Prosthetic Joint Infections
The quest towards a six antibiotic treatment

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Question 12: What is the optimal length of antibiotic treatment after debridement, antibiotics, and implant retention (DAIR) for acute periprosthetic joint infections (PJIs)?

Treatment. A minimum of 6 weeks of antibiotic therapy seems to be sufficient in most cases of PJIs managed by DAIR-provided surgical treatment.

Level of Evidence: Moderate
Delegate Vote: Agree: 91%, Disagree: 8%, Abstain: 1% (Super Majority, Strong Consensus)

• Surgical management: DAIR vs. Implant Removal
• Microbiology
• Antimicrobial treatment
• Host’s baseline features
Prosthetic Joint Infections
Less is (hopefully) more

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Disclosure slide for speaker at “Update on diagnostic and clinical management of complex foreign body infections”

<table>
<thead>
<tr>
<th>(Potential) conflict of interest</th>
<th>None</th>
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<tr>
<td>Potentially relevant company relationships in connection with event</td>
<td>None</td>
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<tr>
<td>• Sponsorship or research funding</td>
<td>None</td>
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<td>• Fee or other (financial) payment</td>
<td>None</td>
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<td>• Shareholder</td>
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<td>• Other relationship, i.e. …</td>
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Outline

• Shorter treatments for DAIR (Implant Retention)
  • Historical recommendations
  • Observational studies
  • Experimental studies
• Shorter treatments for Implant Removal
  • Observational studies
  • Experimental studies

• Final considerations
Heal the infection while keeping the foreign-body

Maximal difficulty

Aggressive treatment

Surgery

Antimicrobials
• High doses
• Long periods

- Intravenous antibiotics (glycopeptides, beta-lactams) ... ≥ 6 weeks
- Oral highly bioavailable antibiotics – fluoroquinolones, rifampin
  • 6 to 9 months
  • 3 to 6 months
One hundred and twelve infected arthroplasties treated with ‘DAIR’ (debridement, antibiotics and implant retention): antibiotic duration and outcome

I. Byren1,2, P. Bejon1,2, B. L. Atkins1–3, B. Angus3, S. Masters1, P. McLardy-Smith1, R. Gundle1 and A. Berendt1

... after an uncertain period of time, prolonging antibiotics does not increase the likelihood of curing the patient...
Evidence I – non-comparative observational studies

Cobo et al. CMI, 2011

- N = 117 cases of PJJ managed by DAIR (various etiologies)
- Median antibiotic duration: 80-84 days
- Treatment success 54%

Soriano et al. CMI, 2009

- N = 47 cases of PJJ managed by DAIR (various etiologies)
- Mean antibiotic duration: 2.7 months
- Treatment success 77%
Evidence II – comparative observational studies

**Six weeks of antibiotic treatment is sufficient following surgery for septic arthroplasty**


Bernard et al. J Infection, 2010

Single center, prospective observational study (1996-2007), n=144 bacterial PJIs
- treatment x 12 weeks: management with DAIR, surgeon’s decision, host’s comorbidity
- treatment x 6 weeks: other surgeries, infectiologist’s decision, host’s comorbidity.

60 cases managed by DAIR
- ≈66% staphylococci, management based on rifampin + FQ
  - 20 cases treated for 6 weeks → 90% success rate
  - 40 cases treated for 12 weeks
Evidence II – comparative observational studies

**Short-course antibiotics for prosthetic joint infections treated with prosthesis retention**

A.-P. Puhto¹, T. Puhto² and H. Syrjala²

Puhto et al. CMI, 2012

Single-center, pre-post design

- prior to 2006, long treatments (3 months hip-arthroplasties, 6 months knee-arthropl).
- after 2006, short treatments (2 months hip-arthropl, 3 months knee-arthropl).

