COMMON CASES 
AND DIFFICULT-TO-TREAT SCENARIOS

MANAGEMENT OF A COMMON CASE 
BASED ON GUIDELINES

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Surgical consultation and photographs courtesy:
Andreas Mavrogenis, Assistant Professor in Orthopaedics, Athens University Hospital ATTIKON
The number of THA and TKA has been increasing

Trends in hip and knee replacement surgery across OECD countries.

As well as the incidence of prosthetic joint infections (PJI):
- Total hip arthroplasty (THA) 0.3 - 2.4%
- Total knee arthroplasty (TKA) 0.6 - 2%
- Revisions 2 - 20%

Edwards JR, Am j Infect Control 2009
Total Arthroplasties Performed and Prosthetic Infections, According to Procedure

Epidemiology and Variability of Orthopaedic Procedures Worldwide

Standard morbidity rate (SMR) and age-standardized incidence rates (ASIR), of total hip and knee arthroplasties worldwide in 2007

Maria de Fatima de Pina, Ana Isabel Ribeiro, and Carlos Santos
European Instructional Lectures, 12th EFORT Lectures, Vol. 11, Copenhagen, Springer 2011
S.T., female, 68 years old

Medical history:
- Parkinson’s disease under levodopa + benserazide (Madopar)
- mild dementia under rivastigmine (Exelon)
- arterial hypertension under tildiazem
ORTHOPAEDIC HISTORY

- Primary degenerative knee arthritis
- Total right knee arthroplasty, 2011
- Total left knee arthroplasty, 2012
ORTHOPAEDIC HISTORY

- Total left knee arthroplasty, 2012 (in another hospital)
- Immediate postoperative wound drainage and dehiscence
Immediate postoperative wound drainage and dehiscence. Which is the best approach?

1. Do nothing. This is common and harmless
2. Close the incision tightly with sutures
3. Take a swab culture and start antibiotics immediately
4. Explore the wound to confirm deep infection
ORTHOPAEDIC HISTORY

• Total left knee arthroplasty, 2012 (in another hospital)

• Immediate postoperative wound drainage and dehiscence

• Wound opening – swab cultures (proven negative)

• Administration of antibiotics (unknown) for 14 days for presumed superficial infection
COMMON ERRORS IN THE TREATMENT OF PROSTHETIC JOINT INFECTIONS

• Delay in the diagnosis of PJIs are often due to psychological reasons

• Any wet wound is suspicious for infection and should be explored

• Any postsurgical hematoma should be surgically treated to avoid contamination from the normal flora

• Error: Starting antibiotic therapy before pathogen identification and infection confirmation

Zimmerli W, 8th Infection Hellenic Society Conference, Athens 2009

Uckay I, Vogt M. In: Infections of the musculoskeletal system, Swiss orthopaedics in-house publisher, Switzerland 2014, p.232-6
Any superficial infection increases the possibility of deep infection 52 times!
CAUTION

1. In early postoperative period, the term superficial wound infection should not be used, because the implant is not hermetically separated from the superficial wound.

2. A short term course of not curative antibiotics may lead to delayed infection.

3. As a rule, specific diagnosis at the earliest possible time-point (especially < 3 months), is very important in order to avoid implant replacement.

Immediate postoperative wound drainage with infected prosthesis.

What kind of arthroplasty infection is it?

