BONE & JOINT INFECTIONS

Henry F. Chambers, MD

Disclosures

- AstraZeneca – advisory board
- Cubist – research grant, advisory panel
- Genentech – advisory board
- Merck – stock
- Pfizer – advisory board
- Theravance – advisory board
Case

- 38 y/o type 2 diabetic women, single, sexually active with 3 days of pain, swelling, loss of ROM of R knee.
- Afebrile, swollen, tender R knee, effusion, resists flexion and extension
- Peripheral WBC 7,000 (70% PMNs)
- ESR = 20 mm/h
- Synovial fluid: WBC 50,000 with 90% PMNs, no crystals, Gram-stain negative
What is the most appropriate initial therapy for this patient?

1. Ceftriaxone 1 g IV q24h
2. Meropenem 1 g IV q8h
3. Vancomycin 15-20 mg/kg q12h
4. Vancomycin + ceftriaxone
5. Withhold antibiotics pending culture results

Differential Diagnosis of Acute Arthritis in the Adult

- Infection (bacteria, fungi, mycobacteria, viruses, spirochetes)
- Rheumatoid arthritis, JRA
- Crystal arthropathy (gout, pseudogout)
- Reactive arthritis, adult Still’s
- Systemic lupus erythematosis
- Osteoarthritis
- About 10 other things
Joints Affected in Septic Arthritis

<table>
<thead>
<tr>
<th>Joint</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip</td>
<td>30-40%</td>
</tr>
<tr>
<td>Knee</td>
<td>40%</td>
</tr>
<tr>
<td>Ankle</td>
<td>5-10%</td>
</tr>
<tr>
<td>Wrist, elbow, hand</td>
<td>10-15%</td>
</tr>
<tr>
<td>Multiple joints</td>
<td>5-10%</td>
</tr>
</tbody>
</table>

Microbiology of Septic Arthritis

**Children**
- *Staph. aureus* (40-60%)
- Streptococci (30%)
  - *S. pneumoniae*
  - GAS
- Gram-negative bacilli (5-20%)
  - *H. influenzae* rare
- *Neisseria* sp.

**Adults**
- *Staph. aureus* (40-60%)
- Streptococci (30%)
  - GAS
  - *S. pneumoniae*
- Gram-negative bacilli (5-20%)
  - Enterics
- *Neisseria* sp.

Culture-negative: 15-30%
Septic Arthritis: Presentation

Joint Pain 85%
History of joint swelling 78%
Fever 57%


Risk Factors for Septic Arthritis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Likelihood Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Positive 2.7</td>
</tr>
<tr>
<td></td>
<td>Negative 0.93</td>
</tr>
<tr>
<td>Recent joint surgery</td>
<td>Positive 6.9</td>
</tr>
<tr>
<td></td>
<td>Negative 0.78</td>
</tr>
<tr>
<td>Hip or knee prosthesis + skin infection</td>
<td>Positive 15.0</td>
</tr>
<tr>
<td></td>
<td>Negative 0.77</td>
</tr>
<tr>
<td>RA</td>
<td>Positive 2.5</td>
</tr>
<tr>
<td></td>
<td>Negative 0.45</td>
</tr>
</tbody>
</table>

## Serum Lab Values

<table>
<thead>
<tr>
<th>Factor</th>
<th>Likelihood Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td>WBC &gt; 10,000</td>
<td>1.4</td>
</tr>
<tr>
<td>ESR &gt; 30 mm/h</td>
<td>1.3</td>
</tr>
<tr>
<td>CRP &gt; 100 mg/L</td>
<td>1.6</td>
</tr>
</tbody>
</table>


## Synovial Fluid Studies

<table>
<thead>
<tr>
<th>Factor</th>
<th>Likelihood Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td>WBC &gt; 100,000</td>
<td>28</td>
</tr>
<tr>
<td>WBC &gt; 50,000</td>
<td>7.7</td>
</tr>
<tr>
<td>WBC &gt; 25,000</td>
<td>2.9</td>
</tr>
<tr>
<td>PMNs &gt; 90%</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Initial Management Of Acute Septic Arthritis

