# Stratégies diagnostiques et thérapeutiques des infections sur prothèses orthopédiques

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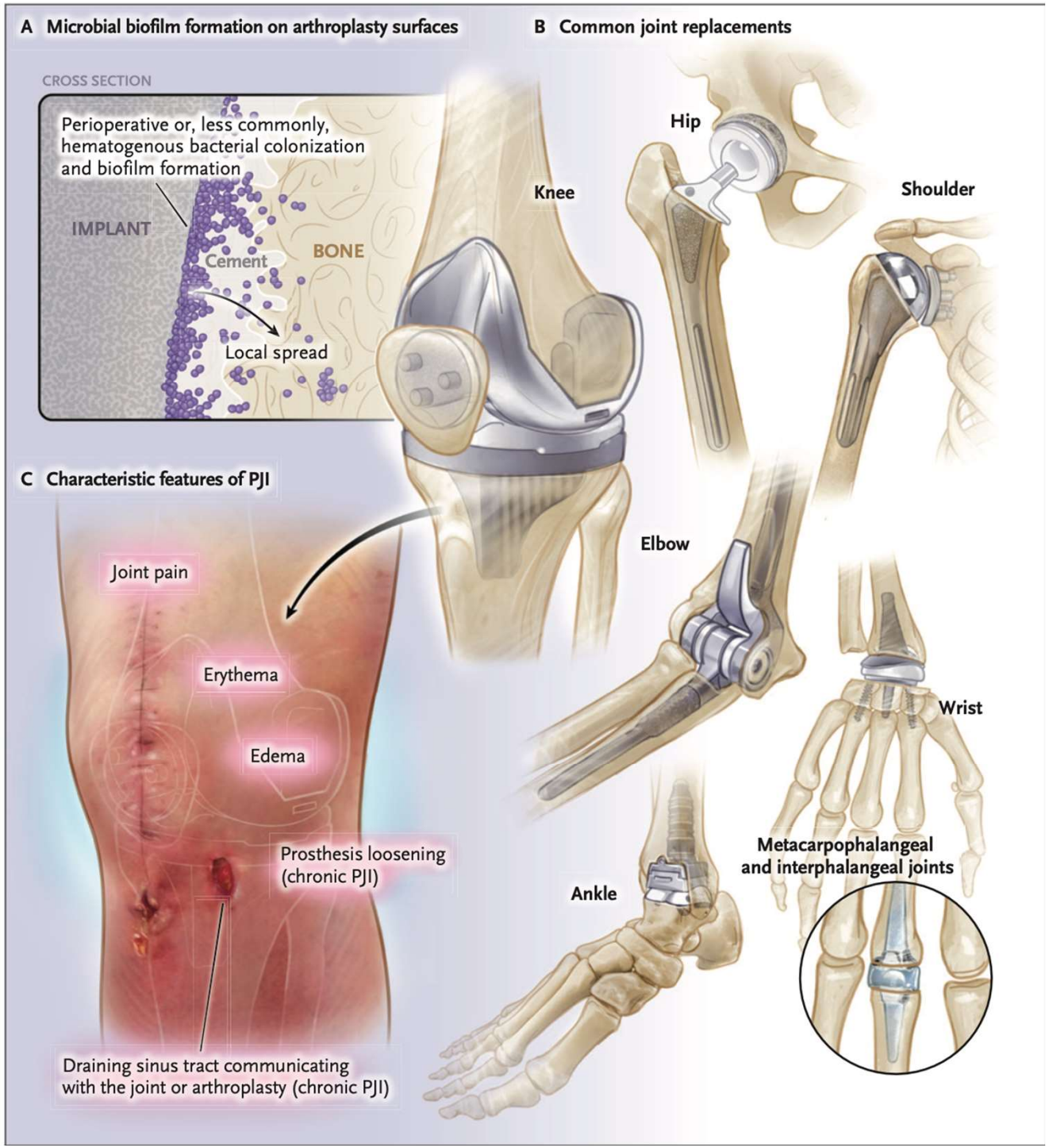


R. Patel
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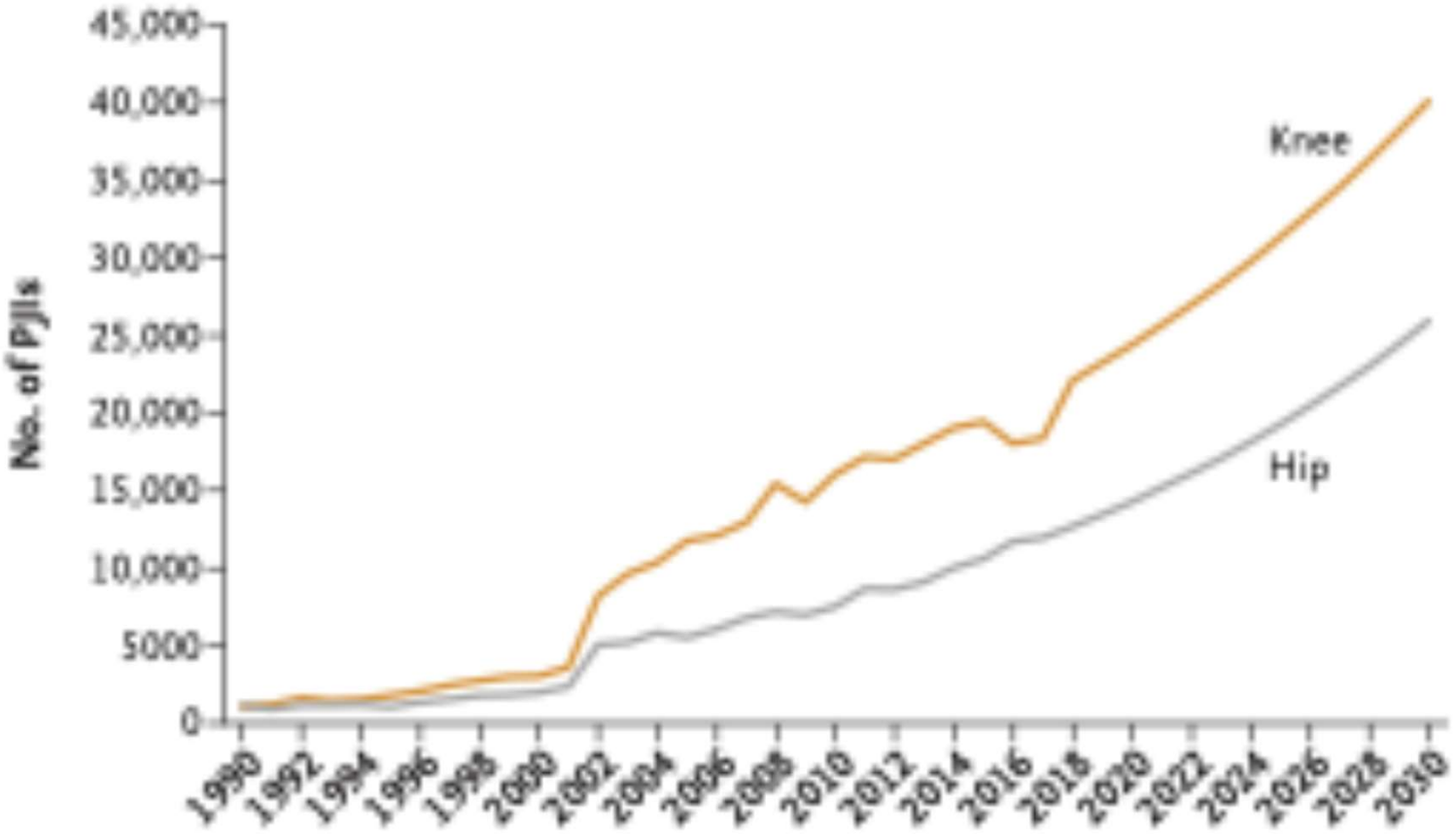
REVIEW ARTICLE

C. Corey Hardin, M.D., Ph.D., *Editor*

# Periprosthetic Joint Infection

Robin Patel, M.D.

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# Periprosthetic Joint Infection

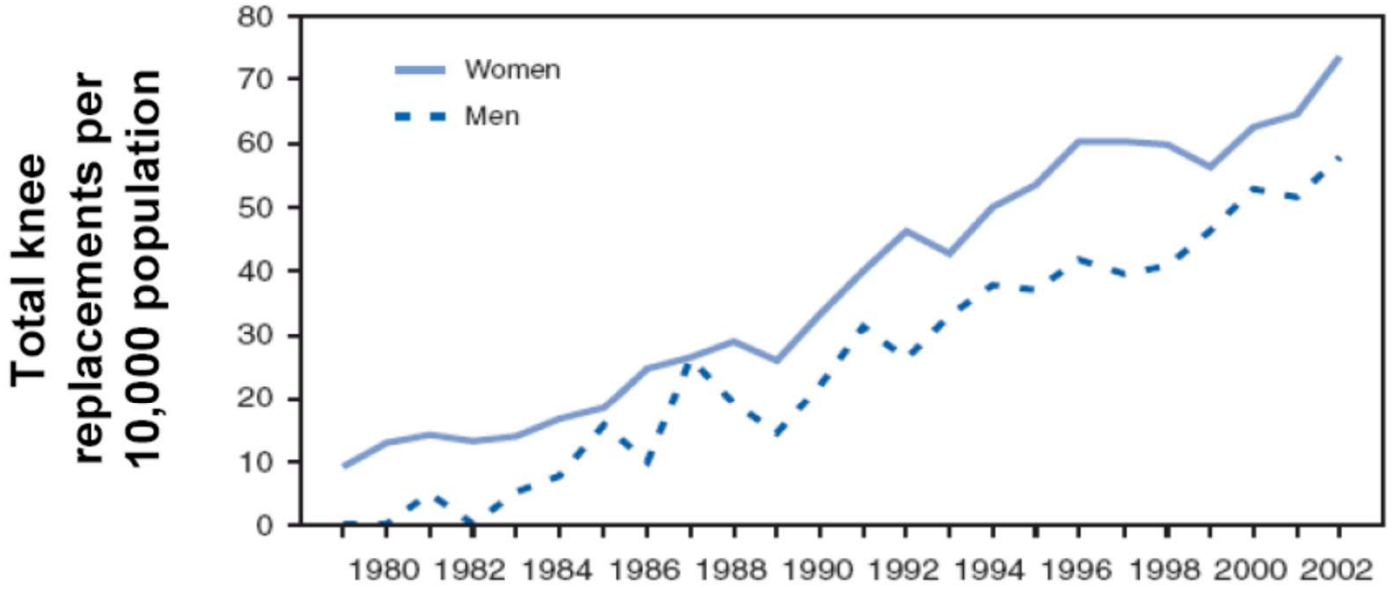
Robin Patel, M.D.

| Microorganism | Frequency (%) |
|---|---|
| Aerobic gram-positive bacteria | 82 |
| Coagulase-negative staphylococcus species (other than *S. lugdunensis*) | 37 |
| *S. aureus* | 24 |
| *S. lugdunensis* | 4 |
| Streptococcus species | 14 |
| Enterococcus species | 8 |
| Corynebacterium species | 5 |
| Aerobic gram-negative bacteria | 11 |
| Enterobacterales | 7 |
| Pseudomonas species | 3 |
| Anaerobic bacteria | 13 |
| Cutibacterium species | 8 |
| Other species | 5 |
| Fungi | 3 |
| Mycobacteria | 0.5 |

R. Patel
NEJM 2024

# Taux d'IPOA croissant

- Augmentation Primo implantations aux USA
- Risque infectieux croissant en cas de reprise de Prothese
- Allongement de durée de vie des patients et des implants




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

# Facteurs de risque

**Potentially modifiable presurgical risk factors**

Anemia

Injection-drug use

Malnutrition

Obesity

Receipt of intraarticular injection in prior 3 mo

Tobacco use

**Operative risk factors**

Allogeneic blood transfusion

Prolonged operative time

Simultaneous bilateral arthroplasty

**Postoperative risk factors**

Discharge to rehabilitation or convalescent care

Prolonged hospitalization

*S. aureus* bacteremia

Wound-healing complications (including superficial skin infection)

**Nonmodifiable presurgical risk factors**

Cardiovascular disease (arrhythmia, coronary artery disease, pulmonary hypertension, congestive heart failure, or peripheral vascular disease)

Diabetes (especially with poor glycemic control)*

Immunocompromised status (owing to cancer or receipt of a transplant)

Inflammatory arthritis

Kidney or liver disease (hepatitis or cirrhosis)

Male sex

Medicaid as primary payer

Mental health disorder (depression or alcohol use)

Relative with PJI

Patellar resurfacing and post-traumatic arthritis (knees)

Prior native joint infection

Prior PJI of same or different joint

Prior revision arthroplasty

Younger age

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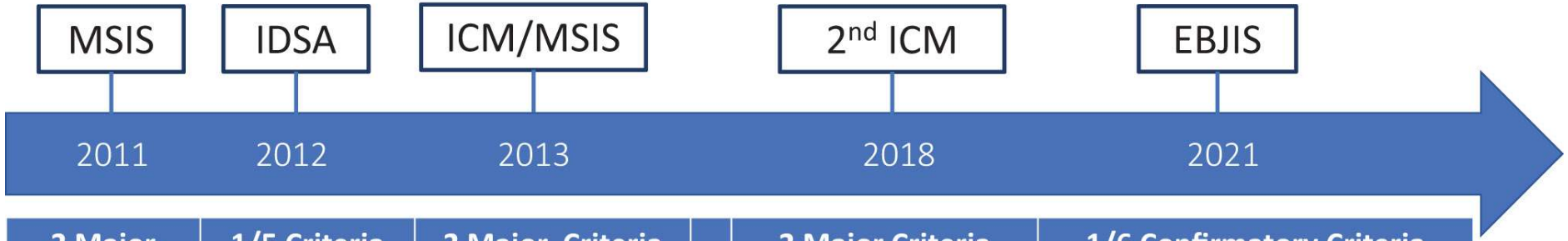
# Periprosthetic Joint Infection

Robin Patel, M.D.

**Table 3. Criteria for Diagnosis of Hip or Knee PJI.***

| EBJIS "Confirmatory" Single Criteria[32] | 2018 Parvizi et al. "Major" Single Criteria[31] |
|---|---|
| Two positive cultures (includes synovial fluid, tissue, and sonicate-fluid cultures) for the same microorganism | Two positive cultures (includes synovial fluid, tissue, and sonicate-fluid cultures) for the same microorganism |
| Sinus tract with communication to joint or prosthesis | Sinus tract with communication to joint or prosthesis |
| Synovial fluid leukocyte count, >3000/ml† | |
| Synovial fluid neutrophils, >80%† | |
| Synovial fluid alpha-defensin positive‡ | |
| Sonicate-fluid culture, >50 CFU/ml for any organism (>200 CFU/ml if centrifuged) | |
| Histopathological assessment (high-power field, 400× magnification) showing ≥5 neutrophils in ≥5 high-power fields (or visible microorganisms)§ | |

# Definitions of PJI




| 2 Major Criteria | 1/5 Criteria | 2 Major Criteria | | 2 Major Criteria | 1/6 Confirmatory Criteria |
|---|---|---|---|---|---|
| Sinus Tract<br>Microbiology<br>2 Cultures | Sinus Tract<br>Purulence<br>Histology<br>Microbiology<br>2 Cultures<br>1 Virulent | Sinus Tract<br>Microbiology<br>2 Cultures | | Sinus Tract<br>Microbiology<br>2 Cultures | Sinus Tract<br>Synovial WCC >3000 (PMN% >80%)<br>Alpha-defensin<br>Microbiology 2 Cultures<br>Sonication >50CFU/ml<br>Histology |
| 4/6 Minor Criteria | | 3/5 Minor Criteria<br>(Acute vs Chronic) | | 10 Minor Criteria<br>Weighted Score ≥6 = PJI | Suggestive Criteria<br>"Infection Likely" |
| CRP & ESR<br>Synovial WCC<br>Synovial PMN%<br>Purulence<br>1 Culture<br>Histology | | CRP & ESR<br>Synovial WCC or LE<br>Synovial PMN%<br>1 Culture<br>Histology | | CRP, D-dimer & ESR<br>Synovial WCC, PMN% & CRP<br>Alpha-defensin<br>Histology<br>Purulence<br>Microbiology 1 Culture | Early Loosening <5 years<br>Poor wound healing<br>Fever<br>Purulence<br>Synovial WCC >1500 (PMN% >65%)<br>Microbiology 1 Culture<br>Nuclear Imaging |

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# The EBJIS definition of periprosthetic joint infection

McNally et al. Bone Joint Journal, January 2021

European Bone & Joint Infection Society EBJIS

| | Infection Unlikely | Infection Likely | Infection Confirmed |
|---|---|---|---|
| | *All findings negative* <br> A ✗ B ✗ C ✗ | *Two positive findings* <br> A ✓ B ✓ or A ✓ C ✓ | *Any positive finding* <br> A ✓ or B ✓ |
| **A CLINICAL** <br> Clinical features | Clear alternative reason for implant dysfunction | • Early radiographic loosening <br> • Wound healing problems <br> • Recent fever/bacteraemia <br> • Purulence around prosthesis <br> • CRP > 10mg/l | Sinus tract communication with the joint +/- visualization of prosthesis |
| C-reactive protein | | | |
| **B LABORATORY** <br> Synovial fluid | • Leukocyte count ≤ 1500 <br> • PMN ≤ 65% | • Leukocyte count > 1500 <br> • PMN > 65% | • Leukocyte count > 3000 <br> • PMN > 80% <br> • Positive Alpha-defensin |
| Microbiology | • All cultures negative <br> • No growth on sonication | • Single positive culture (aspiration or intra-operative) <br> • > 1 CFU/ml any organism on sonication | • ≥ 2 positive samples with the same microorganism <br> • > 50 CFU/ml any organism on sonication |
| Histology | Negative | Presence of ≥ 5 neutrophils in a single HPF | • Presence of ≥ 5 neutrophils in ≥ 5 HPF <br> • Visible microorganisms |
| **C RADIOLOGY** <br> Nuclear imaging | Negative 3-phase isotope bone scan | Positive white blood cell labelled scintigraphy | |

M. Romanova

ESGIAI ESCMID STUDY GROUP FOR IMPLANT-ASSOCIATED INFECTIONS
European Society of Clinical Microbiology and Infectious Diseases

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# « Le Duel »

**Problèmes**

- Tissus osseux
- Matériel
- Bactéries quiescentes
- Résistances bactériennes
- Biofilm
- Adhésion
- Métabolisme lent
- Corrélation in vitro/in vivo ?

**Solutions proposées**

- Chirurgie
- Diagnostic microbiologique complet
- Antibiothérapie forte dose
- Antibiothérapie IV
- Durée traitement prolongée

E. Senneville

# Clinique : aigue vs chronique

## Infections sur prothèse ostéo-articulaire

### Tableau aigu

- Clinique bruyante
- Germe virulent (*S. aureus*)
- Pas de difficulté diagnostique
- Urgence thérapeutique

Pas de problème diagnostic

Urgence thérapeutique

### Tableau chronique

- Clinique difficile
- Bactéries peu virulentes (multiples)
- Difficulté à diagnostiquer et documenter l'infection
- Ne rien faire en urgence

**Difficultés diagnostiques**

**Ne rien faire confier aux spécialistes**

# Infection oui mais ?

## Does This Adult Patient Have Septic Arthritis?

Mary E. Margaretten, MD
Jeffrey Kohlwes, MD, MPH
Dan Moore, PhD
Stephen Bent, MD

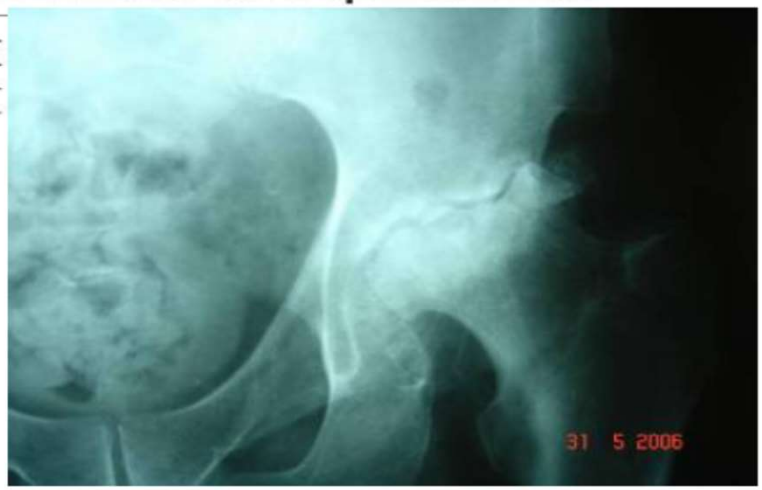



**Table 3.** Sensitivity of Symptoms and Signs*

| Variable | No. of Studies | Sensitivity, % (95% CI) |
|---|---|---|
| Joint pain | 2 | 85 (78-90) |
| History of joint edema | 2 | 78 (71-85) |
| Fever | 7 | 57 (52-62) |
| Sweats | 2 | 27 (20-34) |
| Rigors | 4 | 19 (15-24) |

Abbreviation: CI, confidence interval.
*With the exception of the study by Kortekangas et al,[47] the studies reviewed only included patients with septic arthritis, which permits calculation of only sensitivity and not specificity or likelihood ratios.

**Box 1. Differential Diagnosis for Acute Monoarthritis***

Infection (bacterial, fungal, mycobacterial, viral, spirochete)
Rheumatoid arthritis
Gout
Pseudogout
Apatite-related arthropathy
Reactive arthritis
Systemic lupus erythematosus
Lyme arthritis
Sickle cell disease
Dialysis-related amyloidosis
Transient synovitis of the hip
Plant thorn synovitis
Metastatic carcinoma
Pigmented villonodular synovitis
Hemarthrosis
Neuropathic arthropathy
Osteoarthritis
Intra-articular injury (fracture, meniscal tear, osteonecrosis)

*Adapted from Klippel et al.[18]

Margaretten ME JAMA 2007

# Diagnostic difficile

**Table 1. Criteria for the Diagnosis of a Prosthetic-Joint Infection.***

**The presence of at least one of the following findings:**

Acute inflammation detected on histopathological examination of periprosthetic tissue

Sinus tract communicating with the prosthesis

Gross purulence in the joint space

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

- No universally accepted definition
- Reliable microbiologic diagnosis confirms infection
- Preoperative diagnostic test : aspiration of joint synovial fluid
- Microbiologic identification is critical to choose directed antimicrobial regimen but it takes TIME !

Del Pozo, NEJM 2009

# Démarche diagnostique

- 1. Faisceau d'arguments
  - Clinique >> médecins et/ou chirurgien
  - Imagerie >> radiologue
  - Biologie >> biologiste et/ou microbiologiste
- 2. Suspicion d'infection +/- forte
- 3. Confirmation du diagnostic: **MICROBIOLOGIQUE !!!**

# Examens complémentaires pour confirmer le diagnostic ?

- Aucun n'est sensible ni spécifique !!!
- VS ou CRP normales >>n'élimine pas l'infection.
- Dans le mois qui suit l'implantation, la courbe d'évolution de la CRP a une valeur diagnostique mais pas la VS
- Biologiquement, à 3 mois de l'implantation
  - une VS > 22-30 mm :
    - sensibilité 82 -93 %
    - spécificité 84 %,
  - une CRP > 10 à 13,5 mg/l
    - sensibilité 91- 97 %
    - spécificité entre 86-92 %

OPEN ACCESS Freely available online

PLoS one

# C-Reactive Protein, Erythrocyte Sedimentation Rate and Orthopedic Implant Infection

Kerryl E. Piper[1], Marta Fernandez-Sampedro[1], Kathryn E. Steckelberg[1], Jayawant N. Mandrekar[2], Melissa J. Karau[1], James M. Steckelberg[1], Elie F. Berbari[1], Douglas R. Osmon[1], Arlen D. Hanssen[4], David G. Lewallen[4], Robert H. Cofield[4], John W. Sperling[4], Joaquin Sanchez-Sotelo[4], Paul M. Huddleston[4], Mark B. Dekutoski[4], Michael Yaszemski[4], Bradford Currier[4], Robin Patel[1,3]*

**Table 2.** Descriptive summary and comparison of aseptic failure versus orthopedic implant-associated infection subjects. Median (range) values are shown.

| **Knee arthroplasty (n = 297)** | **Aseptic failure (n = 215)** | **Orthopedic implant-associated infection (n = 82)** | **P-value** |
|---|---|---|---|
| ESR, mm/h | 11 (0–68) | 53.5 (6–128) | <0.0001 |
| CRP, mg/l | 4 (0.1–174) | 51 (3–444) | <0.0001 |
| **Hip arthroplasty (n = 221)** | **Aseptic failure (n = 187)** | **Orthopedic implant-associated infection (n = 34)** | |
| ESR, mm/h | 11 (0–94) | 30 (3–137) | <0.0001 |
| CRP, mg/l | 3 (0.3–141) | 18 (3–288) | <0.0001 |
| **Shoulder arthroplasty (n = 64)** | **Aseptic failure (n = 45)** | **Orthopedic implant-associated infection (n = 19)** | |
| ESR, mm/h | 10 (0–32) | 9 (1–71) | 0.9883 |
| CRP, mg/l | 3 (3–26) | 10 (3–40) | 0.01 |
| **Spine implant (n = 54)** | **Aseptic failure (n = 40)** | **Orthopedic implant-associated infection (n = 14)** | |
| ESR, mm/h | 10 (0–74) | 48.5 (1–83) | 0.0033 |
| CRP, mg/l | 3 (0.5–183) | 20 (3–205) | 0.0011 |

# Inflammatory Blood Laboratory Levels as Markers of Prosthetic Joint Infection

## A Systematic Review and Meta-Analysis

By Elie Berbari, MD, Tad Mabry, MD, Geoffrey Tsaras, MD, Mark Spangehl, MD, Pat J. Erwin, MLS, Mohammad Hassan Murad, MD, James Steckelberg, MD, and Douglas Osmon, MD

*Investigation performed at Mayo Clinic College of Medicine, Rochester, Minnesota*

**Background:** The preoperative diagnosis of prosthetic joint infection in patients with a total hip or knee arthroplasty may rely in part on the use of systemic inflammation markers. These markers have unclear accuracy. The objective of this review was to summarize the evidence on the accuracy of the peripheral white blood-cell count, the erythrocyte sedimentation rate, serum C-reactive protein levels, and serum interleukin-6 levels for the diagnosis of prosthetic joint infection.

**Methods:** We searched electronic databases (MEDLINE, EMBASE, Cochrane Library, Web of Science, and Scopus) from 1950 through 2009. Eligible studies evaluated the accuracy of white blood-cell count, erythrocyte sedimentation rate, serum C-reactive protein level, and serum interleukin-6 level for the intraoperative diagnosis of prosthetic joint infection at the time of revision arthroplasty. Two reviewers working independently extracted study characteristics and data to estimate the diagnostic odds ratio and 95% confidence interval for each result.

**Results:** We included thirty eligible studies that included 3909 revision total hip or knee arthroplasties. The prevalence of prosthetic joint infection was 32.5% (1270 of 3909). The accuracy of assessed inflammation markers, represented with a diagnostic odds ratio, was 314.7 (95% confidence interval, 113.0 to 876.8) for interleukin-6 (three studies), 13.1 (95% confidence interval, 7.9 to 21.7) for C-reactive protein level (twenty-three studies), 7.2 (95% confidence interval, 4.7 to 10.9) for erythrocyte sedimentation rate (twenty-five studies), and 4.4 (95% confidence interval, 2.9 to 6.6) for white blood-cell count (fifteen studies).

**Conclusions:** The diagnostic accuracy for prosthetic joint infection was best for interleukin-6, followed by C-reactive protein level, erythrocyte sedimentation rate, and white blood-cell count. Given the limited numbers of studies assessing interleukin-6 levels, further investigations assessing the accuracy of interleukin-6 for the diagnosis of prosthetic joint infection are warranted.

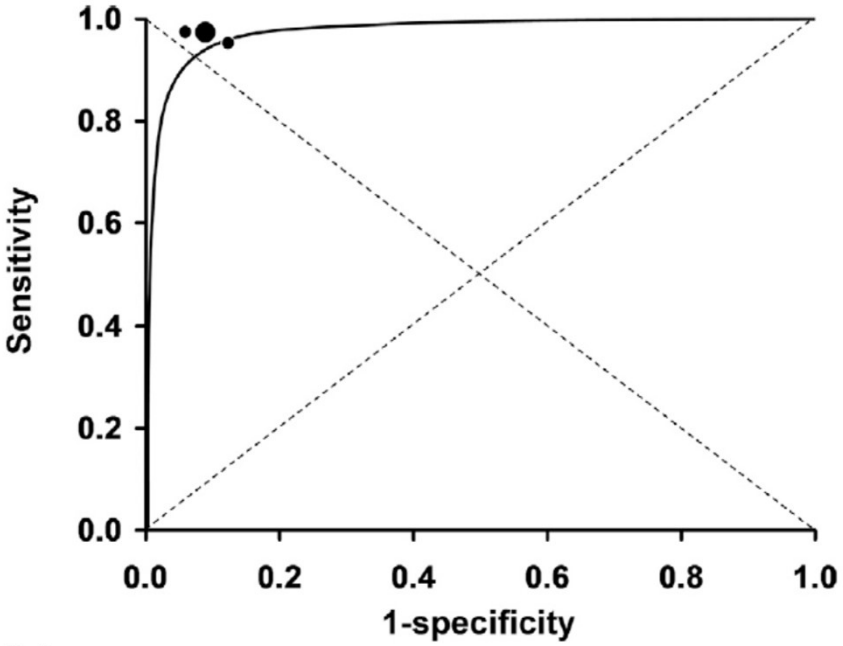



Fig. 5

Summary receiver operator characteristic curve of all included studies that assessed interleukin-6 level as a diagnostic marker for prosthetic joint infection.

- Méta analyse de 30 études (3909 interventions)
- 2 reviewers indépendants
- Prévalence des IPOA : 32,5%
- Comparaison des marqueurs inflammatoires : CRP, VS, IL6

**J Bone Joint Surg Am.** 2010;92:2102-9 • doi:10.2106/JBJS.I.01199

# Intérêt de la ponction pré opératoitre

- Phillips, *Clin Orthop Related Res* 1983 — PPV = 24%, VPN>90%
- Barrack, *JBJS* 1993 — PPV = 6% (58% SCN)
- Duff, *Clin Orthop Related Res* 1996 : — PPV = 100% ; VPN>90%
- Spangehl, *JBJS* 1999 : — PPV = 67% (77% si répétée)
- Somme, *JBS* 2003 : — PPV = 100% ; VPN = 85%

Eric Senneville (Tourcoing)

# Ponction articulaire

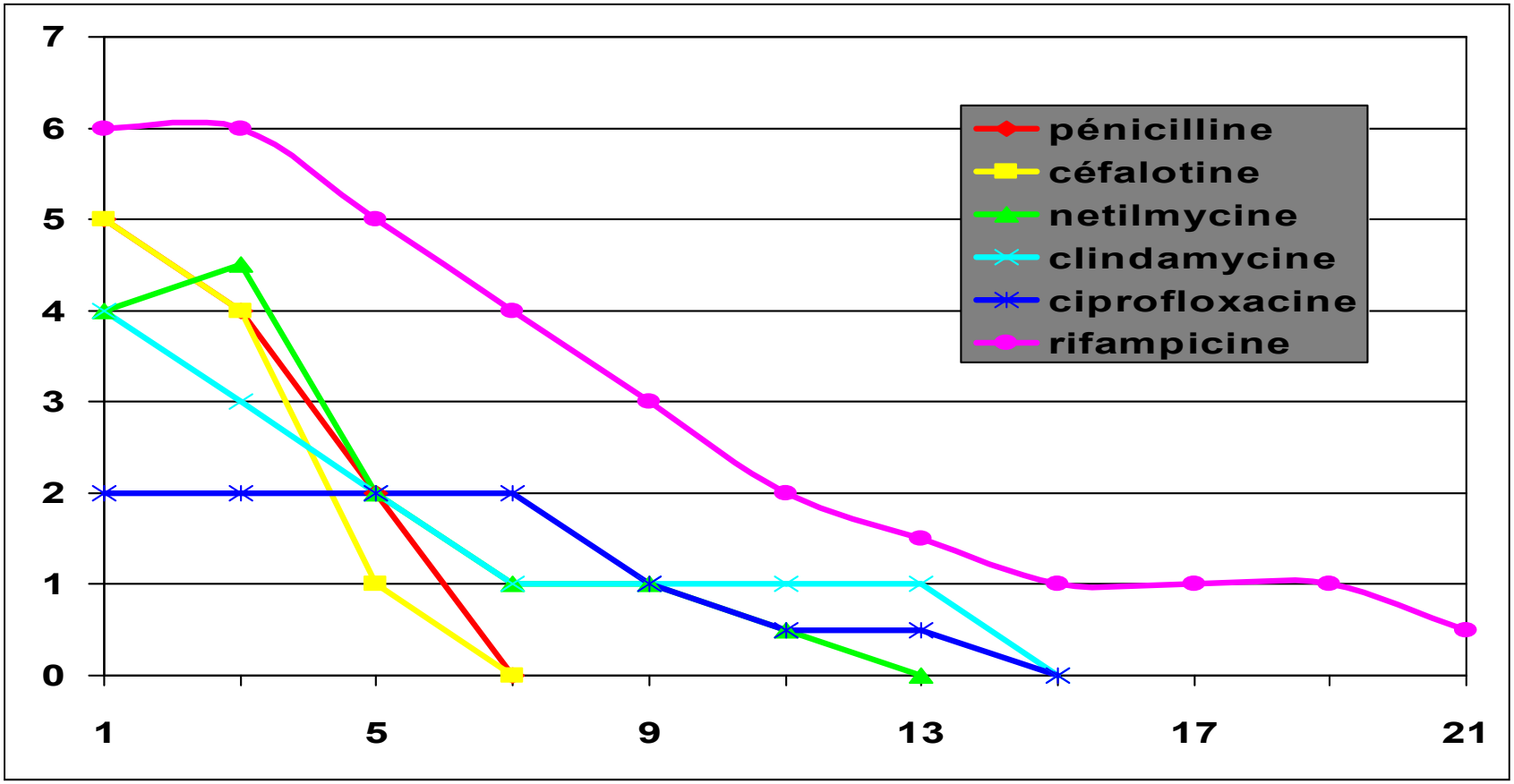
- Se 56-75% ; Spe 95-100%
- Passage en peau saine
- Nécessité
  - Asepsie chirurgicale
  - Pas d'ATB préalable (fenêtre >15j)
- Intérêt d'ensemencement flacon d'hémoculture ?
- A répéter en cas d'identification de germe potentiellement contaminant ?

Trampuz NEJM 2007 ; Fink JBJS 2008 ; Virolainen Scand J Surg 2002 ; Hugues JCM 2001

# Gold Standard = Per opératoire

# «Fenêtre» antibiotique avant biopsie osseuse

## (infection chronique)




Witso et al. *Acta Orthop Scand,* 1999

# Nombre de prélèvements positifs

| N positive specimens | Histology + | Histology - | PPV (%)* |
|---|---|---|---|
| ≥ 3 | 27 | 1 | 96,4** |
| | 19 | 1 | 95 *** |
| 2 | 2 | 6 | 25,2 |
| 1 | 5 | 42 | 10,6 |

* : compared with histology (> 5 PMN/HPF)
** : whatever the microorganism
*** : for CNS

*Atkins et al.JCM 1998*

# Techniques bactériologiques

- L'examen **direct** est semi-quantitatif avec
  - coloration de May-Grünwald Giemsa>> évalue la réponse inflammatoire,
  - Coloration de Gram >> visualise les bactéries présentes.
- Puis **broyage** des échantillons et **culture** en milieux solides et liquides,
- En atmosphère aérobie et anaérobie,
- Puis au **repiquage** des milieux liquides sur milieux solides à J10.
- Une partie congelée à – 80 °C pour une éventuelle analyse par **biologie moléculaire**.

# Culture prolongée nécessaire

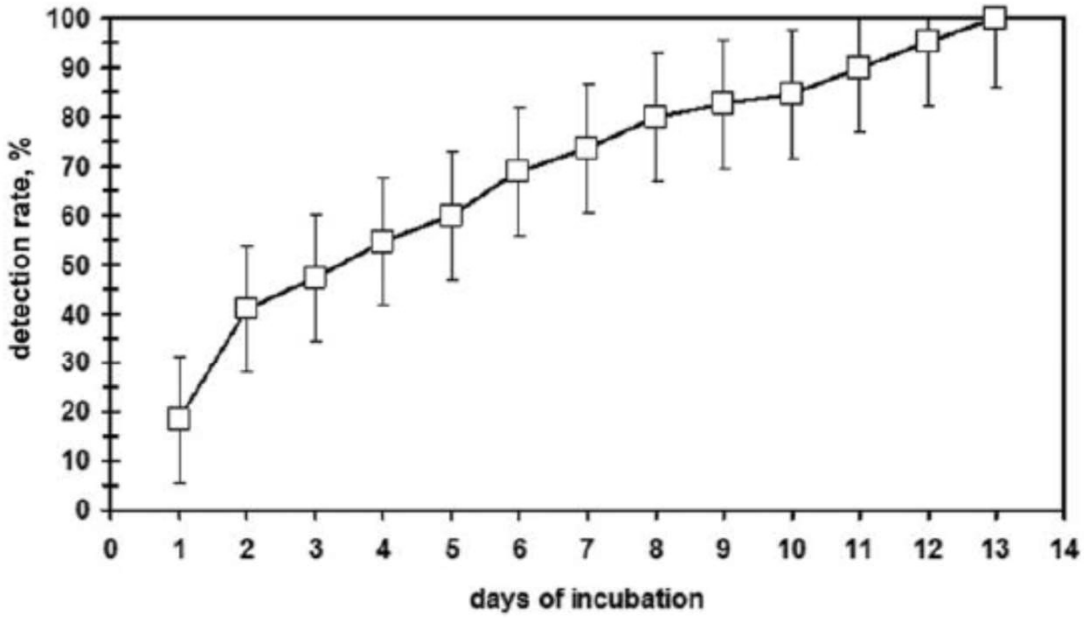
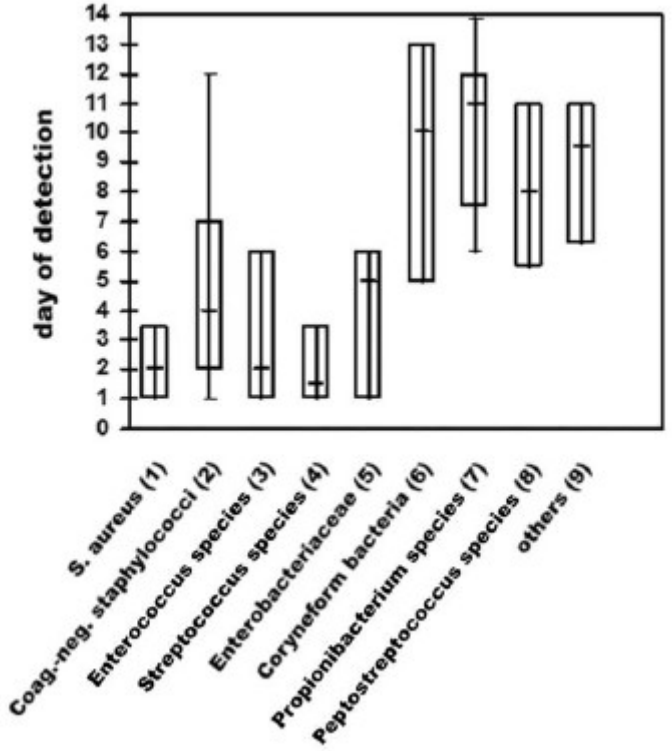



**Figure 1.** Time to diagnosis of infection by culture. Whisker lines span the 95% Hall-Wellner CI.




Schäfer et al CID 2008

# Sonication de matériel

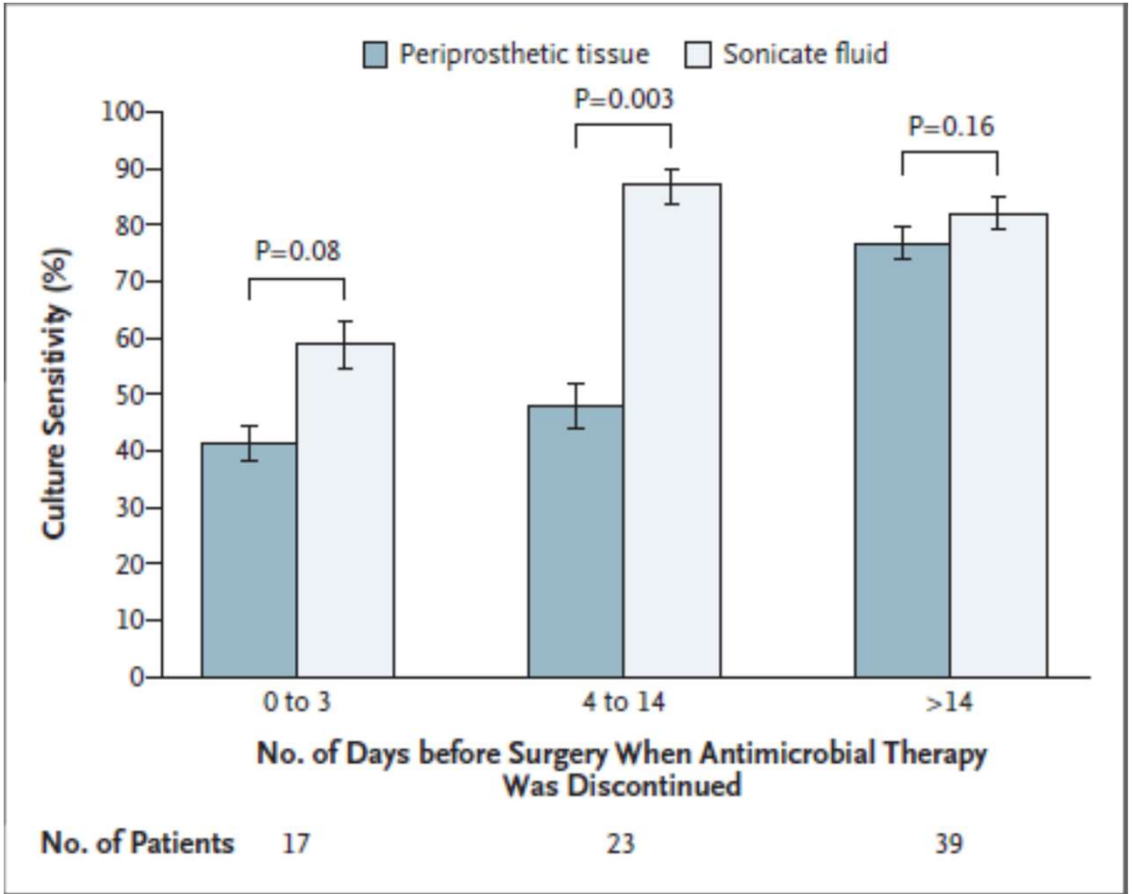



**Figure 2.** Effect of Preoperative Antimicrobial Therapy on Culture Sensitivity in Patients with Prosthetic-Joint Infection.

