Skin-Soft Tissue Infections, Osteomyelitis, Surgical Prophylaxis, Endocarditis & Meningitis

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A 37-year-old man presents for the evaluation of localized swelling and tenderness of the left leg just below the knee. He suspects this lesion developed after a spider bite, although he did not see a spider. Examination of the leg reveals an area of erythema and warmth measuring approximately 5 by 7 cm. At the center of the lesion is a fluctuant area measuring approximately 2 by 2 cm, overlaid by a small area of necrotic skin. The man’s temperature is 38.3°C. The pulse rate is 115 beats per minute. The blood pressure is 116/78 mm Hg. How should this patient be evaluated and treated?

Skin Layers

- Stratum Corneum
  - Impetigo, Folliculitis
  - Furnuncles, Carbuncles, Ecthyma
- Epidermis
  - Erysipelas
  - Cellulitis
- Dermis
  - Necrotic Topical Ulcer
- Fat
  - Necrotizing Fasciitis
- Fascia
  - Myositis
- Muscle
- Bone
  - Osteomyelitis
Infection Development

• Cellulitis: Damage to skin
  – Primary
    • Small break in skin, usually mono-microbial
  – Secondary
    • Abrasions, cuts, bites, pressure (bedsore, diabetic foot)

• Osteomyelitis: infection of the bone
  – Contiguous
    • Spreads from skin-soft tissue
  – Hematogenous
    • Spreads from blood (esp. S. aureus)
# Wound Characteristics

<table>
<thead>
<tr>
<th>Non-Necrotizing</th>
<th>Focal</th>
<th>Necrotizing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-Toxic</strong></td>
<td>Gangrene</td>
<td>Meleney’s Progressive Synergistic Bacterial</td>
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<tr>
<td>Impetigo, Folliculitis Furuncolosis, Carbuncle</td>
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<td><strong>Toxic</strong></td>
<td>Fournier’s Idiopathic Scrotal</td>
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<td>Toxic Shock Syndrome</td>
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<tr>
<td><strong>Cellulitis</strong></td>
<td>Clostridial</td>
<td>Non-Clostridial</td>
</tr>
<tr>
<td>Mild</td>
<td>Cellulitis, Gas gangrene</td>
<td>Necrotizing Fasciitis (1 &amp; 2)</td>
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<tr>
<td>Severe</td>
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<td>High Risk</td>
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<tr>
<td>Complicated</td>
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</table>

## Diffuse

Necrotizing Fasciitis (1 & 2)
**Staphylococcus aureus**

- Colonization
  - 30-50% health adults; 10-20% persistent
- Toxin productions
  - Toxic shock syndrome toxin 1 - TSS
  - Epidermolytic toxin A&B - Staphylococcal Scalded Skin Syndrome (exfoliation)
- Necrosis, pus, abscess, metastatic infection
- Drug Resistance (MR-SA) common & increasing
**Staphylococcus aureus**

- **Penicillin-Sensitive**: high dose penicillin G
  - oxacillin or nafcillin; cefazolin; or vancomycin

- **Methicillin-Sensitive**: oxacillin or nafcillin
  - cefazolin or vancomycin (less active than β-lactams)

- **Methicillin-Resistant**: vancomycin
  - Uncomplicated (Non-Bacteremic, not osteo)
    - TMP/SMX, minocycline, clindamycin*, quinolones
      * D-test to verify susceptibility if erythromycin resistant
  - **streptogramins, linezolid, daptomycin, tigecycline**
Streptococcus pyogenes

• Group A (β-hemolytic) streptococcus (GAS)
• Pyrogenic exotoxins
  – streptococcal toxic shock syndrome
• Antibiotic selection issues
  – Penicillin still drug of choice, resistance limits erythromycin. Other β-lactams ok. Not TMP/SMX
  – Serious infections - penicillin limited by Eagle effect & need to inhibit toxins- add clindamycin
Pyodermas

• Mild - moderate infections of the upper skin
  – Stratum Corneum: Impetigo, Folliculitis
  – Epidermis: Furuncles, Carbuncle & Ecthyma
  – Dermis: Erysipelas & Cellulitis

• Can require IV antibiotics, progress to necrosis/gangrene, & be focus for TSS
Impetigo

- Numerous localized purulent lesions on exposed areas (face & extremities)
- Vesicles then pustules then rupture
  - Thick honey-colored crust usually GAS
    - treat with penicillin (PO or IM), oral cephalosporin
  - Bullous w/varnish-like crust usually *S. aureus*
    - treat with dicloxacillin (PO) or oral cephalosporin
  - Penicillin Allergic: Clindamycin > erythromycin
- Ulcers into epidermis = ecthyma
Folliculitis, Furuncles, & Carbuncles

• Folliculitis
  – Pyodermas centered on hair follicles
  – Caused by *S. aureus*, treat with moist heat
  – Hot tub folliculitis from *P. aeruginosa*

• Furuncles & Carbuncles (aka boils)
  – Extension of folliculitis (coalesce = carbuncle)
  – Moist heat; incision & drainage
  – +/- antibiotics for *S. aureus* & streptococcus
  – If recurs, treat for *S. aureus* carriage w/ mupirocin to nares
Erysipelas

• Superficial layers of skin, lymphatics
  – Raised, demarcated red area of inflammation (peau d’orange) usually involving the face, lower extremities in children & elderly
  – Caused by GAS, sometimes S. aureus
  – Treat with anti-staphylococcal β lactam, penicillin ok if spontaneous & not diabetic
  – 1-2 weeks IV then PO if improved; total 3 wks
Cellulitis

