Objectives

1. Review limitations in current osteomyelitis literature, national guidelines, and practice.
2. Evaluate medical literature investigating treatment modalities of osteomyelitis and comparing oral antibiotics to traditional regimens.
3. Compare pharmacokinetic properties of parenteral and oral antibiotics and their efficacy in treatment of osteomyelitis.
4. Develop evidence-based conclusion for the role of oral antibiotics in osteomyelitis.
Background

I. Relevance to practice
   a. Evidence-based therapy
      i. No Food and Drug Administration (FDA) approved antibiotics for osteomyelitis in last 15 years
      ii. No "Guidance for Industry" standards for osteomyelitis studies
      iii. Paucity of guidelines recommendations
      iv. Several study limitations in current literature
   b. Recurrence
      i. High rates of treatment failures and recurrence of ~20% all cases
   c. Issues with traditional regimens
      i. Patient convenience/quality of life
      ii. Complication of intravenous (IV) therapy
         1. Mechanical: occlusion, thrombosis
         2. Infectious
         3. Recent Veterans Affairs study reported line complication rate of ~6% in their adult patient population
      iii. Cost
         1. Direct medical charges per episode of Staphylococcal osteomyelitis, including average hospital facility charges, professional fees, and postdischarge costs, was estimated to $35,000 in 1995 in a New York hospital; no specification of IV or oral (PO) therapy
         2. $135-263/day for outpatient intravenous antimicrobial therapy versus cost of oral antibiotics

II. Definition of osteomyelitis
   a. Inflammation of bone due to a pathogenic organism leading to destruction of bone

III. Epidemiology
   a. Rare in adults; not well described in literature
   b. Occurs in 3-25% of open fractures depending on grade of trauma
   c. Annual incidence of vertebral osteomyelitis is 2.4/100,000
   d. Osteomyelitis may be present in up to 20% of mild diabetic foot infections (DFI) and in 50-60% of severely infected wounds

Pathophysiology

I. Bone structure
   a. Cortical: dense outer bone
   b. Cancellous: spongy inner bone
   c. Periosteum: dense fibrous membrane covering bone

II. Mechanisms of infection
   a. Adherence
      i. Microorganisms adhere to fibronectin receptors or other proteins of bone marrow
   b. Bone destruction
      i. Ongoing inflammatory cytokines lead to bone destruction
      ii. Ischemia due to compression of vascular channels and subsequent bone necrosis
   c. Necrotic bone
      i. Entrapped bone quickly becomes nonviable
         1. Formation of sequestrum
         2. Organisms can live in sequestrum for years
         3. Formation of new, living involucrum around sequestrum
   d. Biofilms
      i. Microbial community that show altered phenotypes
      ii. Bacterial communication through quorum sensing
      iii. Fibrinogen covering evades host defense mechanisms and antimicrobial penetration
      iv. Allows bacteria to hide intracellularly and achieve slow metabolic rate
      v. Common: Staphylococcus aureus, Streptococcus pneumoniae, Pseudomonas aeruginosa
III. Pathogens

Table 1. Organisms by frequency encountered

<table>
<thead>
<tr>
<th>Common &gt;50% of cases</th>
<th>Encountered occasionally &gt;25% of cases</th>
<th>Rare &lt;5% of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. aureus</em></td>
<td><em>Streptococci spp</em></td>
<td><em>Mycobacterium non-tuberculosis</em></td>
</tr>
<tr>
<td>Coagulase-negative <em>staphylococci</em> (CoNS)</td>
<td><em>Enterococci spp</em></td>
<td>Dimorphic fungi</td>
</tr>
<tr>
<td><em>Pseudomonas spp</em></td>
<td><em>Candida spp</em></td>
<td></td>
</tr>
<tr>
<td><em>Enterobacter spp</em></td>
<td><em>Cryptococcus spp</em></td>
<td></td>
</tr>
<tr>
<td><em>Proteus spp</em></td>
<td><em>Aspergillus spp</em></td>
<td></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td><em>Mycoplasma spp</em></td>
<td></td>
</tr>
<tr>
<td><em>Serratia spp</em></td>
<td><em>Tropheryma whippelli</em></td>
<td></td>
</tr>
<tr>
<td>Anaerobes</td>
<td><em>Brucella spp</em></td>
<td></td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td><em>Salmonella spp</em></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Organisms isolated in select patient population

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patient populations</td>
<td><em>S. aureus</em></td>
</tr>
<tr>
<td>Foreign body associated infections</td>
<td>CoNS, <em>Propionibacterium</em> spp</td>
</tr>
<tr>
<td>Nosocomial infections</td>
<td><em>Enterobacteriaceae, P. aeruginosa, Candida</em> spp</td>
</tr>
<tr>
<td>Diabetic foot lesions and decubitus ulcers</td>
<td><em>Streptococci spp, E. coli, K. pneumonia, Proteus</em> spp, anaerobic bacteria</td>
</tr>
<tr>
<td>Human Immunodeficiency Virus (HIV)</td>
<td><em>Bartonella henselae or B quintana</em></td>
</tr>
<tr>
<td>Immunocompromised patients</td>
<td><em>Aspergillus</em> spp, <em>Candida albicans, or Mycobacteria</em> spp</td>
</tr>
</tbody>
</table>

IV. Classification systems

Table 3. Osteomyelitis classification methods

<table>
<thead>
<tr>
<th>Waldvogel</th>
<th>Contiguous</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Hematogenous</em></td>
<td>Local spread from contaminated source</td>
</tr>
<tr>
<td>Often secondary to seeding from bacteremia; Common in pediatrics</td>
<td>-No generalized vascular disease</td>
</tr>
<tr>
<td><em>Chronic</em></td>
<td>-Generalized vascular disease</td>
</tr>
<tr>
<td>Formation of necrotic bone</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cierny-Mader</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staging</em></td>
<td></td>
</tr>
<tr>
<td>Stage 1: medullary; Stage 2: superficial; Stage 3: localized; Stage 4: diffuse</td>
<td></td>
</tr>
<tr>
<td><em>Host</em></td>
<td></td>
</tr>
<tr>
<td>o Healthy</td>
<td></td>
</tr>
<tr>
<td>o Compromised</td>
<td></td>
</tr>
<tr>
<td>o Bs: Systemic:</td>
<td></td>
</tr>
<tr>
<td>a. Malnutrition, renal/ hepatic failure, diabetes, extreme ages, immunocompromised</td>
<td></td>
</tr>
<tr>
<td>o Bl: Local</td>
<td></td>
</tr>
<tr>
<td>a. Lymphedema, venous stasis, extensive scarring, small-vessel disease, neuropathy</td>
<td></td>
</tr>
<tr>
<td>o Bls: Local and systemic</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chronicity</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Timing</em></td>
<td>o Initial</td>
</tr>
<tr>
<td>o Acute: signs and symptoms &lt;2 weeks</td>
<td></td>
</tr>
<tr>
<td>o Chronic: signs and symptoms ≥2 weeks</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>o Subsequent</td>
</tr>
</tbody>
</table>
Diagnosis

