Prosthetic Joint Infections

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Outline

• Background
• Clinical Presentation
• Risk factors
• Pathogenesis
• Biofilms
• Diagnosis
• Treatment
Background

- Between 1%-5% of all prosthetic joints become infected
  - Significant morbidity
    - Protracted hospitalization
    - Potentially renewed disability
  - Significant cost
    - $50,000-$60,000 per episode

-Sculpo TP. Orthopedics.1995;18:871-873
Risk Factors

- Prior surgery at site of prosthesis
- Rheumatoid arthritis
- Immunocompromised states
- Diabetes mellitus
- Poor nutritional status
- Obesity
- Psoriasis
- Advanced age

• Brause BD. Curr Opin Rheumatolog.1989. 1:194-98
• Hansen Ad et al. J Bone Joint Surg Am. 1998;80;910-922
Pathogenesis

• Locally introduced (60-80%)
  – Operative contamination
  – Wound sepsis contiguous to the prosthesis
    • Common preceding events:
      – Delayed wound healing
      – Infected wound hematomas
      – Wound infection (SSI)
      – Suture abscesses
    • Coagulase negative staphylococci and \textit{S. aureus} are common pathogens in these situations.

Pathogenesis

• Hematogenous (20-40%)
  – Any bacteremic episode may seed a prothetic joint
    • *S. aureus* bacteremia leads to a 34% incidence of prosthetic joint infection
    • Dentogingival infections or manipulations
      – viridans streptococci and anaerobes
    • Genitourinary or gastrointestinal procedures or infections
      – Gram negative rods, enterococci, and anaerobes

Pathogenesis

- Growth of virulent organisms (*S. aureus*) usually indicates infection
- Growth of low-virulence microorganisms that are typical skin commensals (e.g., coagulase-negative staphylococci and *Propionibacterium acnes*) may be either contaminants or pathogens
  - Must consider other factors
    - Growth in more than one specimen
    - Short time to culture positivity
    - Positive Gram's stain
    - Presence of acute inflammation on histopathological examination
    - Radiographic manifestations
Pathogenesis

- **Biofilms** are composed of populations or communities of microorganisms adhering to environmental surfaces and bioprosthetic materials.
- These microorganisms are usually encased in an extracellular polysaccharide that they themselves synthesize.

http://webs.wichita.edu/mschneegurt/biol103/lecture22/catheter_biofilm.gif
Pathogenesis

- Biofilms
  - Biofilm microbes are protected from antimicrobial agents and host immune responses

http://webs.wichita.edu/mschneegurt/biol103/lecture22/catheter_biofilm.gif
Pathogenesis

- Biofilm producing organisms isolated from prosthetic hips
  - Coagulase negative staphylococci
  - Hemolytic streptococci
  - *P. mirabilis*
  - Bacteriodes species
  - *S. aureus*
  - Viridans streptococci
  - *E. coli*
  - *P. aeruginosa*


[http://webs.wichita.edu/mschneegurt/biol103/lecture22/catheter_biofilm.gif](http://webs.wichita.edu/mschneegurt/biol103/lecture22/catheter_biofilm.gif)
## Presenting Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint Pain</td>
<td>95</td>
</tr>
<tr>
<td>Fever</td>
<td>43</td>
</tr>
<tr>
<td>Periarticular swelling</td>
<td>38</td>
</tr>
<tr>
<td>Wound or cutaneous sinus drainage</td>
<td>32</td>
</tr>
</tbody>
</table>

Radiographic Presentation

- Plain radiographs are helpful to detect infection when viewed serially over time after implantation
  - Radiographic changes are typically related to the duration of infection
    - May take 3-6 months to manifest significant radiographic changes
Radiographic Presentation

• Findings in prosthetic joint infections
  – Abnormal lucencies greater than 2mm in width at the bone cement interface
  – Changes in position of the prosthetic components
  – Cement fractures
  – Periosteal reaction
  – Motion of components on stress views

Radiographic Presentation

- Normal prosthesis
  - 1-2mm lucent zones at cement interface
- Indicative/Diagnostic for loosening
  - > 2mm widening with progression
  - Cement fracture
  - Migration or change of position of component

http://www.gentili.net/thr/loosenin.htm
Radiographic Presentation

- Abnormally widened interfaces surrounding cement of femoral component, consistent with loosening

http://www.gentili.net/ thr/loosenin.htm
Other Imaging Studies

- Technetium bone scan of limited value
  - Can remain positive more than a year after implantation due to periprosthetic bone remodeling
- CT scan and MRI of limited value
  - Provides better contrast between normal and abnormal tissue than does plain radiography, however, imaging artifacts caused by metal implants decrease yield