• Skin & subcutaneous infection
  – Erythema, warmth, tenderness, & swelling usually of extremities, can involve lymphatics
  – Caused by *S. aureus*, GAS
    • Severe - rule out necrotizing fasciitis
    • If > 50% MR-SA
      – Mild: PO Clindamycin, Trimethoprim/Sulfamethoxazole
      – Moderate / Severe: IV Vancomycin
    • MS-SA: treat with anti-staphylococcal $\beta$-lactam
    • Treat 7-10 days (>3 days after inflammation gone)
Diabetic foot, decubitus ulcers

- Mild: usually Staph & Strep & may be treated with oral anti-staphylococcal \( \beta \)-lactams
- Moderate-severe: often polymicrobial, requires additional Gram-negative, anaerobic coverage
  - \( \beta \) -lactam/ \( \beta \) -lactamase inhibitor; cefotetan; Clindamycin with gentamicin or quinolone...
  - Life-Threatening: Carbapenem
  - Rule out osteomyelitis
- Wound care, hyperbaric oxygen, relieve pressure, examine skin daily.
Complicated Cellulitis

• Facial / Orbital
  – Medical emergency seen primarily in children
    • caused by *Strep. pneumoniae*, *H.influenzae*, et al;
    • treat with cefuroxime, ampicillin/Sulbactam et al

• Trauma involving water
  – Salt water: Vibrio (hemorrhagic bullous lesion)
    • Ceftazidime & Doxycycline
  – Fresh water: Pseudomonas, Aeromonas
    • β-lactam/ β-lactamase inhibitor or Carbapenem
Complicated Cellulitis 2

• Bites (cats, people, dogs)
  – *Eikenella, Pasteurella multocida* and others
  – Treat with amoxicillin / clavulanate
• Burns (initially not infected)
  – Broad spectrum coverage if becomes infected
• Surgical Wound Infections
  – Staph (including MR-SA), Streptococcus
  +/− gram negative rods or anaerobes if GI surgery
Table 3. Initial Treatment for Cellulitis at Specific Sites or with Particular Exposures.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bacterial Species to Consider*</th>
<th>Standard Antimicrobial Therapy†</th>
<th>Alternative Antimicrobial Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buccal cellulitis</td>
<td><em>H. influenzae</em></td>
<td>Ceftriaxone (1–2 g/day intravenously)</td>
<td>Meropenem or imipenem–cilastatin</td>
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<td>Limb-threatening diabetic foot ulcer</td>
<td>Aerobic gram-negative bacilli (Enterobacteriaceae, <em>P. aeruginosa</em>, acinetobacter), anaerobes</td>
<td>Ampicillin–sulbactam (3 g intravenously every 6 hr)</td>
<td>Meropenem or imipenem–cilastatin; clindamycin plus a broad-spectrum fluoroquinolone (ciprofloxacin or levofloxacin); metronidazole plus a fluoroquinolone or ceftriaxone</td>
</tr>
<tr>
<td>Human bites</td>
<td>Oral anaerobes (bacteroides species, peptostreptococci); <em>Eikenella corrodens</em>, viridans streptococci; <em>S. aureus</em></td>
<td>Amoxicillin–clavulanate (500 mg orally every 8 hr)</td>
<td>Penicillin plus a cephalosporin</td>
</tr>
<tr>
<td>Dog and cat bites</td>
<td><em>P. multocida</em> and other pasteurella species; <em>S. aureus</em>, <em>S. intermedius</em>, Neisseria canis, Haemophilus felix, Capnocytophaga canimorsus; anaerobes</td>
<td>Amoxicillin–clavulanate (500 mg orally every 8 hr)</td>
<td>Moxifloxacin plus clindamycin</td>
</tr>
<tr>
<td>Exposure to salt water at site of abrasion or laceration</td>
<td><em>Vibrio vulnificus</em></td>
<td>Doxycycline (200 mg intravenously initially, followed by 100–200 mg intravenously per day in 2 divided doses)‡</td>
<td>Cefotaxime; ciprofloxacin</td>
</tr>
<tr>
<td>Exposure to fresh water at site of abrasion or laceration or after the therapeutic use of leeches</td>
<td><em>Aeromonas species</em></td>
<td>Ciprofloxacin (400 mg intravenously every 12 hr) or ceftazidime plus gentamicin‡</td>
<td>Meropenem or imipenem–cilastatin</td>
</tr>
<tr>
<td>Working as a butcher, fish or clam handler, veterinarian</td>
<td><em>Erysipelothrix rhusiopathiae</em></td>
<td>Amoxicillin (500 mg orally every 8 hr) for mild skin infections; penicillin G (12 million–20 million units intravenously daily) for bacteremic infections or endocarditis</td>
<td>Ciprofloxacin or cefotaxime or imipenem–cilastatin</td>
</tr>
</tbody>
</table>

* These bacterial species should be considered in addition to the common pathogens.
† Doses given are for adults with normal renal function; the duration of treatment should be 7 to 15 days or longer, depending on the clinical response.
‡ Treatment is to be given along with antimicrobial agents targeted to the common pathogens.
Necrotic Soft Tissue Infections

Tissue death, often rapidly progressing

• Infectious Gangrene
  – subcutaneous tissues & overlying skin
• Necrotizing fasciitis
  – fascia and fat

_Divergent/confusing nomenclature_

• Diagnoses by radiography, CT scan, MRI, ultrasound; skin probe, intra-operative exploration
Treatment of Necrotic Soft Tissue Infection

- Urgent surgical incision or excision
- Empiric treatment for polymicrobial
  *Gram-positive, Gram-negative, & anaerobic organisms*
  - Zoysn, Primaxin, Clinda & Gent;
  - add Vanco for MR-SA
- Clostridial or GAS
  - Clindamycin 900mg IV Q8h & Pen G 4mu IV Q4h
- *S. aureus*
  - Oxacillin or Nafcillin, Cefazolin; Vanco for MR-SA
Case – SSTI: Conclusion

