extremity
- Pain in the chest, back, abdomen or leg, & tenderness over involved vertebrae in patients w/ vertebral osteomyelitis
- Anorexia, vomiting, malaise

Risk Factors

- Chronic wounds w/ exposed bone, tissue necrosis, underlying open fractures or underlying internal fixation
- Advanced age
- Diabetes mellitus (DM)
- Immunosuppression
- IV drug abuse
- Organ transplantation
- Malnutrition
- Cancer
- Renal or hepatic impairment
- Chronic hypoxia
- Peripheral vascular disease
- Radiation fibrosis
- Neuropathy
- Tobacco consumption ≥2 packs/day

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2 HISTORY & PHYSICAL EXAM

History: Elicit predisposing factors (eg vasculopathy, DM, invasive procedures, etc)

Physical Exam Findings

- Warmth, erythema & tenderness over the involved part
  - Tenderness disproportionate to soft tissue findings favors osteomyelitis over soft tissue infection
- Tissue ulceration & draining sinus tracts over the affected bone
- Exposed bone on ulcer bed or a probe used to examine an ulcer encounters bone
- Signs of septicemia

Classification of Osteomyelitis in Children

Acute Hematogenous Osteomyelitis (AHO)

- Bone infection before formation of sequestra (dead bone)
- Primary AHO occurs mainly in infants & children
  - Most patients w/ AHO present w/ symptoms lasting <2 wk
- Long bones are most frequently involved, w/ most infections in children localizing in the metaphysis
  - Most frequently affected sites are the distal femur & proximal tibia, followed by the distal humerus, distal radius, proximal femur & proximal humerus
- Multiple bone involvement is common in infants
- Abscess formation & extension of infection into surrounding soft tissue may occur
- Infection in infants tends to be more diffuse because anatomic barriers are not able to efficiently limit infection
- Vertebral osteomyelitis is uncommon in children & often presents as an indolent infection w/ nonspecific symptoms eg septicemia
  - Often involves infection of the endplates of 2 adjacent vertebrae
- In patients w/ pelvic osteomyelitis, the ilium & ischium are most often involved & usually presents as gait abnormality or hip pain

Contiguous Nonhematogenous Osteomyelitis

- Associated w/ open fractures requiring surgical reduction, orthopedic devices, decubitus & neuropathic ulcers, human & animal bites, puncture wounds esp of the foot or knee
- Presents as an indolent condition often w/o fever & w/ continuous drainage or ulceration over the affected bone
- Has a high rate of recurrence

Classification of Osteomyelitis in Adults

AHO

- Adults usually present in a chronic manner, w/ pain & minimal constitutional symptoms lasting several mth
- Infections usually start in the diaphysis
- Secondary hematogenous osteomyelitis is more common in adults & is usually a reactivation of a childhood infection
- Vertebral osteomyelitis is predominantly a disease of adults, w/ incidence increasing w/ age
  - Condition slowly progresses over wk to mth
  - The lumbar & thoracic spine are most commonly affected
  - Infection may spread from skin & soft tissue, respiratory & genitourinary tract, infected IV sites, endocarditis

Contiguous Nonhematogenous Osteomyelitis

- Associated w/ fractures needing surgical reduction & internal fixation, open fractures, prosthetic devices, soft tissue infections, trauma
- Patients w/ DM are susceptible to osteomyelitis because of impairment of tissue perfusion that is a result of vascular insufficiency
  - Neuropathy & diminished neutrophil function also contribute to the risk
  - Predisposing events include perforating foot ulcers, an ingrown toenail, cellulitis or deep space infection
  - Diabetic patients often develop osteomyelitis even before bone is exposed
    - Positive palpation of bone in probing an infected foot ulcer confirms osteomyelitis

Chronic Osteomyelitis

- Bone infection after sequestra formation
- Diagnosed in patients w/ a history of osteomyelitis w/ recurrence of symptoms ie pain, swelling, erythema, low-grade fever; a sinus tract is pathognomonic
- Pathologic features include presence of necrotic bone, exposed bone, chronic wound over a fracture or surgical hardware, formation of new bone (involucrum) & exudation of polymorphonuclear leukocytes w/ lymphocytes, histiocytes, plasma cells
- An abscess or soft tissue infection may be found, esp if a sinus tract becomes obstructed
- Hematogenous & contiguous-focus osteomyelitis may become chronic

Alternative Diagnoses

- Soft tissue infection
- Osteonecrosis (avascular necrosis of bone) & Charcot arthropathy
- Fracture, gout & bursitis
- Bone infarction esp in patients w/ blood disorders eg hemoglobinopathy
- Bone malignancy