- Drain the joint (controversy as to which is better)
  - Arthrocentesis (knee, ankle, elbow, wrist, hand)
  - Arthroscopy (hip and shoulder)
  - Open drainage (hip and shoulder)
- Obtain cultures
  - Blood (~30% to 50% positive)
  - Synovial fluid, aerobic and anaerobic (consider fungal and mycobacterial if subacute/chronic presentation)
  - STD risk, or polyarticular signs and symptoms, rash: culture blood, fluid, rectum, cervix/urethra, throat for GC

Initial Antimicrobial Therapy of Septic Arthritis

- Synovial fluid crystals: withhold antibiotics
- Gram stain positive
  - Gram-positive cocci: Vancomycin 15-20 mg/kg q8-12h for suspected S. aureus, strep
  - Gram-negative cocci: Ceftriaxone 1 g q24h
  - Gram-negative bacilli: Cefepime 2 gm q8h, meropenem 1 gm q8h, or levofloxacin 750 mg q24h
- Gram-stain negative
  - Vancomycin 15-20 mg/kg q8-12h + ceftriaxone 1 g q24h (or as above for Gram-negative bacilli)
RX of Culture-Positive Septic Arthritis

- **Staphylococcus aureus**
  - MSSA: cefazolin 2 g q8h or nafcillin 2g q4h
  - MRSA: vancomycin 15-20 mg/kg q8-12h
- **Streptococci**
  - Pen G 2 mU q4h or ceftriaxone 2 g q24h
- **Gonococci**
  - Ceftriaxone 1 g q24h (plus azithro, doxy, FQ for chlamydia)
- **Gram-negative bacilli**
  - See previous slide and based on results of susceptibility testing

Duration of Therapy

- **Gonococcal septic arthritis**: 7 days
- **Septic arthritis in a child**
  - 2 weeks (3 weeks if accompanying osteo) (Ped Clin NA 60:425, 2013)
  - 10 days of therapy probably as effective as a 30-day treatment course (Clin Infect Dis 48:1201, 2009)
- **Septic arthritis in an adult**: 2-4 weeks
- **May be a combination of IV (typically ~ 3-7 days) and oral therapy**
Outcomes in Adults

- CRP should normalize in 9-10 days (longer if arthrotomy performed)
- WBC and ESR not useful for f/u
- Relapse or recurrence rare (<1%)
- Except for GC duration of therapy poorly defined, recommendations vary

Oral Regimens

<table>
<thead>
<tr>
<th>Agent</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin 40 mg/kg/d</td>
<td>Children, max dose 450 mg qid</td>
</tr>
<tr>
<td>1st gen ceph 150 mg/kg/d</td>
<td>Children, max dose 1 g qid</td>
</tr>
<tr>
<td>FQ (e.g., cipro 750 mg bid, levo 750 mg q24h, moxi 400 mg qd)</td>
<td>Adult, susceptible Gram-neg.</td>
</tr>
<tr>
<td>SMX-TMP (10-15 mg/kg/d)</td>
<td>Susceptible Gram-neg.</td>
</tr>
<tr>
<td>SMX-TMP + rifampin 300 mg bid</td>
<td>Susceptible MRSA, MSSA</td>
</tr>
<tr>
<td>FQ + rifampin 600 mg/d</td>
<td>Adult, susceptible MRSA, MSSA</td>
</tr>
<tr>
<td>Amox-clav, linezolid, doxycycline</td>
<td>Limited data</td>
</tr>
</tbody>
</table>

