**Société belge d'infectiologie et de microbiologie clinique**

**Belgische vereniging voor infectiologie en klinische microbiologie**

**SYMPOSIUM 26TH OCTOBER 2006**

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

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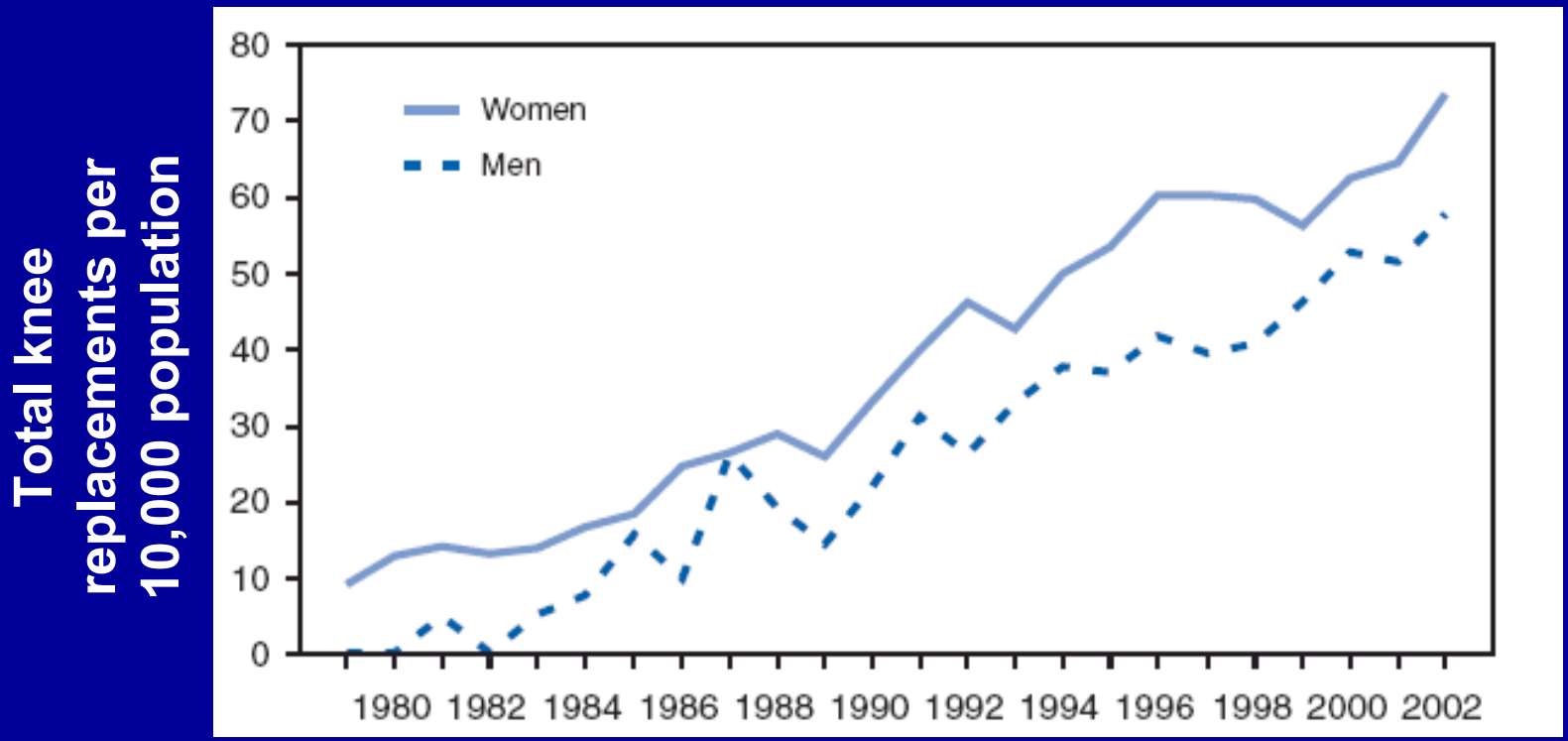
**Werner Zimmerli, *Basel Medical University Clinic Liestal / Switzerland***

