

## BONE & JOINT INFECTIONS

Henry F. Chambers, MD

## SEPTIC ARTHRITIS Native Joint

Curr Rheumatol Rep 15:332, 2013;  
Best Prac Res Clin Rheumatol 25:407, 2011

### Case

- 38 y/o type 2 diabetic woman, 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

Hip	30-40%
Knee	40%
Ankle	5-10%
Wrist, elbow, hand	10-15%
Multiple joints	5-10%

## 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%

Margaretten, et al. JAMA 297:1478, 2007

## Risk Factors for Septic Arthritis

Factor	Likelihood Ratios	
	Positive	Negative
Diabetes	2.7	0.93
Recent joint surgery	6.9	0.78
Hip or knee prosthesis + skin infection	15.0	0.77
RA	2.5	0.45

Margaretten, et al. JAMA 297:1478, 2007

## Serum Lab Values

Factor	Likelihood Ratios	
	Positive	Negative
WBC > 10,000	1.4	0.28
ESR > 30 mm/h	1.3	0.17
CRP > 100 mg/L	1.6	0.44

Margaretten, et al. JAMA 297:1478, 2007

## Synovial Fluid Studies

Factor	Likelihood Ratios	
	Positive	Negative
WBC > 100,000	28	0.75
WBC > 50,000	7.7	0.42
WBC > 25,000	2.9	0.32
PMNs > 90%	3.4	0.34

Margaretten, et al. JAMA 297:1478, 2007

## 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 1<sup>st</sup> generation ceph with similar efficacy

Clin Infect Dis 48:1201, 2009; Clin Micro Infect 18:582, 2011

## 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

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

Clin Infect Dis 56:e1, 2013; J Antimicrobi Chemother 69:309, 2014

## SEPTIC ARTHRITIS Prosthetic Joint Infection (PJI)

Clin Infect Dis 56:e1, 2013; Tsai et al, J Micro Immunol Infect, 2013  
J Antimicrob Chemother 65 (Suppl 3): iii45, 2010

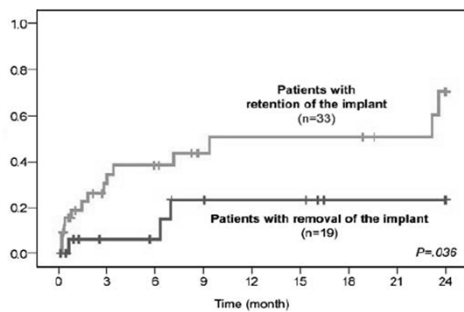
### Microbiology of PJI

Organisms	Rate	Comment
MSSA, MRSA	20-40%	Typically early (w/in 3 mo) or late (> 2 years post implantation)
Coag-neg. staph	30-40%	Typically delayed or late
Strep, enterococci,	10-20%	Also <i>diphtheroids</i> , <i>P. acnes</i>
Gram-neg. bacilli	10-15%	Enterics, <i>Ps. aeruginosa</i>
Culture-negative	15-20%	Hate that!

### Diagnosis of PJI

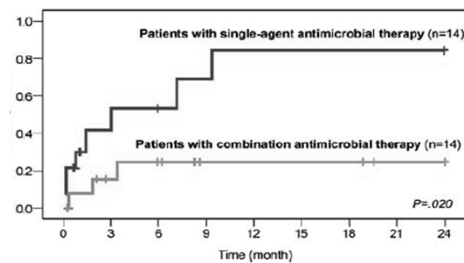
- Orthopedic referral for
  - Sinus tract or persistent drainage
  - Acutely painful prosthesis
  - Chronically painful prosthesis
- ESR, CRP, blood cultures, arthrocentesis
  - Stop if no evidence of infection
  - Suspected infection: Intraoperative exploration for cultures, path, debridement
  - Avoid empirical therapy if at all possible

### Orthopedic Device Related Infections Cumulative Treatment Failure Rate



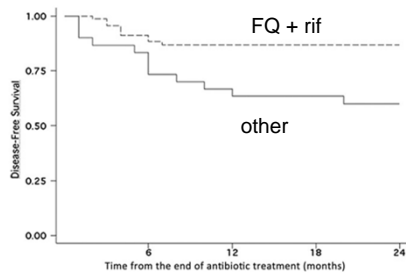
Ferry et al. Eur J Clin Microbiol Infect Dis 29:171-80, 2009

### Orthopedic Device Related Infections Cumulative Treatment Failure Rate



Ferry et al. Eur J Clin Microbiol Infect Dis 29:171-80, 2009

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



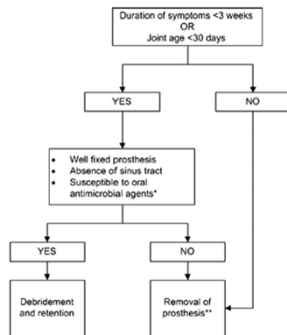
Senneville, et al. Clin Infect Dis 53:334, 2011

