CENTRES DE RÉFÉRENCE
POUR LES INFECTIONS OSTÉO-ARTICULAIRES COMPLEXES
DU GRAND OUEST
CRIOGO

Antibiothérapie de l'infection sur Prothèse Ostéo-articulaire: Spécificité sur sujet âgé ?

Réunion SFGG/SPILF

Louis BERNARD (CHUTours)

Paris, Mercredi 20 nov 2013

Epidémiologie

Fréquence/Incidence : Global des Infections ostéo-articulaires en France

•Données PMSI nationales 2008:

-Prévalence globale 54,6/100 000 (0,2% des hospitalisations):

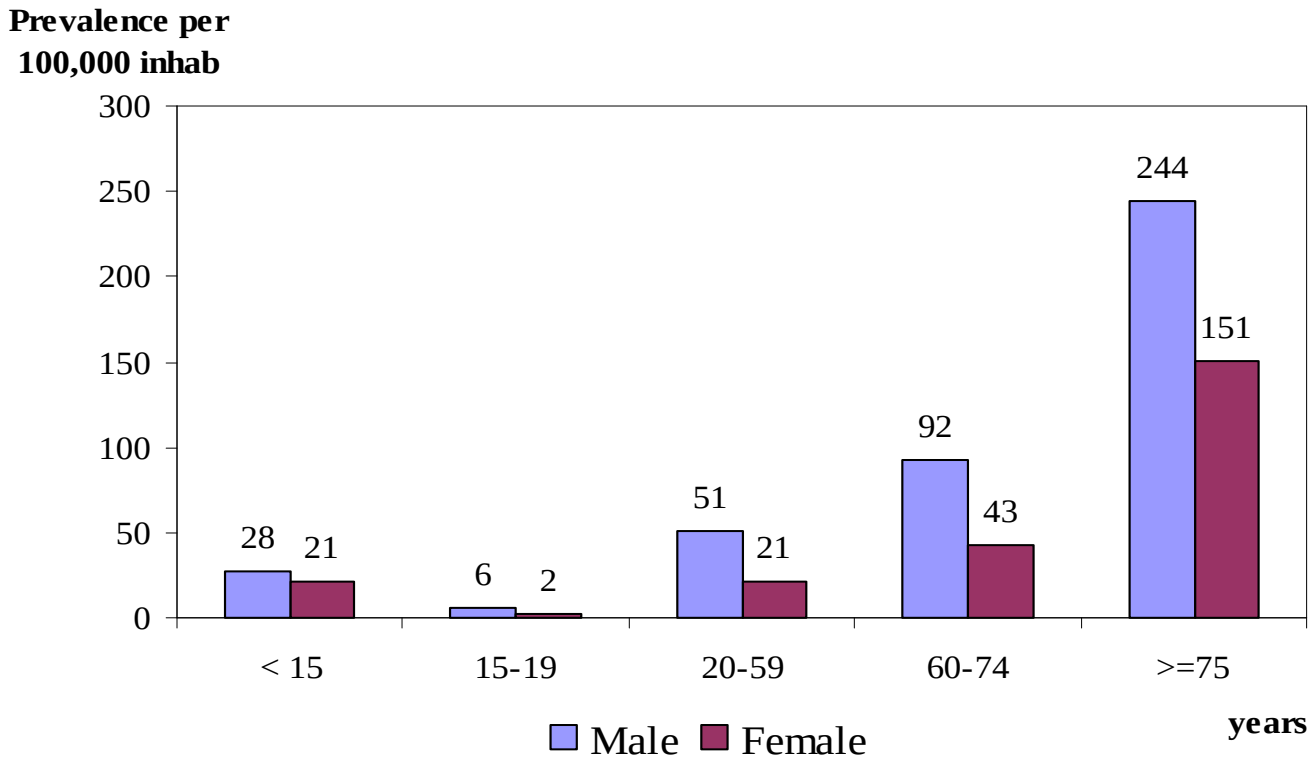
- 21,7 < 15 ans
- 24,5 < 50 ans
- 157 > 70 ans

16 millions de séjours hospitaliers en France en 2008,
36 091 répondaient à la définition de cas d'IOA (0,2%)
28 453 patients distincts

L. Grammatico-Guillon, JHI 2012;82:40-48
L. Grammatico-Guillon, Acta Pædiatrica 2013;102:120-125

Fréquence/Incidence : Age/sexe

Histogram I - Prevalence of BJI by age and sex, France 2008



male:female sex ratio was 1.54

The overall mean age
of BJI cases was 63.1 years (median: 66; range: 15e105); males were significantly younger (mean age: 60 years; median: 62) than females (mean age: 68 years; median: 72).

Fréquence/Incidence : Type d'infection

Séjour 2008 PMSI

Diagnosis	Native BJI	Device-associated BJI
Septic arthritis	8463 (44.3%)	4944 (52.2%)
Osteomyelitis	8157 (42.7%)	1917 (20.2%)
Spondylodiscitis	2480 (13.0%)	212 (2.2%)
Unknown	0	2406 (25.4%)

Difficultés
-Absence de détails précis de la localisation des arthrites et ostéomyélites
-Pied diabétique

Fréquence
-infection sur matériel = 5000/an dont 58% IPOA = 3000/an
-SDI = 2500/an (2008) 1300/an (2002)
-arthrites Genou > Hanche >> autres localisations
-Ostéomyélites: pied diabétique >>tibia > fémur

Fréquence/Incidence :
Infection sur Prothèse Ostéo-Articulaires

Nombre de POA posées/an/France en 2012
-PTH : 135 365 dont 13% de reprise
-PTG : 85 599 (en forte progression)

Calcul/PMSI

200 000 PT/an (HAS)

3 000 IPOA/an (PMSI 2008) soit **1,5% tout confondu**

Calcul/RAISIN

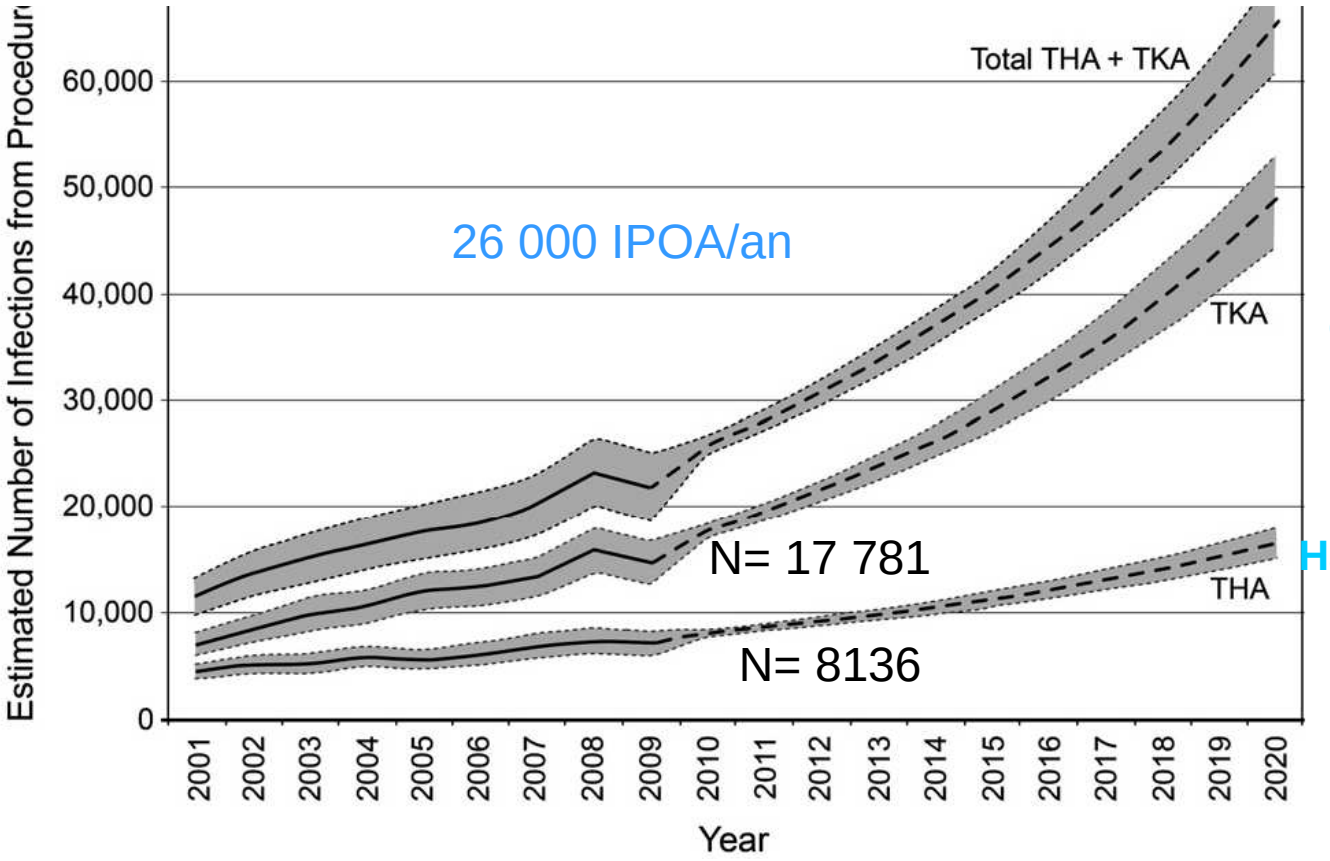
Pour 40 294 intervention: taux = 0,7% mais à J30