UNIVERSITÄT BASEL

- 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

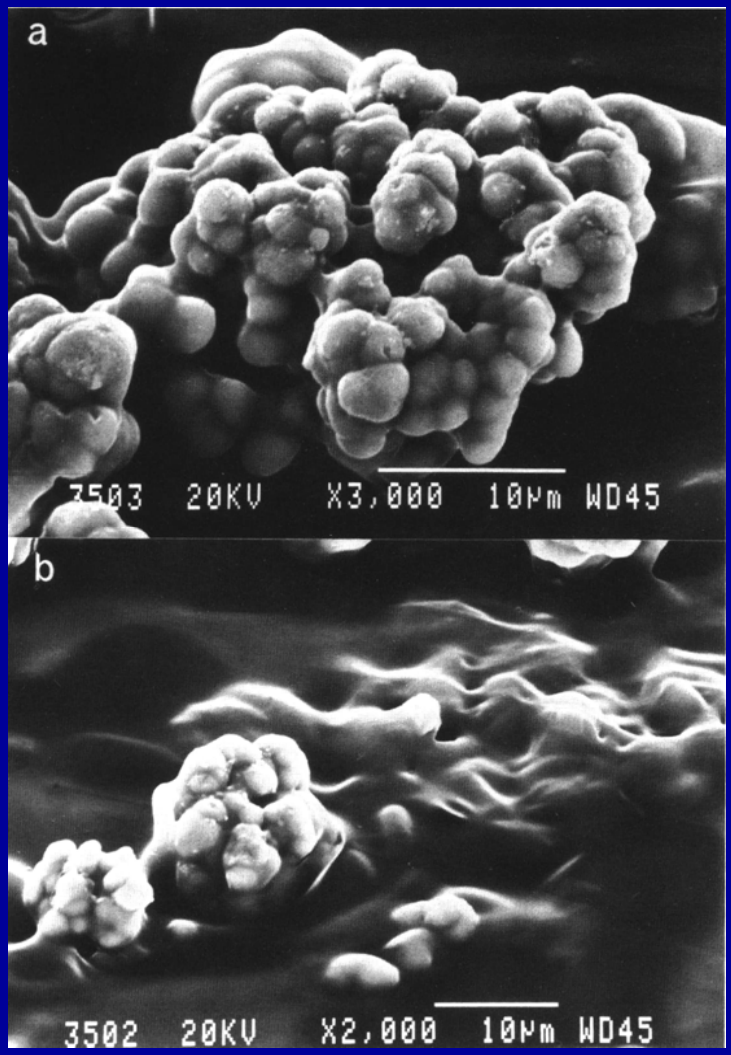
# ABSOLUTE NUMBER OF PJI IS INCREASING

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




*Source: National Center for Health Statistics, www.cdc.gov*

# FAILURE OF LONG-TERM TREATMENT




***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***

***[Scand J Infect Dis 22:611,1990]***

# PROSTHETIC JOINT - ASSOCIATED INFECTION:

## WHAT ARE THE TREATMENT RULES?

## WHAT ARE THE TREATMENT OPTIONS?

# 2005 TEXTBOOK TREATMENT RULES

*„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

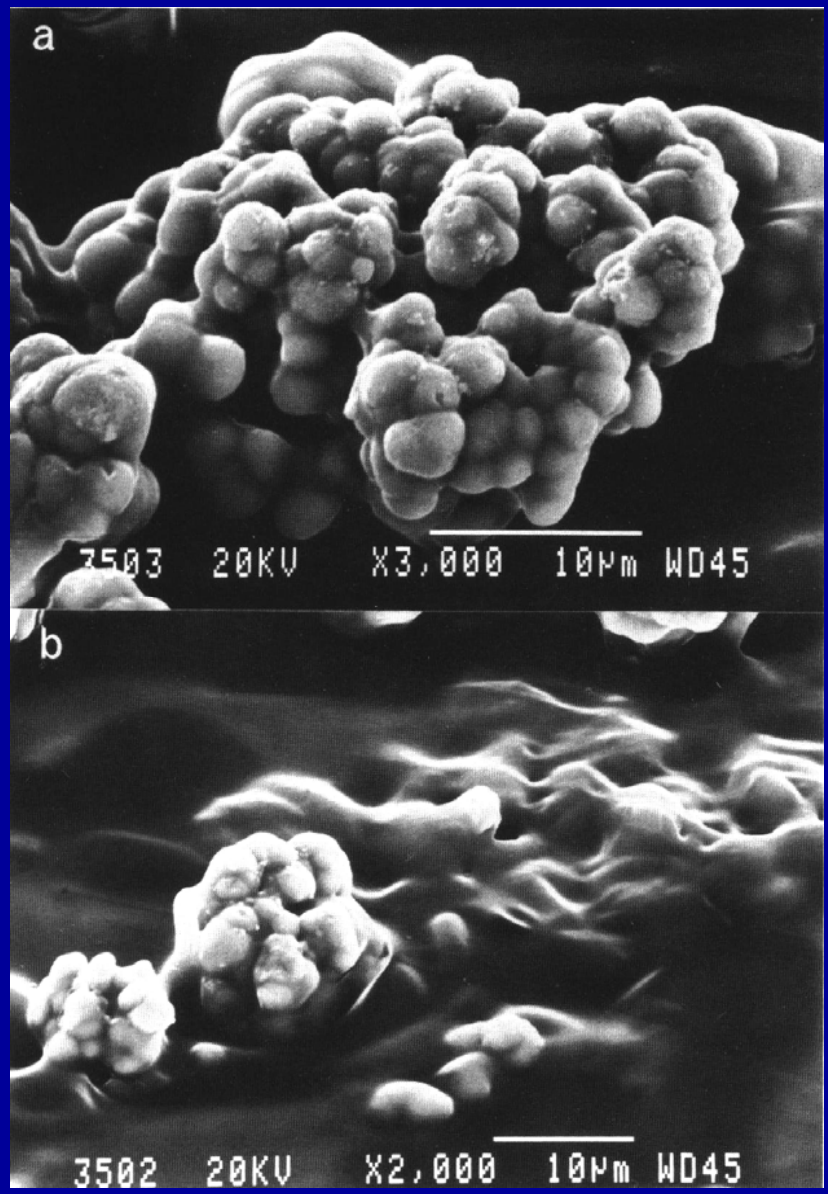
# REQUIREMENTS FOR THE OPTIMAL ANTIMICROBIAL AGENT IN DEVICE-RELATED INFECTIONS

## 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]*

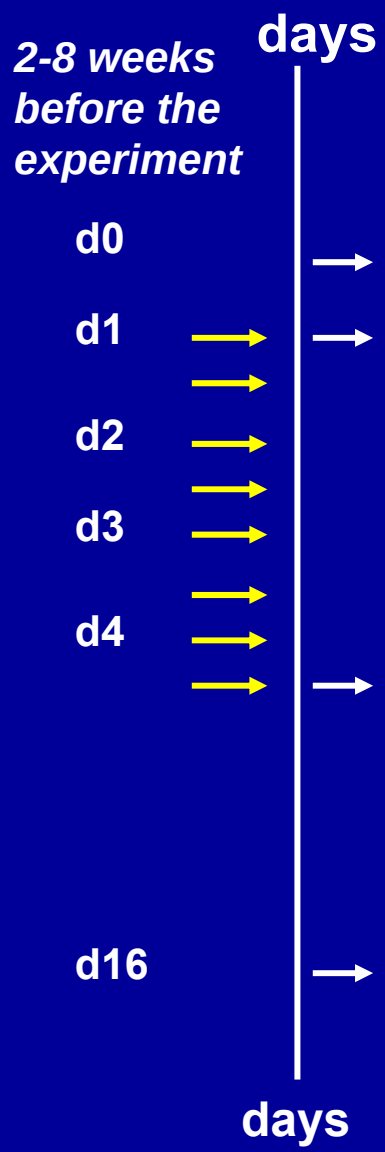
# ROLE OF RIFAMPIN IN THE TREATMENT OF PJI



# 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




Implantation of subcutaneous tissue cages in guinea pigs

Control for sterility and inculation of tissue cages with $10^4$ *S. aureus* ATCC 29213

Start of antibiotic therapy bid

Stop of antibiotic therapy

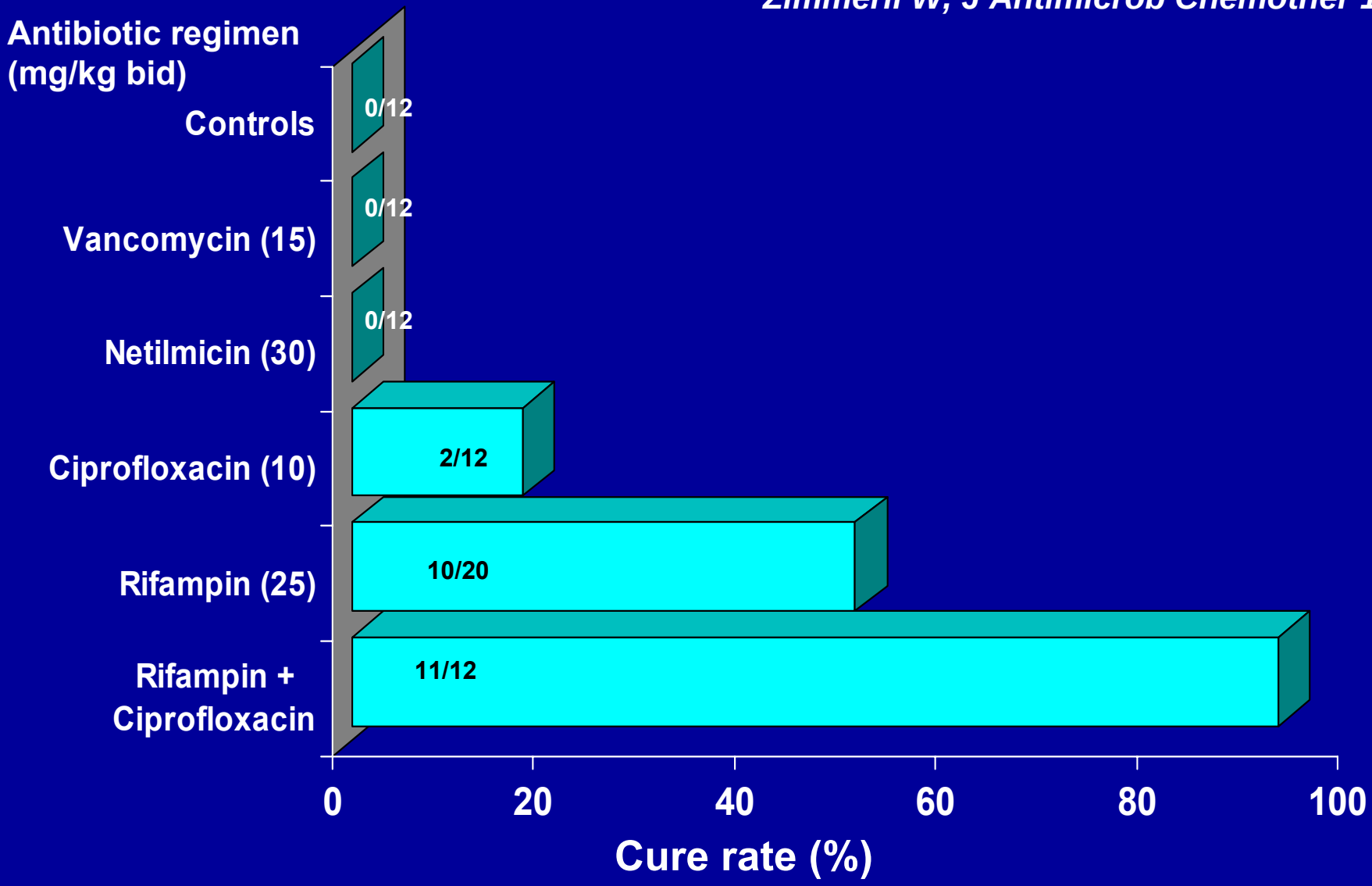
Control: no therapy

(⟶) Quantitative cultures of tissue cage fluid

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

# CURE RATE IN THE TISSUE-CAGE MODEL
## *Staphylococcus aureus* ATCC 29213

*Zimmerli W, J Antimicrob Chemother 1994*



# Minimal bactericidal concentration in different growth phases (local peak level)

| Strain *S.aureus* | Rifampin (8.3 mg/l) $MBC_{log}$ mg/l | Rifampin (8.3 mg/l) $MBC_{stat}$ mg/l | Ciprofloxacin (0.95 mg/l) $MBC_{log}$ mg/l | Ciprofloxacin (0.95 mg/l) $MBC_{stat}$ mg/l |
|---|---|---|---|---|
| KE89 | 1.8 | 3.6 | 0.8 | 133 |
| ZP89 | 2.2 | 7.0 | 1.3 | 175 |
| FB90 | 1.3 | 9.4 | 0.5 | 75 |
| JJ89 | 0.7 | 5.1 | 0.8 | 133 |
| EW90 | 0.7 | 1.8 | 1.1 | 113 |
| HM92 | 1.7 | 1.7 | 0.8 | 150 |