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3 DIAGNOSIS

Imaging exams

Plain X-rays
- First imaging procedure in the work up of patients w/ possible osteomyelitis
- Useful for excluding other diseases & can provide clues for other conditions that may be present
- Positive x-rays are fairly specific for osteomyelitis (75-83%), but negative x-rays cannot be used to rule out the disease
- Bone demineralization by 30-75% needs to occur before a change on plain x-ray is seen; therefore, it takes 10 to 21 days for a bone lesion to become apparent
- In children, early changes may be seen w/in 3 days of symptom onset
  - Focal deep soft tissue swelling in the metaphyseal region may be the 1st sign in children & infants, followed by muscle swelling & loss; tissue planes normally seen around affected bone
  - Soft tissue changes are harder to detect in adults
- Later changes include bone lysis, cortical lucency, osteopenia, periosteal elevation, periosteal new bone formation, single or multiple abscesses, involucrum, sequestration
- Findings in vertebral osteomyelitis include narrowing of the intervetebral disk space, bone destruction & new bone formation at the anterior edge of the vertebral disk
- Radiographs should be repeated at 2-wk intervals in DM patients who have infected foot wounds that do not resolve & whose initial radiographs are normal

Magnetic Resonance Imaging (MRI)
- Highly sensitive for detecting osteomyelitis, test of choice for diabetic foot ulcers
- Useful for differentiating bone infection from soft tissue infection, for confirming the extent of infection in patients w/ established osteomyelitis, & for evaluating intraosseous abscesses
- Able to detect vertebral osteomyelitis early
- Helpful in planning surgical management ie drainage & debridement
- **Limitations:** Not recommended for whole-body exams; metal implants may produce focal artifacts

Bone Scan
- May already be positive 24-48 hr after symptoms start & therefore can detect osteomyelitis earlier than plain radiographs
- Useful for patients in whom multifocal bone involvement is suspected
- Decreased uptake on bone scan may indicate more aggressive infection that has produced thrombosis or ischemia
- **Limitation:** May be positive in other conditions eg malignancy, fracture, bone infarction

Other Imaging Techniques
- Radionuclide studies
  - Not routinely required for evaluation of possible osteomyelitis, but may provide more information about the extent of bone & soft tissue inflammation
  - A gallium scan obtained together w/ a technetium scan or white blood cell (WBC) scan may be more useful than doing either test alone
- Computed tomography (CT) scan
  - Useful for defining the extent of bone & soft tissue infection esp in areas of complex anatomy eg the vertebral column & for guiding biopsies & aspiration procedures
  - Less sensitive than MRI except for detecting sequestra & should not be used routinely for evaluating patients w/ possible osteomyelitis
- Ultrasound
  - Noninvasive technique that may be helpful in detection of fluid collection, abscesses or sinus tracts in soft tissues
  - May be used to guide diagnostic or therapeutic drainage, aspiration or tissue biopsy
- Positron emission tomography & single photon emission computed tomography
  - Detects increased intracellular glucose metabolism that occurs in infection & inflammation
  - Highly accurate for confirming or excluding the diagnosis of chronic osteomyelitis

Lab Exams

Bacterial Culture
- Isolation of the infecting microorganism is extremely important for the diagnosis of long bone osteomyelitis
- Blood, bone & joint fluid should ideally all be cultured to increase the yield of the test
- Sinus tract cultures are reliable for confirming *S aureus* infection but are not useful for detecting gram-negative pathogens
- Gram-stained smear, aerobic & anaerobic cultures should be performed

Blood Tests
- WBC count may be high or normal in acute hematogenous osteomyelitis & is usually normal in chronic osteomyelitis
- Erythrocyte sedimentation rate (ESR) is usually elevated at the onset & may provide a prognostic guide during therapy
- C-reactive protein (CRP) level is elevated, w/ higher levels predicting a possibly greater risk of sequelae

Bone Biopsy
- Bone biopsy samples isolating bacteria w/ findings histologically of osteonecrosis & inflammatory disease are the reference standard for diagnosis of osteomyelitis
- Recommended if the diagnosis of osteomyelitis is still in doubt after imaging
- Frequently needed to diagnose vertebral osteomyelitis because blood cultures are usually sterile in this situation
- Open biopsy is better than needle biopsy & at least 2 samples should be obtained for histopath & for Gram stain & culture

Polymerase Chain Reaction (PCR)
- Helpful in establishing etiology of osteomyelitis when blood & bone cultures are negative