• Incision and drainage are the cornerstones of therapy; purulent material should be cultured. In many patients, particularly those with small lesions (<5 cm in length), incision and drainage alone will be adequate therapy.
• If the skin lesions are large or accompanied by systemic signs of infection or if there is evidence of an increased risk of complicated community associated MRSA disease, antimicrobial therapy that is active against community-associated MRSA is also recommended.
• Therapy ultimately should be guided by the results of susceptibility testing of cultures obtained before the initiation of therapy.
• Clindamycin, trimethoprim–sulfamethoxazole, or doxycycline
Case - Osteomyelitis

- A 62-year-old woman with osteoarthritis presents with a 7-month history of progressively worsening left hip pain radiating to the groin, 8 months after undergoing total left-hip arthroplasty. The pain has not responded to nonsteroidal antiinflammatory drugs. Physical examination reveals a sinus tract overlying her left hip. Her leukocyte count is 8000 per cubic millimeter, and the C-reactive protein (CRP) level is 15.5 mg per liter. A radiograph shows loosening of the prosthesis at the bone-cement interface. Synovial-fluid aspirate shows 15×10³ cells per cubic millimeter (89% neutrophils); cultures of an aspirate from the hip grow *Staphylococcus epidermidis*. How should her case be managed?

Osteomyelitis

• Infection of the bone
  – Contiguous (trauma or skin-soft tissue infection)
    • Often complicated by hardware (foreign bodies)
    • Usually S. aureus; Pseudomonas if exposure to water
  – Hematogenous (primary infection – bacteremia)
    • S. aureus most common
      – Pseudomonas in IVDA
      – Salmonella if asplenic
      – N. gonorrhoeae as STD
Osteomyelitis

• Diagnosis: s/s, WBC, CRP, ESR, surgery, X-ray
  – Need microbiologic sample!

• Treatment: pathogen specific
  – Long term IV (6-8 weeks) +/- oral suppression
  – Need high drug levels, good bone penetration
  – Remove hardware if at all possible
  – Vancomycin for MR-SA (goal trough 15-20)
    • Cipro for susceptible GNR at 750 mg PO Q12h?
    • May add rifampin if hardware retained
Case – Osteomyelitis: Conclusion

- *S. epidermidis* is the likely pathogen. However, since this organism may be a contaminant, additional culture specimens should be obtained for confirmation: synovial fluid (obtained by reaspiration), five or six tissue specimens, or the implant (subjected to vortexing and sonication, with culture of the sonicate fluid). Given the presence of the sinus tract in this case and the duration of the patient’s symptoms, she is not a candidate for debridement and retention of the prosthesis. Instead, arthroplasty with a two-stage exchange plus antibiotics (according to the culture results) administered for 4 weeks would be appropriate.
| Risk of Infection by Surgical Wound Classification and Pathogens by Frequency |
|---|---|
| 1 – 2 % | **Gram-positive** |
| Clean | 19% *Staph. aureus* |
| 3 – 7 % | 14% CoN Staph |
| Clean-contaminated | 12% Enterococci |
| Controlled entry into tract | **Gram-negative** |
| 6 – 16 % | 8% *E. coli* |
| Contaminated | 8% *P. aeruginosa* |
| spillage +/- breaks | 7% *Enterobacter spp* |
| +/- GI / biliary infection. | 3% *K. pneumonia,* |
| 7 – 40 % | **C. albicans,** |
| Dirty and infected | **P. mirabilis,** |
| Infected/contaminated | |
Key Concepts

• **Cover common pathogens**
  – Not every possible pathogen (tb...)
  – Don’t use agents for prophylaxis that you need for treatment (resistance)

• **Achieve bactericidal concentrations at site of incision**
  – Given within 2 hours before incision,
    ideally within 60 minutes (consider infusion time)
  – Re dose intra-operatively at 2 x half life