1. Very early
2. Early
3. Slow
4. Late
5. Delayed
<table>
<thead>
<tr>
<th>PJI classification</th>
<th>MAIN PATHOGENS</th>
<th>CLINICAL PICTURE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EARLY</strong> ≤ 4 wks (3 mo)</td>
<td>Virulent pathogens <em>S. aureus</em> Streptococcus spp (Gram negative bacilli Coagulase negative <em>Staphylococci</em>)</td>
<td>Usually acute onset infection (fever, shivering, joint pain / effusion / erythema, hematoma, edema at implant site, wound drainage, cellulitis, sinus tract)</td>
</tr>
<tr>
<td></td>
<td>29-45 %</td>
<td></td>
</tr>
<tr>
<td><strong>DELAYED</strong> ≥ 4 wks (3 m) – 2 years</td>
<td>Coagulase negative <em>Staphylococci, Propionibacterium</em> spp, Anaerobes <em>S. aureus</em></td>
<td>Low grade infection, usually subtle signs and symptoms, more indolent course: Persistent or deteriorating joint pain + loosening of the implant, Fever &lt;30%, probably sinus tract</td>
</tr>
<tr>
<td></td>
<td>23-41 %</td>
<td></td>
</tr>
<tr>
<td><strong>LATE HAEMATOGENOUS</strong> &gt;2 years</td>
<td>Streptococcus spp <em>S. aureus</em> Gram negative bacilli</td>
<td>Acute (30 %) or subacute onset in a previously well-functioning joint, accompanied by a remote source of infection (UTI, respiratory or dental or skin infection or sepsis)</td>
</tr>
<tr>
<td></td>
<td>30-33 %</td>
<td></td>
</tr>
</tbody>
</table>

Zimmerli W, NEJM 2004
Osmon DR, IDSA Guidelines 2013
Coventry MB, Orthop Clin N Am 1975
Garvin KL, JBJS Am 1995
Early prosthetic joint infection. What is the best therapeutic approach?

1. Debridement + retention of prosthesis
2. One stage replacement
3. Two stage replacement
4. Permanent removal of infected implant or arthrodesis
5. Long-time suppressive antimicrobial therapy alone
Criteria for DAIR.
Adapted from Osmon et al.
IDSA Guidelines 2013

Duration of symptoms:
< 3 weeks
Joint age:
< 3 months
Parvizi J & Gehrke T
International Consensus Meeting on Periprosthetic Joint Infection, 2013

Minassian A M,
J. Antimicrob Chemother 2014;69:i29-i35
Antibiotics is an adjunct to proper surgical technique
August 2013 – Admission to our hospital

Clinical deterioration:
- knee pain, inability to bear weight, knee effusion,
- poor skin condition (scars, thin skin)
- no fever, no fistula
August 2013: Radiographs at presentation. Possible loosening and osteolysis
MANAGEMENT OF A COMMON CASE BASED ON GUIDELINES (continuing)

- August 2013

- Arthrocentesis: *Staphylococcus epidermidis*, MRSE

- Delayed arthroplasty infection

- A 2-stage revision was decided
CAUSATIVE PATHOGENS

• **Coagulase negative Staphylococci (CNS)**: 20-43%
• **Staphylococcus aureus**: 20-25%
• **Mixed flora**: 10-19%
• **Gram-negative bacilli**: 3-11%
• **Streptococcus spp**: 8-10%
• **anaerobes**: 2-10%
• **Enterococcus spp**: 3-7%
• **Candida sp, Brucella sp, Mycobacterium sp, P. acnes**: rare
• **No organism detected**: 8-19%

Chronic bone and joint infections and orthopedic implants infection
Giannitsioti E, ..Papadopoulos A, ... Kanellakopoulou K, Giamarellou H
Hellenic Congress of Infection, Athens 2007

Microbiological evaluation of 177 cases

MRSA 51%, MRSE 60%
What surgical procedure would you prefer for this patient?

1. Debridement + retention of prosthesis

2. One stage replacement

3. Two stage replacement

4. Permanent removal of infected implant or arthrodesis

5. Long-time suppressive antimicrobial therapy alone
Criteria to guide 1-stage or 2-stage revision (evidence graded B III)

Adapted from Osmon et al. IDSA Guidelines 2013

The patient has:
- Total hip arthroplasty
- Good soft tissue
- Identity of the organisms determined preoperatively
- Good bone stock
- Susceptible to highly bioavailable oral agents
- Use of antibiotic-impregnated bone cement for fixation (C-III)
- No bone grafting required (C-III)

One-stage exchange

The patient has:
- Poor soft tissue, OR
- Difficult to treat micro-organisms, AND
- No prior two-stage exchange for infection or prior two-stage exchange and reason for failure AND
- Delayed reimplantation technically feasible AND
- Anticipated good functional outcome

YES

Two-stage exchange (B-III)

NO

See Figure 4

*The guideline states that one-stage revision is uncommon in the USA, but recognizes in the Evidence Summary that this is more commonly undertaken in Europe, that a recent published decision analysis (from authors in the USA) favoured one-stage revision, and that 80%-90% success rates are described in the literature.