*Zimmerli W, Méd Mal Infect 27:181-7,1997*

# 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

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

*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

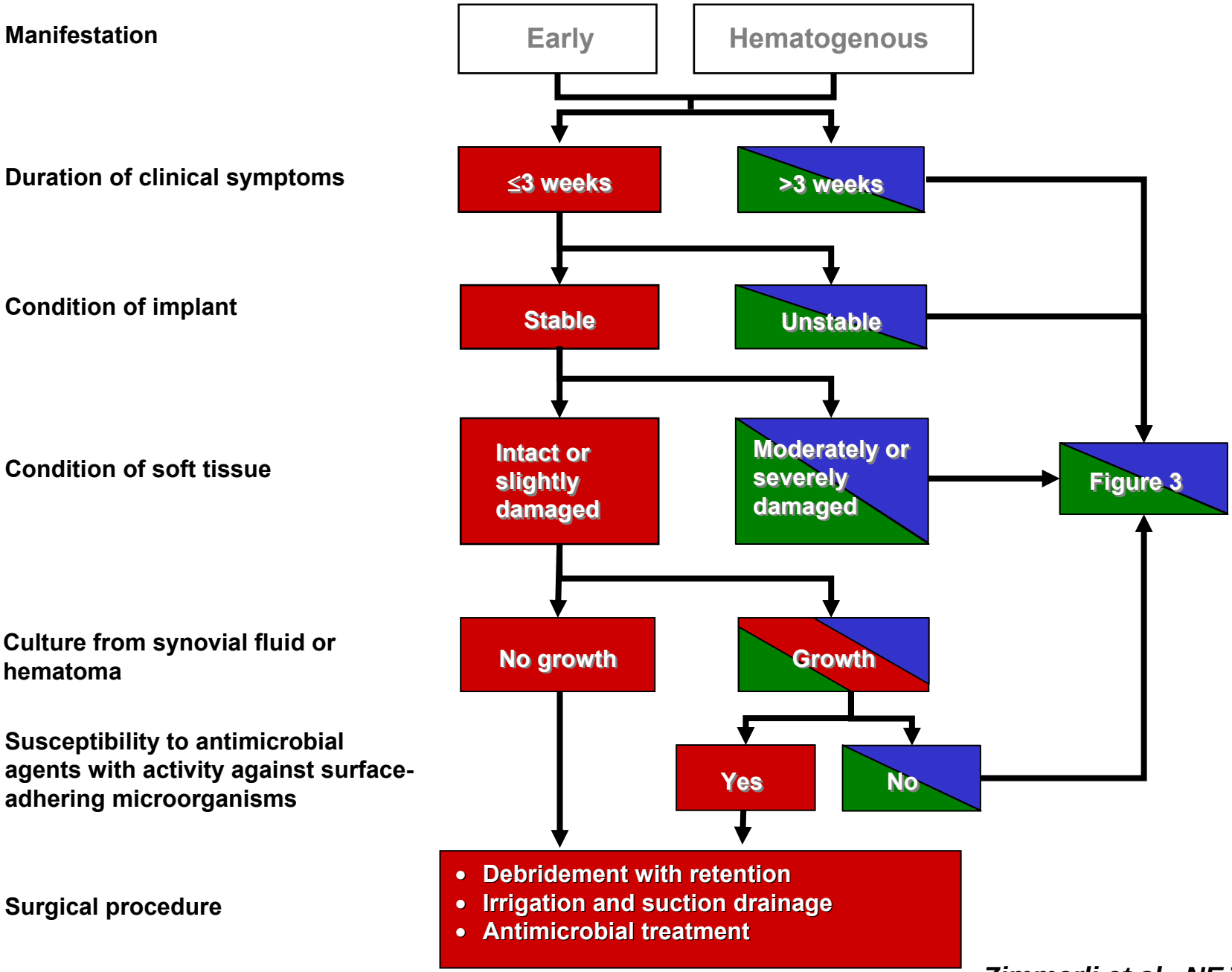
REVIEW ARTICLE

CURRENT CONCEPTS

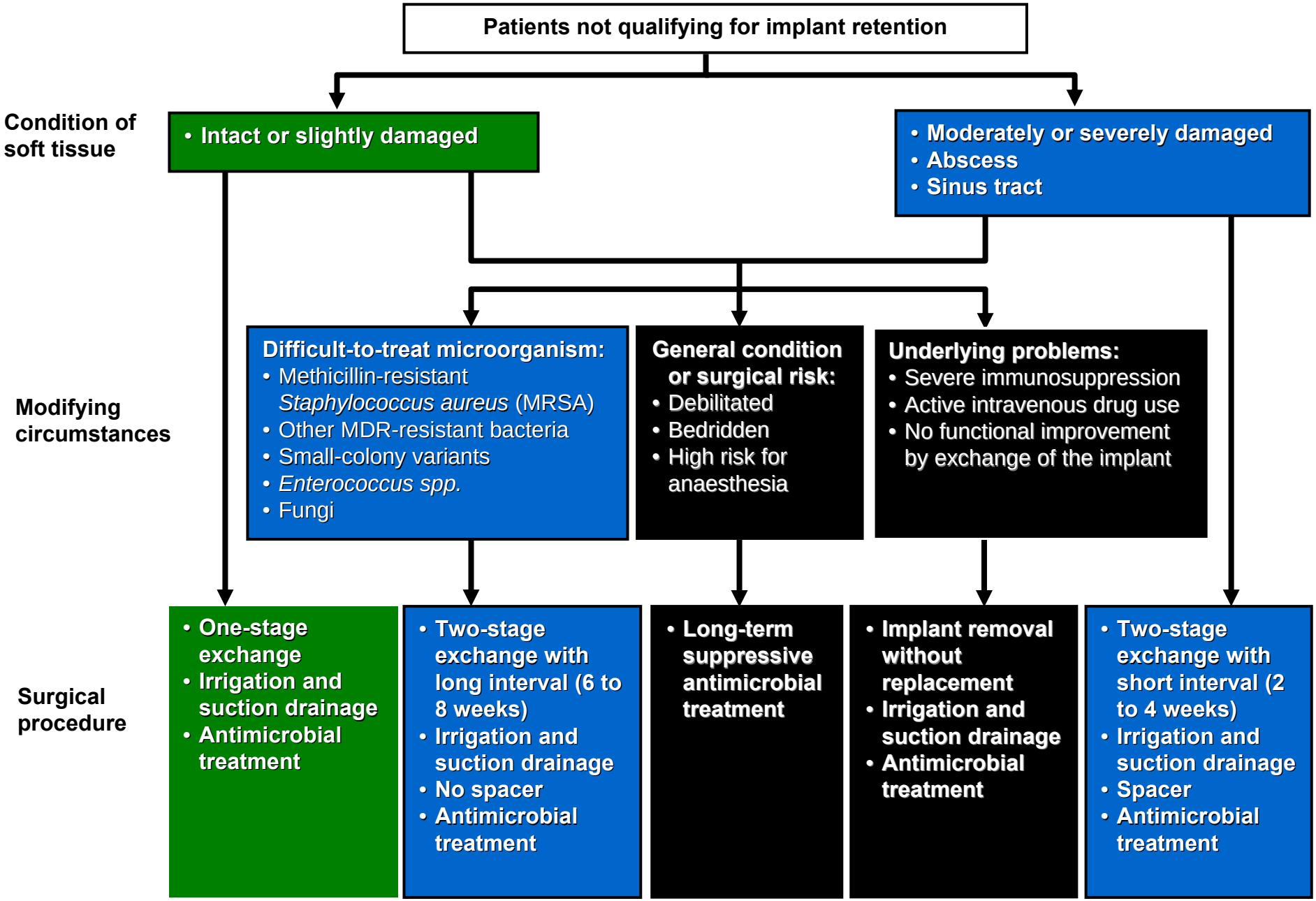
Prosthetic Joint Infections

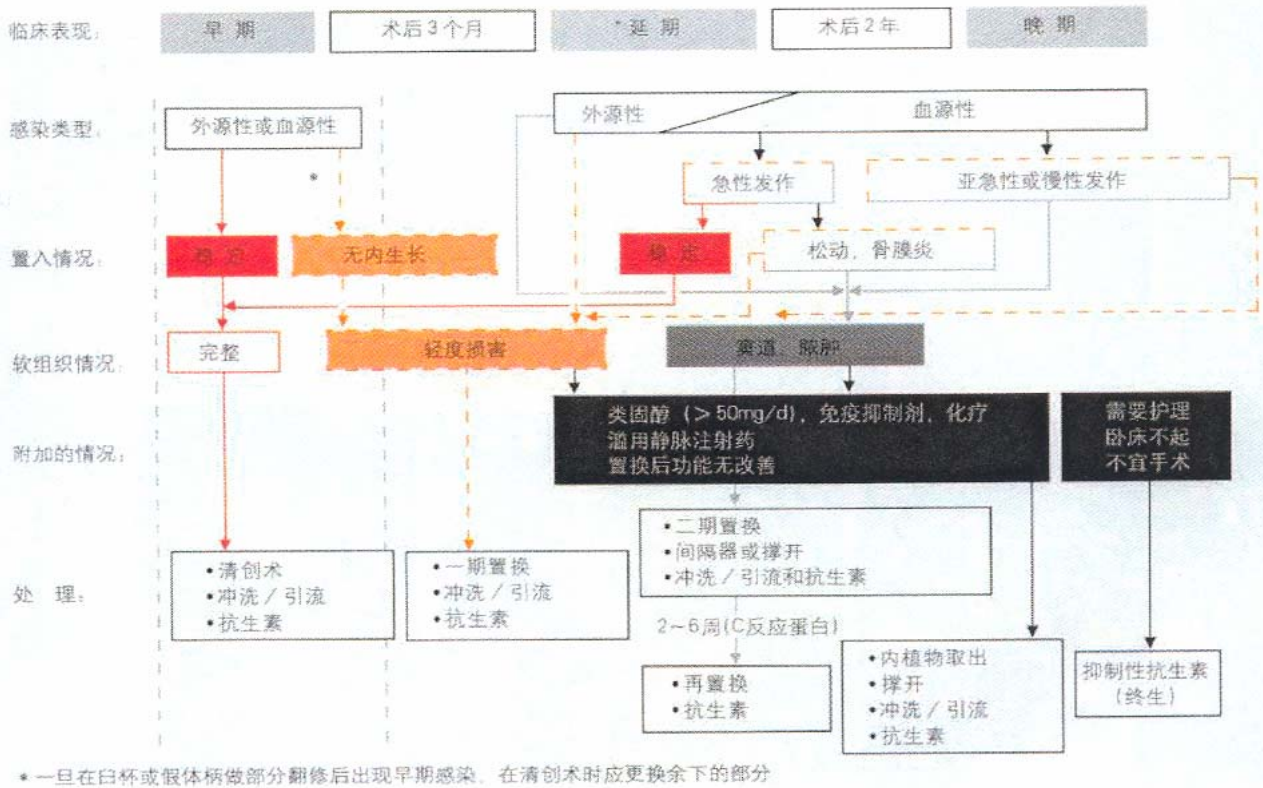
Werner Zimmerli, M.D., Andrej Trampuz, M.D., and Peter E. Ochsner, M.D.