Mais :

- non applicable en pré opératoire
- pas applicable en cas de maintient de l'implant
- 1 seul résultat >> problème des contaminants

Trampuz, NEJM 2007

# Detection of Prosthetic Hip Infection at Revision Arthroplasty by Immunofluorescence Microscopy and PCR Amplification of the Bacterial 16S rRNA Gene

MICHAEL M. TUNNEY,[1] SHEILA PATRICK,[1]* MARTIN D. CURRAN,[3] GORDON RAMAGE,[1] DONNA HANNA,[1] JAMES R. NIXON,[4] SEAN P. GORMAN,[2] RICHARD I. DAVIS,[5] AND NEIL ANDERSON[5]

TABLE 1. Comparison of the detection rates of prosthetic hip infection by different methods

| Method of detection | No. of samples | No. of positive samples | % Positive samples |
|---|---|---|---|
| Culture of tissue only | 120 | 5 | 4 |
| Culture of tissue and implants[a] | 120 | 26 | 22 |
| Immunofluorescence microscopy | 113 | 71 | 63 |
| 16S rRNA gene amplification | 118 | 85 | 72 |
| Inflammatory cell infiltration | 81 | 59[b] | 73 |

JOURNAL OF CLINICAL MICROBIOLOGY, Oct. 1999, p. 3281–3290
0095-1137/99/$04.00+0

Research article

Open Access

# Identification of bacteria on the surface of clinically infected and non-infected prosthetic hip joints removed during revision arthroplasties by 16S rRNA gene sequencing and by microbiological culture

Kate E Dempsey[1], Marcello P Riggio[1], Alan Lennon[1], Victoria E Hannah[1], Gordon Ramage[1], David Allan[2] and Jeremy Bagg[1]

**Table 1**

**Clinical details of the 10 patients studied**

| Patient no. | Sex | Age | CRP (mg/l) | ESR (mm/h) | Hb (g/l) | WCC ($\times 10^9$ g/l) | Clinical diagnosis | Bacteriology results | Duration prosthesis in place (months) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 73 | < 5 | 10 | 117 | 6.1 | Aseptic loosening | No growth | 178 |
| 2 | M | 69 | < 3 | ND | 150 | 6.5 | Aseptic loosening | No growth | 48 |
| 3 | M | 61 | 61 | 49 | 130 | 10.6 | Infected | Coagulase-negative *Staphylococcus* (CF, AM, FM) | 5 |
| 4 | F | 56 | 36 | ND | 134 | 6.9 | Aseptic loosening | No growth | 79 |
| 5 | M | 65 | 36 | 14 | 142 | 6.7 | Infected | No growth | 55 |
| 6 | F | 66 | < 10 | 14 | 148 | 7.7 | Infected | Coagulase-negative *Staphylococcus* (CF, AM, FM) | n.d. |
| 7 | F | 49 | 45 | 60 | 120 | 8.8 | Infected | *Proteus mirabilis* (AM, FM) | n.d. |
| 8 | M | 59 | 60 | 30 | 169 | 4.2 | Aseptic loosening | No growth | 120 |
| 9 | M | 62 | ND | ND | 119 | 3.9 | Aseptic loosening | No growth | n.d. |
| 10 | M | 57 | 131 | ND | 106 | 10.7 | Infected | No growth | n.d. |

**Bacterial genera/groups identified by 16S rRNA gene sequencing of clones from 10 prosthetic hip joints**

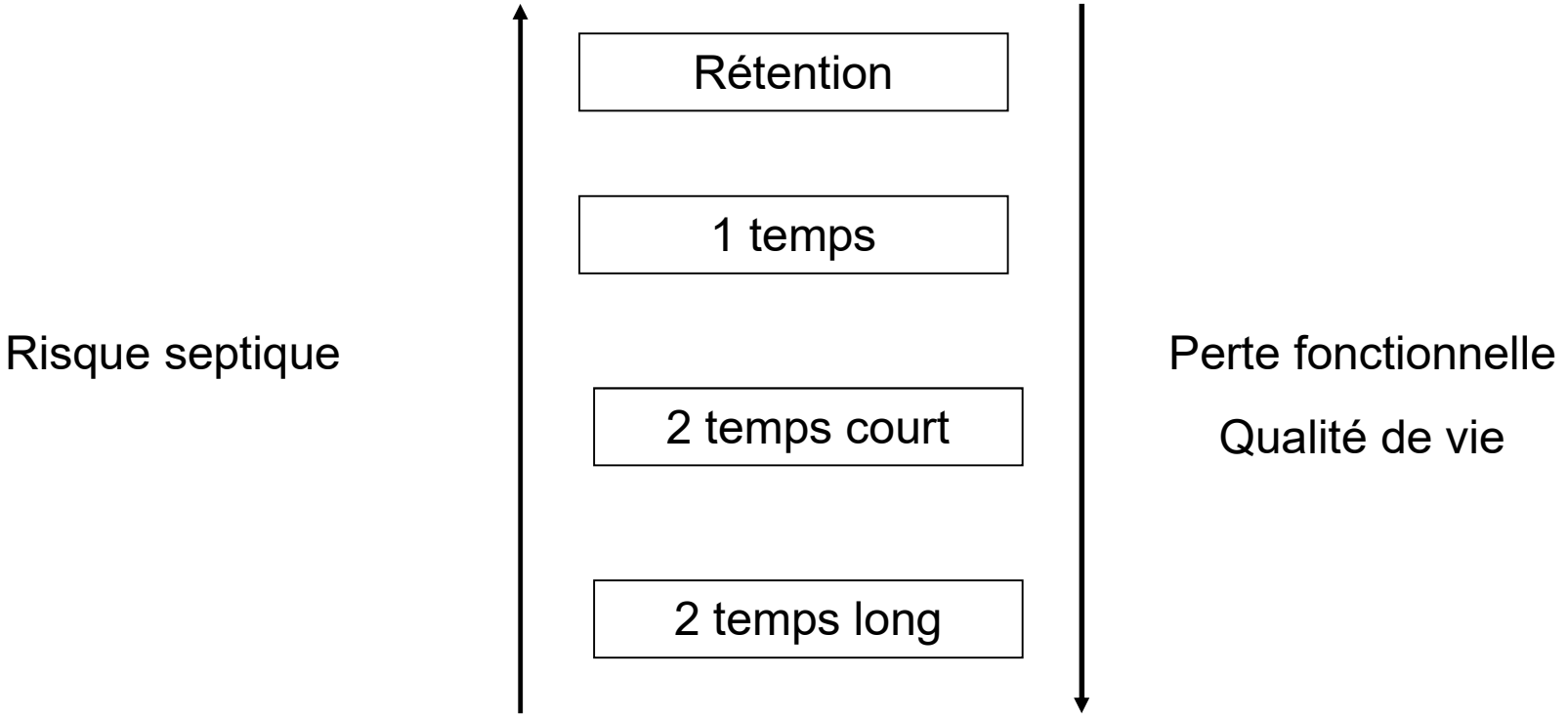
| Genus | Number of clones analysed (percentage) | Number of clones sequenced (percentag |
|---|---|---|
| *Lysobacter* | 312 (60.9) | 52 (44.1) |
| Gamma proteobacterium | 41 (8.0) | 8 (6.8) |
| *Stenotrophomonas* | 34 (6.6) | 9 (7.6) |
| *Methylobacterium* | 24 (4.7) | 5 (4.2) |
| *Staphylococcus* | 24 (4.7) | 5 (4.2) |
| Various bacterial clones | 23 (4.5) | 10 (8.5) |
| *Proteus* | 18 (3.5) | 5 (4.2) |
| *Bradyrhizobium* | 11 (2.1) | 4 (3.4) |
| *Bacteroides* | 6 (1.2) | 3 (2.5) |
| Hydrothermal vent eubacterium | 6 (1.2) | 6 (5.1) |
| Iron-oxidising lithotroph ES-1 | 5 (1.0) | 5 (4.2) |
| Methylobacteriaceae[a] | 4 (0.8) | 2 (1.7) |
| *Acidobacteria* | 1 (0.2) | 1 (0.8) |
| *Eubacterium* | 1 (0.2) | 1 (0.8) |
| Endophytic bacterium | 1 (0.2) | 1 (0.8) |
| *Xylella* | 1 (0.2) | 1 (0.8) |

*Arthritis Research & Therapy* 2007, **9**:R46 (doi:10.1186/ar2201)

# Chirurgie

# Thérapeutique

- D'un point de vue microbiologique il convient de privilégier un changement en 2 temps (long ?)
- Nécessité d'un projet global pour les patients âgés avec en objectif principal la préservation du statut fonctionnel et de l'autonomie.




Young MH. *Drugs aging* 2008

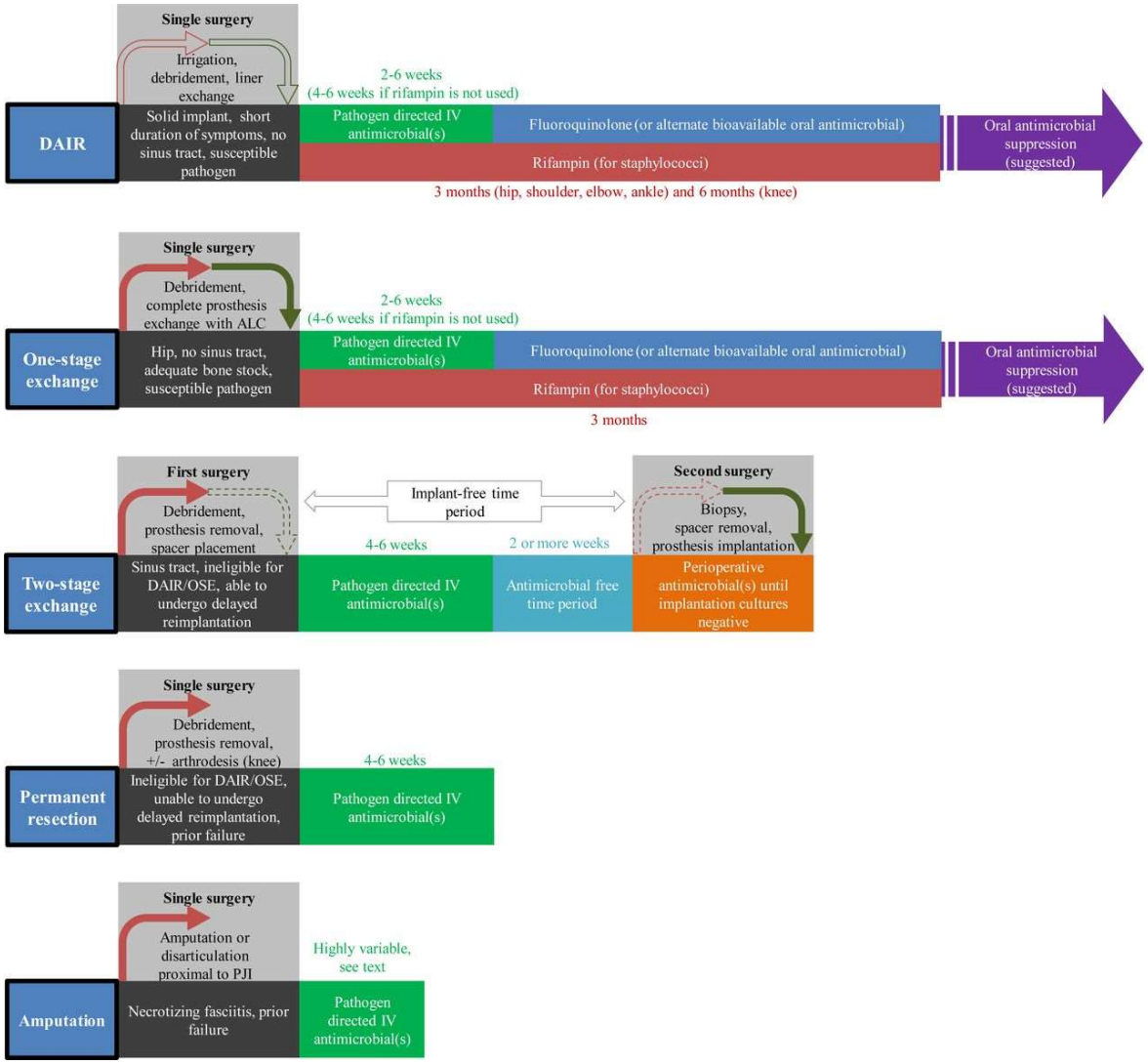
# Peser les arguments

Maintient du matériel

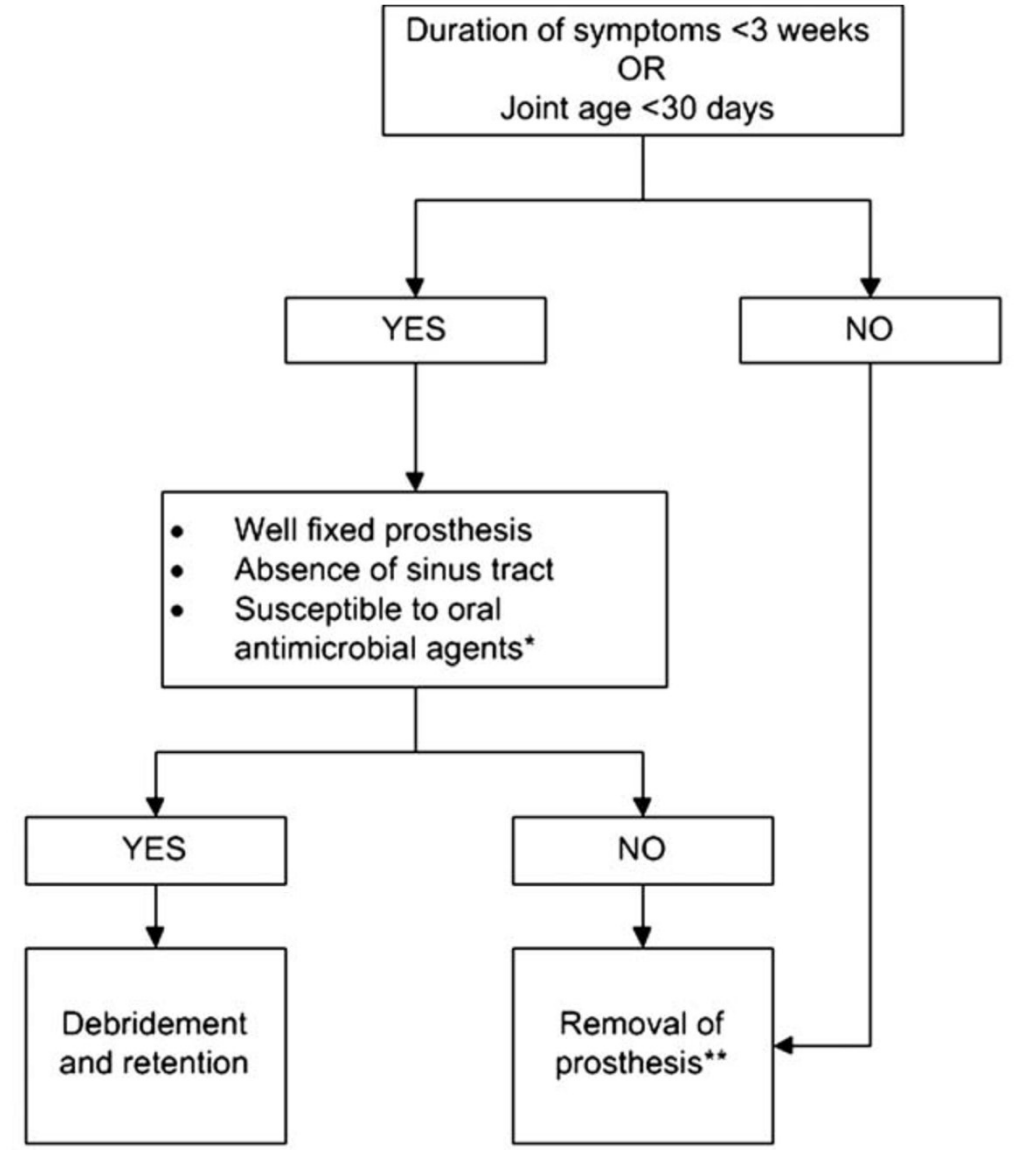
- Matériel récent
- Sujet âgé, comorbidités sévères
- Apparition récente des symptômes
- Peu d'expression clinique de l'infection
- Staphylocoque coagulase négatif en cause

Ablation du matériel

- Pose ancienne du matériel
- Sujet jeune, peu d'ATCD
- Durée d'évolution des symptômes
- État septique sévère
- Staphylocoque doré responsable
- Résistance à un traitement médical bien conduit


Single surgery
Irrigation, debridement, liner exchange
DAIR
Solid implant, short duration of symptoms, no sinus tract, susceptible pathogen
2-6 weeks
(4-6 weeks if rifampin is not used)
Pathogen directed IV antimicrobial(s)
Fluoroquinolone (or alternate bioavailable oral antimicrobial)
Rifampin (for staphylococci)
Oral antimicrobial suppression (suggested)
3 months (hip, shoulder, elbow, ankle) and 6 months (knee)
Single surgery
Debridement, complete prosthesis exchange with ALC
One-stage exchange
Hip, no sinus tract, adequate bone stock, susceptible pathogen
2-6 weeks
(4-6 weeks if rifampin is not used)
Pathogen directed IV antimicrobial(s)
Fluoroquinolone (or alternate bioavailable oral antimicrobial)
Rifampin (for staphylococci)
Oral antimicrobial suppression (suggested)
3 months
First surgery
Debridement, prosthesis removal, spacer placement
Implant-free time period
Second surgery
Biopsy, spacer removal, prosthesis implantation
Two-stage exchange
Sinus tract, ineligible for DAIR/OSE, able to undergo delayed reimplantation
4-6 weeks
Pathogen directed IV antimicrobial(s)
2 or more weeks
Antimicrobial free time period
Perioperative antimicrobial(s) until implantation cultures negative
Single surgery
Debridement, prosthesis removal, +/- arthrodesis (knee)
Permanent resection
Ineligible for DAIR/OSE, unable to undergo delayed reimplantation, prior failure
4-6 weeks
Pathogen directed IV antimicrobial(s)
Single surgery
Amputation or disarticulation proximal to PJI
Amputation
Necrotizing fasciitis, prior failure
Highly variable, see text
Pathogen directed IV antimicrobial(s)

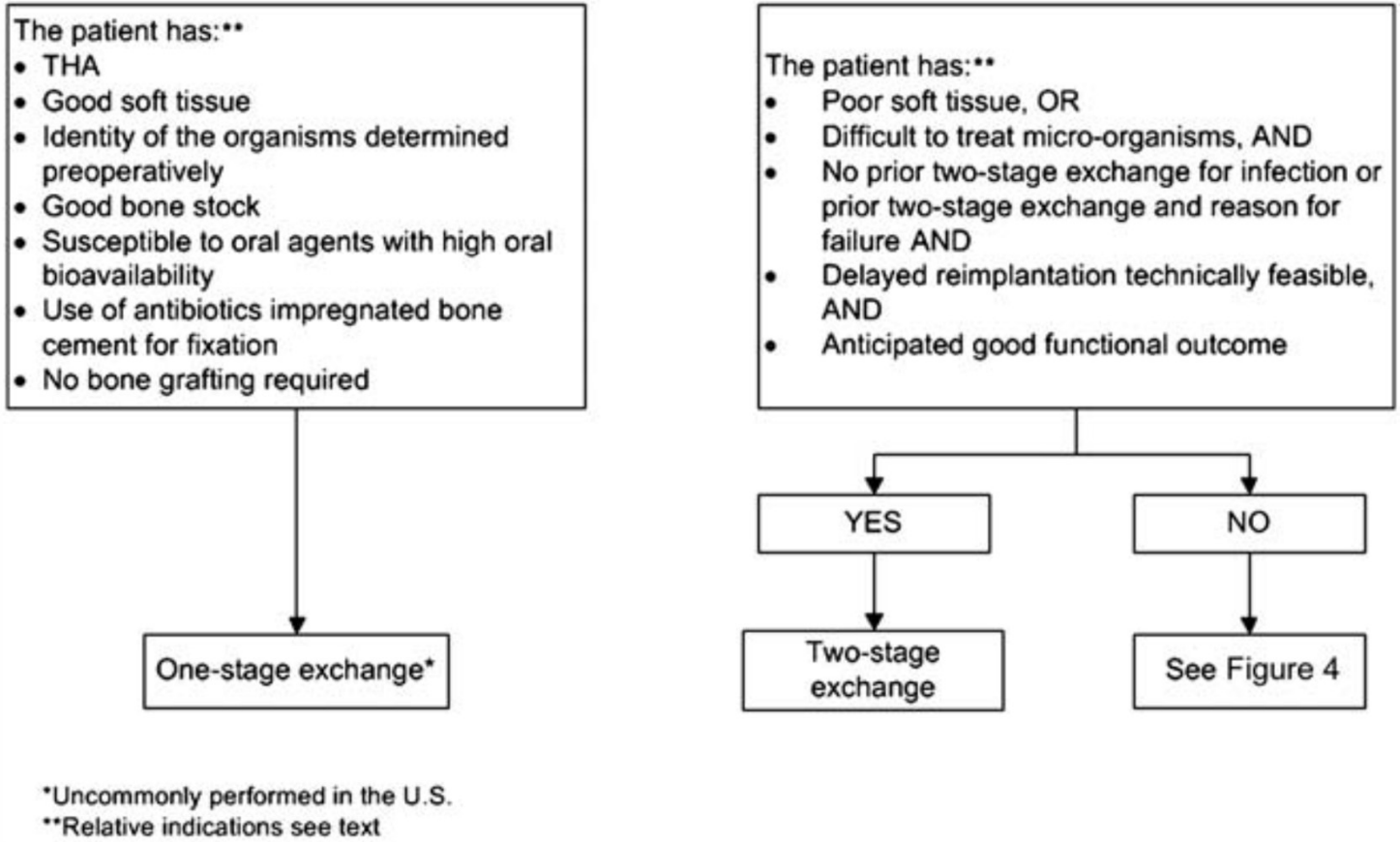
# Management of PJI




IDSA 2013

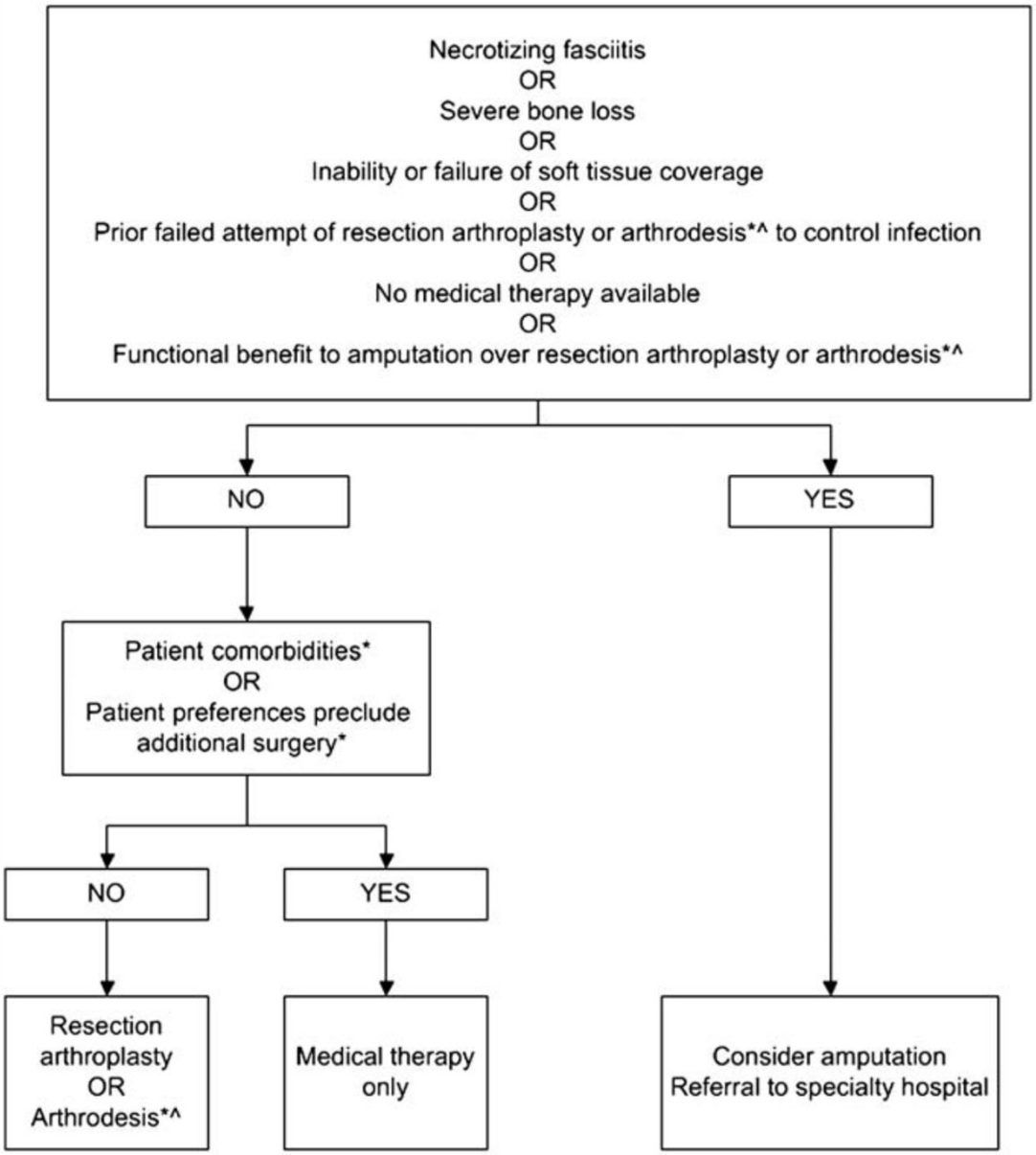
*Antimicrobial agents that are recommended for prolonged use for chronic suppression or treatment of biofilm bacteria (see text for details)
**See Figure 3 and recommendation 18 and accompanying Evidence Summary for possible exceptions

# Changement en 1 temps vs 2 temps




IDSA 2013

# Traitement non conservateur




IDSA 2013

# Antibiothérapie

# Antibioprophylaxie ?

Risque : décapiter les prlvts per op

vs

Bénéfice : Eviter la surinfection

Clin Orthop Relat Res (2010) 468:127–134
DOI 10.1007/s11999-009-1014-4

SYMPOSIUM: PAPERS PRESENTED AT THE ANNUAL MEETINGS OF THE KNEE SOCIETY

# Prophylactic Antibiotics Do Not Affect Cultures in the Treatment of an Infected TKA

A Pro
R. Step

Etude prospective

25 patients 26 infections genou

Recommandation 19

| | |
|---|---|
| AE | L'absence de niveau de preuve suffisant et de consensus sur l'opportunité et les modalités d'une antibioprophylaxie chirurgicale pour éviter une nouvelle infection à un nouveau germe ne permet pas de statuer sur le recours à une antibioprophylaxie chirurgicale lors de la reprise. |

35% *Staph aureus*

Identification per op identique

wheth
would
tively
know
antibi
perfor

aoperatively.
nic (19), and
ion infecting
occus aureus
ic antibiotics
tures and we

nous antibiotic prophylaxis was then administered and the tourniquet inflated. Intraoperative culture swabs and tissue

therefore believe should not be withheld before surgery for an infected TKA when an organism has been identified on aspiration preoperatively, and there has been no recent

# Principe de l'ATB post op

- Après le geste chirurgical : but de l'antibiothérapie initiale : diminuer le plus rapidement l'inoculum bactérien résiduel.
- Antibiothérapie
  - forte dose,
  - IV pour des raisons de tolérance et de biodisponibilité
- Antibiothérapie initiale :
  - probabiliste,
  - adaptée après quelques jours (combien ?).
- Antibiothérapie probabiliste la plus fréquente : glycopeptides+ C3G ou uréidopénicilline
- Avec l'antibiogramme : antibiothérapie prolongée (orale ou parentérale) selon les molécules utilisables et les antécédents du patient.

# Antibiothérapie post opératoire immédiate

**Bénéfice attendu :**

Efficacité immédiate >> ne pas avoir de retard par rapport au geste chirurgical

vs

**Risque :**

Exposition inutile (émergence de résistance, tolérance etc…)

# Outcome and Predictors of Treatment Failure in Total Hip/Knee Prosthetic Joint Infections Due to *Staphylococcus aureus*

**Eric Senneville, Donatienne Joulie, Laurence Legout, Michel Valette, Hervé Dezèque, Eric Beltrand, Bernadette Roselé, Thibaud d'Escrivan, Caroline Loïez, Michèle Caillaux, Yazdan Yazdanpanah, Carlos Maynou, and Henri Migaud**

Centre National de Référence des Infections Ostéo-Articulaires Nord-Ouest, Roger Salengro Faculty Hospital of Lille, Lille, France

***Bac*** ...(PJIs) due to *Staj*

***Met*** ...due to *S. aureus* ...infection assesse

***Resi*** ...ts were in remiss... ...removal. Methic... ...ared with methic... ...ibited no acquired resistance to antibiotics used as definitive therapy, in particular rifampin. In univariate analysis, parameters that differed between patients whose treatment did or did not fail were: American Society of Anesthesiologists (ASA) score, prescription of adequate empirical postsurgical antibiotic therapy, and use of rifampin combination therapy upon discharge from hospital. In multivariate analysis, ASA score ≤2 (odds ratio [OR], 6.87 [95% confidence interval {CI}, 1.45–32.45]; $P = .04$) and rifampin-fluoroquinolone combination therapy (OR, 0.40 [95% CI, 0.17–0.97]; $P = .01$) were 2 independent variables associated with remission.

***Conclusions.*** The results of the present study suggest that the ASA score significantly affects the outcome of patients treated for total hip and knee prosthetic infections due to MSSA or MRSA and that rifampin combination therapy is associated with a better outcome for these patients when compared with other antibiotic regimens.

Etude rétrospective 98 patients

Infection prothèse genou et hanche à *Staph aureus*

Suivi moyen 4 ans

FDR d'échec (univarié): ATB post opératoire non adaptée

- Si pas de documentation pré opératoire (ponction ?)
- Cibler (« tout ») : Staph doré, strepto, entérocoque, entérobactérie.
- Tenir compte écologie du service
- AG si choc septique

**Recommandation 20**

| | |
|---|---|
| AE | Il est recommandé de prescrire : vancomycine et pipéracilline-tazobactam ou vancomycine et céphalosporine de 3e génération (ceftriaxone ou cefotaxime) en attendant l'identification microbiologique. |

# Antibiothérapie probabiliste

Tableau 1. Proposition de traitement antibiotique probabiliste

| ATB | Doses |
|---|---|
| Vancomycine* | 1 000 mg IVL en 1 h (1 250 mg en 1 h - 1 h 30 si poids 80-100 kg ; 1 500 mg si poids > 100 kg)/12 h<br>Réaliser un dosage du taux résiduel à la 72e heure si le traitement est poursuivi pour adapter la dose (objectif de taux résiduel à 20-30 mg/L) |
| Pipéracilline-tazobactam | 4 g IVL/8 h (toutes les 6 h si poids >100 kg) |
| Cefotaxime | 2 g IVL/8 h (3 g/8 h si poids 70-100 kg ; 3 g/6 h si poids > 100 kg) |
| Ceftriaxone | 2 g IVL/24 h (1,5 g/12 h si poids 70-100 kg ; 2 g/12 h si poids > 100 kg) |

**Daptomycine ?** Pas d'AMM
Infection précoce
Dépend du geste chirurgical/des intolérances/ comorbidité du patient
Mais bactéricidie rapide/efficacité immédiate
Pas de perte de chance si SAMS
Risque : émergence de R si monothérapie prolongée

# Antibiothérapie probabiliste

# Outcome and Predictors of Treatment Failure in Total Hip/Knee Prosthetic Joint Infections Due to *Staphylococcus aureus*

**Eric Senneville, Donatienne Joulie, Laurence Legout, Michel Valette, Hervé Dezèque, Eric Beltrand, Bernadette Roselé, Thibaud d'Escrivan, Caroline Loïez, Michèle Caillaux, Yazdan Yazdanpanah, Carlos Maynou, and Henri Migaud**

Centre National de Référence des Infections Ostéo-Articulaires Nord-Ouest, Roger Salengro Faculty Hospital of Lille, Lille, France

- Etude rétrospective 98 patients
- Infection prothèse genou et hanche à Staph aureus
- Suivi moyen 4 ans
- FDR d'échec (univarié): ATB post opératoire non adaptée

***Background.*** Variables associated with the outcome of patients treated for prosthetic joint infections (PJIs) due to *Staphylococcus aureus* are not well known.

***Methods.*** The medical records of patients treated surgically for total hip or knee prosthesis infection due to *S. aureus* were reviewed. Remission was defined by the absence of local or systemic signs of implant-related infection assessed during the most recent contact with the patient.

***Results.*** After a mean posttreatment follow-up period of 43.6 ± 32.1 months, 77 (78.6%) of 98 patients were in remission. Retention of the infected implants was not associated with a worse outcome than was their removal. Methicillin-resistant *S. aureus* (MRSA)–related PJIs were not associated with worse outcome, compared with methicillin-susceptible *S. aureus* (MSSA)–related PJIs. Pathogens identified during revision for failure exhibited no acquired resistance to antibiotics used as definitive therapy, in particular rifampin. In univariate analysis, parameters that differed between patients whose treatment did or did not fail were: American Society of Anesthesiologists (ASA) score, prescription of adequate empirical postsurgical antibiotic therapy, and use of rifampin combination therapy upon discharge from hospital. In multivariate analysis, ASA score ≤2 (odds ratio [OR], 6.87 [95% confidence interval {CI}, 1.45–32.45]; $P = .04$) and rifampin-fluoroquinolone combination therapy (OR, 0.40 [95% CI, 0.17–0.97]; $P = .01$) were 2 independent variables associated with remission.

***Conclusions.*** The results of the present study suggest that the ASA score significantly affects the outcome of patients treated for total hip and knee prosthetic infections due to MSSA or MRSA and that rifampin combination therapy is associated with a better outcome for these patients when compared with other antibiotic regimens.

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- Cibler : Staph doré, strepto, entérocoque, entérobactérie.
- Tenir compte écologie du service

**Recommandation 20**

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|---|---|
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HAS

# Antibiothérapie probabiliste

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| Ceftriaxone | 2 g IVL/24 h (1,5 g/12 h si poids 70-100 kg ; 2 g/12 h si poids > 100 kg) |

# Intérêt des tests rapides

JOURNAL OF CLINICAL MICROBIOLOGY, Dec. 2011, p. 4225–4230 Vol. 49, No. 12
0095-1137/11/$12.00 doi:10.1128/JCM.00334-11


## Direct Detection of *Staphylococcus* Osteoarticular Infections by Use of Xpert MRSA/SA SSTI Real-Time PCR▽

Anne Dubouix-Bourandy,[1]* Aymard de Ladoucette,[2] Valerie Pietri,[1] Nazim Mehdi,[2] David Benzaquen,[2] Régis Guinand,[2] and Jean-Marc Gandois[1]

*Department of Clinical Laboratory[1] and Orthopaedics and Traumatology Department,[2] Clinique de L'Union, Boulevard de Ratalens, 31240 St. Jean, France*

Received 16 February 2011/Returned for modification 29 April 2011/Accepted 23 September 2011

Étude 135 prlvts 105 patients : 46 infections sur prothèse, 3 SDI, 15 arthrites septiques, 33 contrôles

Test Xpert PCR temps réel vs culture

SAMS : sensibilité : 100%/spécificité 98,3%

SAMR : sensibilité : 100% / spécificité 95,3%

Gain de temps : 72min vs 79h

**We evaluate … on periop- erative bone a … ole *Staphy- lococcus aureus* … ant coagu- lase-negative … 5.3%. The median total … id results, appropriate a…**

# Bien choisir ses molécules antibiotiques

- Sensible in vitro
- Bonne diffusion ostéo articulaire
- Bithérapie systématique ?
  - Molécules à risque de mutation
  - Germes particuliers (*Pseudomonas aeruginosa*)
- Forte dose
- Voie parentérale initiale
- RFP si possible sur infection documentée/germe S
- En l'absence de contre indication

# Voie orale possible

- Biodisponibilité bonne
  - **Fluoroquinolones**
  - **Rifampicine**
  - **Clindamycine**
  - **Acide fucidique**
  - **Minocycline**
  - **Linézolide**
- Précautions d'emploi
- Surveillance clinique
- Intérêt dosage sérique antibiotique
- Surveillance interactions médicamenteuses (rifampicine+++)

| | Biodisponibilité orale | Diffusion tissulaire | Choix |
|---|---|---|---|
| B-lactamines | 10-50% | 30% | IV |
| Quinolones | 50-100% | 80% | PO |
| Glycopeptides | 0% | 30% | IV |
| Rifampicine | 80% | 90% | PO |
| Trimetoprime | 80% | 80% | PO |
| Aminosides | 0% | 0-10% | IV |
| Clindamycine | 70-80% ? | 80% | PO |

**Humbert, Clin Pharmacol Ther 1991**

**Nijland, CID 2007**

**Zeller, AAC 2010**

# Durées de traitement

# Durées de traitement

## Antibiotic treatment for 6 weeks versus 12 weeks in patients with pyogenic vertebral osteomyelitis: an open-label, non-inferiority, randomised, controlled trial

*Louis Bernard, Aurélien Dinh, Idir Ghout, David Simo, Valerie Zeller, Bertrand Issartel, Vincent Le Moing, Nadia Belmatoug, Philippe Lesprit, Jean-Pierre Bru, Audrey Therby, Damien Bouhour, Eric Dénes, Alexa Debard, Catherine Chirouze, Karine Fèvre, Michel Dupon, Philippe Aegerter, Denis Mulleman, on behalf of the Duration of Treatment for Spondylodiscitis (DTS) study group**

| | 6-week regimen | 12-week regimen | Difference in proportion of patients* | 95% CI |
|---|---|---|---|---|
| Intention-to-treat analysis, n | 176 | 175 | | |
| Cured | 160 (90·9%) | 159 (90·9%) | +0·1 | −6·2 to 6·3 |
| Cured and alive† | 156 (88·6%) | 150 (85·7%) | +2·9 | −4·2 to 10·1 |
| Cured without further antibiotic treatment‡ | 142 (80·7%) | 141 (80·6%) | +0·1 | −8·3 to 8·5 |
| Per-protocol analysis, n | 146 | 137 | | |
| Cured | 137 (93·8%) | 132 (96·4%) | −2·5 | −8·2 to 2·9 |
| Cured and alive† | 133 (91·1%) | 126 (92·0%) | −0·9 | −7·7 to 6·0 |
| Cured without further antibiotic treatment‡ | NA | NA | NA | NA |

Lancet 2015

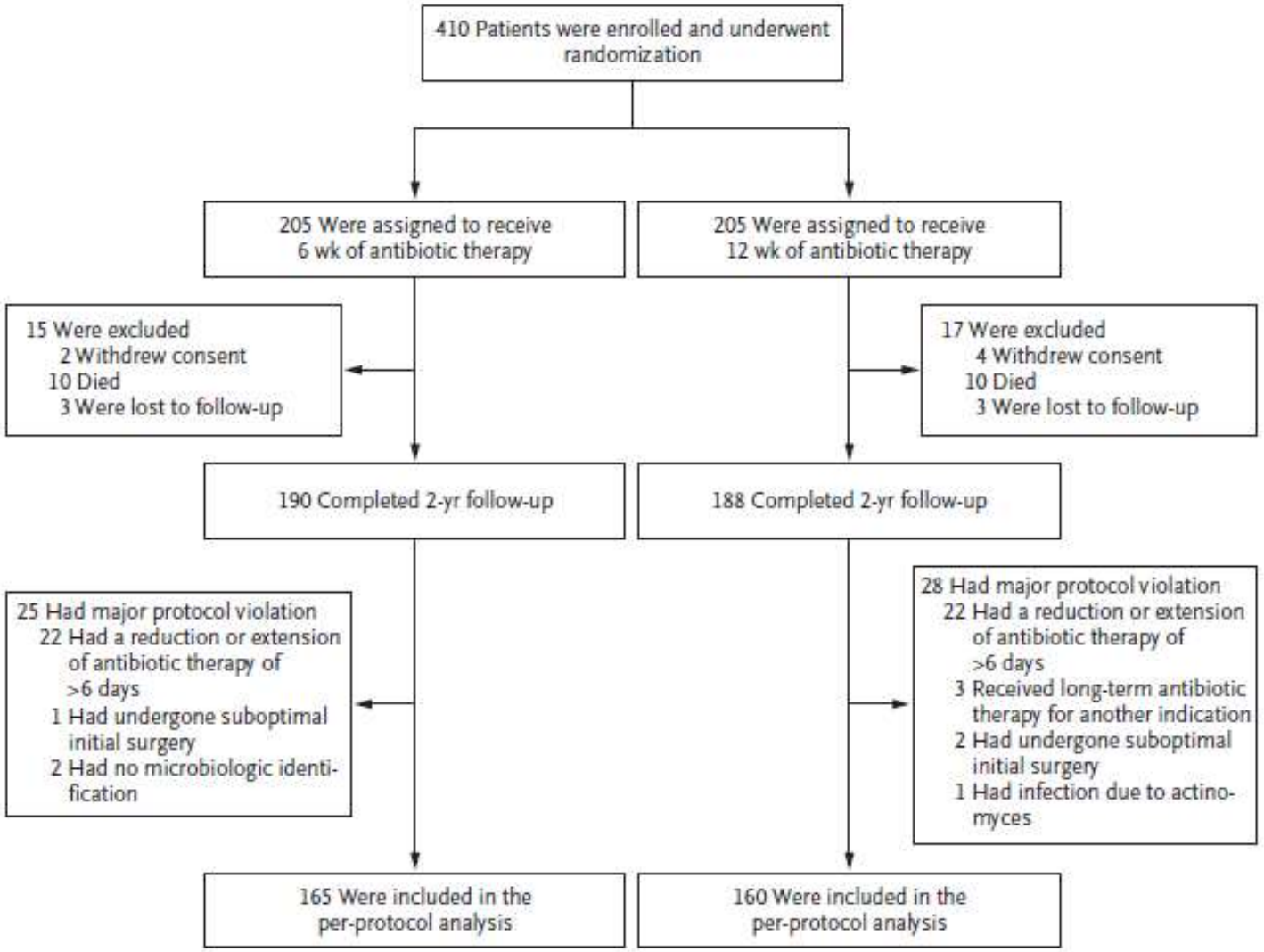
ORIGINAL ARTICLE

## Antibiotic Therapy for 6 or 12 Weeks for Prosthetic Joint Infection

L. Bernard, C. Arvieux, B. Brunschweiler, S. Touchais, S. Ansart, J.-P. Bru, E. Oziol, C. Boeri, G. Gras, J. Druon, P. Rosset, E. Senneville, H. Bentayeb, D. Bouhour, G. Le Moal, J. Michon, H. Aumaître, E. Forestier, J.-M. Laffosse, T. Begué, C. Chirouze, F.-A. Dauchy, E. Devaud, B. Martha, D. Burgot, D. Boutoille, E. Stindel, A. Dinh, P. Bemer, B. Giraudeau, B. Issartel, and A. Caille

