Diagnosis of Periprosthetic Joint Infection

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

- **Research support:**
  - NIH
  - Department of Defense
  - OREF
  - 3M
  - Aesculap
  - AO Spine
  - Biomet
  - Cempra
  - CeramTec
  - DePuy
  - Integra
  - Myoscience
  - NDRI
  - Novartis
  - Pfizer
  - Rotation Medical
  - Simplify Medical
  - Smith and Nephew
  - Stelkast
  - Stryker Orthopedics
  - Synthes
  - TissueGene
  - Tornier
  - Orthospace
  - Zimmer Biomet
Disclosures

- **Consultant**
  - Zimmer Biomet
  - Convatech
  - TissueGene
  - Ceramtec
  - Medtronics
  - Ethicon
  - Theravance

- **Board Member/Adviser**
  - Journal of Arthroplasty
  - Eastern Orthopedic Assoc.
  - 3M
  - JBJS-A
  - Bone and Joint Journal (British)
  - Muller Foundation
  - United Healthcare

- **Royalty**
  - Elsevier
  - Wolters Kluwer
  - Slack
  - Jaypee publishers
  - Datatrace

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The diagnosis of periprosthetic infection has been the subject of considerable research.
This research has produced a large number of peer-reviewed manuscripts.
Obtained using the keyword “peri-prosthetic joint infection”
Infected Revisions 2001-2010
Burden

26,000 infected joints

Kurtz, S, Parvizi J JOA 2012
Infected Revisions 2001-2010
Cost

$1 billion

Kurtz, S, Parvizi J JOA 2012
Diagnosis of PJI

Difficult
Intracellular *S. aureus* in Periprosthetic Tissue

Parham S et al, Clin Infect Dis 2006
No test with absolute accuracy exists

i.e. no gold standard
Problem Diagnosing PJI

Blood CRP

Sensitivity 87%
Specificity 77%

10 mg/L

- Different labs use different units - mg/L vs. mg/dL
- The lab’s normal range has nothing to do with PJI

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Problems with automated cell counters?

- The cutoff is about 3000 cells/ul, not 50,000 cells/ul

<table>
<thead>
<tr>
<th>Synovial Fluid</th>
<th>Sensitivity 89%</th>
<th>Specificity 92%</th>
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</thead>
<tbody>
<tr>
<td>WBC</td>
<td>3000 cells/ul</td>
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</table>

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Problems Diagnosing PJI

Synovial Fluid Culture

Sensitivity 52%
Specificity 95%

Poor Results

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Journal</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>Bare et al.</td>
<td>CORR</td>
<td>53%</td>
<td>94%</td>
</tr>
<tr>
<td>2008</td>
<td>Gallo et al.</td>
<td>New Microbiol</td>
<td>44%</td>
<td>94%</td>
</tr>
<tr>
<td>1999</td>
<td>Spanghel et al.</td>
<td>JBJS</td>
<td>73%*</td>
<td>94%</td>
</tr>
<tr>
<td>2012</td>
<td>Gomez et al.</td>
<td>J Clin Micro</td>
<td>64%</td>
<td>97%</td>
</tr>
<tr>
<td>2014</td>
<td>Shanmugasundaram et al.</td>
<td>HSS Journal</td>
<td>45%</td>
<td></td>
</tr>
</tbody>
</table>
Increasing knowledge has led to many official diagnostic recommendations.
THE DIAGNOSIS OF PERIPROSTHETIC JOINT INFECTIONS OF THE HIP AND KNEE

GUIDELINE AND EVIDENCE REPORT

Adopted by the American Academy of Orthopaedic Surgeons
Board of Directors
June 18, 2010
• 15 recommendations
• Majority strong
• Review of literature

Parvizi et al. JAAOS 2010
Della Valle et al. JAAOS 2010
• Every painful prosthetic joint is potentially infected
Truly Aseptic?

• Infection should always be ruled out
• 12% of so called “aseptic” were infected

Parvizi J, et al CORR 2011
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
Patient at higher probability of hip periprosthetic infection being assessed for infection

2. ESR AND CRP: either positive?
   Yes → Aspirate joint
   No → 6.

3. Aspirate joint
   Yes → 4. Both Cell count/differential AND Culture positive?
   No → 2.

4. Both Cell count/differential AND Culture positive?
   Yes → 5. Infection Likely
   No → 6.

6. Either cell count/differential OR Culture positive?
   Yes → 7. Repeat aspiration: positive?
   No → 6.

7. Repeat aspiration: positive?
   Yes → 9. Frozen section AND/OR Intra-operative synovial cell count: positive?
   No → 8.

