11.30h-12.30h: Therapeutic options in prosthetic joint associated infections

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• Introduction
• Traditional treatment rules
• Requirements for antibiotics in PJI
• Role of rifampin in PJI
• Treatment algorithm
• Case presentations
• “Difficult-to-treat” microrganisms
• Frequent errors
• Conclusions
ABSOLUTE NUMBER OF PJI IS INCREASING

- Increasing number of primary replacements
- Increasing risk with revision replacements
- Longer implantation time *(lifelong risk of infection)*

The traditional rules are based on the observation that device-associated infection can rarely be healed despite the use of antibiotics to which the microorganism is susceptible in vitro.

PROSTHETIC JOINT - ASSOCIATED INFECTION:

WHAT ARE THE TREATMENT RULES?

WHAT ARE THE TREATMENT OPTIONS?
Successful treatment of a TJA infection depends on extensive and meticulous surgical débridement and effective antimicrobial therapy. Simple surgical drainage (with retention of the prosthesis in situ) followed by antibiotic therapy has been successful in only 20 – 36% of cases. For effective treatment complete removal of all foreign material is essential.“

[BD Braude in: Mandell et al 2005]
PROSTHETIC JOINT-ASSOCIATED INFECTION: TREATMENT OPTIONS

• 2-stage replacement
• 1-stage replacement
• Débridement with retention
• Removal without replacement
•Suppressive therapy
2-STAGE EXCHANGE FOR EVERYBODY: WHY SHOULD WE BEND THIS RULE?

- The least invasive possible intervention should be chosen, since each surgery results in tissue destruction.
- Débridement or 1-stage exchange allows resolution of the problem during one single hospital stay.

However, less invasive surgery should not be paid with poorer results.
REQUIREMENTS FOR THE OPTIMAL ANTIMICROBIAL AGENT IN DEVICE-RELATED INFECTIONS
An efficacious antimicrobial agent against device-associated infections should

• penetrate the biofilm
• be active on surface-adhering microorganisms
• be active against stationary-phase bacteria
• have a good oral bioavailability

[Zimmerli et al., J Antimicrob Chemother 1994]
ROLE OF RIFAMPIN IN THE TREATMENT OF PJI
GUINEA PIG MODEL TO TEST THE EFFICACY OF ANTIMICROBIAL AGENTS IN DEVICE-ASSOCIATED INFECTIONS

[AF Widmer et al JID 1990]
TISSUE CAGE INFECTION: TREATMENT PROTOCOL

2-8 weeks before the experiment

- d0
  - Implantation of subcutaneous tissue cages in guinea pigs

- d1
  - Control for sterility and incubulation of tissue cages with $10^4$ S. aureus ATCC 29213
  - Start of antibiotic therapy bid
  - Control: no therapy

- d2

- d3

- d4
  - Stop of antibiotic therapy

- d16
  - Explantation of tissue cages: Semiquantitative and broth cultures of the explanted tissue cages

(→) Quantitative cultures of tissue cage fluid
CURE RATE IN THE TISSUE-CAGE MODEL
Staphylococcus aureus ATCC 29213

Antibiotic regimen (mg/kg bid)

- Controls: 0/12
- Vancomycin (15): 0/12
- Netilmicin (30): 0/12
- Ciprofloxacin (10): 2/12
- Rifampin (25): 10/20
- Rifampin + Ciprofloxacin: 11/12

Cure rate (%)

0 20 40 60 80 100

Zimmerli W, J Antimicrob Chemother 1994
## Minimal bactericidal concentration in different growth phases (local peak level)

<table>
<thead>
<tr>
<th>Strain</th>
<th>Rifampin (8.3 mg/l)</th>
<th>Ciprofloxacin (0.95 mg/l)</th>
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<tr>
<td></td>
<td>$MBC_{\log}$ mg/l</td>
<td>$MBC_{\text{stat}}$ mg/l</td>
</tr>
<tr>
<td>KE89</td>
<td>1.8</td>
<td>3.6</td>
</tr>
<tr>
<td>ZP89</td>
<td>2.2</td>
<td>7.0</td>
</tr>
<tr>
<td>FB90</td>
<td>1.3</td>
<td>9.4</td>
</tr>
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<td>JJ89</td>
<td>0.7</td>
<td>5.1</td>
</tr>
<tr>
<td>EW90</td>
<td>0.7</td>
<td>1.8</td>
</tr>
<tr>
<td>HM92</td>
<td>1.7</td>
<td>1.7</td>
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</table>

ROLE OF RIFAMPIN IN IMPLANT-RELATED BONE INFECTIONS: A randomized controlled trial