## Microbiology of PJI

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Rate</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSA, MRSA</td>
<td>20-40%</td>
<td>Typically early (w/in 3 mo) or late (&gt; 2 years post implantation)</td>
</tr>
<tr>
<td>Coag-neg. staph</td>
<td>30-40%</td>
<td>Typically delayed or late</td>
</tr>
<tr>
<td>Strep, enterococci,</td>
<td>10-20%</td>
<td>Also <em>diphtheroids</em>, <em>P. acnes</em></td>
</tr>
<tr>
<td>Gram-neg. bacilli</td>
<td>10-15%</td>
<td>Enterics, Ps. aeruginosa</td>
</tr>
<tr>
<td>Culture-negative</td>
<td>15-20%</td>
<td>Hate that!</td>
</tr>
</tbody>
</table>
Diagnosis of PJI

• Orthopedic referral for
  – Sinus tract or persistent drainage
  – Acutely painful prosthesis
  – Chronically painful prosthesis

• ESR, CRP, blood cultures, arthrocentesis
  – Stop if no evidence of infection
  – Suspected infection: Intraoperative exploration for cultures, path, debridement
  – Avoid empirical therapy if at all possible

Orthopedic Device Related Infections
Cumulative Treatment Failure Rate

Orthopedic Device Related Infections
Cumulative Treatment Failure Rate


Total Knee/Hip S. aureus Infections
Cumulative Treatment Failure Rate

IDSA Prosthetic Joint Infection Treatment Guidelines

- Obtain cultures prior to starting Rx
- Treatment based on surgical option chosen
  - Debridement, hardware retention
  - 1-stage, direct exchange
  - 2-stage debridement later re-implantation

Clin Infect Dis 56:e1, 2013

Device Retention vs Removal

- Duration of symptoms <3 weeks OR Joint age <30 days
- Well-fixed prosthesis
- Absence of sinus tract
- Susceptible to oral anti-microbial agents*

- Debridement and retention
- Removal of prosthesis**
Synopsis of IDSA Treatment Guidelines

- Prosthesis retained
  - Staph: use iv/po rif combo for 3-6 mo
  - Others: iv/po regimen for 4-6 weeks
- 1-stage procedure
  - Staph: use iv/po rif combo for 3 mo
  - Others: iv/po regimen for 4-6 weeks
- 2-stage procedure
  - Staph: use iv/po rif combo for 4-6 weeks
  - Others: iv/po regimen for 4-6 weeks

Culture-Negative Osteoarticular “Infections”

- Prospective study, 3840 bone and joint samples from 2308 patients
  - Marseille University Hospitals, 2007-09
  - 50% had prosthetic devices
- PCR (16S) performed on culture-neg specimens
- Culture results
  - Positive: 33.1% (S. aureus [33%], CoNS [21%], Gram-neg bacilli [23%] Strep/enterococci [13%])
  - Negative: 67.9%
- PCR results
  - 6.1% of all patients PCR positive
  - 9.1% of culture-neg cases PCR positive

Positive PCR Results in Culture-negative Cases*

<table>
<thead>
<tr>
<th>Organism</th>
<th>% positive (N = 141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fastidious organisms</td>
<td>25</td>
</tr>
<tr>
<td>Staph. aureus§</td>
<td>25</td>
</tr>
<tr>
<td>Coag-neg. staph.</td>
<td>21</td>
</tr>
<tr>
<td>Streptococci, enterococci</td>
<td>16</td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td>11</td>
</tr>
</tbody>
</table>

§ 65% neg on repeat PCR † Prior antibiotic in 42% of cases

Causes of Culture-negative Osteoarticular “Infections”

• Non-infectious cause
• False-negative culture
  – Low inoculum infection, sampling error
  – Prior antibiotics
  – Fastidious organisms
• Other organisms: fungi, MTB, other mycobacteria, brucella, nocardia
Oral Regimens for Culture-negative Septic Arthritis