HAS 2012

The Journal of Arthroplasty Vol. 27 No. 8 Suppl. 1 2012

Economic Burden of Periprosthetic Joint Infection in the United States

Steven M. Kurtz, PhD,*† Edmund Lau, MS,‡ Heather Watson, PhD,‡
Jordana K. Schmier, MA,§ and Javad Parvizi, MD



Genou 1%

Hanche < 1%

36 091 séjours pour IOA en 2008 en France (PMSI)

	IOA native N (%)	IMOA N (%)	p
Caractéristiques des séjours	24 643 (68)	11 448 (32)	
Secteur public d'hospitalisation	20 514 (83,2)	7 919 (69,2)	NS
Passage en chirurgie	11 334 (46,0)	8 513 (74,3)	0,01
Mode de sortie – transfert			
Domicile	17 447 (70,8)	6 711 (58,6)	10^{-3}
Décès	931 (3,8)	391 (3,4)	NS
Long séjour	216 (0,9)	111 (1,0)	NS
SSR	3 485 (14,1)	3 004 (26,2)	10^{-3}
MCO	2 511 (10,1)	1 204 (10,5)	NS
Psychiatrie	53 (0,2)	27 (0,2)	NS

- 1/3 des séjours lié à une infection sur matériel
- La majorité (83%) des séjours = public
- Chirurgie IOA
  - sur matériel : 74,3%
  - sans matériel: 46%
- Sortie
  - IOA sans matériel: domicile (70,8%) SSR (14,1%)
  - IOA sur matériel : domicile (58,6 %) SSR (26,2%)

Mortalité

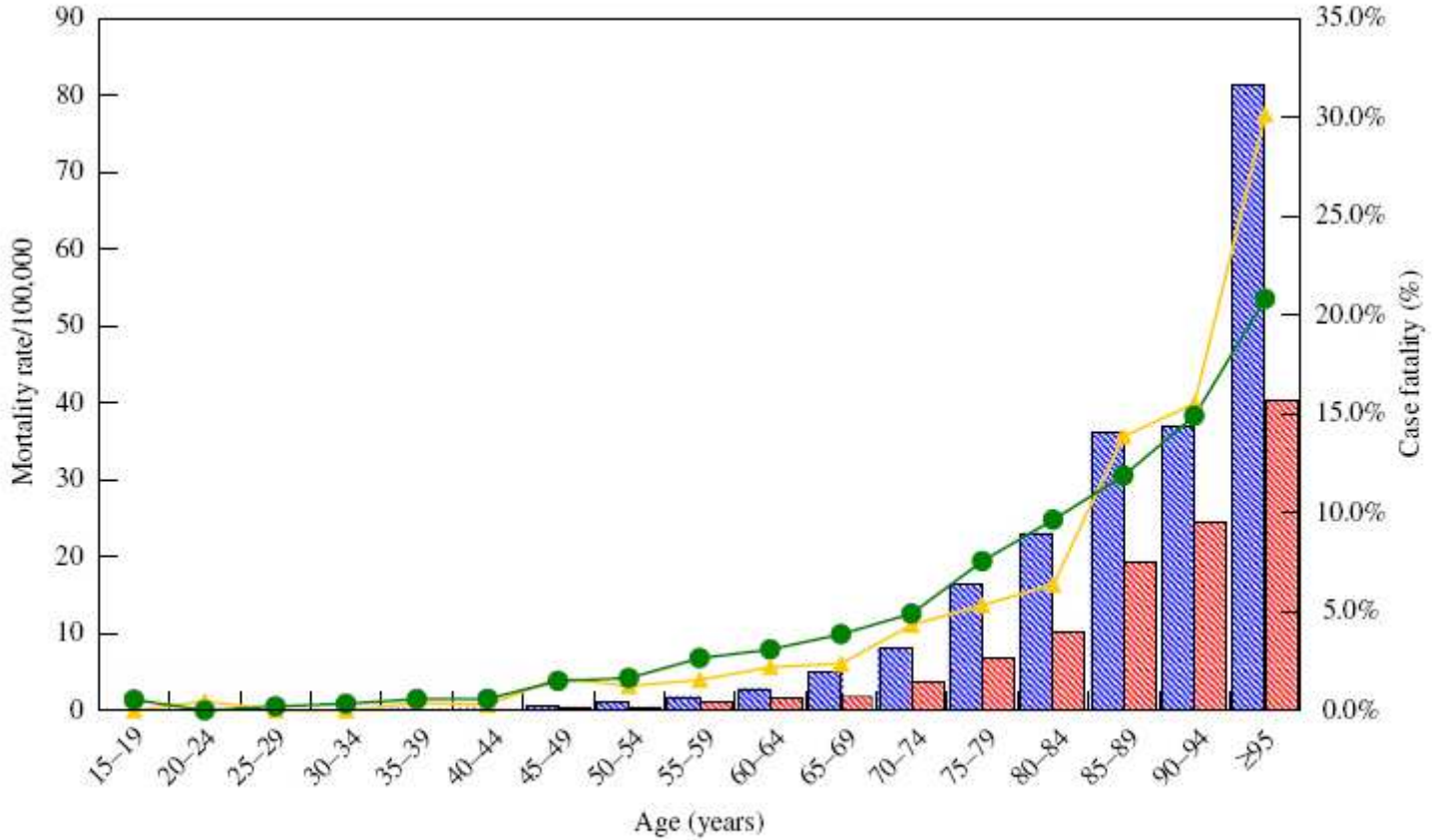
PMSI 2008

Passage en réanimation : 6% (PMSI)

Létalité intra-hospitalière : 4%
significativement associée à
l'infection par Staphylococcus spp (OR=1,3),
à la présence d'ulcères (OR=1,9)
et à l'âge

PHRC DTS (Spondylodiscite n= 359)

Létalité globale : 3% à M1 et 7.3% à 1 an .



[redacted] Mortality rate and device-associated case fatality by sex and age for bone and joint infection with or without device, France, 2008. Blue bars: male mortality rate; red bars; female mortality rate; yellow triangle: device-associated fatality; green circles: native fatality.

36 091 séjours pour IOA en 2008 en France (PMSI)

	IOA native N (%)	IMOA N (%)	p
Caractéristiques des séjours	24 643 (68)	11 448 (32)	
DMS (jours [IC95%])	16,8 [16,6-17,1]	18,9 [18,5-19,3]	0,01
Établissement public	18,2 [17,9-18,5]	20,9 [20,4-21,4]	0,01
Établissement privé[a]	10,2 [9,8-10,6]	14,5 [14,0-15,0]	0,01
Coût moyen par séjour (euros)	6 721	8 161	0,01

- La majorité (83%) des séjours = public
- DMS moyenne 17,5 jours (public= 18,9 vs 12,2 jours en privé)
  - IMOA= 18,9 vs 16,8 jours pour IOA native
  - > 1 comorbidité = 21 jours
  - si endocardite = 27 jours
- Taux de réhospitalisation était de 19,3% surtout si présence de matériel

2 ANTIBIOTHERAPIE

« Le Tripartite »

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

La réalité: Sujet âgé

- Tolérance
- Métabolisme/interaction/ Clairance
- Voie orale/ déglutition

Nécessité d’un diagnostic microbiologique « fiable

- IOA sans microbiologie = diagnostic incertain et incomplet
- IOA sans microbiologie = Perte de chance

Nécessité de suivre les recommandations

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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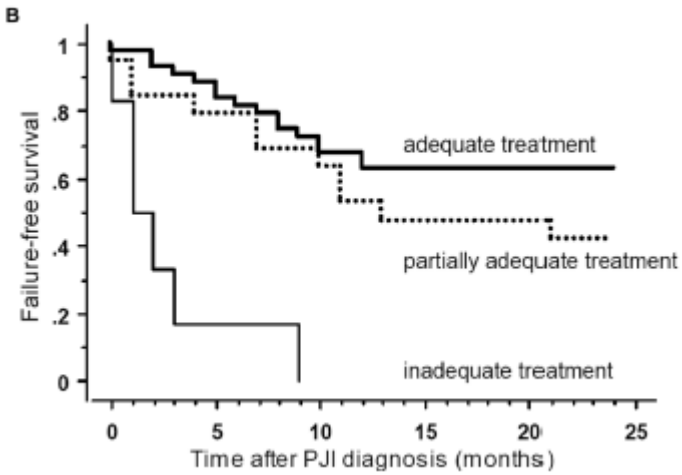


Principe de l'ATB

- 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 (15j ?)
- Antibiothérapie initiale :
  - probabiliste ou guidée par les prélèvements,
  - adaptée après quelques jours.
- Avec l'antibiogramme : antibiothérapie prolongée (orale ou parentérale) selon les molécules utilisables et les antécédents du patient.

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

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

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.