Treatment: Initial débridement and antibiotics:

- 2 weeks iv
  - Flucloxacillin or Vancomycin plus Rifampin or Placebo

followed by:

- 3-6 months p.os
  - Ciprofloxacin plus Rifampin or Placebo

Zimmerli et al. JAMA 279:1537-41,1998
## RESULTS

<table>
<thead>
<tr>
<th></th>
<th>CIP+PLACEBO</th>
<th>CIP+RIF</th>
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</thead>
<tbody>
<tr>
<td>Cure (ITT)</td>
<td>9/15 (60%)</td>
<td>16/18 (89%)</td>
</tr>
<tr>
<td>Drop-out</td>
<td>3/15</td>
<td>6/18</td>
</tr>
<tr>
<td>Cure (as treated)</td>
<td>7/12 (58%)</td>
<td>12/12 (100%)*</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>33 (15-41)</td>
<td>35 (24-46)</td>
</tr>
</tbody>
</table>

*p=0.019 (Fisher’s exact test)
ROLE OF RIFAMPIN IN IMPLANT-RELATED INFECTIONS: SUMMARIZED EVIDENCE

- *In vitro:* Rifampin is able to kill stationary-phase staphylococci which is a prerequisite for its efficacy in device-related infection.

- *Animal model:* Rifampin is more efficacious than other antimicrobial agents in a guinea pig model for device-related infection.

- *Controlled trial:* Among patients with a stable orthopedic implant, a long-term treatment with rifampin-ciprofloxacin combined with débridement surgery was highly efficacious without removal of the device.
PJI: TREATMENT ALGORITHM

CURRENT CONCEPTS

REVIEW ARTICLE

Prosthetic Joint Infections

Werner Zimmerli, M.D., Andrej Trampuz, M.D., and Peter E. Ochsner, M.D.

Surgical procedure
- Debridement with retention
- Irrigation and suction drainage
- Antimicrobial treatment

Condition of implant
- Stable
- Unstable

Condition of soft tissue
- Intact or slightly damaged
- Moderately or severely damaged

Culture from synovial fluid or hematoma
- No growth
- Growth

Susceptibility to antimicrobial agents with activity against surface-adhering microorganisms
- Yes
- No

Duration of clinical symptoms
- ≤3 weeks
- >3 weeks

Manifestation
Early
Hematogenous

Zimmerli et al., NEJM 2004
Patients not qualifying for implant retention

Condition of soft tissue
- Intact or slightly damaged
- Moderately or severely damaged
  - Abscess
  - Sinus tract

Modifying circumstances
- Difficult-to-treat microorganism:
  - Methicillin-resistant Staphylococcus aureus (MRSA)
  - Other MDR-resistant bacteria
  - Small-colony variants
  - Enterococcus spp.
  - Fungi
- General condition or surgical risk:
  - Debilitated
  - Bedridden
  - High risk for anaesthesia
- Underlying problems:
  - Severe immunosuppression
  - Active intravenous drug use
  - No functional improvement by exchange of the implant

Surgical procedure
- One-stage exchange
  - Irrigation and suction drainage
  - Antimicrobial treatment
- Two-stage exchange with short interval (2 to 4 weeks)
  - Irrigation and suction drainage
  - Antimicrobial treatment
- Long-term suppressive antimicrobial treatment
  - Irrigation and suction drainage
  - Antimicrobial treatment
- Implant removal without replacement
  - Irrigation and suction drainage
  - Antimicrobial treatment
- Two-stage exchange with long interval (6 to 8 weeks)
  - Irrigation and suction drainage
  - No spacer
  - Antimicrobial treatment
  - Implant removal without replacement
    - Irrigation and suction drainage
    - Antimicrobial treatment
图5-9  全髋置换术后感染的治疗法则
注：这项计划不能无保留的应用于有感染MRSA的病人和适当的前期治疗而感染复发的病人（表5-1）

- Implants: Hip (78), Knee (22), ankle (10), shoulder (8)
- Median follow-up 37 months
- Median age: 73 y

OUTCOME: 93% infection-free survival at 3 years:
- Débridement with retention (75/81) 91%
- 1-stage exchange (13/14) 93%
- 2-stage exchange (15/15) 100%
- Removal (5/5) 100%

[ICAAC-Poster K-883 2005 WDC ]
CASE PRESENTATIONS
Case 1: 75-y-old man

Posttraumatic ankylosis of the right knee
Fl/Ext 40°/20°/0°

→ Total Knee Arthroplasty
Case 1: 75-y-old man

- Readmission 18 days later
- Complained of pain, swelling and redness during 4d
- Serous discharge since 1 day prior to readmission

