XXVIème congrès de la STPI, 22 avril 2016

Traitement des infections ostéo-articulaires

Aurélien Dinh
Infectiologue
Centre de référence des infections ostéo articulaires complexes
Hôpital R. Poincaré Garches, AP-HP, UVSQ

Une fois que :

- Diagnostic clinique évoqué,
- Confirmation microbiologique réalisée,
- Identification microbiologique fiable…

On peut parler traitement (le plus facile ?)

2 axes :

- Chirurgical
- Médical (ATB et autres)

« 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

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].

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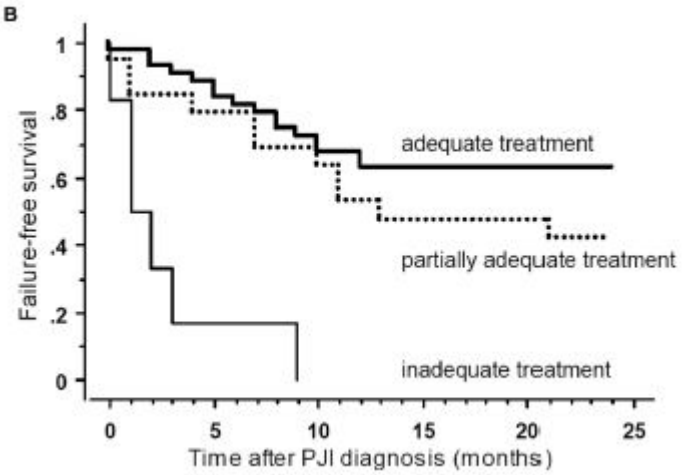


Chirurgie

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

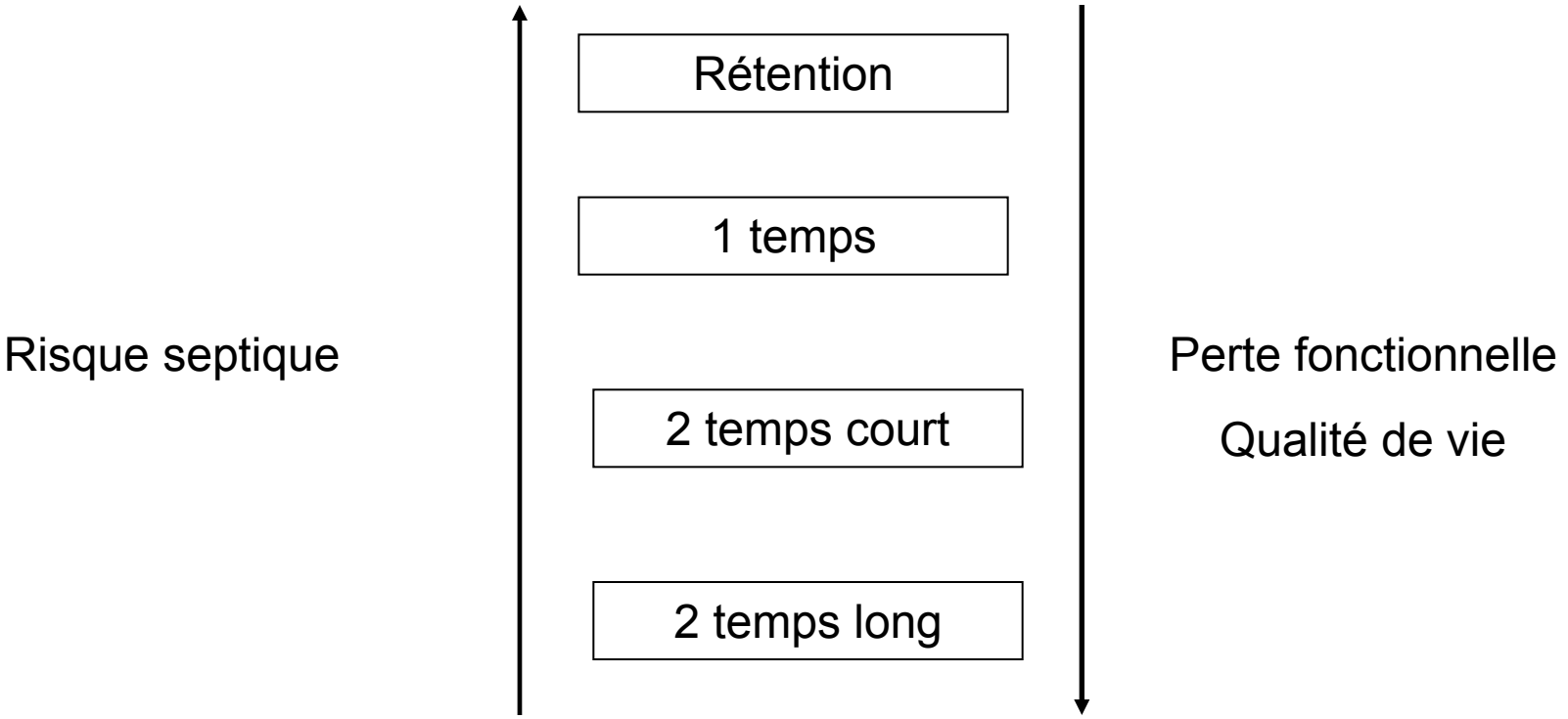
Efficacité lavage débridement fonction de l'âge de la prothèse et de la durée des symptômes

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) 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% >1 mois: 60%	< 2j	Staph (93%)	100%	3
21/34			> 2j		0%	
17/36 cas	6 ans	13 < 1an	< 1mois	Staph (86%)	86.% *	4
19/36 cas		23 > 1an	> 1 mois		NS 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)

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

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 %

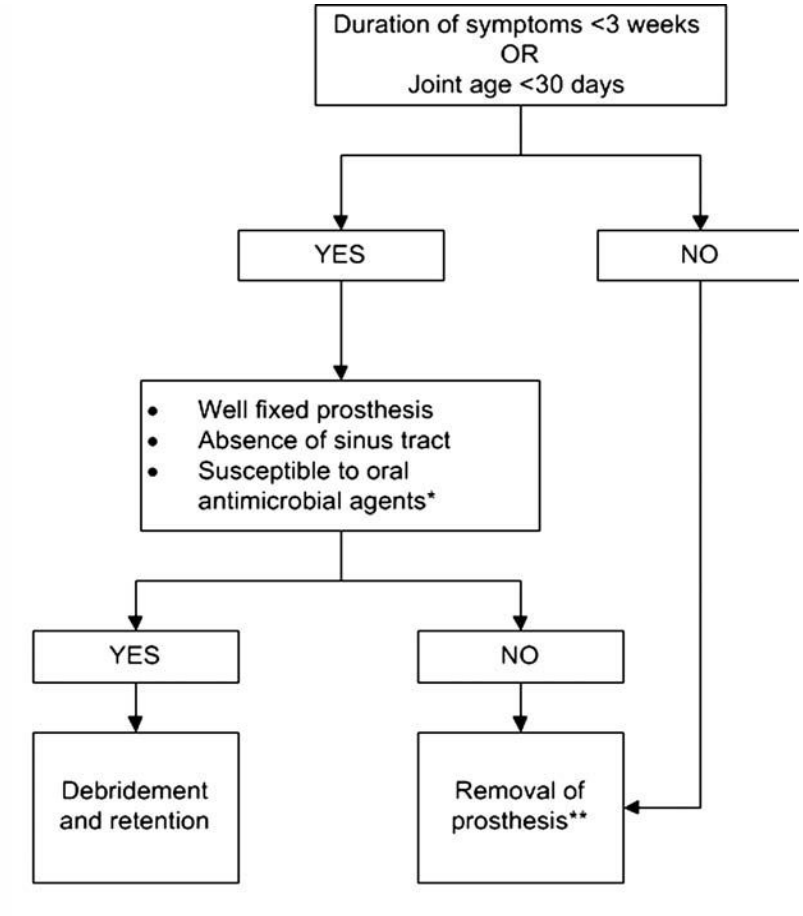
Bengtson S. Acta Orthop Scand 1991 ;
Mont MA. J Bone Joint Surg Am 2000
Hsieh PH. J Bone Joint Surg Am 2004
Mulcahy DM. Ir J Med Sci 1996
Souillac V. Rev Chir Orthop Reparatrice Appar Mot 2006
Hanssen AD. Clin Orthop Relat Res 1994