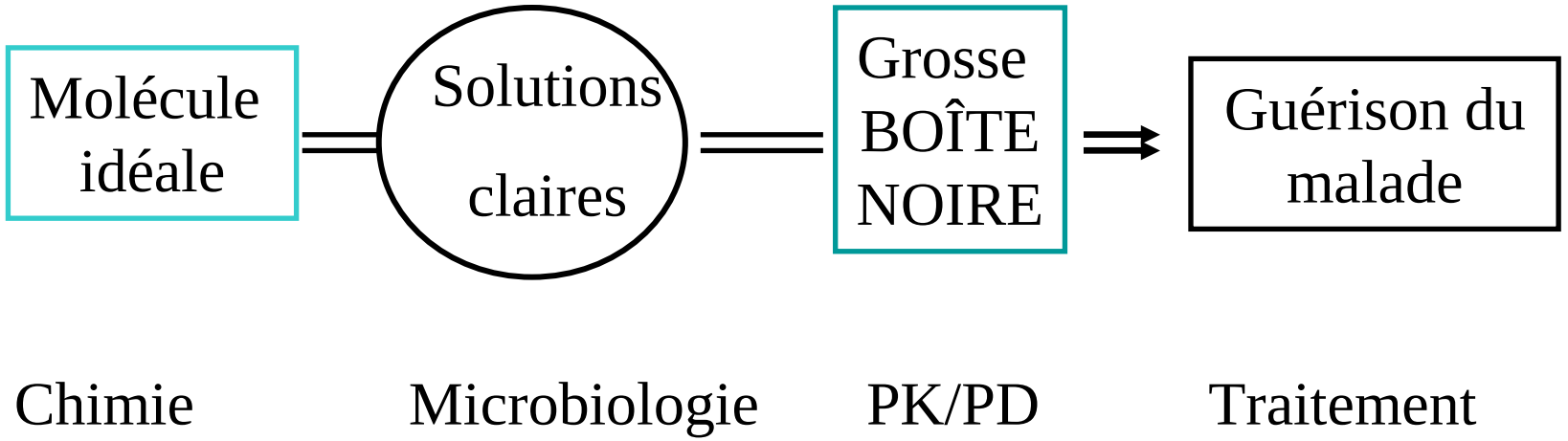
ANTIBIOTHERAPIE

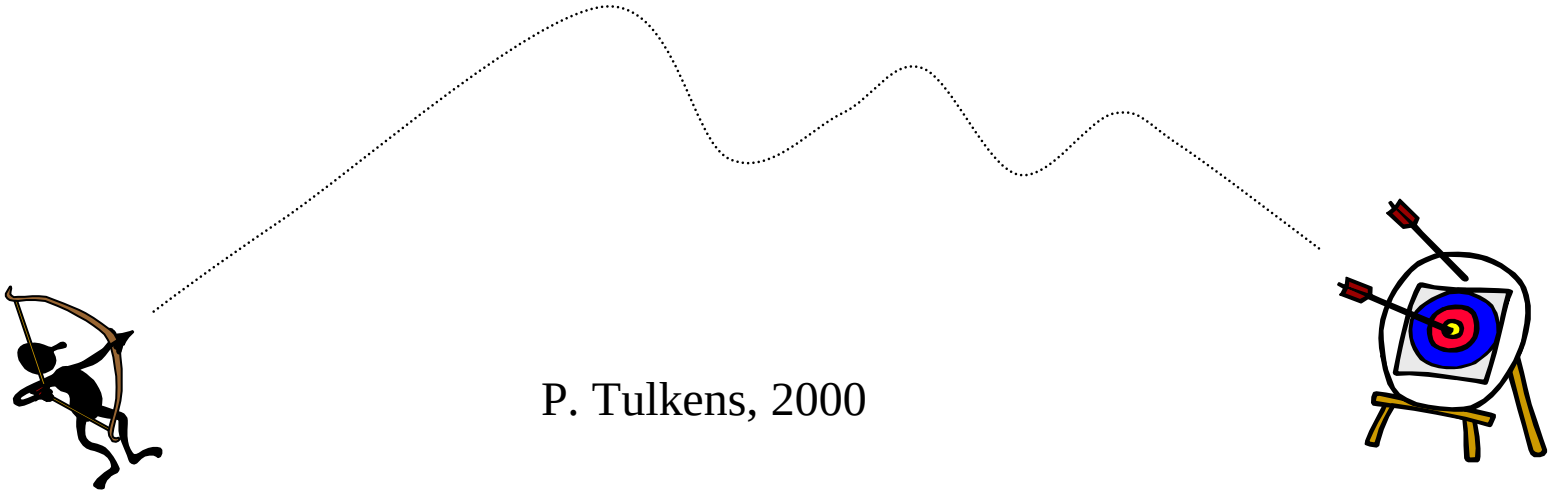
- 1 Molécules
- 2 Voie d’administration
- 3 Mono ou bithérapie
- 4 Durée de l’antibiothérapie

ANTIBIOTHERAPIE

- 1 Molécules

ANTIBIOTIQUE IDEAL





P. Tulkens, 2000

Quel choix ?

Choix en fonction de

- sensibilité du germe CMI
- biodisponibilité orale/IV
- QI tissulaire $\longrightarrow \frac{[ATB]\ t}{CMI}$

Raisonnement en QI tissulaire

- CMI
- [ATB] sérique RESIDUEL++++
- coefficient de diffusion tissulaire CDT

par exemple

- MSSA

	CMI	[ATB]Rsang	CDT	QIt	
peni M:	0.2	20		0.3	**33**
vanco:	1	10		0.3	**3,3**

BUT QI tissulaire >8-10 CMI

PK-PD

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

Rifampicine

Rifampicine

- antibiotique, antituberculeux
- bactéricide temps-dépendant
- biodisponibilité importante
- diffusion; partout (même intracellulaire)
- métabolisme hépatique
- inducteur enzymatique
- anti G+, anaérobies, parfois G-
- posologie variable

Infection à Gram (+) : Rifampicine ?
« In vitro »

100 études « in vitro »:

- essentiellement association d'ATB: synergie ?
- gros problème de méthodologie:

  taille inoculum (10^4 à 10^9), concentration ATB, croissance (stationnaire ou croissance)….

Difficile de conclure: le + souvent : indifférence

Infection à Gram (+) : Rifampicine « Etudes animales »

Trentaine d'études « animales »:

- problème de méthodologie:
  - animaux différents (rat-lapin…)
  - modèles différents

- synergie quinolones-rifampicine
  daptomycine-rifampicine
  linezolide-rifampicine

Expérimentation animale (1)

Travaux de CW NORDEN (1980-1990):

Ostéomyélite tibiale du lapin blanc à S. doré

-injection de *S. aureus*

-puis à J14 : administration d'antibiotique

-pour une durée variable J14 ou J28

-évaluation J70: culture tibia: *S. aureus* + ou -

Expérimentation animale (2)

Ciprofloxacin

JID 1985

Table 2. Results of treatment with ciprofloxacin and tobramycin for experimental osteomyelitis caused by *P. aeruginosa* in rabbits.

Antibiotic*	Duration of therapy (days)	No. of animals surviving†	Severity of disease‡	Rabbits (%) on day 70 with: Sequestra	Rabbits (%) on day 70 with: Positive bone culture
None	. . .	17	2.4 ± 0.8	35	94
Tobramycin	28	18	2.2 ± 0.7	28	94
Ciprofloxacin	14	17	2.1 ± 0.8	18	59
	28	18	1.6 ± 0.7	6	6

Clindamycine

JID 1986

Table 2. Results of treatment with clindamycin for experimental osteomyelitis due to *S. aureus* in rabbits.

Antibiotic	Duration of therapy (days)	No. of animals*	Severity of disease†	Rabbits with positive culture of bone on day 70 (%)
None	. . .	20	2.8 ± 0.3	95
Clindamycin	14	18	1.9 ± 0.8	78
Clindamycin	28	20	2.0 ± 0.8	16

Expérimentation animale (3)

Vancomycine-rifampicine

Table 3. Results of treatment with rifampin and vancomycin alone and in combination for experimental osteomyelitis due to *Staphylococcus aureus* in rabbits.

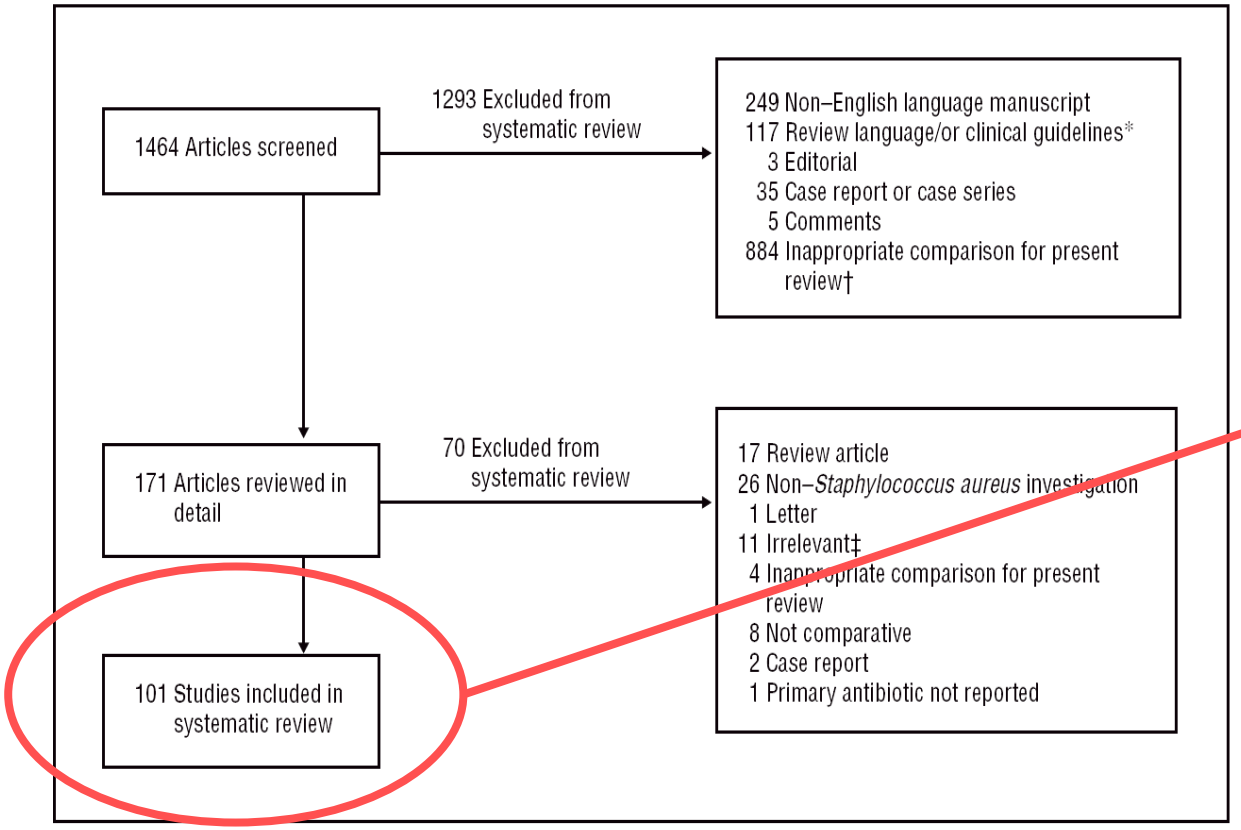
Antibiotic(s)*	Duration of therapy (days)	No. of animals†	Severity of disease‡	Rabbits with sequestra on day 70 (%)	Rabbits with positive bone culture on day 70 (%)
None	. . .	23	2.8 ± 0.3	83	100
Rifampin	14	20	2.1 ± 0.8	40	70
Rifampin	28	21	2.0 ± 0.6	33	43
Vancomycin	14	20	2.4 ± 0.9	60	95
Vancomycin	28	22	2.3 ± 0.8	59	91
Rifampin plus vancomycin	14	19	1.9 ± 0.7	11	16
Rifampin plus vancomycin	28	20	2.0 ± 0.8	10	10