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A SUPPORTIVE MEASURES

- Optimize patient's medical, nutritional & vascular status
- Correct metabolic abnormalities
- Encourage smoking cessation to improve wound healing
- Hyperbaric oxygen therapy & negative pressure wound therapy (NPWT) may be a useful adjunct for treating chronic osteomyelitis

B PHARMACOLOGICAL THERAPY

Factors to consider when choosing an antibiotic for empiric therapy

- Suspected pathogens & their antimicrobial susceptibility pattern
  - Empiric antibiotic coverage for *S aureus* is indicated
- Age of patient esp children
- Severity of infection
- History of recent antibiotic intake
- Current Gram stain results
- Underlying co-morbid conditions
- Antibiotic safety & efficacy

Common Pathogens in Osteomyelitis

AHO

- *S aureus* is the most common etiologic agent in children & adults
  - Children w/ community-acquired Methicillin-resistant *S aureus* (CA-MRSA) infection are more likely to have prolonged fever & be hospitalized for longer periods than children infected w/ Methicillin-sensitive *S aureus* (MSSA)
  - Children w/ MRSA infection are more likely to have multiple foci of infection as well as subperiosteal & intraosseous abscesses
- Other causes of AHO in children include *Streptococcus pneumoniae, S pyogenes, Kingella kingae*; rarely, *Escherichia coli* & other gram-negative enteric bacilli, *Pseudomonas aeruginosa, Haemophilus influenzae* type B, anaerobes
- IV drug abusers are more prone to infections by *P. aeruginosa, Serratia marcescens, S aureus, Salmonella spp* & fungal organisms
- Fungi may be the cause of osteomyelitis in neonates, patients who are immunocompromised eg w/ prolonged neutropenia, those w/ chronic granulomatous disease, catheter-related fungemia, or are in geographic locations indigenous for certain fungal diseases

Contiguous-Infection Osteomyelitis

- Among patients w/o generalized vascular insufficiency, *S aureus* is most frequently isolated from bone, but multiple pathogens may also be isolated including gram-negative bacilli & anaerobes
- Among patients who have generalized vascular insufficiency, esp those w/ DM, multiple pathogens are usually isolated from bone, most commonly coagulase-positive & negative staphylococci, *Streptococcus spp, Enterococcus spp,* gram-negative bacilli & anaerobes
- Anaerobic organisms are common in patients w/ risk factors including surgery, trauma, DM, decubitus ulcers, human bites, chronic otitis media or sinusitis, dental infection, prosthetic devices, fibrous dysplasia of the bone

Vertebral Osteomyelitis

- *S aureus* is the most frequently isolated pathogen
- Spondylitis is the most common form of *Mycobacterium tuberculosis* musculoskeletal infection & should be suspected if symptoms & x-rays indicate chronic infection
- *E coli* may be an etiologic agent in adults esp those w/ a history of recent urinary tract infection or instrumentation
- IV drug abusers are more prone to infections due to *P aeruginosa*, *S aureus*, *Serratia* spp, *Klebsiella* spp, *Enterobacter* spp, or *Candida* spp

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B PHARMACOLOGICAL THERAPY (CONT'D)

Antibiotics for Empiric Therapy
- Antibiotic treatment should be started after specimens for cultures are sent
  - However, treatment in an acutely ill patient should not be delayed to wait for bone debridement
- Empirical therapy of AHO in both children & adults should include coverage against *S aureus*
- IV antibiotics are given at the start of therapy; step-down to PO treatment later may be possible based on clinical response

Antibacterial Combinations
- Eg Co-trimoxazole [Sulfamethoxazole (SMZ) & Trimethoprim (TM)]
- Effective against many MRSA isolates but studies regarding effectiveness in osteomyelitis are limited
- TMP-SMZ is also active against streptococci & enterobacteriaceae

Beta-lactam Antibiotics
- Eg penicillins, cephalosporins, carbapenems
- Achieve therapeutic concentrations in bone
- 1st generation cephalosporins (eg Cefazolin) & Oxacillin are good initial choices for osteomyelitis suspected to be caused by MSSA
  - Cefalexin & Cloxacillin are PO agents that may be used to complete treatment
- Benzylpenicillin is the drug of choice for treating osteomyelitis caused by group A streptococcus, susceptible *S pneumoniae* & enterococci
  - Amoxicillin or Phenoxymethylpenicillin are PO agents recommended for completing treatment
- Antipseudomonal penicillin, or Cefepime, or Ceftazidime &/or an aminoglycoside is an effective combination for osteomyelitis caused by *Pseudomonas*
- Ampicillin is effective against *Salmonella*
  - Cefotaxime or Ceftriaxone may be used for resistant isolates
- Most beta-lactam antibiotics are active against *K kingae*