8. Is surgery planned?
   Yes → 11. Infection Likely
   No → 10.

10. Nuclear imaging: positive?
    Yes → 11. Infection Likely
    No → 12.

12. Infection Unlikely
Patient at lower probability of hip periprosthetic infection being assessed for infection

1. ESR AND CRP: either positive?
   - Yes: 3. Is surgery planned?
     - Yes: 4. Aspiration (pre-or intraoperative) AND/OR Frozen section: positive?
       - Yes: 5. Infection Likely
       - No: 6. Infection unlikely
     - No: 7. Both ESR and CRP positive?
       - Yes: 8. Aspirate joint
       - No: 10. Observe and Re-evaluate at 3 months
   - No: 13. Infection Unlikely

8. Both Cell count/differential AND Culture positive?
   - Yes: 9. Aspirate joint
   - No: 11. Either cell count/differential OR culture positive?
     - Yes: 12. Repeat aspiration: positive?
     - No: 6. Infection unlikely
   - No: 6. Infection unlikely
- CT or MRI
Bone scan (leukocyte labeled) and PET scan is an option for patients not scheduled for reoperation or diagnosis not reached.
Diagnosis of Periprosthetic Joint Infection: The Role of Nuclear Medicine May Be Overestimated

Claudio Diaz-Ledeza, MD, Courtney Lamberton, BS, Paul Lichstein, MD, Javad Parvizi, MD, FRCS

The Rothman Institute at Thomas Jefferson University, Philadelphia, Pennsylvania

ARTICLE INFO

Article history:

ABSTRACT

Although the International Consensus Meeting on Periprosthetic Joint Infection’s definition of periprosthetic joint
New Algorithm

Major Criteria:
- Sinus tract communicating with the joint

Minor Criteria:
- Culture
- Leukocyte Esterase
- Synovial White Blood Cell Count
- Synovial Neutrophil Percentage

Normal ESR and CRP AND Low Probability of Infection (based on history/PE/X-ray)

History
- Physical Examination (PE)
- X-Ray (Joint Specific)
- Serology (ESR and CRP)

Abnormal ESR and/or CRP OR Higher Probability of Infection (based on history/PE/X-ray) without major criteria

All minor criteria negative

Joint Aspiration

No Fluid OR Culture Positive Without Other Positive Minor Criteria OR One or Two Positive Minor Criteria OR Clinical Suspicion Persist without Positive Minor Criteria

All minor criteria negative

Repeat Aspiration With Addition of AFB/ Fungal Cultures

No Fluid OR Culture negative and only one minor criteria positive

Infection Unlikely

Negative

Biopsy (Micro AND Histology)

Positive

Infection Likely

Presence of Major Criteria

Culture Positive and One Positive Minor Criteria OR Minor Criteria ≥ 3 Positive
• Cell count
• Neutrophil differential
• Culture
• ? Biomarkers
Thresholds (Consensus)
Acute PJI

- ESR - No threshold
- CRP > 100 mg/L (hip and knee)
- Synovial WCC = 10,000 cells/ul
- Synovial PMN >90%

Graphs showing sensitivity and specificity for ESR, CRP, ESR+CRP.
Definition of PJI

CDC (National Healthcare Safety Network) adopts the MSIS definition of PJI
- ESR > 30 mm/hr
- CRP > 10 mg/L (hip and knee)
- Synovial WCC > 3,000 cells/ul
- Synovial PMN > 80%
Premature Treatment

- Interferes with isolation of infecting organism
- Affects cell count
- Affects serological markers

Opportunities in Management of PJI

Era of Biomarkers is here

The Journal of Arthroplasty Vol. 26 No. 6 Suppl. 1 2011

Molecular Markers for Diagnosis of Periprosthetic Joint Infection

Christina L. Jacovides, BS, Javad Parvizi, MD, FRCS, Bahar Adeli, BA, and Kwang Am Jung, MD
Biomarkers in Medicine

β-hCG

Cardiac Troponin
Diagnosis of PJI
Simple Test

- UA strips for leukocyte esterase
• 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
# Molecular Markers

## Protein Analysis

<table>
<thead>
<tr>
<th>Category</th>
<th>Proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytokines</strong></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><strong>Adhesion Molecules</strong></td>
<td>ICAM-1, Vascular Cell Adhesion</td>
</tr>
<tr>
<td><strong>Growth Factors</strong></td>
<td>VEG-F, BDNF</td>
</tr>
<tr>
<td><strong>Acute-phase reactants</strong></td>
<td>CRP</td>
</tr>
<tr>
<td><strong>Complement cascade</strong></td>
<td>Complement C3, α-2 macroglobulin, Beta-2-Microglobulin, von Willebrand Factor, Fibrinogen, Factor VII</td>
</tr>
<tr>
<td><strong>Chemotactic proteins</strong></td>
<td>Monocyte Chemotactic Protein 1, Eotaxin-1</td>
</tr>
<tr>
<td><strong>Metalloproteinase compounds</strong></td>
<td>MMP-2, MMP-3, MMP-9, TIMP-1</td>
</tr>
<tr>
<td><strong>Lysis/Destruction</strong></td>
<td>Alpha-1-Antitrypsin, Granulocyte-Macrophage Colony-Stimulating Factor, Macrophage Inflammatory Protein-1 alpha Macrophage Inflammatory Protein-1 beta</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Ferritin, Haptoglobin, Stem Cell Factor, T-Cell-Specific Protein, RANTES, Molecule-1, Vitamin D-Binding Protein</td>
</tr>
</tbody>
</table>
**Biomarker Screen**