### 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



### 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

Levy, et al, Am J Med 126:e25, 2013

### Positive PCR Results in Culture-negative Cases\*

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

<sup>§</sup> 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

Antibiotic	Comments
Moxifloxacin	Misses some MRSA, MRCNS, some GNB
Clindamycin	Misses GNRs, fastidious Gram-negs, enterococci, few to some MRSA
Augmentin	Misses MRSA, MRCNS, resistant GNB
SMX-TMP	Misses enterococci, some GNB, anaerobes
Linezolid	Misses GNBs, anaerobes



## 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  $\geq$  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

Palestro, Love, Miller. Best Pract Res Clin Rheumatol 20:1197, 2006. PMID 17127204

## Diagnosis Conventional Radiography

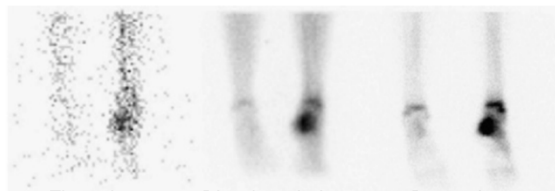
- Insensitive (45-75%):
  - Normal until at least 10-21 after infection onset
  - Lytic changes not seen until extensive (>50%) destruction of bone matrix
- Non-specific (~75%)
  - Early findings
    - Soft tissue swelling
    - Periosteal thickening or elevation
    - Osteopenia
  - Prior bone abnormality 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.)
- Osteo ↑ 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 Calcaneus



Flow phase      Blood pool phase      Bone phase

## 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



See also: Clin Infect Dis 43:172, 2006; Am J Neuroradiol 28:693, 2007

## Treatment

Oral or IV?

## IV Antibiotics

### Achievable Levels (μg/ml)

Drug	Serum	Bone	Bone/MI C
Beta-lactams	50 – 150	5 – 15	2-8
Vancomycin	20 – 40	1 – 4	0.5-2
Daptomycin	40	1	2

**Oral Antibiotics  
Achievable Levels (µg/ml)**

Drug	Serum	Bone	Bone/MI C
Beta-lactams	5 – 10	0.5 – 1	0.5
Ciprofloxacin	2 – 3	0.75 - 1.5	4-8
Levofloxacin	6 – 8	3 – 6	2-16
Metronidazole	20 – 30	15-30	5-10

**Oral Antibiotics  
Achievable Levels (µg/ml)**

Drug	Serum	Bone	Bone/MI C
Linezolid	10 – 20	5 - 10	4-8
TMP / SMX	100 – 150 (sulfa)	15 – 20 (sulfa)	4-16
Clindamycin	5 – 10	2 – 5	1-4
Rifampin	2 – 5	1 - 10	2-16

**Oral Agents:  
Advantages and Disadvantages**

Drug	Advantage	Disadvantage
FQ	Good GNR Low pill burden	Achilles tendon rupture C-diff
TMP-SMX	Adequate Staph and GNR	Allergic rxn Cytopenias
Clindamycin	Good Staph	Pill burden GI Sx, C-diff
Metronidazole	Good anaerobes	Watch for neuropathy
Linezolid	Good GPC	Marrow and nerve toxic
Rifampin	“Synergy”	Drug interactions & LFTs

**Conclusions Cochrane Review 2009  
Treatment of Chronic Osteomyelitis**

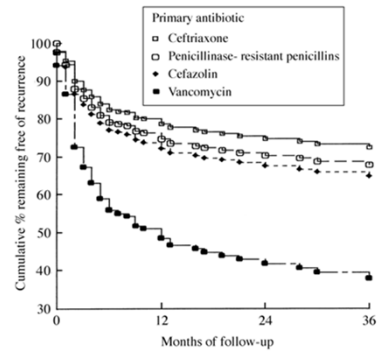
- No difference in outcome between oral and parenteral therapy
- Adverse events rate higher for parenteral (15.5% vs 4.8%, 95% CI 0.13 -1.22)
- No recommendations on duration of therapy or impact of bacterial species or disease severity on outcome

## 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%

Tice et al 2003 Am J Med, J Antimicrob Chemoth

## Out-Patient IV Therapy of Osteomyelitis



## 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
- Excellent review of rifampin for treatment of staphylococcal infection: Perlroth, et al. Arch Intern Med. 168:805-819, 2008

## Summary Clinical Trials of Osteomyelitis

- Rifampin combo superior to single drug therapy for staphylococcal osteomyelitis
  - Van der Auwera 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)
  - Euba, Antimicrob Agents Chemother 2009; 53: 2672, 2009
- 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/moxi (FQ S)
  - Rifampin combination Rx for *S. aureus*
- For MSSA IV beta-lactam is preferable to vanco

\* See oral regimens slide for doses

## Conclusions - 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)