<table>
<thead>
<tr>
<th></th>
<th>Intention-to-treat</th>
<th>Per-protocol</th>
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<tbody>
<tr>
<td></td>
<td>Long N=60</td>
<td>Long N=38</td>
</tr>
<tr>
<td></td>
<td>Short N=72</td>
<td>Short N=48</td>
</tr>
<tr>
<td><strong>Failure</strong></td>
<td>43%</td>
<td>42%</td>
</tr>
<tr>
<td></td>
<td>11%</td>
<td>13%</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>0.28</td>
<td>0.78</td>
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</table>
Evidence II – comparative observational studies

Antibiotic therapy duration for prosthetic joint infections treated by Debridement and Implant Retention (DAIR): Similar long-term remission for 6 weeks as compared to 12 weeks

Hélène Chaussade\textsuperscript{a}, Ilker Üçkay\textsuperscript{b,c}, Albert Vuagnat\textsuperscript{a}, Jérôme Druot\textsuperscript{a}, Guillaume Gras\textsuperscript{a}, Philippe Rosset\textsuperscript{a}, Benjamin A. Lipsky\textsuperscript{b,d}, Louis Bernard\textsuperscript{b}

Retrospective multicenter Cases managed by DAIR

Chaussade et al. Int J ID 2017
Evidence III – clinical trials

- **Design** – open, comparative, randomized clinical trial
- **Setting** – 17 Spanish hospitals (REIPI), from 2009 to 2013

**Eligible Patient**
- Acute staphylococcal infection
- Debridement + Implant Retention

**Hypothesis of non-inferiority**
\[ \Delta = 15\%, \alpha=0.025, 1-\beta=0.80 \]
**Main goal:** cure rate

**Short schedule** = 8 weeks
- Both knee & hip prosthesis

**Rifampin 600 mg/d**
**Levofloxacin 750 mg/d**

**Standard schedule**
- Hip prosthesis = 3 months
- Knee prosthesis = 6 months

Lora-Tamayo et al. IJAA 2016.
Shorter treatments in DAIR

175 patients with acute staphylococcal PJI

112 excluded (64%)*
- 48 (28%) resistance to LVX or RIF
- 19 (11%) other antibiotics > 7 days
- 17 (10%) prosthesis removal
- 12 (7%) debridement delay > 21d
- 16 (9%) other exclusion criteria

63 (36%) randomized
- 33 long arm
- 30 short arm

ITT analysis

19 non-evaluable** patients (see table 1)

44 patients for PP analysis
- 20 long arm
- 24 short arm

Lora-Tamayo et al. IJAA 2016.
**Shorter treatments in DAIR**

<table>
<thead>
<tr>
<th></th>
<th>Long arm (n=33)</th>
<th>Short arm (n=30)</th>
<th>p</th>
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<tbody>
<tr>
<td>Polymicrobial infection</td>
<td>9 (27%)</td>
<td>2 (7%)</td>
<td>0.046</td>
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</table>

**PP analysis**
- Overall success: 93%
- Median follow-up: 355 d
- Mean survival time: 45 m
- \(P = 0.763\)

**ITT analysis**
- Overall success: 41 (65%)
- Mean survival time: 30 m
- \(P = 0.156\)

**Polymicrobial infection**
- Long arm (n=33): 9 (27%)
- Short arm (n=30): 2 (7%)
- \(P = 0.046\)
Shorter treatments in DAIR favors long treatment.
Evidence III – clinical trials

The DATIPO study

Treatment of the Infections on Osteo-articular Prostheses by 6 Versus 12 Weeks of Antibiotherapy (DATIPO)
Shorter treatments in Prosthesis Removal

DAIR (Implant Retention)  Single step revision  Two-staged revision  Amputation

6 weeks after 1st step
Evidence I – non-comparative observational studies

- Single center studies, observational, mainly prospective
- Mainly late-chronic infections, CNS responsible for 33-63% of cases
- Local antibiotic mainly vancomycin + aminoglycoside

<table>
<thead>
<tr>
<th>Ref</th>
<th>n/Loc</th>
<th>Sys ATB</th>
<th>Follow-up</th>
<th>Need 2nd debrid</th>
<th>PIOC at 2nd step</th>
<th>Relapse/Persist</th>
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<tbody>
<tr>
<td>Hoad-Reddick 2005</td>
<td>39/Knee</td>
<td>5 days</td>
<td>56 m</td>
<td>15%</td>
<td>18%</td>
<td>11%</td>
</tr>
<tr>
<td>Hart &amp; Jones 2006</td>
<td>48/Knee</td>
<td>14 days iv</td>
<td>49 m</td>
<td>13%</td>
<td>23%</td>
<td>-</td>
</tr>
<tr>
<td>Stockley 2008</td>
<td>114/Hip</td>
<td>1 day</td>
<td>74 m</td>
<td>4%</td>
<td>16%</td>
<td>12%</td>
</tr>
<tr>
<td>Whittaker 2009</td>
<td>44/Hip</td>
<td>14 days (vanco)</td>
<td>49 m</td>
<td>7%</td>
<td>2%</td>
<td>7%</td>
</tr>
<tr>
<td>McKenna 2009</td>
<td>31/Hip</td>
<td>5 days</td>
<td>35 m</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
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</table>
Evidence II – comparative observational studies