I. Diagnostic testing
   a. Laboratory
      i. White blood cell count (WBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)
      ii. Blood cultures, bone biopsy
   b. Imaging
      i. Initial: conventional radiography; commuted tomography (CT) imaging often unnecessary
      ii. **Standard of care**: magnetic resonance imaging (MRI)—more specific and sensitive
   c. Other
      i. Doppler ultrasonography

Treatment

I. Treatment based on chronicity
   a. Acute
      i. Antibiotics +/- surgical debridement
   b. Chronic
      i. Antibiotics + surgical debridement

II. Surgical debridement and abscess drainage
   a. Goal of debridement is to reach viable, healthy tissue and to remove biofilm
   b. Livorsi and colleagues, 2008
      i. Significantly higher failure rates have been reported in patients with vertebral osteomyelitis who do not receive drainage of abscess, (P<0.04)
   c. Gentry and colleagues, 1990
      i. Patients without debridement had worse outcomes (43% of failures attributed to insufficient debridement)

III. Antibiotics
   a. Traditional regimens
      i. 4-8 weeks of parenteral antibiotics ± subsequent course of oral antibiotics
      ii. Rationale is that it takes 3-4 weeks for bone to revascularize
      iii. Long courses of parenteral antibiotics established in NEJM case series from the 1970’s
      iv. Osteomyelitis cure rate with parenteral antibiotics 67-90% in randomized controlled trials

Current recommendations

I. National guidelines
   a. No current guidelines
   b. Infectious Disease Society of America (IDSA) vertebral osteomyelitis guidelines in development

II. Methicillin-resistant *S. aureus* (MRSA) Guidelines
   a. Debridement and drainage is a mainstay of therapy (A-II)
   b. Optimal route not clearly established—should be decided on individual basis
      i. Vancomycin and daptomycin are recommended parenteral antibiotics (B-II)
         1. Vancomycin remains primary treatment, despite high failure rates
         ii. Trimethoprim/sulfamethoxazole (TMP/SMX), linezolid, and clindamycin are recommended oral antibiotics (BII-BIII)
      iii. Parenteral therapy may offer advantage of better compliance, higher serum level for some drugs, and greater historical experience
      iv. Optimal duration of therapy is unknown—recommend a minimum of 8 weeks (A-II)

III. Diabetic Foot Infection Guidelines
   a. Diagnosis
      i. Suspect osteomyelitis when patients with deep ulcers do not heal after 6 weeks of therapy
      ii. Bone cultures preferred
         1. <50% of bone cultures and soft tissue swabs correspond
         2. Most common organisms are *Staphylococcus aureus* and *Staphylococcus epidermis*
         3. Most common gram-negative bacilli are *E. coli, K. pneumonia*, and *Proteus spp*
b. Treatment
   i. Lack of data suggesting any specific antibiotic, route or duration of therapy is superior
   ii. Initial parenteral antibiotics may be beneficial, but predominantly oral antibiotic therapy with
       high bioavailability is probably adequate

IV. Spellberg B, Lipsky B. Clinical Infectious Diseases, 2012.16
   a. Are certain antibiotics preferred?
      ➞ Data does not suggest that parenteral antibiotics are superior to oral antibiotics for osteomyelitis
   b. Are oral antibiotics acceptable in certain cases?
      ➞ Oral agents with high bioavailability acceptable alternative in most cases
   c. How long should antibiotics be given?
      ➞ Inconclusive
   d. Is surgical debridement always necessary for cure?
      ➞ Surgical resection with antibiotic therapy appears to increase cure rate

V. Cochrane Review, 2013.5
   a. Objectives: to determine the effects of different systemic antibiotic treatment regimens for treating
      chronic osteomyelitis in adults
   b. Inclusion: randomized controlled trials (RCTs) and quasi-RCTs addressing effects of antibiotics after
      surgical debridement
   c. Results
      i. 8 trials, 282 participants; All high risk of bias
      ii. No difference found in four trials comparing parenteral to oral antibiotics (Cl: 0.92-1.18)
   d. Conclusions
      i. Limited evidence suggests route does not affect rate of disease remission
      ii. The main finding was lack of evidence to guide practice

Pharmacokinetics available antibiotics

IV. Background
   a. Bone less vascularized than tissue; cancellous bone achieves higher concentration than cortical bone18
   b. Few reports of higher antimicrobial concentration in inflamed bone16,19
   c. Goal: bone concentration>MIC16

Table 4. Pharmacokinetics of Oral Antibiotics1,16,20,21

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Serum level µg/mL</th>
<th>% Bone Concentration</th>
<th>MIC90± MSSA</th>
<th>CLSI± Breakpoints E. coli</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Free drug)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin (500mg)</td>
<td>5.5-7.5</td>
<td>3-31%</td>
<td>--</td>
<td>≤8</td>
</tr>
<tr>
<td>Amox/clav (875mg)</td>
<td>2.2-11.6</td>
<td>3-30%/1-14%</td>
<td>1</td>
<td>≤8/4</td>
</tr>
<tr>
<td>Cephalaxin (500mg)</td>
<td>12-30</td>
<td>18%</td>
<td>4</td>
<td>≤2 (cefazolin)</td>
</tr>
<tr>
<td>Cefpodoxime (400mg)</td>
<td>4.5-7</td>
<td>15-30%</td>
<td>4</td>
<td>≤2</td>
</tr>
</tbody>
</table>

*milligram; °micrograms per milliliter; °minimum inhibitory concentration that inhibits 90% of isolates; °CLSI: Clinical Laboratory Standard Institute