Laboratory analysis: CRP 114mg/L, leukocytes 8.8 G/L

How would you proceed?
S. epidermidis
in 6/6 biopsies
Case 2: 62-y-old woman

- Case history: 1998 Total hip arthroplasty (left)
- 2 weeks before hospitalisation: Cellulitis of the left foot

During hospitalisation the patient complained of hip pain
X-ray: prosthesis stable
Case 2: 62-y-old woman

Puncture of the total hip arthroplasty revealed growth of group A streptococci susceptible to “all antibiotics”

How would you proceed?
**Manifestation**

- **Early**
  - Duration of clinical symptoms
    - ≤3 wk
  - Condition of implant
    - Stable
  - Condition of soft tissue
    - Intact or slightly damaged
  - Preoperative culture of synovial fluid or hematoma
    - No growth
  - Susceptibility to antimicrobial agents with activity against surface-adhering microorganisms
    - Yes
  - Surgical procedure
    - Débridement with retention
    - Irrigation and suction drainage
    - Antimicrobial treatment

- **Hematogenous**
  - Duration of clinical symptoms
    - >3 wk
  - Condition of implant
    - Unstable
  - Condition of soft tissue
    - Moderately or severely damaged
  - No retention of implant
Case 3: 69-y-old woman

Case history:
2003 Total hip arthroplasty right
2005: New pain at the right hip, fever, and repetitive chills during more than 2 months

Puncture of abscess
Culture: Streptococcus mitis-group

How would you proceed?
No retention of implant

Condition of soft tissue

Intact or slightly damaged

Moderately or severely damaged
Abscess
Sinus tract

Modifying circumstances

Difficult-to-treat microorganism
Methicillin-resistant *Staphylococcus aureus*
Other multidrug-resistant microorganisms
Enterococcus species
Fungi

Surgical procedure

One-stage exchange
Irrigation and suction drainage
Antimicrobial treatment

Two-stage exchange
with long interval (6 to 8 wk)
Irrigation and suction drainage
No spacer
Antimicrobial treatment

Long-term suppressive antimicrobial treatment

Implant removal without replacement
Irrigation and suction drainage
Spacer
Antimicrobial treatment

Two-stage exchange with short interval (2 to 4 wk)
Irrigation and suction drainage
Spacer
Antimicrobial treatment
DIFFICULT-TO-TREAT MICROORGANISMS
Small Colony Variants *Staphylococcus aureus*

Microbiology

- subpopulation of *Staphylococcus aureus*
- naturally occurring
- slow growth (48 – 72h)
- small colony size (10x↓)
- decreased pigmentation
- decreased activities of exoproteins
  [weakly coagulase positive, reduced hemolysis]

Proctor, RA et al., Clin Infect Dis 1988; 27: 419 - 22
Small Colony Variants *Staphylococcus aureus*
small and slow

Day 1  
Day 2  
Day 3

Normal

SCV
SCV S. aureus auxotrophism

Hemin disc on Muller-Hinton (18-h-incubation):

Periphery: growth not yet visible
Center: inhibition by high concentration of hemin
Middle part: growth promotion by hemin
Case 4: 55-y-old male

08/2001 Total hip arthroplasty left side
11/2001 PJ infection with S. aureus → Débridement (2x) + 3 mo AB
07/2002 Relapse with S. aureus:

Persistance of S. aureus for 8 months
Small Colony Variants *Staphylococcus aureus*
Where do they persist?
Small Colony Variants *Staphylococcus aureus*

**Microbiology** → **Clinical relevance**

Slow growth + small colonies, decreased pigmentation → Often overlooked or misinterpreted as CNS

Deficient in electron transport due to auxotrophism → Resistance to aminoglycosides

Intracellular persistence in non-professional phagocytes → Prolonged asymptomatic persistence

Reversal into normal phenotyp *S. aureus* → Recurrent and persistent infection

*Small Colony Variants Staphylococcus aureus are difficult-to-treat microorganisms*
Patients with prosthetic joint infections caused by SCVSA had at least 1 surgical revision and prolonged antimicrobial therapy prior to diagnosis.

A spacer-free, two-stage exchange with a long interval will lead to a successful outcome.
Between 09/2002 – 03/2005 5 patients with hip prosthesis associated infection caused by SCVSA were identified.