Norden CW, JI 1983

Infection à Gram (+) : Rifampicine ?
« Etudes humaines »

Perlroth J, Arch Intern Med. 2008;168:805-19

Bliziotis IA, Eur J Clin Microbiol Infect Dis. 2007;26:849-56.



-72 « in vitro »
-22 « animales »
-9 « humaines »

Infection à Gram (+) : Rifampicine ?
« Etudes humaines »

9 études « humaines »: 6 études randomisées dont 2 contre placebo et 1 étude rétrospective

- problème de méthodologie:
- variation du dosage 600 à 1200 mg/j
- Faible effectif : 15 à 65 patients
- Patients « hétérogènes »
- Ostéomyélites: 5 études

Auteurs	Type d'étude	Patients	Molécule	Effectif	Efficacité
Zimmerli (1998)	DACP	Implants ortho MSSA, S epi	Fluco ou vanco puis cipro +/- rifampicine (450mg x2)	15/18	58% vs 100%
Norden (1986)	RP	Ostéomyélite chronique	Nafcillin +/- rifampicine (300 à 600mg x2)	8 / 10	50% vs 80%
Norden (1983)	RP	Ostéomyélite chronique	Nafcillin +/- rifampicine (300 à 600mg x2)	16/16	x% vs 70%
Van der Auwera (1983)	RP	Infections à S. a dont osteomyélite	Oxa ou vanco puis cipro +/- rifampicine (300mg x2)	29/27	41% vs 67%
Van der Auwera (1985)	DACP	Infections à S. a dont osteomyélite	Oxa ou vanco puis cipro +/- rifampicine (600mg x2)	32/33	56,2% vs 60,6%

DACP: double aveugle contre placebo; RP: randomisée prospective

La Rifampicine: efficacité peu démontrée

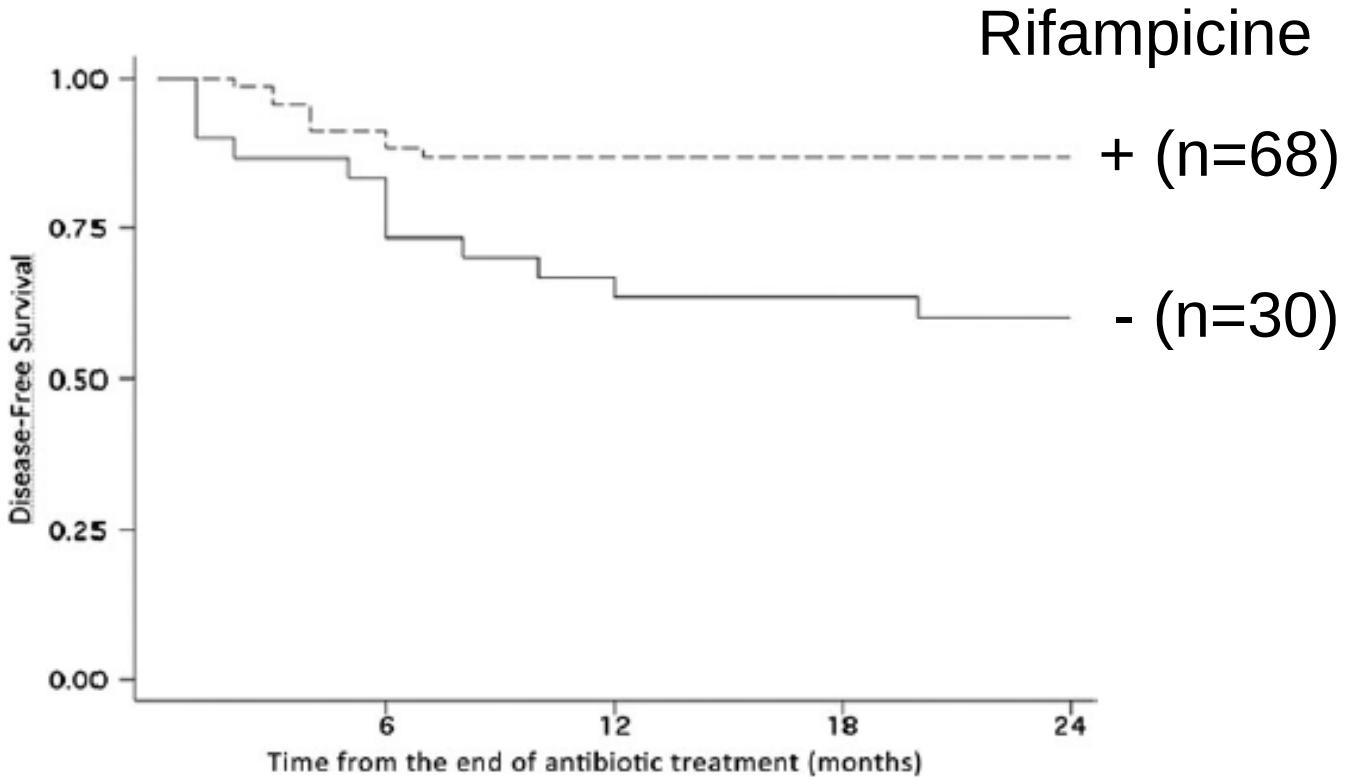
Molécules	Types d'infections microbiologie	Efficacité	
Rifampicin -cipro versus cipro-placébo inclusion en 5 ans	33 inf. avec matériel /15 prothèses MSSA 26/33	100% (12 pts) si rifam-cipro suivi pour 24 pts	Zimmerli, JAMA, 1998
Rifam-autes atb	11 inf matériel en place	88%	Widmer, CID,1992
Rifampicin –oflo inclusion en 6 ans	51 pts changement 1T	74%	Drancourt, AAC, 1993
Rifam-oflo versus ac fusidique	46 inf. avec matériel 29 prothèses	50% versus 55%	Drancourt, JAC, 1997

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

Clinical Infectious Diseases 2011;53(4):334–340

E Sennevile

Etude rétrospective 2000-2006
98 cas: 81 SAMS + 17 SARM



RIFAMPICINE Posologie ?.... Utilité dans les infections à SAMS

Contradiction totale en 6 mois dans CID
pour le traitement des IOA à MSSA

L'article d'E Senneville dit que la rifampicine
(dose 20 mg/kg en 2 fois/j jusqu'à 1800 mg/)
est indispensable pour les IPOA à SAMS

Clinical Infectious Diseases 2011;53(4):334–340

Wieland montre la ceftriaxone est efficace
pour les IOA sans rifampicine (dose 600 mg-900mg/j
associée dans 15% des cas)

Clinical Infectious Diseases 2012;54(5):585–90

En pratique : la Rifampicine

- Peu de molécules répondent à ces critères.
- 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).

Zimmerli JAMA 1998

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%	

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

Les fluoroquinolones

Les fluoroquinolones

- Antibiotique bactéricide
- Temps dépendant- Gram-
- Concentration-dépendant Gram+
- Biodisponibilité : excellente os : 60-70%

Diffusion osseuse/moxifloxacine lévofloxacine

Tissue concentrations of vancomycin and Moxifloxacin in periprosthetic infection in rats

Beckmann J; Acta Orthopaedica,78:6,766-73

Penetration of moxifloxacin and levofloxacin into cancellous and cortical bone in patients undergoing total hip arthroplasty.

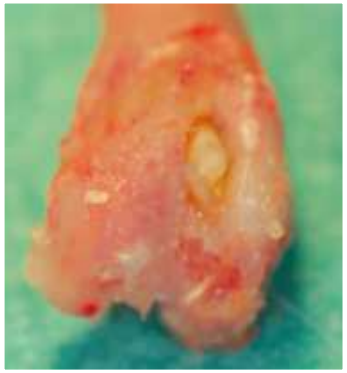
Metallidis S; J Chemother. 2007 ;19(6):682-7.