Figure 1. Human bone:serum ratios for various groups of antibacterials.20

*Lines indicate the group medians, and each symbol indicates the median concentration ratio of one study.
Table 5. Pharmacokinetics of Oral Antibiotics\(^{1,16,20,21}\)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Serum level μg/mL (Free drug)</th>
<th>% Bone Concentration</th>
<th>MIC90 MSSA</th>
<th>CLSI Breakpoints E. coli</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin (750mg)</td>
<td>4.3</td>
<td>27-48%</td>
<td>1</td>
<td>≤1</td>
</tr>
<tr>
<td>TMP-SMX (160mg)</td>
<td>1.72</td>
<td>50%/15%</td>
<td>2/38</td>
<td>≤2/38</td>
</tr>
<tr>
<td>Linezolid (600mg)</td>
<td>11-21.1</td>
<td>40-50%</td>
<td>4</td>
<td>--</td>
</tr>
<tr>
<td>Clindamycin (600mg)</td>
<td>7.5</td>
<td>40-67%</td>
<td>0.5</td>
<td>--</td>
</tr>
<tr>
<td>Doxycycline (100mg)</td>
<td>2.6</td>
<td>2-86%</td>
<td>4</td>
<td>≤4</td>
</tr>
</tbody>
</table>

Evidence Supporting Use of Oral antibiotics

I. Evidence supporting early parenteral to oral transition


<table>
<thead>
<tr>
<th>Study objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Evaluate osteomyelitis cure with early switch from parenteral to oral therapy</td>
</tr>
<tr>
<td>o Apparent cure: no signs/symptoms 6 months after completion</td>
</tr>
<tr>
<td>o Relapse: infection occurring at same site requiring antibiotics or surgery</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Retrospective chart review</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient population</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 72 adults</td>
</tr>
<tr>
<td>• Do not specify chronic versus acute</td>
</tr>
<tr>
<td>• Mostly following trauma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>• IV group received &gt;4 weeks of IV therapy</td>
</tr>
<tr>
<td>• PO group received &lt;4 weeks of IV therapy followed by oral regimen</td>
</tr>
<tr>
<td>• Oral regimens mostly rifampin, quinolones, TMP-SMX, clindamycin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source/Organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bone, blood, deep tissue, abscess</td>
</tr>
<tr>
<td>• MSSA: 35 patients</td>
</tr>
<tr>
<td>• MRSA: 37 patients</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cure rate: 69% for IV group versus 78% for switch group, (P=0.59)</td>
</tr>
<tr>
<td>• Apparent cure rates were similar regardless of duration of intravenous therapy: 83% &lt; 2 weeks, 72% 2–4 weeks, 75% 4–6 weeks and 66% ≥ 6 weeks, (P=0.68)</td>
</tr>
<tr>
<td>• MRSA cure: 65%; methicillin-sensitive S. aureus (MSSA) cure: 83% , (P&lt;0.08)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Authors’ conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Recommend short course of IV antibiotics followed by oral based rifampin combination</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Weaknesses:</td>
</tr>
<tr>
<td>o Small sample size</td>
</tr>
<tr>
<td>o No standard regimen</td>
</tr>
<tr>
<td>• Strengths</td>
</tr>
<tr>
<td>o Included patients with diabetes mellitus (DM), orthopedic implants, traumatic injuries</td>
</tr>
<tr>
<td>o Rifampin treated patients did worse when receiving with concomitant vancomycin</td>
</tr>
</tbody>
</table>
## Treatment by individual antibiotics

### I. Ciprofloxacin Literature

#### Table 7. Ciprofloxacin Randomized and Nonrandomized Studies

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Baseline Characteristics</th>
<th>Intervention</th>
<th>Source/Organism</th>
<th>Follow-up</th>
<th>Clinical Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective, nonblinded, RCT</td>
<td>• N: 5</td>
<td>• Ciprofloxacin 750mg BID or lomefloxacin 800mg BID</td>
<td>• Bone biopsy or aspirate</td>
<td>14-36 months</td>
<td>Ciprofloxacin: 40% (2/5)  Lomefloxacin: 71% (5/7)</td>
</tr>
<tr>
<td></td>
<td>• Chronicity: Chronic</td>
<td>• Debridement: Not reported</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mean age: 38 years</td>
<td>• Mean duration therapy: 60.6 days (28-110)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• S. aureus (4), S. epidermis (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

**Conclusions**

Authors' conclusions:
- Oral quinolone therapy may offer an alternative option in some patients for quinolone susceptible gram-positive organisms

Comments:
- All patients who failed were treated for *Staphylococcus spp* infections

Limitations:
- Do not specify etiologies
- Several patients lost to follow-up
- Small patient population

#### Greenberg et al. 1987

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Baseline Characteristics</th>
<th>Intervention</th>
<th>Source/Organism</th>
<th>Follow-up</th>
<th>Clinical response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective, nonblinded, RCT</td>
<td>• N: 30</td>
<td>• Ciprofloxacin 750mg BID versus “appropriate therapy” for ≥6 weeks</td>
<td>• Blood or from site of infection</td>
<td>1-13 months</td>
<td>Ciprofloxacin: 50% (7/14)  Alternative antibiotic group: 69% (11/16)</td>
</tr>
<tr>
<td></td>
<td>• Chronicity: Chronic</td>
<td>• Debridement: Not reported</td>
<td>• Primarily obtained from biopsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mean age: 52 years</td>
<td>• Mean duration therapy: Ciprofloxacin group: 56 days (44-73)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alternative antibiotic group: 43 days (19-150)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Enterobacteriaceae spp (18), P. aeruginosa (16), S. aureus (4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Conclusions**

Authors' conclusions:
- Oral ciprofloxacin therapy for chronic osteomyelitis appears to be as effective as other antibiotic therapies

Comments:
- Failures were due to noncompliance, foreign body infection, immunosuppression, and superinfection
- More failures with ciprofloxacin over alternative antibiotic group with *P. aeruginosa*
- Alternative antibiotic group often combination therapy of broad-spectrum antibiotics

Strengths:
- Randomized
- Comparator group

Limitations:
- Did not include etiology infection
- Exclusion was severity of disease requiring parenteral therapy
- Debridement not reported
- No standardized comparator
### Gentry et al. 1990

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Baseline Characteristics</th>
<th>Intervention</th>
<th>Source/Organism</th>
<th>Follow-up</th>
<th>Clinical Response</th>
</tr>
</thead>
</table>
| Prospective, RCT | • N: 67  
• Chronicity: Chronic  
• Mean age: 37 years | • Ciprofloxacin 750mg BID versus ceftazidime or nafcillin plus aminoglycoside (AMG)  
• Duration:  
  Oral: at least 6 weeks  
  Parenteral: at least 4 weeks, not to exceed 6 weeks  
• Mean duration of therapy: Ciprofloxacin group: 56 days  
  Alternative antibiotic group: 47 days  
• Debridement: Required | • Bone biopsy  
  S. aureus (20),  
  E. faecalis (7),  
  P. aeruginosa (17),  
  P. mirabilis (8),  
  K. pneumonia (7),  
  S. marcescens (7),  
  Enterobacter spp (5),  
  E. coli (2),  
  M. morganii (2),  
  Providencia spp (2),  
  Acinetobacter spp (2) | 1 year | Ciprofloxacin: 77% (24/31)  
  Ceftazidime or nafcillin plus AMG: 79% (22/28) |