**Treatment:** a spacer-free, two-stage exchange with a long interval

**Follow-up:** clinical examination, laboratory, X-ray

**Successful outcome:** failure free time after reimplantation as ”cured” (≥ 24 mo) or ”probably cured” (<24 mo)

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>55</td>
<td>70</td>
<td>59</td>
<td>71</td>
<td>51</td>
</tr>
<tr>
<td>Prosthesis</td>
<td>Hip</td>
<td>Hip</td>
<td>Hip</td>
<td>Hip</td>
<td>Hip</td>
</tr>
</tbody>
</table>

**Clinical course prior isolating SCVs**

| No. of surgical revisions | 2 | 1 | 1 | 3 | 0 |
| Months of antibiotics | 4 | 6 | 19 | 22 | 6+ |

**Treatment:** *one patient denied reimplantation*

| Removal of implant | yes | yes | yes | yes | yes |
| Antibiotics during implant-free interval | FLUCLOX switched to CIP + RIF | PEN, switched to LEVO + RIF | FLUCLOX, switched to LEV + RIF | FLUCLOX | PEN + LEVO |
| Reimplantation | yes | yes | no* | yes | yes |

**Follow-up (median 32 months)**

| Months until 10/2006 | 50 | 21 | 32 | 41 | 18 |
| Outcome | cured | probably cured | cured* | cured | probably cured |

FLUCOX=flucloxacillin; RIF=rifampicin; PEN=penicillin; LEVO=levofloxacin

+ Patient was treated for PJI on the contralateral side

[Sendi et al CID 2006]
Conclusions regarding SCV S. aureus

In prosthetic joint infections, SCVSA should be considered and actively sought in case of
• persistent and recurrent infections with S. aureus
• poor response to antimicrobial and surgical treatment

Successful treatment in our case series included
• a spacer-free, two-stage exchange
• 8 weeks of implant-free interval
• 6 weeks of antimicrobial therapy during interval
FREQUENT ERRORS IN THE MANAGEMENT OF PJI

*Psychological barrier against the diagnosis of PJ-associated infection results in delay of diagnosis*

- Each wet wound is suspicious and should be revised
- Each postoperative hematoma should be revised in order to avoid superinfection with skin flora
- Postoperative antibiotic treatment without diagnosis is wrong because it results in suppression and later recurrence
Wound healing disturbance
The choice of the treatment option is not based on objective criteria, but on wishful thinking and patient- or surgeon-guided reasoning:

- Prosthetic joint retention should be chosen in patients who qualify according to the presented algorithm, but not in patients in whom the surgeon does not like to perform surgery.
- Antibiotics without débridement will fail.
FREQUENT ERRORS IN THE MANAGEMENT OF PJI

The choice of the treatment option is not based on objective criteria, but on wishful thinking and patient- or surgeon-guided reasoning:

• Débridement with retention in patients with a sinus tract will always fail.

• Open treatment of PJI wounds is not correct. The use of the VAC-system with antibiotics and device retention will always fail.
The optimal surgical treatment of prosthetic-joint-associated infection should consider:

- the type of infection (early, delayed, late)
- the pathogenesis (exogenous, hematogenous)
- the conditions of the soft tissue
- the underlying conditions of the patient
- the susceptibility pattern of the microorganism (susceptibility of surface-adhering and stationary-phase microorganisms)
FUTURE DEVELOPMENTS

In case of quinolone-resistance alternative oral combination drugs for rifampin are needed:
- old drugs: minocycline, trimetho/sulfa, fusidic acid
- newer oral drug: linezolid

In case of rifampin resistance or intolerance, new drugs with efficacy on stationary-phase and adherent staphylococci are needed:
- rifamycin derivatives (ActiveBiotics) [ICAAC 2005: LB-3565] or
- covalently bound rifamycin with second antibiotic (Cumbre)

Antibiofilm coating of devices may decrease the perioperative infection rate
Efficacy of novel rifamycin ABI-0043 against *Staphylococcus aureus* ATCC 29213 in the tissue-cage model

<table>
<thead>
<tr>
<th>Antibiotic regimen (mg/kg bid)</th>
<th>Cure rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>0/12</td>
</tr>
<tr>
<td>LVX (5)</td>
<td>0/12</td>
</tr>
<tr>
<td>RIF (12.5)</td>
<td>11/24</td>
</tr>
<tr>
<td>RIF (12.5) + LVX (5)</td>
<td>21/24</td>
</tr>
<tr>
<td>ABI-0043 (3)</td>
<td>1/12</td>
</tr>
<tr>
<td>ABI-0043 (3) + LVX (5)</td>
<td>12/24</td>
</tr>
<tr>
<td>ABI-0043 (12.5)</td>
<td>5/12</td>
</tr>
<tr>
<td>ABI-0043 (12.5) + LVX (5)</td>
<td>21/24</td>
</tr>
</tbody>
</table>

[Trampuz et al ICAAC 2005]