Clindamycin
- Achieves good bone penetration
- May be used for empirical therapy of osteomyelitis suspected to be due to MSSA & anaerobes
  - However, *S aureus* isolates susceptible to Clindamycin but resistant to Erythromycin should be tested for inducible macrolide-lincosamide-streptogramin B resistance through the D test
  - Treatment failure is more likely in the presence of inducible resistance
- Active against most isolates of *S pyogenes* & *S pneumoniae*

Linezolid
- May be as effective as Vancomycin in treating infections caused by MRSA
- Active against streptococci & Vancomycin-resistant enterococci
- Alternative to prolonged IV therapy because of excellent oral bioavailability

Quinolones
- Eg Ciprofloxacin & Ofloxacin
- May be used for PO treatment of osteomyelitis in adults because of good penetration into the bone & excellent oral absorption
  - Not routinely recommended for use in young children
- May be used to treat osteomyelitis caused by gram-negative organisms including enterobacteriaceae
- Quinolones have variable coverage against *S aureus* & *S epidermidis*; no coverage against *Enterococcus* spp; newer quinolones have better action against *Streptococcus* spp & some anaerobes
- Should be combined w/ another antibiotic to achieve adequate coverage against *S aureus* during empiric therapy

Rifampicin
- May be used in combination w/ cell-wall antibiotics for synergistic action against *S aureus*
- Should never be used as monotherapy because resistance develops rapidly

Tetracyclines
- Effective against many MRSA isolates but studies regarding effectiveness in osteomyelitis are limited
- Tetracycline use in young children may result in stunted bone & tooth growth; should only be considered in >8 yr of age
- Should be avoided in pregnant patients

Vancomycin
- Drug of choice for empiric therapy in areas where CA-MRSA resistance to Methicillin & Clindamycin exceeds 10-15%
- Active against most isolates of *S pyogenes*, *S pneumoniae* & Ampicillin-resistant enterococci

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B PHARMACOLOGICAL THERAPY (CONT'D)

Local Antibiotic Therapy

- Antibiotic-impregnated (usually w/ aminoglycosides or Vancomycin) acrylic beads may be placed to sterilize a dead space while waiting for definitive management
- Limited studies are available to adequately support the superiority of local therapy over systemic antibiotic therapy, though local therapy is associated w/ markedly fewer adverse events

Suppressive Antibiotic Therapy

- Considered for patients in whom surgical treatment is needed but is not feasible
- Choose antibiotics that achieve adequate penetration into bone, have good bioavailability & low toxicity & are active against etiologic agents as based on sensitivity testing results
- Choices include Fusidic acid, quinolones, TMP-SMZ, Rifampicin (combined w/ other antibiotics)
- Treatment duration is usually 6 mth

Duration of Antibiotic Therapy

- Based on extent of infection, etiologic agent & clinical course
- Range is usually between 3-6 wk

C SURGERY

- Indications include persistent fever, erythema, pain & swelling, bacteremia, abscess or sinus tract formation, presence of necrotic bone, & failure to improve after 48-72 hr of antimicrobial therapy
- Long-bone osteomyelitis is classified into stages based on the magnitude of infection; these stages may be used to guide the type of surgical intervention needed
  - Stage 1 (medullary) often requires unroofing & intramedullary reaming
  - Stage 2 (superficial) often requires superficial debridement, coverage & possibly ablation
  - Stage 3 (localized) often needs debridement, dead space management, temporary stabilization & bone grafting
  - Stage 4 (diffuse) often needs stabilization through open reduction w/ internal or external fixation in addition to procedures required for Stage 3

4 EVALUATION

- Response to treatment is evaluated through clinical (ie symptom resolution) & lab parameters
  - ESR levels usually reach peak levels 3-5 days after the start of treatment & return to normal in about 2 wk
  - CRP levels peak 2 days after the start of treatment & return to normal after about 1 wk
- Antibiotic therapy should be revised based on results of culture & sensitivity studies
- If cultures are sterile & symptoms are resolving, empiric antibiotic therapy should be continued
- Assess patient's need to be enrolled in a community-based parenteral anti-infective therapy program
  - A functioning outpatient parenteral antimicrobial therapy (OPAT) program should have a complete & qualified health care team, efficient means of communication, guidelines for follow-up, testing & other interventions, written policies & procedures & outcomes monitoring
  - A candidate for inclusion in an OPAT program should be willing to participate in the program & should have a home environment that is sufficient to support care