**Conclusions**

Authors’ conclusions:
- Oral ciprofloxacin is as safe and effective as parenteral antibiotics in chronic osteomyelitis  
- Debridement is the most important factor for clinical success

Comments:
- Ciprofloxacin group treated 10 days longer on average  
- Failure rates high with *P. aeruginosa* in both groups  
- *S. aureus* as a single pathogen 0/8 cures in ciprofloxacin group

**Strengths:**
- Sufficient follow-up  
- Bone biopsy

**Limitations:**
- Small patient population—stated 6,000 cases to achieve 80% power

### Swedish Study Group, 1988

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Baseline Characteristics</th>
<th>Intervention</th>
<th>Source/Organism</th>
<th>Follow-up</th>
<th>Clinical Response</th>
</tr>
</thead>
</table>
| Prospective, NR, open-label, non-comparative | • N: 34  
• Chronicity: Acute, chronic  
• Etiology: Trauma, DFI, PAD, hematogenous  
• Mean age: 65 years | • Ciprofloxacin 500-1500mg BID  
• Mean duration of therapy: 139 days (15-476 days)  
• Debridement: Not reported, likely as majority of patients had bone biopsies | • Bone biopsy or fistula secretion  
  *P. aeruginosa* (28),  
  Enterobacter spp (2),  
  E. coli (1),  
  P. mirabilis (2),  
  S. aureus, S. epidermis,  
  B. fragilis | ≥2 months | 65% (22/34) |

**Conclusions**

Authors’ conclusions:
- Ciprofloxacin offers an oral treatment alternative in patients with acute and chronic osteomyelitis caused by gram-negative pathogens

Comments:
- Resistance developed in 4 patients; 3/20 *P. aeruginosa*

**Strengths:**
- Bone biopsy in most patients

**Limitations:**
- Small patient population  
- Short follow-up time
### Hessen et al. 1987

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Baseline Characteristics</th>
<th>Intervention</th>
<th>Source/Organism</th>
<th>Follow-up</th>
<th>Clinical Response</th>
</tr>
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<tbody>
<tr>
<td>Prospective, non-randomized (NR)</td>
<td>• N: 23</td>
<td>• Ciprofloxacin 750mg BID for duration determined on individual basis</td>
<td>• Bone or deep soft tissue biopsy</td>
<td>Mean: 43 weeks</td>
<td>86% (19/22)</td>
</tr>
<tr>
<td></td>
<td>• Chronicity: Acute, chronic</td>
<td>• Additional antibiotics acceptable</td>
<td>• P. aeruginosa (15), S. marcescens (5), S. aureus (3), S. epidermis (3), E. coli (3), P. mirabilis (1), K. pneumoniae (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Etiology: Surgery, trauma, DFI, decubitus ulcer</td>
<td>• Mean duration of therapy: 62 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mean age: 58 years</td>
<td>• Debridement: 22/23 patients</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Conclusions

**Authors’ conclusions:**
- Ciprofloxacin was effective and well-tolerated for the treatment of gram-negative bacillary osteomyelitis

**Comments:**
- One failure likely due to non-compliance; another secondary to *S. marcescens* resistance

**Strengths:**
- Majority of patients with bone biopsies
- Debridement performed in most patients
- Reasonable follow-up time

**Limitations:**
- Excluded patient with severe acute underlying disease
- No standardized length of treatment

### Lesse et al. 1987

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Baseline Characteristics</th>
<th>Intervention</th>
<th>Source/Organism</th>
<th>Follow-up</th>
<th>Clinical Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective, NR, non-comparator, on-going at time of publication</td>
<td>• N: 23</td>
<td>• Ciprofloxacin 750mg BID for 6-24 weeks</td>
<td>• Bone biopsy or joint aspirate</td>
<td>2-14 months</td>
<td>100% (14/14)</td>
</tr>
<tr>
<td></td>
<td>• 14 completed therapy</td>
<td>• Mean duration of therapy: 110 days (41-191)</td>
<td>• P. aeruginosa (18), S. marcescens (2), Enterobacter spp (2), M. morganii (2), E. coli (1), Proteus spp CoNS (6), S. aureus 2, Streptococcus spp (3)</td>
<td>Mean: 6.1 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Chronicity: Acute, chronic, recurrent</td>
<td>• Debridement: “Performed as indicated”</td>
<td></td>
<td>(1-13 months)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Etiology: post-surgical (9), post-traumatic (3), DM (2), alcoholism (2), sickle cell disease (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mean age: 51 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Conclusions

**Authors’ conclusions:**
- Ciprofloxacin efficacious for gram-negative osteomyelitis

**Strengths:**
- Included MICs
- Reasonable follow-up time
- Majority of patients with bone biopsies

**Limitations:**
- Small patient population
- No standardized length of treatment
II. Ciprofloxacin summary
a. Several studies from 1980-1990 provide positive evidence for the use of oral ciprofloxacin for the treatment of gram negative osteomyelitis
i. Largest study showing positive results was randomized, included debridement, and obtained bone biopsy cultures
ii. All of the studies were small sample sizes
iii. Cure percentages ranged from 40-100% (40% outlier)
   1. Study with the lowest cure rate was primary treating S. aureus
iv. Several of the studies showed high rates of failure with P. aeruginosa, however, in comparator study, rate of failure were similar between IV and PO
b. Important to consider collateral damage of increased resistance with use of ciprofloxacin

c. Favorable pharmacokinetic profile
   i. Oral bioavailability: 60-80%
   ii. Bone penetration: 37-60%
d. Ciprofloxacin is an efficacious agent in the treatment of gram-negative acute and chronic osteomyelitis