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxifloxacin</td>
<td>Misses some MRSA, MRCNS, some GNB</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Misses GNRs, fastidious Gram-negs, enterococci, few to some MRSA</td>
</tr>
<tr>
<td>Augmentin</td>
<td>Misses MRSA, MRCNS, resistant GNB</td>
</tr>
<tr>
<td>SMX-TMP</td>
<td>Misses enterococci, some GNB, anaerobes</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Misses GNBs, anaerobes</td>
</tr>
</tbody>
</table>

Septic Arthritis - Summary

- Clinical features and patient risk factors are useful in assessing likelihood of septic arthritis
- WBC, ESR, and CRP have limited utility in diagnosis of septic arthritis
  - CRP may be useful for monitoring response
- Synovial fluid WBC and %PMNs are essential for assessment of likelihood of septic arthritis
- IV/oral therapy for 2-3 weeks (less in children) is probably sufficient
- Arthrocentesis, repeated prn, is sufficient for drainage except for hip and shoulder
Case

- 57 y/o newly diagnosed MSSA (Pen R only) vertebral osteomyelitis
- What would you recommend for this patient?
  1. 12 week course of twice daily IV vancomycin
  2. 12 week course of once daily IV daptomycin
  3. 6 week course of six times daily IV oxacillin
  4. 6 week course of IV oxacillin then step-down PO to levo 750 mg + rifampin 600 mg once daily)
  5. Any one of the above with f/u MRI to determine duration of therapy
Classification

• Acute osteomyelitis
  – First episode at given site
  – Potentially cured with antibiotics alone within 6 weeks
  – Bone remains viable

• Chronic osteomyelitis
  – Evolves from acute osteomyelitis
  – Present > 6 weeks
  – Often indolent with few systemic signs/symptoms
  – Fistula formation, dead bone, refractory clinical course

• Orthopedic device-related osteomyelitis

Microbiology

• Staphylococcus aureus (50-60%)
• Streptococci, coagulase-negative staphylococci (orthopedic implants), enteric gram-negative rods, Pseudomonas aeruginosa
Diagnosis
Microbiological Confirmation

- Gold standard = culture of organism from bone (positive blood culture is acceptable)
- Histopathology may give dx if cultures negative
- Swabs from sinus tracts unreliable for predicting organism
  - Isolation of *S. aureus* is more predictive but not sensitive

Diagnosis
ESR, CRP, and WBC

- Case series of patients with osteomyelitis
  - ESR “elevated” in apx. 90% of patients
  - C-reactive protein “elevated” > 90% of patients
- ESR virtually worthless: less predictive of clinical course; longer period of elevation
- CRP levels which are slow to resolve may predict complicated course
- WBC: worthless
Diagnosis
Conventional Radiography

• Insensitive (45-75%):
  – Normal until at least 10-21 after infection onset
  – Lytic changes not seen until extensive (>50%) destruction of bone matrix

• Non-specific (~75%)
  – Early findings
    • Soft tissue swelling
    • Periosteal thickening or elevation
    • Osteopenia
  – Prior bone abnormality major limitation

Diagnosis
Magnetic Resonance Imaging

• T1 weighted images: ↓ (dark) signal intensity
• T2 weighted images: ↑ (bright) signal intensity
• Sensitive because bone marrow appears abnormal (but imperfect specificity)
• May show periosteal reaction, cortical destruction, or joint damage
• Depending on study, sensitivity 60-100%, specificity 50-90%
• Excellent anatomic resolution
MRI for Osteomyelitis
Beware the routine follow-up exam


Treatment

PO or IV?
How Long?
Conclusions Cochrane Review 2009
Treatment of Chronic Osteomyelitis

• No difference in outcome between oral and parenteral therapy
• Adverse events rate higher for parenteral (15.5% vs 4.8%, 95% CI 0.13 -1.22)
• No recommendations on duration of therapy or impact of bacterial species or disease severity on outcome