### Biomarkers Failing Prescreen
- PCT
- TGFα
- LL-37, Human, ELISA kit
- LBP
- CGRP
- Orsomucoid
- Nibrin
- TSG6
- Plekstrin
- SOD2
- Urokinase
- MIF
- PAI-1 (total)
- sFas
- sFasL
- sICAM-1
- sVCAM-1
- Granzyme B
- HSP70
- IL-1α
- IL-10
- IL-17
- MIP-1α
- MIP-1β
- MMP-8

**Total: 45 Markers Screened**

### Biomarkers Passing Prescreen
- IL-1β
- IL-6
- IL-8
- IL-1α
- VEGF
- IP-10
- BFGF (aka FGF2)
- CRP
- a2M
- SKALP
- HNE Enzyme assay

- LE Strip
- Lactoferrin
- Lipocalin-2/NGAL
- Neutrophil Elastase-2 (ELA2)
- Resistin
- Thrombospondin-1 (TSP-1)
- HNP1-3 Human, ELISA kit
- BPI
Alpha-Defensin
Alpha-Defensin

Antimicrobial Peptide Secreted by Neutrophils to fight Infection

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# Overall study data

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Gold Standard</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rothman Institute</td>
<td>149</td>
<td>MSIS Criteria</td>
<td>97% (95% CI: 86-100%)</td>
<td>96% (95% CI: 90-99%)</td>
</tr>
<tr>
<td>Mayo Arizona</td>
<td>61</td>
<td>MSIS Criteria</td>
<td>100% (95% CI: 79-100%)</td>
<td>95% (95% CI: 83-99%)</td>
</tr>
<tr>
<td>Cleveland Clinic</td>
<td>111</td>
<td>MSIS Criteria</td>
<td>96% (95% CI: 82-99%)</td>
<td>99% (95% CI: 93-100%)</td>
</tr>
<tr>
<td>Combined</td>
<td>320</td>
<td>MSIS Criteria</td>
<td>98% (95% CI: 92-100%)</td>
<td>97% (95% CI: 93-99%)</td>
</tr>
</tbody>
</table>
Prophenoloxidase Pathway

Beta Glucan (βG) Fungi

Peptidoglycan (PG) Gram+ & Gram-

Pattern Recognition Receptors

Serine Protease Cascade

Prophenoloxidase

Phenoloxidase

Polymerization of melanin

Melanin clots restrain and kill microbes.

Basis for this colorimetric method:
- Production of melanin is associated with black discoloration and is indicative of presence of PG or βG.
- Time of reaction can be used to estimate the quantity of PG or βG.

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Samples from 8 patients with PJI and 5 patients undergoing primary arthroplasty (control group) have been tested.

In PJI group, the pathogens were S. aureus (4 cases), coagulase negative Staphylococcus (2 cases), Strep. Intermedius and Candida tropicalis.

The test was positive in all PJI cases and negative in all control cases.

The test has been done on two blood (both S. aureus) and two periprosthetic solid tissue samples (S. aureus and Candida tropicalis) at the time of reimplantation and all were positive.
Advantages as diagnostic method

- Directly targets the pathogenic bacteria
  - Most of the pathogens in PJI can be detected.

- Simple

- Inexpensive: (approximate cost will depend on optimization of the method but can be less than 20 $ for each experiment)

- Rapid
  - Time of reaction varies between 30-90 minutes and depends on the quantity of PG/βG.

- Potentially quantitative

- Doable on synovial fluid, solid tissue samples and blood

- Easy to perform
  - In-hospital & out-patient
Issues

- Pathogen
  - Parvizi et al JBJS 2013
Is it really infected?
**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
IBIS 5000: Step 1
Sample Prep and Broad Range PCR
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
IBIS 5000: Step 3
Triangulation Using Multiple Primers

Primer Set
Mass
Blue 18234.970
Blue 17948.926
Blue 18610.017
Blue 18877.118

Base Count
A_{12} G_{17} C_{17} T_{13}
A_{14} G_{14} C_{12} T_{18}
A_{11} G_{19} C_{15} T_{15}
A_{18} G_{15} C_{15} T_{13}

Primer #1

Bacteria
Cytophagales

Spirochetes
Actinobacteria

Fusobacteria
Mollicutes

Firmicutes
Bacilli

Chlamydia
Epsilon

Proteobacteria

Alpha
Beta
Gamma

IBIS 5000: Step 3
Triangulation Using Multiple Primers

Primer Set
Mass
Blue 18234.970
Blue 17948.926
Blue 18610.017
Blue 18877.118

Base Count
A_{12} G_{17} C_{17} T_{13}
A_{14} G_{14} C_{12} T_{18}
A_{11} G_{19} C_{15} T_{15}
A_{18} G_{15} C_{15} T_{13}

Primer #1

Bacteria
Cytophagales

Spirochetes
Actinobacteria

Fusobacteria
Mollicutes

Firmicutes
Bacilli

Chlamydia
Epsilon

Proteobacteria

Alpha
Beta
Gamma
Organisms Profile

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

- **H. influenzae**
  - [A28 G28 C25 T20]
Thank you