III. Trimethoprim/sulfamethoxazole Literature

Table 8. Trimethoprim-Sulfamethoxazole Randomized and Nonrandomized Studies

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Baseline Characteristics</th>
<th>Intervention</th>
<th>Source/Organism</th>
<th>Follow-up</th>
<th>Clinical Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective, NR</td>
<td>N: 88</td>
<td>TMP-SMX 1 DS tablet BID versus dicloxacillin, cloxacillin, or erythromycin</td>
<td>Unspecified</td>
<td>≥11 months</td>
<td>TMP-SMX: 30/66 (45%)</td>
</tr>
<tr>
<td></td>
<td>66 in TMP-SMX group, 22 in penicillin (PCN)/erythromycin group</td>
<td>Debridement: 54% in TMP-SMX group, 56% in penicillin/erythromycin group</td>
<td>TMP-SMX: S. aureus (38), P. aeruginosa (9), Klebsiella spp (6), Enterobacter (2), Streptococcus spp (3)</td>
<td></td>
<td>PCN/erythromycin: 11/22 (50%)</td>
</tr>
<tr>
<td></td>
<td>Chronicity: Chronic</td>
<td>All patients received at least 4 weeks therapy</td>
<td>PCN/erythromycin: S. aureus (16), P. aeruginosa (4), Streptococcus spp (2)</td>
<td></td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>Etiology: unspecified</td>
<td>Treatment duration &lt;12 weeks: 71.6% TMP-SMX group; 92% PCN/erythromycin group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean age: 25.4 years TMP-SMX group, 19.1 years PCN/erythromycin group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusions

Authors’ conclusions:
- TMP-SMX should be another antimicrobial choice in chronic osteomyelitis because low cost, convenient administration

Comments:
- Do not address how organisms like P. aeruginosa were treated
- PCN/erythromycin not recommended for osteomyelitis

Strengths:
- Comparator group
- Statistical analysis

Limitations:
- Do not specify etiology
- Do not specify culture sources
- Only half received debridement
### Nguyen, et al. 2009

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Baseline Characteristics</th>
<th>Intervention</th>
<th>Source/Organism</th>
<th>Follow-up</th>
<th>Clinical Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective, NR</td>
<td>- N: 56</td>
<td>- Linezolid 600mg BID plus rifampicin 10mg/kg BID versus TMP-SMX (TMP 8mg/kg/day) BID plus rifampicin 10mg/kg BID</td>
<td>- Intra-operative samples or joint aspiration</td>
<td>12 months; most patients with 2 year follow-up</td>
<td>Cure: linezolid 89.3%, TMP-SMX 78.6%, (P=0.47) ADRs Linezolid 42.9%, TMP-SMX 46.4%, (P=1)</td>
</tr>
</tbody>
</table>

#### Baseline Characteristics
- 28 in linezolid group, 28 in TMP-SMX group
- Chronicity: Chronic
- Etiology: 36 orthopedic device-related, 6 DFI
- Mean age: 58.5 (22-83)

#### Intervention
- Lead-in of IV antibiotics for 5-7 days
- Debridement: not reported; all patients with foreign body (FB) had surgical intervention

#### Source/Organism
- Linezolid: MRSA (11, 34%), MSSA (4, 13%), MRCoNS (9, 28%), Enterococcus spp (5, 16%)
- TMP-SMX: MRSA (10, 22%), MSSA (7, 16%), MRCoNS (9, 20%)

#### Conclusions
- Authors’ conclusions: Oral linezolid/rifampicin and oral TMP-SMX equally efficacious in treatment osteomyelitis
- Comments: No differences in cure based on surgical intervention, organisms

### Euba et al. 2009

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Baseline Characteristics</th>
<th>Intervention</th>
<th>Source/Organism</th>
<th>Follow-up</th>
<th>Clinical response</th>
</tr>
</thead>
</table>
| Prospective, randomized | - N: 50                                                                                   | - IV cloxacillin 2gm q4h for 6 weeks plus oral cloxacillin for 2 weeks versus oral TMP-SMX (TMP 7-8mg/kg/day) plus rifampin 600mg/day for 8 weeks | - Bone biopsy MSSA | Median: 10 years (IQR 4-13) | Overall cure rate 89.6%(43/48)
  - Cure rate difference between the groups was 1.6% (CI -15.7-33.3)
  - 3 failures per protocol: 1/18 in cloxacillin group, 2/24 in rifampin-TMP-SMX group |

#### Baseline Characteristics
- 22 IV group, 28 PO group
- Chronicity: chronic
- Etiology: 34 postsurgical, 9 hematogenous, 4 trauma, 3 contiguous
- Mean age: 47.7 years (±18.3) cloxacillin group; 41.7 years (±21.1) TMP-SMX+rifampin

#### Intervention
- Debridement: all patients

#### Follow-up
- Median: 10 years (IQR 4-13)
**Euba et al. 2009 (continued)**

Authors' conclusions:
- Oral rifampin-cotrimoxazole therapy is a good alternative in the treatment of chronic staphylococcal osteomyelitis

Comments:
- 2 patients with HIV
- 1 patient with bacteremia
- No factor associated with failure

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>Strengths:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Defined etiology</td>
</tr>
<tr>
<td></td>
<td>• Defined organisms</td>
</tr>
<tr>
<td></td>
<td>• All bone biopsy</td>
</tr>
<tr>
<td></td>
<td>• All received debridement</td>
</tr>
<tr>
<td></td>
<td>• Long follow-up time</td>
</tr>
<tr>
<td></td>
<td>• Unblinded</td>
</tr>
</tbody>
</table>

**IV. TMP-SMX Summary**

a. TMP-SMX is a potentially useful option in the treatment of chronic, gram-positive osteomyelitis

i. Cure percentages ranged from 45-89.6%

   1. The study with the lowest cure rate by Saengnipanthkul, et al. included patients with only *P. aeruginosa* osteomyelitis \(^\text{30}\)

   ii. Treatment with TMP-SMX was generally well-tolerated

   iii. All studies had long follow-up times which increases the strength of this recommendation

b. Favorable pharmacokinetic profile\(^{16,20}\)

   i. Oral bioavailability: 90-100%

   ii. Bone penetration: 50% TMP, 15% SMX

c. The MRSA Guidelines give TMP-SMX with rifampin combination a B-II recommendation\(^{17}\)

**V. Linezolid Literature**

**Table 9. Linezolid Randomized and Nonrandomized Studies**

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Baseline Characteristics</th>
<th>Intervention</th>
<th>Source/Organism</th>
<th>Follow-up</th>
<th>Clinical Response</th>
</tr>
</thead>
</table>
| Retrospective, NR | • N: 56  
• 28 in linezolid group, 28 in TMP-SMX group  
• Chronicity: Chronic  
• Etiology: 36 orthopedic device-related, 6 DFI  
• Mean age: 58.5 (22-83) | • Linezolid 600mg BID plus rifampicin 10mg/kg BID versus TMP-SMX (TMP 8mg/kg/day) BID plus rifampicin 10mg/kg BID  
• Lead-in of IV antibiotics for 5-7 days  
• Debridement: not reported; all patients with FB had surgical intervention | • Intra-operative samples or joint aspiration  
Linezolid: MRSA (11, 34%), MSSA (4, 13%), MRCOnS (9, 28%), *Enterococcus spp* (5, 16%)  
TMP-SMX: MRSA (10, 22%), MSSA (7, 16%), MRCOnS (9, 20%) | 12 months; most patients with 2 year follow-up | Cure: linezolid 89.3%, TMP-SMX 78.6%, (P=0.47)  
ADRs Linezolid 42.9%, TMP-SMX 46.4%, (P=1) |
## Nguyen et al. 2009 (continued)