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Dosage Guidelines

AMINOGLYCOSIDES		
Drug	**Dosage**	**Remarks**
Amikacin	15 mg/kg/day IM/IV divided 8, 12, or 24 hrly **Max dose:** 1.5 g/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, local pain & inflammation **Special Instructions** • Ototoxicity & nephrotoxicity are most likely in geriatric, 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, Parkinson's); vestibular or cochlear impairment • Should be avoided in patients w/ gastrointestinal ulceration
Bekanamycin	400-600 mg/day IM divided 8 or 12 hrly **Childn:** 10-20 mg/day IM divided 12 hrly	
Gentamicin	3-5 mg/kg/day IM/IV divided 6 or 8 hrly **Max dose:** 5 mg/kg/day IM/IV divided 6 or 8 hrly **Childn:** 2-2.5 mg/kg IM/IV 8 hrly **Gentamicin 7.5 mg/Zirconium dioxide 20 mg bead:** 10-90 beads to fill cavity	
Kanamycin	1-2 g/day IM divided 12-24 hrly **Childn:** 30-50 mg/kg/day IM divided 12-24 hrly	
Netilmicin	4-6 mg/kg/day IM/IV divided 8-12 hrly Up to 7.5 mg/kg/day IM/IV divided 8 hrly **Childn:** 6-7.5 mg/kg/day IM/IV divided 8 hrly	
Sisomicin	3-5 mg/kg/day IM/IV divided 8 hrly	
Tobramycin	3-5 mg/kg/day IM/IV divided 8 hrly **Childn:** 1.5-1.9 mg/kg IM/IV 6 hrly or 2-2.5 mg/kg IM/IV 8 hrly	

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Dosage Guidelines

ANTIBACTERIAL COMBINATIONS		
Drug	**Dosage**	**Remarks**
Co-trimoxazole [Sulfamethoxazole (SMZ) & Trimethoprim (TM)]	800 mg SMZ/ 160 mg TM PO 12 hrly **Childn:** 6 mg/kg/day based on TMP divided 12 hrly	**Adverse Reactions** • GI effects (N/V, anorexia, diarrhea, rarely antibiotic-associated diarrhea/colitis, glossitis); Dermatologic effects (rash, pruritus, photosensitivity); Hypersensitivity reactions can range from mild (eg rash) to severe/life threatening (eg Stevens-Johnson syndrome); Urogenital effect (crystallization in the urine) • Rarely hematologic effects which may be more common if given for long periods or w/ high doses; Rarely hepatic effects, renal effects; Aseptic meningitis has occurred **Special Instruction** • 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)

CEPHALOSPORINS		
Drug	**Dosage**	**Remarks**
Cephalosporins (1st Generation)		
Cefadroxil	1-2 g PO 24 hrly or divided 12 hrly **<40 kg:** 25-50 mg/kg/day PO divided 12 hrly	**Adverse Reactions** • Hypersensitivity reactions (urticaria, pruritus, rash, severe reactions such as anaphylaxis can occur); GI effects (diarrhea, N/V, rarely antibiotic associated diarrhea/colitis); Other effect (Candidal infections) • High doses may be associated w/ CNS effects (encephalopathy, convulsions); Rarely hematologic effects; 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 & occur most frequently w/ NMTT side chain-containing cephalosporins **Special Instructions** • May be taken w/ food to decrease gastric distress • Use w/ caution in patients allergic to Penicillin, there may be 10% chance of cross sensitivity • Use w/ caution in patients w/ renal impairment
Cefalexin (Cephalexin)	250-500 mg PO 6-8 hrly **Max dose:** 6 g/day **Childn:** 25-100 mg/kg/day PO divided 6-12 hrly **Max dose:** 4 g/day	
Cefaloridine (Cephaloridine)	0.5-1 g IM/IV 6-12 hrly **Max dose:** 6 g/day **Childn:** 50 mg/kg/day IM/IV divided 12 hrly	
Cefalotin (Cephalotin)	1-6 g IM/IV/day divided 4-6 hrly **Childn:** 20-80 mg/kg/day divided 4-6 hrly	
Cefazolin	1-4 g/day IM/IV divided 8-12 hrly **Childn:** 25-50 mg/kg/day IM/IV divided 6-8 hrly	
Cefradine (Cephradine)	1 g IV 6 hrly **Max dose:** 8 g/day **Childn:** 50-100 mg/kg/day IV divided 6-12 hrly	