Zimmerli et al. NEJM 351;16 1645-54, 2004
Arthrocentesis

- Synovial-fluid leukocyte count >1700 per cubic millimeter or a finding of more than 65 percent neutrophils
  - Sensitivity for prosthetic infection of 94 and 97 percent
  - Specificities of 88 and 98 percent

# Diagnostic Value of Positive Operative Cultures

Number of positive cultures for the same organism when 3-6 operative specimens are examined

<table>
<thead>
<tr>
<th>Number Positive</th>
<th>Probability of Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>94.8</td>
</tr>
<tr>
<td>2</td>
<td>20.4</td>
</tr>
<tr>
<td>1</td>
<td>13.3</td>
</tr>
<tr>
<td>0</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Histopathology

- Periprosthetic tissue
  - Variable presence of PMN infiltrate
    - secondary to sampling error
  - Definition of acute inflammation in the periprosthetic tissue varies:
    - 1-10 or more neutrophils per high-power field at 400X magnification
    - sensitivity of 80 percent and a specificity of 90 percent
- Single most accurate predictor of infection:
  Isolation of the pathogen by arthrocentesis or surgical debridement

## Bacteriology of Prosthetic Joint Infections

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase negative staphylococci</td>
<td>22</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>22</td>
</tr>
<tr>
<td>Streptococci</td>
<td>14</td>
</tr>
<tr>
<td>Enterococci</td>
<td>7</td>
</tr>
<tr>
<td>Gram negative rods</td>
<td>25</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>10</td>
</tr>
</tbody>
</table>

Treatment

Goal of treating infection associated with a prosthetic joint is a pain-free, functional joint.
Surgical Therapy

• Debridement with retention of prosthesis
• One stage exchange of implant
• Two stage exchange of implant
  – With long interval (6-8 wks)
  – With short interval (2-4 wks)
• Implant removal without replacement
Principles of Therapy

• Historically- simple surgical drainage with retention of prosthesis followed by antibiotics
  – Success rate 20-36%

• In select patients: retention of prostheses
  – Early symptom duration (< 1 month) with debridement and retention of prosthesis, and 4-6 weeks of antibiotics
  – Success rate of 71%

• Brandt CM et al. CID. 1997;24:914-919
Principles of Therapy

• Two stage surgical procedure
  – 90% to 96% success with hips
  – 97% success with knees
    • Removal of prosthesis and cement
    • Placement of antibiotic impregnated spacer
    • 6 week course of bactericidal antibiotic therapy preferably based on pathogen identification and susceptibility testing.
    • Reimplantation of prosthesis at the conclusion of antibiotic therapy.

Criteria for Retention of Prosthesis

• Duration of clinical symptoms is less than three weeks
• Stable implant
• Soft tissue is on good condition
• Organism identified is susceptible to antimicrobial agents with activity against surface adhering organisms
Criteria for Surgical Debridement With Retention of Prosthesis

- Reported success rate of 82-100% for staphylococcal infections fulfilling the following criteria:
  - Duration of clinical symptoms is less than three weeks
  - Stable implant
  - Soft tissue is on good condition
  - Organism identified is susceptible to antimicrobial agents with activity against surface adhering organisms
    - 4-6 weeks of IV antimicrobial therapy
    - Followed by oral antibiotic therapy for 3 months (Hips) or 6 months (knees)

Zimmerli et al. NEJM 351;16 1645-54, 2004
Algorithm for the Treatment of Early or Hematogenous Infection Associated with a Prosthetic Joint

Zimmerli et al. NEJM 351;16 1645-54, 2004
Surgical Options When Implant Retention is Not Applicable

• One step approach prerequisites:
  – Satisfactory condition of soft tissue
  – Absence of severe coexisting illnesses
    • Diabetes mellitus, Rheumatoid arthritis, steroid use
  – Absence of difficult to treat organisms
    • MRSA, Enterococci, MDR GNRs, Fungi
Surgical Therapy: Two Step Approach

• Two step approach is generally preferred
  – Compromised soft tissue
  – Difficult to treat organisms

• Early (2-4wk) vs. late (6-8wk) interval reimplantation?
  – Infections with difficult-to-treat microorganisms such as MRSA, MDR gram negative rods, enterococci, or fungi, an interval of six to eight weeks between removal of the first prosthesis and placement of the second (late reimplantation)

Zimmerli et al. NEJM 351;16 1645-54, 2004
Surgical 2 Step Therapy: What About The Use of a Spacer?

- Antimicrobial-impregnated cement is frequently suggested
  - Data from randomized, controlled trials are lacking
- If multidrug-resistant microorganisms are isolated, instead of implanting a spacer, the preferred treatment is:
  - limb extension (hip)
  - external fixation or stabilization with a brace (in a procedure involving the knee)

Zimmerli et al. NEJM 351;16 1645-54, 2004
Surgical 2 Step Therapy: What About Duration of Antibiotics?