Difficult-to-treat microorganisms include microorganisms resistant to antibiotics with good oral bioavailability, rifampin-resistant staphylococci, enterococci, and quinolone-resistant gram-negative bacilli and fungi.
2-STAGE REVISION

1st stage
- Excision of arthroplasty
- Necrotic bone
- Bone defect
- Extensive lavage
2-STAGE REVISION

1st stage

After extensive lavage and excision of necrotic bone
2-STAGE REVISION

1st stage
Insertion of articulating antibiotic-loaded PMMA (Poly-Methyl-Meth-Acrylate) cement spacers (with 2 gr vancomycin)
For better range of motion, even after the 2nd stage.
Radiographs after 1st stage
• 1st stage – intraoperative cultures
• 6 tissue specimens for culture
• Prosthetic material for sonication
• Both positive for *Staphylococcus epidermidis*, MRSE

**Antibiogram**

- VANCOMYCIN S (MIC 0.5 μg/ml)
- TEICoplanin S
- Rifampin R
- Oxacillin R
- Cefotixin R
- Ceftriaxone R
- Erythromycin R
- Ciprofloxacin R
- Moxifloxacin R
- Gentamycin R
- Minocycline R
- Linezolid S
- Clindamycin S
- Daptomycin S
- TMP/SMX S
ANTIBIOTIC TREATMENT AFTER 1ST STAGE REVISION

- **Vancomycin** 1 gr iv every 12 h for 3 weeks, followed by

- **Cotrimoxazole** DS (160/800 mg) every 8 h for 3 weeks

- Follow up in the outpatient clinic (efficacy, toxicity)
- After 6 weeks: ESR and CRP normal,
  Antibiotics discontinued
1 month after therapy discontinuation:

2nd STAGE of revision arthroplasty

- Intraoperative cultures taken, then
- Antibiotic prophylaxis with 1 gr vancomycin iv
- Removal of the spacer
- No sign of infection
- New prosthesis implantation
2\textsuperscript{nd} stage: removal of the articulating spacer, no evidence of infection
2\textsuperscript{nd} stage: more curettage, insertion of stemmed TKA (revision type prosthesis with central stem with rotating ability, choice due to instability - ligament insufficiency and bone defect)
After 2nd stage: immediate postop radiographs. Last FU: 1.5 yrs
2nd STAGE of revision arthroplasty

No microorganism detected (after 14 days incubation)
Vancomycin discontinued
Uneventful outcome
No recurrence after follow up for more than 1.5 year
RECENT INTERNATIONAL GUIDELINES

- **FRENCH** (in English !!): Recommendations for bone and joint prosthetic device infections in clinical practice (prosthesis, implants, osteosynthesis) *Medecine et maladies infectieuses* 2010;40: 185-211

- **ITALIAN**: Italian Guidelines for the diagnosis and infectious disease management of osteomyelitis and prosthetic joint infections in adults *Infection* 2009; 37(6): 478-496

- **USA (for MRSA)**: Clinical Practice Guidelines by the IDSA for the treatment of MRSA infections in adults and children, *Clinical Infectious Diseases* 2011; 52: 1-38

- **IDSA (USA)**: Diagnosis and management of prosthetic joint infection. Clinical practice Guidelines by the Infectious Disease Society of America. *Clinical Infectious Disease* 2013; 56(1): e1-25