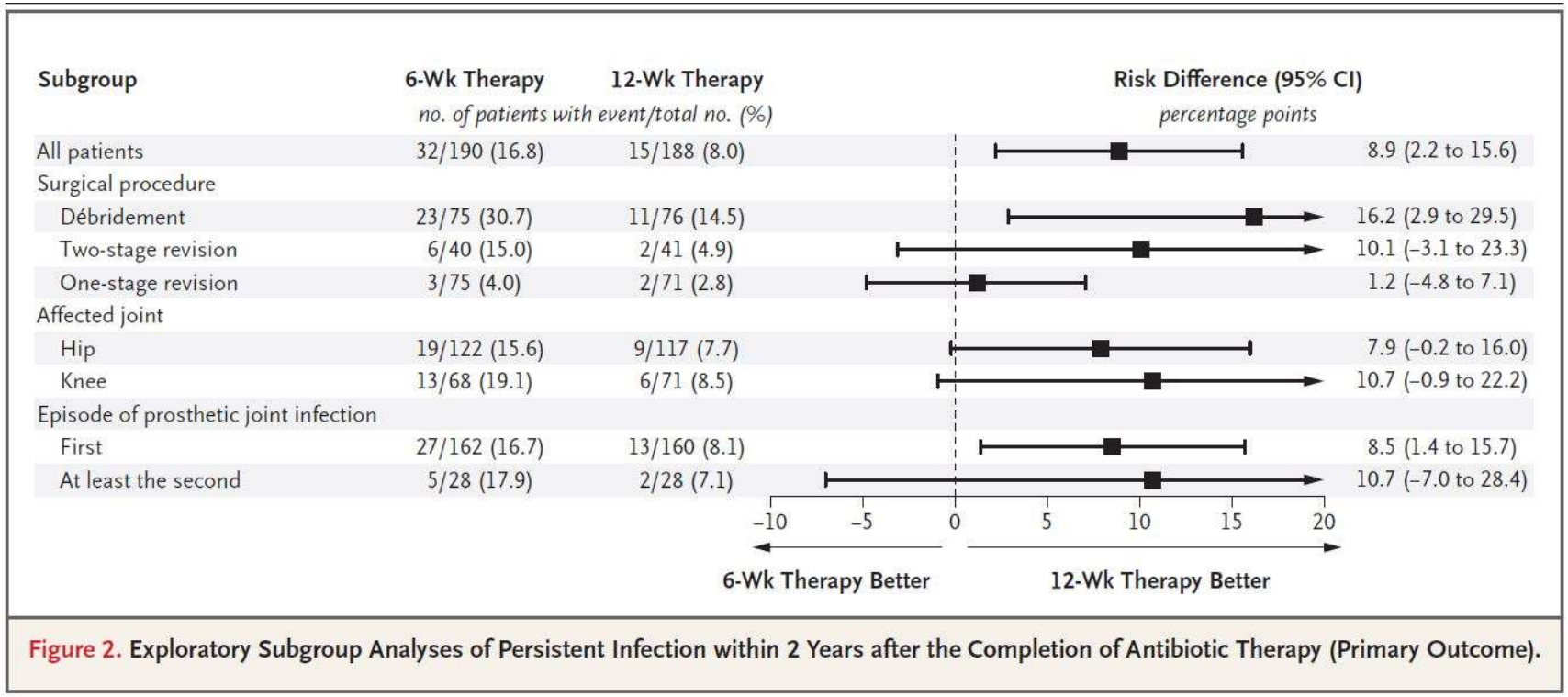
| Analysis | 6-Wk Therapy | 12-Wk Therapy | Risk Difference | Adjusted Risk Difference* |
|---|---|---|---|---|
| | *no. of patients with event/total no. (%)* | | *Percentage points (95% CI)* | |
| **Modified intention-to-treat** | | | | |
| Main analysis in which missing outcomes for patients who were lost to follow-up were considered to be persistent infections and data from patients who died removed† | 35/193 (18.1) | 18/191 (9.4) | 8.7 (1.8–15.6) | 9.0 (2.3–15.7) |
| Sensitivity analyses in which data from patients who were lost to follow-up or died were removed† | | | | |
| Analysis in which all persistent infections were counted | 32/190 (16.8) | 15/188 (8.0) | 8.9 (2.2–15.6) | 9.1 (2.6–15.5) |
| Post hoc analysis in which only persistent infections that were diagnosed after 6 weeks of antibiotic therapy were counted‡ | 29/187 (15.5) | 13/186 (7.0) | 8.5 (2.1–15.1) | 8.8 (2.5–15.0) |
| **Per-protocol§** | | | | |
| Analysis in which all persistent infections were counted | 29/165 (17.6) | 11/160 (6.9) | 10.7 (3.6–17.9) | 10.6 (3.7–17.5) |
| Post hoc analysis in which only persistent infections that were diagnosed after 6 weeks of antibiotic therapy were counted¶ | 27/163 (16.6) | 11/160 (6.9) | 9.7 (2.7–16.8) | 9.7 (2.9–16.5) |

NEJM 2021


410 Patients were enrolled and underwent randomization
205 Were assigned to receive 6 wk of antibiotic therapy
205 Were assigned to receive 12 wk of antibiotic therapy
15 Were excluded
2 Withdrew consent
10 Died
3 Were lost to follow-up
17 Were excluded
4 Withdrew consent
10 Died
3 Were lost to follow-up
190 Completed 2-yr follow-up
188 Completed 2-yr follow-up
25 Had major protocol violation
22 Had a reduction or extension of antibiotic therapy of >6 days
1 Had undergone suboptimal initial surgery
2 Had no microbiologic identification
28 Had major protocol violation
22 Had a reduction or extension of antibiotic therapy of >6 days
3 Received long-term antibiotic therapy for another indication
2 Had undergone suboptimal initial surgery
1 Had infection due to actinomyces
165 Were included in the per-protocol analysis
160 Were included in the per-protocol analysis

| Characteristic | 6-Wk Therapy (N=203) | 12-Wk Therapy (N=201) |
|---|---|---|
| Age — yr† | 68.4±11.7 | 69.5±10.7 |
| Male sex — no./total no. (%) | 143/203 (70.4) | 130/201 (64.7) |
| History of prosthetic joint infection — no./total no. (%)‡ | 30/203 (14.8) | 29/201 (14.4) |
| Baseline surgical procedure — no./total no. (%) | | |
| Débridement with implant retention | 82/203 (40.4) | 85/201 (42.3) |
| One-stage prosthetic joint implant exchange | 77/203 (37.9) | 73/201 (36.3) |
| Two-stage prosthetic joint implant exchange | 44/203 (21.7) | 43/201 (21.4) |
| Affected joint — no./total no. (%) | | |
| Hip | 129/203 (63.5) | 126/201 (62.7) |
| Knee | 74/203 (36.5) | 75/201 (37.3) |
| BMI§ | 29.9±5.8 | 29.9±6.2 |
| Coexisting medical condition — no./total no. (%) | | |
| Obesity§ | 91/192 (47.4) | 78/186 (41.9) |
| ASA score ≥3¶ | 51/178 (28.7) | 60/179 (33.5) |
| Clinical presentation — no./total no. (%) | | |
| Infection after surgery | 68/203 (33.5) | 66/201 (32.8) |
| Acute blood-borne infection | 46/203 (22.7) | 37/201 (18.4) |
| Fever | 83/196 (42.3) | 62/196 (31.6) |
| Fistula | 81/201 (40.3) | 76/192 (39.6) |
| Median time between symptom onset and surgical procedure (IQR) — days‖ | 17 (5–85) | 18 (5–110) |
| CRP level at diagnosis of infection — mg/liter** | 108.4±99.0 | 113.2±100.8 |
| Positive blood culture — no./total no. (%) | 29/203 (14.3) | 23/201 (11.4) |
| Mono-microorganism — no./total no. (%) | 166/203 (81.8) | 170/201 (84.6) |
| Multidrug resistance — no./total no. (%)†† | 17/196 (8.7) | 19/192 (9.9) |
| Pathogens identified — no./total no. (%)‡‡ | | |
| *Staphylococcus aureus* | 90/237 (38.0) | 70/233 (30.0) |
| Coagulase-negative staphylococcus | 70/237 (29.5) | 82/233 (35.2) |
| Streptococcus species | 32/237 (13.5) | 26/233 (11.2) |
| Gram-negative organisms | 21/237 (8.9) | 26/233 (11.2) |
| Other pathogens§§ | 24/237 (10.1) | 29/233 (12.4) |
| Antibiotic treatment | | |
| Median duration of intravenous administration (IQR) — days¶¶ | 9 (5–15) | 9 (5–15) |
| ≥1 Oral antibiotic agent — no./total no. (%)‖‖ | 191/203 (94.1) | 189/201 (94.0) |
| Rifampin | 144/191 (75.4) | 123/189 (65.1) |
| Quinolone | 137/191 (71.7) | 123/189 (65.1) |
| Clindamycin | 35/191 (18.3) | 52/189 (27.5) |
| Trimethoprim–sulfamethoxazole | 22/191 (11.5) | 34/189 (18.0) |
| Amoxicillin with or without clavulanic acid | 19/191 (9.9) | 21/189 (11.1) |

# Durées de traitement : individualisation ?



| Subgroup | 6-Wk Therapy | 12-Wk Therapy | Risk Difference (95% CI) |
|---|---|---|---|
| | *no. of patients with event/total no. (%)* | | *percentage points* |
| All patients | 32/190 (16.8) | 15/188 (8.0) | 8.9 (2.2 to 15.6) |
| Surgical procedure | | | |
| Débridement | 23/75 (30.7) | 11/76 (14.5) | 16.2 (2.9 to 29.5) |
| Two-stage revision | 6/40 (15.0) | 2/41 (4.9) | 10.1 (–3.1 to 23.3) |
| One-stage revision | 3/75 (4.0) | 2/71 (2.8) | 1.2 (–4.8 to 7.1) |
| Affected joint | | | |
| Hip | 19/122 (15.6) | 9/117 (7.7) | 7.9 (–0.2 to 16.0) |
| Knee | 13/68 (19.1) | 6/71 (8.5) | 10.7 (–0.9 to 22.2) |
| Episode of prosthetic joint infection | | | |
| First | 27/162 (16.7) | 13/160 (8.1) | 8.5 (1.4 to 15.7) |
| At least the second | 5/28 (17.9) | 2/28 (7.1) | 10.7 (–7.0 to 28.4) |



**Figure 2.** Exploratory Subgroup Analyses of Persistent Infection within 2 Years after the Completion of Antibiotic Therapy (Primary Outcome).

# Relais per os

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Oral versus Intravenous Antibiotics for Bone and Joint Infection

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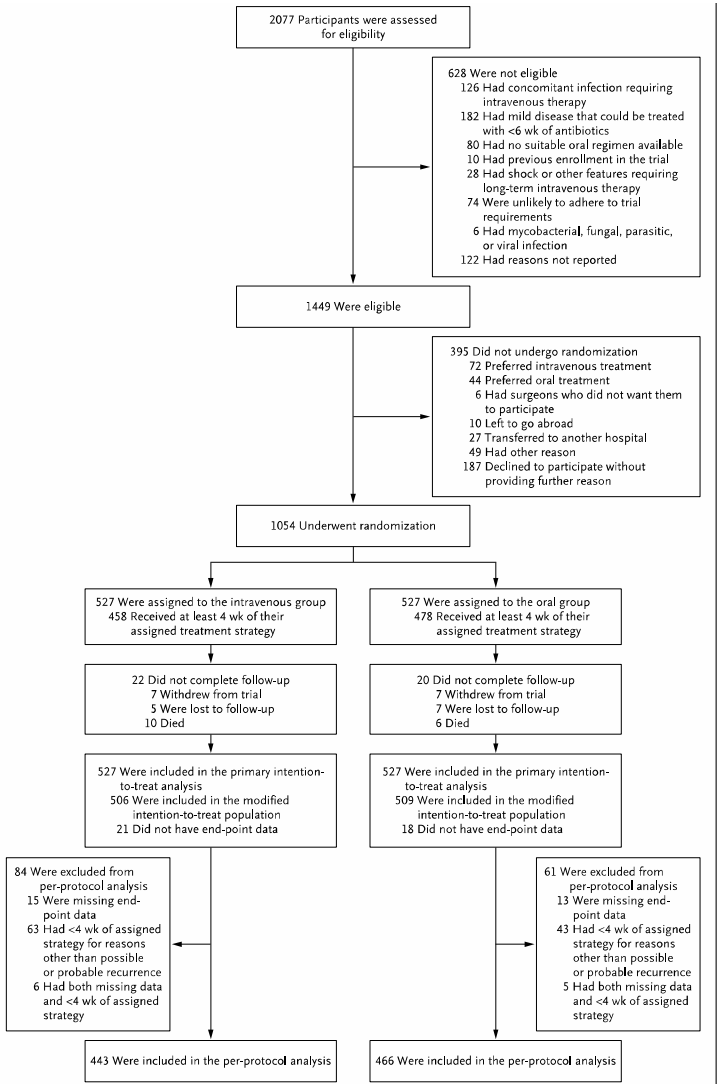

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| Characteristic | Intravenous Group (N=527) | Oral Group (N=527) | Total (N=1054) |
|---|---|---|---|
| Age — yr | | | |
| Median (interquartile range) | 61 (49–70) | 60 (49–70) | 60 (49–70) |
| Range | 18–92 | 18–91 | 18–92 |
| Male sex — no. (%) | 320 (60.7) | 358 (67.9) | 678 (64.3) |
| Baseline surgical procedure — no. (%) | | | |
| No implant or device present; débridement of chronic osteomyelitis performed | 153 (29.0) | 169 (32.1) | 322 (30.6) |
| No implant or device present; débridement of chronic osteomyelitis not performed | 25 (4.7) | 29 (5.5) | 54 (5.1) |
| Débridement and implant retention | 124 (23.5) | 123 (23.3) | 247 (23.4) |
| Removal of orthopedic device for infection | 89 (16.9) | 78 (14.8) | 167 (15.8) |
| Prosthetic joint implant removed | 68 (12.9) | 67 (12.7) | 135 (12.8) |
| Prosthetic joint implant, one-stage revision | 47 (8.9) | 43 (8.2) | 90 (8.5) |
| Surgery for diskitis, spinal osteomyelitis, or epidural abscess; débridement performed | 8 (1.5) | 5 (0.9) | 13 (1.2) |
| Surgery for diskitis, spinal osteomyelitis, or epidural abscess; débridement not performed | 13 (2.5) | 13 (2.5) | 26 (2.5) |
| Deep-tissue histologic result — no. (%) | | | |
| Infected | 266 (50.5) | 277 (52.6) | 543 (51.5) |
| Equivocal | 13 (2.5) | 17 (3.2) | 30 (2.8) |
| Uninfected | 31 (5.9) | 32 (6.1) | 63 (6.0) |
| Not done or missing† | 217 (41.2) | 201 (38.1) | 418 (39.7) |
| Microbiologic diagnostic sampling — no. (%) | | | |
| Two or more samples positive for same organism | 357 (67.7) | 338 (64.1) | 695 (65.9) |
| Two or more samples taken but only one positive for a given pathogenic organism | 20 (3.8) | 32 (6.1) | 52 (4.9) |
| Only one sample taken, which was found to be positive for a pathogenic organism by closed biopsy | 25 (4.7) | 30 (5.7) | 55 (5.2) |
| Two or more samples taken but only one positive for a given nonpathogenic organism | 21 (4.0) | 25 (4.7) | 46 (4.4) |
| Sampling undertaken but no organisms identified | 77 (14.6) | 78 (14.8) | 155 (14.7) |
| Not done or missing‡ | 27 (5.1) | 24 (4.6) | 51 (4.8) |
| Organisms identified — no./total no. (%)§ | | | |
| *Staphylococcus aureus* | 196/500 (39.2) | 182/503 (36.2) | 378/1003 (37.7) |
| Coagulase-negative staphylococcus | 137/500 (27.4) | 135/503 (26.8) | 272/1003 (27.1) |
| Streptococcus species | 72/500 (14.4) | 73/503 (14.5) | 145/1003 (14.5) |
| Pseudomonas species | 28/500 (5.6) | 23/503 (4.6) | 51/1003 (5.1) |
| Other gram-negative organisms | 84/500 (16.8) | 84/503 (16.7) | 168/1003 (16.7) |
| Culture negative | 77/500 (15.4) | 78/503 (15.5) | 155/1003 (15.5) |

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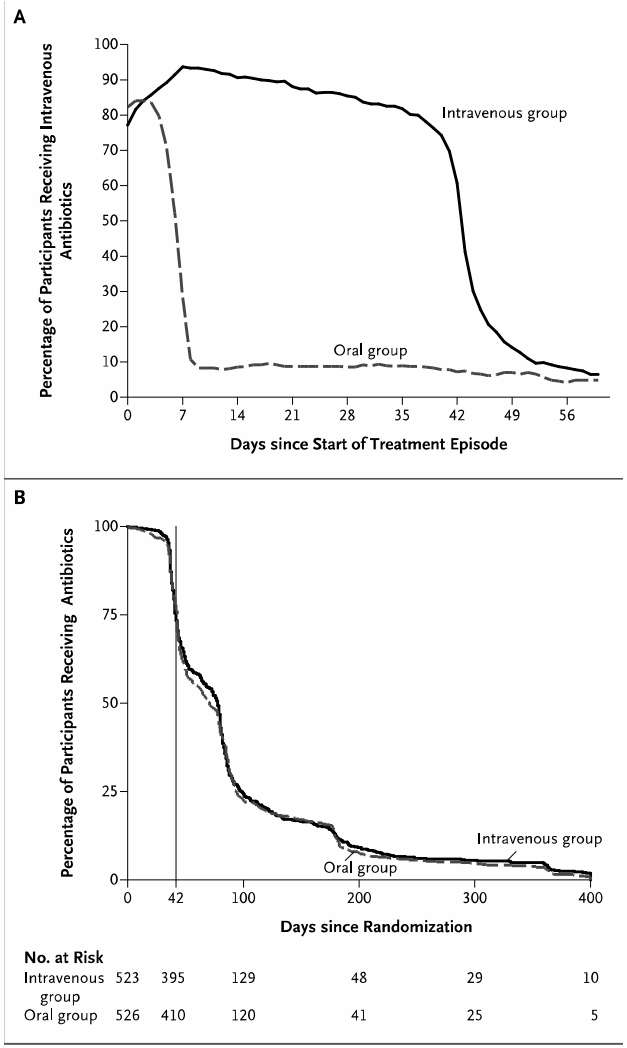

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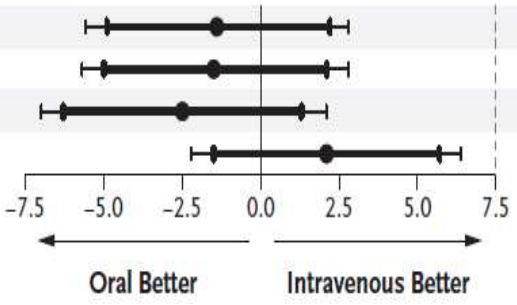
| Subgroup | Oral Group | Intravenous Group | Risk Difference (90% CI; 95% CI) |
|---|---|---|---|
| | *patients with treatment failure/ total no. of participants* | | |
| Intention-to-treat population | 70.0/527 | 77.3/527 | −1.4 (−4.9 to 2.2; −5.6 to 2.9) |
| Modified intention-to-treat population | 67/509 | 74/506 | −1.5 (−5.0 to 2.1; −5.7 to 2.8) |
| Per-protocol population | 61/466 | 69/443 | −2.5 (−6.3 to 1.3; −7.0 to 2.1) |
| Worst-case sensitivity analysis | 85/527 | 74/527 | 2.1 (−1.5 to 5.7; −2.2 to 6.4) |




NEJM 2019

CLINICAL PRACTICE

# Infection Associated with Prosthetic Joints

Jose L. Del Pozo, M.D., Ph.D., and Robin Patel, M.D.

## AREAS OF UNCERTAINTY

Although surgical intervention is generally recommended, the optimal surgical strategy in a given patient remains controversial. Likewise, the optimal antimicrobial regimen and its duration are incompletely defined. The optimal care for patients who are initially thought to have aseptic failure but who have intraoperative culture results that suggest infection is also uncertain; although a variety of medical treatments have been successful, further studies are needed to identify patients who can be treated with oral antimicrobial agents alone and those who may not need medical treatment.[48]

# Recommandations

- **USA** : PTH 3 mois, PTG 6 mois
- **Suisse** (Zimmerli) : PTH 3 mois, PTG 6 mois
- **France** : au moins 6 semaines ; justifier

pour traitement >12 semaines si ostéo

arthrite pas plus de 6 semaines

- **Chez l'enfant** : 3 semaines habituellement

Une étude récente valide 10j d'antibiothérapie

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

Louis Bernard [a,d], Laurence Legout [a], Line Zürcher-Pfund [a], Richard Stern [a], Peter Rohner [b], Robin Peter [a], Mathieu Assal [a], Daniel Lew [c], Pierre Hoffmeyer [a], Ilker Uçkay [a,c,*]

*Results:* A total of 144 PJI (62 hip arthroplasties, 62 knee arthroplasties, and 20 hip hemiarthroplasties) were included with a prolonged follow-up ranging from 26 to 65 months. Surgical treatment included 60 débridements with implant retention, 10 one-stage exchanges of the prosthesis, 57 two-stage exchanges, and 17 Girdlestone procedures or knee arthrodeses. Seventy episodes (49%) received 6 weeks antibiotic therapy and 74 episodes, 12 weeks. Cure was achieved in 115 episodes (80%). Cure rate did not change according to the duration of intravenous antibiotics (>8 days, 8–21 days, >21 days) (Kruskal–Wallis-test; $p = 0.37$). In multivariate analysis, none of the following parameters was statistically significantly associated with cure: two-stage exchange (odds ratio 1.1,95%CI 0.2–4.8); number of débridements (0.9, 0.4–1.9); six weeks antibiotherapy (2.7, 0.96–8.3); duration of intravenous course (1.0, 0.96–1.03); sinus tract (0.6, 0.2–1.7); or MRSA infection (0.5, 0.2–1.5), although implant retention showed a tendency for less cure (0.3, 0.1–1.1).

**Table 4** Logistic regression with outcome "overall cure of prosthetic joint infection".

| Associations | Univariate analysis | Multivariate analysis |
|---|---|---|
| | Odds ratio with 95% confidence intervals | Odds ratio with 95% confidence intervals |
| Twelve weeks of antibiotic therapy | 1 | |
| Six weeks of antibiotic therapy | 3.8 (1.5–9.6) | 2.7 (0.9–8.3) |

# Mono vs bithérapie

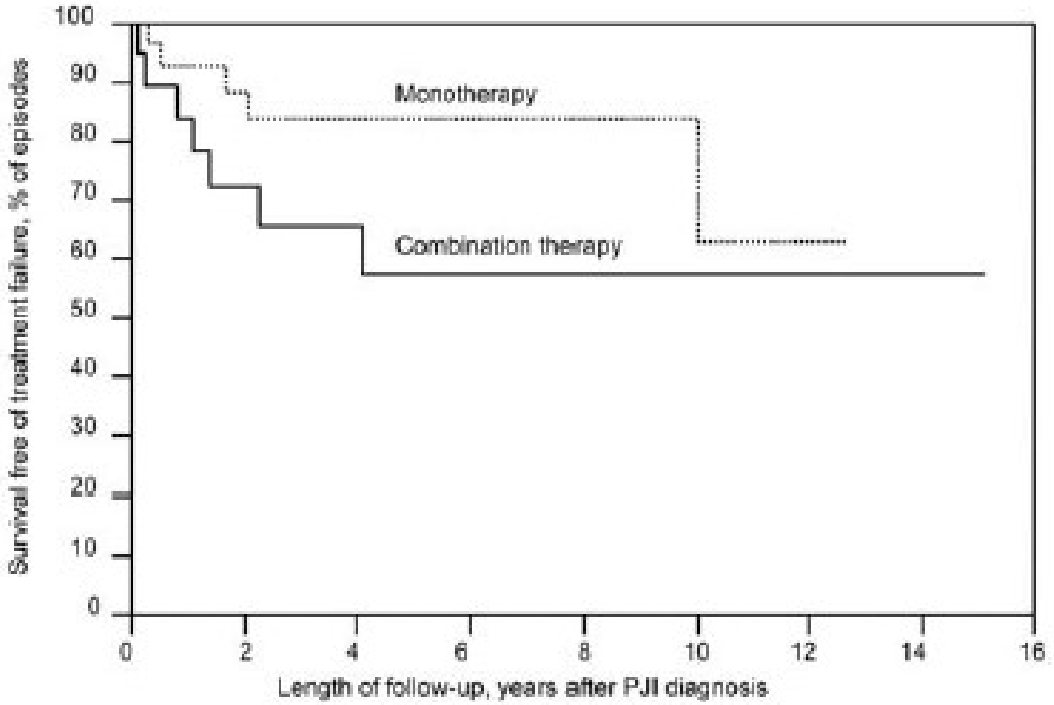
# Bithérapie

Plutôt, surtout si :

- Staphylocoque ou *Pseudomonas aeruginosa*
- Inoculum fort
- Utilisation de
  - Rifampicine
  - Quinolones
  - Fosfomycine ou ac. Fucidique

# Outcome of Enterococcal Prosthetic Joint Infection: Is Combination Systemic Therapy Superior to Monotherapy?

Odette C. El Helou,[1] Elie F. Berbari,[1] Camelia E. Marculescu,[3] Wissam I. El Atrouni,[1] Raymund R. Razonable,[1] James M. Steckelberg,[1] Arlen D. Hanssen,[2] and Douglas R. Osmon[1]




Number of episodes in patients at risk

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Monotherapy | 31 | 20 | 15 | 10 | 8 | 4 | 2 | 2 |
| Combination therapy | 19 | 12 | 8 | 8 | 6 | 4 | 2 | 2 |

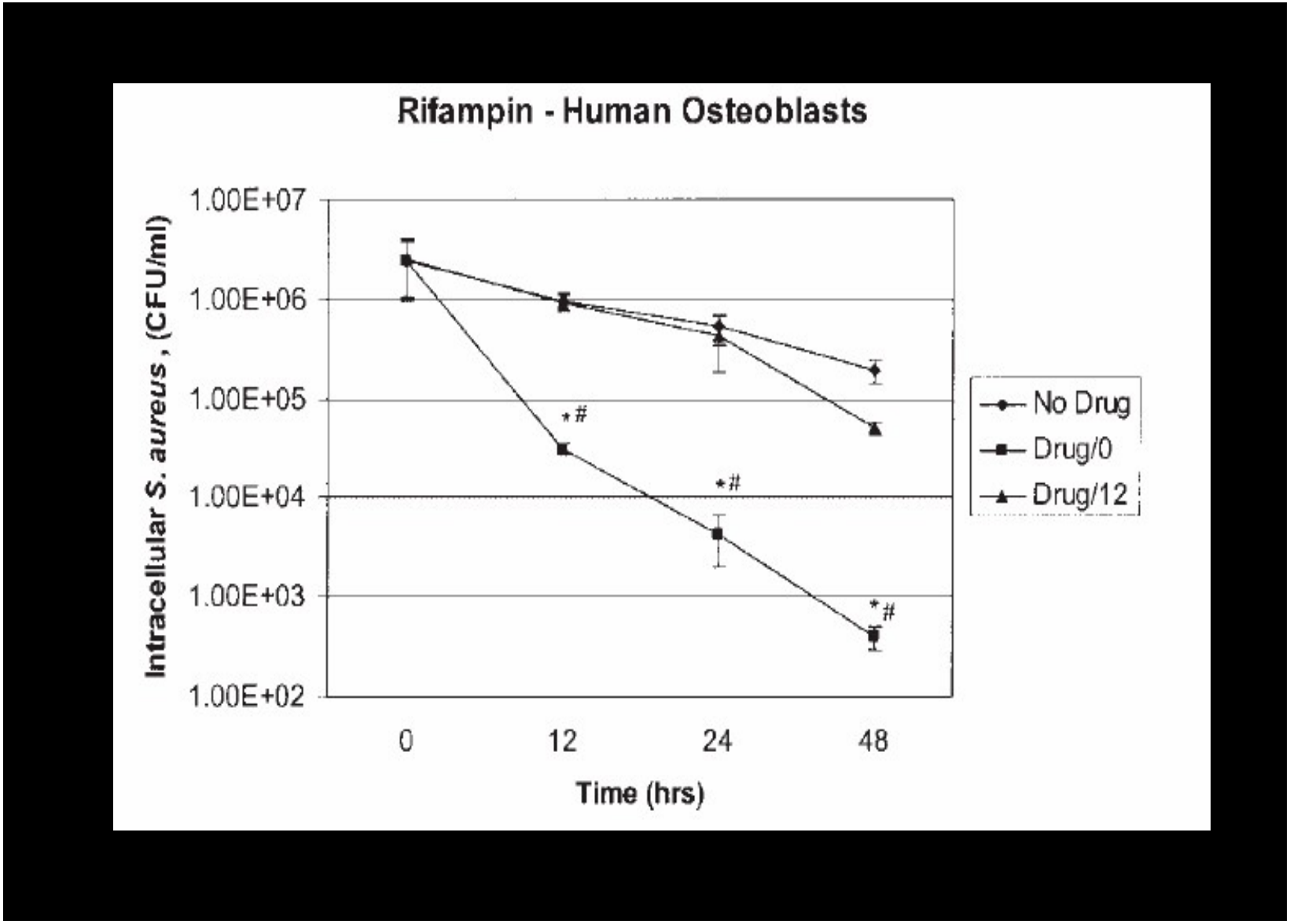
CID 2008:47 (1 October)

# Rifampicine

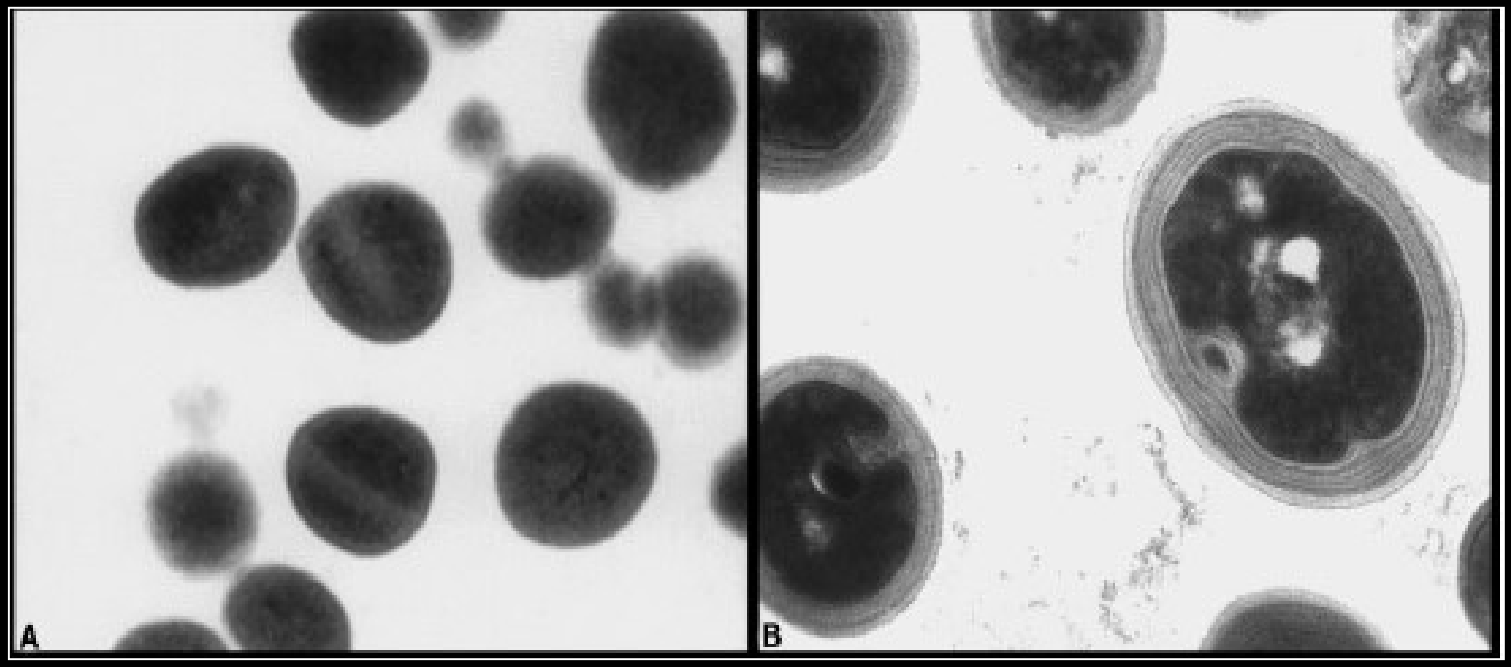
# *S. aureus* intra ostéoblastique = résistance aux antibiotiques (rifampicine)

- Modèle in vitro/ ostéomyélite chronique
  - Ostéoblastes + *S. aureus*
  - Lavage + gentamicine (destruction *S.a*. extra cellulaire)
  - Ajout rifampicine à T0, T12

JL Ellington, J. of Ortho Research 2006 ; 24 : 87-93


Rifampin - Human Osteoblasts
Intracellular S. aureus , (CFU/ml)
1.00E+07
1.00E+06
1.00E+05
1.00E+04
1.00E+03
1.00E+02
0
12
24
48
Time (hrs)
*#
*#
*#
No Drug
Drug/0
Drug/12

..*aureus* extracellulaire  *S.aureus* intra-ostéoblastique



# En pratique : la Rifampicine !

- Peu de molécules répondent aux critères nécessaires.
- La sensibilité à la rifampicine est un **élément clé** du pronostic
- MAIS : capacité **importante** à sélectionner des mutants résistants
- DONC utilisation obligatoire en bithérapie (+++FQ).

1 seule étude prospective randomisée double aveugle vs placebo : lavage débridement quand infection précoce sur prothèse puis 3 à 6 mois de traitement antibiotique :

| Antibiothérapie | Succès | Emergence de résistance à la CPF |
|---|---|---|
| CPF + RFP | 100% | +++ |
| CPF + placebo | 58% | |

Zimmerli JAMA 1998

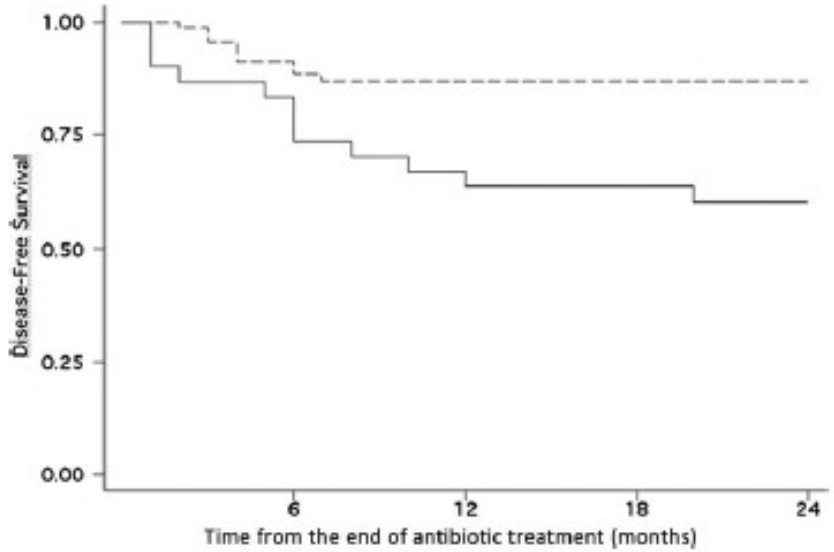
**La rifampicine**: oui mais pas seule 10-15 mg/Kg x 1 ou 2

# Outcome and Predictors of Treatment Failure in Total Hip/Knee Prosthetic Joint Infections Due to *Staphylococcus aureus*

**Eric Senneville, Donatienne Joulie, Laurence Legout, Michel Valette, Hervé Dezèque, Eric Beltrand, Bernadette Roselé, Thibaud d'Escrivan, Caroline Loïez, Michèle Caillaux, Yazdan Yazdanpanah, Carlos Maynou, and Henri Migaud**

**Table 2. Characteristics of Surgical Procedures and Antibiotic Therapy in 98 Patients With Total Hip or Knee Prosthesis Infection Due to *Staphylococcus aureus* According to Outcome**

| Characteristic | Remission ($n$ = 77) | Treatment failure ($n$ = 21) | $P$ |
|---|---|---|---|
| Delay from onset of infection to revision, mean days ± SD | 119.4 ± 238.2 | 79 ± 111.7 | .80 |
| Removal of all infected implants | 45 (58.4) | 12 (57.1) | .99 |
| Gentamicin-loaded cement spacer[a] | 27 (35.1) | 7 (33.3) | .84 |
| Adequate empirical postsurgical antibiotic therapy[b] | 73 (94.8) | 17 (80.9) | .04 |
| Rifampin-fluoroquinolone combination therapy | 37 (48.1) | 2 (9.5) | .001 |
| Rifampin combination therapy | 58 (75.3) | 10 (47.6) | .002 |
| Total duration of antibiotic therapy, mean days ± SD | 165.7 ± 108.8 | 145.1 ± 101.6 | .44 |




FQ + RFP

CID 2011:53 (15 August)

Open Forum Infectious Diseases
MAJOR ARTICLE

Predictors of Treatment Success After Periprosthetic Joint Infection: 24-Month Follow up From a Multicenter Prospective Observational Cohort Study of 653 Patients

Davis J. *et al* OFID 2022

**Table 5. Factors Associated With Treatment Success in Patients With Periprosthetic Infection Managed With Debridement, Antibiotics and Implant Retention as the Main Management Strategy Within 90 Days of Diagnosis (n = 352)**

| | OR Rx Success | 95% CI | *P* | aOR | 95% CI | *P* |
|---|---|---|---|---|---|---|
| Age | 0.988 | 0.968–1.008 | .259 | | | |
| Presentation type (vs early) | | | | | | |
| Late-acute (n = 163) | 0.26 | 0.15–0.46 | <.001 | | | |
| Chronic (n = 44) | 0.16 | 0.07–0.35 | <.001 | | | |
| Early presentation type (vs all others) | **4.26** | **2.47–7.36** | **<.001** | **2.99** | **1.57–5.71** | **.001** |
| Time post implant (months)[a] | 0.987 | 0.982–0.992 | <.001 | | | |
| Duration of Sx (days) | 0.984 | 0.970–0.997 | .02 | | | |
| Symptom duration <21 days | **3.34** | **1.45–7.69** | **.005** | **6.32** | **2.01–19.49** | **.001** |
| Symptom duration <7 days | 1.71 | 1.01–2.89 | .03 | | | |
| Extensive debridement | 1.45 | 0.70–1.88 | .592 | | | |
| Change of liners | 1.07 | 0.63–1.80 | .808 | | | |
| *Staphylococcus aureus* vs all others | **0.49** | **0.32–0.77** | **.002** | **0.39** | **0.22–0.68** | **.001** |
| Knee vs all others | 0.41 | 0.26–0.66 | <.001 | | | |
| Duration of IV ABs | 0.99 | 0.97–1.00 | .109 | | | |
| Duration of PO ABs | 1.004 | 0.993–1015 | .474 | | | |
| Received rifampicin | 1.10 | 0.71–1.71 | .67 | | | |
| Received rifampicin if Gram positive | 1.25 | 0.85–1.85 | .55 | | | |
| Received ciprofloxacin | 1.01 | 0.65–1.57 | .96 | | | |
| Received ciprofloxacin if Gram negative | 1.49 | 0.42–5.24 | .54 | | | |
| Body mass index (kg/m$^2$) | 1.02 | 0.99–1.05 | .234 | | | |
| At least 1 comorbidity | **0.43** | **0.27–0.67** | **<.001** | **0.44** | **0.24–0.76** | **.003** |
| Baseline CRP | 0.997 | 0.995–0.999 | <.001 | | | |
| Baseline CRP >100 | 0.49 | 0.29–0.82 | .007 | | | |
| Decreasein CRP baseline to day 90 (absolute) | 0.997 | 0.994–0.999 | .007 | | | |
| Decreasein CRP baseline to day 90 (%) | 1.005 | | .232 | | | |
| Decrease in CRP by ≥50% (%) | 1.62 | 0.48–5.49 | .434 | | | |
| Baseline albumin | **1.05** | **1.01–1.09** | **.007** | **1.05** | **1.006–1.095** | **.008** |

*Clinical Infectious Diseases*

MAJOR ARTICLE

# If, When, and How to Use Rifampin in Acute Staphylococcal Periprosthetic Joint Infections, a Multicentre Observational Study

Mark Beldman,[1] Claudia Löwik,[1] Alex Soriano,[2] Laila Albiach,[2] Wierd P. Zijlstra,[3] Bas A. S. Knobben,[4] Paul Jutte,[1] Ricardo Sousa,[5] André Carvalho,[5] Karan Goswami,[6] Javad Parvizi,[6] Katherine A. Belden,[7] and Marjan Wouthuyzen-Bakker[8]

| | Total patient group (n= 669) | | |
|---|---|---|---|
| | Rifampin (n = 407) | No rifampin (n = 262) | *P* value |
| Baseline characteristics | | | |
| Male sex | 43.5% (177/407) | 43.9% (115/262) | .92 |
| Age >80 years | 23.4% (95/406) | 18.3% (47/257) | .12 |
| BMI >30 kg/m$^2$ | 48.1 % (177/368) | 55.6% (138/248) | .07 |
| Medical history | | | |
| Diabetes | 20.6% (84/407) | 17.9% (47/262) | .39 |
| Renal failure | 6.9% (28/407) | 6.9% (18/262) | .99 |
| COPD | 18.4% (75/407) | 15.6% (41/262) | .35 |
| Liver cirrhosis | 3.7% (15/407) | 5.3% (14/262) | .30 |
| Malignancy | 14.3% (58/407) | 14.5% (38/262) | .93 |
| Rheumatoid arthritis | 7.4% (30/407) | 3.3% (22/262) | .63 |
| Characteristics implant | | | |
| Primary | 83% (338/407) | 80.5% (206/256) | .40 |
| Cemented | 77.3% (310/401) | 64.7% (152/235) | .001 |
| Fracture as indication prosthesis | 15.5% (63/407) | 16.5% (42/254) | .72 |
| Clinical presentation | | | |
| Serum CRP >115 mg/L | 31.1% (124/399) | 34.3% (87/254) | .40 |
| Serum Leucocytes >12 cells/µL | 28.5% (113/396) | 26.9% (60/223) | .66 |
| Late acute PJI | 3.2% (13/406) | 15.4% (39/253) | <.001 |
| Identified micro-organism | | | |
| *Staphylococcus aureus* | 61.9% (252/407) | 56.9% (149/262) | .19 |
| Polymicrobial | 37.8% (154/407) | 37.8% (99/262) | .98 |
| Surgical treatment | | | |
| Exchange modular components | 45.6% (182/399) | 45.2% (104/230) | .92 |
| DAIR >4 wks after surgery[a] | 18.6% (73/393) | 19.6% (42/214) | .75 |