### Authors’ conclusions:
- Oral linezolid/rifampicin and oral TMP-SMX equally efficacious in treatment osteomyelitis

### Comments:
- No differences in cure based on surgical intervention, organisms

## Conclusions

### Strengths:
- Included patients with comorbidities
- Comparator
- Statistical analysis
- Sufficient follow-up

### Limitations:
- Small sample size

---

## Lipsky et al. 2012

### Study Design | Baseline Characteristics | Intervention | Source/Organism | Follow-up | Clinical response |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective, RCT</td>
<td>N: 371</td>
<td>Linezolid 600mg q12h either IV or PO versus ampicillin-sulbactam (1.5-3gm q6h) or amoxicillin-clavulanate (500-875mg q12-8h)</td>
<td>Suitable tissue wound specimens</td>
<td>15-21 days following treatment</td>
<td>Linezolid group: 27/44 (61%)&lt;br&gt;Amino-penicillin/β-lactamase inhibitor: 69% (11/16)&lt;br&gt;CI: -34.3-19.5</td>
</tr>
<tr>
<td>N: 241 in linezolid group</td>
<td>Total 77 patients with osteomyelitis</td>
<td>Could add vancomycin for MRSA infections in amino-penicillin/β-lactamase inhibitor group</td>
<td>Staphylococcus aureus (158 isolates), Staphylococcus epidermis (60 isolates), Enterococcus spp (59 isolates), Streptococcus agalactiae (52 isolates)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etiology: DFI</td>
<td>Mean age: 63 years old</td>
<td>Could add aztreonam for gram-negative infections in linezolid group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age: 63 years old</td>
<td></td>
<td>Median duration: 19 (±9) days for osteomyelitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Debridement: Not required, but wounds with necrotic areas were sharply debrided</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Authors’ conclusions:
- Oral linezolid equally efficacious to IV amino-penicillin/β-lactamase inhibitor combination in treatment osteomyelitis

### Comments:
- Most common ADRs were thrombocytopenia, anemia, nausea
- Shorter duration of treatment

### Limitations:
- Did not require debridement
- Did not include patients with critical ischemia or foreign bodies
- Could use additional antibiotics
- Short follow-up time

### Strengths:
- Prospective, randomized
# Rayner et al. 2004

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Baseline Characteristics</th>
<th>Intervention</th>
<th>Source/Organism</th>
<th>Follow-up</th>
<th>Clinical Response</th>
</tr>
</thead>
</table>
| Prospective, NR, open-label | • N: 55  
• Chronic; 53% long bone, 18% DFI, 15% vertebral osteomyelitis  
• Included 3 immunosuppressed patients  
• Compassionate use  
• All failed prior treatment  
• Mean age: 58 year (30-81) | • Linezolid 600mg BID IV or PO  
• 19 received IV lead-in period (34.5%)  
• 27 received PO only (49.1%)  
• Duration 5 days to 3 months  
• 13 (23.6%) received <28 days  
• 42 (76.4%) received >28 days  
• Debridement: not required | • 49 had surgically obtained positive cultures (89% bone, remaining aspirate)  
MRSA (25; 45.5%), vancomycin-resistant *E. faecium* (VRE) (17, 30.9%), MSSA (3, 5.5%), MRSE (2), VRE faecalis (2), VRE spp. (1), other | • Short-term follow-up median: 21.5 days (5-31)  
• Long-term follow-up median: 195 days (31-540) | • Short-term follow-up cure: 79% (38/48)  
• Long-term follow-up cure: 81.8% (18/22)  
• 2 patients with failure of oral |

## Conclusions

**Authors’ conclusions:**  
- Oral linezolid efficacious in treatment of chronic, MDR osteomyelitis  
**Comments:**  
- Most common ADR was GI disturbances; 10 patients developed anemia-6 requiring D/C; 9 decrease PLT counts-7 requiring D/C  
- No specific factor was more likely to result in failure  
- 63.6% (7) cure with MRSA  

**Strengths:**  
- Defined etiology  
- Defined organisms  
- Majority bone biopsy  

**Limitations:**  
- Non-comparator  
- Many patients did not receive long-term follow-up

---

**VI. Linezolid Summary**

a. Based on these three small studies, linezolid is a potential option in the treatment of gram-positive osteomyelitis  
i. Rayner et al. and Nguyen et al. included several patients with multi-drug resistant (MDR) organisms  
ii. Cure percentages ranged from 61-89.3%  
1. The study with the lowest reported cure rate was in osteomyelitis secondary to diabetic foot infections  
2. Patients were treated for a median duration of 19 days (±9 days)  
3. Comparator group had similar rates of cure  
iii. Small sample sizes weaken the strength of this recommendation  
iv. Adverse drug reactions may limit use, although this was not significant in the trials presented

b. Favorable pharmacokinetic profile  
i. Oral bioavailability: 100%  
ii. Bone penetration: 40-51%  

C. The MRSA Guidelines give linezolid a B-II recommendation
## VII. Clindamycin Literature

### Table 10. Clindamycin Randomized and Nonrandomized Studies

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Baseline Characteristics</th>
<th>Intervention</th>
<th>Source/Organism</th>
<th>Follow-up</th>
<th>Clinical Response</th>
</tr>
</thead>
</table>
| NR, case-series | • N: 12  
• Chronicity: chronic, refractory to other therapy  
• Etiology: unspecified  
• Mean age: 47 years | • Clindamycin 150mg q6h  
• Surgical debridement: not required  
• Mean duration of therapy: 124 days (48-288) | • Source unspecified  
S. aureus (7), CoNS (1), micrococcus (1), others unidentified | Not specified | • Cure: 5/12 (41.7%) |