Clinical Infectious Diseases Advance Access published December 6, 2012

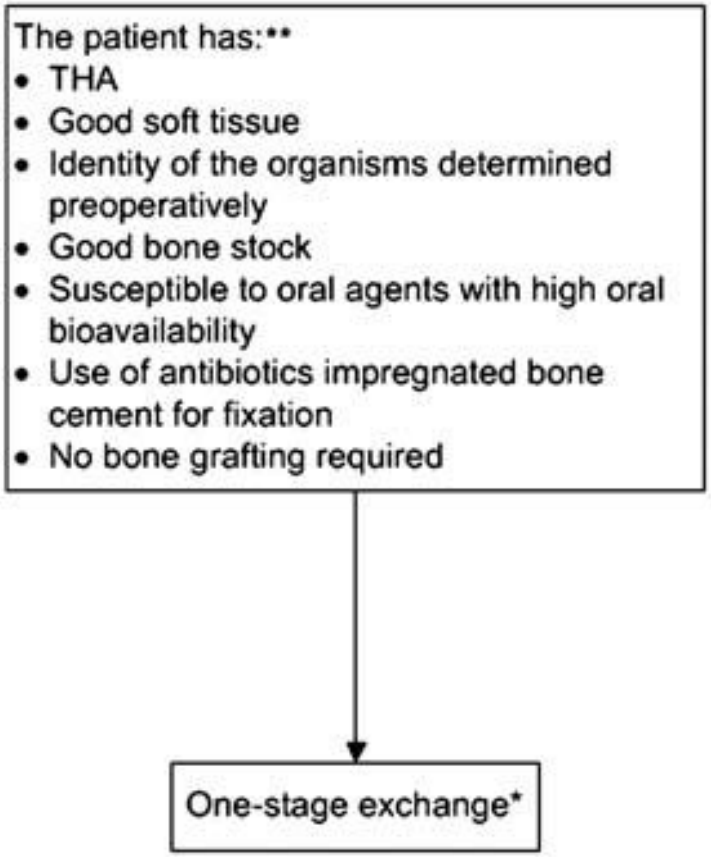
IDSA GUIDELINES

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

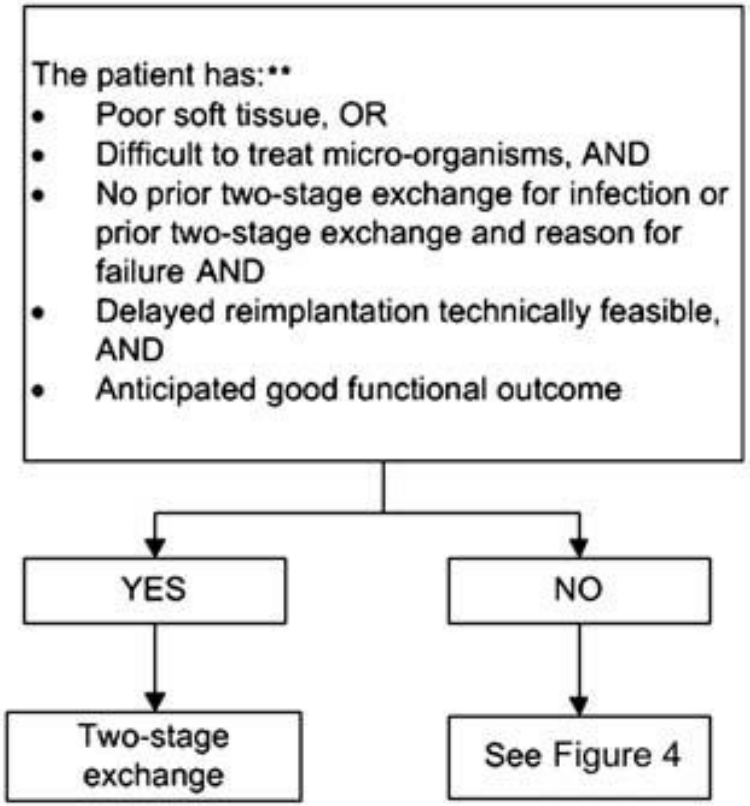
Douglas R. Osmon,[1] Elie F. Berbari,[1] Anthony R. Berendt,[2] Daniel Lew,[3] Werner Zimmerli,[4] James M. Steckelberg,[1] Nalini Rao,[5,6] Arlen Hanssen,[7] and Walter R. Wilson[1]