*N Engl J Med 351:1645-54, 2004*




*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 long interval (6 to 8 weeks)
• Irrigation and suction drainage
• No spacer
• Antimicrobial treatment
• Long-term suppressive antimicrobial treatment
• Implant removal without replacement
• Irrigation and suction drainage
• Antimicrobial treatment
• Two-stage exchange with short interval (2 to 4 weeks)
• Irrigation and suction drainage
• Spacer
• Antimicrobial treatment




* 一旦在臼杯或假体柄做部分翻修后出现早期感染，在清创术时应更换余下的部分

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）

*In: PE Ochsner (ed.) Total Hip Replacement (Chinese Edition 2004)*

# RETROSPECTIVE 10-y-STUDY IN 118 PATIENTS WITH PJI (Univ.Hosp.Basel 1994-2003)

- 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:*

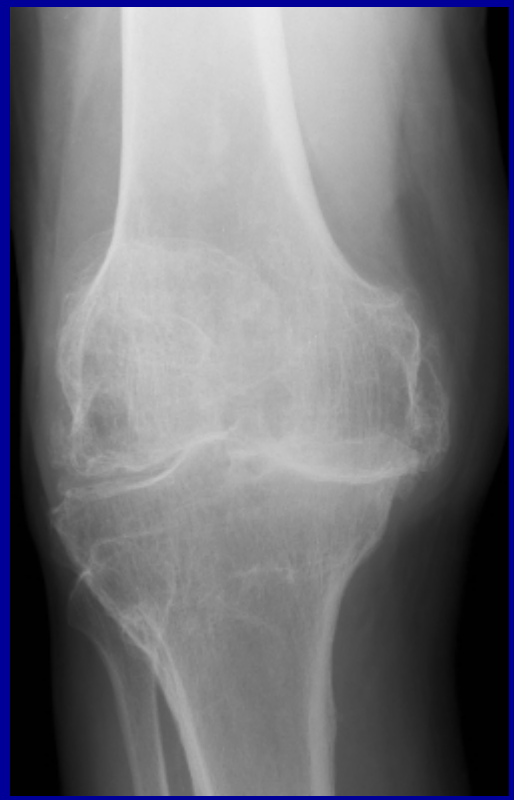
- Débridement with retention (75/81) 91%
- 1-stage exchange (13/14) 93%
- 2-stage exchange (15/15) 100%
- Removal (5/5) 100%