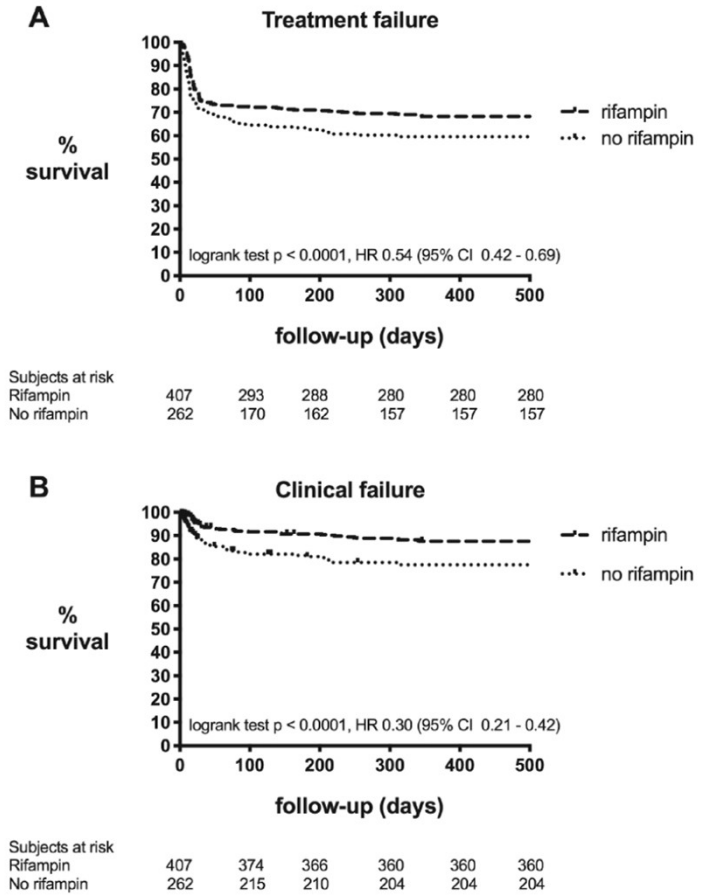



**Figure 1.** Treatment failure (A) and clinical failure (B) rifampin versus no-rifampin according to the type of joint.

*Clinical Infectious Diseases*, 10 May 2021

*Clinical Infectious Diseases*
MAJOR ARTICLE

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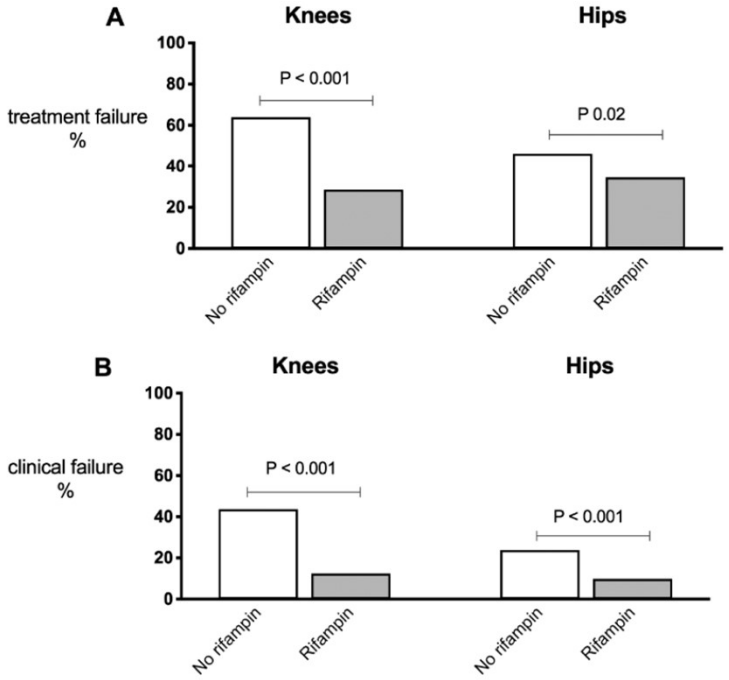
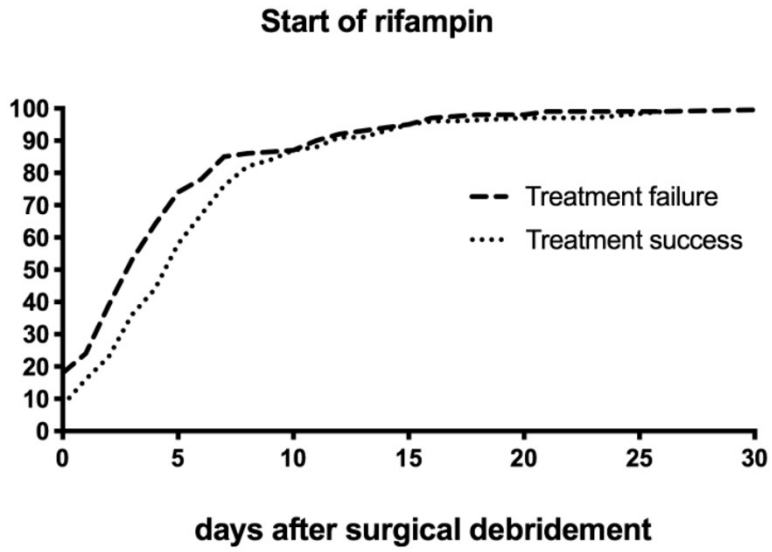
Mark Beldman,[1] Claudia Löwik,[1] Alex Soriano,[2] Laila Albiach,[2] Wierd P. Zijlstra,[3] Bas A. S. Knobben,[4] Paul Jutte,[1] Ricardo Sousa,[5] André Carvalho,[5] Karan Goswami,[6] Javad Parvizi,[6] Katherine A. Belden,[7] and Marjan Wouthuyzen-Bakker[8]



ACCEPTED MANUSCRIPT

# If, when, and how to use rifampin in acute staphylococcal periprosthetic joint infections, a multicentre observational study

Mark Beldman, Claudia Löwik, Alex Soriano, Laila Albiach, Wierd P Zijlstra, Bas A S Knobben, Paul Jutte, Ricardo Sousa, André Carvalho, Karan Goswami, Javad Parvizi, Katherine A Belden, Marjan Wouthuyzen-Bakker ✉

*Clinical Infectious Diseases*, ciab426, https://doi.org/10.1093/cid/ciab426

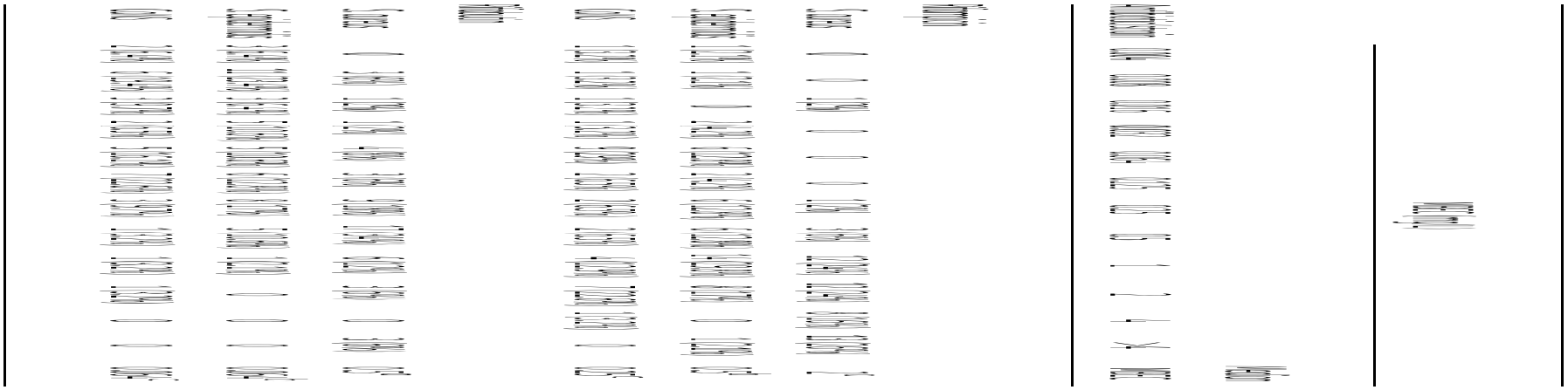
**Published:** 10 May 2021 **Article history** ▾

- Meilleur pronostic
- Association préférentielle : FQ ou clinda
- Peu importe la dose
- >5j

*Clinical Infectious Diseases*, 10 May 2021

# Rifabutin versus rifampicin bactericidal and antibiofilm activities against clinical strains of *Staphylococcus* spp. isolated from bone and joint infections

Pauline Thill [1]*, Olivier Robineau [1,2], Gabrielle Roosen[3], Pierre Patoz[3], Benoit Gachet[1,2], Barthélémy Lafon-Desmurs[1], Macha Tetart[1], Safia Nadji[3], Eric Senneville[1,2] and Nicolas Blondiaux[3,4]



JAC 2022

# Propositions

| | Traitement initial | Relais oral exclusif[1] |
|---|---|---|
| **Staphylocoques multisensibles[2]** | | |
| Poids ≤ 70 kg | Oxacilline ou cloxacilline[3] IV 1,5 g/4 h<br>**OU**<br>Cefazoline[4] 1 g/6 h IV | Ofloxacine[5,6,7] à la dose de 200 mg 2x/j<br>**ET**<br>rifampicine[8,9] 900 mg 1x/j |
| Poids > 70 kg | Oxacilline ou cloxacilline3 IV 2 g/4 h<br>**OU**<br>Cefazoline[4] 2 g/8 h IV | Ofloxacine[5,6,7] à la dose de 200 mg 3x/j<br>**ET**<br>rifampicine[8,9] 600 mg 2x/j |
| **Entérobactéries sensibles[10]** | | |
| Poids ≤ 70 kg | Cefotaxime 2 g/8 h IV<br>**OU**<br>Ceftriaxone 2 g/24 h IV | Ofloxacine[5,6] à la dose de 200 mg 2x/j<br>**OU**<br>ciprofloxacine[6] 500 mg 2x/j |
| Poids > 70 kg | Cefotaxime 9 à 12 g/j IV en 3 à 6 injections<br>**OU**<br>Ceftriaxone 1,5 à 2 g/12 h IV | Ofloxacine[5,6] à la dose de 200 mg x3/j<br>**OU**<br>ciprofloxacine[6] 750 mg 2x/j |

# Propositions (bis)

| | Traitement initial | Relais oral exclusif[1] |
|---|---|---|
| Streptocoques (sauf entérocoques) | | |
| Si poids ≤ 70 kg | Amoxicilline 1,5 g/4 h IV<br>**OU**<br>ceftriaxone[2,3] 2 g/24 h IV | Clindamycine[4] 600 mg x3/j<br>**OU**<br>amoxicilline[5] 2 g 3x/j |
| Si poids > 70 kg | Amoxicilline 2 g/4 h IV<br>**OU**<br>ceftriaxone[2,3] 1,5 à 2 g/12 h IV | Clindamycine[4] 600 mgx4/j<br>**OU**<br>amoxicilline[5] 3 g 3x/j |

# Administration IV prolongée

- Administration IV en post op systématique : intolérance digestive, identification bactérienne en cours
- Administration IV prolongée (>7j) si
  - Intolérance digestive
  - Septicémie
  - Etudes microbiologique en cours
- Dans ce cas voie d'abord centrale ex : Picc line (pb de l'utilisation en HAD)

# Commentaires

- Vérifier sensibilité à érythro et clinda
- Amoxicilline pdt repas (tolérance)
- RFP :
  - A prendre en **dehors de toute prise alimentaire** (30min avant ou 1h30 après)
  - Attention aux **interactions** (AVK, CO)
  - Jamais jamais : probabiliste, monothérapie
- FQ :
  - **Introduction précoce possible** en association avec ttt IV
  - **Risque** comitialité, photosenibilté, tendinopaties
  - Ne pas associer avec **anti acide** (Ulcar Maalox)
  - Elimination rénale ++++

# Suivi et tolérance

- **Efficacité** :
  - Clinique, CRP hebdomadaire initialement, redon ?
- **Tolérance** :
  - Clinique (digestive, allergie
  - Biologie : tolérance hémato (tazo), hépatique (béta lactamine) rénale (AG, vanco)
  - Dosage vanco efficacité/ AG tolérance/obésité
  - Pas de dosage en dehors de ces situations

# The Value of Suction Drainage Fluid Culture during Aseptic and Septic Orthopedic Surgery: A Prospective Study of 901 Patients

**L. Bernard,[1,2,3,4,5,6] B. Pron,[4] A. Vuagnat,[2] V. Gleizes,[3] F. Signoret,[3] P. Denormandie,[5] A. Si-Ali,[4] C. Perrone,[6] J. M. Feron,[3] J. L. Gaillard,[4] and the Groupe d'Etude sur l'Ostéite**

[1]Division of Infectious Diseases, Geneva University Hospital, Geneva, Switzerland; [2]Department of Statistics, St. Michel Hospital, Angoulème, [3]Department of Orthopedic Surgery, Tenon Hospital, and Departments of [4]Microbiology, [5]Orthopedic Surgery, and [6]Infectious Diseases, Raymond-Poincaré Hospital, Garches, France

There are no guidelines on the value of suction drainage fluid culture (SDC), and it is difficult to determine whether the organisms cultured from suction drainage fluid samples are pathogenic or simply contaminants. We performed 2989 cultures of suction drainage fluid samples obtained, during a 1-year period, from 901 patients who underwent aseptic or septic orthopedic surgery (946 operations). The culture results were analyzed to evaluate their ability to detect postoperative infection after aseptic operations or to detect either a persistent or new episode of sepsis in patients known to have infection. For aseptic operations, the sensitivity of SDC was 25%, the specificity was 99%, the positive predictive value was 25%, and the negative predictive value was 99%. For septic operations, the sensitivity of SDC was 81%, the specificity was 96%, the positive predictive value was 87%, and the negative predictive value was 94%. We conclude that, for aseptic orthopedic surgery, SDC is not useful in detecting postoperative infection. However, for septic orthopedic surgery, it is of clinical importance.

# Interactions

- LNZ - RFP >> protectrice ? (L. Legout *et al.* JAC 2010)
- Clindamycine – RFP >> baisse efficacité ?
- **Intérêt des dosages**
- Utilisés pour
  - Vancomycine (objectif 25-35mg/l)
  - Aminoglycosides (Toxicité)

- Fluoroquinolones ? Hétérogénéité des concentrations (C. Pucini *et al.* Presse med. 2004)
- Autres ?
- Daptomycine ?

# Suivi du traitement

- Efficacité :
  - Clinique
  - Paraclinique
  - Liquide de redon (L. Bernard *et al.* CID)
- Tolérance :
  - AG>> insuffisance rénale
  - FQ >> tendinopathie/photosensibilité
  - Béta lactamine : allergie/cytolyse
  - Rifampicine
  - Linézolide
  - Daptomycine
  - Vancomycine
- Modification si nécessaire de l'antibiothérapie (20 à 30%)

# Treatment of Joint Prosthesis Infection in Accordance with Current Recommendations Improves Outcome

**Belinda Y. Betsch,[1] Stefan Eggli,[2] Klaus A. Siebenrock,[2] Martin G. Täuber,[1,3] and Kathrin Mühlemann[1,3]**

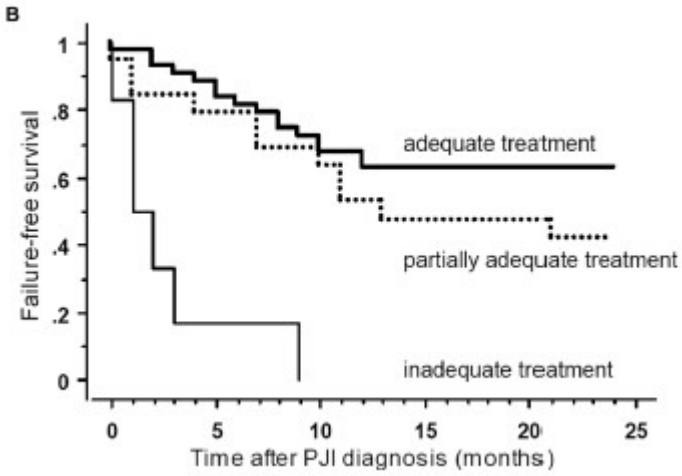
Departments of [1]Infectious Diseases and [2]Orthopedic Surgery, University Hospital Bern, and [3]Institute for Infectious Diseases, University of Bern, Bern, Switzerland

**Table 5. Univariate analysis of risk factors for treatment failure among 68 patients with prosthetic joint infection.**

| Variable | Treatment failure ($n$ = 29) | Healed ($n$ = 39) | HR[a] (95% CI) | $P$ |
|---|---|---|---|---|
| Age, mean years ± SD | 70.6 ± 12.5 | 64.5 ± 10.4 | 1.03 (0.99–1.10) | .12 |
| Charlson Comorbidity Index, mean score ± SD | 1.9 ± 2.0 | 1.4 ± 1.3 | 1.09 (0.89–1.30) | .42 |
| Immunosuppression | 4 (13.8) | 2 (5.1) | 1.87 (0.66–5.30) | .24 |
| Duration of symptoms <3 weeks | 13 (44.8) | 24 (61.5) | 1.71 (0.80–3.40) | .14 |
| Mean infection score ± SD | 9.4 ± 2.8 | 7.1 ± 2.7 | 1.29 (1.10–1.40) | <.001 |
| Sinus tract | 10 (34.5) | 4 (10.3) | 2.35 (1.10–5.0) | .02 |
| Inadequate antimicrobial treatment | 9 (31.0) | 2 (5.1) | 3.45 (1.50–7.60) | .002 |
| Surgical strategy not as recommended[a] | 12 (41.4) | 8 (20.5) | 2.34 (1.10–4.70) | .01 |

**NOTE.** Data are number (%) of patients, unless otherwise indicated. HR, hazard ratio.

[a] Based on Giulieri et al. [8].



# Recommandations

IDSA GUIDELINES

## Diagnosis and Management of Prosthetic Joint Infection: Clinical Practice Guidelines by the Infectious Diseases Society of America[a]

Douglas R. Osmon,[1] Elie F. Berbari,[1] Anthony R. Berendt,[2] Daniel Lew,[3] Werner Zimmerli,[4] James M. Steckelberg,[1] Nalini Rao,[5,6] Arlen Hanssen,[7] and Walter R. Wilson[1]

CID 2013:56 (1 January)

## Recommandations de pratique clinique

*Infections ostéo-articulaires sur matériel*

**(prothèse, implant, ostéosynthèse)**

*Médecine et Maladies Infectieuses 2008*

# IDSA Clinical Practice Guidelines for the treatment of MRSA infections

First IDSA guidelines on the treatment of MRSA

Projected publication : late 2010

# What is the management of MRSA Bone and Joint Infections?

- Debride and drain associated soft tissue abscesses (AII)

| Adults | Children |
|---|---|
| Vancomycin (BII) | Vancomycin (AII) |
| Daptomycin (BII) | Clindamycin (AII) |
| Linezolid (BII) | Daptomycin (CIII) |
| Clindamycin (BIII) | Linezolid (CIII) |
| TMP-SMX + Rifampin (BII) | |

- Some experts recommend adding rifampin 300-450 BID (BIII)
  - Animal models, small human trials of MSSA osteo
  - Retrospective studies : cure rates of up to 80%; no benefit if debridement

Crompton J Chemotherapy 2009; Rayner Infection 2004; Rao DMID 2007; Euba AAC 2009; Martinez-Aguilar PIDJ 2003, Pelroth Arch Int Med 2008; Van der Auwera AAC 1985, Nordern SMJ 1986; Priest SMJ 2005; Livorsi J Infect 2008

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2009, p. 4252–4257 Vol. 53, No. 10
0066-4804/09/$08.00+0 doi:10.1128/AAC.00208-09


# Efficacy of High Doses of Daptomycin versus Alternative Therapies against Experimental Foreign-Body Infection by Methicillin-Resistant *Staphylococcus aureus*▽

O. Murillo,[1]* C. Garrigós,[1] M. E. Pachón,[1] G. Euba,[1] R. Verdaguer,[2] C. Cabellos,[1] J. Cabo,[3] F. Gudiol,[1] and J. Ariza[1]

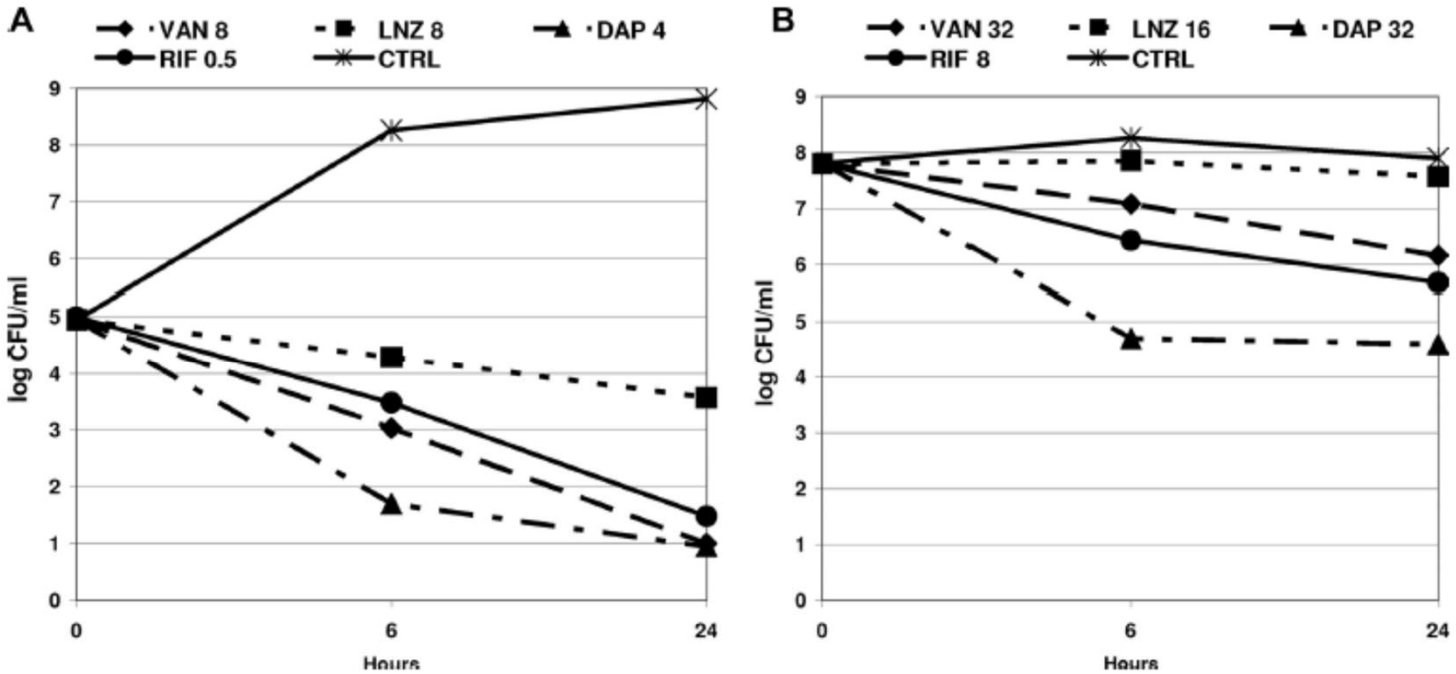
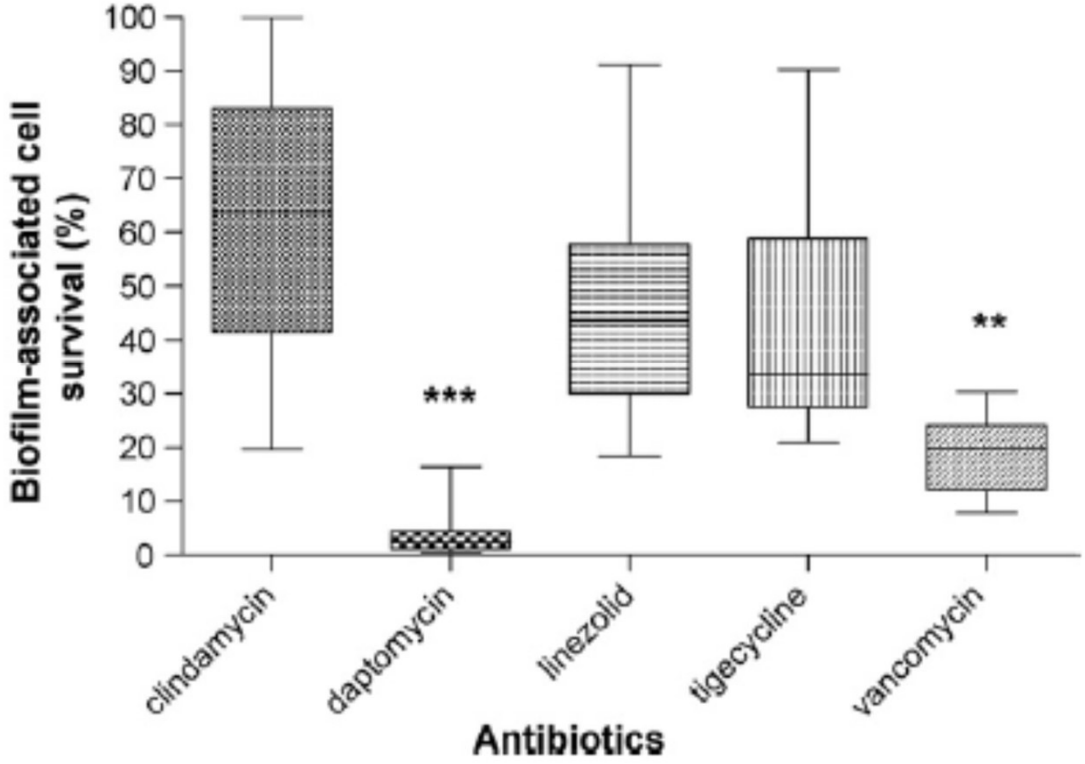



FIG. 1. Time-kill curves for log-phase (A) and stationary-phase (B) bacteria with clinically representative drug concentrations (in micrograms per milliliter). Abbreviations: DAP, daptomycin; RIF, rifampin; LNZ, linezolid; VAN, vancomycin; CTRL, controls.

Short communication

# Comparison of biofilm-associated cell survival following in vitro exposure of meticillin-resistant *Staphylococcus aureus* biofilms to the antibiotics clindamycin, daptomycin, linezolid, tigecycline and vancomycin

Karen Smith [a], Ana Perez [a], Gordon Ramage [b,1], Curtis G. Gemmell [c], Sue Lang [a,*,1]

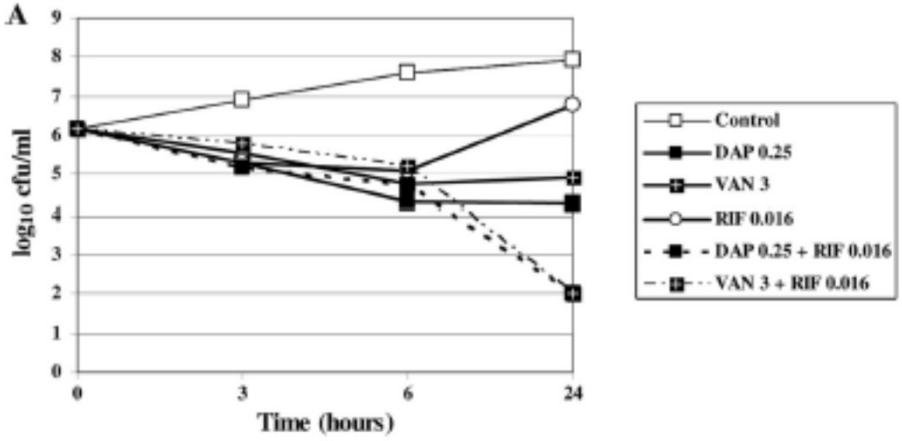


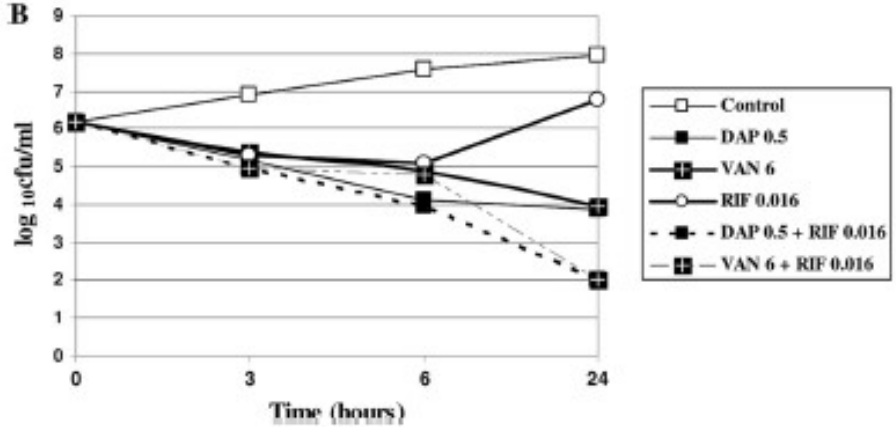

International Journal of Antimicrobial Agents 33 (2009) 374–378

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2011, p. 4589–4593 Vol. 55, No. 10
0066-4804/11/$12.00 doi:10.1128/AAC.00675-11


# Adjunctive Rifampin Is Crucial to Optimizing Daptomycin Efficacy against Rabbit Prosthetic Joint Infection Due to Methicillin-Resistant *Staphylococcus aureus*▽†

Azzam Saleh-Mghir,[1,2] Claudette Muller-Serieys,[3] Aurélien Dinh,[1,2] Laurent Massias,[4] and Anne-Claude Crémieux[1,2]*



# Les tendances

- Raccourcissement durée de traitement
- Relais per os précoce (molécules à bonne diffusion +++)
- Changement en 1 temps ?
- SIMPLIFICATION DE LA PRISE EN CHARGE ?
- +++ si molécules à bonne diffusion utilisée
- Si acte chirurgical optimisé

# Nouveaux antibiotiques

*Review*

**Dalbavancin for the Treatment of Prosthetic Joint Infections: A Narrative Review**

Luis Buzón-Martín [1,2,*], Ines Zollner-Schwetz [3], Selma Tobudic [4], Emilia Cercenado [5,6,7] and Jaime Lora-Tamayo [2,8,9]

Antibiotics 2021

Dalbavancin treatment for prosthetic joint infections in real-life: a national cohort study and literature review

Morgan Matt[a], Clara Duran[a], Johan Courjon[b], Romain Lotte[c], Vincent Le Moing[d], Boris Monnin[d], Patricia Pavese[e], Pascal Chavanet[f], Lydie Khatchatourian[g], Pierre Tattevin[h], Vincent Cattoir[i], Catherine Lechiche[j], Gabriella Illes[k], Flore Lacassin-Beller[k], Eric Senneville[l], Aurélien Dinh[a,*], on behalf of the Dalbavancin French Study Group

JGAR 2021

| Reference | *n* | Bone & Joint Infection (Other than PJI) | Episodes of PJI | PJI Outcome (Success, %) |
|---|---|---|---|---|
| Bouza et al., 2017 [51] | 69 | 13 | 20 | 80% |
| Morata et al., 2019 [50] | 64 | NP | 26 | NP |
| Tobudic et al., 2019 [45] | 72 | 20 | 8 | 75% |
| Wunsch et al., 2019 [49] | 101 | 30 | 32 | 94% |
| Martín et al., 2019 [48] | 16 | 0 | 16 | 88% |
| Dinh et al., 2019 [52] | 75 | 48 | NP | NP |

NP: not provided. PJI: prosthetic joint infection.

antibiotics

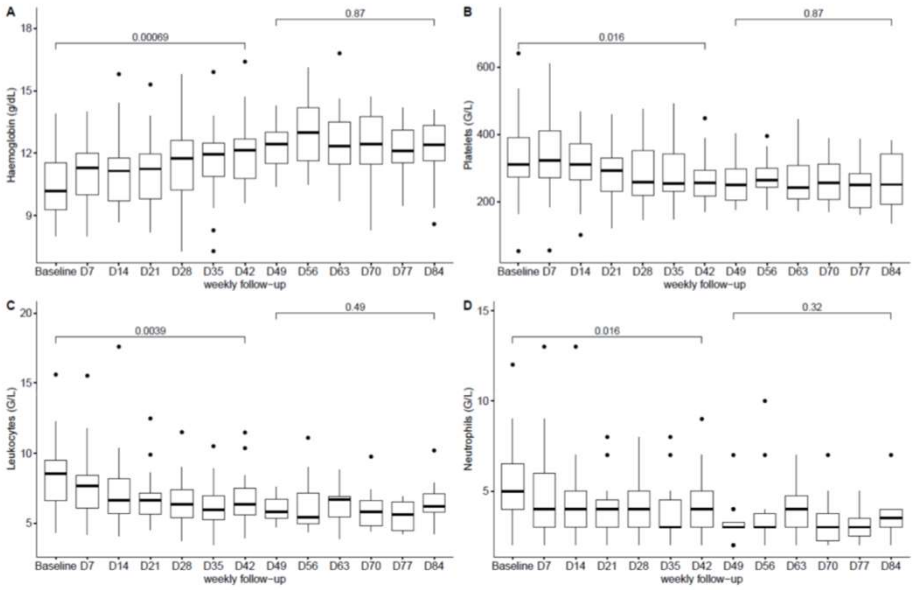
MDPI

*Article*

# Tolerance of Prolonged Oral Tedizolid for Prosthetic Joint Infections: Results of a Multicentre Prospective Study

Eric Senneville [1,2,3,*], Aurélien Dinh [4,5], Tristan Ferry [6,7], Eric Beltrand [3,8], Nicolas Blondiaux [3,9] and Olivier Robineau [1,2,3]

Etude prospective multicentrique
33 patients infection prothèse ostéo articulaires : hanche (*n* = 19), genou (*n* = 13) et épaule (*n* = 1)
DAIR (33.3%), changement en 1 et 2 temps 17/5 (51.5%/15.2%),
Bactéries : *Staphylococci* et *enterococci*
Durée moyenne de ttt 8.0 ± 3.27 semaines(6–12).
Arrêt prématuré chez 6 patients (18.2%)
Intolerance au TZD (*n* = 2),
2 cas d'anémie (hémorragie)
2 échecs septiques




Antibiotics 2020

Safety of Tedizolid as Suppressive Antimicrobial Therapy for Patients With Complex Implant-Associated Bone and Joint Infection due to Multidrug-Resistant Gram-Positive Pathogens: Results From the TediSAT Cohort Study

Tristan Ferry,[1,2,3] Anne Conrad,[1,2,3] Eric Senneville,[4,5,6] Sandrine Roux,[1,2] Céline Dupieux-Chabert,[1,2,3] Aurélien Dinh,[7,8] Sébastien Lustig,[2,9] Sylvain Goutelle,[1,2,10] Thomas Briot,[1,2] Truong-Thanh Pham,[1,2,11] Florent Valour[1,2,3]

Cohorte prospective

multicentrique

17 patients

ATB suppressive par tedizolide

Suivi moyen 6 mois

Pas d'EIG

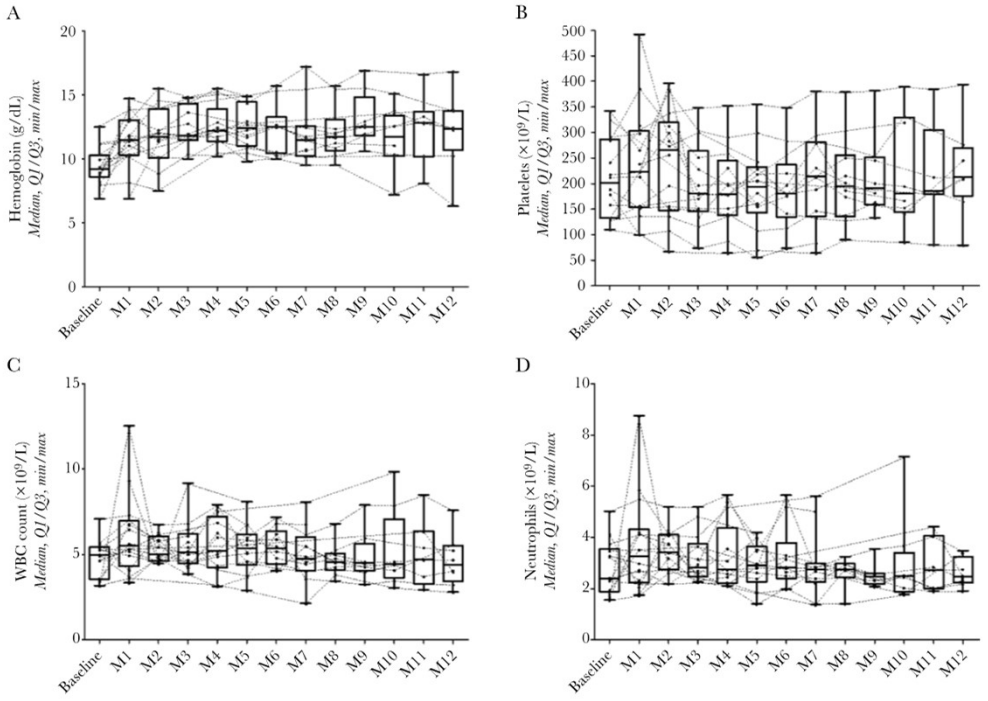



**Figure 1.** Evolution of hemoglobin (*A*), platelet count (*B*), white blood cell (WBC) count (*C*), and neutrophil count (*D*) during the first 12 months of suppressive antimicrobial therapy with tedizolid.

OFID 2021

# Absence d’antibiotique

# Phage Therapy as Adjuvant to Conservative Surgery and Antibiotics to Salvage Patients With Relapsing *S. aureus* Prosthetic Knee Infection

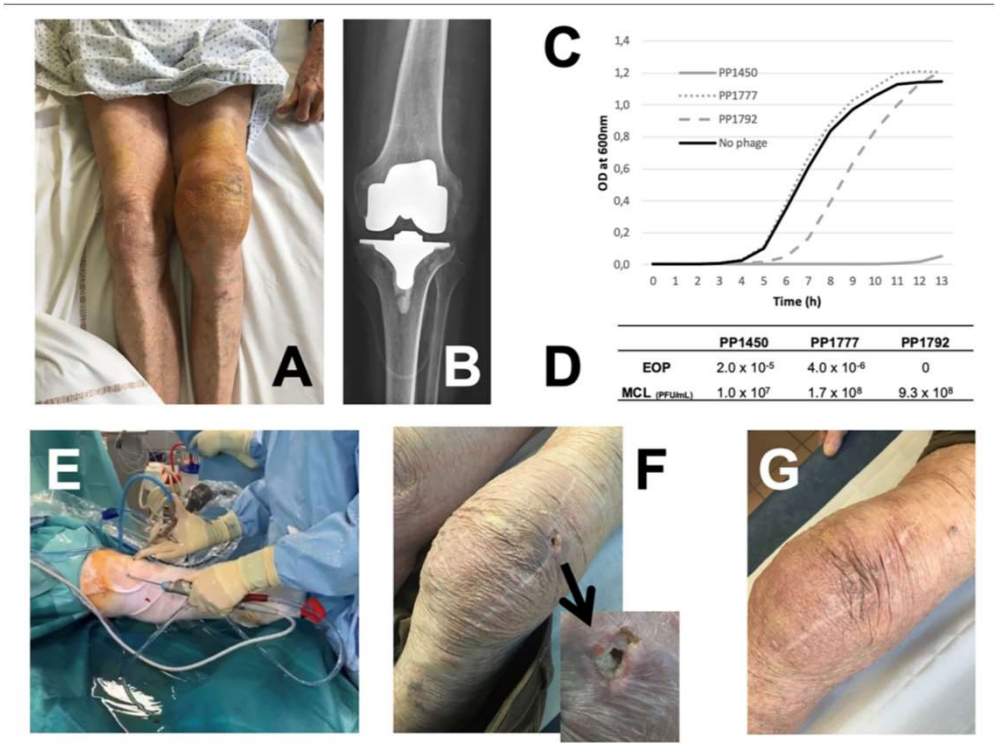
*Tristan Ferry[1,2,3,4]*, Camille Kolenda[2,3,4,5], Cécile Batailler[2,3,6], Claude-Alexandre Gustave[2,3,4,5], Sébastien Lustig[2,3,6], Matthieu Malatray[3,6], Cindy Fevre[7], Jérôme Josse[2,3,4,5], Charlotte Petitjean[7], Christian Chidiac[1,2,3,4], Gilles Leboucher[8] and Frédéric Laurent[2,3,4,5] on behalf of the Lyon BJI Study group*

| Patient ID | Age (sex) | Putative mechanism of inoculation | Time since prosthesis implantation (months) | Duration of clinical symptoms before the PhagoDAIR procedure (days) | Delay from the previous surgery performed for the current infection to the PhagoDAIR procedure (days) | Antimicrobial resistance | Successive primary antimicrobial therapies after the PhagoDAIR procedure (duration in days) | Successive SAT after the primary antimicrobial therapy(ies) until the last follow-up (duration in days) |
|---|---|---|---|---|---|---|---|---|
| Patient 1 | 80 (male) | Perioperative | 40 | 976 | One-stage exchange (1,371) | Penicillin G | Daptomycin–cloxacillin (4)*<br>Levofloxacin–rifampin (123) | Doxycycline (45)***<br>Cephalexin (739) |
| Patient 2 | 84 (male) | Hematogenous | 35 | 82 | Open DAIR without PE exchange (78) | Erythromycin | Daptomycin–levofloxacin (14)**<br>Ofloxacin–doxycycline (72) | Doxycycline (189) |
| Patient 3 | 83 (female) | Perioperative | 11 | 122 | Open DAIR without PE exchange (98) | Penicillin G | Daptomycin–cefepime–rifampin (14)**<br>Levofloxacin–rifampin (111) | Doxycycline (200) |

*SAT, suppressive antimicrobial therapy; DAIR, debridement antibiotics and implant retention; PE, polyethylene.*

Front med 2020

**Case Report: Arthroscopic "Debridement Antibiotics and Implant Retention" With Local Injection of Personalized Phage Therapy to Salvage a Relapsing *Pseudomonas Aeruginosa* Prosthetic Knee Infection**

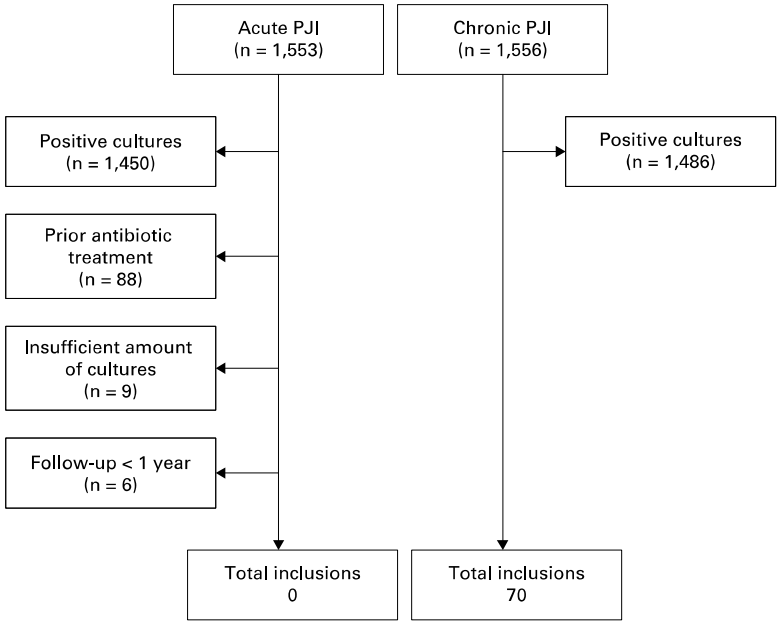


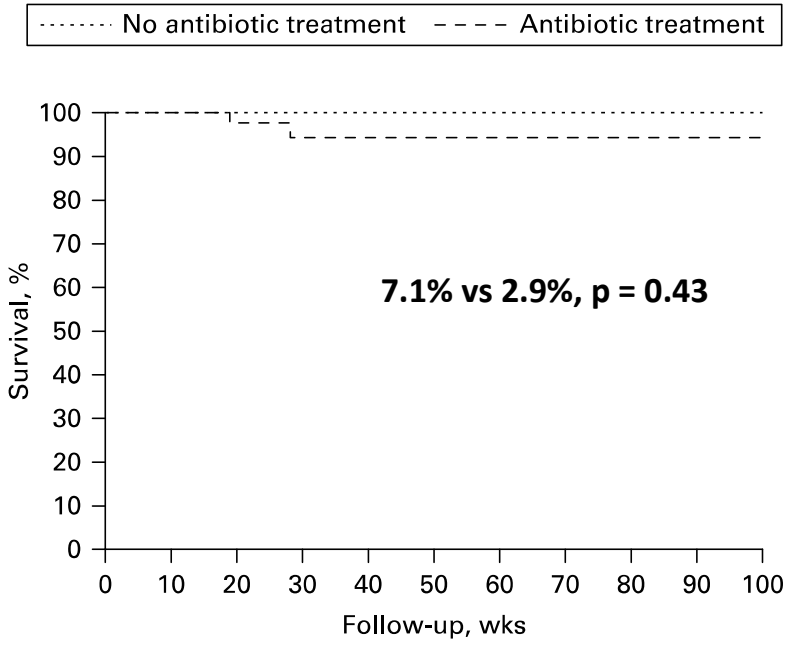

Front med 2021

■ GENERAL ORTHOPAEDICS

# Should all patients with a culture-negative periprosthetic joint infection be treated with antibiotics?

A MULTICENTRE OBSERVATIONAL STUDY




Joint bone J. 2022

# The efficacy of suppressive antibiotic treatment in patients managed non-operatively for periprosthetic joint infection and a draining sinus