## ANTIMICROBIAL TREATMENT (IV/PO) OF COMMON MICROORGANISMS CAUSING PJIs (B-III)

<table>
<thead>
<tr>
<th>MICROORGANISM</th>
<th>PREFERRED TREATMENT iv</th>
<th>ALTERNATIVE TREATMENT iv/po</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSA / MSSE</td>
<td>Cefazolin</td>
<td>Vancomycin</td>
<td>± Rifampicin</td>
</tr>
<tr>
<td></td>
<td>Nafcillin</td>
<td></td>
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<tr>
<td></td>
<td>Flucloxacillin</td>
<td></td>
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<tr>
<td></td>
<td>Ceftriaxone ?</td>
<td>Daptomycin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Linezolid</td>
<td></td>
</tr>
<tr>
<td>MRSA / MRSE</td>
<td>Vancomycin</td>
<td>Daptomycin</td>
<td>± Rifampicin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Linezolid</td>
<td></td>
</tr>
</tbody>
</table>

## Italian guidelines 2009: antibiotic treatment of S. aureus bone and prosthetic joint infections

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Antibiotics</th>
<th>Grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSA</td>
<td>Oxacillin ± rifampin</td>
<td>A-II</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin/clavulanic acid ± rifampin</td>
<td>A-II</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin or levofoxacin or moxifloxacin + rifampin</td>
<td>A-I</td>
</tr>
<tr>
<td></td>
<td>Co-trimoxazole or minocycline ± rifampin</td>
<td>A-III</td>
</tr>
<tr>
<td></td>
<td>Clindamycin</td>
<td>A-III</td>
</tr>
<tr>
<td>MRSA</td>
<td>Teicoplanin or vancomycin ± rifampin</td>
<td>A-II</td>
</tr>
<tr>
<td></td>
<td>Co-trimoxazole or minocycline ± rifampin</td>
<td>A-II</td>
</tr>
<tr>
<td></td>
<td>Linezolid ± rifampin</td>
<td>A-II</td>
</tr>
<tr>
<td></td>
<td>Daptomycin</td>
<td>A-II</td>
</tr>
</tbody>
</table>

# Antimicrobial Treatment (IV/PO) of Common Microorganisms Causing PJI (B-III)

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Preferred Treatment  iv</th>
<th>Alternative Treatment iv/po</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-hemolytic Streptococci</td>
<td>Penicillin G</td>
<td>Vancomycin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ampicilline</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ceftriaxone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterococci</td>
<td>Penicillin G</td>
<td>Vancomycin</td>
<td>± aminoglycoside</td>
</tr>
<tr>
<td></td>
<td>Ampicilline</td>
<td>Daptomycin</td>
<td>Ampicilline + Rif</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Linezolid</td>
<td>Linezolid + Rif</td>
</tr>
<tr>
<td>Gram - negative</td>
<td>Cefepime</td>
<td>Ciprofloxacin</td>
<td>Ciprofloxacin + Rif</td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolones</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ertapenem</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>Cefepime</td>
<td>Ciprofloxacin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Meropenem</td>
<td>Ceftazidime</td>
<td></td>
</tr>
<tr>
<td>Propionibacterium acnes</td>
<td>Penicillin G</td>
<td>Clindamycin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ceftriaxone</td>
<td>Vancomycin</td>
<td></td>
</tr>
</tbody>
</table>

Surgical intervention, route, and duration of antimicrobial therapy

IV, Intravenous route; PO, oral route; * = Microbiological sampling, † = Continuation with the same antibiotic regimen. Samples are cultured for 10 to 14 days in most centers that are specialized centers for periprosthetic joint infection. If microbiologic results are confirmed to be negative, the antimicrobial treatment can be stopped.