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Dosage Guidelines

CEPHALOSPORINS (CONT'D)		
Drug	**Dosage**	**Remarks**
Cephalosporin (2nd Generation)		
Cefamandole	1-2 g IM/IV 4, 6, or 8 hrly **Childn:** 50-100 mg/kg/day IM/IV divided 4-8 hrly May increase dose to 150 mg/kg/day	**Adverse Reactions** • Hypersensitivity reactions (urticaria, pruritus, rash, severe reactions such as anaphylaxis can occur); GI effects (diarrhea, N/V, rarely antibiotic-associated diarrhea/colitis); Other effect (Candidal infections) • High doses may be associated w/ CNS effects (encephalopathy, convulsions); Rarely hematologic effects; 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 & occur most frequently w/ NMTT side chain-containing cephalosporins **Special Instructions** • May be taken w/ food to decrease gastric distress • Use w/ caution in patients allergic to Penicillin, there may be 10% chance of cross sensitivity • Use w/ caution in patients w/ renal impairment
Cefmetazole	1-2 g/day IM/IV divided 12 hrly May increase dose to 4 g/day IM/IV divided 6-12 hrly **Childn:** 25-100 mg/kg/day IM/IV divided 6-12 hrly May increase dose to 150 mg/kg/day	
Cefotiam	0.5-2 g/day IM/IV divided 6-12 hrly May increase dose to 4 g/day 200-400 mg PO 8 hrly **Childn:** 40-80 mg/kg/day IV divided 6-8 hrly	
Cefoxitin	1-2 g IM/IV 8 hrly May increase dose to 3 g IM/IV 6 hrly **Max dose:** 12 g/day **Childn:** 20-40 mg/kg IM/IV 6-12 hrly	
Ceftizoxime	1-4 g/day IM/IV divided 6-12 hrly **Childn:** 40-80 mg/kg/day IM/IV divided 6-12 hrly	
Cefuroxime	1.5 g IV 6-8 hrly **Childn:** 70-150 mg/kg/day IV divided 8 hrly	
Cephalosporins (3rd Generation)		
Cefoperazone	2-8 g IM/IV 12 hrly **Max dose:** 16 g/day **Childn:** 50-100 mg/kg/day IM/IV divided 12 hrly **Max dose:** 300 mg/kg/day	
Cefotaxime	1-2 g IM/IV 6-8 hrly **Max dose:** 12 g/day **Childn:** 50-100 mg/kg/day IM/IV divided 6-12 hrly **Max dose:** 200 mg/kg/day IM/IV divided 6-8 hrly	
Ceftazidime	2 g IV 12 hrly **Max dose:** 9 g/day **Childn:** 30-100 mg/kg/day divided 8-12 hrly **Max dose:** 6 g/day	
Ceftriaxone	1-4 g IV 24 hrly 20-80 mg/kg/day IV 24 hrly	
Cephalosporin (3rd Generation) w/ Beta-Lactamase Inhibitor		
Cefoperazone/ Sulbactam	2-4 g/day IV divided 12 hrly **Max dose:** 8 g/day (4 g of Cefoperazone) **Childn:** 40-80 mg/kg/day IV divided 6-12 hrly **Max Sulbactam dose:** 80 mg/kg/day	

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Dosage Guidelines

PENICILLINS		
Drug	**Dosage**	**Remarks**
Benzylpenicillin (Penicillin G, Penicillin G Na, Penicillin G K)	0.6-3.6 g/day divided 4-6 hrly	**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 effects; renal & hepatic effects have occurred; 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
Phenoxymethylpenicillin (Penicillin V, Penicillin V K)	50 mg/kg/day PO divided 6 hrly	
Aminopenicillins w/ or w/o Beta-Lactamase Inhibitors		
Amoxicillin (Amoxycillin)	250 mg-1 g PO 8 hrly 250-500 mg IM/IV 6-8 hrly **Max dose:** 6 g/day **Childn:** 25-50 mg/kg/day PO divided 8 hrly 25-40 mg/kg/day IM/IV divided 6-8 hrly	
Amoxicillin/clavulanic acid (Co-amoxiclav, Amoxicillin/clavulanate)	625 mg-1 g PO 12 hrly 1.2 g IV 6-8 hrly **Childn:** 25-50 mg/kg/day PO divided 8 hrly	
Ampicillin	500 mg IM/IV 4-6 hrly	
Ampicillin/sulbactam (Sultamicillin: Pro-drug of Ampicillin/sulbactam, the 2 drugs are linked chemically w/ a double ester)	1.5-12 g/day IM/IV divided 6, 8, or 12 hrly **Max dose:** 4 g of Sulbactam or 16 g/day **Childn:** 150 mg/kg IM/IV 6-8 hrly	
Antipseudomonal Penicillins w/ or w/o Beta-Lactamase Inhibitors		
Piperacillin	2-4 g IM/IV 4-6 hrly	
Piperacillin/tazobactam	2.25-4.5 g IV 6-8 hrly	
Ticarcillin/clavulanic acid (Ticarcillin/clavulanate)	3.2 g IV 4-6 hrly	
Antistaphylococcal Penicillins		
Cloxacillin	250 mg IM 4-6 hrly 500 mg IV 4-6 hrly 250-500 mg PO 6 hrly **Max dose:** 6 g/day **Childn:** 250-500 mg PO 6 hrly	
Dicloxacillin	250-500 mg PO 6 hrly **Childn:** 125-250 mg PO 6 hrly	
Flucloxacillin	8 g/day IM/IV divided 6-8 hrly 250-500 mg PO 6 hrly	
Oxacillin	500 mg-1 g IM/IV 4-6 hrly 500 mg-1 g PO 6 hrly **Childn <40 kg:** 50-100 mg/kg/day IM/IV divided 6 hrly	