Tissue concentrations of vancomycin and Moxifloxacin in periprosthetic infection in rats

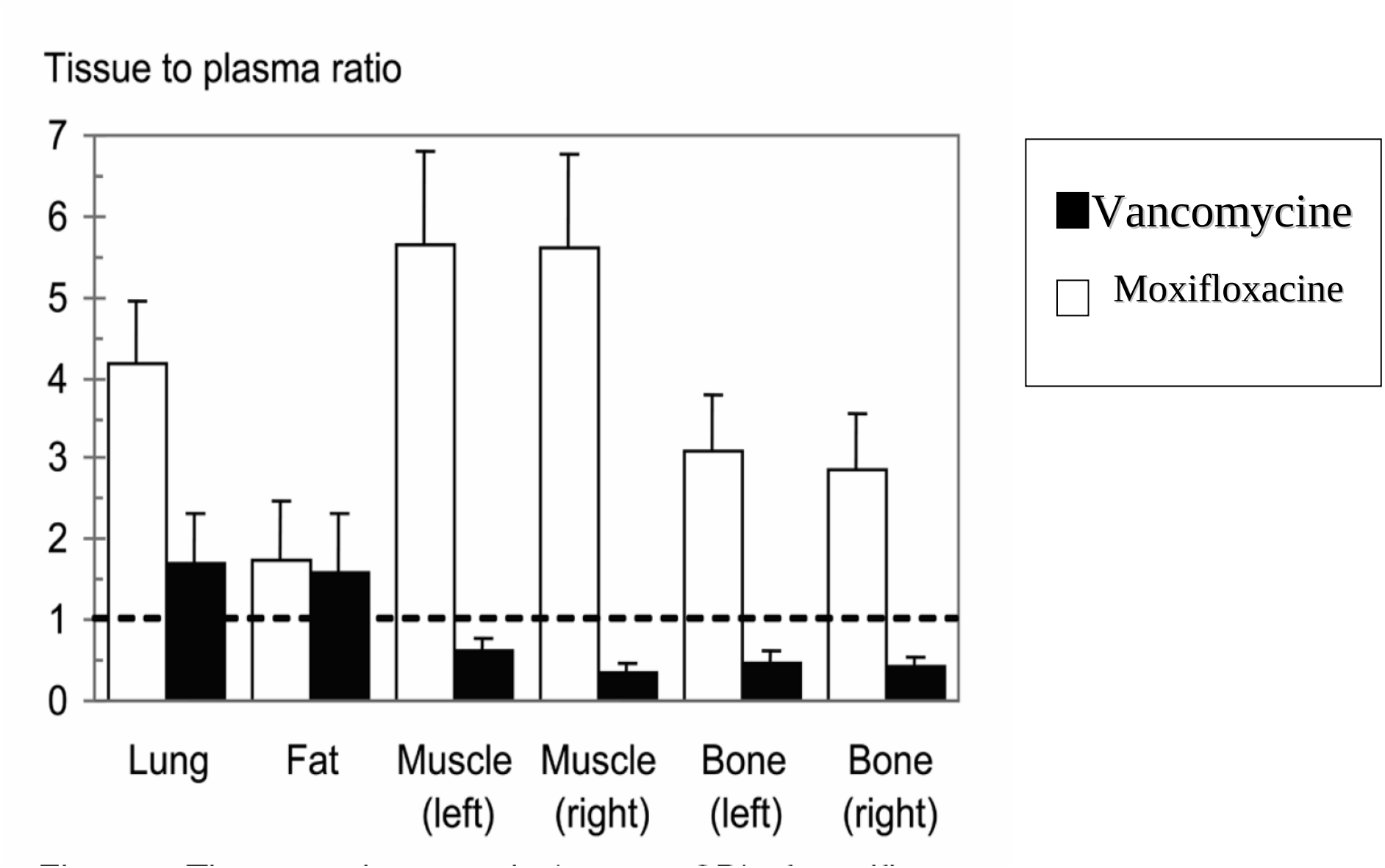
36 rats + enclouage tibial + infection MSSA

Puis de J7 jusqu'à J21

- (12) moxifloxacine 10 mg/kg x 2/j
- (12) vancomycine 15mg/kg x 2/j
- (12) sérum physiologique



Beckmann J; Acta Orthopaedica,78:6,766-73


Tissue to plasma ratio
7
6
5
4
3
2
1
0
Lung
Fat
Muscle (left)
Muscle (right)
Bone (left)
Bone (right)
Vancomycine
Moxifloxacine

Penetration of moxifloxacin and levofloxacin into cancellous and cortical bone in patients undergoing total hip arthroplasty.

16 patients-PTH:

- 8 moxifloxacine 400 mg
- 8 ofloxacine 500 mg

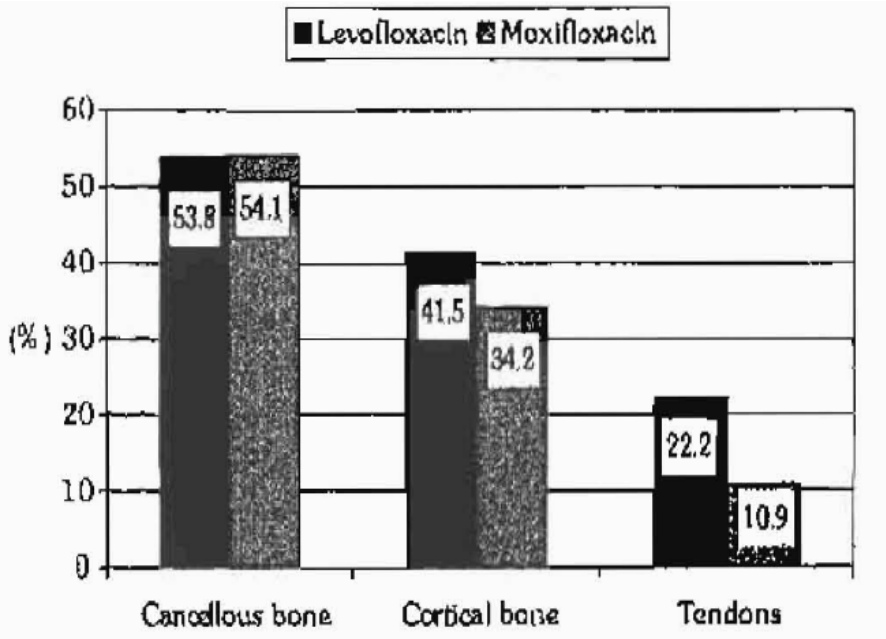


FIGURE 1 - Penetration of levofloxacin and moxifloxacin in osteoarticular tissues of patients undergoing total hip arthroplasty.

Metallidis S; J Chemother. 2007 ;19(6):682-7.

Les Quinolones

Molécules	Types d'infections microbiologie	Efficacité	
Lévofloxacine-Rifampicine	60 IPOA, matériel en place genou: 28, hanche:32 SCN, MSSA, MRSA	65% 83,4% si symptômes < 1 mois 30,8% si symptômes >6 mois	Barberan AJM 2006
Lévofloxacine-Rifampicine	47 IPOA matériel en place	76,9%	Soriano CMI, 2006
Ciprofloxacine-Rifampicin	29 pts matériel en place	83%	Derdal, CMI, 2005
Rifam-oflo versus ac fusidique	46 inf. avec matériel 29 prothèses	50% versus 55%	Drancourt, JAC, 1997

Lévofloxacine ? Moxifloxacine ? Ciprofloxacine ?

Les autres anciens

Co-trimoxazole

Molécules	Types d'infections microbiologie	Efficacité	
Co-trimoxazole inclusion en 8 ans	39 inf. avec matériel /19 prothèses MRSA ,SE	50% hanche 62.5% genou	Stein, AAC, 1997

Glycopeptides

Vancomycine

Teicoplanine

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;

AAC Antimicrobial Agents and Chemotherapy

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]

AAC Antimicrobial Agents and Chemotherapy

Continuous **clindamycin** infusion,
an innovative approach
to treating bone and joint infections.

Zeller V, Dzeing-Ella A, Kitzis MD,
Ziza JM, Mamoudy P, Desplaces N.
. 2010 Jan;54(1):88-92..

Clindamycine

-Bactériostatique
-Anti G+
-Bonne biodisponibilté
-Diffusion +++
-Peu sélectionnant
- « américain »

Les autres « nouveaux »
Daptomycine
Linézolide

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Efficacy of daptomycin combined with rifampicin for the treatment of experimental meticillin-resistant *Staphylococcus aureus* (MRSA) acute osteomyelitis

M. Lefebvre, C. Jacqueline, G. Amador, V. Le Mabecque, A. Miegeville, G. Potel, J. Caillon, N. Asseray*

Université de Nantes, Faculté de Médecine, EA3826, 1 rue Gaston Veil, F-44035 Nantes, France

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]

Laboratory of Experimental Infection, Infectious Diseases Service,[1] and Departments of Microbiology[2] and Orthopaedic Surgery,[3] IDIBELL, Hospital Universitari de Bellvitge, Barcelona, Spain

Received 16 February 2010/Returned for modification 8 August 2010/Accepted 26 September 2010

