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 erythematosus
- 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

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint Pain</td>
<td>85%</td>
</tr>
<tr>
<td>History of joint swelling</td>
<td>78%</td>
</tr>
<tr>
<td>Fever</td>
<td>57%</td>
</tr>
</tbody>
</table>

Risk Factors for Septic Arthritis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Likelihood Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.7</td>
</tr>
<tr>
<td>Recent joint surgery</td>
<td>6.9</td>
</tr>
<tr>
<td>Hip or knee prosthesis + skin infection</td>
<td>15.0</td>
</tr>
<tr>
<td>RA</td>
<td>2.5</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
Disseminated Gonococcal Infection

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)

Initial Therapy 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 Children

- CRP normalizes in 9-10 days
  - Faster resolution in those with needle aspiration versus more invasive drainage procedure
- WBC and ESR not useful for f/u
- Relapse or recurrence rare (<1%)
- Clindamycin and 1st generation ceph with similar efficacy


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>


SEPTIC ARTHRITIS
Prosthetic Joint Infection (PJI)

J Antimicrob Chemother 68 (Suppl 3): ii45, 2010
### 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 diphtheroids, <em>P. acnes</em></td>
</tr>
<tr>
<td>Gram-neg. bacilli</td>
<td>10-15%</td>
<td>Enterics, <em>P. aeruginosa</em></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**

**Total Knee/Hip S. aureus Infections**

Cumulative Treatment Failure Rate

- **FQ + rif**
- **other**


**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 cultures, 3-6 weeks

Joint age, >60 days

- **Y**es
  - Viable host prosthesis
  - Absence of abscess
to joint or adjacent bone
  - Meningitis/acroinfection

- **N**o
  - 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

**OSTEOMYELITIS**

**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. 6-8 week course of six times daily IV oxacillin
  4. 6-8 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: Imaging

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

Radionuclide Scintigraphy

- 3-phase bone scan with technetium 99m diphosphonates
  1. Flow or angiogram phase
  2. Blood pool phase
  3. Delayed or bone phase (usually 3, up to 24 hrs.)
- Osteomyelitis uptake phases 1-2 with focal, intense uptake delayed images
- Cellulitis uptake phases 1-2 with mild, diffuse uptake delayed images
- Useful if multiple sites suspected

Bone Scan Osteomyelitis

Osteomyelitis of the Right Calcaneous

Diagnosis

Radionuclide Scintigraphy

- Indium 111-labeled WBCs often combined with bone scan to improve specificity
  - Process is complex
  - Takes 24 hours
  - High dose radiation
- WBC scan may be more useful in acute disease; prosthesis, peripheral skeleton - normal axial marrow takes up WBCs
- Bone scan + WBC scan: one study reports sensitivity ~70%, specificity ~90%, PPV~90%

Jacobson et al., Am J Roentgenol 1991;157:807-12
**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**

Oral or IV?

**IV Antibiotics**

Achievable Levels (μg/ml)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Serum</th>
<th>Bone</th>
<th>Bone/MI C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-lactams</td>
<td>50 – 150</td>
<td>5 – 15</td>
<td>2-8</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>20 – 40</td>
<td>1 – 4</td>
<td>0.5-2</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>40</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
### Oral Antibiotics

**Achievable Levels (μg/ml)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Serum</th>
<th>Bone</th>
<th>Bone/MI C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-lactams</td>
<td>5 – 10</td>
<td>0.5 – 1</td>
<td>0.5</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>2 – 3</td>
<td>0.75 - 1.5</td>
<td>4 - 8</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>6 – 8</td>
<td>3 – 6</td>
<td>2 - 16</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>20 – 30</td>
<td>15-30</td>
<td>5-10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Serum</th>
<th>Bone</th>
<th>Bone/MI C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linezolid</td>
<td>10 – 20</td>
<td>5 - 10</td>
<td>4 - 8</td>
</tr>
<tr>
<td>TMP / SMX (sulfa)</td>
<td>100 – 150</td>
<td>15 – 20</td>
<td>4 - 16</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>5 – 10</td>
<td>2 – 5</td>
<td>1 - 4</td>
</tr>
<tr>
<td>Rifampin</td>
<td>2 – 5</td>
<td>1 - 10</td>
<td>2 - 16</td>
</tr>
</tbody>
</table>

### 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</td>
<td>Achilles tendon rupture</td>
</tr>
<tr>
<td></td>
<td>Low pill burden</td>
<td>C-diff</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>Adequate Staph and GNR</td>
<td>Allergic rxn</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Good Staph</td>
<td>Cytopenias</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Good anaerobes</td>
<td>GI Sx, C-diff</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Good GPC</td>
<td>Watch for neuropathy</td>
</tr>
<tr>
<td>Rifampin</td>
<td>“Synergy”</td>
<td>Marrow and nerve toxic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug interactions &amp; LFTs</td>
</tr>
</tbody>
</table>

### 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
Out-Patient IV Therapy of Osteomyelitis

- Retrospective reviews of OP IV Rx for osteo at an ID private practice from 1982-1998
- 454 pts evaluated
- *S. aureus* 54%, CoNS 14%, Strep spp. 14%, *Pseudomonas* 4%, others 14%


Summary of Animal Model Data

- 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)
  - Oral FQ equivalent to parenteral regimens (beta-lactams, aminoglycosides)
    - Greenberg Am J Med ‘87; Peacock Am J Med ‘89; Gentry AAC ‘90, ’91; Lipsky, CID ‘97
### Duration of Therapy
Vertebral Osteomyelitis

- Unblinded, non-inferiority RCT:
  - 6 wks (n=176) versus 12 wks (n=175) IV/PO Rx
- Patients
  - 52% febrile
  - 68% blood culture positive, 20% with endocarditis
  - *S. aureus* 41%, CoNS 15%, Strep 18%
- FQ + rif most frequent oral Rx
- Cure rates: 91% both groups
  - 85% power to detect a 10% difference

Dinh, et al, Abstract # L-338, ICAAC 2013, Denver Co

### Conclusions – 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/maxi (FQ S)
  - Rifampin combination Rx for *S. aureus*
- For MSSA IV beta-lactam is preferable to vanco

* See oral regimens slide for doses