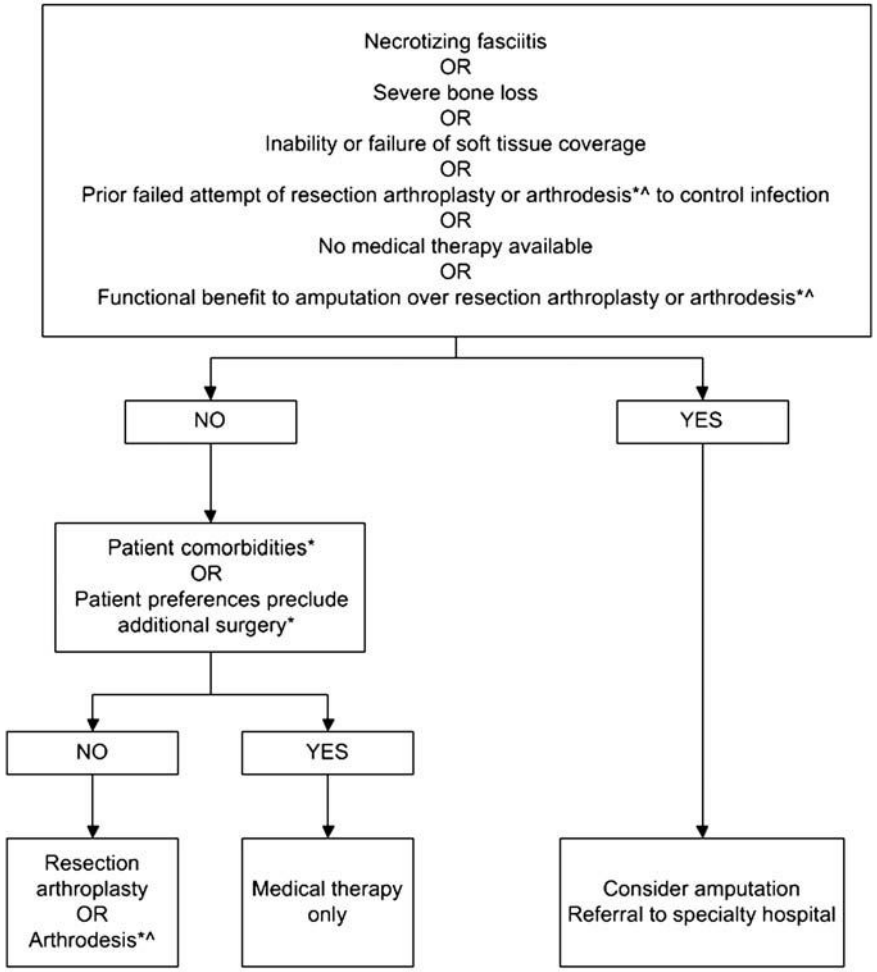
Changement en 1 temps



Changement en 2 temps



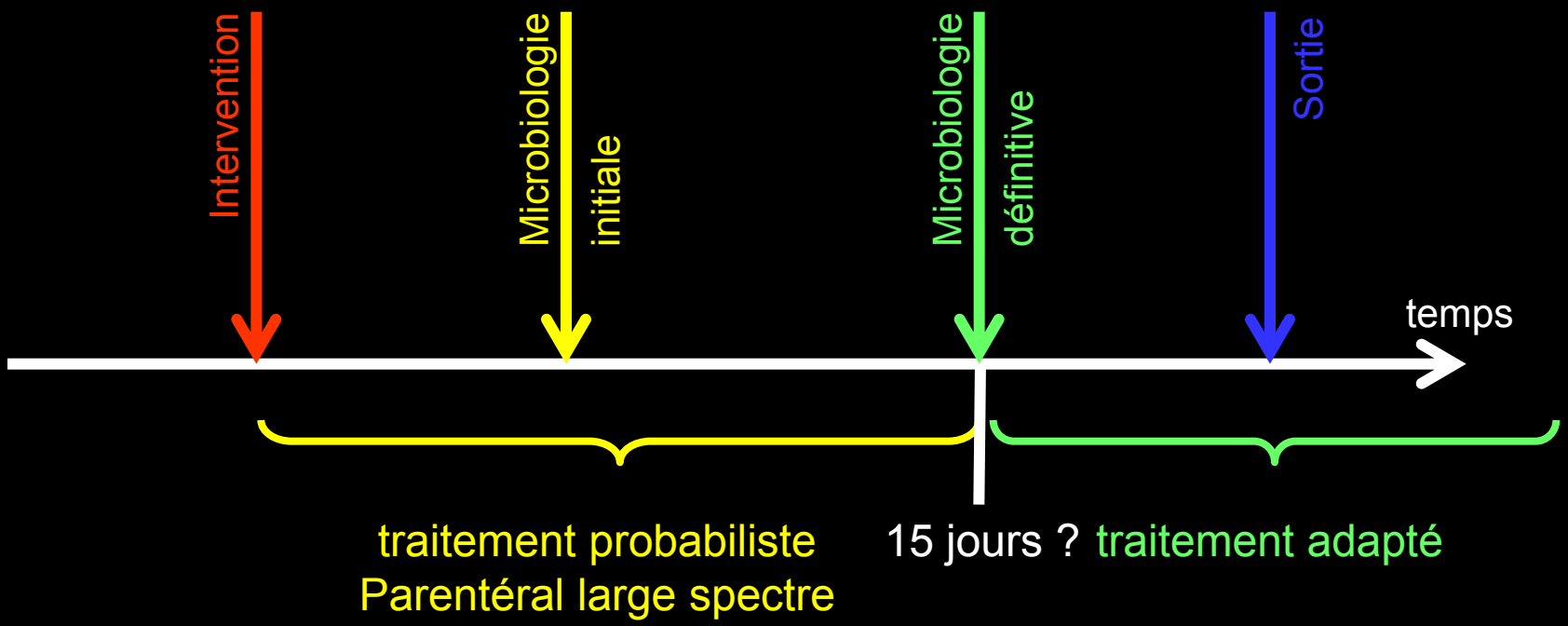
Autres ?


Necrotizing fasciitis
OR
Severe bone loss
OR
Inability or failure of soft tissue coverage
OR
Prior failed attempt of resection arthroplasty or arthrodesis*^ to control infection
OR
No medical therapy available
OR
Functional benefit to amputation over resection arthroplasty or arthrodesis*^
NO
YES
Patient comorbidities*
OR
Patient preferences preclude additional surgery*
NO
YES
Resection arthroplasty
OR
Arthrodesis*^
Medical therapy only
Consider amputation
Referral to specialty hospital

Antibiothérapie

UNIVERSITE DE VERSAILLES
SAINT-QUENTIN-EN-YVELINES

Chronogramme de la prise en charge



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…)

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

We evaluated the Xpert MRSA/SA SSTI real-time PCR assay (Cepheid, Sunnyvale, CA) directly on perioperative bone and joint samples. The sensitivity and specificity for detection of methicillin-susceptible *Staphylococcus aureus* (MSSA), methicillin-resistant *Staphylococcus aureus* (MRSA), and methicillin-resistant coagulase-negative *Staphylococcus* were, respectively, 100% and 98.3%, 100% and 100%, and 100% and 95.3%. The median total test turnaround time was 72 min for PCR versus 79 h for culture. Using these rapid results, appropriate antibiotic treatment could be rapidly initiated.

- 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.

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 ıred with methic ıibited 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

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 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

HAS 2014

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

Propositions

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

HAS 2014

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)

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]

Service de Chirurgie Osseuse et Traumatologique, Groupe Hospitalier Diaconesses-Croix Saint-Simon, 125, rue d'Avron, Paris 75020, France[1]; Service de Médecine Interne et Rhumatologie, Groupe Hospitalier Diaconesses-Croix Saint-Simon, 125, rue d'Avron, Paris 75020, France[2]; Laboratoire de Microbiologie, Groupe Hospitalier Paris Saint-Joseph, 68, rue des Plantes, Paris 75014, France[3]; and Laboratoire de Biologie Médicale, Groupe Hospitalier Diaconesses-Croix Saint-Simon, 125, rue d'Avron, Paris 75020, France[4]

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.

Propositions (bis)

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

HAS 2014

Administration IV prolongée ?

- Administration IV en post op systématique : intolérance digestive, idenification 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)

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

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 ++++

Durée de traitement

The NEW ENGLAND JOURNAL of MEDICINE

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)

Evolution

	Six weeks $n = 70$	Twelve weeks $n = 74$
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 χ^2 – tests).

