Cutibacterium (ex. Propionibacterium) acnes & Shoulders

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Disclosure and Objectives

• Disclosures:
  – Johnson & Johnson
  – Collidion

• Objectives:
  – Describe why *C. acnes* is a leading cause of prosthetic shoulder infection
  – Discuss critical gaps in the diagnosis and treatment of *C. acnes* PJI
Shoulder surgeries: U.S.

- Rotator cuff repairs & shoulder arthroplasty
  - ↑ 600% since 1996
- 53,000 shoulder replacements (2016)
Infectious Arthritis Due to Propionibacterium acnes in a Prosthetic Joint

Author(s): Mark S. Sulkowski, Igor Z. Abolnik, Edward I. Morris and Donald L. Granger
Published by: Oxford University Press

1990s: ID View:

Usually a contaminant
Rare cause of significant infection

1994
Case Report from Duke University

71M total shoulder replacement 1984
1990: loosening, replacement
--note of extensive inflammation

Despite negative aspiration cx
OR Cultures x 3: P acnes

World arthritis literature:
12 cases to date, 6 prosthetic
**P. acnes – Shoulder**

**Propionibacterium acnes** Postoperative Shoulder Arthritis: An Emerging Clinical Entity

Pierre Yves Levy, Florence Fenollar, Andreas Stein, Frederic Borrione, Emile Cohen, Bernhard Lebail, and Didier Raoult

1. Unité des Rickettsies, Faculté de Médecine, Université de la Méditerranée.
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3. Hôpital Ambroise Paré, Marseille, and 4. Clinique la Casamance, Aubagne, France

- Rotator cuff & arthroplasty
- Used extended culture (10-14d v. 5d)
- Reason for predilection not initially understood
- Treatment: amoxicillin + rifampin

**Table 1. Clinical investigation and systematic microbiological analysis of Propionibacterium acnes infection.**

<table>
<thead>
<tr>
<th>Site of infection</th>
<th>No. of patients (n = 276)</th>
<th>No. of patients with positive culture (n = 247)</th>
<th>No. of patients with infection due to P. acnes*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder</td>
<td>19</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Lower limb</td>
<td>257</td>
<td>233</td>
<td>1</td>
</tr>
</tbody>
</table>

*P value for comparison of shoulder infection versus lower limb infection was <.001.
What’s most important in the skin microbiome?

- Coag-neg Staph
  - Not just a weed
  - Appears to help
    - Modulate inflammation
    - Assist skin repair
    - Antimicrobial effects
    - Control malignancy

*The multifaceted roles of S. epidermidis in skin physiology*

*S. epidermidis* guards skin against inflammation, infections, and cancer through interactions with keratinocytes, T cells, and other members of the skin microbiota. These interactions are strain- and context-dependent, with some leading to negative outcomes for the host, including inflammation and infection.
Cutibacterium (P.) acnes

- Gram positive rod, anaerobe
  - Commensal, low pathogenicity
    - 2% of skin microbiome flora
  - Sebaceous follicles
- Slow growth, aerotolerant
  - Tissue: 10-14d
  - Blood: mean 6.4d (range: 2-15d)
  - Frequent contaminant
- Phylogenetic subtypes
  - IA1, IA2, IB, IC, II and III
  - IB and II associated with deep, joint infections
- Resistant to lysozyme, chymotrypsin, hydrogen peroxide, human serum factors
- Propensity to form biofilm
Association of *Cutibacterium avidum* Colonization in the Groin With Obesity: A Potential Risk Factor for Hip Periprosthetic Joint Infection

Laura Böni, Stefan P. Kuster, Bianka Bartik, Reinhard Zbinden, Patrick O. Zingg, and Yvonne Achermann

1Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, 2Department of Orthopedics, University Hospital Balgrist, and 3Institute of Medical Microbiology, University of Zurich, Switzerland

- Associated with THRls
  - Achermann CID 2018;66:54
- Microbiome:
  - Moist sweat glands, esp. groin
- 21/65 (32.5%) colonized
  - Mostly anterior or lateral thigh
  - BMI increases risk
  - OR per BMI unit increase 1.15
    95% CI 1.03-1.29, p = 0.01
C. acnes Virulence/Biofilm

- All phylotypes produce biofilm
  - Less for acnes vulgaris isolates
  - Dermatan-sulfate adhesion
  - Resistance to neutrophilic action, antimicrobials

- Immune responses
  - Best studied in acne vulgaris
Additional Studies/Background
Shoulder surgeries

- Infection rates:
  - Rotator cuff repair: 0.27-1.9%
  - Arthroplasty: 0-15%, 1% average
    - Reverse arthroplasty--higher
- *C. (P.) acnes*:
  - Commonly identified infectious complication of shoulder arthroplasty
    - #1 C. acnes > Staph
  - Delayed/late >> early
  - Incidence primary vs. revision arthroplasty
    - 1-3% vs. 29%
Additional Studies/Background
Shoulder surgeries

Recovery in primary arthroscopy & open surgery
• Complicates interpretation
  – Culture contamination?
  – Deep tissue contamination?
  – Some implicate in primary joint disease?