### Conclusions

**Authors’ conclusions:**
- Clindamycin would appear distinctly inferior to lincomycin and cloxacillin

**Comments:**
- Likely underdosed

**Strengths:**
- Reported organisms

**Limitations:**
- Did not require debridement
- Did not specify follow-up

---

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Baseline Characteristics</th>
<th>Intervention</th>
<th>Source/Organism</th>
<th>Follow-up</th>
<th>Clinical response</th>
</tr>
</thead>
</table>
| Prospective, RCT | • N: 50  
• Pediatric patients  
• Chronicity: acute  
• Etiology: hematogenous; 8 had joint involvement  
• Median age: 9 years old | • 150mg/kg/d cephadrine divided q6h vs 40mg/kg/day clindamycin divided q6h  
• Treatment initiated IV, but switched to oral within 4 days in most cases (85%)  
• Mean duration: 23 days  
• Debridement: ~50% of patients—purposefully kept at a minimum  
• Treatment Duration: 3-4 weeks | • Bone biopsy or blood cultures  
S. aureus | ≥1 year (Median 27 months) | • Cure: 100% (50/50) patients |

### Conclusions

**Authors’ conclusions:**
- Treatment of pediatric acute *S. aureus* osteomyelitis can be simplified and cost reduced by keeping surgery at a minimum, shortening the course of antimicrobials, and switching quickly to the oral route

**Comments:**
- No mention MRSA

**Strengths:**
- Well-designed
- Long-term follow-up

**Limitations:**
- Homogenous patient population
- Bone biopsy not required
- Surgical intervention discouraged
**Study Design** | **Baseline Characteristics** | **Intervention** | **Source/Organism** | **Follow-up** | **Clinical Response**
---|---|---|---|---|---
Prospective, RCT | • N: 131  
• 67 patients in the short-term treatment group; 64 in the long-term group  
• Pediatric patients  
• Chronicity: acute  
• Etiology: hematogenous  
Median age: 9 years | • Clindamycin (40 mg/kg per day divided q6h) or first-generation cephalosporin  
• Randomized to 20 or 30 days, including an IV phase for the first 2 to 4 days  
Debridement: purposefully kept at a minimum | • Bone biopsy and blood cultures  
MSSA | 1 year follow-up in 126/131 patients | • Cure: 122/131 (93%)  
• 5 modifications to therapy made in short-term group  
4 modifications to therapy made in long-term group

### Baseline Characteristics
- N: 131 patients
- 67 patients in the short-term treatment group; 64 in the long-term group
- Pediatric patients
- Chronicity: acute
- Etiology: hematogenous
- Median age: 9 years

### Intervention
- Clindamycin (40 mg/kg per day divided q6h) or first-generation cephalosporin
- Randomized to 20 or 30 days, including an IV phase for the first 2 to 4 days
- Debridement: purposefully kept at a minimum

### Source/Organism
- Bone biopsy and blood cultures
- MSSA

### Follow-up
- 1 year follow-up in 126/131 patients

### Clinical Response
- Cure: 122/131 (93%)
- 5 modifications to therapy made in short-term group
- 4 modifications to therapy made in long-term group

### Conclusions
**Authors’ conclusions:**
- Most cases of childhood acute hematogenous osteomyelitis can be treated for 20 days with large doses of a well-absorbed antimicrobial, such as clindamycin or a first-generation cephalosporin, provided the clinical response is good and CRP normalizes within 7 to 10 days

**Strengths:**
- Well-designed
- Long-term follow-up

**Weaknesses:**
- Homogenous patient population
- Bone biopsy not required
- Surgical intervention discouraged

**Comments:**
- Did not consider modifications in therapy failure

#### VIII. Clindamycin Summary
- Strong data supporting the use of clindamycin in pediatric populations with acute, hematogenous osteomyelitis
  - **The cure percentage was 41.7%, however, clindamycin was likely under-dosed and surgical debridement was not required**
- Favorable pharmacokinetic profile\textsuperscript{16,20}
  - **Oral bioavailability: 90%**
  - **Bone penetration: 40-67%**
- The MRSA Guidelines give clindamycin a B-III recommendation\textsuperscript{17}

#### IX. Tetracycline Literature

**Table 11. Tetracycline case reports**

<table>
<thead>
<tr>
<th>Report</th>
<th>Patient</th>
<th>Intervention</th>
<th>Etiology/Chronicity</th>
<th>Organisms</th>
<th>Response</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan et al. 2012\textsuperscript{38}</td>
<td>45 year old, Chinese male, Shoulder w/ implant placement</td>
<td>Oral doxycycline 100mg BID x6 weeks</td>
<td>Chronic/contiguous from implant-related septic arthritis</td>
<td><em>Kytococcus Schroeteri</em></td>
<td>Inflammatory markers resolved after 1 week; no relapse at 3 years</td>
<td>Oral doxycycline potentially effective for osteomyelitis w/ surgical intervention</td>
</tr>
</tbody>
</table>
### Table 11. Tetracycline Case Reports (continued)

<table>
<thead>
<tr>
<th>Report</th>
<th>Patient Description</th>
<th>Intervention</th>
<th>Etiology/Chronicity</th>
<th>Organisms</th>
<th>Response</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gupta et al. 1992</td>
<td>31 year old female, HIV, lower extremity osteomyelitis</td>
<td>Minocycline 600mg qday and rifampin 600mg qday</td>
<td>Unknown source—possibly hematogenous</td>
<td><em>Mycobacterium haemophilum</em></td>
<td>Pain/leg swelling improved with 6 weeks of minocycline</td>
<td>Optimal therapy for <em>M. haemophilum</em> is unknown; empiric treatment with minocycline could be considered</td>
</tr>
<tr>
<td>Preininger 1973</td>
<td>33 year old, male with spinal fusion with intermittent drainage from his left iliac crest</td>
<td>Unsuccessful Initial trial with erythromycin Successful Minocycline 100mg BID x unknown duration (recurrence) Minocycline 100mg BID x7 weeks</td>
<td>Surgical procedures</td>
<td>2 separate <em>S. aureus</em> species resistant to penicillin and ampicillin</td>
<td>Drainage ceased, wound closed, and patient reported no signs/symptoms osteomyelitis</td>
<td>Response was rapid with both treatment courses of minocycline No imaging reported Minocycline may be a useful agent for <em>S. aureus</em> osteomyelitis</td>
</tr>
</tbody>
</table>

### Tetracyclines Summary

a. Tetracyclines use in osteomyelitis is not well-reported in the literature
b. Based on available case reports, it may be an effective option
c. Favorable pharmacokinetic profile
   i. Oral bioavailability: 90%
   ii. Bone penetration: 2-86%
d. The MRSA Guidelines do not give specific recommendations for tetracyclines, but do mention its use in the narrative