• Short interval reimplantation (2-4wks)
  – 2-4 weeks of antibiotic therapy prior to reimplantation with a spacer or external fixator device
  – Then antimicrobial treatment is administered for:
    • A total of three months (hip replacement)
    • A total of six months (knee replacement)

Zimmerli et al. NEJM 351;16 1645-54, 2004
Surgical 2 Step Therapy: What About Duration of Antibiotics?

- Long interval (6-8wk) reimplantation (for MRSA, enterococci, fungi MDR organisms)
  - Six to eight weeks of antimicrobials prior to reimplantation, without the use of a spacer
  - Antibiotics are discontinued two weeks prior to reimplantation in order to obtain reliable tissue specimens for culture
  - If on repeat culture specimens show:
    - no growth and no acute inflammation
      - antimicrobial treatment is discontinued.
    - growth and acute inflammation
      - continue antibiotics for a total of:
        » three months (hip)
        » six months (knee)

Zimmerli et al. NEJM 351;16 1645-54, 2004
Two Stage Exchange-Summary

- Current data supports the superiority of a two stage exchange vs. one step exchange
- Decision to proceed with 2 step exchange of with either long or short interval is a matter of expert opinion and is not supported by rigorous clinical data
- Not using an antibiotic impregnated spacer given infection with MRSA or MDR organisms is a matter of expert opinion
Algorithm for the Treatment of Patients with Infections Not Qualifying for Implant Retention

Zimmerli et al. NEJM 351;16 1645-54, 2004
Antibiotic Therapy Principles

• Important Antibiotic Properties:
  – Antimicrobial agents should have bactericidal activity against surface-adhering, slow-growing, and biofilm-producing microorganisms
    • Rifampin has effective antimicrobial properties within a biofilm
    • Rifampin should never be administered alone
      – staphylococci rapidly develop resistance
Antibiotic Considerations

• Quinolones are excellent combination agents
  – Excellent bioavailability, antimicrobial activity, and tolerability
  – Can be combined with rifampin
• Ciprofloxacin and ofloxacin
  – Well studied in bone and joint infections
• Levofloxacin
  – Better gram positive coverage
  – Not well studied for the management of bone and prosthetic joint infections
Antibiotic Considerations

• Trimethoprim–sulfamethoxazole, minocycline, and linezolid can also be combined with rifampin
  – no data on these combination regimens have been reported.

• There is a paucity of data available for the treatment of prosthetic joint infections with GNRs
New Antibiotics

• Linezolid
  – Oxazolidinone
    • FDA approved for VRE/MRSA infections, pneumonia, skin/soft tissue infections
  – Side effects
    • Thrombocytopenia
    • Serotonin syndrome with concomitant SSRI use
  – Not FDA approved for prosthetic joint infections
    • Case report data exists supporting the use of Linezolid for MRSA infected hip prosthesis
New Antibiotics

• Daptomycin
  – Lipopeptide antibiotic
    • FDA approved for management of complicated skin and soft tissue infections
    • Excellent bactericidal activity against MRSA and VRE
    • IV formulation
  – Side effect- myositis
  – No clinical information on penetration into bone, synovial fluid and no data on the management of bone and prosthetic joint infections
New Antibiotics