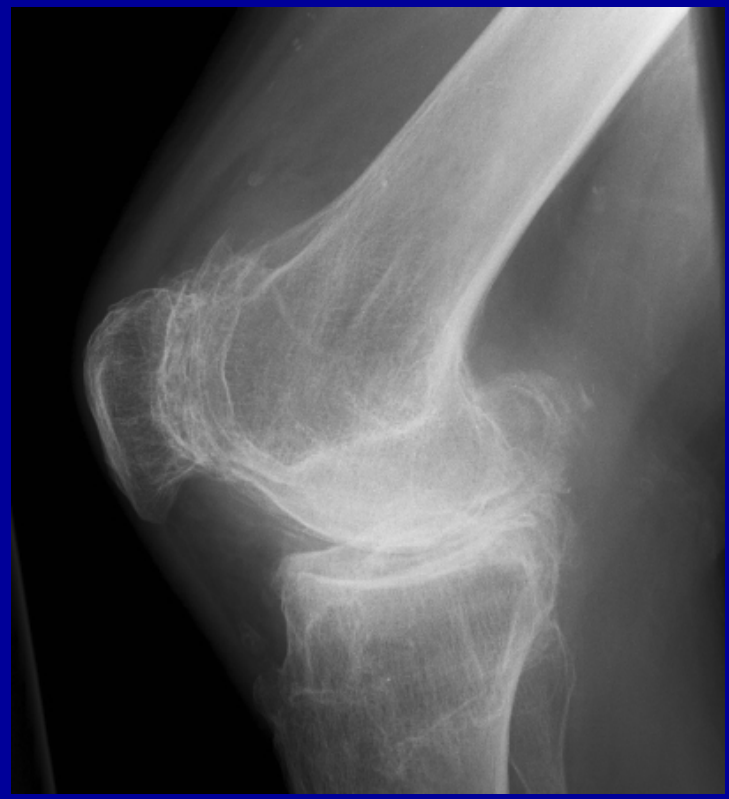
*[ICAAC-Poster K-883 2005 WDC ]*

# CASE PRESENTATIONS

# Case 1: 75-y-old man

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

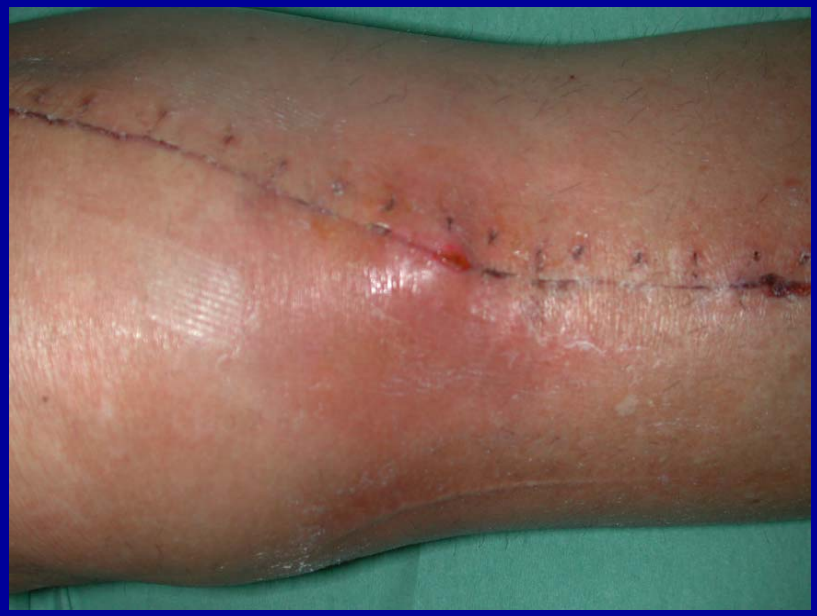


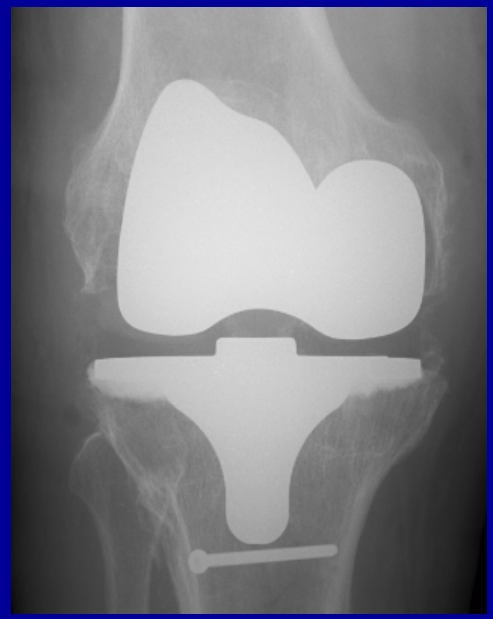


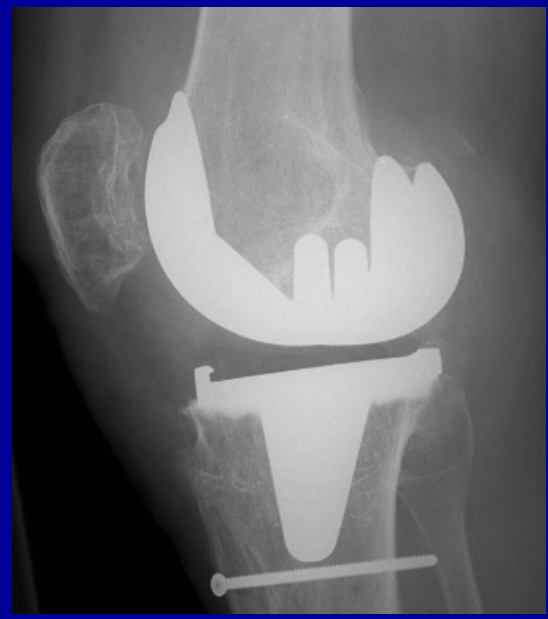
**→ Total Knee Arthroplasty**

# 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

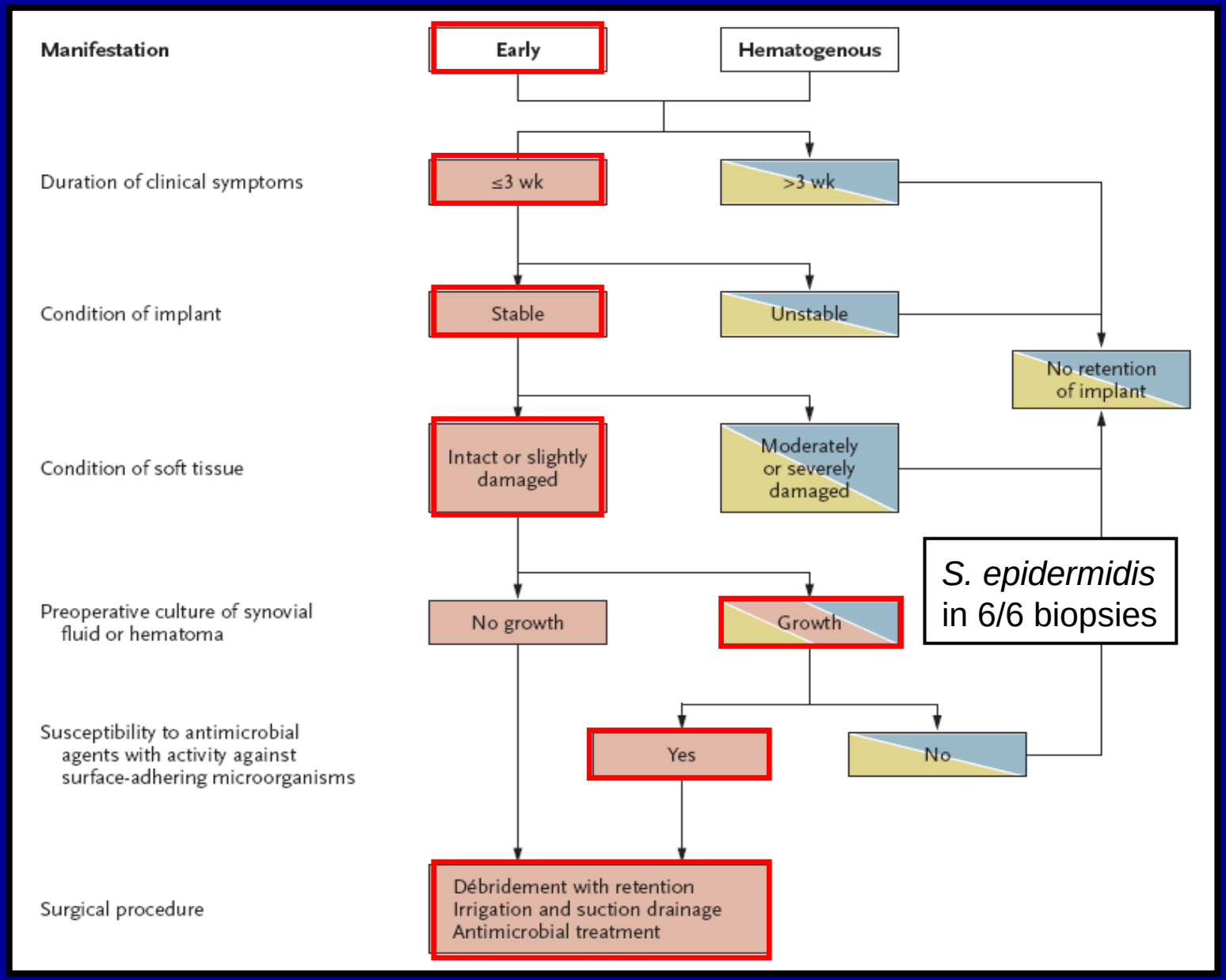






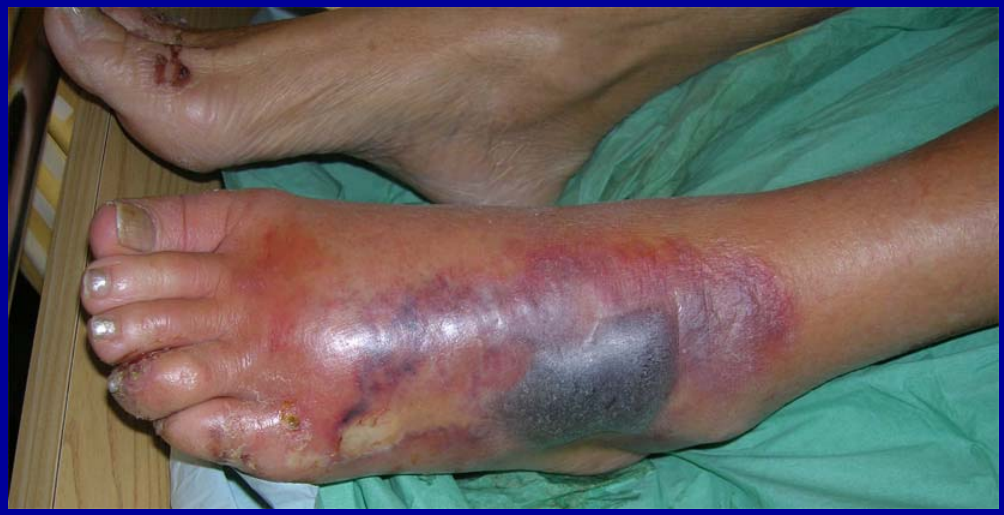
**Laboratory analysis: CRP 114mg/L, leukocytes 8.8 G/L**

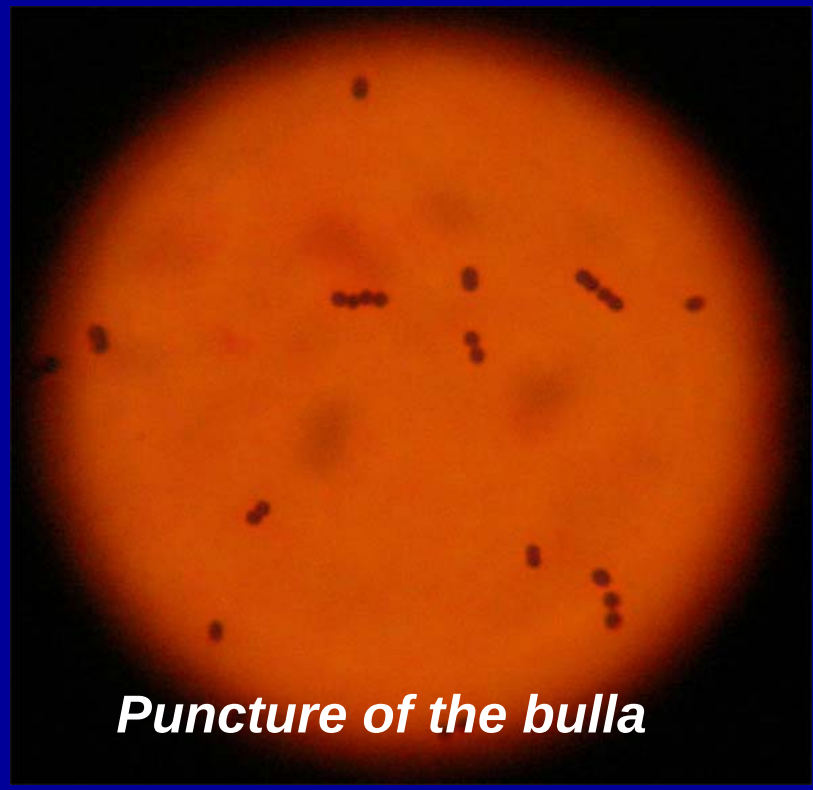
**How would you proceed?**


Manifestation
Early
Hematogenous
Duration of clinical symptoms
≤3 wk
>3 wk
Condition of implant
Stable
Unstable
No retention of implant
Condition of soft tissue
Intact or slightly damaged
Moderately or severely damaged
S. epidermidis in 6/6 biopsies
Preoperative culture of synovial fluid or hematoma
No growth
Growth
Susceptibility to antimicrobial agents with activity against surface-adhering microorganisms
Yes
No
Surgical procedure
Débridement with retention
Irrigation and suction drainage
Antimicrobial treatment

# Case 2: 62-y-old woman

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





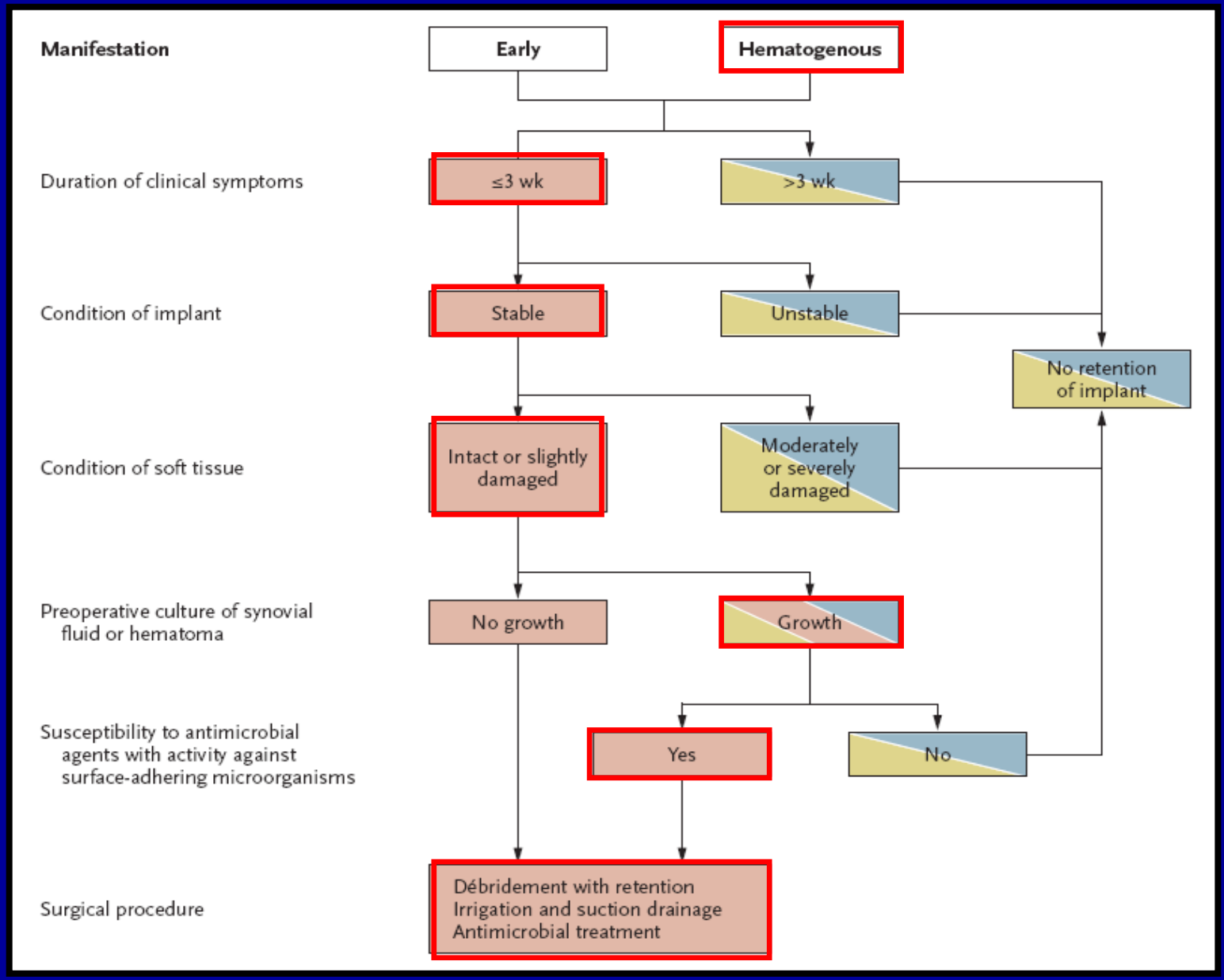
*Puncture of the bulla*

During hospitalisation the patient complained of hip pain
X-ray: prosthesis stable