Most propose:
- Hip 3 mo
- Knee 6 mo
**ANTIBIOTIC TREATMENT – DURATION AND CHOICE**

**DEBRIDEMENT AND IMPLANT RETENTION**

with polyethylene modular components removed and exchanged

<table>
<thead>
<tr>
<th>INITIAL TREATMENT</th>
<th>SUCCESSIVE THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>iv</strong></td>
<td><strong>po</strong></td>
</tr>
<tr>
<td><strong>IDSA 2013</strong></td>
<td></td>
</tr>
<tr>
<td>Staphylococcal PJIs</td>
<td>2-6 weeks</td>
</tr>
<tr>
<td>Pathogen-specific antibiotic + Rifampicin</td>
<td>A-II</td>
</tr>
<tr>
<td>If no Rif (resistance, toxicity):</td>
<td></td>
</tr>
<tr>
<td>Pathogen-specific antibiotic for 4-6 weeks</td>
<td>B-III</td>
</tr>
<tr>
<td>PJIs due to other organisms:</td>
<td>4-6 wks iv/po B-II</td>
</tr>
</tbody>
</table>

**INTERNATIONAL CONSENSUS 2013**

5-10 days

β-lactams or glycopeptides

(to reduce bacterial inoculum, no anti-biofilm)

<table>
<thead>
<tr>
<th>Duration ≤ 3-6 months suggested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Abs with high bioavailability eg</td>
</tr>
<tr>
<td>Rifampicin (in combination)</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
</tr>
<tr>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Fusidic acid</td>
</tr>
<tr>
<td>Clindamycin</td>
</tr>
<tr>
<td>Linezolid</td>
</tr>
</tbody>
</table>


## ANTIBIOTIC TREATMENT – DURATION AND CHOICE
### 1-STAGE (SINGLE) EXCHANGE
### IDSA 2013 AND INTERNATIONAL CONSENSUS 2013

<table>
<thead>
<tr>
<th>INITIAL TREATMENT</th>
<th>SUCCESSIVE THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IDSA 2013</strong></td>
<td></td>
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<tr>
<td>Staphylococcal PJIs</td>
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<tr>
<td>2-6 weeks</td>
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</tr>
<tr>
<td>Pathogen-specific antibiotic + Rifampicin</td>
<td>C-III</td>
</tr>
<tr>
<td>If no Rif (resistance, toxicity):</td>
<td></td>
</tr>
<tr>
<td>pathogen-specific antibiotic for 4-6 weeks</td>
<td>B-III</td>
</tr>
<tr>
<td><strong>PJIs due to other organisms:</strong></td>
<td>4-6 wks iv/po</td>
</tr>
<tr>
<td>Duration: total 3 months</td>
<td>C-III</td>
</tr>
<tr>
<td>Ciprofloxacin + Rifampicin</td>
<td>A-I</td>
</tr>
<tr>
<td>Levofloxacin + Rifampicin</td>
<td>A-II</td>
</tr>
<tr>
<td>If no FQ: Cotrimoxazole + Rif</td>
<td>A-II</td>
</tr>
<tr>
<td>Minocycline/Doxycycline + Rif</td>
<td>B-III</td>
</tr>
<tr>
<td>Cephalexin + Rif</td>
<td></td>
</tr>
<tr>
<td>Dicloxacillin +Rif</td>
<td></td>
</tr>
<tr>
<td><strong>INTERNATIONAL CONSENSUS</strong></td>
<td></td>
</tr>
<tr>
<td>2-6 weeks</td>
<td></td>
</tr>
<tr>
<td>(IDSA Guidelines are mentioned)</td>
<td></td>
</tr>
<tr>
<td>Duration longer than the iv suggested</td>
<td>(IDSA Guidelines are mentioned)</td>
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</tbody>
</table>
ANTIBIOTIC TREATMENT – DURATION AND CHOICE
2-STAGE EXCHANGE
IDSA 2013 AND INTERNATIONAL CONSENSUS 2013

