Periprosthetic Joint Infection
What is on the horizon

Javad Parvizi MD, FRCS
Rothman Institute at Thomas Jefferson University, Philadelphia
Disclosures

- **Research support:**
  - NIH
  - OREF
  - Stryker Orthopedics
  - Depuy
  - Zimmer
  - Baxter
  - 3M
  - Biomemetics
  - Ceramtec
  - Smith and Nephew

- **Consultant:**
  - Zimmer
  - Smith and Nephew
  - Convatech
  - TissueGene
  - Ceramtec
  - OsteoMEM
  - 3M
  - Cadence

- **Intellectual Property/Royalty/Ownership**
  - SmarTech
  - Elsevier
  - Wolters Kluwer
  - Slack
  - Hip Innovation Technology
  - CD Diagnostics
  - Jaypee publishers
  - Datatrace

- **Board Member/Adviser**
  - Journal of Arthroplasty
  - Philadelphia Orthopaedic Soc
  - Eastern Orthopedic Assoc.
  - United Healthcare
  - Magnifi Group (Publishers)
  - 3M
  - JBJS-A

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Thomas Jefferson University
Periprosthetic Joint Infection

- Incidence 1-4% of primary lower limb arthroplasties
- May occur in >30% after revision arthroplasty
THA Infection: Medicare Data

% of Prosthesis Infection – Free at Time (T)

Years Since Hip Arthroplasty

Age  
65–69  
70–74  
75–79  
80–84  
85+

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TKA Infection: Medicare Data
Infected Revisions: 1990-2003

Kurtz, S, Parvizi J JOA 2008
Infected Revisions 2001-20
Cost

Total Cost (millions) of Patients with Infected Procedures

Year


THA
TKA
Total THA + TKA
Annual Cost

$600 Million
Periprosthetic Joint Infection

- Prevention
- Diagnosis
- Treatment
Periprosthetic Joint Infection

- Prevention of SSI
Optimize Host
Diabetes

• Control of glucose
  • HbA1C <7%
  • glucose <180
• Ulcerations
• Neuropathy
Control Nidus

- GI/GU (urine)
- Skin/nails
- No role for routine dental clearance
Rheumatoid Arthritis

• Disease modifying agents (antimonomoclonal antibodies)
• Steroids (taper)
• Skin (ensure there is no ulcers)
Preoperative Optimization

- Malnutrition
- Obesity
- Skin (psoriasis, eczema, ulcerations)
- Vascular insufficiency ??
- Smoking
Peri-operative Factors

- Skin prep
- Gloves
- Draping
- Room
- Antibiotics

- Exposure
- Bleeding control
- Closure
- Dressing
Antibiotics
Prophylactic antibiotics

Vancomycin (needs 1 hour)

MRSA carriers

Remote or recent MRSA Infection

Institutionalized patients

Healthcare workers
Skin Prep

Starts at home
Preoperative Optimization

- Skin decontamination
  - Betadine shower
  - Chlorhexidine wipes/showers
  - Shaving (save until the OR)
Skin prep

- 9 step

Matar W, et al JBJS 2012

Skin prep

- Most important agent is ALCOHOL
Skin Prep

- Contamination of skin during draping
- May repeat skin prep (Duraprep™)
Drapes

- Skin recolonizes
- Adhesive draping

Lack of adequate science

- Laminar flow
- Space suits
- Size/volume
OR Environment

- Wound Contamination
  - Direct Fall-out
  - Gloves Or Instruments

- The Primary Source Of Bacteria In OR Is OR Personnel
People Shed up to 10,000 bacteria/min.

“Dispersers”

- 13% of Men
- 5% of Post-menopausal Woman
- 1% of Pre-menopausal Women

• Traffic--- terrible
- Puncture all cases > 3 hrs
- Cotton outer gloves reduce risk
- Change every 2 hrs
Approach

- Gentle soft tissue handling
- Expeditious surgery
- Irrigation
Wound Complications

- Drainage
- Hematoma
- Cellulitis

Treat Aggressively
Hip do not lie
- Aspirin for majority
- As effective as any agent
- Less complication
SSI caused by MRSA

Screening and Decolonization?
Handheld PCR Machines

- Point of care
- Portable
- Isothermal Recombinase polymerase amplification (RPA)
- Peptide covalently attached to microbead anchor and reporter molecule
Decolonization

- One time application
- One hour before surgery
- 12 hour effect
- 99% eradication
- Lowers SSI
  - Phillips MS et al. IDSA 2012
I. a dicaticionic porphyrin drug
II. rapid Gram-positive antibacterial activity
III. unique abilities to prevent bacterial resistance
IV. may be used to prevent potentially fatal SA infections
V. undergoing clinical trials for the nasal decolonization of Staphylococcus aureus, including methicillin-resistant Staphylococcus aureus (MRSA)
Screening