Oral Agents:
Advantages and Disadvantages

<table>
<thead>
<tr>
<th>Drug</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>FQ</td>
<td>Good GNR, Low pill burden</td>
<td>Achilles tendon rupture, C-diff</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>Adequate Staph, GNR</td>
<td>Allergic rxn, cytopenias</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Good Staph</td>
<td>Pill burden, GI Sx, C-diff</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Good anaerobes</td>
<td>Watch for neuropathy</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Good GPC</td>
<td>Marrow and nerve toxic</td>
</tr>
<tr>
<td>Rifampin</td>
<td>“Synergy”</td>
<td>Drug interactions &amp; LFTs</td>
</tr>
</tbody>
</table>
Rifampin for Osteomyelitis in Animal Models

- Rifampin combos consistently superior to single drug regimens (beta-lactams, macrolide, clindamycin, vancomycin) in animal models of *S. aureus* osteomyelitis
- Resistance occurs rapidly if rifampin is used alone

Summary
Clinical Trials of Osteomyelitis

- Rifampin combo superior to single drug therapy for staphylococcal osteomyelitis
  - Van derAuwera AAC ’85; Norden South Med J ’86; Zimmerli JAMA ’98
- Oral rifampin + TMP-SMX for 8 weeks equivalent to IV/PO oxacillin (6+2 weeks)
Patient Characteristics

- Unblinded, non-inferiority (10% margin) RCT:
  - 6 wks (n=176) versus 12 wks (n=175) IV/PO Rx
- Patients: all culture positive
  - 68% blood culture positive, 20% with endocarditis
    - S. aureus 41% (only 13 MRSA cases), CoNS 17%, Strep 18%
  - 19% with abscess, only 3/68 needed
  - 5% perioperative specimen
- Other characteristics
  - 15% with diabetes
  - 89% with single vertebral body
  - 16% with neurological signs
**PO and IV Therapy**

- **IV therapy**
  - Median of 14 days (IQR 7-27)
  - 26% for < 1 week
- **PO therapy**
  - 73% received FQ or RIF, or the combination
    - 44% received FQ + RIF
  - 28% received oral aminopenicillin

**Results**

<table>
<thead>
<tr>
<th>ITT, N</th>
<th>6 wk RX</th>
<th>12 wk RX</th>
<th>Δ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cured &amp; alive @ 6 mo</td>
<td>156 (88.6%)</td>
<td>150 (85.7%)</td>
<td>2.9 (-4.2, 10.1)</td>
</tr>
<tr>
<td>Cured, no further Rx</td>
<td>142 (80.7%)</td>
<td>141 (80.6%)</td>
<td>0.1 (-8.3, 8.5)</td>
</tr>
<tr>
<td>Back pain @ 1 yr</td>
<td>44/145 (30%)</td>
<td>41/138 (30%)</td>
<td></td>
</tr>
</tbody>
</table>

Failure associated with age > 75 yr and *S. aureus* infection
Conclusions

• 6 weeks as good as 12 weeks
• Predominantly PO therapy seemed to work
• Limitations:
  – Not much MRSA, other multiple drug resistant organism
  – Few cases with larger abscesses, multiple vertebral bodies or other subgroups that may require longer courses of therapy

Summary – I

• Gram negative oral options*
  • Fluoroquinolone or TMP-SMX
• Anaerobic oral choice
  • Clindamycin or metronidazole
• Gram positive oral options
  • TMP-SMX, clinda, linezolid, cipro/levo/moxi (FQ S)
  • Rifampin combination Rx for S. aureus
• For MSSA IV beta-lactam is preferable to vanco

* See oral regimens slide for doses
Summary – II

• Oral therapy is probably as effective as parenteral therapy
• 6 weeks of therapy generally effective in cases of acute hematogeneous vertebral osteo (longer if large undrained abscess, implant)
• Monitoring response to therapy
  + CRP: persistently elevated CRP is suggestive of persistent osteomyelitis
  + Routine MRI: findings often do not correlate with clinical status (although worsening soft tissue abnormalities may be significant)