**Karel-Jan Dag François Lensen[1], Rosa Escudero-Sanchez[2], Javier Cobo[2], Rihard Trebše[3], Camelia Gubavu[4], Sara Tedeschi[5], Jose M. Lomas[6], Cedric Arvieux[7], Dolors Rodriguez-Pardo[8], Massimo Fantoni[9], Maria Jose Garcia Pais[10], Francisco Jover[11], Mauro José Costa Salles[12], Ignacio Sancho[13], Marta Fernandez Sampedro[14], Alex Soriano[15], Marjan Wouthuyzen-Bakker[1], and ESCMID Study Group of Implant Associated Infections (ESGIAI)✚**

# The efficacy of suppressive antibiotic treatment in patients managed non-operatively for periprosthetic joint infection and a draining sinus

Karel-Jan Dag François Lensen[1], Rosa Escudero-Sanchez[2], Javier Cobo[2], Rihard Trebše[3], Camelia Gubavu[4], Sara Tedeschi[5], Jose M. Lomas[6], Cedric Arvieux[7], Dolors Rodriguez-Pardo[8], Massimo Fantoni[9], Maria Jose Garcia Pais[10], Francisco Jover[11], Mauro José Costa Salles[12], Ignacio Sancho[13], Marta Fernandez Sampedro[14], Alex Soriano[15], Marjan Wouthuyzen-Bakker[1], and ESCMID Study Group of Implant Associated Infections (ESGIAI)✚

**Table 3.** Primary and secondary end points of suppressive antibiotic treatment (SAT) vs. no SAT.

| | SAT ($n = 63$) | No SAT ($n = 9$) | $p$ value |
|---|---|---|---|
| **Primary end point** | | | |
| Prosthesis retention | 79.4 % | 88.9 % | 0.68 |
| **Secondary end points** | | | |
| Prosthetic loosening in initially fixed implants | 42 % | 0 % | 0.08 |
| Need for surgical debridement | 6.3 % | 0 % | 0.44 |
| Sinus tract closure at last follow-up | 42.1 % | 12.5 % | 0.14 |
| Resolution of pain | 35.2 % | 14.3 % | 0.22 |
| Bacteremia with same micro-organism as in PJI | 3.2 % | 0 % | 1.00 |
| CRP > 50 mg/L at last follow-up | 12.5 % | 16.7 % | 0.78 |
| CRP (mg/L)<br>– Baseline (range)<br>– Last follow-up (range)<br>Difference | <br>32.0 (12.0–75.0)<br>11.7 (4.0–37.0)<br>−12.5 (−41.0 to −0.7) | <br>36.5 (24.5–42.0)<br>23.0 (14.5–23.0)<br>−10.5 (−22.8–10.4) | <br>0.93<br>0.26 |
| Haemoglobin < 6 mmol/L at last follow-up | 4.7 % | 20 % | 0.18 |
| Haemoglobin (mmol/L)<br>– Baseline<br>– Last follow-up<br>Difference | <br>7.1 (6.6–8.1)<br>7.3 (6.6–8.1)<br>−0.1 (−0.6–0.4) | <br>6.83 (6.5–7.2)<br>6.95 (6.3–7.5)<br>0.06 (−0.2–0.3) | <br>0.90<br>0.94 |
| Side effects of SAT | 27 % | | |

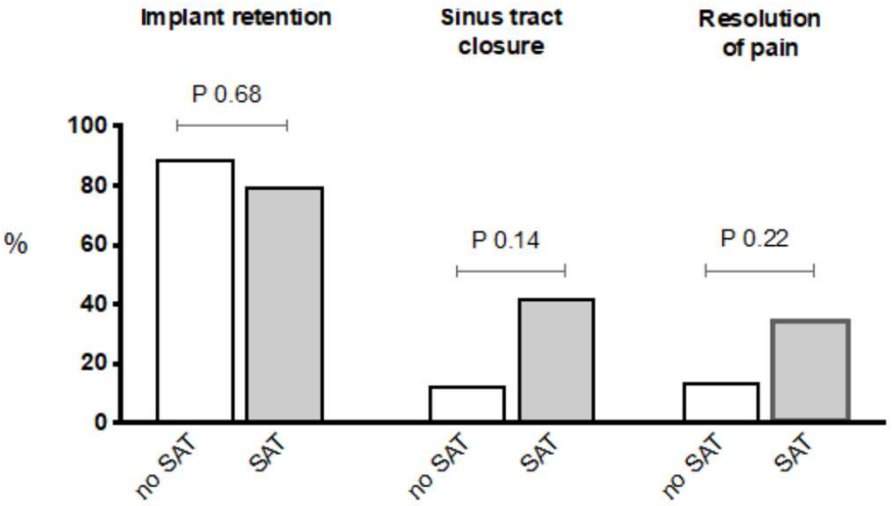


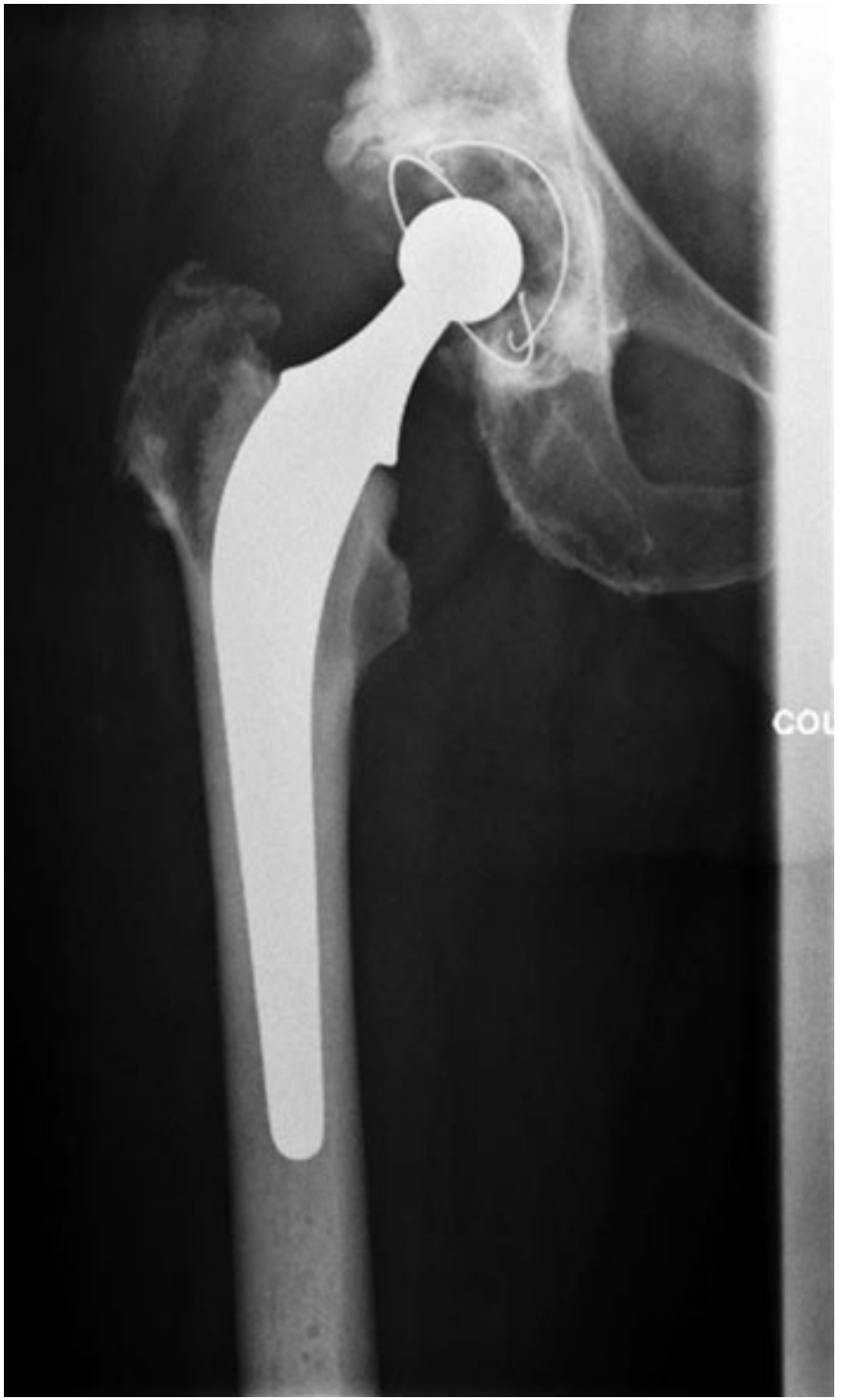

**Figure 1.** Clinical outcome of patients with and without SAT (suppressive antibiotic treatment).

J Bone Jt Infect. 2021

# Les « clefs »

- Identification microbiologique fiable +++
- Rarement des urgences
- Enlever le matériel
- Voie IV au début (large spectre)
- Molécules à bonne diffusion
- Intérêt de la rifampicine
- Forte doses / durée prolongée ?
- Bi antibiothérapie ?
- Surveiller efficacité et tolérance

# MERCI !



# Evolution

| | Six weeks<br>$n = 70$ | Twelve weeks<br>$n = 74$ |
|---|---|---|
| Outcome | | |
| Median time delay begin of treatment–failure | 3 weeks | 3 weeks |
| Persistence of infection | 6 (85%) | 18 (82%) |
| New infection | 1 (14%) | 5 (23%) |
| Death of all causes during follow-up | 15 (21%) | 24 (32%) |
| Death due to prosthetic joint infection | 1 (1%) | 2 (3%) |

**Table 3** Cure incidences stratified according key parameters (Fisher exact or $\chi^2$ – tests).

| | | | *p* value |
|---|---|---|---|
| Parenteral antibiotic treatment | For $\leq$ 8 days<br>37/44 | For $\geq$ 21 days<br>50/65 | 0.47 |
| Removal vs. retention of arthroplasty | Removal<br>75/84 | Retention<br>40/60 | <0.01 |
| Time of onset of infection | Early infection<br>38/42 | Late infection<br>56/71 | 0.13 |

*Journal of Antimicrobial Chemotherapy* (2009) **64**, 392–397
doi:10.1093/jac/dkp177
Advance Access publication 28 May 2009

JAC

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

Pang-Hsin Hsieh[1,2]*, Kuo-Chin Huang[2,3], Po-Cheng Lee[1,2] and Mel S. Lee[1,2]

[1]*Department of Orthopedics, Chang Gung Memorial Hospital, Taoyuan, Taiwan;* [2]*College of Medicine, Chang Gung University, Taoyuan, Taiwan;* [3]*Department of Orthopedics, Chang Gung Memorial Hospital, Chia-Yi, Taiwan*

***Patients and methods***: We reviewed 99 patients with PHI who were managed with SEA using an ALCS from February 2002 to October 2005. A standard (4–6 week) antibiotic treatment course was administered in the first 46 patients and a short-term (1 week) therapy was adopted in the subsequent 53 patients.

***Conclusions***: Short-term antibiotic therapy was not associated with a higher rate of treatment failure.

# Durée de traitement ?

- 6 à 12 semaines
- Pas recommandé au delà de 3 mois

- PHRC DATIPO : inclusions terminées

# Nécessité d'un diagnostic microbiologique « fiable »

- IOA sans microbiologie = diagnostic incertain et incomplet

- IOA sans microbiologie = Perte de chance

# Remarques

- Propositions car **faible niveau de preuve**
- Prendre en compte allergies, co morbidité (responsabilité médicale ?)
- Poso non en mg/kg !
- **Dosages** à réaliser chez obèse
- **Monothérapie FQ** pour entérobactérie
- Péni M IV (jamais per os)
- **Si SAMS**
  - FQ : Oflo > Lévo et CPF
  - Rifam :
    - prescription décalée (éviter monothérapie fonctionnelle)
    - Posologie (discutée 5 mg/kg/j – 20mg/kg/j)

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 2009, p. 883–887 Vol. 53, No. 3
0066-4804/09/$08.00+0 doi:10.1128/AAC.00389-08


# Continuous Cefazolin Infusion To Treat Bone and Joint Infections: Clinical Efficacy, Feasibility, Safety, and Serum and Bone Concentrations▽

Valérie Zeller,[1,2]* Frédérick Durand,[1,2] Marie-Dominique Kitzis,[3] Luc Lhotellier,[1] Jean-Marc Ziza,[2] Patrick Mamoudy,[1] and Nicole Desplaces[1,4]

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Received 22 March 2008/Returned for modification 30 April 2008/Accepted 3 December 2008

**Cohorte rétrospective de 100 patients**
**Céfazoline IVSE au moins 15j**
**Mesures des concentrations sérique et osseuse de céfazoline**
**suivi 1 an et 2 ans**
**Taux sériques et osseux : thérapeutiques**
**2 EI**
**88 patients suivis : 55 guéris et 29 probablement guéris**

**months), 52 were considered cured and 29 were considered probably cured. Thus, the treatment of bone and joint infections with a prolonged continuous intravenous cefazolin infusion was feasible, effective, well-tolerated, safe, and convenient, making it a strong candidate for home therapy.**

ELSEVIER

International Journal of Antimicrobial Agents 30 (2007) 202–209

INTERNATIONAL JOURNAL OF Antimicrobial Agents

www.ischemo.org

Review

# Daptomycin for treatment of patients with bone and joint infections: a systematic review of the clinical evidence

Matthew E. Falagas[a,b,*], Konstantina P. Giannopoulou[a], Fotinie Ntziora[a], Panayiotis J. Papagelopoulos[a,c]

The treatment of bone and joint infections, mainly caused by Gram-positive pathogens, can be difficult and quite challenging since it frequently involves prolonged administration of antibiotics as well as appropriate surgical procedures. First-line drugs have failed in some cases to cure the underlying infection. We performed a systematic review of the available evidence to clarify further the effectiveness and safety of daptomycin in the treatment of bone and joint infections. Cure of infection was achieved in 43/53 cases (81.1%). The results of the reviewed articles are promising with regard to the effectiveness and safety profile of this new antibiotic for bone and joint infections that are not responsive to other traditionally used antimicrobial agents. Although these reports are encouraging, the relatively frequent emergence of antimicrobial resistance associated with prolonged administration of daptomycin should be considered seriously.

Arch Orthop Trauma Surg (2009) 129:1495–1504
DOI 10.1007/s00402-008-0772-x

ORTHOPAEDIC SURGERY

# Daptomycin in bone and joint infections: a review of the literature

Dennis A. K. Rice · Luke Mendez-Vigo

# Antibiothérapie définitive/ciblée

- Identifier **les difficultés** (recours CRIOA)
  - Staph R méti/RFP/FQ
  - Entérobactéries gpe I et II R C3G et/ou FQ (acide nalidixique)
  - Entérobactérie groupe III/*Pseudomonas aeruginosa*/entérocoque/anaérobies/fongique
  - Infection plurimicrobienne
- **Relais per os**

Pas de données comparatives dans la littérature (5j à 6 semaines) >> au moins 7 j si septicémie (14 si septicémie à *Staph aureus*)

Relais immédiat si évolution locale staisfaisante (Redon ?)

- **AG**

si sepsis sévère ou choc septique (pyo ?) cf reco ANSM

CLINICAL MICROBIOLOGY REVIEWS, Jan. 2010, p. 14–34 Vol. 23, No. 1
0893-8512/10/$12.00 doi:10.1128/CMR.00034-09


# Rifampin Combination Therapy for Nonmycobacterial Infections

Graeme N. Forrest[1,2]* and Kimberly Tamura[1]

*Portland Veterans Affairs Medical Center[1] and Oregon Health and Science University,[2] Portland, Oregon*

TABLE 1. Nonantimicrobial drugs with major drug interactions or contraindications when used with rifampin[a]

| Immunosuppressive drug | Endocrine drug | Cardiac drug | Neurologic drug | Other drug |
|---|---|---|---|---|
| Tacrolimus | Simvastatin | Diltiazem | Diazepam | Cimetidine |
| Sirolimus | Repaglinide | Digoxin | Barbiturates | Methadone |
| Corticosteroids | Clofibrate | Disopyramide | Buspirone | Opiates |
| Mycophenolate | Contraceptives | Lorcainide | Haloperidol | Ondansetron |
| Cyclosporine | Estrogen | Metoprolol | Midazolam | Sulfasalazine |
| | Glyburide | Mexiletine | Nitrazepam | Theophylline |
| | Tamoxifen | Nifedipine | Nortriptyline | Bendamustine |
| | Thyroxine | Propafenone | Phenytoin | Imatinib |
| | Rosiglitazone | Propranolol | Sertraline | |
| | Pioglitazone | Quinidine | Zolpidem | |
| | Ranolazine | Tocainide | Clozapine | |
| | Bosentan | Verapamil | Lamotrigine | |
| | | Losartan | | |
| | | Warfarin | | |

TABLE 4. Significant clinical studies of rifampin combination therapy[a]

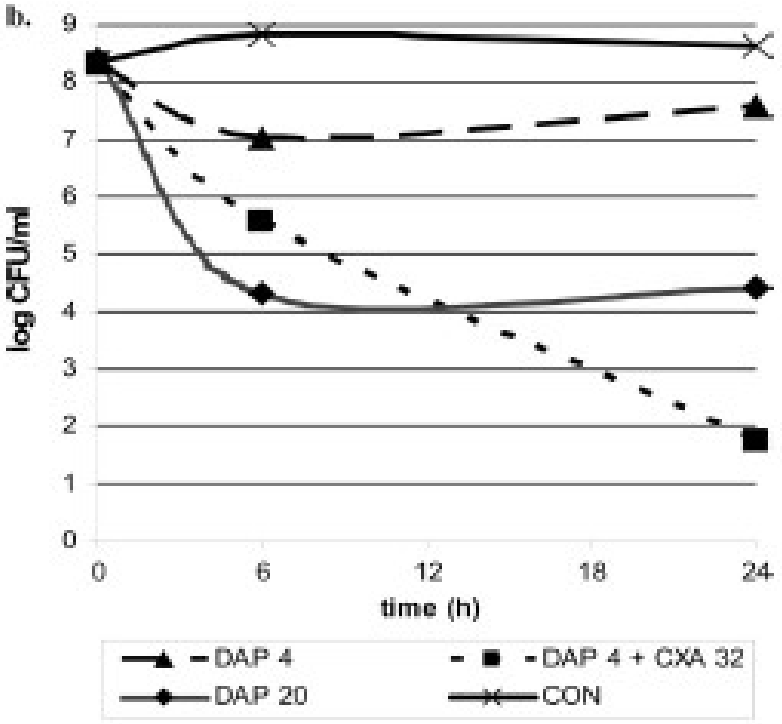
| Disease and authors (reference) | Study design | No. of cases | Organism(s) | Antibiotic(s) | Outcome | Rifampi resistanc |
|---|---|---|---|---|---|---|
| Prosthetic valve endocarditis | | | | | | |
| Karchmer et al. (141) | Retrospective | 75 | CoNS | Nafcillin +/− gentamicin | 10/20 cured; poorer response than vancomycin | N |
| | | | | Vancomycin +/− gentamicin | 21/26 | N |
| Karchmer et al. (140) | Retrospective | 23 | CoNS | Vancomycin +/− gentamicin | 16/23 cured | Y (2 case |
| Prosthetic joint infections | | | | | | |
| Zimmerli et al. (279) | Prospective, randomized | 33 | MSSA | Ciprofloxacin | 12/12 cured vs 7/12 | N |
| Barberán et al. (21) | Retrospective | 25 | MSSA, CoNS | Levofloxacin | 18/25 cured | N |
| Laffer et al. (153) | Retrospective | 35 | MSSA (14/33) | Multiple | 92% success | N |
| Choong et al. (47) | Retrospective | 14 | Multiple | Quinolone | Salvage therapy effective | N |
| Aboltins et al. (1) | Retrospective | 20 | MSSA/MRSA | Ciprofloxacin | 10/11 MRSA responded | N |
| Berdal et al. (29) | Retrospective | 29 | MSSA (18/29) | Fusidic acid | 24/29 successful | NT |
| Donaldson et al. (69) | Retrospective | 2 | MRSA | Ciprofloxacin | Failed | Y |
| Barberán et al. (20) | Retrospective | 60 | CoNS, MRSA | Fusidic acid | Higher MRSA failure rate | N |
| Chronic osteomyelitis | | | | | | |
| Norden et al. (186) | Retrospective | 28 | MSSA | Nafcillin | 70% cure | N |
| Senneville et al. (226) | Retrospective | 20 | MSSA | Ofloxacin | 88.2% cure | N |
| Senneville et al. (225) | Retrospective | 50 | Mixed | Quinolone | 2/4 MRSA cases failed therapy | NT |
| Daver et al. (65) | Retrospective | 72 | MRSA/MSSA | Vancomycin | MRSA cases responded poorly (65%) vs MRSA cases (83%) | Y |

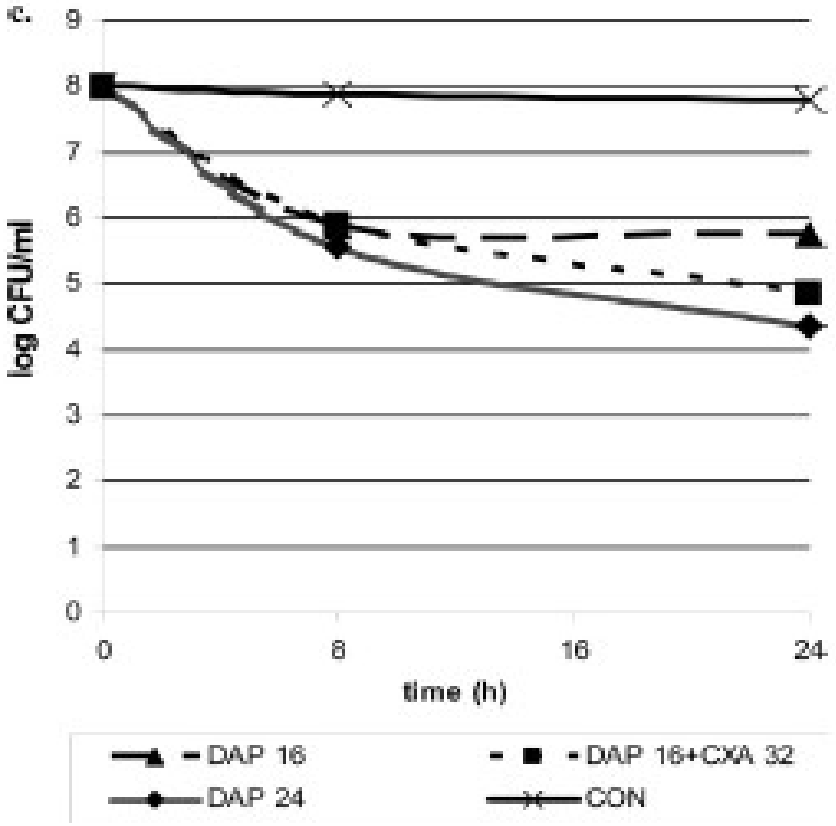
There is a lack of compelling clinical information to support the use of rifampin combination therapy for osteomyelitis. Another important observation was that the vancomycin-rifampin combination for the treatment of osteomyelitis due to MRSA was again associated with clinical failure (65). Unfortunately, the published literature on the diagnosis, treatment, and management of osteomyelitis is inadequate to make any conclusions about antibiotic therapy in general (154).

AAC
JournalsASM.org

# Efficacy of Daptomycin-Cloxacillin Combination in Experimental Foreign-Body Infection Due to Methicillin-Resistant *Staphylococcus aureus*

C. Garrigós,[a] O. Murillo,[a] J. Lora-Tamayo,[a] R. Verdaguer,[b] F. Tubau,[b] C. Cabellos,[a] J. Cabo,[c] and J. Ariza[a]



# Daptomycine (1)

- Pas d'AMM dans les IOA
- Bactéricidie rapide
- Dose dépendance (4mg/kg-12mg/kg)
- Tolérance : surveillance des EI (Dosage CPK, taux résiduel, fonction du morphotype)
- Intérêt +++ si matériel >> activité sur le biofilm et bactérie quiescente

# Daptomycine (2)

- Association à la rifampicine si possible
- Indications : infection à Cocci Gram + résistant ou intolérant au glycopeptides et autres anti staph
- Plus maniable et facilité d'utilisation par rapport à la vancomycine
- Limites : prix, posologie encore non définie

# PHRC : DATIPO

- Évaluer l'efficacité de 2 Durées d'Antibiothérapie (6 s versus 12 s) dans le Traitement des Infections sur Prothèses Ostéo-articulaires (IPOA), avec changement prothétique (en 1T ou 2T long) ou non (lavage articulaire)
- Étude multicentrique, de non infériorité, prospective, randomisée, ouverte
- Stratification sur :
  - la technique chirurgicale (changement prothétique en 1T ou 2T, ou lavage avec maintien de l'implant)
  - la topographie de l'articulation (hanche/genou)
  - le rang de l'infection (1er épisode/2ème épisode et plus)

# Molécules recommandées

| **Bactérie** | **Traitement de 1re intention** | **Autre proposition** |
|---|---|---|
| Staphylocoque méti-sensible | - IV pendant 10 jours avant relais oral : pénicilline M +/- gentamycine<br>- Rifampicine + fluoroquinolone | -Clindamycine + rifampicine<br>- Cotrimoxazole + rifampicine<br>- Fluoroquinolone + acide fusidique<br>- rifampicine+acide fucidique |
| Staphylocoque méti-résistant | Glycopeptide + (rifampicine ou acide fusidique ou fosfomycine) | Rifampicine + acide fusidique<br>Cotrimoxazole + rifampicine<br>Fosfomycine + rifampicine ou acide fusidique |
| Entérocoque | Amoxicilline +/- aminoside (10 j) si résistance de bas niveau | Glycopeptides (teicoplanine) |
| Streptocoque | Amoxicilline+/- rifampicine | Céphalosporine 3e génération |
| Bacille Gram – (sauf *Pseudomonas aeruginosa*) | Céphalosporine 3e génération + fluoroquinolone | Fluoroquinolone + fosfomycine |
| *Pseudomonas aeruginosa* | Ceftazidime en perfusion continue + ciprofloxacine ou amikacine ou tobramycine | Ceftazidime ou imipénème + fosfomycine |

Table VII: doses and ways of administration of antibiotics used for bone and joint infections on osteosynthesis material

| Antibiotics (DCI) | Dose/24h | Regimen |
|---|---|---|
| amoxicillin | 100-200 mg/kg | 4-6 injections IVL<br>3-4 oral intakes |
| cloxacillin<br>oxacillin | 100-200 mg/kg (doses superior to approval – expert advice) | 4-6 injections IVL |
| amoxicillin- clavulanic acid | 100 mg/kg | 4-6 injections IVL<br>3-4 oral intakes |
| cefazolin | 60-80 mg/kg | 4-6 injections IVL or<br>Infusion pump[1] |
| cefotaxim | 100-150 mg/kg | 3 injections IVL |
| ceftriaxone | 30-35 mg/kg | 1-2 injection(s) IVL |
| ceftazidim | 100 mg/kg | Infusion pump[1] or<br>3-4 injections IVL |
| imipenem | 2 à 3 g | 3 to 4 administrations IV or IM |
| meropenem | 3 à 6 g | 3 administrations IV |
| vancomycin[2] | 40-60 mg/kg | Infusion pump[1] |
| teicoplanin[2] | 12 mg/kg/12h for 3-5 days<br>then 12 mg/kg | IVL, IM or s/c |
| gentamycin[3] | 3-4 mg/kg | 1 administration IV<br>30 minutes |
| amikacin[3] | 15 mg/kg | 1 administration IV<br>30 minutes |

Table VII bis: doses and ways of administration of antibiotics used for bone and joint infections on osteosynthesis material

| Antibiotics (DCI) | Dose/24h | Regimen |
|---|---|---|
| ofloxacin | 400-600 mg | 2 à 3 oral intakes<br>2 à 3 injections IVL |
| pefloxacin | 800 mg | 2 oral intakes<br>2 injections IVL |
| levofloxacin<br>(not government approved) | 500 à 750 mg | 1 oral intake<br>1 injection IVL |
| ciprofloxacin | 1,500-2,000 mg<br>800 à 1,200mg | 2 to 3 oral intakes<br>2 to 3 injections IVL |
| clindamycin | 1,800-2,400mg | 3-4 injections IVL<br>3 oral intakes |
| rifampicin | 20 mg/kg | 2 administrations IV<br>30 minutes<br>2-3 oral intakes |
| fusidic acid | 1,500 mg | 2-3 oral intakes<br>2-3 injections IVL |
| fosfomycin | 150-200 mg/kg | 3-4 administrations<br>120 minutes |
| cotrimoxazole | 3,200 mg/640 mg | 2 oral intakes<br>2 injections |
| minocyclin<br>doxycyclin | 200 mg | 2 oral intakes<br>2 injections IV (doxycyclin) |
| linezolid<br>(not government approved) | 1,200 mg | 2 oral intakes<br>2 injections IVL |

JRIOA du 6 mars 2015

Recommandations HAS : Prise en charge d'une infection de prothèse dans le premier mois post opératoire

# Traitement médical

Aurélien Dinh
Infectiologie
Hôpitaux Paris Ile de France Ouest
CRIOA

# Vers une simplification ?

**SPILF/SOFCOT 2007**

- Aminosides initialement systématique
- Atb IV 15j
- Bithérapie le plus longtemps possible
- Dosage AG au pic et dosage des Atb associés à la rfp
- RFP 20 mg/kg/j

**HAS 2014**

- Aminosides si sepsis sévère ou choc
- Atb IV 7j
- Monothérapie dés que possible
- Pas de dosage sauf vanco et AG au résiduel
- RFP 15 mg/kg/j

Merci

## Recommandation 21

| | |
|---|---|
| **AE** | Il est recommandé d'utiliser un aminoside en association avec l'antibiothérapie probabiliste ou avec l'antibiothérapie adaptée si sepsis sévère ou choc septique (cf. bonnes pratiques d'utilisation des aminosides). |

## Recommandation 22

| | |
|---|---|
| **AE** | Il est recommandé d'utiliser les antibiotiques suivants (cf. tableau 2) après identification du micro-organisme et obtention de l'antibiogramme : soit après une antibiothérapie probabiliste soit d'emblée si un micro-organisme a été isolé en préopératoire.<br><br>Il est recommandé d'adapter les doses au poids du patient et à sa fonction rénale. |

Les propositions thérapeutiques dans les tableaux suivants sont données à titre indicatif en l'absence d'études de haut niveau de preuve et ne sont pas limitatives. L'infectiologue en charge du traitement médical adaptera au cas par cas (terrain, allergie, intolérance, etc.).

Il a été décidé de ne pas exprimer les doses en mg/kg afin de faciliter la prescription et la préparation, éviter les surdosages en particulier chez les patients en surpoids.

Chez les patients obèses, il est recommandé de doser les antibiotiques.

Concernant le staphylococcus aureus meticilline sensible (SAMS) et l'utilisation des fluoroquinolones, la ciprofloxacine et la lévofloxacine sont des alternatives à l'ofloxacine. Le recul d'utilisation de l'ofloxacine est supérieur à celui de la lévofloxacine. À noter que la ciprofloxacine a un spectre plus large (anti-*Pseudomonas*) que l'ofloxacine et devrait être réservée aux infections à bactéries Gram négatif.

Concernant le SAMS et l'utilisation de la rifampicine, le choix de ne pas l'introduire immédiatement est dicté par le souci de ne pas induire de résistance en cas d'évolution défavorable (inoculum élevé persistant).

IDSA GUIDELINES

# Diagnosis and Management of Prosthetic Joint Infection: Clinical Practice Guidelines by the Infectious Diseases Society of America[a]

**Douglas R. Osmon,[1] Elie F. Berbari,[1] Anthony R. Berendt,[2] Daniel Lew,[3] Werner Zimmerli,[4] James M. Steckelberg,[1] Nalini Rao,[5,6] Arlen Hanssen,[7] and Walter R. Wilson[1]**

[1]Division of Infectious Diseases, Mayo Clinic College of Medicine, Rochester, Minnesota; [2]Bone Infection Unit, Nuffield Orthopaedic Centre, Oxford University Hospitals NHS Trust, United Kingdom; [3]Division of Infectious Diseases, Department of Internal Medicine, University of Geneva Hospitals, [4]Basel University Medical Clinic, Liestal, Switzerland; [5]Division of Infectious Diseases, Department of Medicine, and [6]Department of Orthopaedic Surgery, University of Pittsburgh School of Medicine, Pennsylvania, and [7]Department of Orthopedics, Mayo Clinic College of Medicine, Rochester, Minnesota

# Procédure diagnostique

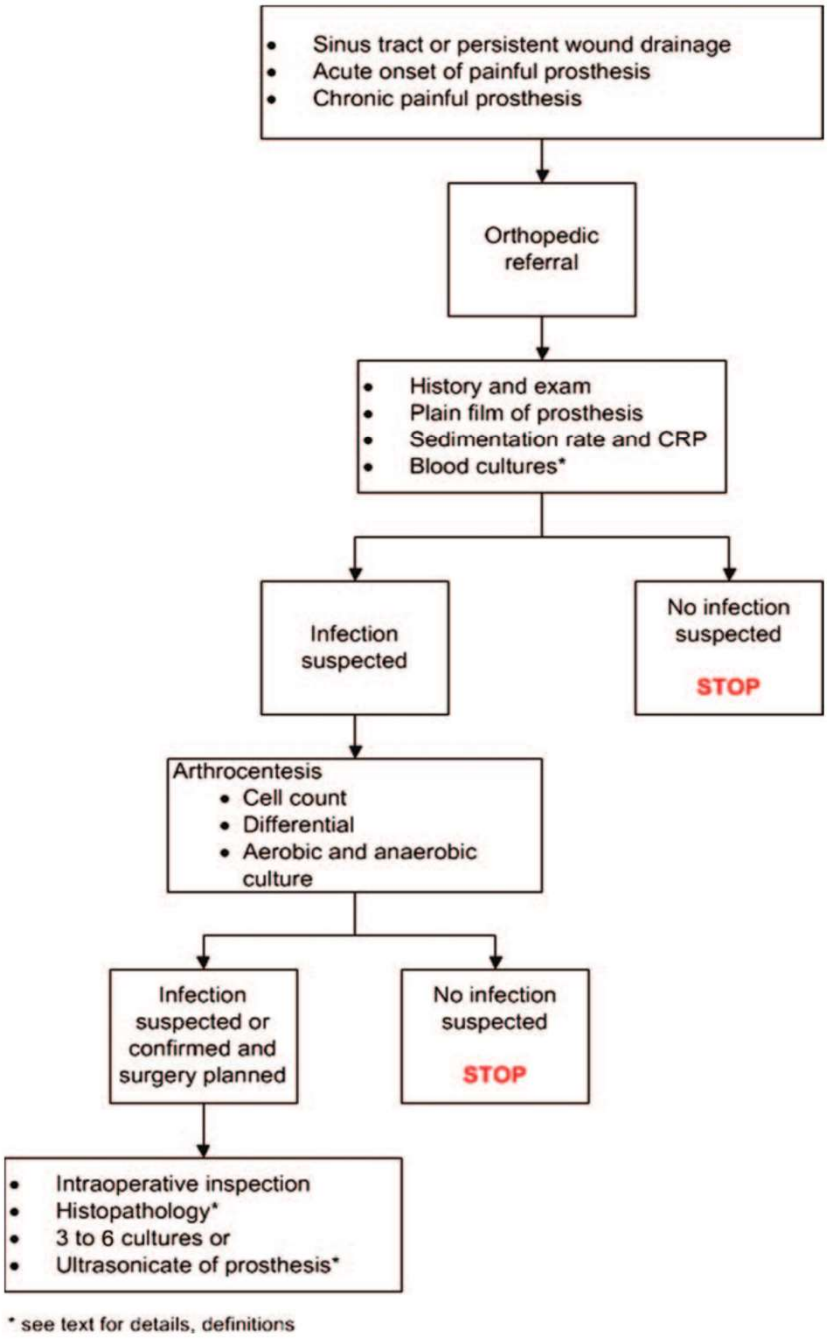



**Figure 1.** Preoperative and intraoperative diagnosis of prosthetic joint infection. Abbrevation: CRP, C-reactive protein.

IDSA 2014

**Table 2. Intravenous or Highly Bioavailable Oral Antimicrobial Treatment of Common Microorganisms Causing Prosthetic Joint Infection (B-III Unless Otherwise Stated in Text)**

| Microorganism | Preferred Treatment[a] | Alternative Treatment[a] | Comments |
|---|---|---|---|
| Staphylococci, oxacillin-susceptible | Nafcillin[b] sodium 1.5–2 g IV q4-6 h<br>or<br>Cefazolin 1–2 g IV q8 h<br>or<br>Ceftriaxone[c] 1–2 g IV q24 h | Vancomycin IV 15 mg/kg q12 h<br>or<br>Daptomycin 6 mg/kg IV q 24 h<br>or<br>Linezolid 600 mg PO/IV every 12 h | See recommended use of rifampin as a companion drug for rifampin-susceptible PJI treated with debridement and retention or 1-stage exchange in text |
| Staphylococci, oxacillin-resistant | Vancomycin[d] IV 15 mg/kg q12 h | Daptomycin 6 mg/kg IV q24 h<br>or<br>Linezolid 600 mg PO/IV q12 h | See recommended use of rifampin as a companion drug for rifampin-susceptible PJI treated with debridement and retention or 1-stage exchange in text |
| *Enterococcus* spp, penicillin-susceptible | Penicillin G 20–24 million units IV q24 h continuously or in 6 divided doses<br>or<br>Ampicillin sodium 12 g IV q24 h continuously or in 6 divided doses | Vancomycin 15 mg/kg IV q12 h<br>or<br>Daptomycin 6 mg/kg IV q24 h<br>or<br>Linezolid 600 mg PO or IV q12 h | 4–6 wk. Aminoglycoside optional<br>Vancomycin should be used only in case of penicillin allergy |
| *Enterococcus* spp, penicillin-resistant | Vancomycin 15 mg/kg IV q12 h | Linezolid 600 mg PO or IV q12 h<br>or<br>Daptomycin 6 mg IV q24 h | 4–6 wk. Addition of aminoglycoside optional |
| *Pseudomonas aeruginosa* | Cefepime 2 g IV q12 h<br>or<br>Meropenem[e] 1 g IV q8 h | Ciprofloxacin 750 mg PO bid<br>or 400 mg IV q12 h<br>or<br>Ceftazidime 2 g IV q8 h | 4–6 wk<br>Addition of aminoglycoside optional<br>Use of 2 active drugs could be considered based on clinical circumstance of patient. If aminoglycoside in spacer, and organism aminoglycoside susceptible than double coverage being provided with recommended IV or oral monotherapy |
| *Enterobacter* spp | Cefepime 2 g IV q12 h<br>or<br>Ertapenem 1 g IV q24 h | Ciprofloxacin 750 mg PO or 400 mg IV q12 h | 4–6 wk. |
| Enterobacteriaceae | IV β-lactam based on in vitro susceptibilities<br>or<br>Ciprofloxacin 750 mg PO bid | | 4–6 wk |
| β-hemolytic streptococci | Penicillin G 20–24 million units IV q24 h continuously or in 6 divided doses<br>or<br>Ceftriaxone 2 g IV q24 h | Vancomycin 15 mg/kg IV q12 h | 4–6 wk<br>Vancomycin only in case of allergy |

**Table 3. Common Antimicrobials Used for Chronic Oral Antimicrobial Suppression (B-III Unless Otherwise Stated in Text)[a,b]**

| Microorganism | Preferred Treatment | Alternative Treatment |
|---|---|---|
| Staphylococci, oxacillin-susceptible | Cephalexin 500 mg PO tid or qid<br>or<br>Cefadroxil 500 mg PO bid | Dicloxacillin 500 mg PO tid or qid<br>Clindamycin 300 mg PO qid<br>Amoxicillin-clavulanate 500 mg PO tid |
| Staphylococci, oxacillin-resistant | Cotrimoxazole 1 DS tab PO bid<br>Minocycline or doxycycline100 mg PO bid | |
| β-hemolytic streptococci | Penicillin V 500 mg PO bid to qid<br>or<br>Amoxicillin 500 mg PO tid | Cephalexin 500 mg PO tid or qid |
| *Enterococcus* spp, penicillin susceptible | Penicillin V 500 mg PO bid to qid<br>or<br>Amoxicillin 500 mg PO tid | |
| *Pseudomonas aeruginosa* | Ciprofloxacin 250–500 mg PO bid | |
| Enterobacteriaceae | Cotrimoxazole 1 DS tab PO bid | β-lactam oral therapy based on in vitro susceptibilities |
| *Propionibacterium* spp | Penicillin V 500 mg PO bid to qid<br>or<br>Amoxicillin 500 mg PO tid | Cephalexin 500 mg PO tid or qid<br><br>Minocycline or doxycycline 100 mg PO bid |

# Daptomycine : Données expérimentales

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## Efficacy of Usual and High Doses of Daptomycin in Combination with Rifampin versus Alternative Therapies in Experimental Foreign-Body Infection by Methicillin-Resistant *Staphylococcus aureus* ▽†

C. Garrigós,[1]* O. Murillo,[1] G. Euba,[1] R. Verdaguer,[2] F. Tubau,[2] C. Cabellos,[1] J. Cabo,[3] and J. Ariza[1]

TABLE 1. Decreases in bacterial counts from TCF at day 8 and day 11 and bacterial counts recovered from CVs at day 11

| Therapy regimen or group[a] | Bacterial count, mean log CFU/ml ± SD (no. of samples)[b] | | |
|---|---|---|---|
| | TCF | | CVs |
| | Day 8 | Day 11 | |
| Monotherapies | | | |
| RIF | −2.59 ± 0.91 (20)** | −2.75 ± 1.35 (19)* | 1.69 ± 1.26 (19)* |
| DAP100 | −3.14 ± 0.74 (15)** | −3.59 ± 0.49 (15)*** | 1.88 ± 0.92 (15) |
| DAP45 | −2.54 ± 1.21 (25)* | −2.71 ± 1.56 (22)* | 2.11 ± 1.41 (22) |
| Combination therapies | | | |
| LNZ+RIF | −2.38 ± 1.17 (20) | −3.23 ± 1.45 (19) | 1.76 ± 1.27 (19) |
| VAN+RIF | −2.62 ± 1.19 (20) | −3.73 ± 1.48 (20) | 1.23 ± 0.52 (20) |
| DAP100+RIF | −4.57 ± 0.69 (17)†† | −4.58 ± 0.68 (17)†† | 0.95 ± 0.13 (17)†† |
| DAP45+RIF | −4.21 ± 0.99 (18)†† | −4.38 ± 0.92 (18)† | 0.91 ± 0.32 (18)†† |
| Control | 0.66 ± 1.24 (19) | 1.14 ± 1.16 (11) | 5.58 ± 0.97 (11) |

[a] RIF, rifampin; DAP100, daptomycin at 100 mg/kg/day; DAP45, daptomycin at 45 mg/kg/day; LNZ, linezolid; VAN, vancomycin.
[b] Data for vancomycin and linezolid alone are not shown. All therapeutic groups performed significantly better than controls ($P < 0.05$). Among monotherapies, *, $P < 0.05$ versus linezolid; **, $P < 0.05$ versus linezolid and vancomycin; and ***, $P < 0.05$ versus linezolid, vancomycin, rifampin, and daptomycin at 45 mg/kg/day. Among combination therapies, †, $P < 0.05$ versus linezolid-rifampin, and ††, $P < 0.05$ versus linezolid-rifampin and vancomycin-rifampin.