- It appears that screening and decolonization reduces the incidence of SSI
- Logistic issues
- How to?
- Perhaps most important is identifications
  - Appropriate antibiotics
  - Isolation

Stay tuned
Periprosthetic Joint Infection

- Prevention
- Diagnosis
- Treatment
Diagnosis of PJI

- No absolute test for diagnosis
- No standard definition/criteria for PJI
# Culture – “gold standard”

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>◦ Inexpensive</td>
<td>◦ Polymicrobial results</td>
</tr>
<tr>
<td>◦ Result can be used in further testing</td>
<td>◦ Time limitations</td>
</tr>
<tr>
<td></td>
<td>- pathogen growth</td>
</tr>
<tr>
<td></td>
<td>- result to treatment</td>
</tr>
<tr>
<td></td>
<td>◦ False positive</td>
</tr>
<tr>
<td></td>
<td>- contamination</td>
</tr>
<tr>
<td></td>
<td>◦ False negatives</td>
</tr>
<tr>
<td></td>
<td>- biofilms</td>
</tr>
<tr>
<td></td>
<td>- prior antibiotic treatment</td>
</tr>
<tr>
<td></td>
<td>- hard-to-culture organisms</td>
</tr>
</tbody>
</table>

Malekzadeh CORR 2010
Definition of PJI (MSIS)

- There is a sinus tract communicating with the prosthesis; or

Parvizi J et al CORR 2011
Definition of PJI (MSIS)

- There is a sinus tract communicating with the prosthesis; or

- A pathogen is isolated by culture from at least two separate tissue or fluid samples obtained from the affected prosthetic joint; or

Parvizi J et al CORR 2011
Definition of PJI (MSIS)

- There is a sinus tract communicating with the prosthesis; or
- A pathogen is isolated by culture from two separate tissue or fluid samples obtained from the affected prosthetic joint; or
- When four out of the following six criteria exists

Parvizi J et al CORR 2011
Definition of PJI

- ESR or CRP,
- Synovial WBC count,
- Synovial PMN%,
- Presence of purulence,
- Isolation of a microorganism in one culture of periprosthetic tissue or fluid, or
- ≥ 5 neutrophils per hpf in 5 hpf observed from histological analysis of periprosthetic tissue at x 400 times magnification.
Craig Della Valle
Javad Parvizi
Mark Spangehl
Tom Bauer
Paul DiCesare
Richard Evans
John Segreti

AAOS Guidelines

Committee
15 recommendations
Majority strong or moderate
Review of literature
Patients were divided into high and low risk groups (consensus).

ESR and CRP for all patients undergoing revision arthroplasty.

Aspiration of joint before any further imaging.
Patients be off antibiotics before aspiration (2 weeks)

No Antibiotics until diagnosis reached or refuted

No role for intraoperative gram stain
Cannot recommend bone scan, CT, or MRI

Frozen section for suspected but not confirmed cases

Perioperative antibiotic not to be withheld
1. Patient at higher probability of hip periprosthetic infection being assessed for infection

2. ESR AND CRP: either positive?
   
3. Aspirate joint
   
4. Both Cell count/differential AND Culture positive?
   
5. Infection Likely

6. Either cell count/differential OR culture positive?
   
7. Repeat aspiration: positive?
   
8. Is surgery planned?
   
9. Frozen section AND/OR Intra-operative synovial cell count: positive?

10. Nuclear imaging: positive?

11. Infection Likely

12. Infection Unlikely
Target:

- Segment of the 16S ribosomal RNA gene unique to eubacteria

Report:

- Sensitivity 100%
- Specificity 89%

(Mariani & Tuan 1985)
(Tuan et al JBJS 2008)
Protein profiling has been successfully used to diagnose
- Pregnancy
- Urinary tract infections

Inflammatory proteins elevated in cases of PJI in both
- Serum, and
- Synovial fluid

Di Cesare JBJS 2007
Shah CORR 2009
Deirmengian CORR 2010
Pregnancy Test for PJI

- Neutrophil enzymes
- Detected in joint aspirate
- 1 minute for response
Leukocyte esterase in Urinalysis strips

<table>
<thead>
<tr>
<th>Leukocytes</th>
<th>neg.</th>
<th>trace</th>
<th>+</th>
<th>++</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 - 120 sec</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results

- Prospective study
- Rothman Institute
- 31 infected / 83 uninfected

* sensitivity = 81%
* specificity = 100%
* positive predictive value = 100%
* negative predictive value = 93.3%

Parvizi et al. JBJS 2011
• The Area under the Curve (AUC): 0.988
Leukocyte esterase strip test is highly accurate for diagnosis of PJI