Two-stage revision of infected hip arthroplasty using an antibiotic-loaded spacer: retrospective comparison between short-term and prolonged antibiotic therapy

Pang-Hsin Hsieh¹,², Kuo-Chin Huang²,³, Po-Cheng Lee¹,² and Mel S. Lee¹,²

Retrospective, pre-post, single centre

Local antibiotics variable, mainly vancomycin + gentamicin.

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<tr>
<th></th>
<th>2002-03</th>
<th>2004-05</th>
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<tbody>
<tr>
<td>ATB duration</td>
<td>ATB 4 w. (iv) ± 2 w. (oral)</td>
<td>ATB 1 w. (iv)</td>
</tr>
<tr>
<td>N</td>
<td>N=46</td>
<td>N=53</td>
</tr>
<tr>
<td>Need for a</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>repeated 1st-step</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse after</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>reimplantation</td>
<td></td>
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</table>

Hsieh et al. JAC 2009
Evidence III – clinical trials

Shorter treatments in Prosthesis Removal

ClinicalTrials.gov

Short or Long Antibiotic Regimes in Orthopaedics (SOLARIO)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03806166

Recruitment Status: Recruiting
First Posted: January 16, 2019
Last Update Posted: May 13, 2019
See Contacts and Locations
Evidence III – clinical trials

Four versus six weeks of antibiotic therapy for osteoarticular infections after implant removal: a randomized trial

Mohamed Benkabouche¹‡, Guillaume Racloz²,³‡, Hervé Spechbach¹, Benjamin A. Lipsky⁴, Jean-Michel Gaspoz¹ and Ilker Uçkay¹

• Design – open, comparative, randomized clinical trial
• Setting – single centre, from 2015 to 2019

Eligible Patient
• Bone and joint infections managed with implant removal without immediate re-osteosynthesis / prosthetic reimplantation

Hypothesis of non-inferiority
\[ \Delta = 10\%, \, \alpha=0.05, \, 1-\beta=0.80 \]
Main goal: cure rate

Short schedule = 4 weeks ± 3 d

Standard surgical and antimicrobial treatment

Long schedule = 6 weeks ± 3 d

Benkabouche et al. JAC 2019
N=123

4 weeks 62

6 weeks 61

4 weeks 60

6 weeks 57

• Similar baseline features
• Similar microbiology
  • S. aureus 46 cases (37%) (4 cases MRSA)
  • CNS 44 cases
  • Streptococci 15 cases
  • GNB 31 cases
• Similar type of bone and joint infection
  • Metal-plate infection – 44
  • Intramedullary nail infection – 11
  • Other Osteo-synthesis material inf – 30
• **Prosthetic Joint Infection (2-step)** – 39
  • Spacer in 27/39 (69%), but only with ATB in 2
  • Re-implantation 30/39 (77%).

**ITT analysis**

- 4-weeks – Recurrence 4/62 (6.5%)
- 6-weeks – Recurrence 3/61 (4.9%)

\[ \Delta = 1.6\% \ (95\%CI \ -9.8\% \ - +6.8\%) \]

Similar results in PP analysis, per etiologies, per type of infection

Benkabouche et al. JAC 2019
• There is consistent scientific evidence suggesting that short treatments may perform as well as long standard treatments, although it is difficult to set a precise cut-off, which is probably dependant on the specific characteristics of the infection and the treatment provided.
• Regarding DAIR, 8 weeks of treatment is probably enough as long as surgical and antimicrobial treatment have been optimized. Less than that (i.e. 6 weeks) may also work in certain scenarios, but in my opinion we do not have enough evidence to generalize its recommendation.
• Regarding PJI managed with implant removal,
  • 4 weeks seems enough after complete foreign-material removal, although these results should be confirmed
  • the use of high concentrations of local antibiotics seems to allow very short treatments, but we need larger comparative trials.
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