# Case 2: 62-y-old woman

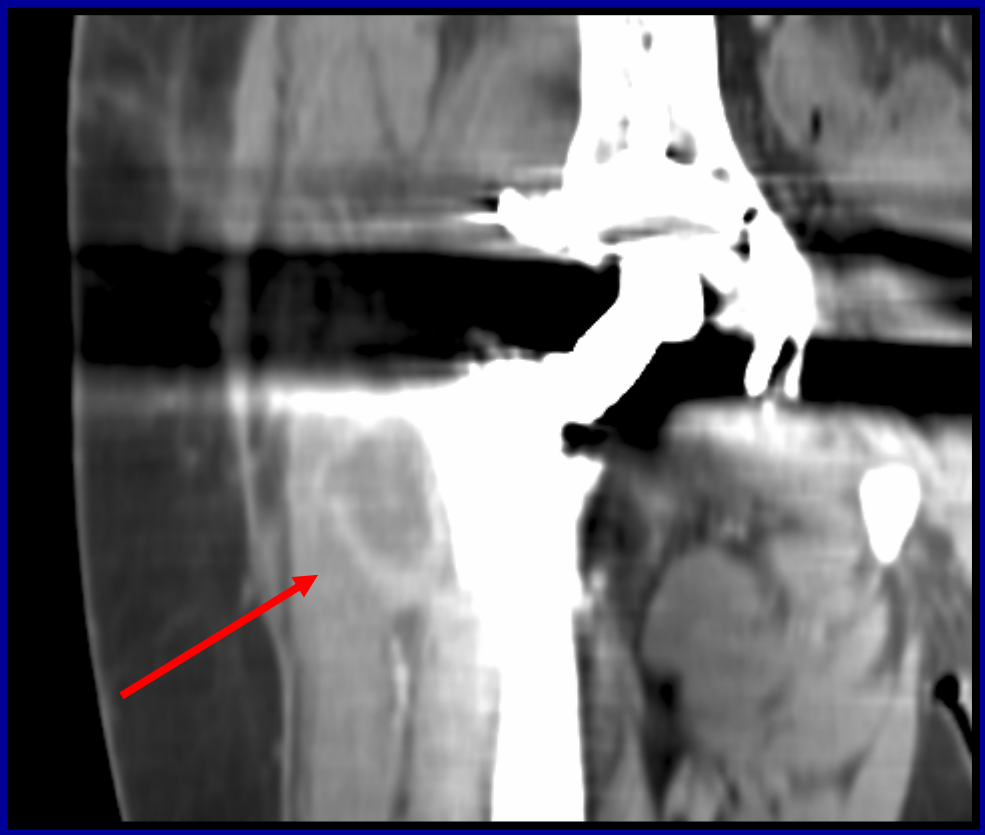
Puncture of the total hip arthroplasty revealed growth of group A streptococci susceptible to “all antibiotics”

How would you proceed?


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

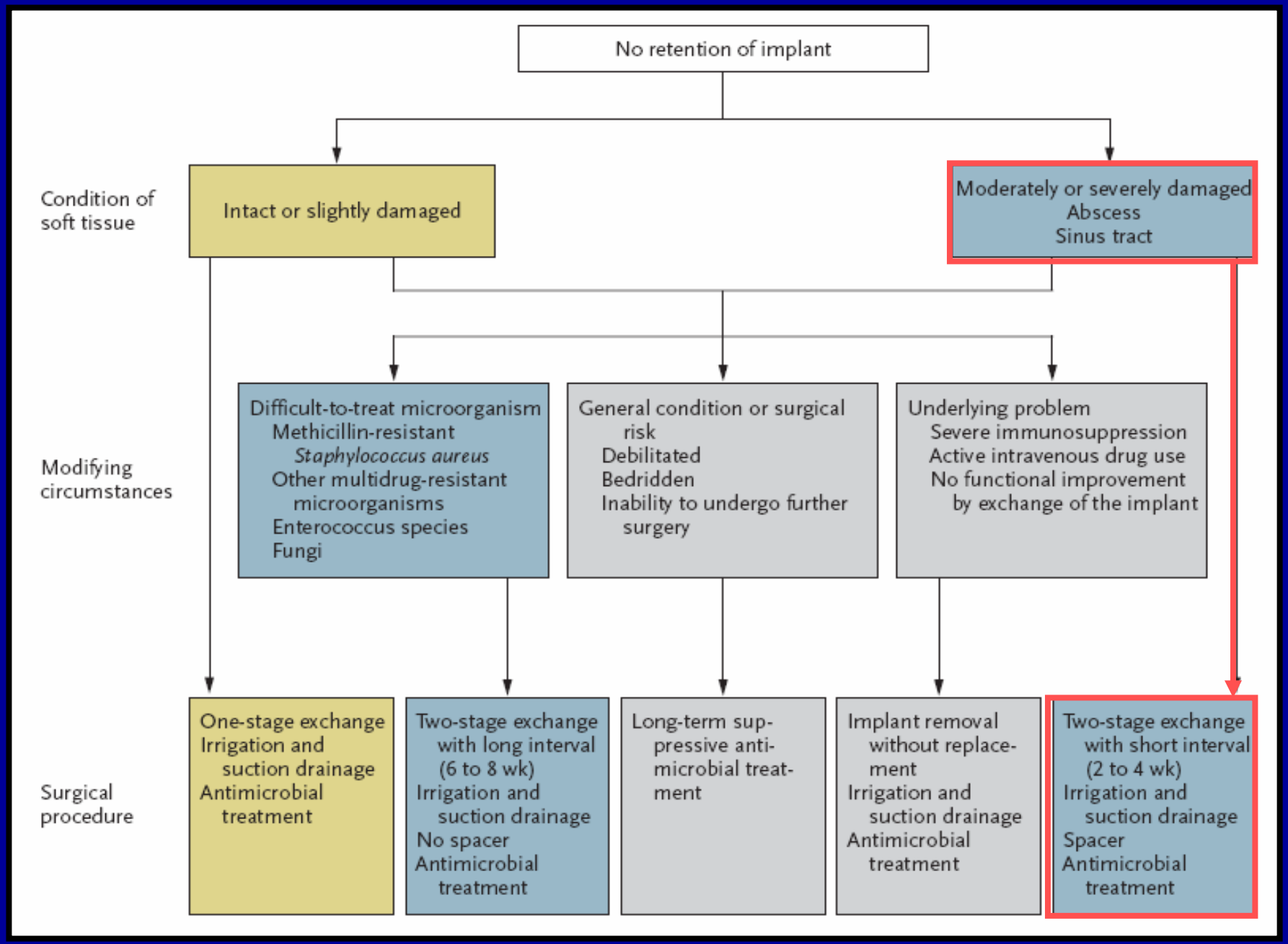
# Case 3: 69-y-old woman

**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
General condition or surgical risk
Debilitated
Bedridden
Inability to undergo further surgery
Underlying problem
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 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
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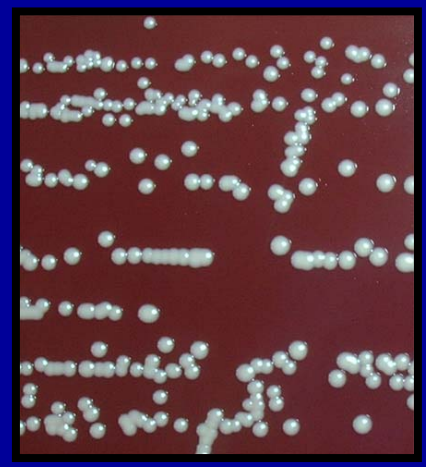
Two-stage exchange with short interval (2 to 4 wk)
Irrigation and suction drainage
Spacer
Antimicrobial treatment