• Variable presentation, often indolent infection w/ foreign material present

• Lack of traditional signs/symptoms
  – Pain, stiffness #1
  – +/- swelling
  – Fever unusual
  – Pus may or may not be present
  – Radiolucencies about implant
  – ESR, CRP often normal
Typical presentation

- Male, shoulder prosthesis
- Higher BMI
- Concern for mechanical failure or loosening of prosthesis

Also increased risk if:
- Immunosuppressed
- Diabetic
- Replacement done for trauma
Labs: C. acnes PJI

- Low sensitivity and predicative values
  - Especially later infections
  - Cannot exclude infection if normal!

<table>
<thead>
<tr>
<th>Metric</th>
<th>Percentage elevated</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>6.8%</td>
<td>Often when overt pus exists</td>
</tr>
<tr>
<td>ESR</td>
<td>37.6%</td>
<td>Also less specific</td>
</tr>
<tr>
<td>CRP</td>
<td>62.1%</td>
<td></td>
</tr>
</tbody>
</table>
Imaging for C. acnes

- Plain radiographs
  - Concern for bone loss in setting of pain
  - OR 3.0-10.0, if humeral component loosening

- Other imaging methods?
  - CT or MRI: difficult due to artifact
  - Nuclear medicine: poor
    - WBC scan
    - Bone scan
Synovial fluid markers

• Ready for prime time? Limited studies
• IL-6 ↑
• IL-6 + TNF α + IL-2: ↑ more accurate
• Alpha-defensin: ↑
Case from March 2019

- 77M diabetic, shoulder replacement 2 yrs prior
  - Pain, stiffness, mild swelling over 6 mos.
  - ESR and CRP normal
  - Aspiration: positive culture D8, C. acnes
  - Placed on doxycycline
  - To OR: reverse prosthesis, negative cultures
Cultures: Pre-operative?

• Must be held for 10-14d for maximum sensitivity
  – May rule in, but not reliably exclude infection (AAOS 2018)

• Culture
  – Aspiration: 16.7%
  – Biopsy tissue, arthroscopic: ~100%
Operative Testing:

• If not obvious infection: terminology
  – Failed arthroplasty w/ (+) cultures
  – Unexpected positive cultures

• Do all failed joints/revisions need cultures?

• Are definitions different for *C. acnes*?
Definitions of infection

- No gold standard for *C. acnes*
  - Aspiration: less specific, sensitive
    - >2000 PMNs suggestive of late PJI
  - Tissue: definitions for hip/knee (frozen histopath, \( \geq 5 \) PMNs/hpf)
    - Since indolent infection, frozen sections as not reliable, compared to hip/knee infections, < 10% = > 5 PMNs/hpf
    - Proposed as more specific*: tissue microscopy, 5 samplings
      - 10 PMNs in 5 HPF
      - Sensitivity 72%, specificity 100%

- OR: at least 4 tissue samples
  - Avoid swabs
  - Procure near implant
  - Sonication, limited data suggests no benefit, shoulder PJI
Characteristics and Treatment Outcomes of \textit{Propionibacterium acnes} Prosthetic Shoulder Infections in Adults

- 24 PJIs, shoulder surgery 2000-2013
- PJI definition based on standard criteria
  - $\geq$ 2 culture specimens
  - 1 culture specimen and
    - joint purulence
    - histopathologic inflammation
    - sinus tract communicating
- 92\% diagnosed by extended cultures x 14d [2009]
  - Brucella media
  - Chopped meat broth
## Microbiology and outcomes

### Outcomes (median abx 6.3 mos)

<p>| Table 3. Treatment Outcomes for <em>Propionibacterium acnes</em> Shoulder Prosthetic Joint Infection |</p>
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total Treated No. (%)</th>
<th>Favorable Outcomea No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of treatment*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotic therapy only</td>
<td>7 (29)b</td>
<td>4 (67)</td>
</tr>
<tr>
<td>Antibiotic therapy + surgery</td>
<td>14 (58)</td>
<td>10 (71)</td>
</tr>
<tr>
<td>Surgical type*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-stage exchange</td>
<td>4 (27)c</td>
<td>3 (75)</td>
</tr>
<tr>
<td>2-stage exchange</td>
<td>7 (47)</td>
<td>6 (86)</td>
</tr>
<tr>
<td>Rifampin therapy*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15 (71)d</td>
<td>11 (73)</td>
</tr>
<tr>
<td>No</td>
<td>5 (24)</td>
<td>3 (60)</td>
</tr>
</tbody>
</table>

* Data are number (% of treated cases).
* Data are number (% of all cases).
* Data are number (% of surgical cases).
* Data are number (% of cases receiving antibiotic therapy).
* P > .05.