• **Discontinue within 24 hours of end of surgery**
<table>
<thead>
<tr>
<th>Nature of Operation</th>
<th>Common Pathogens</th>
<th>Recommended Antimicrobials</th>
<th>Adult Dosage Before Surgery¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac</strong></td>
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<tr>
<td></td>
<td><em>Staphylococcus aureus, S. epidermidis</em></td>
<td>Cefazolin</td>
<td>1-2 g IV</td>
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<td></td>
<td></td>
<td>OR vancomycin²</td>
<td>1 g IV</td>
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<tr>
<td><strong>Gastrointestinal</strong></td>
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<tr>
<td>Esophageal, gastroduodenal</td>
<td>Enteric gram-negative bacilli, gram-positive cocci</td>
<td><em>High risk</em> only: cefazolin³</td>
<td>1-2 g IV</td>
</tr>
<tr>
<td>Biliary tract</td>
<td>Enteric gram-negative bacilli, enterococci, clostridia</td>
<td><em>High risk</em> only: cefazolin⁵</td>
<td>1-2 g IV</td>
</tr>
<tr>
<td>Colorocral</td>
<td>Enteric gram-negative bacilli, anaerobes, enterococci</td>
<td>Oral: neomycin + erythromycin base⁷ OR + metronidazole⁷ Parenteral: cefoxitin⁵ or cefotetan⁵ OR cefazolin + metronidazole</td>
<td>1-2 g IV OR ampicillin/subactam⁵ 0.5 g IV 3 g IV</td>
</tr>
<tr>
<td>Appendectomy, non-perforated</td>
<td>Same as for colorectal</td>
<td>Cefoxitin⁵ or cefotetan⁵ OR cefazolin OR cefopetan OR ampicillin/subactam⁵</td>
<td>1-2 g IV 1-2 g IV 0.5 g IV 3 g IV</td>
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<tr>
<td><strong>Genitourinary</strong></td>
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<tr>
<td>Cystoscopy alone</td>
<td>Enteric gram-negative bacilli, enterococci</td>
<td><em>High risk</em>³ only: ciprofloxacin OR trimethoprim-sulfamethoxazole</td>
<td>500 mg PO or 400 mg IV 1 DS tablet</td>
</tr>
<tr>
<td>Cystoscopy with manipulation or Upper tract instrumentation</td>
<td>Enteric gram-negative bacilli, enterococci</td>
<td>Ciprofloxacin OR trimethoprim-sulfamethoxazole</td>
<td>500 mg PO or 400 mg IV 1 DS tablet</td>
</tr>
<tr>
<td>Open or laparoscopic surgery</td>
<td>Enteric gram-negative bacilli, enterococci</td>
<td>Cefazolin⁵</td>
<td>1-2 g IV</td>
</tr>
<tr>
<td>Gynecologic and Obstetric</td>
<td>Vaginal, abdominal or laparoscopic hysterectomy</td>
<td>Enteric gram-negative bacilli, anaerobes, Gp B strep, enterococci</td>
<td>cefoxitin&lt;sup&gt;5&lt;/sup&gt;, cefotetan&lt;sup&gt;5&lt;/sup&gt; or cefazolin&lt;sup&gt;5&lt;/sup&gt; OR ampicillin/sulbactam&lt;sup&gt;5&lt;/sup&gt;</td>
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<tr>
<td>Cesarean section</td>
<td>same as for hysterectomy</td>
<td>cefazolin&lt;sup&gt;5&lt;/sup&gt;</td>
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<tr>
<td>Abortion</td>
<td>same as for hysterectomy</td>
<td>doxycycline</td>
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<tr>
<td>Head and Neck Surgery</td>
<td>Incisions through oral or pharyngeal mucosa</td>
<td>Anaerobes, enteric gram-negative bacilli, &lt;i&gt;S. aureus&lt;/i&gt;</td>
<td>clindamycin OR cefazolin + metronidazole</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td></td>
<td>&lt;i&gt;S. aureus, S. epidermidis&lt;/i&gt;</td>
<td>cefazolin OR vancomycin&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>&lt;i&gt;S. epidermidis, S. aureus, streptococci, enteric gram-negative bacilli, Pseudomonas spp.&lt;/i&gt;</td>
<td>gentamicin, tobramycin, ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, ofloxacin or neomycin-gramicidin-polyoxymyxin B</td>
<td>ceftazolin or multiple drops topically over 2 to 24 hours</td>
</tr>
<tr>
<td>Orthopedic</td>
<td>&lt;i&gt;S. aureus, S. epidermidis&lt;/i&gt;</td>
<td>cefazolin&lt;sup&gt;13&lt;/sup&gt; or cefuroxime&lt;sup&gt;13&lt;/sup&gt; OR vancomycin&lt;sup&gt;3,13&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Thoracic (Non-Cardiac)</td>
<td>&lt;i&gt;S. aureus, S. epidermidis, streptococci, enteric gram-negative bacilli&lt;/i&gt;</td>
<td>cefazolin or cefuroxime OR vancomycin&lt;sup&gt;3&lt;/sup&gt;</td>
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<tr>
<td>Vascular</td>
<td>Arterial surgery involving a prosthesis, the abdominal aorta, or a groin incision</td>
<td>&lt;i&gt;S. aureus, S. epidermidis, enteric gram-negative bacilli&lt;/i&gt;</td>
<td>cefazolin OR vancomycin&lt;sup&gt;3&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Lower extremity amputation for ischemia</td>
<td>&lt;i&gt;S. aureus, S. epidermidis, enteric gram-negative bacilli, clostridia&lt;/i&gt;</td>
<td>cefazolin OR vancomycin&lt;sup&gt;3&lt;/sup&gt;</td>
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<tr>
<td>Principals and antibiotic selection</td>
<td>Consensus position</td>
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<tr>
<td><strong>General principles</strong></td>
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<tr>
<td>Antibiotic timing</td>
<td>Infusion of the first antimicrobial dose should begin within 60 minutes before the surgical incision is made.*</td>
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<tr>
<td>Duration of prophylaxis</td>
<td>Prophylactic antimicrobials should be discontinued within 24 hours of the end of surgery.</td>
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<tr>
<td>Screening for β-lactam allergy</td>
<td>For those operations for which the cephalosporins represent the most appropriate antimicrobials for prophylaxis, the medical history should be adequate to determine if the patient has a history of allergy or serious adverse antibiotic reaction. Alternative testing strategies (eg, skin testing) may be useful in patients with reported allergy [35–37].</td>
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<tr>
<td>Antimicrobial dosing</td>
<td>The initial antimicrobial dose should be adequate based on the patient’s weight, adjusted dosing weight, or body mass index. An additional dose of antimicrobial should be given intraoperatively if the operation is still continuing two half-lives after the initial dose.†</td>
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<tr>
<td>Antibiotic selection</td>
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<tr>
<td>Abdominal or vaginal hysterectomy</td>
<td>Cefotetan is preferred; cefazolin or cefoxitin are alternatives; metronidazole monotherapy.‡</td>
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<tr>
<td>If β-lactam allergy</td>
<td>Cefotetan or cefoxitin</td>
<td></td>
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<tr>
<td>Clindamycin combined with gentamicin or ciprofloxacin§ or aztreonam</td>
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<tr>
<td>Metronidazole combined with gentamicin or ciprofloxacin§</td>
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<tr>
<td>Clindamycin monotherapy</td>
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<tr>
<td>Hip or knee arthroplasty</td>
<td>Cefazolin or cefuroxime</td>
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<tr>
<td>If β-lactam allergy</td>
<td>Vancomycin</td>
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<tr>
<td>Clindamycin</td>
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<tr>
<td>Cardiothoracic and vascular surgery</td>
<td>Cefazolin or cefuroxime</td>
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<td>Vancomycin</td>
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<td>Clindamycin</td>
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<tr>
<td>Colon surgery</td>
<td>Oral antimicrobial prophylaxis:</td>
<td></td>
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<tr>
<td>Neomycin plus erythromycin base</td>
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<td>Neomycin plus metronidazole</td>
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<tr>
<td>Parenteral antimicrobial prophylaxis:</td>
<td>Cefotetan or cefoxitin</td>
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<tr>
<td>Cefazolin plus metronidazole</td>
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<td>Metronidazole with gentamicin or ciprofloxacin§</td>
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</tbody>
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Beta-lactam Allergy & MRSA