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

Mono vs bithérapie

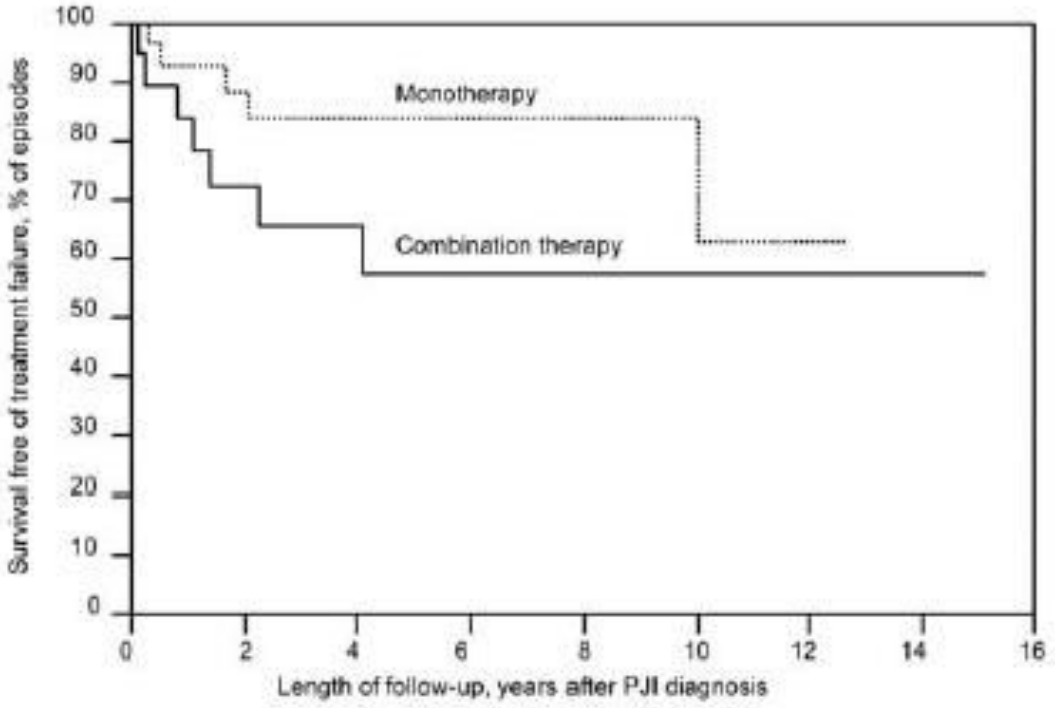
Bithérapie

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

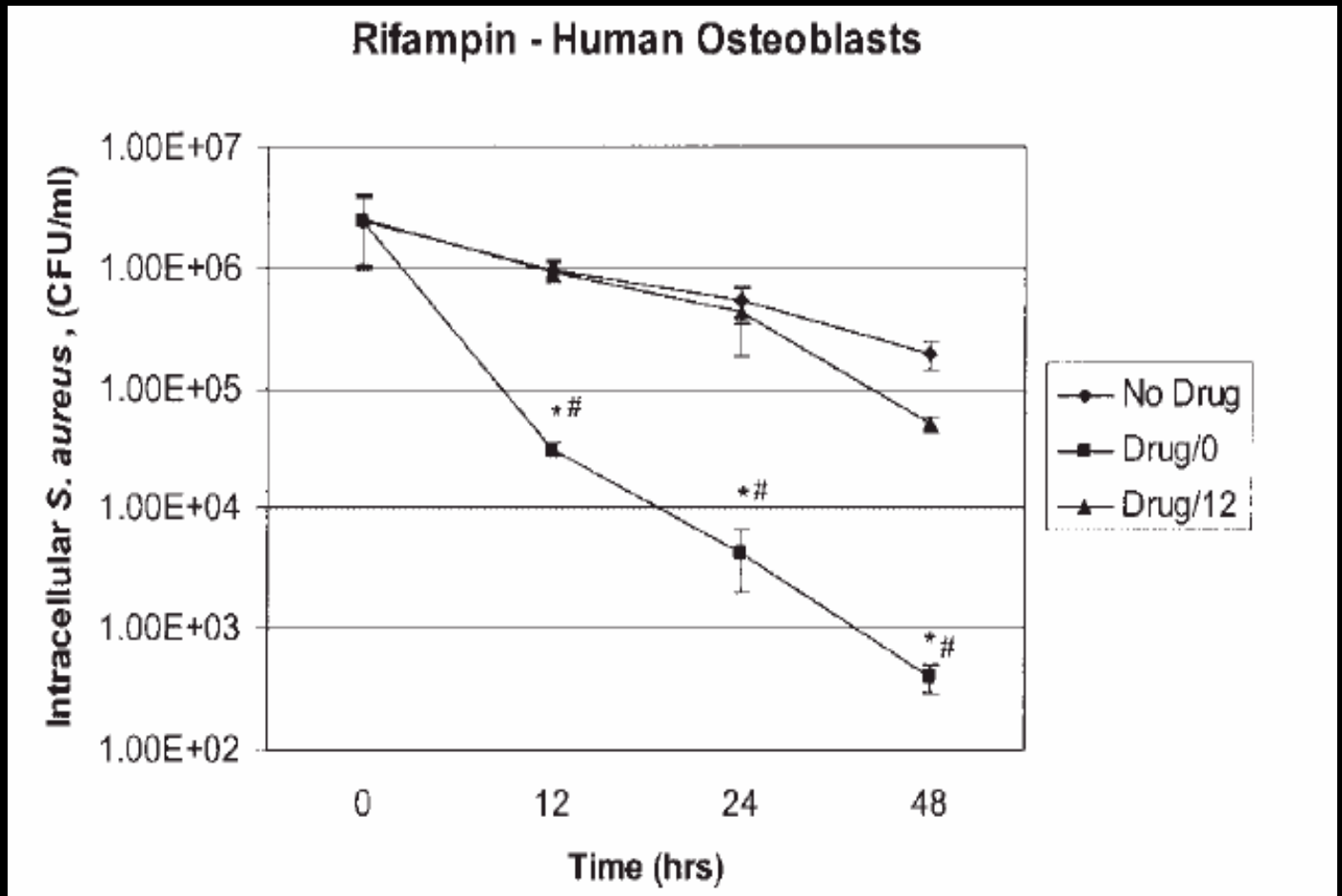
CID 2008:47 (1 October)