### Susceptibilities

<p>| Table 2. Microbial Susceptibility Patterns of <em>Propionibacterium acnes</em> Isolates |</p>
<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>No. (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>19 (100)</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Rifampin</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>14 (100)</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>17 (94)</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Minocycline MIC 0.03–0.25 µg/mLb</td>
<td></td>
</tr>
</tbody>
</table>
ID Consultant v. Ortho Surgeon v. Micro lab—who are you going to believe?

<table>
<thead>
<tr>
<th>Study</th>
<th>Operation</th>
<th>Rate (+) culture, usually <em>C. acnes</em> recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mooks (2015)</td>
<td>Negative controls: sterile gauze</td>
<td>13%</td>
</tr>
<tr>
<td>Kelly (2009)</td>
<td>Primary shoulder*</td>
<td>29%</td>
</tr>
<tr>
<td>Levy</td>
<td>Primary shoulder/OA*</td>
<td>41.8%</td>
</tr>
<tr>
<td>Hudek (2014)</td>
<td>Primary shoulder*</td>
<td>36.4%</td>
</tr>
<tr>
<td>Maccioni (2015)</td>
<td>Primary shoulder* ▲</td>
<td>3.125%</td>
</tr>
<tr>
<td>Wong (2018)</td>
<td>Primary shoulder*</td>
<td>38% 1 (+) cx 19% ≥ 2 (+) cxs</td>
</tr>
</tbody>
</table>
Can you be a little bit pregnant?

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>No infection</td>
<td>All cultures are negative and no pre- or intraoperative infection finding.</td>
</tr>
<tr>
<td>Possible infection</td>
<td>1 positive intraoperative culture and no pre- or intraoperative infection finding.</td>
</tr>
<tr>
<td>Probable infection</td>
<td>&gt;1 positive intraoperative culture and no pre- or intraoperative infection finding or 1 positive intraoperative culture and ≥1 positive pre- or intraoperative infection finding.</td>
</tr>
<tr>
<td>Definite infection</td>
<td>&gt;1 positive intraoperative culture and ≥1 positive pre- or intraoperative infection finding or 1 positive intraoperative culture and 1 positive preoperative (aspirate) culture.</td>
</tr>
</tbody>
</table>

Pre- or intraoperative infection findings include the following: (1) preoperative clinical signs (eg, swelling, sinus tract, erythema, drainage), (2) elevated erythrocyte sedimentation rate or C-reactive protein level, (3) positive frozen section, and (4) intraoperative gross findings (eg, pus, drainage, necrosis).
Management

- Limited data: case series, retrospective/observational
- Approaches:
  - Observation
    - Assuming contaminant
  - Irrigation and debridement
    - < 1 month post-op (early infxn)
  - One stage exchange revision
    - Often unintended (medico-legal care?)
  - Two stage exchange revision
    - Favored by surgeons for late
  - Antibiotic therapy and suppression
  - Check susceptibility profile
- Favored approach: replacement
  - Success: 94%, f/u 1-13 years (42 pts, single stage)
  - Limited f/u data otherwise
- Many report 4-6 weeks IV antibiotic therapy
  - Some use combination therapy, often with rifampin
  - IDSA PJI Guideline: PCN G or ceftriaxone, alt: clindamycin
- One-stage
  - IV followed by 6-12 mos oral abx
Why do we give 4-6 weeks of IV antibiotic therapy for PJI/Osteo?

In our experience, clinically recurrent osteomyelitis is rarely controlled without the combination of careful, complete surgical debridement and prolonged (four to six weeks) parenteral antibiotic therapy at high dosage.
Does the OVIVA trial give any insight to treatment?
OVIVA: Pragmatic trial