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Dosage Guidelines

OTHER BETA-LACTAMS

Drug	Dosage	Remarks
Carbapenems		
Ertapenem	1 g IM/IV 24 hrly **Childn:** 15 mg/kg IM/IV 12 hrly **Max dose:** 1 g/day	**Adverse Reactions** • GI effects (diarrhea, N/V, antibiotic-associated diarrhea/colitis, tongue/tooth discoloration, altered taste); Hypersensitivity reactions ranging from mild (eg rash) to severe (eg anaphylaxis) can occur; Other effect (Candidal infections) • CNS effects (mental disturbances, confusion; Imipenem/cilastatin: Seizures & convulsions have been reported 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)
Imipenem/ Cilastatin	1-2 g/day IV divided 6-8 hrly **Max dose:** 4 g/day **Childn ≥3 mth, <40 kg:** 15 mg/kg IV 6 hrly **Max dose:** 2 g/day	
Meropenem	0.5-1 g/day IV divided 8-12 hrly **Max dose:** 2 g/day **Childn:** 10-20 mg/kg IV 8 hrly	
Monobactam		
Aztreonam	1-2 g/day IM/IV 8-12 hrly May increase dose to 2 g/day IM/ IV 6-8 hrly **Childn:** 50 mg/kg IM/IV 6-8 hrly	

QUINOLONES

Drug	Dosage	Remarks
Ciprofloxacin	400 mg IV 8-12 hrly 500-750 mg PO 12 hrly	**Adverse Reactions** • GI effects (N/V, diarrhea, abdominal pain, dyspepsia, diarrhea, rarely antibiotic-associated diarrhea/colitis); CNS effects (headache, dizziness, sleep disorders, restlessness, drowsiness); Dermatologic effects (rash, pruritus, photosensitivity); Hypersensitivity reactions can range from mild (eg rash) to severe/ life-threatening (eg Stevens-Johnson syndrome) • Rarely hematologic, hepatic & renal effects- • Some quinolones have the potential to prolong the QT interval **Special Instructions** • Administer at least 2 hr before or 3 hr after Al- or Mg-containing antacids, dietary supplements containing Zn or Fe or buffered ddI preparations • Avoid exposure to strong sunlight or tanning beds • Use w/ caution in patients w/ epilepsy or history of CNS disorders, in patients w/ impaired renal or hepatic function & in those w/ G6PD deficiency
Levofloxacin	500 mg IV 24 hrly 250-500 mg PO 12-24 hrly	
Ofloxacin	200 mg IV 12 hrly 400 mg PO 24 hrly	
Pefloxacin	8 mg/kg IV 12 hrly or 800 mg/day	

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Dosage Guidelines

TETRACYCLINES		
Drug	**Dosage**	**Remarks**
Doxycycline	**Initial dose:** 100 mg PO 12 hrly **Maintenance dose:** 100 mg PO 24 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 effect (photosensitivity); Other effects (Candidal infections, discoloration of teeth, interference w/ bone growth in young infants/pregnant women) • Rarely renal dysfunction, hepatotoxicity, hematologic effects, intracranial pressure w/ headache & visual disturbances; Hypersensitivity reactions have occurred **Special Instructions** • Avoid long exposure to sunlight or tanning beds - Take w/ plenty of fluid while sitting or standing & well before retiring to bed • Avoid in children ≤8 yr & pregnant women; avoid in patients w/ SLE • Use w/ caution in renal or hepatic impairment
Tetracycline	250 mg PO 3-6 hrly 500 mg PO 12 hrly **Childn:** 20-40 mg/kg/day PO divided 6 hrly	