Rifampicine

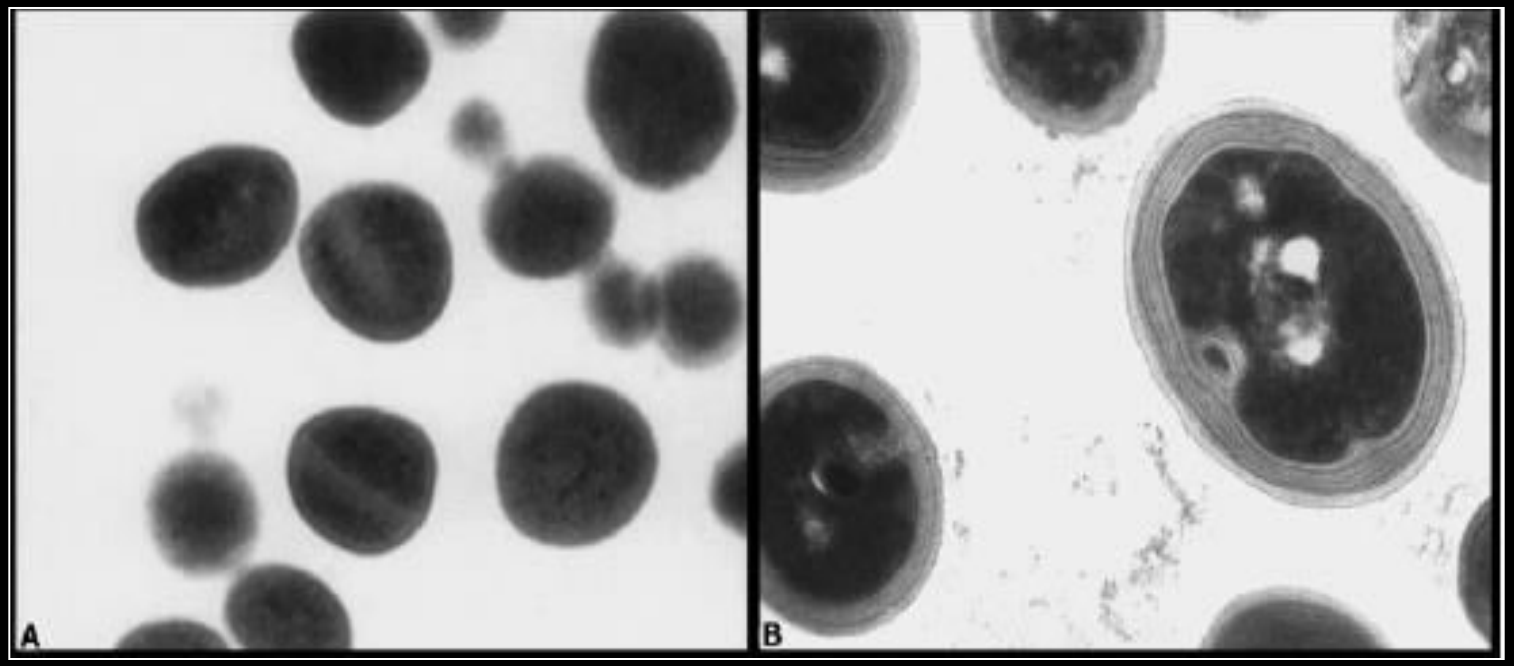
S. aureus intra ostéoblastique = résistance aux antibiotiques (rifampicine)

- 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

S..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

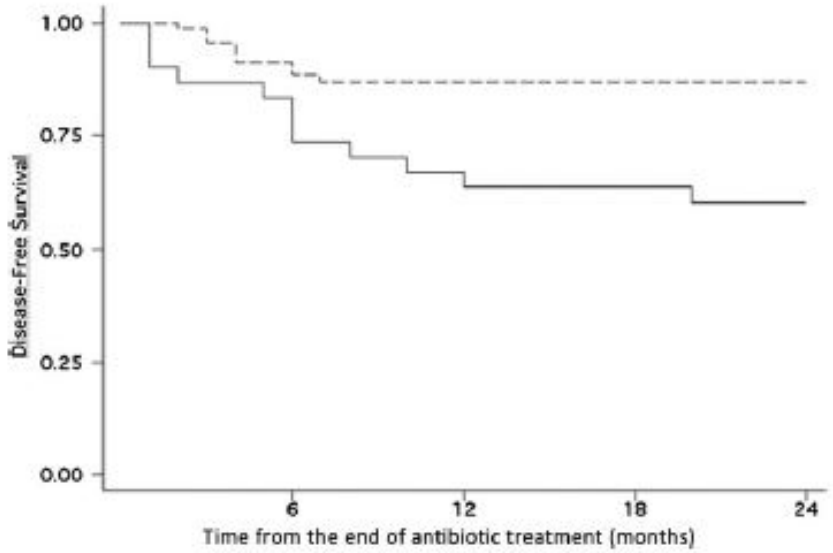
La rifampicine: oui mais pas seule 10-15 mg/Kg x 1 ou 2

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

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%)

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.

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

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

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]