- UK 26 centers, bone or joint infections
- Arms: PO or IV for first six weeks
  - Enter trial within 7d of diagnosis/surgery
  - Clinicians chose abx
    - Rifampin allowed
  - Abx could continue for longer
  - $1^\circ$ endpoint: treatment failure within 1 yr
- $N = 1054$, noninferiority 7.5%
  - Upper limb infection in 102 (9.67%)
## Selected OVIVA Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IV (n=527)</th>
<th>Oral (n=527)</th>
<th>Total (n=1054)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implant-related</td>
<td>328 (62%)</td>
<td>311 (59%)</td>
<td>639 (61%)</td>
</tr>
<tr>
<td>Debride/retain</td>
<td>124 (23.5)</td>
<td>123 (23.3)</td>
<td>247 (23.4)</td>
</tr>
<tr>
<td>Removal</td>
<td>89 (16.9)</td>
<td>78 (14.8)</td>
<td>135 (12.8)</td>
</tr>
<tr>
<td>One-stage</td>
<td>47 (8.9)</td>
<td>43 (8.2)</td>
<td>90 (8.5)</td>
</tr>
<tr>
<td><strong>Pathogens (total)</strong></td>
<td>500</td>
<td>503</td>
<td>1003</td>
</tr>
<tr>
<td>S. aureus</td>
<td>196 (39.2)</td>
<td>182 (36.2)</td>
<td>378 (37.2)</td>
</tr>
<tr>
<td>Coag-neg Staph</td>
<td>137 (27.4)</td>
<td>135 (26.8)</td>
<td>272 (27.1)</td>
</tr>
<tr>
<td>Strep spp.</td>
<td>72 (14.4)</td>
<td>73 (14.5)</td>
<td>145 (14.5)</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>38 (5.6)</td>
<td>23 (4.6)</td>
<td>51 (5.1)</td>
</tr>
<tr>
<td>Other Gram-neg</td>
<td>84 (16.8)</td>
<td>84 (16.7)</td>
<td>168 (16.7)</td>
</tr>
<tr>
<td>Culture neg</td>
<td>77 (15.4)</td>
<td>78 (15.5)</td>
<td>155 (15.5)</td>
</tr>
</tbody>
</table>
OVIVA: Antibiotics Received

Receiving IV ABX

Receiving any ABX
OVIVA

95% CI thin lines; 90% CI thick lines
Modified ITT: included only those with endpoint data
Worst-case: those with missing data
Oral: all assumed to fail; IV: no failures
OVIVA

• Serious ADRs:
  – IV: 146/527 (27.7%)
  – Oral: 138/527 (26.2)
  – Catheter complications: IV (9.4%), oral (1.0%)

• Conclusion: Oral noninferior to IV
  – No difference if rifampin included or not
Suppression?

• Who is cured with initial therapy or not?
• Some recent data
  – Byron (2019): 112 pts, long-term abx only appeared to postpone relapse
  – Kiss (2019): Australia survey ID docs
    • 74% willing to enroll pts in RCT re: stopping?
  – Lau (2017): most abx given > 1 yr for incurable infections, e.g., “vascular grafts”
Unintended consequences?

• Likely over-diagnosis and over-treatment
  – Especially late positive cultures, post-operative after revision of TSR.
  – Genie out of the bottle
  – Devasting consequences if infected/not treated

• Surgeons requesting extended cultures
  – Spine/discs
  – Prosthetic joints (hips, knees)
Shoulder microbiome?

- Microbial 16S rRNA Illumina MiSeq
- *C. acnes* only recovered from skin
- Other microbial DNA
  - True microbiome?
  - Contaminants from scalpel?

**Conclusions:**
- *C. acnes* shoulder infection from surgical contamination
Prevention *C. acnes*

- Cefazolin customary antimicrobial agent periop prophylaxis
  - Clindamycin may be inadequate for *P. acnes*
- Surgical skin preps: no difference
  - ChloraPrep, DuraPrep, and povidone-iodine
    - 6% (axillary) - 16.7% (anterior/posterior shoulder)
    - 5% Benzoyl peroxide may be helpful addition
      - 1/20 positive vs. 7/20 chlorhexidine
- Perioperative doxycycline: no effect, decreasing skin flora
- No current standards exist for prevention *C. acnes*
Prevention

- Recommended OR maneuvers
  - Frequent glove changes
    - Post-gown draping
  - Discard skin incision scalpel
  - Copious irrigation before closure
- Operative ABX: no high level evidence
  - Antibiotic cement
  - Vancomycin powder
Conclusions

• Indolent infection
  – Pain common, inflammatory markers may be normal

• Extended cultures for tissue: 10-14d

• Surgical skin preps may be inadequate

• Talk to your surgeons:
  – Multiple samples (4 or more)
  – Discuss their surgical techniques
Conclusion: So Many Questions

• Clinical Struggles and Research Gaps:
  – What is a gold standard for C. acnes PJI?
  – Can biomarkers help distinguish true PJI diagnosis
  – Best treatment approaches
    • Drug choices
    • Surgical decisions
      – Replacement always necessary?
    • Duration