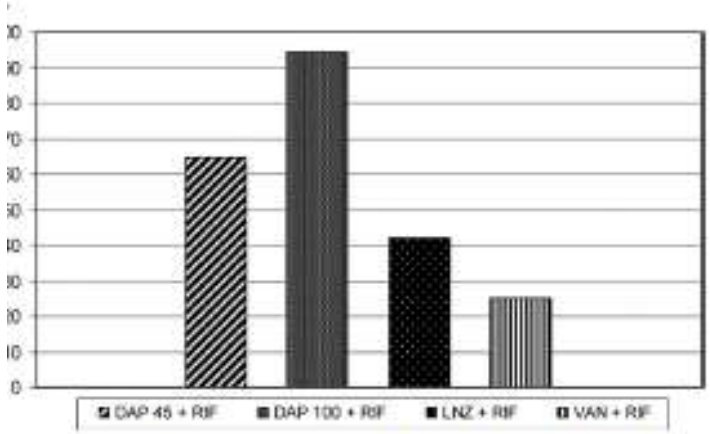


FIG. 2. Cure rates of infection for antibiotic combinations with rifampin at day 11. Data for antibiotics alone are not shown. LNZ, linezolid; VAN, vancomycin; RIF, rifampin; DAP45, daptomycin at 45 mg/kg/day; DAP100, daptomycin at 100 mg/kg/day.

« N’ayez pas peur »

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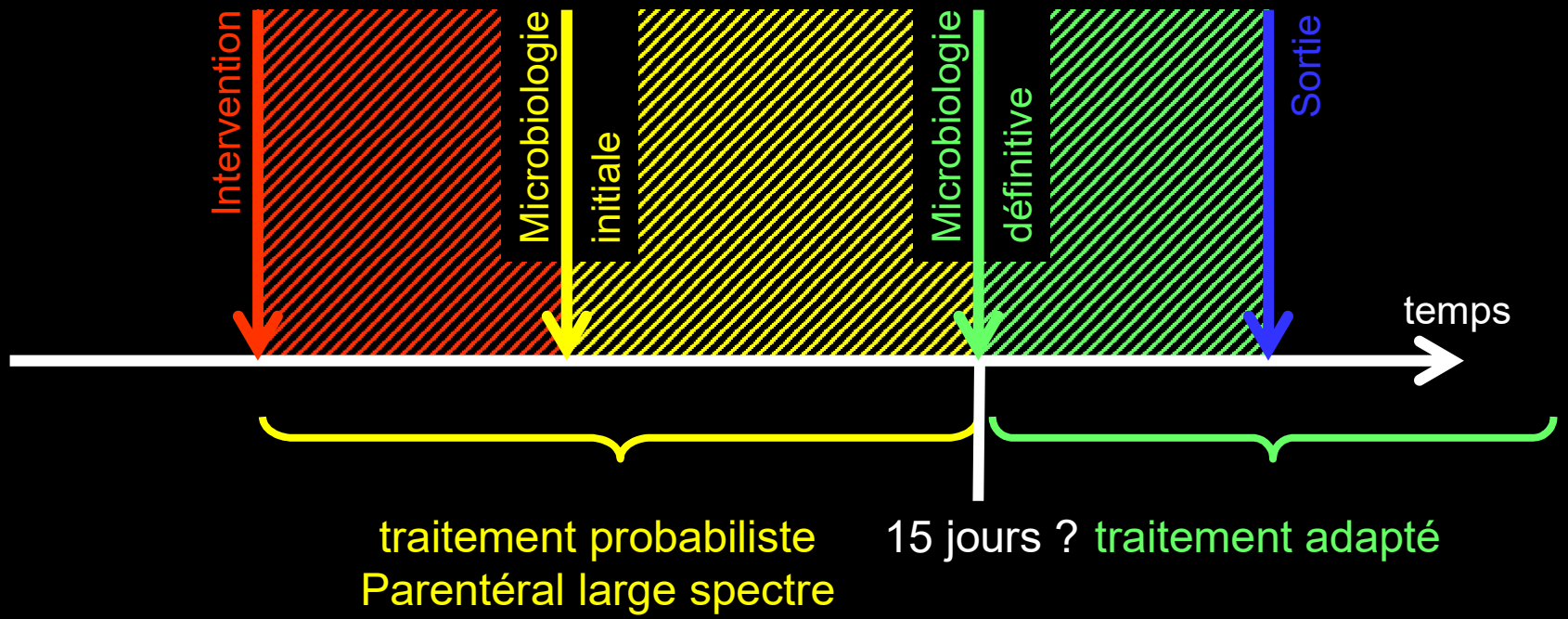
# Chronogramme de la prise en charge



# Efficacité de l'antibiothérapie post opératoire immédiate

## Outcome and Predictors of Treatment Failure in Total Hip/Knee Prosthetic Joint Infections Due to *Staphylococcus aureus*

**Eric Senneville, Donatienne Joulie, Laurence Legout, Michel Valette, Hervé Dezèque, Eric Beltrand, Bernadette Roselé, Thibaud d'Escrivan, Caroline Loïez, Michèle Caillaux, Yazdan Yazdanpanah, Carlos Maynou, and Henri Migaud**

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***Background.*** Variables associated with the outcome of patients treated for prosthetic joint infections (PJIs) due to *Staphylococcus aureus* are not well known.

***Methods.*** The medical records of patients treated surgically for total hip or knee prosthesis infection due to *S. aureus* were reviewed. Remission was defined by the absence of local or systemic signs of implant-related infection assessed during the most recent contact with the patient.

***Results.*** After a mean posttreatment follow-up period of 43.6 ± 32.1 months, 77 (78.6%) of 98 patients were in remission. Retention of the infected implants was not associated with a worse outcome than was their removal. Methicillin-resistant *S. aureus* (MRSA)–related PJIs were not associated with worse outcome, compared with methicillin-susceptible *S. aureus* (MSSA)–related PJIs. Pathogens identified during revision for failure exhibited no acquired resistance to antibiotics used as definitive therapy, in particular rifampin. In univariate analysis, parameters that differed between patients whose treatment did or did not fail were: American Society of Anesthesiologists (ASA) score, prescription of adequate empirical postsurgical antibiotic therapy, and use of rifampin combination therapy upon discharge from hospital. In multivariate analysis, ASA score ≤2 (odds ratio [OR], 6.87 [95% confidence interval {CI}, 1.45–32.45]; $P = .04$) and rifampin-fluoroquinolone combination therapy (OR, 0.40 [95% CI, 0.17–0.97]; $P = .01$) were 2 independent variables associated with remission.

***Conclusions.*** The results of the present study suggest that the ASA score significantly affects the outcome of patients treated for total hip and knee prosthetic infections due to MSSA or MRSA and that rifampin combination therapy is associated with a better outcome for these patients when compared with other antibiotic regimens.

# Perfusion continue Vancomycine

- **Perfusion continue de vancocine ou de ß-lactamines**

  -plusieurs études : efficacité+++

  -os = tissu peu perméable
  taux sérique constant élevé = diffusion
  taux constant > 8xCMI

  -efficace
  -économique
  -meilleure qualité de vie

  } Antibiothérapie Parentérale Ambulatoire

L. Bernard, J Clin Pharm Ther. 2001 Dec;

INVITED ARTICLE CLINICAL PRACTICE

Ellie J. C. Goldstein, Section Editor

# Systemic Antibiotic Therapy for Chronic Osteomyelitis in Adults

**Brad Spellberg[1,2] and Benjamin A. Lipsky[3,4]**

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**Table 1. Bone Penetration of Parenteral Antibiotics: Data From Clinical Studies**

| Drug (Dose) | Patients, No. | Serum Level, Mean, μg/mL | Bone Level, Mean, μg/g | Ratio of Bone/Serum Levels, % |
|---|---|---|---|---|
| Agents Predominantly Used to Treat Gram-Positive Infections | | | | |
| Oxacillin (2 g) | NA | NA | NA | 10[a] |
| Ampicillin (2 g) | 20 | NA | 12 | 17[b] |
| Sulbactam (1 g) | | | 7 | 12[b] |
| Ampicillin (1 g) | 40 | NA | 20 | 33[b] |
| Sulbactam (0.5 g) | | | 5 | 17[b] |
| Cefazolin (1 g) | 35 | 80 | 10 (knee), 30 (hip) | 13 (knee), 37 (hip) |
| Cefazolin (1 g) | 20 | 45 | 8 | 18 |
| Cefazolin (1 g) | 17 | 52 | 6 | 11.5 |
| Cefazolin (2 g) | 6 | 98 | 15 | 15 |
| Cefazolin (1 g) | 48 | NA | 6 | 7.5[b] |
| Cefazolin (1–2 g) | 16 | 25–216 | 3–10 | <10 |
| Vancomycin (1 g) | 14 | 22 (medullary) | 2.3 (medullary) | 10 |
| | | 22 (cortical) | 1.1 (cortical) | 5 |
| | | 16.8 (infected) | 3.6 (infected) | 21 |
| Daptomycin (6 mg/kg) | 4 | 73 | 5 | 7 |
| Agents Predominantly Used to Treat Gram-Negative Infections | | | | |
| Ceftriaxone (1 g) | 13 | 104 | 20 ± 6 | 19 |
| Ceftriaxone (2 g) | 40 | 130 | 19 ± 7 (medullary) | 15 |
| | | | 6.5 ± 1.6 (cortical) | 5 |
| Ceftriaxone (2 g) | 42 | NA | 17 ± 9 (medullary) | NA |
| | | | 3 ± 0.7 (cortical) | NA |
| Ceftazidime (2 g) | 10 | 150 | 5 (ischemic legs) | 3 |
| Ceftazidime (1 g) | 43 | NA | 20 | 27[c] |
| Imipenem (500 mg) | 6 | NA | 6 (infected) | 48[c] |
| Cefepime (2 g) | 10 | 73 ± 24 | 74 ± 16 (cancellous) | 100 |
| | | | 68 ± 12 (cortical) | 87 |
| Imipenem (1 g) | 16 | NA | 4 | 16[c] |
| Imipenem (500 mg) | 10 | 13 | 2.6 (infected) | 20 |
| Meropenem (500 mg) | 15 | 30 | 5.75 | 17 |
| Piperacillin (3 g)/tazobactam (0.375 g) | 10 | NA | NA | 20/25[d] |
| Piperacillin (4 g) | NA | 200 | 15 | 7.5 |
| Piperacillin (2 g) | 18 | 95 | 5 | 5 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Ciprofloxacin | 7 | 500 mg | Oral | 1.4 (0.4–2) | 0.4 (0.2–0.9) | 30 |
| | 7 | 750 mg | Oral | 2.6 (0.9–4) | 0.7 (0.2–1.4) | 27 |
| | 6 | 500 mg | Oral | 2.0 (0.9–3) | 0.7 (0.2–1.4)[a] | 35 |
| | 4 | 750 mg | Oral | 2.9 (1–6) | 1.4 (0.6–2.7)[a] | 48 |
| Ciprofloxacin | 20 | 200 mg | Intravenous | NA | 2 (medullary) | 66 |
| | | | | | 1.4 (cortical) | 47[b] |
| Ciprofloxacin | 15 | 200 mg | Intravenous | NA | 0.1–0.9 | 3–30[b] |
| Levofloxacin | 9 | 500 mg | Intravenous | 8 | 6 (medullary) | 75 |
| | | | | | 3 (cortical) | 38 |
| Levofloxacin | 12 | 500 mg | Intravenous | 7.5 | 7.4 (medullary) | 99 |
| | | | | | 3.9 (cortical) | 50 |
| Enoxacin | 24 | 400 mg | Oral or | 2.4 | 0.9 | 37.5 |
| | 7 | | Intravenous | | 1.3[b] | 55 |
| Moxifloxacin | 10 | 400 mg | Intravenous | 4.9 | 1.9 (medullary) | 39 |
| | | | | | 1.3 (cortical) | 27 |
| | 10 | 400 mg | Oral | 3.7 | 1.8 (medullary) | 49 |
| | | | | | 1.6 (cortical) | 43 |
| Linezolid | 13 | 600 mg | Oral | NA | 4 | 40[c] |
| Linezolid | 12 | 600 mg | Oral | NA | 9 | 51[c] |
| Linezolid | 10 | 600 mg | Oral | 23 | 8.5 | 37 |
| TMP-SMX | 14 | 1 DS tablet twice daily for 2 d | Oral | 7.4/143 | 3.7/19 | 50/15 |
| Doxycycline | 6 | 200 mg | Intravenous | NA | 2.6 | 86[a] |
| Doxycycline | 25 | 200 mg | Intravenous | NA | 0.2 | 6[a] |
| Doxycycline | 34 | 200 mg | Intravenous | 6 | 0.13 | 2 |
| Clindamycin | 13 | 600 mg | Intravenous or intramuscular | NA | 5 | 67[a] |
| Clindamycin | 27 | 300 mg | Intramuscular | 7.33 | 2.63 | 40 |
| Clindamycin | 23 | 600 mg | Intravenous | 8.5 | 3.8 | 45 |
| Metronidazole | 16 | 500 mg | Intravenous | NA | 14 | 100[a] |
| Metronidazole | 17 | 1500 mg | Intravenous | 34 | 27 | 79 |
| Rifampin | 32 | 300 mg | Intravenous | 2 | 5 (1.4–8.8) | >100[c] |
| Fusidic acid in infected bone[d] | 15 | 500 mg 3 times daily | Oral | NA | 7.3 (1.7–14.9) | |
| | 14 | 1 g 3 times daily | Oral | NA | 9.8 (3.4–14.8) | |
| Fusidic acid in uninfected bone | 9 | 500 mg 3 times daily for 5 d | Oral | 27 (2–109) | 12 (1–40) | 44 |
| | 15 | 500 mg 3 times daily for 6–10 d | Oral | 45 (5–166) | 21 (2–75) | 47 |
| | 14 | 500 mg 3 times daily for >10 d | Oral | 27 (3–59) | 25 (3–79) | 93 |

**Table 4. Cure Rates in Nonrandomized Clinical Trials for Oral Treatment of Chronic Osteomyelitis With or Without Infected Prosthesis in Adults**

| Drug | Dose (Duration)[a] | Follow-up | Cure,[b] % (No. of Patients) | Comment |
|---|---|---|---|---|
| Fluoroquinolones | | | | |
| Ciprofloxacin | 500–750 mg twice daily (3–4 mo) | 1 y | 33 (12/36) | All cured patients had foreign material removed; 1/3 underwent debridement |
| Ciprofloxacin | 750 mg twice daily (3–4 mo) | 6 mo | 91 (21/23) | Cure defined as resolution or improvement |
| Ciprofloxacin | 750 mg twice daily (3 mo) | 7–21 mo | 65 (13/20) | Only 7/13 *Pseudomonas* infections cured; all debrided |
| Ciprofloxacin | 750 mg twice daily (2–4 mo) | 1–17 mo | 77 (17/22) | 4 patients who failed therapy with *Pseudomonas*; 20 debrided |
| Ciprofloxacin | 750 mg twice daily (1–6 mo) | 0–22 mo | 48 (14/29) | 7/12 *Pseudomonas* and 4/9 *Staphylococcus aureus* infections cured |
| Ciprofloxacin or nafcillin, clindamycin, or gentamicin | 750 mg by mouth twice daily (12–64 d) (ciprofloxacin); or varying doses and durations | 25–39 mo | 79 (11/14) for ciprofloxacin vs 83 (10/12) for intravenous therapy | Not randomized; patients were sequentially enrolled in the 2 arms |
| Ciprofloxacin | 200 mg intravenous twice daily, then 750 mg by mouth twice daily | ? | 67 (6/9) | Unknown duration of treatment; 5/7 *Pseudomonas* infections cured |
| Ciprofloxacin | 200 mg intravenous twice daily, then 750 mg by mouth twice daily | ? | 83 (10/12) | Unknown duration of treatment |
| Ciprofloxacin | 500–1500 mg twice daily (0.5–18 mo) | ? | 68 (30/44) | *Pseudomonas* eradicated microbiologically in 20/28 |
| Levofloxacin | 500 mg/d | ? | 60 (9/15 ) | Failure of cure in 6 patients with *S. aureus* and 1 with *Pseudomonas* infection |
| Pefloxacin | 400 mg/12 h intravenous for 4 doses, then 400 mg/12 h by mouth (3–6 mo) | ? | 76 (29/38) | All cured patients had foreign material removed; 1/3 underwent debridement |
| Ofloxacin | 200 mg/8–12 h (3–6 mo) | | | |
| Ciprofloxacin | 500–750 mg/12 h (3–6 mo) | | | |
| Ofloxacin | 200 mg 3 times daily (4–6 wk) | >6 mo | 85 (98/115) | Failure of cure in 3/15 patients with *Pseudomonas* and 5/74 with *S. aureus* infection; debridement in 113 |
| Ciprofloxacin | 750–1000 mg twice daily (3 mo) | 12 mo | 61 (19/31) | No benefit from higher dose; all had soft tissue, but not bone, debrided |
| Ofloxacin + rifampin | Ofloxacin: 200 mg 3 times daily; rifampin: 300 mg 3 times daily (both, 6–9 mo) | >6 mo | 71 (35/49) | All infections of prostheses |
| Levofloxacin + rifampin | Levofloxacin: 500 mg/d; rifampin: 600 mg/d (both, >6 wk) | >6 mo | 72 (18/25) | All had prosthetic bone implants; mean duration of therapy, 5 mo for those cured and 2.6 mo for those without cure |
| Rifampin + (ofloxacin or fusidic acid) | Rifampin: 900 mg/d; ofloxacin: 200 mg 3 times daily; fusidic acid: 500 mg 3 times daily for 5 d, then twice daily (both, >6 mo) | Mean, 24 mo (range, 12–36 mo) | 55 (11/20) | All patients had orthopedic implants, only 14 of which were removed; patients were assigned to treatment arm by year of birth (ofloxacin for even years, fusidic acid for odd years) |

*Table 4 continued.*

| Drug | Dose (Duration)[a] | Follow-up | Cure,[b] % (No. of Patients) | Comment |
|---|---|---|---|---|
| | | | 50 (11/22) | |
| Other Agents | | | | |
| Rifampin + various other antibiotics | 600 mg/d (6 mo) | Variable | 50 (7/14) | All cases refractory to prior therapy |
| Rifampin + quinolone vs other antibiotics | When used, rifampin at 20 mg/kg, divided into 2 daily doses (not to exceed 1800 mg/d) | Mean, 44 ± 32 mo | 98 (37/39) vs 68 (40/59) | All patients had *S. aureus* prosthetic joint infections; 29 received rifampin in combination with nonquinolone antibiotics; in multivariate analysis, rifampin-quinolone combination had an odds ratio of 0.4 (95%, CI 0.17–0.97) for failure |
| Rifampin + levofloxacin (prospective) vs historical cohort with variable antibiotics, without or with rifampin | When used, rifampin at 900 mg/d (3–6 mo) | ? | 93 (13/14) (prospective) vs 63 (34/56) (historical without rifampin) vs 68 (21/31) (historical with rifampin) | All had retained prosthetic joints; by multivariate analysis, hazard ratio for treatment failure was 1.0 for historical cohort without rifampin, 0.55 (95%, CI 0.25–1.26) for historical cohort with rifampin, 0.11 (95%, CI 0.01–0.84) for prospective rifampin cohort ($P = .03$) |
| Linezolid | 600 mg/12 h | ? | 60 (45/89) | Compassionate use program |
| Clindamycin | 50–150 mg/6 h (mean, 16 wk) | Variable | 42 (5/12) | … |
| TMP-SMX | 1–2 DS tablet twice daily | ? | 83 (5/6) | No patients had debridement |
| TMP-SMX | 1 DS tablet twice daily (4–8 wk) | 11–70 mo | 45 (30/66) | 55% of patients had debridement |
| TMP-SMX + rifampin | TMP: 3.5 mg/kg twice daily; rifampin: 600–1200 mg/d (mean, 5 wk for both) | 6 mo to 5 y | 100 (27/27) | All patients had debridement |
| TMP-SMX with or without rifampin | DS tablet twice daily; rifampin: 300–450 mg twice daily (median, 10 wk for both) | 2 y | 82 (28/34) | 10 patients had debridement, all of whom were cured |
| TMP-SMX | TMP: 5 mg/kg twice daily (6–9 mo) | 24–75 mo | 67 (26/39) | 11 patients had device removed |
| TMP-SMX | Dose unclear (6 mo) | 12–60 mo | 98 (59/60) | All patients had debridement |
| (TMP-SMX or linezolid) + rifampin | TMP: 8 mg/kg; linezolid: 600 mg twice daily; rifampin: 10 mg/kg twice daily (all given intravenously for 1 wk and then by mouth) | ≥12 mo | 89 (37/41) | 20 patients with chronic osteomyelitis and 56 with orthopedic implant infections; mean treatment durations were 15 wk (range, 1–53 wk) for TMP-SMX–based therapy and 18 wk (8–36 wk) for linezolid-based therapy; adverse event rates were similar (46% vs 43%), as were discontinuation rates (14% vs 21%) |
| | | | 79 (29/38) | |

**Table 5. Cure Rates in Randomized Clinical Trials of Antibiotics for Chronic Osteomyelitis With or Without Infected Prosthesis in Adults**

| Drug | Dose (Duration) | Follow-up | Cure,[a] % (No. of Patients) | Comment |
|---|---|---|---|---|
| Ceftazidime vs ticarcillin + tobramycin | Ceftazidime: 2 g/12 h intravenous; ticarcillin: 3 g/4 h intravenous; tobramycin: 1.5 mg/kg/8 h intravenous (mean, 35 d; range, 26–63 d) | 2–31 mo | 67 (6/9) vs 100 (9/9) | Open label; all patients had debridement |
| (Vancomycin or oxacillin) + (rifampin vs pyridium placebo) | Vancomycin: 1 g/12 h intravenous; oxacillin: 3 g/6 h intravenous; rifampin: 600 mg/d by mouth | ? | 90 (9/10) vs 62 (8/13) | Double-blind study |
| Nafcillin vs (nafcillin + rifampin) | Nafcillin: 20 mg/kg/4 h intravenous; rifampin: 600 mg/12 h by mouth (mean, 6 wk) | 9–36 mo | 80 (8/10) vs 50 (4/8) | Open label; 16 patients had debridement |
| Linezolid vs (ampicillin-sulbactam or amoxicillin-clavulonate) | Linezolid: 600 mg twice daily, by mouth or intravenous; ampicillin-sulbactam: 1.5–3 g/6 h intravenous; amoxicillin-clavulonate: 500–875 mg by mouth 2 or 3 times daily | ? | 61 (27/44) vs 69 (11/16) | Open label; part of larger trial of diabetic patients with soft-tissue infections; patients requiring >4 wk of therapy were excluded |
| Ciprofloxacin + (rifampin vs placebo) | Ciprofloxacin: 750 mg by mouth twice daily; rifampin: 450 mg by mouth twice daily (3–6 mo) | Median, 3 y | 100 (12/12) vs 58 (7/12) | Double-blind study |
| Ciprofloxacin vs ''appropriate antimicrobial therapy'' | 750 mg by mouth twice daily (treatment for ≥6 wk) | ? | 50 (7/14) vs 69 (11/16) | For patients infected with *Pseudomonas*, cure rate were 3/8 for ciprofloxacin vs 7/9 for comparator antibiotics |
| Ciprofloxacin vs ceftazidime | Ciprofloxacin: 200 mg intravenous twice daily, then 500 mg by mouth twice daily; ceftazidime: 2 g/12 h intravenous | ? | 67 (2/3) vs 100 (3/3) | Part of larger study of serious gram-negative infections; open label |
| Ciprofloxacin vs (ceftazidime or nafcillin + amikacin) | Ciprofloxacin: 750 mg by mouth twice daily; other antibiotics: ? doses (mean, 8 wk) | 1 y | 77 (24/31) vs 79 (22/28) | Open label; all patients had debridement |
| Ciprofloxacin vs lomefloxacin | Ciprofloxacin: 750 mg by mouth twice daily; lomefloxacin: 800 mg by mouth twice daily | Median, 8 mo (range, 0–36 mo) | 40 (2/5) | Open label; 5 failures with ofloxacin were due to infections with *Pseudomonas* (n = 2) or *Staphylococcus aureus* (n = 3) |
| | | | 71 (5/7) | |
| Ofloxacin vs (ceftazidime or cefazolin) | Ofloxacin: 400 mg by mouth twice daily (mean, 8 wk); ceftazidime: 2 g/12 h intravenous (mean, 4 wk); cefazolin: 1 g/8 h intravenous (mean, 4 wk) | Mean, 1.5 y | 74 (14/19) vs 86 (12/14) | Open label; part of larger study of soft-tissue foot infections in diabetic patients |
| Ofloxacin vs ampicillin-sulbactam followed by amoxicillin-clavulonate | Ofloxacin: 400 mg by mouth twice daily; ampicillin-sulbactam: 1–2 g/6 h intravenous; amoxicillin-clavulonate: 500 mg by mouth 3 times daily | 3–4 wk | 39 (6/16) vs 20 (1/5) | Open label |
| Ofloxacin vs imipenem | Ofloxacin: 400 mg by mouth twice daily; imipenem: | ? | 69 (11/16) vs 50 (8/16) | All patients had debridement |
| | 500 mg/6 h intravenous | | | |
| Cloxacillin vs (TMP-SMX + rifampin) | Cloxacillin: 2 g/4 h intravenous; TMP: 7–8 mg/kg by mouth twice daily; rifampin: 600 mg/d by mouth (8 wk) | Mean, 10 y | 90 (19/21) vs 89 (24/27) | Open label; all patients had debridement |

INVITED ARTICLE CLINICAL PRACTICE
Ellie J. C. Goldstein, Section Editor

# Systemic Antibiotic Therapy for Chronic Osteomyelitis in Adults

**Brad Spellberg[1,2] and Benjamin A. Lipsky[3,4]**

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## Randomized Clinical Trials

There have been few randomized trials of systemic therapy for osteomyelitis in adults. A systematic review published in 2009 found only 8 small trials, with a total of 228 evaluable subjects [158]. A composite analysis of the 5 trials that compared oral with parenteral treatment found no significant difference in remission rate at ≥12 months of follow-up, but the rate of moderate or severe adverse events was significantly higher with parenteral than with oral agents (15.5% vs 4.8%, respectively).

INVITED ARTICLE CLINICAL PRACTICE

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Adjunctive rifampin therapy has been studied in 2 randomized clinical trials of patients with chronic osteomyelitis caused by *S. aureus* [159, 160] (Table 5). Summarizing their results, more patients who received rifampin in addition to other antibiotics were cured compared with those who did not (17 of 20 [85%] vs 12 of 21 [57%]; $P = .05$ by Fisher's exact test), and no patient terminated therapy due to rifampin-related adverse effects. In another trial, Zimmerli et al [163] randomized patients with prosthetic devices infected with *Staphylococcus* spp. to receive either rifampin or placebo, plus ciprofloxacin, for 3–6 months. In the per-protocol population, cure rates were 100% for rifampin-treated versus 58% for placebo-treated patients ($P < .02$). Of note, the causative pathogen in 4 of the 5 patients whose infection failed to respond to ciprofloxacin monotherapy developed resistance to ciprofloxacin.

INVITED ARTICLE CLINICAL PRACTICE
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## Parenteral Therapy

In nonrandomized studies of adults with chronic osteomyelitis, 4–6 weeks of parenteral β-lactam antibiotic therapy has cured 60%–90% of cases (Table 3). The varying cure rates may be related to variable diagnostic criteria, use of concomitant surgical debridement (specifically reported in only 2 studies [107, 108]), or duration of follow-up. In multiple studies, the cure rates of infections caused by *Pseudomonas* were lower than those for other pathogens [108, 109, 112].

### Oral Therapy: Fluoroquinolones

There are more studies of fluoroquinolones for treating chronic osteomyelitis than of all other antibiotic classes (Table 4). Cross-study comparisons are difficult because of the varied criteria for enrollment, utilization of debridement, antibiotic dosing regimens, duration of follow-up, and definitions of cure. Nevertheless, we draw several general inferences from these studies.

1. Most studies reported cure rates of 60%–80% [129, 138, 139].
2. Cure rates were similar to debridement rates (when reported), but because none of the studies specifically reported cure rates of patients who did and did not undergo debridement, the benefit of debridement can only be inferred.
3. The majority of failures occurred in patients infected with *Pseudomonas*, and to a lesser extent, patients infected with *S. aureus*.
4. Therapy was typically given for 12–16 weeks, and at doses higher than those used for most other infections (eg, ciprofloxacin at ≥1500 mg/d), but it is not possible from the available data to conclude that this high-dose and prolonged treatment is necessary.

Clinical Infectious Diseases Advance Access published December 6, 2012

IDSA GUIDELINES

# Diagnosis and Management of Prosthetic Joint Infection: Clinical Practice Guidelines by the Infectious Diseases Society of America[a]

Douglas R. Osmon,[1] Elie F. Berbari,[1] Anthony R. Berendt,[2] Daniel Lew,[3] Werner Zimmerli,[4] James M. Steckelberg,[1] Nalini Rao,[5,6] Arlen Hanssen,[7] and Walter R. Wilson[1]

## III. What is the medical treatment for a patient with PJI following debridement and retention of the prosthesis?

### *Recommendations*

*Staphylococcal PJI*

23. Two to 6 weeks of a pathogen-specific intravenous antimicrobial therapy (Table 2) in combination with rifampin 300–450 mg orally twice daily followed by rifampin plus a companion oral drug for a total of 3 months for a THA infection and 6 months for a total knee arthroplasty (TKA) infection (**A-I**). Total elbow, total shoulder, and total ankle infections may be managed with the same protocols as THA infections (**C-III**). Recommended oral companion drugs for rifampin include ciprofloxacin (**A-I**) or levofloxacin (**A-II**).

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Secondary companion drugs to be used if in vitro susceptibility, allergies, intolerances, or potential intolerances support the use of an agent other than a quinolone include but are not limited to co-trimoxazole (**A-II**), minocycline or doxycycline (**C-III**), or oral first-generation cephalosporins (eg, cephalexin) or antistaphylococcal penicillins (eg, dicloxacillin; **C-III**). If rifampin cannot be used because of allergy, toxicity, or intolerance, the panel recommends 4–6 weeks of pathogen-specific intravenous antimicrobial therapy (B-III).

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25. Indefinite chronic oral antimicrobial suppression may follow the above regimen with cephalexin, dicloxacillin, co-trimoxazole, or minocycline based on in vitro susceptibility, allergies, or intolerances (Table 3; **B-III**). Rifampin alone is

**Table 2. Intravenous or Highly Bioavailable Oral Antimicrobial Treatment of Common Microorganisms Causing Prosthetic Joint Infection (B-III Unless Otherwise Stated in Text)**

| Microorganism | Preferred Treatment[a] | Alternative Treatment[a] | Comments |
|---|---|---|---|
| Staphylococci, oxacillin-susceptible | Nafcillin[b] sodium 1.5–2 g IV q4-6 h<br>or<br>Cefazolin 1–2 g IV q8 h<br>or<br>Ceftriaxone[c] 1–2 g IV q24 h | Vancomycin IV 15 mg/kg q12 h<br>or<br>Daptomycin 6 mg/kg IV q 24 h<br>or<br>Linezolid 600 mg PO/IV every 12 h | See recommended use of rifampin as a companion drug for rifampin-susceptible PJI treated with debridement and retention or 1-stage exchange in text |
| Staphylococci, oxacillin-resistant | Vancomycin[d] IV 15 mg/kg q12 h | Daptomycin 6 mg/kg IV q24 h<br>or<br>Linezolid 600 mg PO/IV q12 h | See recommended use of rifampin as a companion drug for rifampin-susceptible PJI treated with debridement and retention or 1-stage exchange in text |
| *Enterococcus* spp, penicillin-susceptible | Penicillin G 20–24 million units IV q24 h continuously or in 6 divided doses<br>or<br>Ampicillin sodium 12 g IV q24 h continuously or in 6 divided doses | Vancomycin 15 mg/kg IV q12 h<br>or<br>Daptomycin 6 mg/kg IV q24 h<br>or<br>Linezolid 600 mg PO or IV q12 h | 4–6 wk. Aminoglycoside optional<br>Vancomycin should be used only in case of penicillin allergy |
| *Enterococcus* spp, penicillin-resistant | Vancomycin 15 mg/kg IV q12 h | Linezolid 600 mg PO or IV q12 h<br>or<br>Daptomycin 6 mg IV q24 h | 4–6 wk. Addition of aminoglycoside optional |
| *Pseudomonas aeruginosa* | Cefepime 2 g IV q12 h<br>or<br>Meropenem[e] 1 g IV q8 h | Ciprofloxacin 750 mg PO bid<br>or 400 mg IV q12 h<br>or<br>Ceftazidime 2 g IV q8 h | 4–6 wk<br>Addition of aminoglycoside optional<br>Use of 2 active drugs could be considered based on clinical circumstance of patient. If aminoglycoside in spacer, and organism aminoglycoside susceptible than double coverage being provided with recommended IV or oral monotherapy |
| *Enterobacter* spp | Cefepime 2 g IV q12 h<br>or<br>Ertapenem 1 g IV q24 h | Ciprofloxacin 750 mg PO<br>or 400 mg IV q12 h | 4–6 wk. |
| Enterobacteriaceae | IV β-lactam based on in vitro susceptibilities<br>or<br>Ciprofloxacin 750 mg PO bid | | 4–6 wk |
| β-hemolytic streptococci | Penicillin G 20–24 million units IV q24 h continuously or in 6 divided doses<br>or<br>Ceftriaxone 2 g IV q24 h | Vancomycin 15 mg/kg IV q12 h | 4–6 wk<br>Vancomycin only in case of allergy |

**Table 3. Common Antimicrobials Used for Chronic Oral Antimicrobial Suppression (B-III Unless Otherwise Stated in Text)[a,b]**

| Microorganism | Preferred Treatment | Alternative Treatment |
|---|---|---|
| Staphylococci, oxacillin-susceptible | Cephalexin 500 mg PO tid or qid<br>or<br>Cefadroxil 500 mg PO bid | Dicloxacillin 500 mg PO tid or qid<br>Clindamycin 300 mg PO qid<br>Amoxicillin-clavulanate 500 mg PO tid |
| Staphylococci, oxacillin-resistant | Cotrimoxazole 1 DS tab PO bid<br>Minocycline or doxycycline100 mg PO bid | |
| β-hemolytic streptococci | Penicillin V 500 mg PO bid to qid<br>or<br>Amoxicillin 500 mg PO tid | Cephalexin 500 mg PO tid or qid |
| *Enterococcus* spp, penicillin susceptible | Penicillin V 500 mg PO bid to qid<br>or<br>Amoxicillin 500 mg PO tid | |
| *Pseudomonas aeruginosa* | Ciprofloxacin 250–500 mg PO bid | |
| Enterobacteriaceae | Cotrimoxazole 1 DS tab PO bid | β-lactam oral therapy based on in vitro susceptibilities |
| *Propionibacterium* spp | Penicillin V 500 mg PO bid to qid<br>or<br>Amoxicillin 500 mg PO tid | Cephalexin 500 mg PO tid or qid<br><br>Minocycline or doxycycline 100 mg PO bid |

*Infections ostéo-articulaires sur matériel*

# (prothèse, implant, ostéosynthèse)

## Texte court

**Organisées par**
**la Société de Pathologie Infectieuse de Langue Française (SPILF)**
**avec la participation des sociétés savantes et organismes :**

**Collège des Universitaires de Maladies Infectieuses et Tropicales (CMIT)**
**Groupe de Pathologie Infectieuse Pédiatrique (GPIP)**
**Société Française d'Anesthésie et de Réanimation (SFAR)**
**Société Française de Chirurgie Orthopédique et Traumatologique (SOFCOT)**
**Société Française d'Hygiène Hospitalière (SFHH)**
**Société Française de Médecine Nucléaire (SFMN)**
**Société Française de Médecine Physique et de Réadaptation (SOFMER)**
**Société Française de Microbiologie (SFM)**
**Société Française de Radiologie (SFR-Rad)**
**Société Française de Rhumatologie (SFR-Rhu)**

### 3.3.2 Quelle antibiothérapie systémique, comment l'administrer, quelle durée, quelle surveillance ?

#### 3.3.2.1 Principes généraux

La prescription de l'antibiothérapie au cours des infections ostéo-articulaires sur matériel répond à certaines obligations :

- documenter l'infection (en cas de sepsis [annexe 2], l'antibiothérapie sera débutée de façon probabiliste après réalisation des prélèvements microbiologiques et en attente de leurs résultats),
- antibiothérapie débutée en association ;
- obtention de concentrations plasmatiques élevées ;
- utilisation de molécules ayant une bonne diffusion osseuse ;
- en cas d'infection staphylococcique, ne jamais utiliser la rifampicine, l'acide fusidique, les fluoroquinolones et la fosfomycine en monothérapie ;
- le linézolide, la daptomycine, la tigécycline n'ont pas, en 2009, d'AMM dans le traitement des infections ostéo-articulaires **(grade C)**.

##### 3.3.2.1.1 Voie d'administration

Il est recommandé d'administrer initialement le traitement par voie intraveineuse. La durée de l'antibiothérapie parentérale n'est validée par aucune étude. Elle est habituellement de 15 jours **(avis d'expert).** À ce terme, il est recommandé de proposer un relais par voie orale à condition :

- que les antibiotiques aient une bonne biodisponibilité et une bonne diffusion osseuse,
- que la tolérance digestive du traitement soit bonne

| | | |
|---|---|---|
| | **ou**<br>rifampicine + clindamycine[2] (si souche érythromycine sensible)<br><br>**ou**<br>(ofloxacine ou péfloxacine[3] ou ciprofloxacine ou lévofloxacine[4]) + acide fusidique<br><br>**ou**<br>clindamycine (si souche érythromycine sensible) + acide fusidique<br><br>**ou**<br>rifampicine + cotrimoxazole<br>(en l'absence d'autre alternative) | |

1 : Durée maximale de prescription : 5 à 7 jours.

2 : La rifampicine diminue de moitié les concentrations plasmatiques de la clindamycine ; cela peut entraîner des sous-dosages importants de la clindamycine qu'elle soit prescrite par voie orale ou par voie intraveineuse (dosage de clindamycine recommandé).

3 : Se référer aux mises en garde de l'AFSSAPS.

4 : La prescription de lévofloxacine dans cette indication hors AMM doit être validée par un référent en infectiologie.

5 : Cette association nécessite une surveillance régulière de la biologie hépatique.

| | |
|---|---|
| | (vancomycine[1] ou teicoplanine[2]) + doxycycline<br>**ou**<br>clindamycine (si souche érythromycine sensible)<br>+ gentamicine[4]<br>**puis**<br>clindamycine + rifampicine[5] |
| **Relais oral si la sensibilité de la bactérie le permet** | rifampicine + acide fusidique[6]<br>**ou**<br>rifampicine + clindamycine[5] (si souche érythromycine sensible)<br>**ou**<br>rifampicine + cotrimoxazole<br>**ou**<br>rifampicine + (minocycline[7] ou doxycycline)<br>**ou**<br>rifampicine + linézolide[8] |

1 : Pour obtenir une efficacité maximale des glycopeptides dans le traitement des IOA, il est indispensable d'utiliser la vancomycine en perfusion IV continue à la seringue électrique (IVSE).

2 : La teicoplanine ne peut être utilisée qu'après détermination de la CMI.

3 : En cas d'association d'un glycopeptide avec l'acide fusidique ou avec la rifampicine, il est conseillé de différer la prescription de ces 2 dernières molécules de 48 heures afin d'avoir des taux sériques suffisants du glycopeptide.

4 : Durée maximale de prescription : 5 à 7 jours.

5 : La rifampicine diminue de moitié les concentrations plasmatiques de la clindamycine ; cela peut entraîner des sous-dosages importants de la clindamycine qu'elle soit prescrite par voie orale ou par voie intraveineuse (dosage de clindamycine recommandé).

6 : Cette association nécessite une surveillance régulière de la biologie hépatique.

7 : La minocycline (se référer aux mises en garde de l'AFSSAPS) a une meilleure CMI que la doxycycline mais est moins bien tolérée.