### Metronidazole Literature

### Table 12. Metronidazole case reports

<table>
<thead>
<tr>
<th>Report</th>
<th>Patient Description</th>
<th>Intervention</th>
<th>Etiology/chronicity</th>
<th>Organisms</th>
<th>Response</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chazan et al. 2001</td>
<td>17 year old, male, vertebral osteomyelitis</td>
<td>Metronidazole 500mg q8h x8 weeks</td>
<td>Acute osteomyelitis Anal dilation</td>
<td><em>B. fragilis</em></td>
<td>2 months following treatment patient without back pain, decrease ESR, and imaging showed arrest of destructive process</td>
<td>Oral metronidazole may be effective for the treatment of acute, vertebral osteomyelitis</td>
</tr>
</tbody>
</table>
Table 12. Metronidazole case reports (continued)

<table>
<thead>
<tr>
<th>Report</th>
<th>Patient</th>
<th>Intervention</th>
<th>Etiology/chronicity</th>
<th>Organisms</th>
<th>Response</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Tawfig, 2008</td>
<td>18 year old F with sickle cell disease &amp; osteomyelitis</td>
<td>Ceftriaxone + gentamicin initially, then metronidazole 500mg q8h x6 wks</td>
<td>Acute osteomyelitis</td>
<td>Blood cultures</td>
<td>NS</td>
<td>No follow-up; cannot assess outcomes</td>
</tr>
</tbody>
</table>

XII. Metronidazole Summary
   a. The use of oral metronidazole is not well-reported in the literature
   b. Based on available case reports, it may be an effective option for anaerobic infections
   c. Favorable pharmacokinetic profile
      i. Oral bioavailability: 80%
      ii. Bone penetration: >100%

XIII. Summary Oral Antibiotics

Table 13. Antibiotic Summary

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Organisms*</th>
<th>Doses</th>
<th>Oral bioavailability</th>
<th>Bone:Serum Concentration</th>
<th>Bone penetration (ug/g)</th>
<th>Supporting Literature</th>
<th>ADRs/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>Gram-negative</td>
<td>750mg BID</td>
<td>60-80%</td>
<td>0.27-1.2</td>
<td>0.1-1.4</td>
<td>+++</td>
<td>ADRs: QTc prolongation, peripheral neuropathies, Resistance</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>TMP/SMX</td>
<td>S. aureus, CoNS</td>
<td>7-10mg/kg/d TMP</td>
<td>90-100%</td>
<td>0.42</td>
<td>1.4 (cortical); 2 (medullary)</td>
<td>+++</td>
<td>ADRs: rash, agranulocytosis</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>S. aureus</td>
<td>450mg q6h-600mg q8h</td>
<td>90%</td>
<td>0.21-0.45</td>
<td>2.63-5</td>
<td>+++</td>
<td>ADRs: Increased risk of C. difficile</td>
</tr>
<tr>
<td>Linezolid</td>
<td>S. aureus, Streptococci, agalactia, CoNS, Enterococci spp</td>
<td>600mg BID</td>
<td>100%</td>
<td>0.37-0.51</td>
<td>4-9</td>
<td>+++</td>
<td>ADRs: Anemia, thrombocytopenia, peripheral neuropathy, optic neuritis, serotonin syndrome, Monitoring of CBC with &gt;2 weeks use</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>S. aureus, Brucella spp</td>
<td>100mg BID</td>
<td>90%</td>
<td>0.13-2.6</td>
<td>0.13-2.6</td>
<td>+</td>
<td>ADRs: Erosive esophagitis</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>B. fragilis</td>
<td>500mg q8h</td>
<td>80%</td>
<td>0.79-1</td>
<td>14-27</td>
<td>+</td>
<td>ADRs: Peripheral neuropathy, leukopenia</td>
</tr>
</tbody>
</table>

Evidence supporting use: +++ Randomized controlled studies; ++ Non-randomized studies; + Case report
*Could expect coverage of additional organisms with antimicrobials listed, but not present in current literature
Future directions

I. Standards for Industry
   a. Need for FDA “Guidance for Industry” standards to lead to new drug approval

II. Current ongoing studies
   a. Dellitt and colleagues, 2011
      i. Oral TMP-SMX versus IV vancomycin for the treatment of osteomyelitis
      ii. Study no longer ongoing secondary to poor enrollment in vancomycin IV group
   b. Efficacy of Oral Antibiotic Therapy Compared to Intravenous Antibiotic Therapy for the Treatment of Diabetic Foot Osteomyelitis (CRO-OSTEO)
      i. Randomized, phase II trial
      ii. Patients will receive six weeks of IV or oral antibiotic therapy depending upon their randomization group. Primary outcomes at six months clinical follow-up will include:
         1. No evidence of bone infection
         2. Resolution of ulcer
      iii. IV antibiotics: piperacillin/tazobactam, cefepime, metronidazole, aztreonam, vancomycin, daptomycin, linezolid, meropenem
      iv. PO antibiotics: sulfamethoxazole/trimethoprim, clindamycin, linezolid, moxifloxacin, ciprofloxacin, metronidazole

Conclusions

I. Summary
   a. Osteomyelitis is a difficult to treat disease state secondary to the complex pathogenesis and scarcity of literature to guide practice
   b. Traditional treatment with only parenteral antibiotics is not well-supported by the literature
   c. Advantages oral antibiotics
      i. Patient convenience
      ii. Eliminates risk of line complications (infection, thrombosis)
      iii. Decreased cost
   d. Disadvantages oral antibiotics
      i. Possibility for decreased compliance
      ii. Potentially less predictable antimicrobial bone concentrations

II. Flaws in study design and literature
   a. Unclear definition of acute versus chronic
   b. Several studies do not identify etiology of osteomyelitis
   c. Many studies did not require bone biopsy or surgical debridement
   d. No standardized follow-up times
   e. Mostly small sample size
   f. Endpoints, such as remission and cure, not well defined

III. Patient populations in which oral antibiotics may be appropriate
   a. Chronic osteomyelitis in immunocompetent patients
   b. Acute osteomyelitis the data is less clear, but looking at the chronic data and MRSA guidelines, it is likely a suitable alternative

IV. Patient populations in which oral antibiotics may not be appropriate
   a. Understudied populations: immunocompromised, patients with critical ischemia, patients with gangrene
   b. Patients who may not have adequate gastrointestinal absorption
   c. Patients with history or potential for noncompliance

V. Final Recommendations
   a. Similar rates of cure regardless of route of administration
      i. RCT suggest percentage cure rate with IV antibiotics to be 67-90%\(^\text{16}\)
   b. Pharmacokinetic data supports use of select oral antibiotics
   c. Immunocompetent patients with either acute or chronic osteomyelitis should be considered for 4-8 weeks of oral antibiotics if no contraindications exist
References