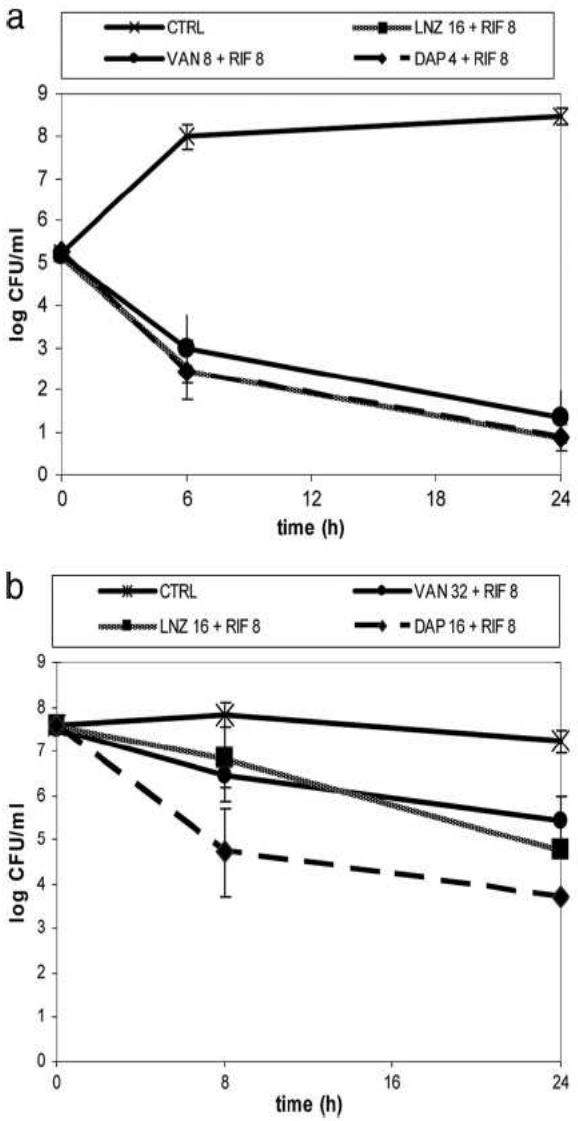


FIG. 1. Time-kill curves in log (a) and stationary (b) phases with various antibiotics in combination with rifampin. Data for antibiotics alone are not shown. Concentrations are given in μg/ml. Error bars indicate standard deviations. LNZ, linezolid; VAN, vancomycin; RIF, rifampin; DAP, daptomycin.

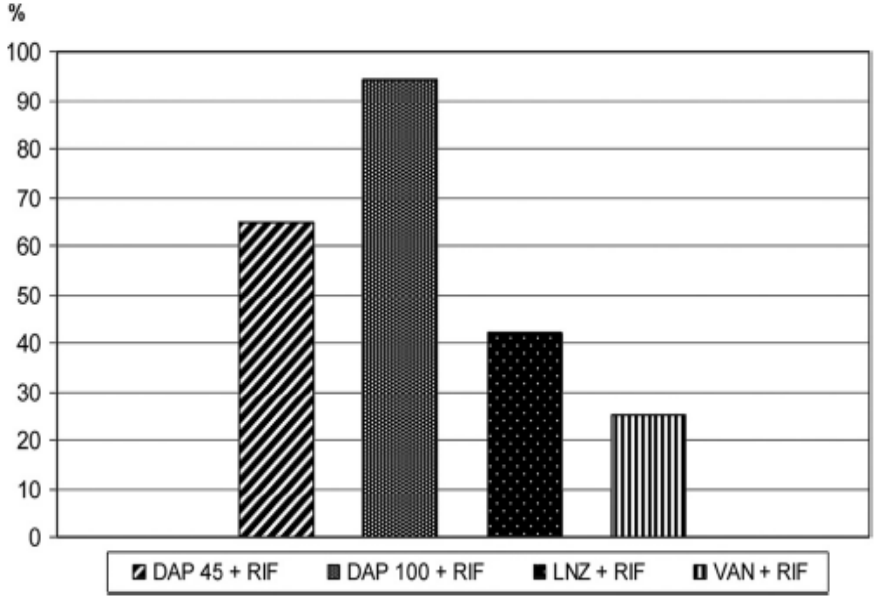


FIG. 2. Cure rates of infection for antibiotic combinations with rifampin at day 11. Data for antibiotics alone are not shown. LNZ, linezolid; VAN, vancomycin; RIF, rifampin; DAP45, daptomycin at 45 mg/kg/day; DAP100, daptomycin at 100 mg/kg/day.

CHICAACGO
51st ICAAC ~ SEPT. 17-20, 2011 ~ CHICAGO

Penetration of Daptomycin into Bone and Joint

C. Chirouze - *Physician*, P. Muret - *Pharmacologist*, F. Berthier - *anesthesiology*, G. Leclerc - *Surgeon*, A. Serre - *Surgeon*, L. Jeunet - *Surgeon*, M. Berard - *Laboratory technician*, A. Denis - *Pharmacologist*, L. Vettoretti - *Research ingeneer*, J. Leroy - *Physician*, B. Hoen - *Physician*;
Univ. medical center, Besançon, France.

	Plasma C_{max} mg/L	Bone mg/g	Synovial fluid mg/L	Plasma C_{mrt} mg/L
Median [range], mg/L	71.3 [39.4:110.3]	3.1 [1.4:5.7]	22.4 [13.1:35.0]	43.0 [21.6:69.9]

$\frac{3.1}{43} = 7\%$

2012; 56: 5626–5632

Randomized Controlled Trial of the Safety and Efficacy of Daptomycin versus Standard-of-Care Therapy for Management of Patients with Osteomyelitis Associated with Prosthetic Devices Undergoing Two-Stage Revision Arthroplasty

Ivor Byren,[a] Shruta Rege,[b] Ed Campanaro,[b] Sara Yankelev,[b] Diane Anastasiou,[b] Gennady Kuropatkin,[c] and Richard Evans[d]*
Nuffield Orthopaedic Center, Oxford, United Kingdom[a]; Cubist Pharmaceuticals, Inc., Lexington, Massachusetts, USA[b]; Samara Regional Clinical Hospital, Samara, Russia[c]; and UAMS College of Medicine, Little Rock, Arkansas, USA[d]

Clinical success rates for the mITT population
at TOC were:
14 of 24 (58.3%) 6mg/kg groups
14 of 23 (60.9%) 8-mg/kg groups
8 of 21(38.1%) in the comparator group (vanco ou teico)

LINEZOLIDE

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2011, p. 4308–4310 Vol. 55, No. 9
0066-4804/11/$12.00 doi:10.1128/AAC.00352-11

Linezolid plus Rifampin as a Salvage Therapy in Prosthetic Joint Infections Treated without Removing the Implant[▽]

J. Gómez,[1] E. Canovas,[1] V. Baños,[1] L. Martínez,[2] E. García,[1]* A. Hernández-Torres,[1] M. Canteras,[4] J. Ruiz,[3] M. Medina,[2] P. Martínez,[2] A. Canovas,[2] A. Soriano,[5] and M. Clavel[2]

Services of Infectious Diseases,[1] Traumatology,[2] and Microbiology,[3] University Hospital Virgen de la Arrixaca, Murcia, Spain; Department of Biostatistic, Faculty of Medicine, University of Murcia, Murcia, Spain[4]; and Service of Infectious Diseases, Hospital Clinic, Barcelona, Spain[5]

Received 16 March 2011/Returned for modification 19 April 2011/Accepted 9 June 2011

- Etude prospective 2000-2007
- 161 infections sur prothèse,
- 49 patients étudiés
  - 45 (27.9%) en échec de traitement préalable (teicoplanine, ciprofloxacine, triméthoprime + rifampicine)
  - 4 intolérances au traitement préalable

TABLE 1. Characteristics of patients treated with linezolid as second-line therapy according to outcome after 2 years of follow-up

Characteristic	No. (%) of patients[a]		P[b]
	Success (n = 34)	Failure (n = 15)	
Male sex	14 (50)	7 (26.6)	
Diabetes mellitus	11 (32.3)	5 (33.3)	0.59
Primary arthroplasty	15 (44.1)	7 (46.6)	0.88
Revision arthroplasty	19 (55.9)	8 (53.3)	
Age of implant (days)[c]			0.99
<30	22 (64.7)	9 (60)	
30–90	7 (20.6)	3 (20)	
>90	5 (14.7)	3 (20)	
Type of prosthesis[d]			0.34
Hip	18 (60)	6 (40)	
Knee	12 (40)	9 (60)	
Grade III of drainage[c,d]	5 (14.7)	9 (60)	0.004
Baseline C-reactive protein concn (mg/dl)			
≤5	16 (47)	7 (46.7)	0.77
>5	18 (53)	8 (53.3)	
Reason for switching to linezolid			
Failure (n = 45)	30 (88.2)	15 (100)	
Adverse event (n = 4)	4 (11.8)	0	0.21
Open debridement[c,d]	21 (70)	14 (93.3)	0.08
Microbiology[c,d]			
Culture negative	16 (36.5)	1 (6.6)	0.006[e]
Culture positive for:	14 (31.1)	14 (93.3)	
S. epidermidis (all MR)	11	11	
Methicillin-resistant *S. aureus*	3	3	

[a] The median (SD) ages of the patients in the success and failure groups were 65.3 (11.5) and 62.3 (12.4) years, respectively (P = 0.50). The mean (SD) durations of linezolid treatment were 77.5 (31.9) and 84.4 (26.1) days, respectively (P = 0.45).
[b] Chi-square test or Fisher exact test, as necessary.
[c] At the moment that linezolid treatment was started.
[d] Considering only patients who failed previous treatment (n = 45).
[e] Comparing the outcomes of culture-negative and culture-positive patients.

mean (SD) duration of antibiotic regimen was 80.2 (29.7) days, with a range of from 21 to 180 days.

Effets secondaires

- Digestifs: n = 6 (12.2%), Candidose: n = 6 (12.2%)

- Hématologiques
  - Thombopénie: n = 3 (6.1%)
  - Anémie: n = 3 (6.1%) dont 2 transfusions

- Pas de neuropathie périphérique

J Antimicrob Chemother 2010; **65**: 2224–2230
doi:10.1093/jac/dkq281 Advance Access publication 29 July 2010

Journal of Antimicrobial Chemotherapy

Tolerability of prolonged linezolid therapy in bone and joint infection: protective effect of rifampicin on the occurrence of anaemia?