8 : Le linézolide n'a pas l'AMM dans cette indication. Il doit être prescrit uniquement en cas d'infection documentée et sous surveillance clinique et biologique rapprochée, sans dépasser 28 jours de traitement (toxicité hématologique et neurologique ; en particulier chez le sujet > 58 ans). Sa prescription doit être validée par un référent en infectiologie.

| | | |
|---|---|---|
| | | **ou**<br>ceftriaxone + gentamicine[1] |
| Relais oral | amoxicilline<br>**ou**<br>clindamycine (si souche érythromycine sensible) | |
| **Entérocoques** | | |
| Antibiothérapie initiale par voie IV | amoxicilline + gentamicine[1]<br><br>**puis**<br>amoxicilline ± rifampicine | (vancomycine[2] ou teicoplanine) + gentamicine[1]<br><br>**puis**<br>(vancomycine[2] ou teicoplanine) + rifampicine |
| Relais oral | amoxicilline ± rifampicine | Avis spécialisé |
| **Anaérobies à Gram (+)**<br>*(P. acnes, Peptostreptococcus)* | amoxicilline **ou** céfazoline **ou** ceftriaxone **ou** clindamycine (si souche érythromycine sensible) | clindamycine |
| **Anaérobies à Gram (-)**<br>*(Bacteroides spp...)* | clindamycine **ou** métronidazole[3] **ou** amoxicilline-ac. clavulanique | clindamycine **ou** métronidazole[3] |

Tableau VI : Propositions d'antibiothérapie en cas d'infections à bacilles à Gram négatif, adaptées l'antibiogramme et le terrain

| | |
|---|---|
| **Antibiothérapie initiale par voie IV**<br><br>*Pseudomonas aeruginosa* | (céfotaxime ou ceftriaxone) + (ciprofloxacine ou ofloxacine)<br>**ou**<br>(céfotaxime ou ceftriaxone) + gentamicine[1]<br>**ou**<br>(imipénem ou méropénem[2] ou doripénem[2]) + gentamicine[1]<br><br>(ceftazidime ou céfépime) **ou**<br>(imipénem ou méropénem[2] ou doripénem[2])<br>+<br>(amikacine[1] ou tobramycine[1]) **ou** ciprofloxacine **ou** fosfomycine |
| **Relais par voie orale**<br><br>(si souche sensible aux fluoroquinolones et en l'absence de fort inoculum bactérien) | ofloxacine<br>**ou**<br>ciprofloxacine si *Pseudomonas aeruginosa* |

| Antibiotiques (DCI) | Posologie/24h | Rythme et voie D'administration |
|---|---|---|
| amoxicilline | 100-200 mg/kg | 4-6 injections IVL<br>3-4 prises orales |
| cloxacilline<br>oxacilline | 100-200 mg/kg (posologies majorées par rapport au Vidal – avis d'expert) | 4-6 injections IVL |
| amoxicilline-acide clavulanique | 100 mg/kg | 4-6 injections IVL<br>3-4 prises orales |
| céfazoline | 60-80 mg/kg | 4-6 injections IVL ou IVSE[1] |
| céfotaxime | 100-150 mg/kg | 3 injections IVL |
| ceftriaxone | 30-35 mg/kg | 1-2 injection(s) IVL |
| ceftazidime | 100 mg/kg | IVSE[1] ou<br>3-4 injections IVL |
| imipénem | 2 à 3 g | 3 à 4 administrations IV ou IM |
| méropénem | 3 à 6 g | 3 administrations IV |
| vancomycine[2] | 40-60 mg/kg | IVSE[1] |
| teicoplanine[2] | 12 mg/kg/12h pendant 3-5 jours puis 12 mg/kg | IVL, IM ou s/c |
| gentamicine[3] | 3-4 mg/kg | 1 administration IV<br>30 minutes |

Tableau VII bis : Posologies et voies d'administration des antibiotiques utilisés au cours des infections ostéo-articulaires sur matériel d'ostéosynthèse

| Antibiotiques (DCI) | Posologie/24h | Rythme et voie D'administration |
|---|---|---|
| ofloxacine | 400-600 mg | 2 à 3 prises orales<br>2 à 3 injections IVL |
| péfloxacine | 800 mg | 2 prises orales<br>2 injections IVL |
| lévofloxacine<br>(hors AMM) | 500 à 750 mg | 1 prise orale<br>1 injection IVL |
| ciprofloxacine | 1 500-2 000 mg<br>800 à 1 200mg | 2 à 3 prises orales<br>2 à 3 injections IVL |
| clindamycine | 1 800-2 400mg | 3-4 injections IVL<br>3 prises orales |
| rifampicine | 20 mg/kg | 2 administrations IV<br>30 minutes<br>2-3 prises orales |
| acide fusidique | 1 500 mg | 2-3 prises orales<br>2-3 injections IVL |
| fosfomycine | 150-200 mg/kg | 3-4 administrations<br>120 minutes |
| cotrimoxazole | 3 200 mg/640 mg | 2 prises orales<br>2 injections |
| minocycline<br>doxycycline | 200 mg | 2 prises orales<br>2 injections IV (doxycycline) |
| linézolide<br>(hors AMM) | 1 200 mg | 2 prises orales<br>2 injections IVL |

## CONCLUSION

There is a minimal amount of compelling data to support rifampin combination antimicrobial therapy for the treatment of nonmycobacterial infections. There is a lack of significantly controlled clinical studies, and it is doubtful that any large randomized clinical trials will be performed in the future to assess rifampin combination therapy. Therefore, its use is reliant upon noncomparable *in vitro* or *in vivo* data or retrospective case reviews with their subsequent limitations and biases. There has been no standard practice used to define the appropriate rifampin dose required, when to initiate the rifampin with another antibiotic, and for how long a patient should remain on therapy. The most prominent observation from this review is that rifampin combination therapy appears to have improved treatment outcomes when there is a low organism burden for infections such as those with biofilms (i.e., PJI and PVE) but in general does not offer any benefits over antibiotic monotherapy for high-organism-burden infections such as NVE. Also, the failure to obtain source control through surgical debridement or removal of the focus of infection results in frequent treatment failures and the emergence of rifampin-resistant strains.

| pe | % SSI | | |
|---|---|---|---|
| | Locums | Non-locums | OR (95% C |
| | 6.7% (11/163) | 1.4% (33/2385) | 5.16 (2.30-10 |
| egistrar | 6.7% (3/45) | 0.9% (3/336) | 7.93 (1.02-60 |

| ype | % SSI | | |
|---|---|---|---|
| | Specialist registrars | Consultants | OR (95% C |
| sis | 2.4% (10/421) | 1.9% (37/1950) | 1.61 (0.74-3 |
| esis | 3.7% (12/322) | 2.2% (29/1359) | 1.78 (0.85-3 |
| racture | 1.9% (6/318) | 1.4% (3/212) | 1.34 (0.28-8 |
| plasty | 5.6% (13/233) | 3.5% (4/114) | 1.63 (0.49-6 |

# Effets indésirables

- DONC : antibiothérapie prolongée forte dose et complexe
- DONC : surveillance clinique et biologique + éducation du patient (gestion des effets secondaires).

# Les petits nouveaux

- Daptomycine : actif sur le biofilm ?
- Tigécycline : intérêt contre les BMR
- Linezolid : bactériostatique mais bonne diffusion
- Doripenem : actif sur pyo multi R
- Ceftobiprol : pas d'accord FDA
- Ceftaroline : en attente

# RFP+ CTX vs RFP+LNZ

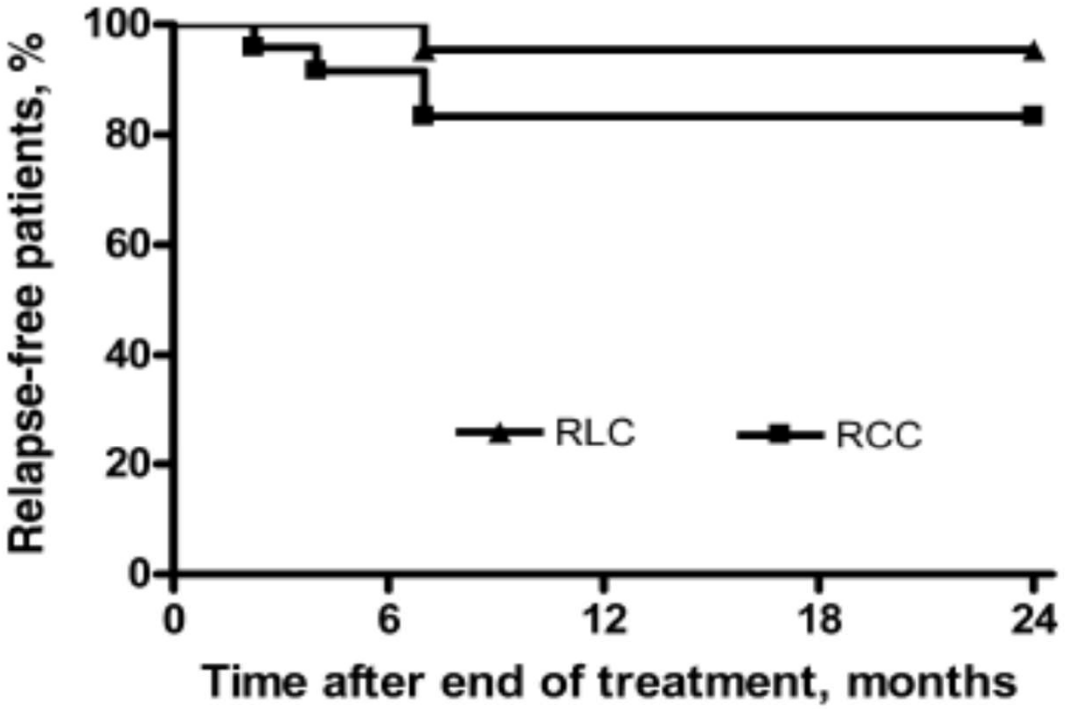



**FIG. 1.** Relapse-free survival at 2 years after end-of-treatment in the rifampicin–linezolid combination (RLC) and rifampicin–cotrimoxazole combination (RCC) groups.

Nguyen *et al.* CMI 2009

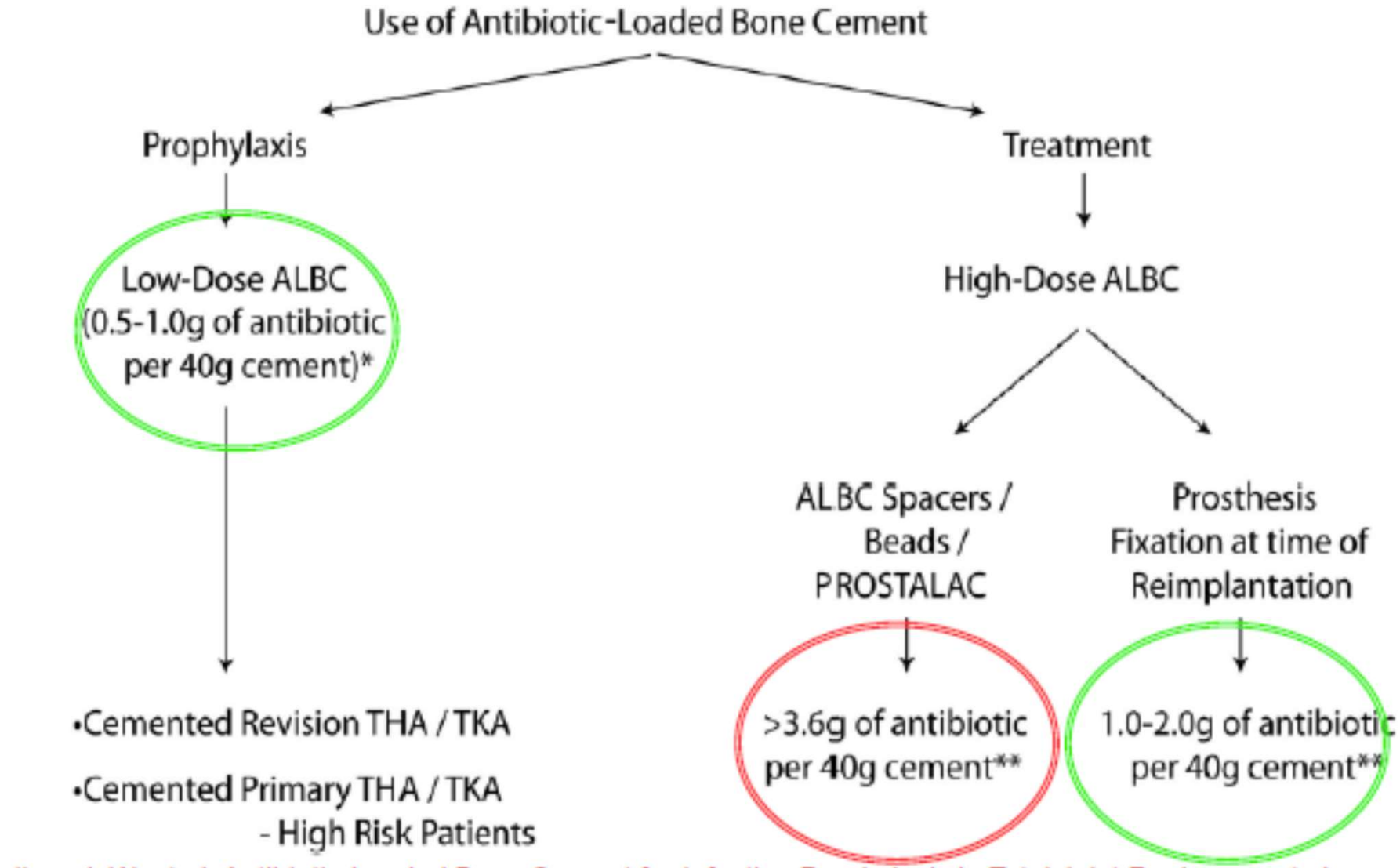
# Antibiotics for treating chronic osteomyelitis in adults (Review)

**Conterno LO, da Silva Filho CR**

**COCHRANE DATA BASE**

"No trials compared different durations of antibiotic treatment for chronic osteomyelitis"

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library*
2009, Issue 3
http://www.thecochranelibrary.com




*Jiranek W; et al. Antibiotic-Loaded Bone Cement for Infection Prophylaxis in Total Joint Replacement. Journal Bone & Joint Surgery · 2006; 88-A · 11 ·*

# Principes généraux de la prise en charge des infections sur matériel chirurgical

- **Principes du traitement médical**
  - Ne pas utiliser la vancomycine en cas d'infection à SAMS
  - Traitement empirique efficace envers SAMR en l'absence de données bactériologiques
  - Utiliser la rifampicine en cas d'infection à Staphylocoque
  - En cas de réimplantation utiliser une antibiothérapie efficace sur les germes initialement retrouvés

- **Principes du traitement chirurgical**
  - La guérison de l'infection impose la dépose du matériel surtout en présence de staphylocoque doré et de candida
  - Retirer le matériel est indispensable en cas d'échec d'une antibiothérapie appropriée
  - Il faut enlever tous les composants des implants pour éviter les récidives
  - Il faut s'assurer de l'absence clinique et si possible microbiologique d'infection avant de reposer du matériel

# Conclusions

- Tendances :
  - 1 temps,
  - Durée Atb courte,
  - relai per os précoce
- Nécessité de
  - réunion pluridisciplinaire,
  - communication inter services et collégialité
  - mettre en place des protocole et les évaluer

RICAI 2010, le 2 décembre

# Évolution des schémas thérapeutiques en infection ostéo-articulaire : Nouvelles molécules et données nouvelles sur la durée de traitement

Groupe TIRESIAS

A. Dinh,

Unité des Maladies Infectieuses, CHU R. Poincaré, AP-HP, UVSQ

# Daptomycine : Données expérimentales

***In vivo* studies**

Table2. Effect of antibiotic Rx on experimental MRSA prosthetic knee infection in rabbits

| Rx[a] | No. of rabbits with sterile bone/Total | $log_{10}$ CFU/g of bone mean ± SD | Decreased susceptibility to DAP/Total |
|---|---|---|---|
| None | 0/9 | 5.93 ± 1.15 | 2/9 |
| DAP | 2/12 | 4.23 ± 1.44[b] | 7/12 |
| VAN | 0/12 | 4.63 ± 1.08[b] | 4/12 |
| DAP+ RIF | 11/11 | 1.47±0.04[c] | - |
| VAN+ RIF | 6/8 | 1.50 ± 0.12[c] | 0/2* |

[a]Rabbits were treated for 7 days with DAP (22 mg/kg, iv., od.) or VAN (60 mg/kg, im, bid.) alone and combined with RIF (10 mg/kg, im, bid).

[b]Significantly different from untreated controls ($p<0.01$).

[c] Significantly different from monotherapy($p<0.01$).

* Other rabbits had sterile bones

**A. SALEH MGHIR, C. MULLER-SERIEYS, L. MASSIAS, A.C. CREMIEUX.** 2010. COMBINING HIGH-DOSE DAPTOMYCIN AND RIFAMPIN IS CRUCIAL FOR THE TREATMENT OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* RABBIT PROSTHETIC JOINT INFECTION. *Interscience Conference Antimicrobial Agent Chemotherapy,* Boston B 698

| | Group I | Group II |
|---|---|---|
| Number | 46 | 53 |
| Average age, years (range) | 59 (22–81) | 62 (28–76) |
| Gender (male/female) | 27/19 | 33/20 |
| Average follow-up period, months (range) | 50 (24–60) | 37 (24–48) |
| Previous surgery[a] | | |
| primary total hip arthroplasty | 18 | 25 |
| revision total hip arthroplasty | 16 | 20 |
| bipolar hemiarthroplasty | 9 | 8 |
| unipolar hemiarthroplasty | 3 | 0 |
| ASA status (I/II/III)[b] | 1/10/35 | 0/12/41 |

**Table 2.** Antibiotics used in the cement spacers

| | Group I ($n=46$) | Group II ($n=53$) |
|---|---|---|
| Vancomycin + aztreonam | 20 | 12 |
| Vancomycin + gentamicin | 12 | 21 |
| Vancomycin | 6 | 7 |
| Gentamicin | 7 | 12 |
| Teicoplanin | 1 | 1 |

| Patient | Group | Infecting organism | Antibiotic(s) in spacer | Treatment | Outcome |
|---|---|---|---|---|---|
| 1 | I | *S. aureus*, methicillin-resistant | vancomycin + aztreonam | repeated 1st-stage surgery | infection eradicated, followed by 2nd-stage surgery |
| 2 | I | *Staphylococcus*, coagulase-negative | vancomycin + aztreonam | repeated 1st-stage surgery | infection eradicated, followed by 2nd-stage surgery |
| 3 | I | *S. aureus*, methicillin-susceptible | vancomycin + gentamicin | repeated 1st-stage surgery | persistent infection, followed by repeated debridement without re-implantation |
| 4 | I | *S. aureus*, methicillin-resistant | vancomycin | repeated 1st-stage surgery | persistent infection, followed by repeated debridement without re-implantation |
| 5 | II | *S. aureus*, methicillin-resistant | vancomycin + gentamicin | repeated 1st-stage surgery | infection eradicated, followed by 2nd-stage surgery |
| 6 | II | *S. aureus*, methicillin-resistant | vancomycin + gentamicin | repeated 1st-stage surgery | persistent infection, followed by repeated debridement without re-implantation |
| 7 | II | *P. aeruginosa* | vancomycin + aztreonam | repeated 1st-stage surgery | persistent infection, followed by repeated debridement without re-implantation |
| 8 | II | *P. aeruginosa* | vancomycin + gentamicin | no further surgery due to severe cardiovascular disease | persistent infection, treated with long-term antibiotic suppression |

AAOS

AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS

# THE DIAGNOSIS OF PERIPROSTHETIC JOINT INFECTIONS OF THE HIP AND KNEE

## GUIDELINE AND EVIDENCE REPORT

**Adopted by the American Academy of Orthopaedic Surgeons**
**Board of Directors**
**June 18, 2010**

3. We recommend joint aspiration of patients being assessed for periprosthetic **knee** infections who have abnormal erythrocyte sedimentation rate ***AND/OR*** C-reactive protein results. We recommend that the aspirated fluid be sent for microbiologic culture, synovial fluid white blood cell count and differential.

   Strength of Recommendation: Strong

4. We recommend a selective approach to aspiration of the **hip** based on the patient's probability of periprosthetic joint infection and the results of the erythrocyte sedimentation rate (ESR) AND C-reactive protein (CRP). We recommend that the aspirated fluid be sent for microbiologic culture, synovial fluid white blood cell count and differential.

# Treatment of staphylococcal prosthetic joint infections with debridement, prosthesis retention and oral rifampicin and fusidic acid

*C. A. Aboltins*[1], *M. A. Page*[1], *K. L. Buising*[1], *A. W. J. Jenney*[1], *J. R. Daffy*[1], *P. F. M. Choong*[2] *and P. A. Stanley*[1]

[1]Department of Infectious Diseases and [2]Department of Orthopaedic Surgery, St Vincent's Hospital, Melbourne, Victoria, Australia

## ABSTRACT

There is growing evidence of the efficacy of treating early staphylococcal infections of prosthetic joints with surgical debridement and prosthesis retention, combined with oral antibiotic regimens that include rifampicin in combination with a fluoroquinolone. With rising rates of fluoroquinolone-resistant staphylococci, evidence concerning the efficacy of alternative combinations of antibiotics is required. Twenty patients with staphylococcal prosthetic joint infections who had been treated with surgical debridement and prosthesis retention, and a combination of rifampicin and fusidic acid were analysed. The mean duration of symptoms before initial debridement was 16 (range 2–75) days. The median time of follow-up was 32 (range 6–76) months. Treatment failure occurred in two patients. The cumulative risk of treatment failure after 1 year was 11.76% (95% CI 3.08–39.40%). Two patients had their treatment changed because of nausea. Ten of 11 patients with infections involving methicillin-resistant *Staphylococcus aureus* had successful outcomes. Debridement without prosthesis removal, in combination with rifampicin and fusidic acid treatment, was effective and should be considered for patients with early staphylococcal prosthetic joint infections, including those with infections involving fluoroquinolone-resistant organisms.

**Keywords** Antibiotic regimens, debridement, fusidic acid, prosthetic joint infection, rifampicin, *Staphylococcus* spp.

**Original Submission:** 3 September 2006; **Revised Submission:** 26 November 2006; **Accepted:** 3 December 2006

*Clin Microbiol Infect* 2007; **13**: 586–591

# Posologies et administration

| Antibiotiques | Posologies/24h | Rythme et voie d'administration |
|---|---|---|
| **Amoxicilline** | 100-200 MKJ | 4-6 IVL<br>3-4 po |
| **Cloxacilline oxacilline** | 100-200 MKJ | 4-6 IVL |
| **Cefotaxime** | 100-150 MKJ | 3 IVL |
| **Ceftriaxone** | 30-35 MKJ | 1-2 IVL |
| **Ceftazidime** | 100 MKJ | IVSE |
| **Vancomycine** | 40-60 MKJ | IVSE |
| **Ofloxacine** | 400-600 mg | 2-3 po |
| **Ciprofloxacine** | 1500-200 mg | 2-3 po |
| **Fosfomycine** | 150-200MKJ | 3-4 IVL |
| **cotrimoxazole** | 2400/480mg | 3 po |

Séminaire de gérontologie pratique, Paris 15 janvier 2010

# Infections ostéo-articulaires :

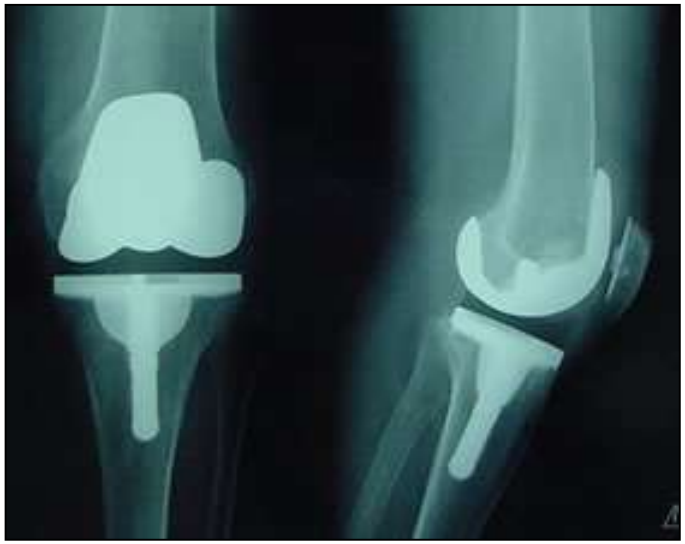
## infections sur prothèse articulaire

Dr Aurélien DINH, Pr Louis BERNARD

Service des Maladies Infectieuses,

CHU Garches, CHRU Tours

# Généralités

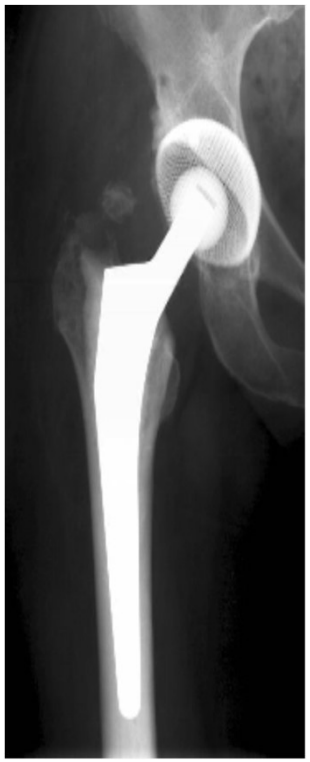


Pourquoi c’est compliqué !

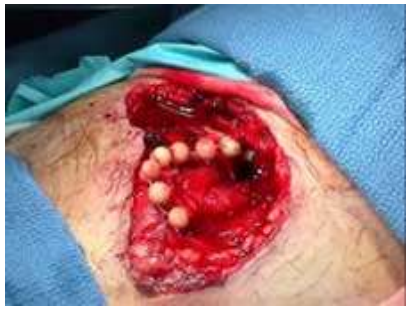
# Pourquoi ce n'est pas facile

- Absence de **définition consensuelle**
- **Diagnostic** ardu : faisceau d'argument + divers entité nosologique
- Identification **bactériologique** difficile : pas de gold standard
- **Chirurgie** difficile : peu d'étude + dépend du terrain et…du chirurgien
- **Antibiothérapie** complexe : site d'accès difficile pour les ATB (peu de vascularisation, corps étrangers, séquestres…)
- Une **évaluation** retardée : 12 mois sans rechute ?

# Différents types de chirurgie



**Inoculum:**
-drainage ?

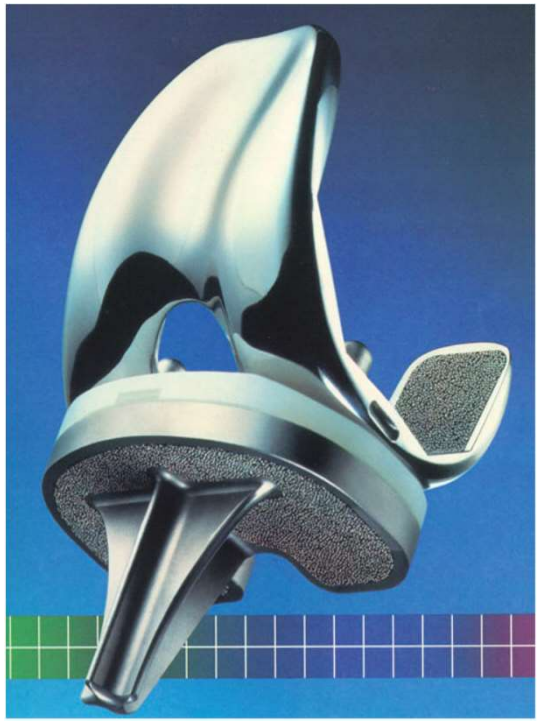


**Matériel:**
-différents types
-ablation ou non / changement (1T, 2T)

**Antibiotiques locaux:**
-ciments
-billes

# Et pourtant

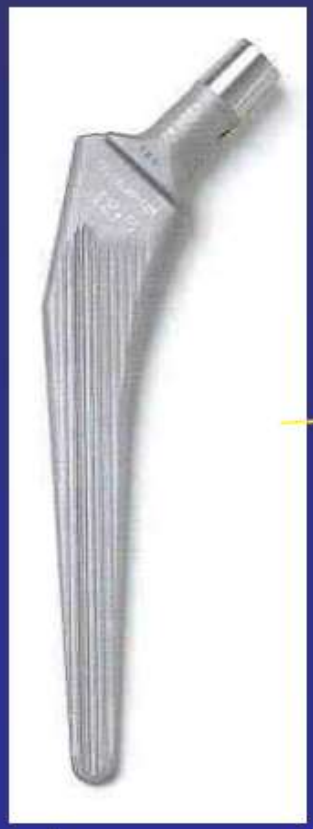
- C’est fréquent
- C’est grave
- Coût (fonctionnel et financier) important pour le patient et la société



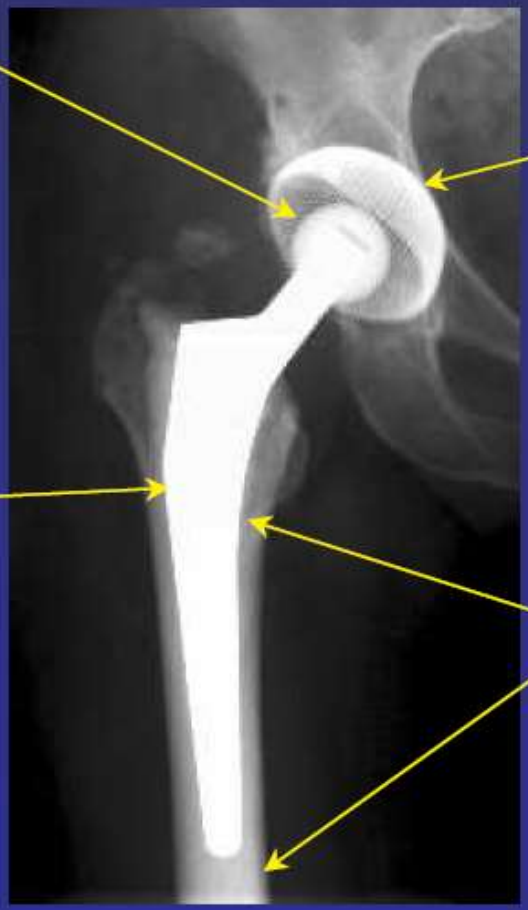
# 1-Infection sur prothèse articulaire

# Prothèse de hanche: composants

Tête
céramique



Tige
alliage chrome-cobalt



Cupule
titane et polyéthylène

Ciment
méthyl-méthacrylate

# Pourquoi s'intéresser à l'infection de prothèse articulaire ?

**En France**

- 100 000 prothèses de hanche / an
- 40 000 prothèses de genou / an

**Aux USA**

- 300 000 prothèses de hanche / an
- 200 000 prothèses de genou / an

L'incidence des infections = 1-2%,

L 'incidence des descellement = 2-3% ???

Parmi les descellements à 20-50% d'infection ?

# IOA sur matériel

- France:
  - En 1994 --> 60 000 Prothèses Tx Infection 1% 600 patients par an
  - 290 000 matériels ortho posés Tx infection 1,1% à 2% --> ≈ 5000 patients infectés
- USA 1,9-2,2%
- Scandinavie 0,7%

Espehaug et al Registre norvegien2006
Gillespie et al The Cochrane Collaboration 2008

# Fréquence des IPOA

- Pour les **PTH ?**

  entre 1 et 2 %

- Pour les **PTG ?**

  probablement 3 %

- Cela malgré les mesures de prophylaxie :
  - **Antibioprophylaxie**,
  - Utilisation **d'enceinte à flux laminaire** lors de la pose.

# Commentaires

- Une enquête CCLIN Sud-Est (1999 et 2000) :
  - parmi 3 881 patients opérés d'une PTH,
  - 87 ISO
  - soit prévalence globale = 2 %

- Donc les IPOA en France estimées entre 2 000 et 2 500 par an.
- IPOA = complications graves de la chirurgie orthopédique avec morbidité et surmortalité importante

http://cclin-sudest.chu-lyon.fr/reseaux/iso/rapport_ISO/RAP9900.pdf

# Proportion des différentes IOA

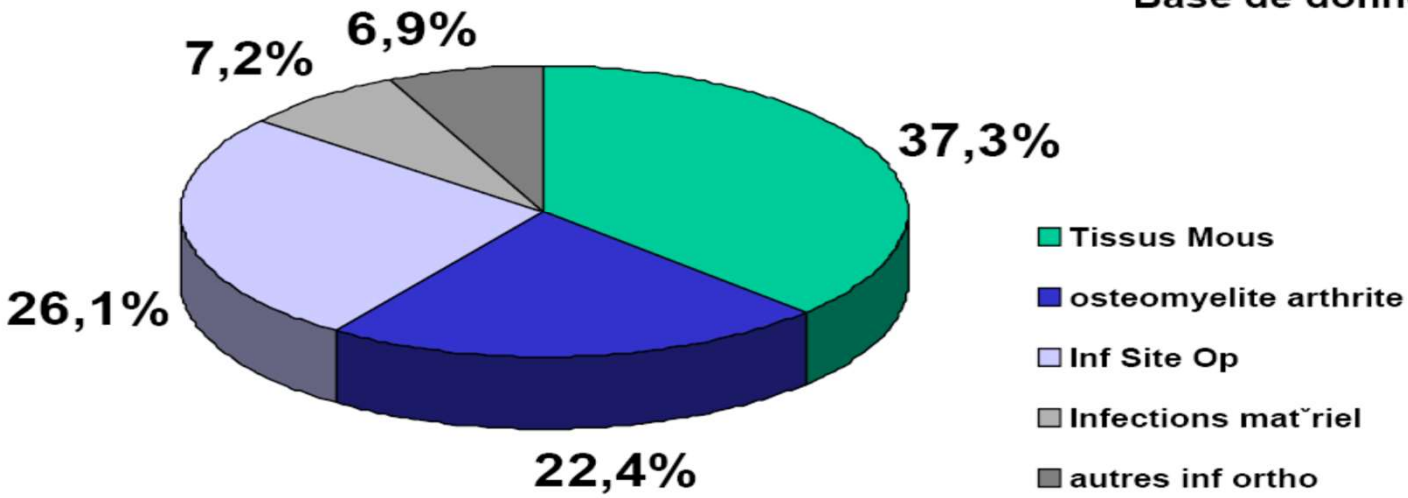
INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY NOVEMBER 2007, VOL. 28, NO. 11

ORIGINAL ARTICLE

## Skin, Soft Tissue, Bone, and Joint Infections in Hospitalized Patients: Epidemiology and Microbiological, Clinical, and Economic Outcomes

Benjamin A. Lipsky, MD; John A. Weigelt, MD; Vikas Gupta, PharmD, BCPS; Aaron Killian, PharmD, BCPS; Michael M. Peng, PhD, MPH

12 506 Patients avec
Culture Positive
134 centres 2002-2003
**Base de données Vet's**



# Quels sont les facteurs de risque d'infection du site opératoire (ISO) ?

- Les facteurs de risque connus sont liés :
- – soit au **terrain** :
  - polyarthrite rhumatoïde, diabète, néoplasie, traitement immunosuppresseur, âge > 65 ans…
- – soit aux facteurs **périopératoires** :

**Locaux** : reprises chirurgicales multiples, hématome postopératoire, cicatrisation difficile,

**Généraux** : absence d'antibioprophylaxie, existence d'un autre foyer infectieux, séjour préopératoire supérieur à 4 jours.

SPILF RCP Infections ostéoarticulaires sur matériel (Version préliminaire) Juin 2008.
Mader JT. Clin Infect Dis 1997

# Autres facteurs de risque d'ISO

- Il existe des facteurs de risque discutables ou majorant faiblement le risque d'ISO :
  - l'obésité,
  - la dénutrition,
  - la corticothérapie,
  - la réalisation d'une radiothérapie récente sur le site opératoire.

SPILF RCP Infections ostéoarticulaires sur matériel (Version préliminaire) Juin 2008.
Mader JT. Clin Infect Dis 1997

# Classification de Coventry

- Cette classification en 3 phases différentes d'infection sur prothèse :
- – **type I** : aiguë et précoce, période postopératoire immédiate (< 1 mois) ;
- – **type II** : chronique, plus tardive, prothèse douloureuse ;
- – **type III** : aiguë, tardive, par voie hématogène, prothèse le plus souvent asymptomatique.

# Changement en 1 ou 2 temps ?

- Choix repose sur l'**habitude** de chaque équipe
- Pas sur des d'études prospectives comparatives
- Ablation de la prothèse si signes radiologiques de **descellement** (accord professionnel)
- Possibilités de repose plus élevées si pas de maladie générale sous-jacente

Zimmerli W. NEJM 2004
Crockarell JR. J Bone Joint Surg Am 1998 ;
Widmer AF. Clin Infect Dis 2001 ;
Mc Pherson EJ. Clin Orthop Relat Res 2002 ; 403 : 8-15.

# 1 ou 2 temps ?

- Recommandation pour le changement prothétique (accord professionnel) :
- – en 2 temps :
  - – Si un (des) germe(s) multirésistant(s),
  - – et/ou lorsque l'articulation a déjà fait l'objet d'un changement de prothèse,
  - – et/ou s'il existe des lésions osseuses importantes ;
- – en 1 temps :
  - – si l'infection est bactériologiquement documentée avant l'intervention,
  - – sans germe multirésistant,
  - – Pas de destruction osseuse importante, Si l'excision chirurgicale est considérée de bonne qualité.

# Efficacité du 2 temps

- Le changement en 2 temps, ± espaceur contenant ou non des antibiotiques,
- associé à une antibiothérapie systémique,
- permet d'obtenir un taux d'éradication de l'infection entre
  - Au niveau de la hanche : 85 et 100 % (généralement supérieur à 95 %)
  - Au niveau du genou : généralement entre 85 et 90 %
- Quelle que soit la sensibilité des bactéries aux antibiotiques

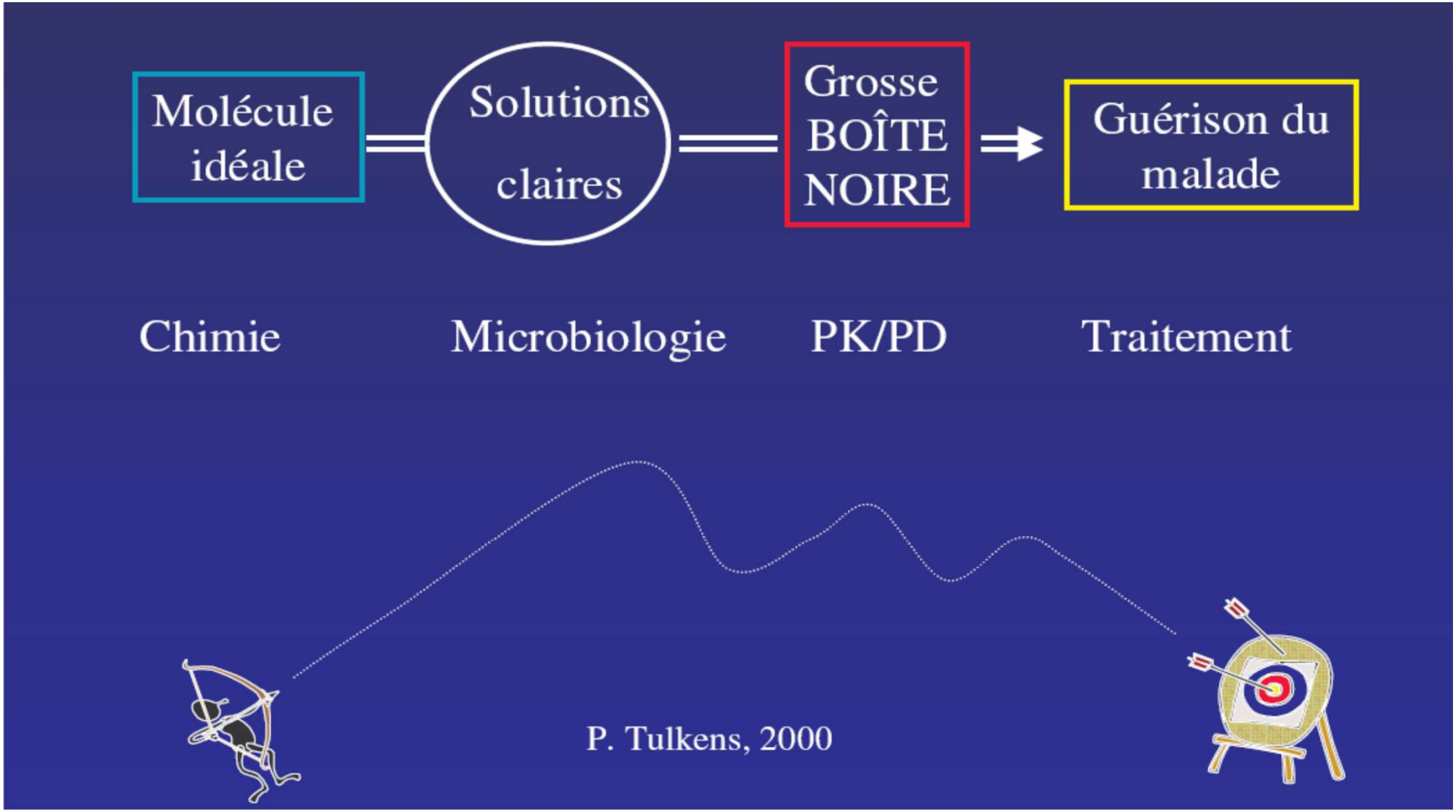

Brandt CM. Clin Infect Dis 1997
Hanssen AD. Clin Orthop Relat Res 1994
Lecuire F. Rev Chir Orthop Reparatrice Appar Mot 1999
Windsor RE. J Bone Joint Surg Am 1990
Hsieh PH. J Bone Joint Surg Br 2005
Souillac V. Rev Chir Orthop Reparatrice Appar Mot 2006
Volin SJ. Clin Orthop Relat Res 2004
Hirakawa K. J Arthroplasty 1998
Nazarian DG. J Arthroplasty 2003
Hsieh PH. J Trauma 2004

# Repose et stérilité du site

- Ponction-biopsie préopératoire avant réimplantation afin de s'assurer de la stérilité du site.
- Repose de la prothèse au moins 15 jours après l'arrêt des antibiotiques.
- Prélèvements profonds avant l'introduction du traitement antibiotique (comprenant l'antibioprophylaxie).
- Ce traitement antibiotique sera arrêté à la réception des cultures négatives des prélèvements peropératoires.
- En cas, exceptionnel, de positivité de ces cultures, une antibiothérapie adaptée sera poursuivie 6 à 12 semaines.

# Traitement antibiotique

# Antibiotique idéal



# Antibiothérapie

- **Antibiothérapie générale**
- **Ce qui est habituel :**

- ATB indispensable, (quelle que soit la technique chirurgicale)
- concentrations plasmatiques élevées
- durée prolongée (6 semaines…1an)

- **Choix de la molécule**

- sensibilité *in vitro* des germes en cause (CMI)
- stabilité vis à vis des mutations résistantes (pyo, staph)
- capacité de diffusion tissulaire,
- toxicité/tolérance.

- **En pratique clinique**,

-dosages plasmatiques,

-résultats d'études pharmacocinétiques.

-taux sériques élevés (surtout résiduel)

-pouvoir bactéricide du sérum ?

- **Ce qui est incertain**

-mono- ou bi-thérapie ?

-parentérale ou orale ?

-critères de surveillance ?

-méthodologie dans les dosages osseux (sain et pathologique)

# Principe de l'ATB post op

- Après le geste chirurgical , but de l'antibiothérapie initiale : diminuer le plus rapidement l'inoculum bactérien résiduel.
- Antibiothérapie
  - forte dose,
  - IV pour des raisons de tolérance et de biodisponibilité
- Antibiothérapie initiale :
  - probabiliste ou guidée par les prélèvements préopératoires,
  - adaptée après quelques jours.
- Antibiothérapie probabiliste la plus fréquente : glycopeptides.
- Avec l'antibiogramme : antibiothérapie prolongée (orale ou parentérale) selon les molécules utilisables et les antécédents du patient.

# Principe de l'ATB en relais

- Le choix de l'antibiothérapie par voie orale pour le traitement prolongé est complexe.
- Infections sur prothèses articulaires >> capacité de fixation de certaines bactéries sur le matériel implanté (biofilm).
- Donc il faut utiliser des antibiotiques :
- – avec une bonne activité sur les bactéries isolées ;
- – avec une bonne pénétration dans le site d'implantation de la prothèse ;
- – efficaces sur des bactéries en phase de croissance lente ou protégées par un biofilm.

# Effets indésirables

- DONC : antibiothérapie prolongée forte dose et complexe
- DONC : surveillance clinique et biologique + éducation du patient (gestion des effets secondaires).