- Duration: **4-6 weeks** of pathogen specific iv / oral high bioavailable Ab Rx – A-II
- Duration in studies: 6-12 weeks (iv 4-6 weeks – oral 2-8 weeks)
- Ideal duration unknown
- **Initial iv regimen preferred** - oral antibiotics is an appropriate choice afterwards
- High bioavailable oral antibiotics (eg Linezolid, FQs) alternative in some cases
- Optimal duration of Ab Rx determined by clinical signs and markers (CRP, ESR)
  - no ideal cut-off value for discontinuing Rx
  - new markers (?): procalcitonin, IL-6, leucocyte esterase etc
- No conclusive evidence for the need of a holiday period (eg. 2-8 weeks) in order to ensure eradication of infection

When foreign material remains present (DAIR and one-stage revision), treatment with a combination of a fluoroquinolone and rifampicin (A-I) for 3–6 months is recommended, following on from 2–6 weeks of intravenous or oral (with highly bioavailable drugs) antibiotics (A-I for DAIR; C-III for one-stage revision).

Where rifampicin combinations are not possible due to intolerance or bacterial resistance patterns, 4–6 weeks of pathogen-specific intravenous antibiotic therapy is recommended (B-III).

When the prosthesis has been removed, for the purposes of a long-term excision arthroplasty or a two-stage revision, 4–6 weeks of pathogen-specific antimicrobials are recommended either as intravenous or oral (highly bioavailable) therapy (A-II).
ROLE OF RIFAMPIN (RIF)

- Mainly for staphylococcal (S.aureus, CNS) PJIs
- Rifampin should be used in case of retained hardware:
  - after debridement and implant retention (DAIR)
  - in 1st-stage exchange
  - after early reimplantation in 2-stage exchange
- No convincing evidence for use after infected hardware removal
- Not in suppressive therapy
- Only in combination, preferably with fluoroquinolones (levo, Cipro)
- Preferably after a few days of primary IV antibiotic administration to avoid R
- After any bacteremia has cleared

RESEARCH GAPS – UNANSWERED QUESTIONS

- Optimal strategies for surgical and medical strategies
- Diagnostics (PCR, sonication, incubation time, biomarkers, imaging)
- Optimal time interval between 1\textsuperscript{st} and 2\textsuperscript{nd} stage (reports: 2 weeks to several months)
- Monotherapy vs combination therapy
- Parenteral vs oral therapy
- Alternatives to vancomycin for MRSA/MRSE
- Prediction markers for PJI outcome
- \textit{S.aureus} screening and decolonization
- Etc, etc..
Co-operation between orthopaedic surgeons, infectious diseases experts and laboratory physicians is absolutely necessary for ultimate success
THANK YOU
Table 1. Criteria for the Diagnosis of a Prosthetic-Joint Infection

<table>
<thead>
<tr>
<th>The presence of at least one of the following findings:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute inflammation detected on histopathological examination of periprosthetic tissue</td>
</tr>
<tr>
<td>Sinus tract communicating with the prosthesis</td>
</tr>
<tr>
<td>Gross purulence in the joint space</td>
</tr>
</tbody>
</table>

| Isolation of the same microorganism from two or more cultures of joint aspirates or intraoperative periprosthetic-tissue specimens, isolation of the organism in substantial amounts (e.g., ≥20 CFU per 10 ml from the implant in a total volume of 400 ml of sonicate fluid), or both |

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*Data are from Berbari et al.,9 Trampuz et al.,12 Piper et al.,16 Berbari et al.,18 Marculescu et al.,20 and Betsch et al.21 CFU denotes colony-forming units.*

DelPozo J & Patel R, NEJM 2009
Relative bacteriostatic and bactericidal activity of antibiotic agents

Criteria for DAIR.
Adapted from Osmon et al. IDSA Guidelines 2013

*If organism susceptibility permits, use rifampicin (A-I) partnered with ciprofloxacin (A-I) or levofloxacin (A-II). Other agents advised are co-trimoxazole (A-II), minocycline or doxycycline (C-III), or oral first-generation cephalosporins (C-III).

*Some patients not meeting these criteria may be considered for DAIR, but the panel considered there was more likelihood of failure (B-III).