Use alternative agent if:

• True Beta-lactam Allergy:
  – urticaria, pruritus, angioedema, bronchospasm, hypotension, or arrhythmia

• Severe ADR to Beta-lactam
  – Drug-induced hypersensitivity syndrome, drug fever, or toxic epidermal necrolysis

• Documented MRSA
  – Colonized patient or high rate of post-operative wound infections caused by MRSA
Endocarditis

• Microbial infection of endocardium
  – Usually on Heart valves; also septal defect...
  – Vegetation (Characteristic lesion):
    Platelets, fibrin, microorganisms & inflammatory cells

• 1.7-6.2 cases per 100,000 person years
  – 150-2,000 per 100,000 py in IV Drug users
  – 100 per 100,000 py with mitral valve prolapse
  – 1% at 12, 3% at 60 months w/ Prosthetic valves
  – Males > Females (1.7:1);
  – Poor dental hygiene, hemodialysis, diabetics
Native Valve
Left Sided
Aortic Valve
Mitral Valve

Right Sided
Tricuspid

IVDU

Aortic valve
Left atrium
Mitral valve
Left ventricle
Tricuspid valve
Right atrium
Right ventricle
Aorta
Pathogenesis

- Colonization of tissue, mucus membrane
- Trauma (including procedures)*
- Bacteremia*
- Adherence
- Colonization
- Mature Vegetation

* incidence of bacteremia varies by procedure
## Clinical Manifestations of IE

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>80% Fever</td>
<td>90% Fever</td>
</tr>
<tr>
<td>40% Chills</td>
<td>85% Heart Murmur</td>
</tr>
<tr>
<td>40% Weakness</td>
<td>5-10% Changing murmur</td>
</tr>
<tr>
<td>25% Dyspnea</td>
<td>3-5% New Murmur</td>
</tr>
<tr>
<td>25% Sweat</td>
<td>&gt;50% Embolic Phenom.</td>
</tr>
<tr>
<td>Anorexia</td>
<td>18-50% Skin Manifestation</td>
</tr>
<tr>
<td>Wt Loss</td>
<td>10-23% Osler nodes</td>
</tr>
<tr>
<td>Malaise</td>
<td>15% Splinter hemorrhage</td>
</tr>
<tr>
<td>Cough</td>
<td>20-40% Petechiae</td>
</tr>
<tr>
<td></td>
<td>&lt;10% Janeway lesions</td>
</tr>
<tr>
<td></td>
<td>20-57% Splenomegaly</td>
</tr>
<tr>
<td></td>
<td>20% Septic Complications</td>
</tr>
</tbody>
</table>
Diagnosis of IE

Modified Duke criteria (CID 2000;30:633)

• Definite IE by Clinical Criteria
  – 2 major criteria; or
  – 1 major criterion and 3 minor criteria or
  – 5 minor criteria

• Possible IE:
  – 1 major criterion and 1 minor criterion; or
  – 3 minor criterion

• Rejected
  – Firm alternative diagnosis explaining evidence of IE; or
  – Resolution of IE syndrome with antibiotic therapy for < 4 days; or
  – does not meet criteria for possible IE, as above
Major & Minor Criteria

• Major criteria (abbreviated)
  – Blood culture positive for & consistent with IE
  – Evidence of endocardial involvement
  – Echocardiogram positive for IE
  – New valvular regurgitation (not pre-existing)

• Minor criteria (abbreviated)
  – Predisposition, predisposing heart condition or IDU
  – Fever, Temperature > 38°C
  – Vascular phenomena consistent with IE
  – Immunologic phenomena consistent with IE
  – Microbiological evidence not entirely consistent with IE
<table>
<thead>
<tr>
<th>Percentage</th>
<th>Cause</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-80%</td>
<td><strong>Streptococci</strong> (10-20% Mortality)</td>
<td></td>
</tr>
<tr>
<td>30-40%</td>
<td>Viridans streptococci</td>
<td></td>
</tr>
<tr>
<td>5-18%</td>
<td>Enterococci</td>
<td></td>
</tr>
<tr>
<td>15-25%</td>
<td>Other streptococci</td>
<td></td>
</tr>
<tr>
<td>20-35%</td>
<td><strong>Staphylococci</strong> (38% Mortality with SA)</td>
<td></td>
</tr>
<tr>
<td>10-27%</td>
<td>Coagulase-positive (S. aureus)</td>
<td></td>
</tr>
<tr>
<td>1-3%</td>
<td>Coagulase-negative</td>
<td></td>
</tr>
<tr>
<td>1.5-13%</td>
<td>Gram-negative aerobic bacilli (50% Mortality)</td>
<td></td>
</tr>
<tr>
<td>2-4%</td>
<td>Fungi</td>
<td></td>
</tr>
<tr>
<td>&lt;5-24%</td>
<td>Culture Negative</td>
<td></td>
</tr>
</tbody>
</table>
Native Valve - Empiric Rx