Laurence Legout[1]*, Michel Valette[1], Hervé Dezeque[2], Sophie Nguyen[1], Xavier Lemaire[1], Caroline Loïez[3], Michèle Caillaux[4], Eric Beltrand[5], Luc Dubreuil[1,4], Yazdan Yazdanpanah[1], Henri Migaud[2] and Eric Senneville[1]

[1]Infectious Diseases Department, Dron Hospital of Tourcoing, Tourcoing, France; [2]Department of Orthopaedic Surgery, Centre Hospitalier Universitaire de Lille, Lille, France; [3]Microbiology Laboratory of the Centre Hospitalier Universitaire de Lille, Lille, France; [4]Microbiology Laboratory, Dron Hospital of Tourcoing, Tourcoing, France; [5]Department of Orthopaedic Surgery, Dron Hospital of Tourcoing, Tourcoing, France

94 patients +
LZD

Table 1. Baseline characteristics and outcomes for 94 patients receiving rifampicin/linezolid combination therapy, linezolid alone or other linezolid-containing regimens

Characteristics of the study population	Linezolid/rifampicin combination ($n=43$)	Linezolid alone ($n=25$)	Other linezolid-containing regimen ($n=26$)
Mean duration of linezolid therapy, weeks ± SD	18 ± 7	12 ± 8	13 ± 7
Haematologic values			
baseline haemoglobin, mean ± SD, g/dL	11.6 ± 1.9	11.7 ± 2	11.2 ± 2
anaemia events,[a] *n* (%)	4 (9.3)	11 (44)	13 (50)**
anaemia events leading to linezolid discontinuation, *n* (%)	4/4 (100)	6/11 (54.5)	5/13 (38.5)
baseline platelet count, mean ± SD, 10^9/L	317.078 ± 117.696	340.957 ± 120.986	379.818 ± 136.167
thrombocytopenia events[b] *n* (%)	19 (44.2)	12 (48)	15 (57.7)
thrombocytopenia events leading to linezolid discontinuation, *n* (%)	0 (0)	0 (0)	0 (0)
Neuropathy events, *n* (%)	5 (11.6)	1 (4)	3 (11.5)
Outcomes			
success, *n* (%)	37/41 (90.2)	18/21 (85.7)	18/21 (85.7)
failure, *n* (%)	4/41 (9.8)	2/21 (9.5)	3/21(14.3)
loss to follow-up, *n* (%)	2 (4.7)	4 (16)	5 (19.2)
mean follow-up time, months ± SD	15.7 ± 4.5	17.8 ± 7.6	13.6 ± 5.4

Diminution de 30% de l'AUC si ajout de rifampicine ?

Gandelman, K., et al. 2010. J. Clin. Pharmacol. **51:**229–236

Quelle durée ?

Recommandations

- **USA** : SARM > 8 s
- **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

The NEW ENGLAND JOURNAL of MEDICINE

THE NEW ENGLAND JOURNAL OF MEDICINE

Jan 29, 1970

MEDICAL PROGRESS

OSTEOMYELITIS: A REVIEW OF CLINICAL FEATURES, THERAPEUTIC CONSIDERATIONS AND UNUSUAL ASPECTS (Second of Three Parts)*

FRANCIS A. WALDVOGEL, M.D., GERALD MEDOFF, M.D., AND MORTON N. SWARTZ, M.D.

Résultats du traitement de 82 cas d' « ostéomyélite » (2 cas d'IPOA)

en fonction du traitement INTENSIF :

> 2 semaines de pénicilline haute dose (6 mU/j)

Et il faut toujours traiter le *S.aureus*

The NEW ENGLAND JOURNAL of MEDICINE

Osteomyelitis

Daniel P. Lew, M.D., and Francis A. Waldvogel, M.D.

Treatment

Basic Principles

Early antibiotic treatment, before extensive destruction of bone or necrosis, produces the best results and must be administered parenterally for at least four — and usually six — weeks to achieve an acceptable rate of cure (Table 2). To reduce costs,

April 3, 1997

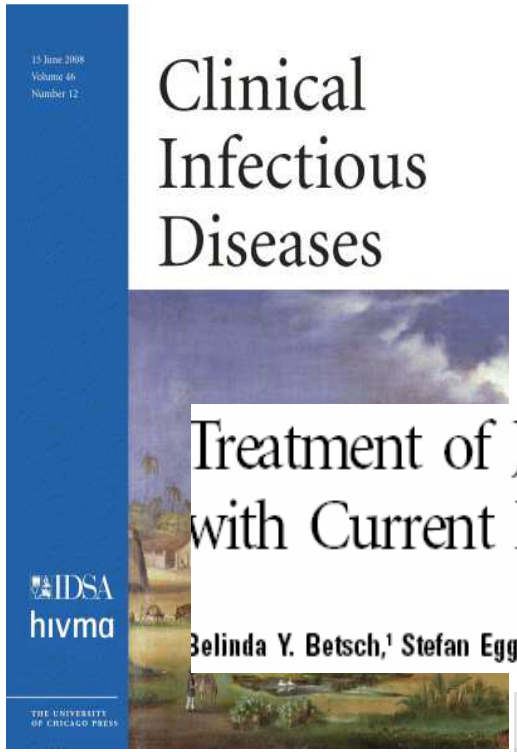
CURRENT CONCEPTS

Prosthetic-Joint Infections

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

Antimicrobial treatment is administered for a total of three months in the case of hip replacement and six months in the case of knee replacement. In in-

October 14, 2004



CID 2008:46 (15 April)

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]

Antimicrobial treatment category

(1) Adequate (total duration of ⩾3 months, duration of therapy administered intravenously ⩾2 weeks, use of agent-appropriate drugs according to susceptibility testing and clinical studies, use of antibiotics with efficacy against surface-adhering bacteria, if possible), (2) partially adequate (duration of at least 2 but <3 months and/or <2 weeks of therapy administered intravenously), (3) inadequate (antimicrobial treatment not corresponding to the above or no antimicrobial treatment) [8]

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.

Journal of Infection (2010) 61, 125-132

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,*]

[a] *Orthopaedic Surgery Service, Geneva University Hospitals & Medical School, Geneva, Switzerland*
[b] *Laboratory of Bacteriology, Geneva University Hospitals & Medical School, Geneva, Switzerland*
[c] *Service of Infectious Diseases, Geneva University Hospitals & Medical School, Geneva, Switzerland*
[d] *Division of Infectious Diseases, Bretionneau Hospital, University Hospitals of Tours, France*

- **70 épisodes (49%) traitées pendant 6 semaines**
- **74 traitées pendant 12 semaines d'antibiotiques**

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

Prosthetic joint infection: surgical treatment associated with 6 weeks antibiotic is effective

H. Chaussade[1], G. Gras[1], A. Vuagnat[2], I. Uckay[3], J. Druon[1], P. Rosset[1], L. Bernard[1]

[1] Univ. Hosp. Tours, France
[2] DREES Inst, Paris, France,
[3] Univ. Hosp. Geneva, Switzerland

Dr H. Chaussade
helene.chaussade@univ-tours.fr

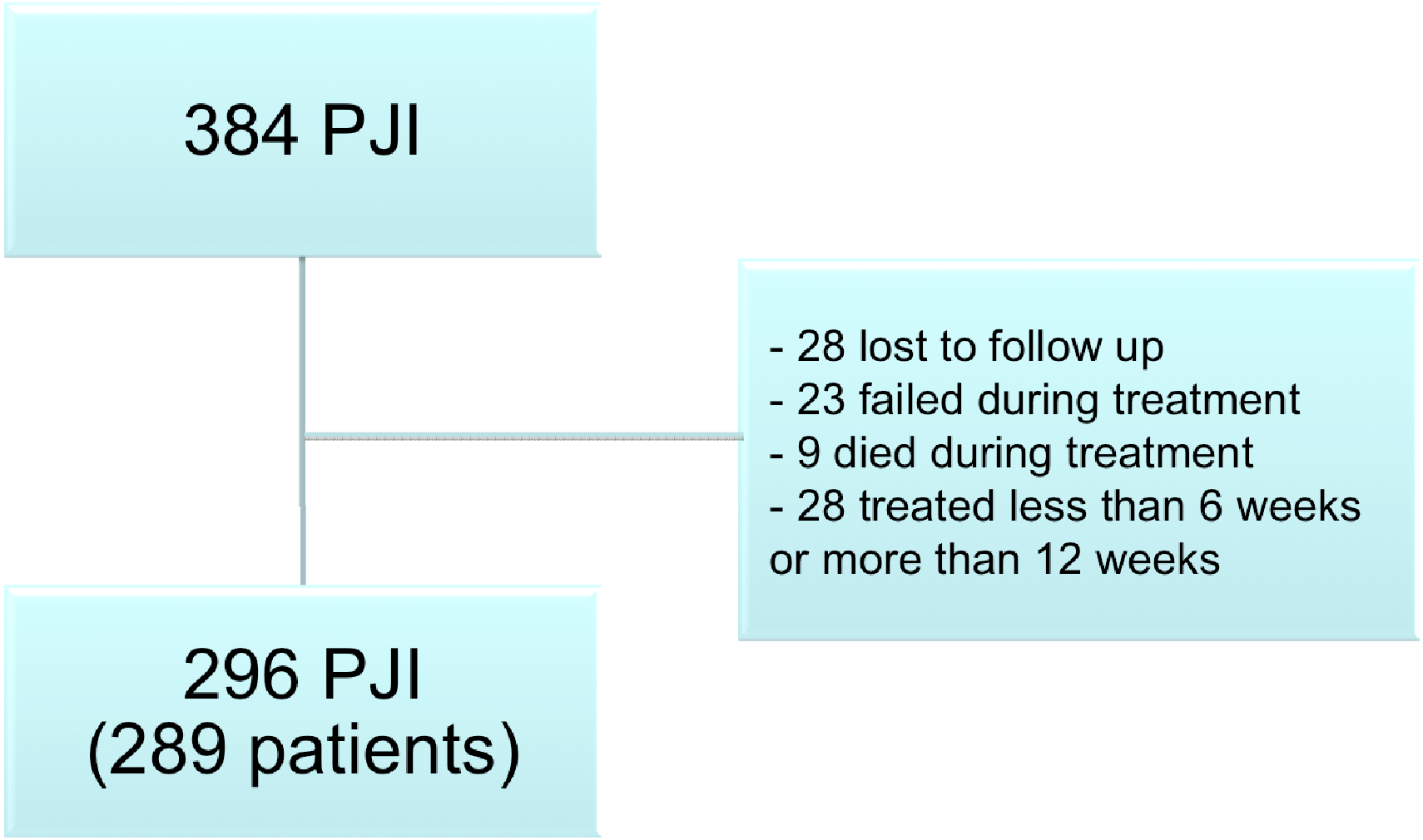
ICAAC 2013, Denver SEPT 12

Objective

Evaluate the optimal duration of antibiotic treatment after adequate surgical procedure in PJI