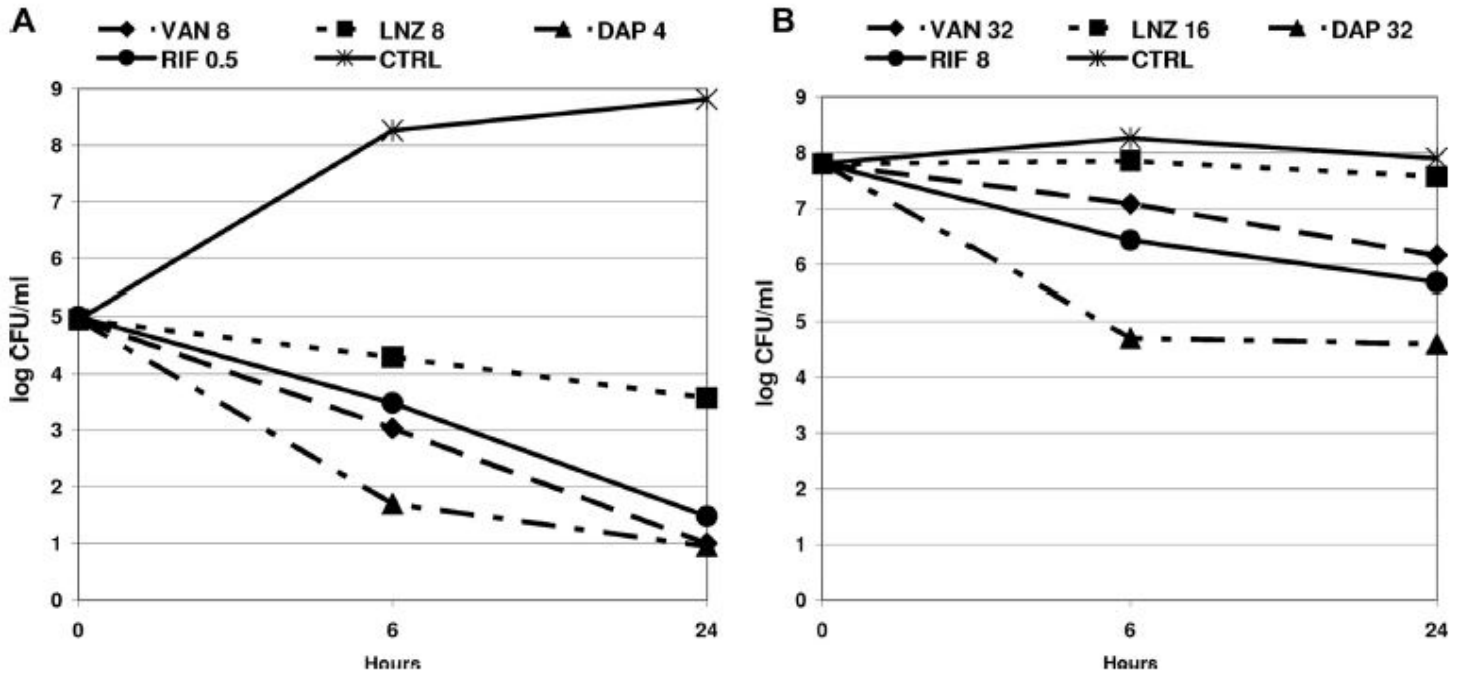
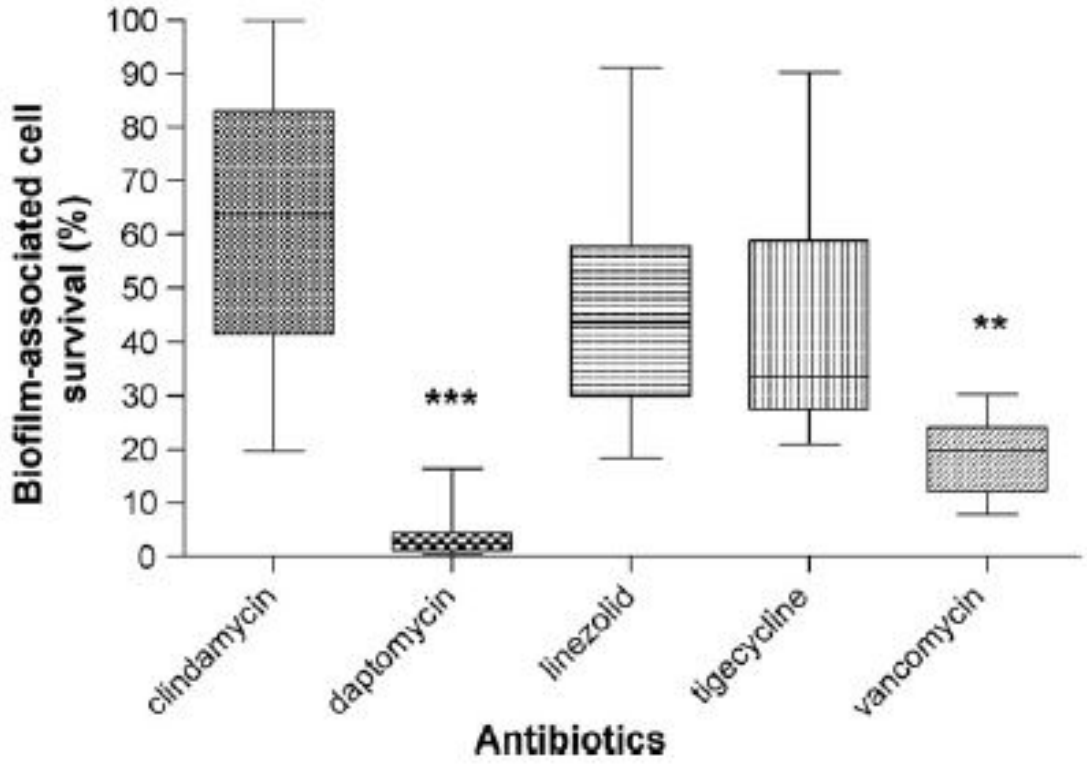


FIG. 1. Time-kill curves for log-phase (A) and stationary-phase (B) bacteria with clinically representative drug concentrations (in micrograms per milliliter). Abbreviations: DAP, daptomycin; RIF, rifampin; LNZ, linezolid; VAN, vancomycin; CTRL, controls.

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

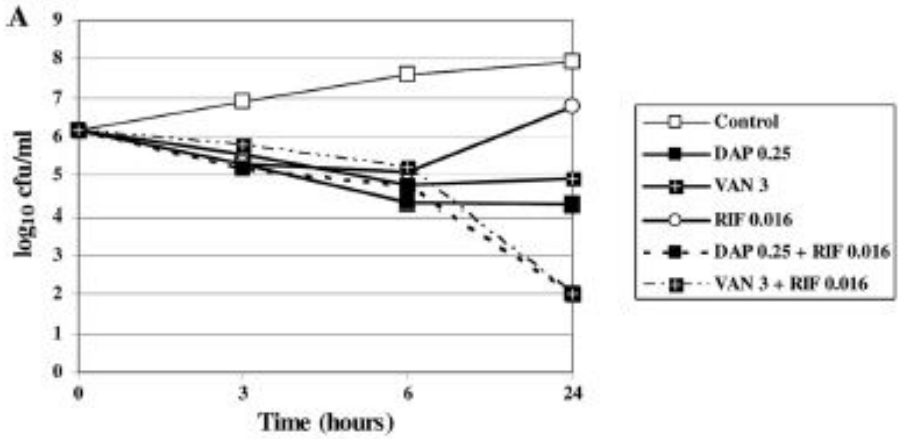
Karen Smith [a], Ana Perez [a], Gordon Ramage [b,1],
Curtis G. Gemmell [c], Sue Lang [a,*,1]

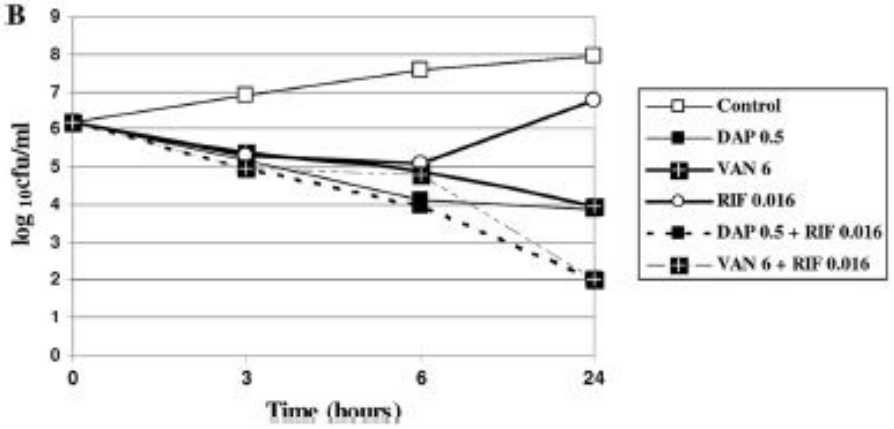


ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2011, p. 4589–4593 Vol. 55, No. 10
0066-4804/11/$12.00 doi:10.1128/AAC.00675-11