# Molécules recommandées

| **Bactérie** | **Traitement de 1re intention** | **Autre proposition** |
|---|---|---|
| Staphylocoque méti-sensible | - IV pendant 10 jours avant relais oral : pénicilline M +/- gentamycine<br>- Rifampicine + fluoroquinolone | -Clindamycine + rifampicine<br>- Cotrimoxazole + rifampicine<br>- Fluoroquinolone + acide fusidique<br>- rifampicine+acide fucidique |
| Staphylocoque méti-résistant | Glycopeptide + (rifampicine ou acide fusidique ou fosfomycine) | Rifampicine + acide fusidique<br>Cotrimoxazole + rifampicine<br>Fosfomycine + rifampicine ou acide fusidique |
| Entérocoque | Amoxicilline +/- aminoside (10 j) si résistance de bas niveau | Glycopeptides (teicoplanine) |
| Streptocoque | Amoxicilline+/- rifampicine | Céphalosporine 3e génération |
| Bacille Gram – (sauf *Pseudomonas aeruginosa*) | Céphalosporine 3e génération + fluoroquinolone | Fluoroquinolone + fosfomycine |
| *Pseudomonas aeruginosa* | Ceftazidime en perfusion continue + ciprofloxacine ou amikacine ou tobramycine | Ceftazidime ou imipénème + fosfomycine |

# Posologies recommandées

| Antibiotique | Posologie | Rythme et voie d'administration | Concentration plasmatique |
|---|---|---|---|
| **Bêtalactamines** | | | |
| Oxacilline ou cloxacilline | 100 à 150 mg/kg | IV 4 à 6 injections /j | |
| Amoxicilline | 150 200 mg/kg/j | IV 4 à 6 injections/j<br>*PO* en 3 à 4 fois | |
| Céfotaxime | 100-150 mg/kg | IV 3 à 4 injections /j | |
| Ceftriaxone | 30-50 mg/kg/j | IV 1 à 2 injections /j | |
| Ceftazidime | 50-100 mg/kg/j | IV perfusion continue ou 3 à 4 injections /j | |
| Imipénème | 2 à 3 g/j | IV 3 à 4 injections /j | |
| Céfépime | 50-100 mg/kg/j | IV 4 à 6 injections /j | |
| **Glycopeptides** | | | |
| Teicoplanine | 12 mg/kg/j | IV 1 fois par jour après une dose de charge (12 mg/12 h pour les 5 premières injections) | C min 30-35 |
| Vancomycine | 30-40 mg/kg/j | IV dose de charge puis perfusion continue | C min 30-35 |
| **Aminosides*** | | | |
| Amikacine | 15 mg/kg/j | IV 1 injection/j | C min < 5 |
| Gentamycine | 3 mg/kg/j | IV 1 injection/j | C min < 1 |
| Tobramycine | 3 mg/kg/j | IV 1 injection/j | C min < 1 |
| **Fluoroquinolone*** | | | |
| Ofloxacine | 400-600 mg/j | *PO* en 2 fois/j | |
| Lévofloxacine | 500-1 000 mg/j | *PO*/IV en 1 à 2 fois/j | |
| Ciprofloxacine | 1 500-2 000 mg/j<br>600-1 200 mg/j | *PO* en 2 à 3 fois /j<br>IV en 2 à 3 fois/j | |
| **Divers** | | | |
| Rifampicine* | 20 mg/k/j | *PO*/IV en 2 à 3 fois/j | |
| Acide fusidique* | 1500 mg/j | *PO*/IV en 3 fois/j | |
| Fosfomycine* | 150-200 mg/kg/j | IV en 3 à 4 injections de 1 à 2 h | |
| Clindamycine | 1,8 à 2,4 g/j | *PO*/IV en 3 ou 4 fois/j | |
| Triméthoprime – sulfaméthoxazole | 480 mg/2,4 g | *PO*/IV en 2 à 3 fois/j | |

# Durée de traitement des IPOA : Revue de la littérature

**20 Articles:**

- Aucune étude prospective de durée
- de 15 à 186 patients par étude (total n= 1196)
- 12 études avec durée 6s
- 2 études avec durée 3 mois
- 5 études avec  durée variable 6s à 6 mois
- 1 étude avec  durée variable < à  >6 mois

# Durée de traitement des IPOA : Revue de la littérature

**Efficacité:**

- entre 67% et 100%
- majorité des études entre 85% et 95%
- 1 étude : 67%
  malgré une durée 18 s
  mais multiples reprises
- difficiles à interpréter car différentes stratégies chirurgicales

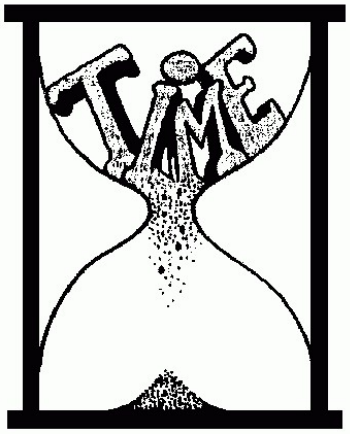
# Quelle durée ?

- Durée du traitement antibiotique non standardisée.
- Études récentes : possibilité d'une durée de traitement de 6 semaines après la dépose (PTH et PTG).
- En pratique courante : le plus souvent 6 à 12 semaines.

Choutet P, Desplaces N, Evrard P *et al. Traitement des infections ostéoarticulaires bactériennes en dehors des infections à mycobactéries.* Med Mal Infect 1991 ; 21 : 546-550.
Bernard L, Hoffmeyer P, Assal M *et al. Trends in the treatment of orthopaedic prosthetic infections.* J Antimicrob Chemother 2004 ; 53 : 127-129.
Hoad-Reddick DA, Evans CR, Norman P, Stockley I. *Is there a role for extended antibiotic therapy in a two-stage revision of the infected knee arthroplasty ?* J Bone Joint Surg Br 2005 ; 87 (2) : 171-174.
Galpérine T, Bernard L. *Antibiotic therapy of osteoarticular infections in the adult.* Rev Prat 2007 ; 57 (9) : 995-1002.

# Alors 6 ou12 semaines ?

Il faut faire des études !




LEVOS: Lévofloxacine-rifampicine 6s
Changement de prothèse en 2T

DATIPO: Durées d'Antibiothérapie (6 semaines versus 12 semaines) dans le Traitement des Infections sur Prothèses Ostéo-articulaires

# Principes généraux de la prise en charge des infections sur matériel chirurgical

- **Principes du traitement médical**
  - Ne pas utiliser la vancomycine en cas d'infection à SAMS
  - Traitement empirique efficace envers SAMR en l'absence de données bactériologiques
  - Utiliser la rifampicine en cas d'infection à Staphylocoque
  - En cas de réimplantation utiliser une antibiothérapie efficace sur les germes initialement retrouvés

- **Principes du traitement chirurgical**
  - La guérison de l'infection impose la dépose du matériel surtout en présence de staphylocoque doré et de candida
  - Retirer le matériel est indispensable en cas d'échec d'une antibiothérapie appropriée
  - Il faut enlever tous les composants des implants pour éviter les récidives
  - Il faut s'assurer de l'absence clinique et si possible microbiologique d'infection avant de reposer du matériel

# Efficacité lavage débridement fonction de l'âge de la prothèse et de la durée des symptômes

| Nombre de cas | Délai d'inclusion | Age de la PT | Durée des symptômes | Bactério. | Efficacité | Ref |
|---|---|---|---|---|---|---|
| 19 cas | 29 ans | 2 mois-5ans | <10j (1-10)<br>Mediane 4j | Strepto. peniS | 89.5% | 1 |
| 13/34 cas | 16 ans | 1.5 à 3ans | 5 j | Staph (75%) | 100% | 2 |
| 21/34 cas | | | 54 j | | 0% | |
| 12/34 | 11 ans | < 1mois: 40%<br>>1 mois: 60% | < 2j | Staph (93%) | 100% | 3 |
| 21/34 | | | > 2j | | 0% | |
| 17/36 cas | 6 ans | 13 < 1an<br>23 > 1an | < 1mois | Staph (86%) | 86.% *<br>NS | 4 |
| 19/36 cas | | | > 1 mois | | 27% | |
| 11/33 cas | 8 ans | < 4 s | Variable 14j | Staph (?%) | 61% | 5 |
| 22/33 cas | | > 4 s | | | | |

1: Meehan, CID 2003(36: 845-9)
2: Tattevin, CID 1999 (29:292-5)
3: Brandt, CID, 1997(24:914-9)
4: RAO, Clin Ortho Rel Research, 2003(414: 55-60)
5: Hartman, Clin Ortho Rel Research, 1991(273: 113-8)

# Efficacité globale

- La comparaison des différentes études : difficile.
- Mais en globalité pour hanche et genou on obtient :
  - Changement en 1 temps : efficacité entre 85 et 90 %
  - Changement en 2 temps : 85 et 95 %

Bengtson S. Acta Orthop Scand 1991 ;
Mont MA. J Bone Joint Surg Am 2000
Hsieh PH. J Bone Joint Surg Am 2004
Mulcahy DM. Ir J Med Sci 1996
Souillac V. Rev Chir Orthop Reparatrice Appar Mot 2006
Hanssen AD. Clin Orthop Relat Res 1994

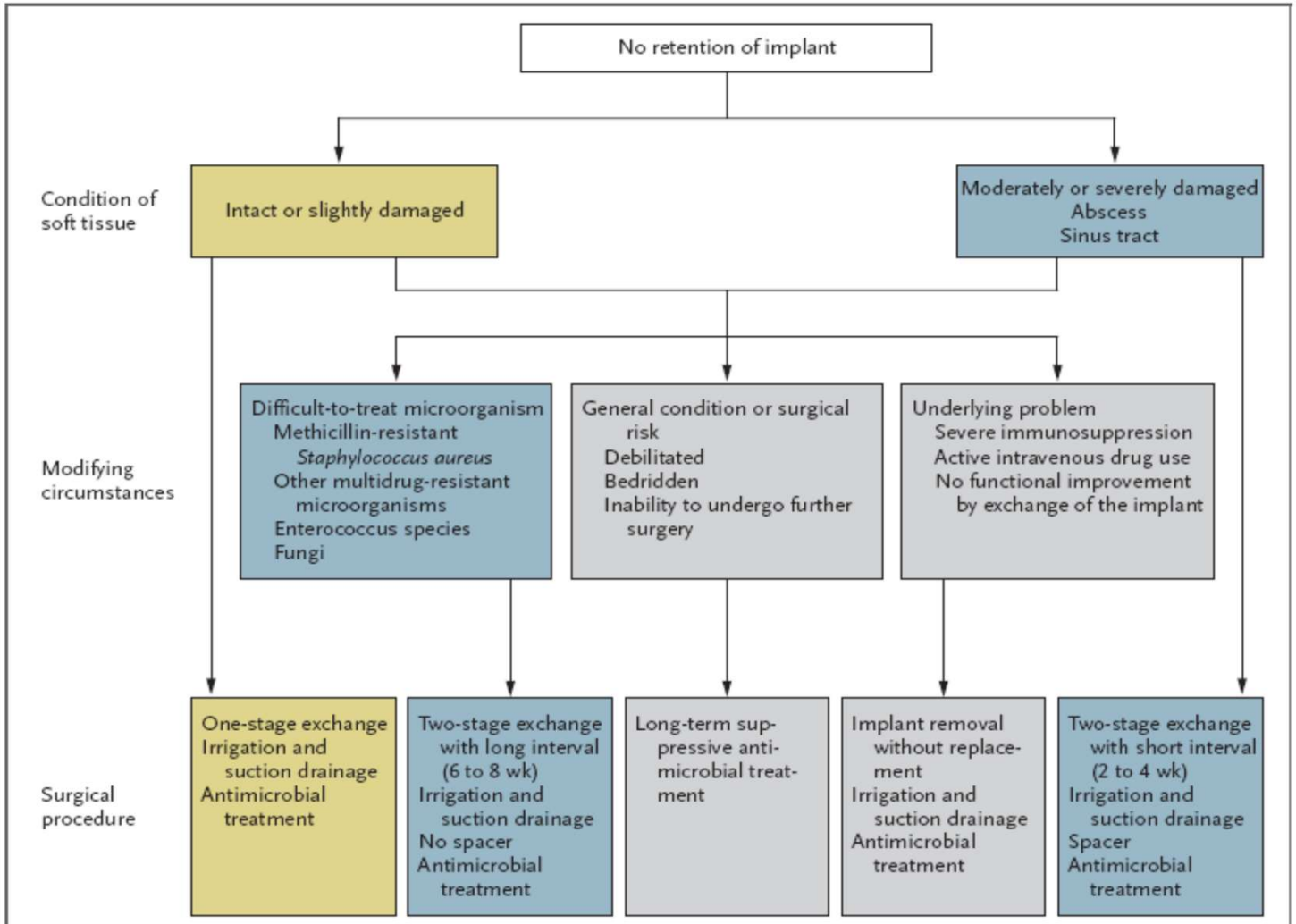



**Figure 3. Algorithm for the Treatment of Patients with Infections Not Qualifying for Implant Retention.**

This algorithm has been developed for patients with a hip prosthesis who have delayed or late infection, symptoms of more than three weeks' duration, infection with difficult-to-treat microorganisms, severely compromised soft tissue, or a severe coexisting illness. In patients with a knee prosthesis, arthrodesis is performed after resection arthroplasty. If the soft tissue is intact or only slightly damaged, a one-stage exchange (green boxes) may be possible. In patients with compromised soft tissue or difficult-to-treat microorganisms, a two-stage exchange (blue boxes) is preferred. Permanent explantation or joint arthrodesis is usually performed in severely immunocompromised patients, those with active intravenous drug use, and those in whom arthroplasty will not provide any functional benefit (gray boxes).

# Confirmation microbiologique

- Élément majeur du diagnostic positif car **INDISPENSABLE** à la bonne conduite de l'antibiothérapie
- En l'absence d'une documentation microbiologique FIABLE (ponction articulaire, prélèvements per opératoires, biopsie percutanée, hémocultures),
- >> Diagnostic incomplet, traitement antibiotique hasardeux

D'après E. Senneville

**Features of selected antimicrobials used for outpatient parenteral antibiotic therapy**

| Anti-infective | Oral bioavailability (percent)* | Doses per day¶ | Infusion time | Delivery device△ | Monitoring frequency◇ | | | Most common potentially serious ADRs | Torsades de Pointes risk§ | Other comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | CBC-diff | BMP↓ including K, Cr, BUN | Liver profile: ALT, AST, ALK, Tbil | | | |
| Amikacin | NA | 1 to 3 | 30 to 60 minutes depending on dose | Grav, Elas | Once weekly | Twice weekly | Not required routinely | Nephrotoxicity; ototoxicity | | Refer to aminoglycoside monitoring# |
| Ampicillin | 50 | 4 to 6 | 3 to 5 minutes push or 10 to 15 minutes infusion | Grav, EID, IVP | Once weekly | Once weekly | Once weekly | Hypersensitivity including anaphylaxis | | Stable once reconstituted for only 3 days; refer to stability footnote* |
| Ampicillin-sulbactam | NA | 3 to 4 | 10 to 15 minutes push or 15 to 30 minutes infusion | Grav, EID, Elas, IVP | Once weekly | Once weekly | Once weekly | Hypersensitivity including anaphylaxis | | Stable once reconstituted for only 3 days; refer to stability footnote* |
| Azithromycin | 28 to 52 | 1 | 60 minutes | Grav | Once weekly | Not required routinely | Not required routinely | | Known | Consider change to po |
| Aztreonam | NA | 2 to 4 | 3 to 5 minutes push or 20 to 60 minutes infusion | Grav, EID, Elas, IVP | Once weekly | Once weekly | Once weekly | | | Rare cross-allergenicity with other beta-lactams |
| Cefazolin | NA | 3 to 4 | 3 to 5 minutes push or 30 to 60 minutes infusion | Grav, Elas, IVP | Once weekly | Once weekly | Not required routinely | Hypersensitivity including anaphylaxis | | Dialysis-only dosing possible |
| Cefepime | NA | 2 to 3 | 5 minutes push or 30 minutes infusion | Grav, Elas, IVP | Once weekly | Once weekly | Not required routinely | Hypersensitivity including anaphylaxis | | Dialysis-only dosing possible |
| Cefoxitin | NA | 3 to 4 | 3 to 5 minutes push or 20 to 30 minutes infusion | Grav, Elas, IVP | Once weekly | Once weekly | Not required routinely | Hypersensitivity including anaphylaxis | | |
| Ceftaroline | NA | 2 to 3 | 5 minutes push or 5 to 60 minutes | Grav, IVP | Once weekly | Once weekly | Not required routinely | Hypersensitivity including anaphylaxis | | |
| Ceftazidime | NA | 3 | 3 to 5 minutes push or 15 to 30 minutes infusion | Grav, Elas, IVP | Once weekly | Once weekly | Not required routinely | Hypersensitivity including anaphylaxis | NA | Dialysis-only dosing possible |
| Ceftazidime-avibactam | NA | 3 | 120 minutes | Grav, EID | Once weekly | Once weekly | Not required routinely | Hypersensitivity including anaphylaxis | | … |
| Ceftolozane-tazobactam | NA | 3 | 60 minutes | Grav, EID | Once weekly | Once weekly | Not required routinely | Hypersensitivity including anaphylaxis | | … |
| Ceftriaxone | NA | 1 to 2 | 1 to 4 minutes push or 30 minutes infusion | Grav, Elas, IVP | Once weekly | Once weekly | Once weekly | Hypersensitivity including anaphylaxis | | Refer to monitoring footnote* |
| Ciprofloxacin | 50 to 85 | 2 to 3 | 60 minutes | Grav, Elas | Not required routinely | Not required routinely | Not required routinely | Tendonitis/tendon rupture; peripheral neuropathy | Known | Consider change to po; refer to monitoring footnote◇ |
| Clindamycin | 90 | 3 to 4 | 10 to 60 minutes (not to exceed 30 mg/minute) | Grav, Elas | Once weekly | Once weekly | Once weekly | | | Consider change to po; refer to monitoring footnote◇ |
| Colistin | NA | 2 to 4 | 3 to 5 minutes IVP; 30 minutes for infusion | Grav, IVP | Once weekly | Twice weekly | Not required routinely | Nephro- and neurotoxicity | | Inhaled colistin may be an option for respiratory tract infections |
| Daptomycin | NA | 1 | 2 minutes push or 30 minutes infusion | Grav, Elas, IVP | Once weekly | Once weekly | Not required routinely | Myopathy; rhabdomyolysis | | Baseline and weekly CK, discontinue if symptomatic and CK >1000 units/L (~5× ULN) or asymptomatic and CK >2000 units/L (~10 minutes ULN); dialysis-only dosing possible |
| Dalbavancin | NA | Once per week | 30 minutes | Grav | Not required routinely | Not required routinely | Not required routinely | Hypersensitivity including anaphylaxis | | Vancomycin flushing reaction more likely if infusion <30 minutes; monitoring requirements unknown for treatment duration greater than 2 weeks |
| Ertapenem | NA | 1 | 30 minutes | Grav, Elas | Once weekly | Once weekly | Once weekly | Hypersensitivity including anaphylaxis | NA | Refer to stability footnote* |
| Gentamicin | NA | 1 to 3 | 30 to 120 minutes depending on dose | Grav, EID, Elas | Once weekly | Twice weekly | Not required routinely | Nephrotoxicity; ototoxicity | | Refer to aminoglycoside monitoring# |
| Imipenem | NA | 3 to 4 | 20 to 60 minutes depending on dose | Grav | Once weekly | Once weekly | Once weekly | Hypersensitivity including anaphylaxis; seizures | | Refer to stability footnote* |
| Levofloxacin | 90 | 1 | 60 to 90 minutes depending on dose | Grav | Not required routinely | Not required routinely | Not required routinely | Tendonitis/tendon rupture; cardiac arrhythmias; peripheral neuropathy | Known | Consider change to po; refer to monitoring footnote◇ dialysis-only dosing possible |
| Linezolid | 100 | 2 | 30 to 120 minutes | Grav, EID | Once weekly | Not required routinely | Once weekly | Thrombocytopenia; leukopenia; anemia; peripheral neuropathy; optic neuritis | | Consider change to po; monitor for neuropathy, optic neuritis in prolonged use; refer to monitoring footnote◇ potential for drug interactions |
| Meropenem | NA | 3 to 4 | 30 minutes | Grav, Elas | Once weekly | Once weekly | Once weekly | Hypersensitivity including anaphylaxis | | Dialysis-only dosing possible; refer to stability footnote* |
| Metronidazole | 100 | 2 to 4 | 30 to 60 minutes | Grav, EID, Elas | Once weekly | Not required routinely | Not required routinely | Peripheral neuropathy | Conditional | Consider change to po |
| Nafcillin | NA | 4 to 6 | 30 to 60 minutes | Grav, EID | Once weekly | Once weekly | Once weekly | Hypersensitivity including anaphylaxis | | Central line commonly used because of concern for phlebitis risk |
| Oritavancin | NA | Once | 180 minutes | Grav | Not required routinely | Not required routinely | Not required routinely | Hypersensitivity including anaphylaxis; infusion related | | Vancomycin flushing reaction more likely if infusion <60 minutes; monitoring requirements unknown for treatment duration greater than a single dose |
| Oxacillin | NA | 4 to 6 | 10 to 30 minutes | Grav, Elas | Once weekly | Once weekly | Once weekly | Hypersensitivity including anaphylaxis; hepatotoxicity | | Central line commonly used because of concern for phlebitis risk |
| Penicillin G | 25 to 73 | 4 to 6 | 15 to 30 minutes | Grav, EID | Once weekly | Once weekly | Once weekly | Hypersensitivity including anaphylaxis | | Oral penicillin V K is not a substitute for IV treatment of most clinical conditions requiring IV penicillin, eg, syphilis |
| Piperacillin-tazobactam | NA | 3 to 4 | 30 to 240 minutes (extended infusion) | Grav, EID | Once weekly | Once weekly | Once weekly | Hypersensitivity including anaphylaxis | | |
| Polymyxin B | NA | 1 | 60 to 90 minutes | Grav | Once weekly | Twice weekly | Not required routinely | Nephro- and neurotoxicity | | Monitor for nephrotoxicity, neurotoxicity |
| Rifampin | 70 to 90 | 1 to 3 | 30 minutes | Grav | Once weekly | Once weekly | Once weekly | Hepatitis; hypersensitivity | NA | Potential for drug-drug interactions; consider change to po |
| Tedizolid | 91 | 1 | 60 minutes | Grav | Once weekly | Not required routinely | Once weekly | Thrombocytopenia; leukopenia; anemia; peripheral neuropathy; optic neuritis | | Consider change to po; monitor for neuropathy, optic neuritis in prolonged use; potential for drug interactions; refer to monitoring footnote◇ |
| Telavancin | NA | 1 | 60 minutes | Grav | Once weekly | Twice weekly | Not required routinely | Nephrotoxicity; hypersensitivity including anaphylaxis; infusion-related prolongation of QTc | Possible | High rate of renal injury in patients aged >65 years, with preexisting renal impairment or other nephrotoxins; vancomycin flushing reaction more likely if infusion <60 minutes |
| Tigecycline | NA | 2 | 30 to 60 minutes | Grav | Once weekly | Once weekly | Once weekly | Nausea/vomiting | | |
| Tobramycin | NA | 1 to 3 | 30 to 120 minutes depending on dose | Grav, EID, Elas | Once weekly | Twice weekly | Not required routinely | Nephrotoxicity; ototoxicity | | Refer to aminoglycoside monitoring# |
| Trimethoprim/sulfamethoxazole | 85 | 2 to 4 | 60 to 90 minutes | Grav | Once weekly | Once weekly | Once weekly | Hyperkalemia; rash; nephrotoxicity; Stevens Johnson syndrome | Special | Consider change to po; potential for drug-drug interactions; high fluid requirement; spurious increase in serum creatinine |
| Vancomycin | NA | 1 to 2 | 60 to 120 minutes depending on dose | Grav, EID, Elas | Once weekly | Once weekly | Not required routinely | Nephrotoxicity; infusion-related reactions | | Dialysis-only dosing possible; vancomycin trough levels or area under the curve/minimum inhibitory concentration weekly and with dose changes; vancomycin flushing reaction more likely if infusion <60 minutes |

Use of the information presented in this table should be tailored to individual patient circumstances.

CBC: complete blood cell count; BMP: basic metabolic profile; K: potassium; Cr: creatinine; BUN: blood urea nitrogen; ALT: alanine transaminase; AST: aspartate transaminase; ALK: alkaline phosphatase; Tbil: total bilirubin; ADR: adverse drug reaction; NA: not applicable/no oral formulation; Grav: gravity; Elas: elastomeric; EID: electronic infusion device; IVP: intravenous push; po: by mouth; CK: creatine kinase; ULN: upper limit of normal; IV: intravenous; QTc: corrected QT-interval; LFT: liver function tests.

* Bioavailability: changing to oral medications when possible is part of good antimicrobial stewardship. Clinicians should consider the full clinical situation, including the appropriateness of oral antimicrobials for the condition being treated. Potential for interaction with foods and other medications as well as concomitant illnesses and the potential for impaired gut absorption must also be considered.

¶ Doses per day: assumes normal renal and hepatic function. More than 2 to 3 doses per day may be impractical for pediatric outpatient parenteral antimicrobial therapy (OPAT) that requires adult infusion assistance for every dose. Dosing more frequently than once daily is typically not practical for patients who receive care in infusion centers.

△ Devices: very limited published information on the use of these devices in OPAT. Individual infusion pharmacies have variable policies and device availability. Not all drugs are compatible with all delivery options. EIDs can be programmed to automatically deliver multiple doses per day but they require that the patient be connected to a small device virtually continuously and are not covered by all insurance carriers. Elas are very simple to use but also are not covered by all insurance carriers. Gravity delivery (infusion without a pump, using a roller clamp) is less expensive but also less convenient due to longer infusion times and complexity for patients to learn. Depending upon care setting, use of a traditional infusion pump may be selected in lieu of gravity for rate control. IVP is very convenient because of rapid infusion time.

◇ These are recommendations based on frequency and seriousness of reported adverse events. The monitoring plan for an individual patient may be different based on the comorbid conditions and anticipated duration of OPAT. For instance, for shorter courses of linezolid, ceftriaxone, or clindamycin, it may not be necessary to monitor LFTs and/or renal function. Alternatively, for longer courses of fluoroquinolones, weekly lab monitoring may be appropriate. For patients with normal baseline labs, less intense monitoring may be appropriate.

§ Risk of Torsades de Pointes (TdP): known, known to prolong QTc interval and cause TdP even when taken as recommended; possible, can cause QTc prolongation but not known to cause TdP when taken as recommended; conditional, associated with TdP but only under certain conditions (ie, excessive dose, with hypokalemia, with other interacting drugs) or by creating conditions that induce TdP (inhibiting metabolism of QTc prolonging drugs); special, high risk of TdP in patients with congenital long QT syndromes due to other actions. Source for TdP risk[1].

# Aminoglycoside monitoring: monitor concentrations minimum weekly. Goal aminoglycoside trough values differ according to the drug, infection, and dosing strategy.

* For medications with limited stability, home delivery more frequently than once weekly will be required. Some drugs may be reconstituted in the home using a use-activated container, if available.


References:
1. Woosley RL, Heise CW, Gallo T, et al. QTdrugs List. Ore Valley, AZ: AZCERT, Inc. Available at: https://www.crediblemeds.org.

**Suppression of osteomyelitis or prosthetic joint infection in adults: Oral antibiotic regimens***

| Infectious agent | Antibiotic regimen¶ | Dosing |
|---|---|---|
| **Staphylococci, methicillin susceptible** | **One of the following:** | |
| | Cefadroxil | 500 to 1000 mg twice daily |
| | Cephalexin | 500 mg 3 or 4 times daily, or 1000 mg 2 or 3 times daily |
| | Dicloxacillin | 500 mg 3 or 4 times daily |
| | Flucloxacillin | 500 mg 3 or 4 times daily |
| **Staphylococci, methicillin resistantΔ** | **One of the following:** | |
| | Trimethoprim-sulfamethoxazole | 1 double-strength tablet twice daily |
| | Doxycycline | 100 mg twice daily |
| | Minocycline | 100 mg twice daily |
| | Clindamycin | 600 mg 3 times daily |
| **Gram-negative organisms** | **One of the following:** | |
| | Trimethoprim-sulfamethoxazole | 1 double-strength tablet twice daily |
| | Ciprofloxacin◇ | 500 mg twice daily |
| | Levofloxacin◇ | 500 mg once daily |
| **Penicillin-sensitive streptococci and enterococci** | **One of the following:** | |
| | Amoxicillin | 500 mg 2 to 3 times daily |
| | Penicillin V K | 500 mg 2 to 4 times daily |
| ***Cutibacterium* (formerly *Propionibacterium*) *acnes*** | **One of the following:** | |
| | Amoxicillin | 500 mg 2 to 3 times daily |
| | Penicillin V K | 500 mg 2 to 3 times daily |

The doses recommended above are intended for adults with normal renal function; the doses of some of these agents must be adjusted in patients with renal insufficiency. Refer to the drug-specific monographs included within UpToDate for renal dose adjustments.

PJI: prosthetic joint infection.

* Initial treatment of PJI consists of definitive antibiotic therapy (refer to the separate UpToDate table); suppressive therapy is warranted only for individuals with retained hardware and/or necrotic bone not amenable to complete debridement. The optimal duration of oral suppressive antibiotic therapy is uncertain. Refer to the UpToDate topic on the treatment of PJI for further discussion.

¶ The choice of antibiotic regimen should be based on susceptibility, as well as patient drug allergies, intolerances, and potential drug-drug interactions or contraindications to a specific agent.

Δ The agents listed for methicillin-resistant staphylococci may be used for suppression of methicillin-susceptible staphylococci in patients with beta-lactam allergy or intolerance, provided the organism is susceptible.

◇ Ciprofloxacin and levofloxacin have activity against *Pseudomonas aeruginosa*.

*Data from:*

1. *Osmon DR, Berbari EF, Berendt AR, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2013; 56:e1.*
2. *Berbari EF, Kanj SS, Kowalski TJ, et al. 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. Clin Infect Dis 2015; 61:e26.*

**Treatment of Staphylococcus aureus prosthetic joint infection in adults with retained hardware following debridement and completion of intravenous therapy: Oral antibiotic continuation therapy*¶**

| Antibiotic regimen | Dosing |
|---|---|
| **Preferred regimens include:** | |
| **One of the following:** | |
| Levofloxacin | 500 to 750 mg daily |
| Ciprofloxacin | 500 to 750 mg twice daily |
| **plus** | |
| Rifampin$^{\Delta}$ | 300 to 450 mg twice daily$^{\diamond}$ |
| **Alternative regimens include:** | |
| **One of the following agents:**§ | |
| Trimethoprim-sulfamethoxazole | 1 double-strength tablet twice daily |
| Doxycycline | 100 mg twice daily |
| Minocycline | 100 mg twice daily |
| Dicloxacillin | 500 mg 3 or 4 times daily |
| Cefadroxil | 500 mg twice daily |
| Cephalexin | 500 mg 3 or 4 times daily |
| Flucloxacillin | 500 mg 3 or 4 times daily |
| Fusidic acid (where available)¥ | 500 mg 3 times daily |
| **plus** | |
| Rifampin$^{\Delta}$ | 300 to 450 mg twice daily$^{\diamond}$ |

The doses recommended above are intended for adults with normal renal function; the doses of some of these agents must be adjusted in patients with renal insufficiency. Refer to the drug-specific monographs included within UpToDate for renal dose adjustments.

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PJI: prosthetic joint infection.

* For patients with *S. aureus* PJI with retained hardware following debridement (eg, debridement and retention of prosthesis or 1-stage exchange), antibiotic therapy consists of pathogen-specific intravenous therapy in combination with rifampin for 2 to 6 weeks (refer to the UpToDate topic on treatment of PJI for further discussion). Thereafter, subsequent therapy for patients who undergo debridement and retention of hip, elbow, shoulder, or ankle PJI consists of pathogen-specific oral therapy in combination with rifampin to complete a total duration of 3 months. Subsequent therapy for patients who undergo debridement and retention of knee PJI consists of pathogen-specific oral therapy in combination with rifampin to complete a total duration of 6 months. Subsequent therapy for patients who undergo 1-stage exchange consists of pathogen-specific oral therapy in combination with rifampin to complete a total duration of 3 months.

¶ Following administration of antibiotic therapy as summarized in this table, indefinite antibiotic suppression with an oral regimen may be warranted in some patients; refer to the UpToDate topic on treatment of PJI for further discussion.

Δ Patients who cannot take rifampin because of drug resistance, allergy, toxicity, intolerance, or drug-drug interactions should remain on intravenous antistaphylococcal therapy for 4 to 6 weeks (before transitioning to antibiotic suppression with an oral regimen, if warranted).

◇ We favor administration of rifampin 450 orally twice daily; the dose may be reduced to 300 mg orally twice daily in the setting of nausea.

§ Alternative agents given with rifampin are recommended for patients who cannot take a fluoroquinolone due to allergies, intolerances, or resistance. If an alternative agent is used, confirm susceptibility.

¥ Not available in the United States. Fusidic acid should not be used alone; it must be combined with a second active agent to reduce the likelihood of selection for drug resistance. When rifampin is combined with fusidic acid, fusidic levels may be reduced.

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*Data from:*

1. *Osmon DR, Berbari EF, Berendt AR, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2013; 56:e1.*
2. *Berbari EF, Kanj SS, Kowalski TJ, et al. 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. Clin Infect Dis 2015; 61:e26.*
3. *Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis 2011; 52:e18.*
4. *Leijtens B, Elbers JB, Sturm PD, et al. Clindamycin-rifampin combination therapy for staphylococcal periprosthetic joint infections: a retrospective observational study. BMC Infect Dis 2017; 17:321.*
5. *Zimmerli W, Widmer AF, Blatter M, et al. Role of rifampin for treatment of orthopedic implant-related staphylococcal infections: a randomized controlled trial. Foreign-Body Infection (FBI) Study Group. JAMA 1998; 279:1537.*
6. *Byren I, Bejon P, Atkins BL, et al. One hundred and twelve infected arthroplasties treated with 'DAIR' (debridement, antibiotics and implant retention): antibiotic duration and outcome. J Antimicrob Chemother 2009;63:1264.*
7. *Berdal JE, Skråmm I, Mowinckel P, et al. Use of rifampicin and ciprofloxacin combination therapy after surgical debridement in the treatment of early manifestation prosthetic joint infections. Clin Microbiol Infect 2005; 11:843.*
8. *Senneville E, Poissy J, Legout L, et al. Safety of prolonged high-dose levofloxacin therapy for bone infections. J Chemother 2007; 19:688.*
9. *Soriano A, García S, Bori G, et al. Treatment of acute post-surgical infection of joint arthroplasty. Clin Microbiol Infect 2006; 12:930.*
10. *Pushkin R, Iglesias-Ussel MD, Keedy K, et al. A randomized study evaluating oral fusidic acid (CEM-102) in combination with oral rifampin compared with standard-of-care antibiotics for treatment of prosthetic joint infections: A newly identified drug-drug interaction. Clin Infect Dis 2016; 63:1599.*

**Pathogen-specific antibiotic therapy for treatment of osteomyelitis or prosthetic joint infection in adults**

| Infectious agent | Antibiotic regimen | Dosing |
|---|---|---|
| Staphylococci, methicillin susceptible* | Nafcillin | 2 g IV every 4 hours |
| | Oxacillin | 2 g IV every 4 hours |
| | Cefazolin | 2 g IV every 8 hours |
| | Flucloxacillin | 2 g IV every 6 hours |
| | Ceftriaxone¶ | 2 g IV every 24 hours |
| Staphylococci, methicillin resistant* | **Regimen of choice:** | |
| | Vancomycin[Δ] | Loading dose[◇]: 20 mg/kg<br>Initial maintenance dose and interval determined by nomogram[§]: typically 15 to 20 mg/kg every 8 to 12 hours for most patients with normal renal function<br>Subsequent dose and interval adjustments based on AUC-guided or trough-guided serum concentration monitoring[¥] |
| | **Alternative regimens:**[†] | |
| | Daptomycin[†] | 6 to 10 mg/kg IV once daily |
| | Teicoplanin (where available)**,¶¶ | 12 mg/kg IV every 12 hours for 3 to 5 doses, followed by 12 mg/kg once daily |
| Staphylococci, adjunctive agents* | Rifampin | 300 to 450 mg orally twice daily |
| | Fusidic acid (where available)** | 500 mg orally 3 times daily |
| Gram-negative organisms | Ciprofloxacin[ΔΔ,◇◇,§§] | 750 mg orally twice daily or 400 mg IV every 12 hours; if treating *Pseudomonas*, increase IV dose to 400 mg IV every 8 hours |
| | Levofloxacin[◇◇,§§] | 750 mg orally or IV once daily |
| | Ceftriaxone[¥¥] | 2 g IV every 24 hours |
| | Ceftazidime[◇◇] | 2 g IV every 8 hours |
| | Cefepime[◇◇] | 2 g IV every 8 to 12 hours |
| | Ertapenem[¥¥] | 1 g IV every 24 hours |
| | Meropenem[◇◇] | 1 g IV every 8 hours |
| Enterococci** | **Monotherapy regimens:** | |
| | Ampicillin | 12 g IV every 24 hours, either continuously or in 6 equally divided doses |
| | Aqueous crystalline penicillin G | 20 to 24 million units IV every 24 hours, either continuously or in 6 equally divided doses |
| | Vancomycin[Δ] | 20 mg/kg loading dose, then 15 mg/kg IV every 12 hours, not to exceed 2 g per dose |
| | Daptomycin[†] | 6 to 10 mg/kg IV once daily |
| | Teicoplanin (where available)**,¶¶ | 12 mg/kg IV every 12 hours for 3 to 5 doses, followed by 12 mg/kg once daily |
| | **Combination therapy regimen:** | |
| | Ampicillin | 12 g IV every 24 hours, given either continuously or in 6 equally divided doses |
| | **plus** | |
| | Ceftriaxone | 2 g IV every 12 to 24 hours |
| Streptococci, penicillin sensitive | **One of the following:** | |
| | Aqueous crystalline penicillin G | 20 to 24 million units IV every 24 hours, either continuously or in 6 equally divided doses |
| | Ampicillin | 12 g IV every 24 hours, either continuously or in 6 equally divided doses |
| | Ceftriaxone | 2 g IV every 24 hours |
| | Vancomycin[Δ] | 20 mg/kg loading dose, then 15 mg/kg/dose IV every 12 hours, not to exceed 2 g per dose, initially |
| *Cutibacterium* (formerly *Propionibacterium*) *acnes*** | **One of the following:** | |
| | Aqueous crystalline penicillin G | 20 million units IV every 24 hours, either continuously or in 6 divided doses |
| | Ceftriaxone | 2 g IV every 24 hours |

In stable patients, antibiotics may be held pending establishment of microbiologic diagnosis or obtaining cultures from bone debridement or biopsy. The total duration of antibiotic therapy depends on individual patient circumstances (refer to the UpToDate content on treatment of osteomyelitis and prosthetic joint infection for further discussion). The doses in this table are intended for adults with normal renal function. The doses of many of these agents must be adjusted in the setting of renal insufficiency; refer to the drug-specific monographs included within UpToDate for renal dose adjustments.

NSAIDs are useful for treatment of acute and chronic painful and inflammatory conditions and may reduce opioid requirements. The indications for use of NSAIDs in specific disorders, adverse effects, and toxicities are presented in the relevant UpToDate topics including reviews of NSAID-associated adverse cardiovascular effects, gastroduodenal toxicity, acute kidney injury, etc.

UpToDate contributors generally avoid use of NSAIDs, or use them with particular caution and at reduced doses, in older adults and patients (regardless of age) with existing or increased risk for cardiovascular, GI, or kidney disease. Concurrent gastroprotection (eg, a proton pump inhibitor) may be warranted. For information on gastroprotective strategies, including use of selective COX-2 inhibitors and other options, refer to the UpToDate topic reviews of COX-2 selective NSAIDs and NSAIDs (including aspirin) and primary prevention of gastroduodenal toxicity.

Short- to moderate-acting NSAIDs (eg, naproxen, ibuprofen) are preferred for most patients. Use the lowest effective dose for the shortest duration of time. For chronic inflammatory conditions, a trial of ≥2 weeks is advised to assess full efficacy. For patients who experience an inadequate response to an NSAID of 1 class, it is reasonable to substitute an NSAID of another class.

Dosing in this table is for immediate-release preparations in patients with normal organ (eg, kidney) function. For treatment of acute pain, a loading dose of some NSAIDs may be used; refer to UpToDate Lexidrug monographs.

Drug interactions may be determined by use of the drug interactions program included within UpToDate.

AUC: area under the 24-hour time-concentration curve; IV: intravenously; PJI: prosthetic joint infection.

* For patients with staphylococcal PJI and residual hardware following surgery, we favor use of adjunctive rifampin. To mitigate the emergence of resistance, rifampin should not be started until the patient has received several days of anti-staphylococcal therapy. We favor administration of rifampin 450 orally twice daily; the dose may be reduced to 300 mg orally twice daily in the setting of nausea. There should be careful screening drug-drug interactions prior to initiation of rifampin.

¶ Use of ceftriaxone for treatment of staphylococcal osteomyelitis is not universally accepted. In our practice, we use it as an alternative regimen for isolates with oxacillin minimum inhibitory concentration <0.5 mcg/mL in the absence of concomitant bacteremia; once-daily dosing is a convenient outpatient regimen.

Δ In adults, vancomycin is dosed based on actual body weight. Target troughs for vancomycin should be chosen with the guidance of a local infectious disease physician based on the pathogen, in vitro susceptibility, and the use of rifampin or local vancomycin therapy, with a target trough concentration of at least 10 mcg/mL. It is unknown if a higher vancomycin trough level of 15 to 20 mcg/mL is routinely needed. Refer to the UpToDate topic review on vancomycin parenteral dosing and serum concentration monitoring in adults.

◇ Most patients with osteomyelitis or prosthetic joint infection due to methicillin-resistant *Staphylococcus aureus* (MRSA) are clinically stable; a loading dose of 20 mg/kg is adequate in such cases. For patients with critical illness and serious MRSA infection, a loading dose of up to 35 mg/kg may be warranted. The vancomycin loading dose is based on actual body weight, rounded to the nearest 250 mg increment and not exceeding 3000 mg.

§ Refer to the UpToDate topic on vancomycin dosing for sample nomogram.

¥ Refer to the UpToDate topic on vancomycin dosing for discussion of AUC-guided and trough-guided vancomycin dosing.

# Ceftaroline has been used successfully for treatment of osteomyelitis but has been associated with increased risk of neutropenia. Pending further study, use of ceftaroline should be reserved for patients unable to receive other therapies. Ceftaroline susceptibility must be confirmed; the prevalence of resistance is high in some regions. Daptomycin may be used for vancomycin-resistant enterococci; confirm susceptibility.

† Standard daptomycin dosing (as approved by the US Food and Drug Administration) for treatment of bacteremia or osteomyelitis is 6 mg/kg IV once daily. Because daptomycin exhibits concentration-dependent killing, some experts recommend doses of up to 8 to 10 mg/kg IV once daily, which appear safe; further study is needed.

** Not available in the United States. Fusidic acid should not be used alone; it must be combined with a second active agent to reduce the likelihood of selection for drug resistance. When rifampin is combined with fusidic acid, fusidic levels may be reduced.

¶¶ The teicoplanin dose should be adjusted to attain a trough concentration of >20 mcg/mL.

ΔΔ Oral ciprofloxacin at dose shown in table achieves therapeutic levels for treatment of *Pseudomonas aeruginosa*.

◇◇ Ciprofloxacin, levofloxacin, ceftazidime, cefepime, and meropenem have activity against *P. aeruginosa*; confirm susceptibility.

§§ The possibility of prolonged QTc interval, tendinopathy, neuropathy, or development of an aneurysm should be reviewed and monitored when using fluoroquinolones. For more information, please refer to the UpToDate topic on fluoroquinolones.

¥¥ Ceftriaxone and ertapenem have no activity against *P. aeruginosa*, but are appropriate for other gram-negative organisms, if susceptible.

** For treatment of infection due to penicillin-susceptible enterococci, it is unclear whether combination therapy is superior to monotherapy, particularly if thorough debridement is performed. In the setting of retained hardware, we favor combination therapy for PJI due to *Enterococcus faecalis* with ampicillin and ceftriaxone. We do not use this approach for treatment of PJI due to non-*faecalis* species of penicillin-susceptible enterococci because synergy with these agents in vitro is variable and clinical data are not available in patients with PJI due to non-*faecalis* species[11]. If antibiotic-impregnated material containing gentamicin is implanted at the time of debridement, then monotherapy is likely sufficient and we favor treatment with either intravenous ampicillin or penicillin (vancomycin or daptomycin are acceptable alternative agents for patients with proven beta-lactam hypersensitivity). For treatment of infection due to penicillin-resistant enterococci, the preferred agent is vancomycin; daptomycin or teicoplanin (where available) are acceptable alternative agents.

†† For patients with *Cutibacterium* spp infection and beta-lactam hypersensitivity, reasonable alternative agents include vancomycin, a tetracycline (doxycycline or minocycline), or moxifloxacin.


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