- Oxacillin or Nafcillin 2g IV Q4h with Penicillin 4mu IV Q4h and Gentamicin 1mg/kg IV Q8+h
- Alternative if Penicillin allergic or Risk of MRSA (i.e. Memphian or IV-DA)
  - Vancomycin 15mg/kg IV Q12+h
  - with Gentamicin 1mg/kg IV Q8+h
## Prosthetic Valve - Etiology

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>&lt; 1 year</th>
<th>&gt; 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strep sps</td>
<td>8%</td>
<td>32%</td>
</tr>
<tr>
<td>S. aureus</td>
<td>12%</td>
<td>17%</td>
</tr>
<tr>
<td>S. epidermidis</td>
<td>33%</td>
<td>11%</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td>Other</td>
<td>35%</td>
<td>30%</td>
</tr>
</tbody>
</table>
Prosthetic Valve - Empiric Rx

- Vancomycin 15mg/kg IV Q12^{+}h
  with Gentamicin 1mg/kg IV Q8^{+}h
  and Rifampin 600mg PO Q24h
  or 300 mg PO Q8h

  Will likely need valve replacement surgery
Definitive Treatment of IE


• Must read this!
## Native Valve - Streptococci
Highly Penicillin Susceptible

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Cell-Wall Active Drug</th>
<th>Gentamicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td><strong>Penicillin</strong> 12-18 million Units daily</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Divided Q4-6 hours</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><strong>Ceftriaxone</strong> 2 gram IV every 24 hours</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td><strong>Penicillin</strong> 12-18 million units daily</td>
<td>3 mg /kg IV once daily</td>
</tr>
<tr>
<td></td>
<td>Divided Q4 hours</td>
<td>Or 1 mg/kg IV Q8h (T = 1)</td>
</tr>
<tr>
<td>2</td>
<td><strong>Ceftriaxone</strong> 2 gram IV every 24 hours</td>
<td>3 mg / kg IV once daily</td>
</tr>
<tr>
<td>4</td>
<td><strong>Vancomycin</strong> 15 -20 mg /kg every 12 hours</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>targeting troughs 15-20 mcg/mL</td>
<td></td>
</tr>
</tbody>
</table>
## Native Valve S. aureus

<table>
<thead>
<tr>
<th>Bug</th>
<th>Weeks</th>
<th>Cell-Wall Active Drug</th>
<th>Gentamicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS-SA</td>
<td>6</td>
<td><strong>Nafcillin 12</strong> grams daily Divided Q4-6 hours</td>
<td>Optional 3 mg / kg IV daily divided for 3-5 days</td>
</tr>
<tr>
<td>MR-SA</td>
<td>6</td>
<td><strong>Vancomycin</strong> 15 -20 mg /kg every 12 hours targeting troughs 15-20 mcg/mL</td>
<td>None</td>
</tr>
<tr>
<td>Either</td>
<td>6</td>
<td>Daptomycin 6 mg/kg IV Q24h</td>
<td></td>
</tr>
</tbody>
</table>
# Prosthetic Valve

<table>
<thead>
<tr>
<th>Bug</th>
<th>Weeks</th>
<th>Primary Drug(s)</th>
<th>Gentamicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCN-S Strep</td>
<td>6</td>
<td>Penicillin 24 million Units daily divided Q4-6 hrs</td>
<td>+/- 2 weeks of 3 mg/kg once daily</td>
</tr>
<tr>
<td>PCN-S Strep</td>
<td>6</td>
<td>Ceftriaxone 2 gram IV every 24 hrs</td>
<td>+/- 2 weeks of 3 mg/kg once daily</td>
</tr>
<tr>
<td>PCN-S Strep</td>
<td>6</td>
<td>Vancomycin 15 -20 mg /kg every 12 hrs targeting troughs 15-20 mcg/mL</td>
<td></td>
</tr>
<tr>
<td>MS-SA</td>
<td>&gt;6</td>
<td>Nafcillin 12 grams IV daily divided Q4-6 hrs</td>
<td>2 weeks of 3 mg / kg IV divided Q8+ hours</td>
</tr>
<tr>
<td>MR-SA</td>
<td>&gt;6</td>
<td>Vancomycin 15 -20 mg /kg every 12 hrs targeting troughs 15-20 mcg/mL</td>
<td>2 weeks of 3 mg / kg IV divided Q8+ hours</td>
</tr>
</tbody>
</table>
Definitive Antibiotic Treatment

• Special Problems
  – Penicillin with MIC > 0.12 (treat longer)
  – Enterococci: VRE, ARE, HLARE
    • Get an ID consult!
  – Fastidious (HACEK)
  – Prosthetic Valve IE with
    • Pseudomonas
      – (Piperacillin, Ceftazidime, or Cefepime)
        and Tobramycin 8 mg / kg daily x 6 weeks
    • Fungus (candida or aspergillus)
      – Amphoteracin +/- replace valve
Endocarditis Prophylaxis: Indications

• Prosthetic cardiac valve
• Previous IE
• Cardiac transplantation recipients who develop cardiac valvulopathy
• Congenital heart disease (CHD)*
  – Unrepaired cyanotic CHD, including palliative shunts & 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†
  – Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
Dental Procedures for Which Endocarditis Prophylaxis Is Recommended

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

• *The 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.