# DIFFICULT-TO-TREAT MICROORGANISMS

# Small Colony Variants *Staphylococcus aureus* Microbiology

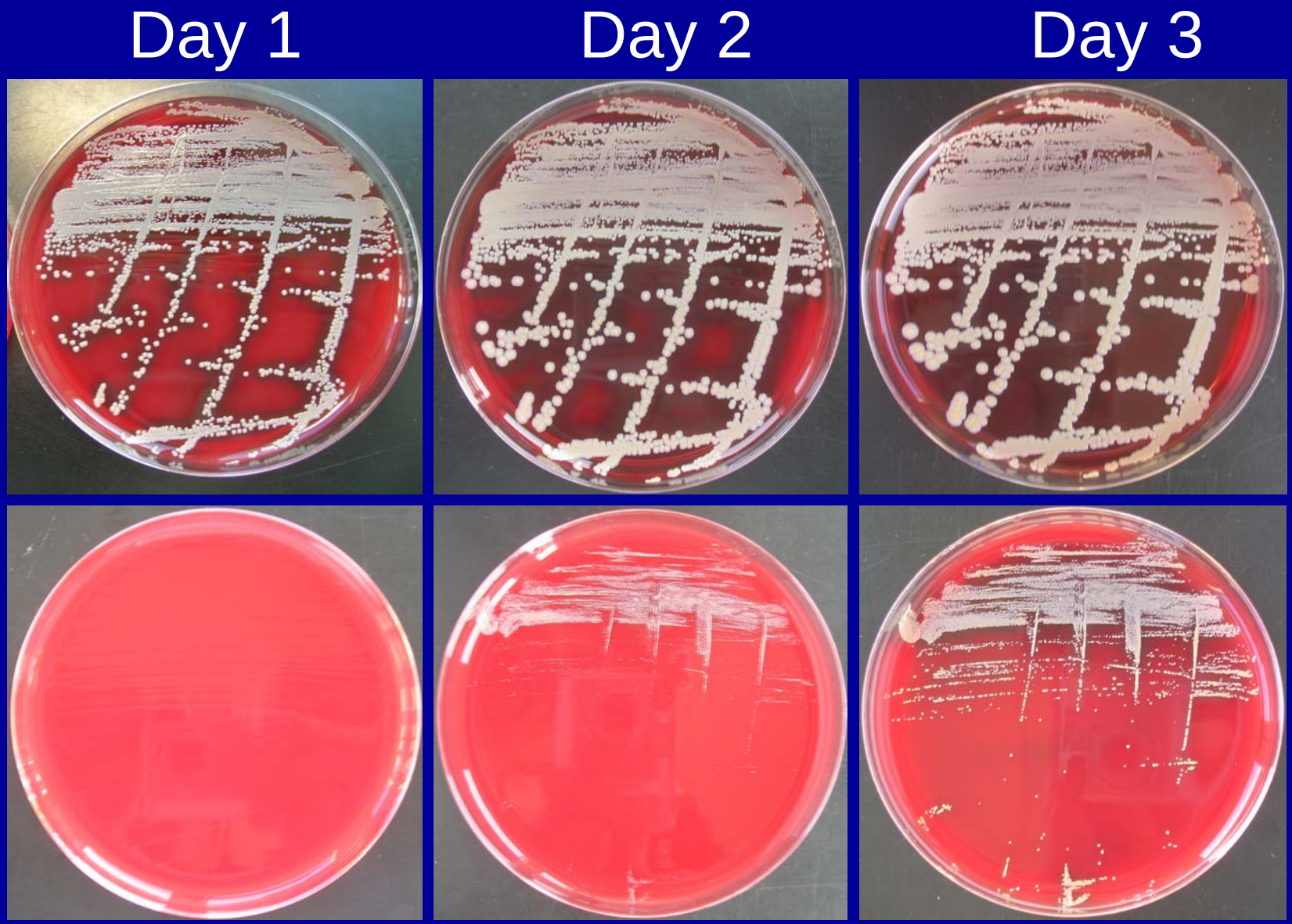
- subpopulation of *Staphyloccocus aureus*
- naturally occurring
- slow growth (48 – 72h)
- small colony size (10x↓)
- decreased pigmentation
- decreased activities of exoproteins

  [weakly coagulase positive, reduced hemolysis]



Proctor, RA et al., Clin Infect Dis 1988; 27: 419 - 22

# Small Colony Variants *Staphylococcus aureus*
## small and slow



# SCV S.aureus auxotrophism

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

***Spavetti***

**Periphery: growth not yet visible**

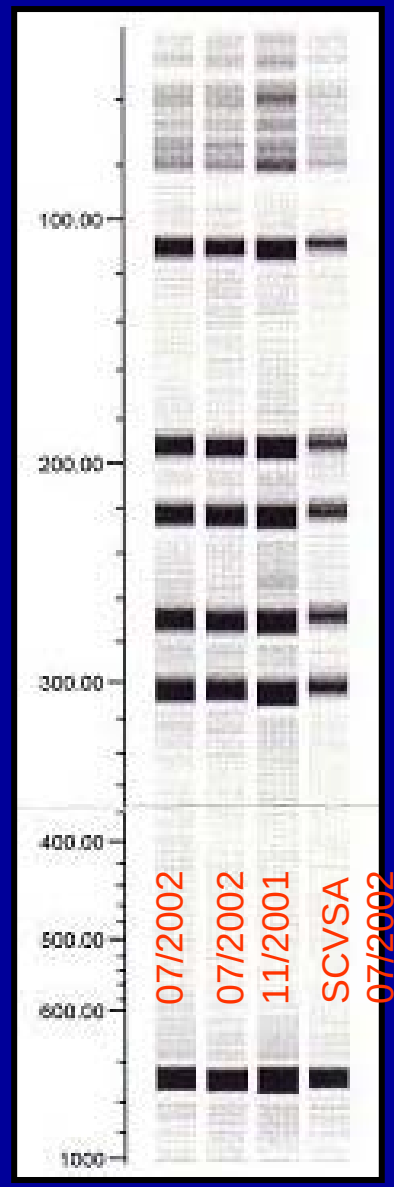
**Center: inhibition by high concen-tration of hemin**