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]*

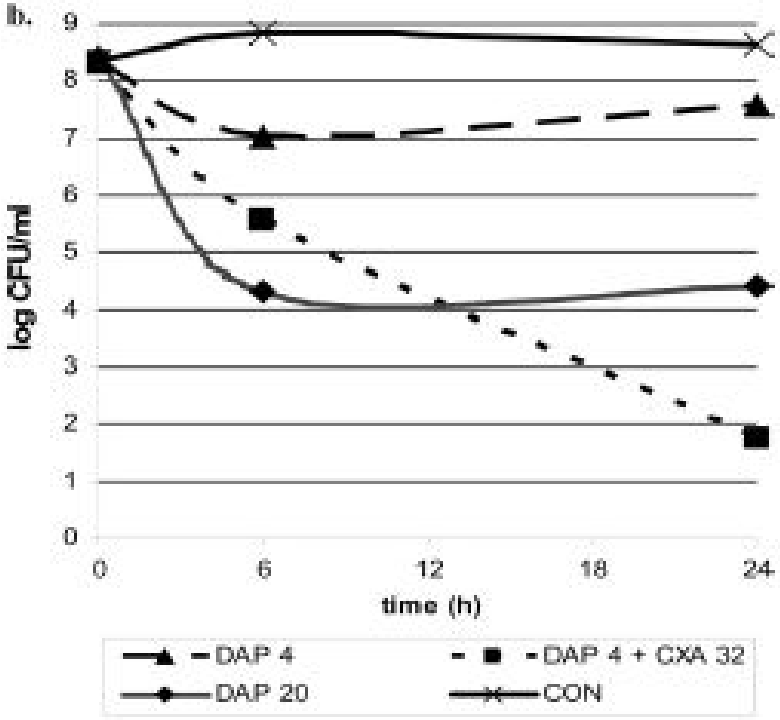


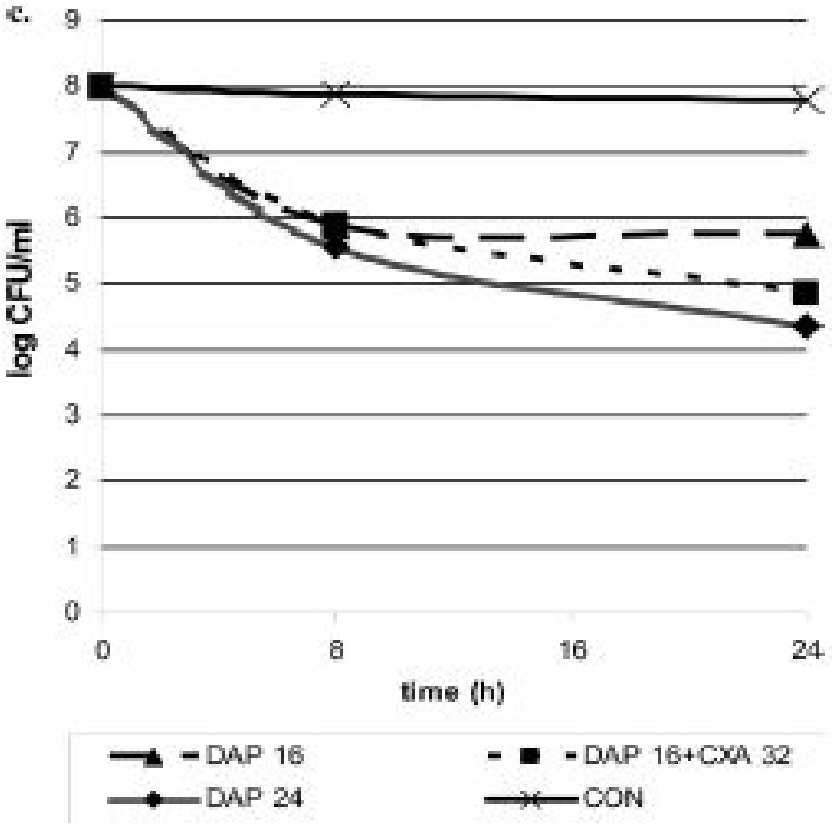


AAC
JournalsASM.org

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

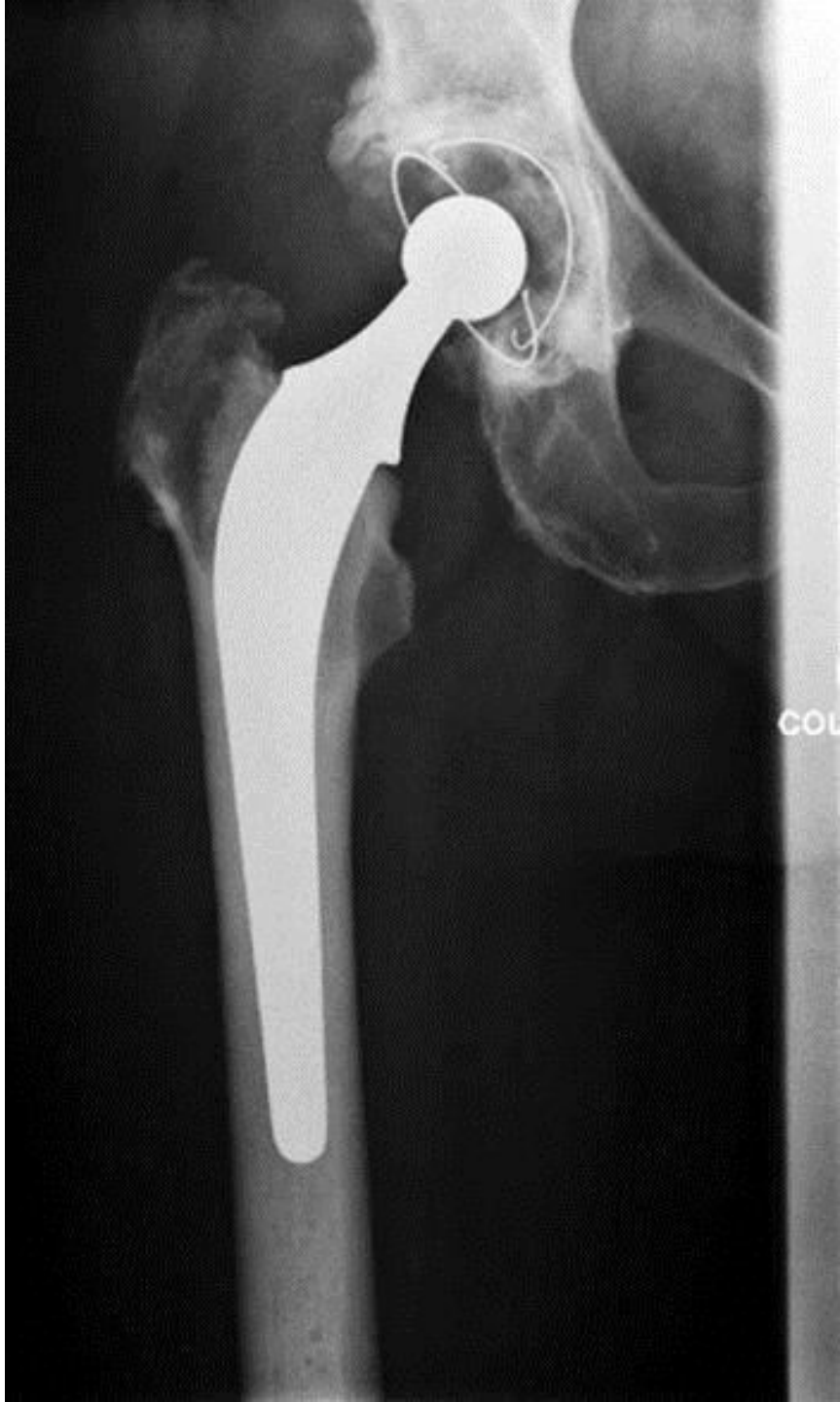
Les tendances

- 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

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 !