OTHER ANTIBIOTICS		
Drug	**Dosage**	**Remarks**
Fusidate		
Fusidic acid	500 mg diluted to 250-500 mL slow IV infusion for 2 hr **Na fusidate:** 500 mg 12 hrly **Childn:** 20 mg/kg/day slow IV infusion for 2-4 hr **Oral susp:** **1-5 yr:** 250 mg PO 8 hrly **5-12 yr:** 500 mg PO 8 hrly	**Adverse Reactions** • GI effects (anorexia, N/V, dyspepsia); Hepatic effects (jaundice & changes in liver function which returns to normal once drug is discontinued); CNS effects (headache, dizziness) **Special Instructions** • Use w/ caution in patients w/ liver dysfunction & monitoring of hepatic function is recommended during systemic therapy
Glycopeptides		
Teicoplanin	**Loading dose:** 400 mg IM/IV 12 hrly for 1st 3 doses **Maintenance dose:** 400 mg/day IM/IV **Childn:** **Loading dose:** 10 mg/kg IV 12 hrly for 1st 3 doses **Maintenance dose:** 6-10 mg/kg/day IM/IV	**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); CNS effects (dizziness, headache); GI effect (GI disturbances); Hematologic & hepatic effects; Renal effects (renal impairment, but less often than Vancomycin); Ototoxic effects have occurred but less frequently than w/ Vancomycin **Special Instructions** • Use w/ caution in patients w/ preexisting renal dysfunction & monitor renal & auditory function if on prolonged therapy • Periodic monitoring of CBC & LFTs are advised

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Dosage Guidelines

OTHER ANTIBIOTICS (CONT'D)		
Drug	**Dosage**	**Remarks**
Glycopeptides (Cont'd)		
Vancomycin	500 mg IV 6 hrly 1 g IV 12 hrly **Childn:** 10 mg/kg IV 6 hrly or 20 mg/kg IV 12 hrly	**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 have occurred; 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 & the elderly • 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 • Use w/ caution in premature neonates & young infants because of their renal immaturity & potential to have increased serum concentrations
Lincosamides		
Clindamycin	1.2-2.7 g/day IM/IV divided 6-8 hrly 300-450 mg PO 12 hrly **Childn:** 25-40 mg/kg/day IM/IV divided 6-8 hrly 8-25 mg/kg/day PO 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); Hematologic & hepatic effects have occurred; Other effect (polyarthritis) **Special Instructions** • Use w/ caution in patients w/ GI disease esp w/ history of colitis • Use w/ caution in atopic patients & in patients w/ renal or hepatic impairment • Discontinue if diarrhea occurs
Lincomycin	600 mg IM 12-24 hrly 600 mg IV 8-12 hrly 500 mg PO 6-8 hrly **Childn:** 30-60 mg/kg/day PO divided 6-8 hrly	

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Dosage Guidelines

OTHER ANTIBIOTICS (CONT'D)		
Drug	**Dosage**	**Remarks**
Nitroimidazole Derivative		
Metronidazole	500 mg/100 mL IV infusion 8-12 hrly **Childn:** 1.5 mL/kg IV infusion 8-12 hrly Then 7.5 mg/kg PO 8-12 hrly	**Adverse Reactions** • GI effects (N/V, metallic taste, diarrhea, constipation); CNS effects have been reported (weakness, dizziness, headache, mood changes, peripheral neuropathy has occurred at high/prolonged doses); Other effects (Candidal infection, darkening of urine) • Hematologic & hepatic effects have occurred, rarely hypersensitivity reactions • High dose or prolonged use has caused peripheral neuropathy & epileptiform seizures **Special Instructions** • When given w/ alcohol, a disulfiram-like reaction can occur • Use w/ caution in patients w/ severe hepatic impairment • If given >10 days, recommend monitoring CBC & clinical monitoring for CNS effects
Oxazolidinone		
Linezolid	600 mg IV 12 hrly 600 mg PO 12 hrly	**Adverse Reactions** • GI effects (diarrhea, N/V, metallic taste, constipation, antibiotic-associated diarrhea/colitis can occur); CNS effects (headache, insomnia, dizziness); Hepatic effect (abnormal LFTs); 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	450 mg PO 24 hrly **Childn:** 10 mg/kg/day PO 24 hrly **Max dose:** 600 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

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