**Middle part: growth promotion by hemin**

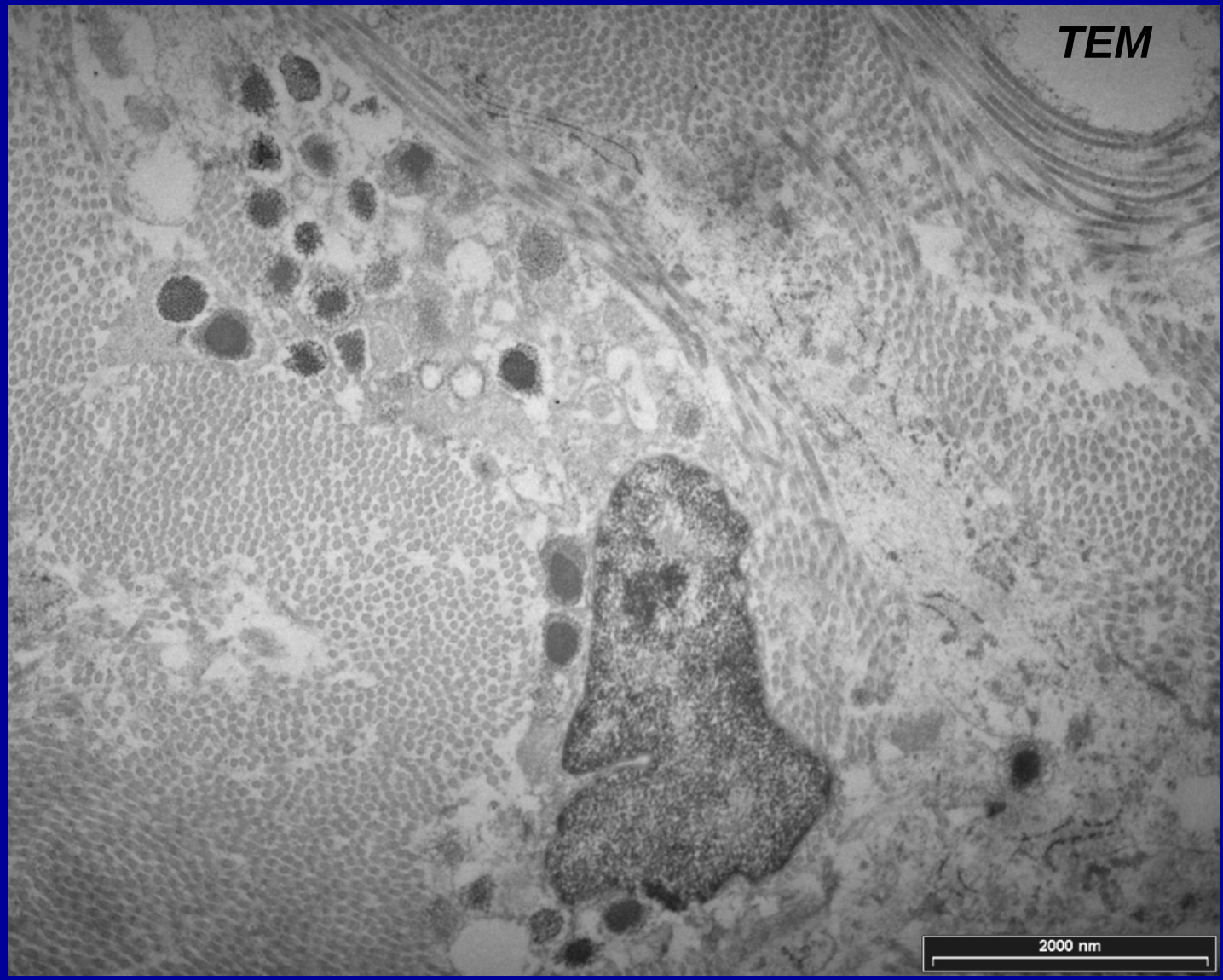
# Case 4: 55-y-old male

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



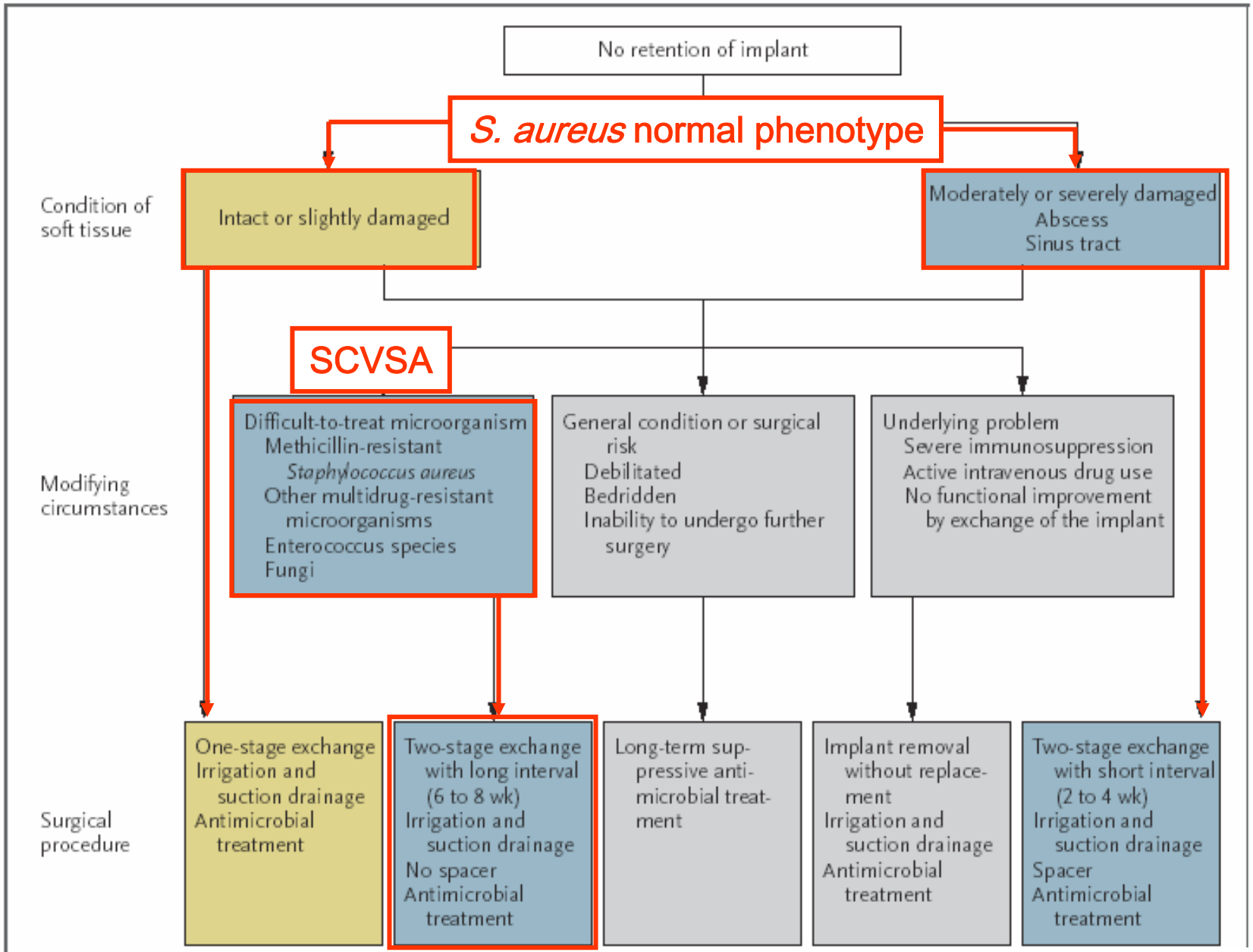
# Small Colony Variants *Staphylococcus aureus*
# Where do they persist?



# 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 |

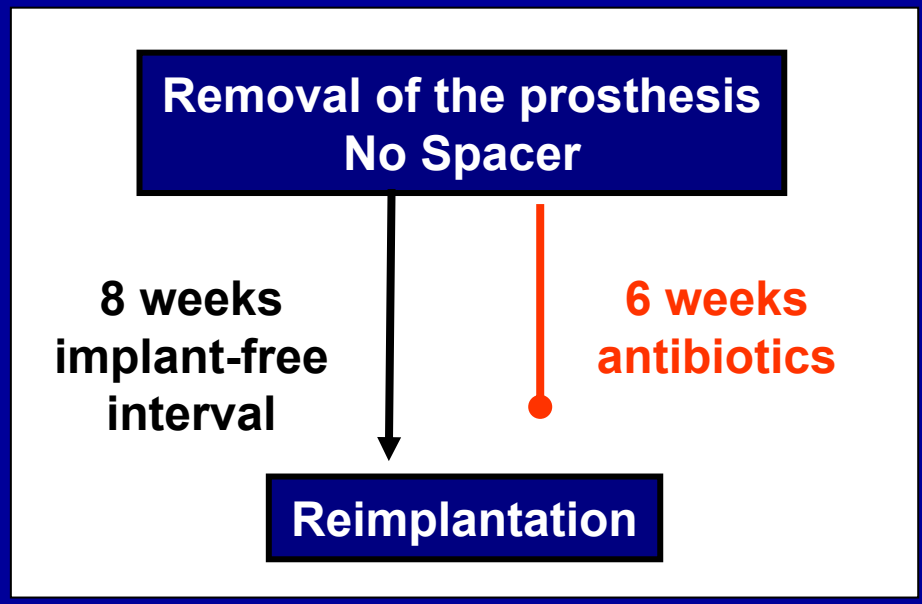
**Small Colony Variants *Staphylococcus aureus* are difficult-to-treat microorganisms**




Zimmerli, W. et al. 2004: NEJM 351: 1645

**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)**

***Sendi et al. Staphylcoccus aureus small colony variants in prosthetic joint infection. Clin Infect Dis 43:961-7,2006.***

| Patient | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| **Age** | 55 | 70 | 59 | 71 | 51 |
| **Prosthesis** | Hip | Hip | Hip | Hip | Hip |
| **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***

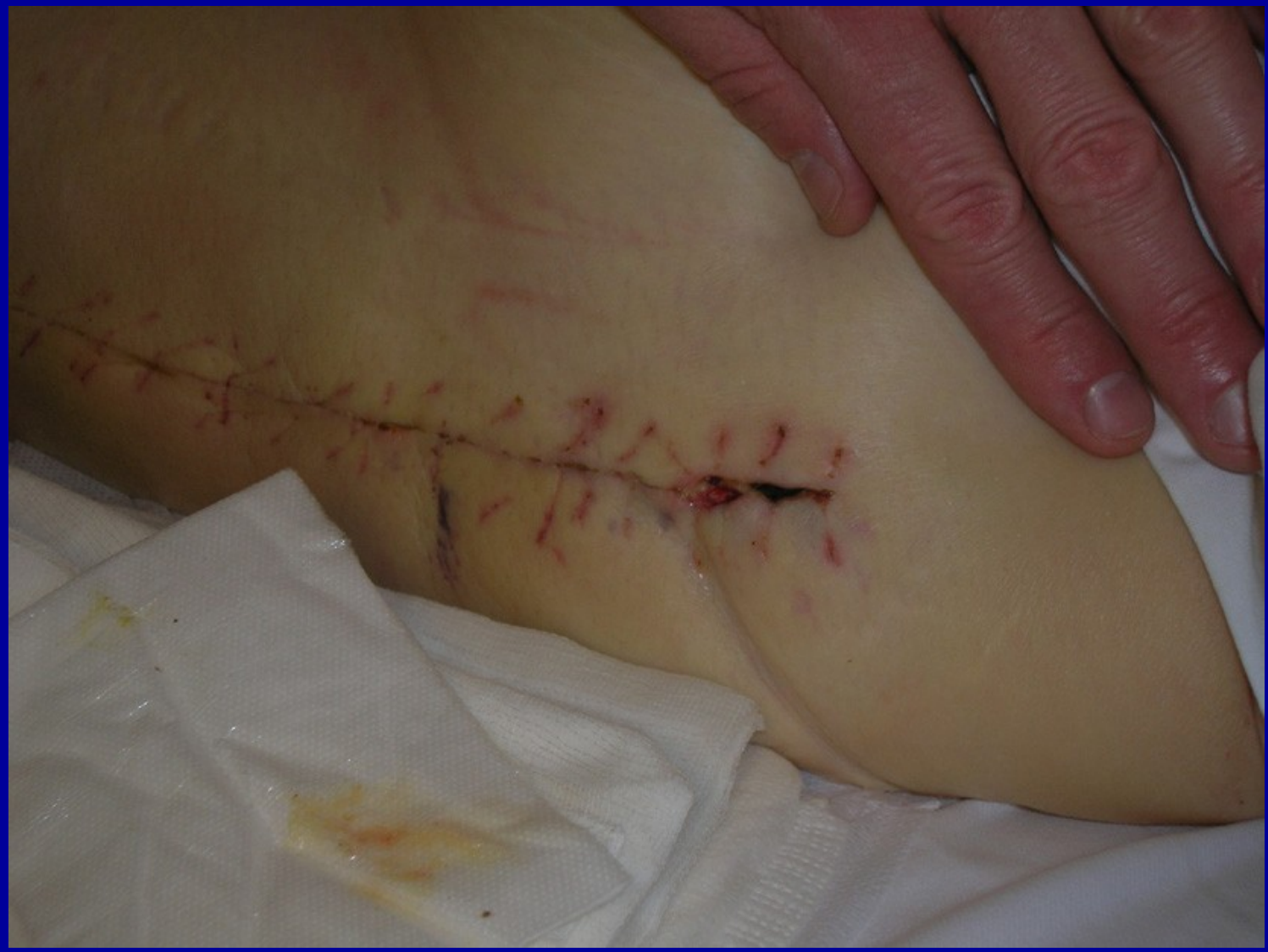
- **a spacer-free, two-stage exchange**
- **8 weeks of implant-free interval**
- **6 weeks of antimicrobial therapy during interval**

# 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 postopearative 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



# 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:*

- **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.**

# CONCLUSIONS

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