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]

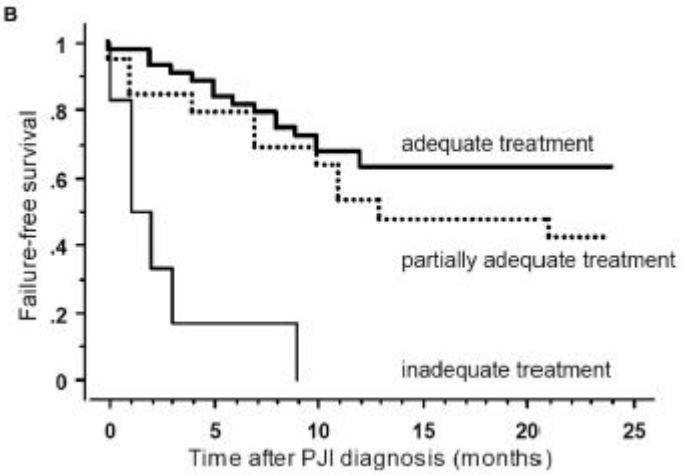
Departments of [1]Infectious Diseases and [2]Orthopedic Surgery, University Hospital Bern, and [3]Institute for Infectious Diseases, University of Bern, Bern, Switzerland

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].



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

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)

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
- Si pb : CRIOA ?

Durée de traitement ?

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

- PHRC DATIPO : inclusions terminées

Microorganism	Preferred Treatment[a]	Alternative Treatment[a]
Staphylococci, oxacillin-susceptible	Nafcillin[b] sodium 1.5–2 g IV q4-6 h or Cefazolin 1–2 g IV q8 h or Ceftriaxone[c] 1–2 g IV q24 h	Vancomycin IV 15 mg/kg q12 h or Daptomycin 6 mg/kg IV q 24 h or Linezolid 600 mg PO/IV every 12 h
Staphylococci, oxacillin-resistant	Vancomycin[d] IV 15 mg/kg q12 h	Daptomycin 6 mg/kg IV q24 h or Linezolid 600 mg PO/IV q12 h
Enterococcus spp, penicillin-susceptible	Penicillin G 20–24 million units IV q24 h continuously or in 6 divided doses or Ampicillin sodium 12 g IV q24 h continuously or in 6 divided doses	Vancomycin 15 mg/kg IV q12 h or Daptomycin 6 mg/kg IV q24 h or Linezolid 600 mg PO or IV q12 h
Enterococcus spp, penicillin-resistant	Vancomycin 15 mg/kg IV q12 h	Linezolid 600 mg PO or IV q12 h or Daptomycin 6 mg IV q24 h
Pseudomonas aeruginosa	Cefepime 2 g IV q12 h or Meropenem[e] 1 g IV q8 h	Ciprofloxacin 750 mg PO bid or 400 mg IV q12 h or Ceftazidime 2 g IV q8 h
Enterobacter spp	Cefepime 2 g IV q12 h or Ertapenem 1 g IV q24 h	Ciprofloxacin 750 mg PO or 400 mg IV q12 h
Enterobacteriaceae	IV β-lactam based on in vitro susceptibilities or Ciprofloxacin 750 mg PO bid	
β-hemolytic streptococci	Penicillin G 20–24 million units IV q24 h continuously or in 6 divided doses or Ceftriaxone 2 g IV q24 h	Vancomycin 15 mg/kg IV q12 h

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

HAS 2014

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

Daptomycine : Données expérimentales

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2010, p. 5251–5256 Vol. 54, No. 12
0066-4804/10/$12.00 doi:10.1128/AAC.00226-10

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.

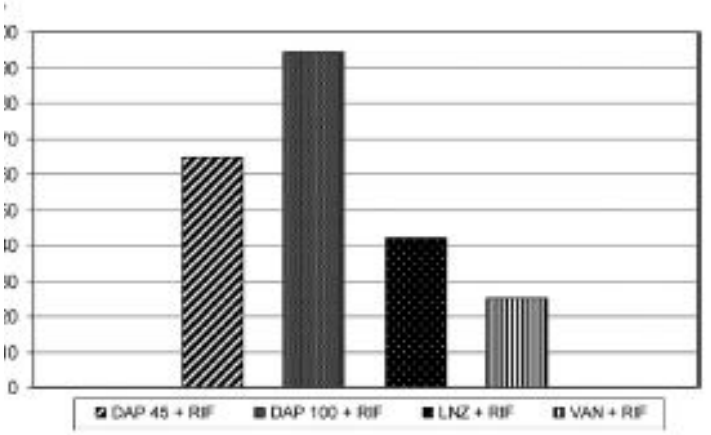


FIG. 2. Cure rates of infection for antibiotic combinations with rifampin at day 11. Data for antibiotics alone are not shown. LNZ, linezolid; VAN, vancomycin; RIF, rifampin; DAP45, daptomycin at 45 mg/kg/day; DAP100, daptomycin at 100 mg/kg/day.

Antibiothérapie suppressive

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

Molécules recommandées

Bactérie	Traitement de 1re intention	Autre proposition
Staphylocoque méti-sensible	- IV pendant 10 jours avant relais oral : pénicilline M +/- gentamycine - Rifampicine + fluoroquinolone	-Clindamycine + rifampicine - Cotrimoxazole + rifampicine - Fluoroquinolone + acide fusidique - rifampicine+acide fucidique
Staphylocoque méti-résistant	Glycopeptide + (rifampicine ou acide fusidique ou fosfomycine)	Rifampicine + acide fusidique Cotrimoxazole + rifampicine 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 3-4 oral intakes
cloxacillin 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 3-4 oral intakes
cefazolin	60-80 mg/kg	4-6 injections IVL or 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 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 then 12 mg/kg	IVL, IM or s/c
gentamycin[3]	3-4 mg/kg	1 administration IV 30 minutes
amikacin[3]	15 mg/kg	1 administration IV 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 2 à 3 injections IVL
pefloxacin	800 mg	2 oral intakes 2 injections IVL
levofloxacin (not government approved)	500 à 750 mg	1 oral intake 1 injection IVL
ciprofloxacin	1,500-2,000 mg 800 à 1,200mg	2 to 3 oral intakes 2 to 3 injections IVL
clindamycin	1,800-2,400mg	3-4 injections IVL 3 oral intakes
rifampicin	20 mg/kg	2 administrations IV 30 minutes 2-3 oral intakes
fusidic acid	1,500 mg	2-3 oral intakes 2-3 injections IVL
fosfomycin	150-200 mg/kg	3-4 administrations 120 minutes
cotrimoxazole	3,200 mg/640 mg	2 oral intakes 2 injections
minocyclin doxycyclin	200 mg	2 oral intakes 2 injections IV (doxycyclin)
linezolid (not government approved)	1,200 mg	2 oral intakes 2 injections IVL

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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).