• Not GI or GU procedures anymore
Table 1. Endocarditis Prophylaxis for Dental Procedures\(^1\)

<table>
<thead>
<tr>
<th>Oral</th>
<th>Adult Dosage (30-60 minutes before procedure)</th>
<th>Pediatric Dosage (30-60 minutes before procedure)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin(^2,3) (Amoxil, and others)</td>
<td>2 g</td>
<td>50 mg/kg</td>
</tr>
<tr>
<td><strong>Penicillin allergy:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalexin(^4,5) (Keflex, and others)</td>
<td>2 g</td>
<td>50 mg/kg</td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clindamycin (Cleocin, and others)</td>
<td>600 mg</td>
<td>20 mg/kg</td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin(^3) (Zithromax, and others)</td>
<td>500 mg</td>
<td>15 mg/kg</td>
</tr>
<tr>
<td>or clarithromycin(^3) (Biaxin, and others)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parenteral (for patients unable to take oral drugs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin(^3)</td>
<td>2 g IM or IV</td>
<td>50 mg/kg IM or IV</td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefazolin or ceftriaxone (Rocephin, and others)</td>
<td>1 g IM or IV</td>
<td>50 mg/kg IM or IV</td>
</tr>
<tr>
<td><strong>Penicillin allergy:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefazolin(^4) or ceftriaxone(^4) (Rocephin, and others)</td>
<td>1 g IM or IV</td>
<td>50 mg/kg IM or IV</td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clindamycin (Cleocin Phosphate, and others)</td>
<td>600 mg IM or IV</td>
<td>20 mg/kg IV</td>
</tr>
</tbody>
</table>

1. Viridans streptococci are the most common cause of endocarditis after dental procedures.
2. Amoxicillin remains the drug of choice for patients without penicillin allergy because of its excellent bioavailability and generally good activity against streptococci.
4. Not recommended for patients with history of severe or immediate-type (urticaria, angioedema, anaphylaxis) allergy to penicillin.
5. Or another first- or second-generation oral cephalosporin in equivalent dosage.
Bacterial Meningitis

• Inflammation of the membranes (meninges) which surround the brain and spinal cord
  – vs Aseptic vs Encephalitis vs Ventriculitis

• Impact:
  – 25% mortality
  – Substantial morbidity (learning deficits, hearing loss, seizure disorder, hydrocephalus)
Anatomy & Physiology of the CNS

1. Brain
2. Brain Stem
3. Spinal Cord
The Meninges

- Membrane lining CNS:
  - Dura mater
  - Arachnoid,
  - Pia mater

- Isolates & protects the CNS from pathogens, toxins, etc
Pathogenesis

Sources of bacteria:

- Translocation / inoculation (trauma, surgery)
- Parameningeal seeding (otitis media, sinusitis)
- Hematogenous

  Mucosal colonization
    ➞ Local Invasion
    ➞ Bacteremia
    ➞ Meningeal Invasion (Cross BBB)
    ➞ Bacterial Replication
    ➞ Inflammation
Presentation

- Acute (s/s within 24hrs) vs Subacute (1 week)
- Neonates: lethargy, irritability, poor feeding
- Children & Adults: fever, headache, photophobia, leukocytosis (w/ left shift), stiff neck (nucal rigidity) and back, nausea, vomiting, & altered mental status
  + Brudzinski’s sign:
    flexing neck of supine pt causes flexion of hips & knees
  + Kernig’s sign:
    Can’t passively extend leg after touching thigh to abdomen with knee flexed.
- Elderly: fever & altered mental status
Laboratory findings

- Leukocytosis with left shift (bandemia)
- Bacteremia (reseeding CNS)
- CSF analysis in all patients suspected of Meningitis (unless papilledema, trauma, or coagulopathy).
- +/- CT Scan (do if can’t do lumbar tap)
<table>
<thead>
<tr>
<th>CSF</th>
<th>Bacterial</th>
<th>AFB/Fungus</th>
<th>Viral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure</td>
<td>↑</td>
<td>↑</td>
<td>WNL or ↑</td>
</tr>
<tr>
<td>Organisms</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Cells</td>
<td>&gt;500</td>
<td>&lt;500</td>
<td>&lt;500</td>
</tr>
<tr>
<td></td>
<td>(500-50,000)</td>
<td>(25-1,000)</td>
<td>(6-1,000)</td>
</tr>
<tr>
<td>Diff</td>
<td>Neutrophils (90-95%)</td>
<td>Monos (85%)</td>
<td>Monos</td>
</tr>
<tr>
<td>Glucose</td>
<td>↓</td>
<td>↓</td>
<td>WNL</td>
</tr>
<tr>
<td></td>
<td>(0-35)</td>
<td>(15-35)</td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td>↑</td>
<td>↑</td>
<td>WNL or ↑</td>
</tr>
<tr>
<td></td>
<td>(50-500)</td>
<td>(50-1,000)</td>
<td></td>
</tr>
</tbody>
</table>
CSF Examination 2

• Gram Stain
  – Pneumococcus (S. pneumoniae)
    • Gram-Positive Lancet-shaped Diplococcus
  – Meningiococcus (N. meningitidis)
    • Gram-Negative Diplococcus

• Latex agglutination (Capsular polysaccharide antigens)
  – Strep. pneumoniae
  – H. influenzae type B (invasive)
  – N. meningitidis Group A and C
  – Group B streptococcus
Antibiotic Issues

• Optimal outcome demands bactericidal effect in the cerebrospinal fluid
  – Penetration into the fluid & concentration there
    • Inflamed meninges allow increased permeability of BBB
  – Characteristics of the antibiotic
    • Small molecular size, Low degree of binding to protein
    • Low degree of ionization at physiologic pH, High solubility in lipids
## Antibiotic Penetration

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Mg/kg</th>
<th>$C_{\text{csf}}/C_{\text{serum}}$ (%)</th>
<th>PSSP</th>
<th>PRSP</th>
<th>NM</th>
<th>HI</th>
<th>PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>50-70</td>
<td>13-14</td>
<td>++</td>
<td>+/-*</td>
<td>++</td>
<td>++**</td>
<td>-</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>80</td>
<td>8-16</td>
<td>++</td>
<td>+/-*</td>
<td>++</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>100-150</td>
<td>20-40</td>
<td>+</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>60</td>
<td>7-14</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