Fast (real time), simple, cheap
<table>
<thead>
<tr>
<th>Category</th>
<th>Proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokines</td>
<td>IL-1α, IL-1β, IL1ra, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12 subunit p40, IL-12 subunit p70, IL-15, IL-17, IL-23, IFN-γ, TNF-α, TNF-β, TNF receptor-like 2</td>
</tr>
<tr>
<td>Adhesion Molecules</td>
<td>ICAM-1, Vascular Cell Adhesion</td>
</tr>
<tr>
<td>Growth Factors</td>
<td>VEG-F, BDNF</td>
</tr>
<tr>
<td>Acute-phase reactants</td>
<td>CRP</td>
</tr>
<tr>
<td>Complement cascade</td>
<td>Complement C3, α-2 macroglobulin, Beta-2-Microglobulin, von Willebrand Factor, Fibrinogen, Factor VII</td>
</tr>
<tr>
<td>Chemotactic proteins</td>
<td>Monocyte Chemotactic Protein 1, Eotaxin-1</td>
</tr>
<tr>
<td>Metalloproteinase compounds</td>
<td>MMP-2, MMP-3, MMP-9, TIMP-1</td>
</tr>
<tr>
<td>Lysis/Destruction</td>
<td>Alpha-1-Antitrypsin, Granulocyte-Macrophage Colony-Stimulating Factor, Macrophage Inflammatory Protein-1 alpha Macrophage Inflammatory Protein-1 beta</td>
</tr>
<tr>
<td>Other</td>
<td>Ferritin, Haptoglobin, Stem Cell Factor, T-Cell-Specific Protein, RANTES, Molecule-1, Vitamin D-Binding Protein</td>
</tr>
</tbody>
</table>
2.44 fold difference between highest aseptic sample and lowest septic sample.
Recursive Partitioning

Suspected Infection

- LE ++
  - LE reading
  - Synovial Fluid
  - Start

- LE +, Trace, Negative
  - CRP
    - > or = 3.75 mg/dL
      - 100% Probability of PJI
    - < 3.75 mg/dL
      - 62.5% Probability of PJI

- Decision
- End
Is it really infected?
IBIS T5000 Biosensor

1) Amplification
   - Multiple pairs of species specific primers

2) ESI-MS: Electrospray Ionization Mass Spectrometry

3) Base composition analysis compared to database

4) Microorganisms identified
   - Pathogen status
   - Genomes/Well
   - Confidence
   - *mecA* gene
IBIS 5000: Step 1
Sample Prep and Broad Range PCR

Microbe Mixture

Extract Nucleic Acids

Broad Range Primers

PCR Amplification

Primer Set 1
Primer Set 2
Primer Set 3

PCR Products

Internal Calibrant
IBIS 5000: Step 2
MS Analysis and Signal Processing

Mass Spectrometer

Spectral Signal

Signal Processing
Masses to Base Compositions

<table>
<thead>
<tr>
<th>ORGANISM</th>
<th>Mass</th>
<th>Base Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacillus anthracis</td>
<td>35278.823</td>
<td>A26 G34 C27 T27</td>
</tr>
<tr>
<td>Borrelia burgdorferi</td>
<td>33770.606</td>
<td>A29 G31 C23 T26</td>
</tr>
<tr>
<td>Clostridium botulinum</td>
<td>35843.944</td>
<td>A29 G33 C30 T24</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>35641.855</td>
<td>A22 G39 C29 T25</td>
</tr>
<tr>
<td>Staph aureus</td>
<td>35240.807</td>
<td>A24 G35 C30 T25</td>
</tr>
<tr>
<td>Strep pneumoniae</td>
<td>35270.806</td>
<td>A24 G35 C28 T27</td>
</tr>
<tr>
<td>Strep pyogenes</td>
<td>35281.808</td>
<td>A23 G37 C30 T24</td>
</tr>
</tbody>
</table>

Base Compositions Map to Microbes
### Primer Set 1

<table>
<thead>
<tr>
<th>Primer</th>
<th>Mass</th>
<th>Base Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blue</td>
<td>18234.970</td>
<td>A$<em>{12}$G$</em>{17}$C$<em>{17}$T$</em>{13}$</td>
</tr>
<tr>
<td>Blue</td>
<td>17948.926</td>
<td>A$<em>{14}$G$</em>{14}$C$<em>{12}$T$</em>{18}$</td>
</tr>
<tr>
<td>Blue</td>
<td>18610.017</td>
<td>A$<em>{11}$G$</em>{19}$C$<em>{15}$T$</em>{15}$</td>
</tr>
<tr>
<td>Blue</td>
<td>17936.912</td>
<td>A$<em>{11}$G$</em>{17}$C$<em>{16}$T$</em>{14}$</td>
</tr>
<tr>
<td>Blue</td>
<td>18877.118</td>
<td>A$<em>{18}$G$</em>{15}$C$<em>{15}$T$</em>{13}$</td>
</tr>
</tbody>
</table>