Determine the risk factors of failure

Results


384 PJI
- 28 lost to follow up
- 23 failed during treatment
- 9 died during treatment
- 28 treated less than 6 weeks or more than 12 weeks
296 PJI
(289 patients)

Results, description

Infection characteristics	6 weeks N = 183 (%)	12 weeks N = 113 (%)	*P*
Median age	72	73	0.78
Total hip prosthesis	123 (67.2)	72 (63.7)	0.54
Total knee prosthesis	60 (32.8)	41 (36.3)	0.54
Infection			
Early (< 3 months)	75 (41)	71 (62.8)	
Delayed	35 (19.1)	24 (21.2)	
Late (> 12 months)	73 (39.9)	18 (15.9)	<0.0001
Microbiology			
MRSA	20 (10.9)	18 (15.9)	0.21
CNS	59 (32.2)	27 (23.9)	0.12

Results, treatment characteristics

Variables	Subjects (Nb)	Success rate (%)	Univariate	*P*	Multivariate	*P*
Surgical management						
Early <15 days	111	80 (72)	1			
Late >14 days	185	146 (79)	1.45 (0.84-2.5)	0.16		
Surgical treatment						
Débridement	118	78 (66)	1		1	
One-stage	20	14 (70)	1.20 (0.43-3.35)		1.15 (0.41-3.25)	0.79
Two-stage	95	81 (85)	**2.97** (1.5-5.88)		**3.05** (1.5-6.19)	**0.002**
Resection	63	53 (84)	**2.72** (1.25-5.9)	**0.0003**	**3.05** (1.36-6.89)	**0.007**
Antibiotherapy						
Others	194	150 (77)	1			
FQ + Rifampicin	102	76 (75)	0.86 (0.49-1.5)	0.59		
Antibiotherapy						
6 weeks	183	143 (78)	1		1	
12 weeks	113	83 (73.5)	0.77 (0.45-1.34)	0.36	1.10 (0.61-1.97)	0.76

Discussion

- 76.4% of PJI cured after surgical and medical treatment

- **Associated with remission rate**
  - Microbiology : non MRSA
  - Surgical treatment :
    - Two-stage exchange
    - Débridement

- **Not associated with remission rate**
  - Duration of antibiotic treatment (6 or 12 weeks)
  - Rifampicin
  - Combination treatment / monotherapy

IntraVeineux

ou

Per os

IV ou Per Os (1)

IPOA « aiguës » avec maintien de l'implant

- Suivi de 39 patients: 30 traités per os, 9 en IV
- Levofloxacine 500 mg + rifampicine 450 mg/j
- durée moyenne: 2,7 mois

Table 2. Patient outcome according to antimicrobial treatment

Antimicrobial	Mean duration (SD) in months	No. cured/No. evaluable[a] (%)
Lev + Rif	2.5 (1.1)	12/13 (92.3)
Clin + Rif	3 (1.3)	7[2]/10 (70)
Tei (alone or in combination)	2.8 (1)	5[b]/8 (62.5)
Other regimens	2.5 (0.7)	6[c]/8 (75)
Total		30/39 (76.9)

Soriano, CMI;12:9 Sept 2006

IV ou Per Os (2)

Comparaison traitement/ostéomyélites à S. doré

	36 patients IV > 4s	36 patients IV puis per os
	IV group (*N* = 36), *N* (%)	Switch group (*N* = 36), *N* (%)
MSSA	17 (47)	18 (50)
MRSA	19 (53)	18 (50)
IV duration (median) (days)	42	14
Oral duration (median) (days)	21	42
Total duration (median) (days)	60	56

Daver, J of Inf. 2007;54:39-44

Table 3 Outcomes for methicillin-sensitive *Staphylococcus aureus* (MSSA) oteomyelitis by treatment groups and antibiotic regimens

Treatment group	Therapies given	Cured (*N*)	Relapsed (*N*)	% Cured
IV		12	4	75[a]
	IV only	4	2	67
	IV with orals	8	2	80
Switch		17	2	89
	Rifampin based	10	1	91
	Other oral therapies	7	1	88

[a] $P = 0.26$ comparing IV to switch group outcomes for MSSA.

Daver, J of Inf. 2007;54:39-44

Association d’antibiotique

Association d'antibiotique (1)

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

CID 2008:47 (1 October)

Table 1. Type of parenteral antimicrobial therapy administered in 50 episodes of enterococcal prosthetic joint infections treated at the Mayo Clinic (Rochester, Minnesota), 1969–1999.

Type of antimicrobial therapy	No. (%) of episodes
Monotherapy (*n* = 31)	
Penicillin G or ampicillin	16 (52)
Vancomycin	5 (16)
Other[a]	10 (32)
Combination therapy (*n* = 19)	
Penicillin G or ampicillin and gentamicin	13 (68)
Vancomycin and gentamicin	2 (11)
Other[b]	4 (21)

[a] Includes episodes treated with <14 days of aminoglycoside (median du-

	Episodes treated with monotherapy (n = 31)	Episodes treated with combination therapy (n = 19)	P
Treatment failure	5 (16)	7 (37)	.2
Nephrotoxicity	2 (6)	5 (26)	.09
Cranial nerve VIII toxicity	0 (0)	6 (32)	.002

Systematic review and meta-analysis of antibiotic therapy for bone and joint infections

Lancet Infectious Diseases 2001; 1: 175–188

Dirk Stengel, Kai Bauwens, Jalid Sehouli, Axel Ekkernkamp, and Franz Porzsolt

« No significant differences in therapeutic efficacy were found among trials comparing oral fluoroquinolones with intravenous beta-lactam drugs for both end-of treatment. »

« A trend towards improved, long-lasting infection control was observed in favour of a rifampicin-ciprofloxacin combination versus ciprofloxacin monotherapy for the treatment of staphylococcal infections related to orthopaedic devices ».

Bithérapie

Plutôt, surtout si :

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

Interactions

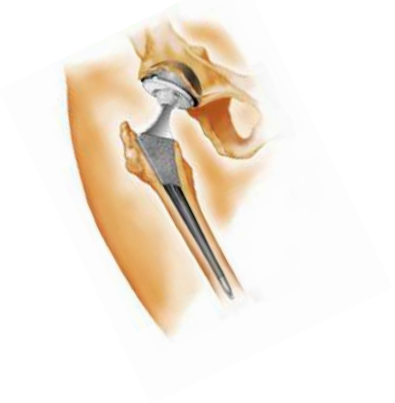
- LNZ - RFP >> protectrice ? (L. Legout *et al.* JAC 2010)
- Clindamycine – RFP >> baisse efficacité ?
- **Intérêt des dosages**
- Utilisés pour
  - Vancomycine (objectif 25-35mg/l)
  - Aminoglycosides (Toxicité)

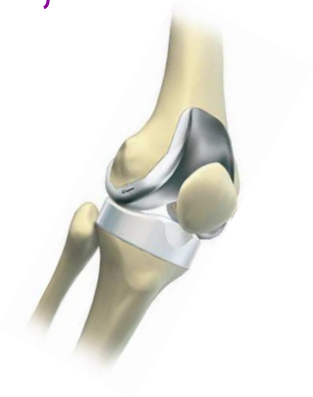
- Fluoroquinolones ? Hétérogénéité des concentrations (C. Pucini *et al.* Presse med. 2004)
- Autres ?
- Daptomycine ?

DATIPO

PHRC 2009

- **2 Durée d'Antibiothérapie** (6 semaines vs 12semaines) dans le Traitement des **IPOA** avec changement en 1T ou 2T long ou lavage articulaire
- Étude multicentrique, de non infériorité, prospective, randomisée, ouverte





410 patients - 34 centres

Nov 2011 - Nov 2014

CHRU HOPITAUX DE TOURS

SOFCOT

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

Références

- **http://www.invs.sante.fr/Publications-et-outils/BEH-Bulletin-epidemiologique hebdomadaire/Archives/2013/BEH-n-4-5-2013**
- **www.invs.sante.fr/.../Rapport_Surveillance_infections_site_opératoire**
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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

Clinical Infectious Diseases Advance Access published December 6, 2012

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CENTRES DE RÉFÉRENCE
POUR LES INFECTIONS OSTÉO-ARTICULAIRES COMPLEXES
DU GRAND OUEST
CRIOGO

Merci

-Aurélien DINH

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