SP: Strep. pneumoniae, Pen Susceptible (PS) or Pen Resistant (PR)

NM: N. meningitidis  HI: H. influenzae  PA: P. aeruginosa

- $C_{\text{MIC}_{90}} < 1$
- $C_{\text{MIC}_{90}} 1-10$
- $C_{\text{MIC}_{90}} > 10$

* Intermediately & Highly penicillin - resistant strains

** Non-Beta-lactamase producing strains
Usual adult antibiotic doses

- Ceftriaxone 2 grams IV Q12 hours
- Ampicillin 2 grams IV Q 4 hours*
- Penicillin 4 million units IV Q 4 hours*
- Vancomycin 20 mg / kg IV Q 8 hours*
  - Target trough of 15-20
  - Consider loading dose of 25 - 30 mg / kg

* adjust dose for renal dysfunction at GFR < 60 mL/minute
## Empiric Therapy

<table>
<thead>
<tr>
<th>Age</th>
<th>Bugs</th>
<th>Drugs</th>
</tr>
</thead>
</table>
| < 1 Month    | *S. agalactiae, E. coli,*  
* L. monocytogenes,  
* Klebsiella species* | Ampicillin plus cefotaxime  
or ampicillin plus an aminoglycoside |
| 1–23 months | *S. pneumoniae,*  
* N. meningitidis,*  
* S. agalactiae,*  
* H. influenzae,*  
* E. coli* | Vancomycin plus a  
third-generation cephalosporin |
| 2–50 years  | *N. meningitidis,*  
* S. pneumoniae* | Vancomycin plus a  
third-generation cephalosporin |
| > 50 years  | *S. pneumoniae,*  
* N. meningitidis,*  
* L. monocytogenes,*  
* aerobic GNR* | Vancomycin plus  
ampicillin plus a  
third-generation cephalosporin |
| Head Trauma | MR-SA & GNR (PA)                  | Vanco plus  
Ceftazidime or Cefepime or Meropenem |
# Pathogen-Specific Therapy

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Susceptibilities</th>
<th>Drug of Choice (all high dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. pneumoniae</em></td>
<td>Penicillin &lt; 0.1 mcg/mL</td>
<td>Penicillin</td>
</tr>
<tr>
<td></td>
<td>Penicillin 0.1 - 1 mcg/mL</td>
<td>Ceftriaxone</td>
</tr>
<tr>
<td></td>
<td>Penicillin &gt; 2 mcg/mL</td>
<td>Vancomycin &amp; Ceftriaxone</td>
</tr>
<tr>
<td><em>N. meningitidis</em></td>
<td>Penicillin &lt; 0.1 mcg/mL</td>
<td>Penicillin</td>
</tr>
<tr>
<td></td>
<td>Penicillin 0.1 - 1 mcg/mL</td>
<td>Ceftriaxone</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>Negative Beta-Lactamase</td>
<td>Ampicillin</td>
</tr>
<tr>
<td></td>
<td>Positive Beta-Lactamase</td>
<td>Ceftriaxone</td>
</tr>
<tr>
<td><em>L. monocytogenes</em></td>
<td>NA</td>
<td>Ampicillin (alt = Trimeth/Sulfa)</td>
</tr>
</tbody>
</table>
Adjunctive Dexamethasone?

- Children with documented *H. Influenzae*
- Adults with documented *S. pneumoniae*
  - 10 mg (0.15 mg/kg) 4 times daily for 2-4 days before or with first dose of antibiotic.
- Still controversial for empiric therapy
Duration of treatment

- *S. pneumoniae*: 10-14 days
- *H. influenzae*: 7 days
- *N. meningitidis*: 7 days
- *L. monocytogenes*: 14-21 days
- *S. agalactiae*: 14-21 days
- Enterobacteriaceae: 21 days
- *P. aeruginosa*: 21+ days
Prevention - Chemoprophylaxis

• H. influenzae type b (invasive)
  – Rifampin 20mg/kg PO (max 600mg) Qday x 4 doses
    • Household and/or day care contact residing with index case or \( \geq \) 4hrs
    • Day care contact: same day care as index case for 5-7 days before onset
    • See also Pediatric Redbook 2009
Prevention - Chemoprophylaxis

• N. meningitidis

  Ciprofloxacin 500mg PO x 1 dose
  or Ceftriaxone 250mg IM x 1 dose
  or Rifampin 600mg PO Q12hrs x 4 doses

• Close contacts (droplets): > 4 hrs or exposure to nasopharyngeal secretions
Prevention - Vaccination

*S. pneumoniae*:
- Pneumovax 23, Pnu-Immune, Pneumo23
  - Immunocompromised (HIV, Malignancy, meds, or nephrotic syndrome)
  - Asplenic, >65yo
- Prevnar (7 valent conjugate vaccine)
  - Children: 3 doses at 2-6 months, 4th at 12-15 months

*H. influenzae* type b:
- Children: 4 shot series

*N. Meningitidis*:
- ?Asplenia, epidemics, at risk (college, military)
Other CNS Infections

- HSV encephalitis: Acyclovir 10mg/kg IV Q8h
- Tuberculosis: RIPE = INH, RIF, ETB, PZA
- Cryptococcal: Amphi B + 5FC (HIV: +/- 5FC)
- Brain Abscess: Streptococci & Bacteroides
  - Metronidazole Plus (Ceftriaxone or high dose Penicillin G)
- Drug-induced Aseptic
  - NSAID’s especially if patient has lupus
  - Trimethoprim / Sulfamethoxazole
  - Ciprofloxacin
  - Penicillin, Cephalosporins
  - Isonazid, Pyrazinamide