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**Bacteria**

- **Cytophaga**
  - Mesoacidiphilus lacus
  - Alcaligenes fecalis
  - Clostridium perfringens
  - Bacillus subtilis

- **Chlamydia**
  - Chlamydia psittaci
  - Chlamydia granulomatis
  - Chlamydia pneumoniae

- **Spirocheta**
  - Leptospira interrogans
  - Borrelia burgdorferi
  - Treponema pallidum

- **Actinobacteria**
  - Mycobacterium tuberculosis
  - Mycobacterium leprae

- **Proteobacteria**
  - Escherichia coli
  - Salmonella enterica

- **Fusobacteria**
  - Fusobacterium nucleatum

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**IBIS 5000: Step 3**

**Triangulation Using Multiple Primers**
**Organisms Profile**

- **S. pyogenes**
  - [A27 G32 C24 T18]

- **H. influenzae**
  - [A28 G28 C25 T20]
**PLEX-ID**

1) Amplification
   - Broad identification (3100 species)

2) Targeted identification (spectroscopy)

1) Characterization (high resolution subtyping and drug resistance)
   - Pathogen status
   - Genomes/Well
   - Confidence
   - *mecA* gene

Rothman Institute Orthopaedics
Thomas Jefferson University
Periprosthetic Joint Infection

- Prevention
- Diagnosis
- Treatment
Treatment of PJI

Options Available

- Antibiotic suppression alone
- Debridement and antibiotics
- Prosthesis Removal
  - One stage reimplantation
  - Two stage reimplantation
- Arthrodesis
- Amputation
Traditional Indications Revisited

Azzam K JOA 2010
- Acute symptoms (<48 hr)
- Susceptible organism
- Good soft-tissue coverage
- Well-fixed prosthesis
Success rates:

- 37%  
  our experience
- 17%  
  Salgado et al, CORR 2007
- 29%  
- 11%  
  Kilgus et al, CORR 2002

Average success rate: 24%
“True” success rate (no infection, no mechanical failure, no reoperation)----

65%

Parvizi et al CORR 2009
Intracellular *S. aureus* in Periprosthetic Tissue

Parham S et al, Clin Infect Dis 2006
New Antibiotics

- **New Glucopeptides:** dalbavancin, telavancin, oritavancin
- **New betalactam:** ceftobiprole
- **New rifamycin:** AB-0043
- **New inhibitor of DHFR:** iclapram
Staphylococcus aureus (MSSA)

peptidoglycan

PBP 1 2 3 4

B-lactactam
Staphylococcus aureus (MSSA)

peptidoglycan

PBP 1 2 3 4

B-lactam

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Staphylococcus aureus (MRSA)

peptidoglycan

PBP 1 2 2a 3 4

B-lactam ceftobiprole

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Staphylococcus aureus (MRSA)

B-lactam

Ceftobiprole

PBP 1 2 2a 3 4

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Biofilm

- Smart Implants
- Natural barriers (opsonins, defensins)
- Biofilm disruption technologies
- Immunization
  - fragments of RNA to elicit cellular immunity
  - Staph aureus vaccine (University of Rochester/Pfizer)
Vancomycin Tethered To Ti Prevents Infection

Modification of Bone Allograft

a. Naturally-occurring amines in bone protein

EDTA as needed

AEEA Linker 2X

Addition of linkers

Vancomycin-modified bone

b. Modified Fluorescamine

Stained Background

Vancomycin

Control

Modified

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Bacterial Challenge: S. aureus

5 hours

12 hours

Control

VAN-Bone

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Thomas Jefferson University
Cortical Bone Struts

Control

VAN-Bone
Anti-infective Coating

N,N- dodecyl,methyl polyethylenimine (DM-PEI)
- Microbicidal “bubble bursting porcupine”

Permanent Passive Coating
- Intra-operative dipping
- Non-leaching attachment
- Long chain polycationic molecules
- Disrupts lipid membranes or cell walls of bacteria

U.S.S.N. 61/543,981 “Antibacterial Coatings that Inhibit Biofilm Formation on Orthopedic and Dental Implants.”
Developed by Dr. Paul Savage

- Synthetic analog of naturally occurring antimicrobial peptides (such as magainin—African Clawed Frog)

- Eradicates high inocula of bacteria—including those in a biofilm

- Can be coated alone or with polymer conjugate onto the surface of metal or polymer

- Sterilized by ETO, gamma irradiation or autoclave

Musculoskeletal Infection Society
International Consensus Meeting

- Review of literature (if available)
- Consensus/recommendations
- 400 delegates/80 countries/societies
- Representation from FDA/CMS/NIH/NQF/AHRQ and so on
THANK YOU.