• Tigecycline
  – Gyicylcycline antibiotic
    • Bacteriostatic activity against MRSA, VRE, MDR GNR, ESBL enterobacteriaceae
    • FDA approved for skin/soft tissue infections, complicated intra-abdominal infections
    • Not FDA approved for prosthetic joint infections
  – No data available for the treatment of prosthetic joint infections with Tigecycline
<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Antimicrobial Agent</th>
<th>Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em> or <em>coagulase-negative</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>methicillin-susceptible</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Methicillin-susceptible</td>
<td>Nafcilin or floxacillin plus</td>
<td>2 g every 6 hr</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>Rifampin for 2 wk, followed by</td>
<td>450 mg every 12 hr</td>
<td>PO or IV</td>
</tr>
<tr>
<td></td>
<td>Rifampin plus</td>
<td>450 mg every 12 hr</td>
<td>PO</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin or</td>
<td>750 mg every 12 hr</td>
<td>PO</td>
</tr>
<tr>
<td></td>
<td>Levofoxacin</td>
<td>750 mg every 24 hr to</td>
<td>PO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>500 mg every 12 hr</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methicillin-resistant</td>
<td>Vancomycin plus</td>
<td>1 g every 12 hr</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>Rifampin for 2 wk, followed by</td>
<td>450 mg every 12 hr</td>
<td>PO or IV</td>
</tr>
<tr>
<td></td>
<td>Rifampin plus</td>
<td>450 mg every 12 hr</td>
<td>PO</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin plus</td>
<td>750 mg every 12 hr</td>
<td>PO</td>
</tr>
<tr>
<td></td>
<td>Levofoxacin plus</td>
<td>750 mg every 24 hr to</td>
<td>PO</td>
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<tr>
<td></td>
<td></td>
<td>500 mg every 12 hr</td>
<td></td>
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<tr>
<td></td>
<td>Telithromycin</td>
<td>400 mg every 24 hr</td>
<td>IV or IM</td>
</tr>
<tr>
<td></td>
<td>Fusidic acid</td>
<td>500 mg every 8 hr</td>
<td>PO</td>
</tr>
<tr>
<td></td>
<td>Trimethoprim–sulfamethoxazole</td>
<td>1 DS tablet every 8 hr</td>
<td>PO</td>
</tr>
<tr>
<td></td>
<td>Minocycline</td>
<td>100 mg every 12 hr</td>
<td>PO</td>
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<td></td>
</tr>
<tr>
<td><em>Streptococcus species</em> (except <em>Streptococcus</em></td>
<td>Penicillin G or</td>
<td>5 million U every 6 hr</td>
<td>IV</td>
</tr>
<tr>
<td><em>agalactiae</em>)</td>
<td>Ceftriaxone for 4 wk, followed by</td>
<td>2 g every 24 hr</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin</td>
<td>750–1000 mg every 8 hr</td>
<td>PO</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Enterococcus species (penicillin-susceptible) and</td>
<td>Penicillin G or</td>
<td>5 million U every 6 hr</td>
<td>IV</td>
</tr>
<tr>
<td><em>Streptococcus</em> <em>agalactiae</em>)</td>
<td>Amoxicillin or amoxicillin plus</td>
<td>2 g every 4–6 hr</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>Aminoglycoside† for 2–4 wk,</td>
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<tr>
<td></td>
<td>followed by</td>
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<td></td>
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<tr>
<td></td>
<td>Amoxicillin</td>
<td>750–1000 mg every 8 hr</td>
<td>PO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae (quinolone-susceptible)</td>
<td>Ciprofloxacin</td>
<td>750 mg every 12 hr</td>
<td>PO</td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td>Nonfermenters (e.g., <em>Pseudomonas aeruginosa</em>)</td>
<td>Ceftazidime or cefepime†</td>
<td>2 g every 8 hr</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>Aminoglycoside† for 2 wk,</td>
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<td></td>
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<tr>
<td></td>
<td>followed by</td>
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<tr>
<td></td>
<td>Ciprofloxacin</td>
<td>750 mg every 12 hr</td>
<td>PO</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Anaerobes</td>
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<td></td>
<td>Clindamycin for 2–4 wk,</td>
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<tr>
<td></td>
<td>followed by</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clindamycin</td>
<td>300 mg every 6 hr</td>
<td>PO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed infections (without methicillin-resistant</td>
<td>Amoxicillin–clavulanic acid‡ or</td>
<td>2.2 g every 8 hr</td>
<td>IV</td>
</tr>
<tr>
<td>staphylococci)</td>
<td>Ampicillin–sulbactam or</td>
<td>3 g every 6 hr</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>Carbapenem for 2–4 wk, followed</td>
<td>According to com-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>by individual regimens</td>
<td>pound</td>
<td></td>
</tr>
</tbody>
</table>
Suppressive antibiotics

- Prosthesis removal contraindicated by medical or surgical conditions or patient refusal
- Life long suppressive antibiotics
  - Pathogen is relatively avirulent
  - Pathogen is sensitive to an oral antibiotic
  - Prosthesis is not loose
- Successful joint function has been variably maintained in 26%-82% of patients

Conclusion

• Prosthetic joint infections have both high morbidity and cost.

• Risk factors for prosthetic joint infections include age, rheumatoid arthritis, DM, obesity, poor nutritiona status and psoriasis.

• Prosthetic joint infections occur by local introduction or by hematogenous spread.
Conclusion

• Common presenting symptoms include:
  – Fever, pain, swelling & draining sinus tract

• Radiographic tests
  – Loosening of prosthesis

• Peri-articular operative cultures and histopathologic evaluation
  – Greatest diagnostic yield
Conclusion

• Surgical Treatments
  – One step exchange of prosthesis
    • For patients with short duration of symptoms, intact periprosthetic tissue, organism not MDR
  – Two step exchange of prosthesis
    • Greatest efficacy and greatest opportunity for cure and preservation of mobility
Conclusion

• Antibiotic therapy is used in conjunction with surgical intervention
  – Choice should be pathogen directed and should include an agent with biofilm activity

• Suppressive antibiotic therapy may be an option for non-surgical candidates
The End