DIU Infections ostéo-articulaires
Lyon, 28 novembre 2018

Place de la rifampicine dans les IOA

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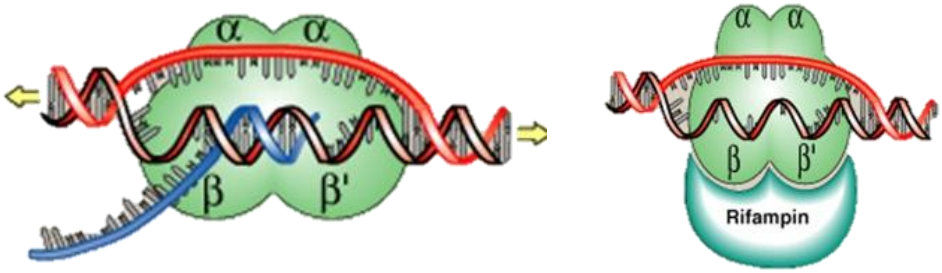
Centre de Référence inter-régional pour la prise en charge des IOA complexes
Hospices Civils de Lyon

INSERM U1111 – Centre International de Recherche en Infectiologie
Université Claude Bernard Lyon 1

Rifampicine : rappels

Cible : sous-unité B de l'ARN polymérase – Inhibition de la synthèse d'ARN bactérien
Action bactéricide [C]dpdte



Rifampicine : rappels

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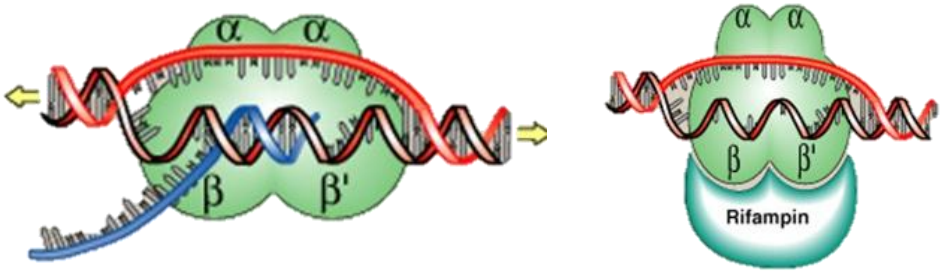
Action bactéricide [C]dpdte

Gram+ et intracellulaires



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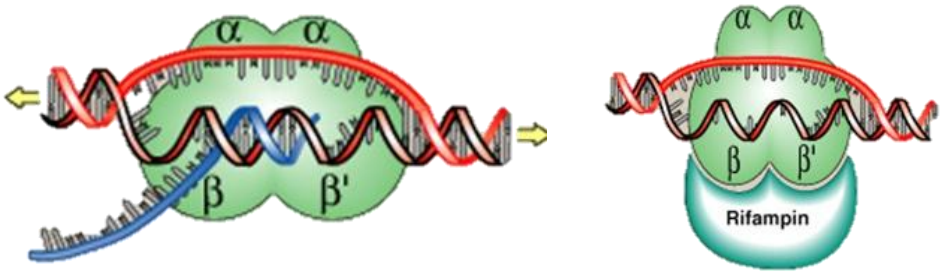
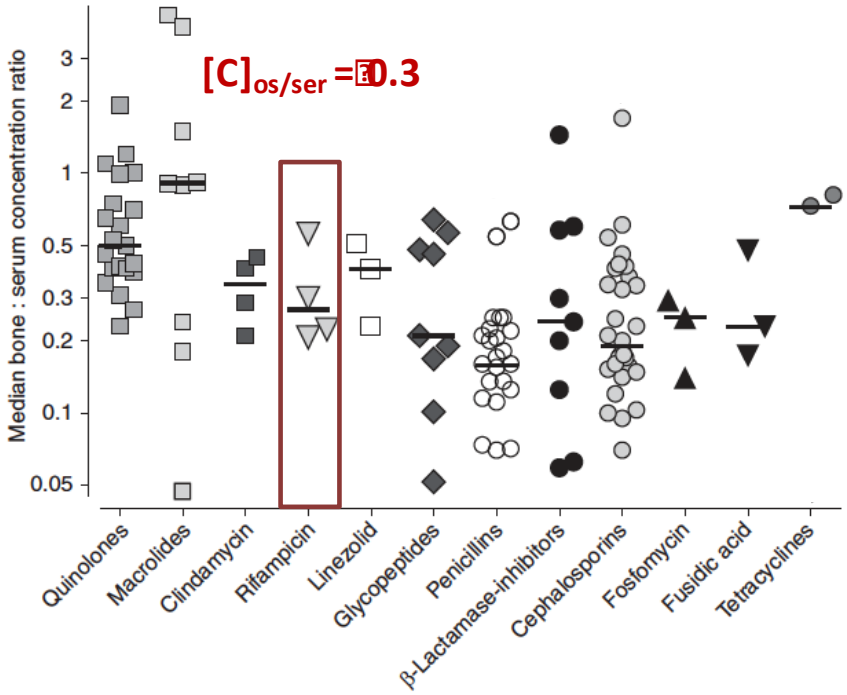


Gram+ et intracellulaires

Biodisponibilité > 90% (si prise à jeun : +30%)
Diffusion tissulaire +++ dont osseuse



Landersdorfer, 2009

Rifampicine : rappels

Cible : sous-unité B de l'ARN polymérase – Inhibition de la synthèse d'ARN bactérien
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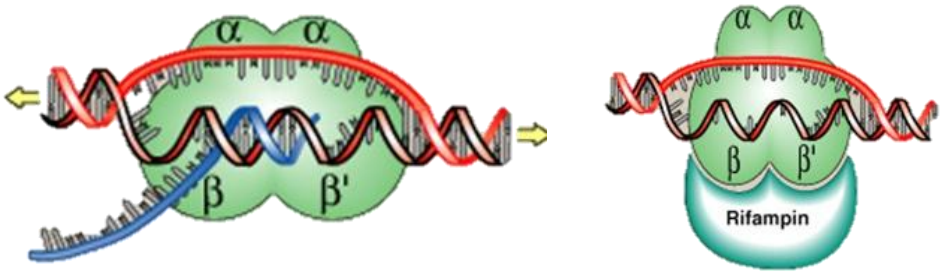

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A UTILISER EN ASSOCIATION

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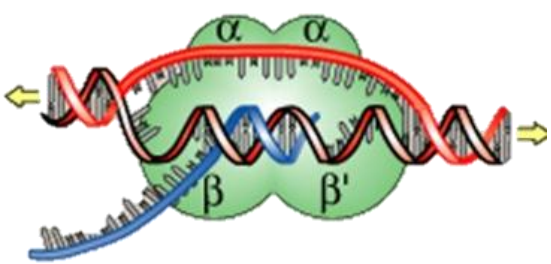
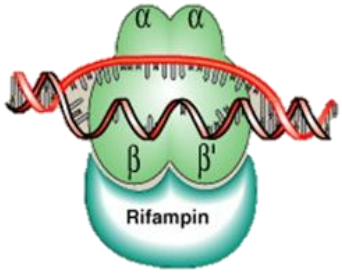




Gram+ et intracellulaires

Biodisponibilité > 90% (si prise à jeun : +30%)
Diffusion tissulaire +++ dont osseuse

A UTILISER EN ASSOCIATION

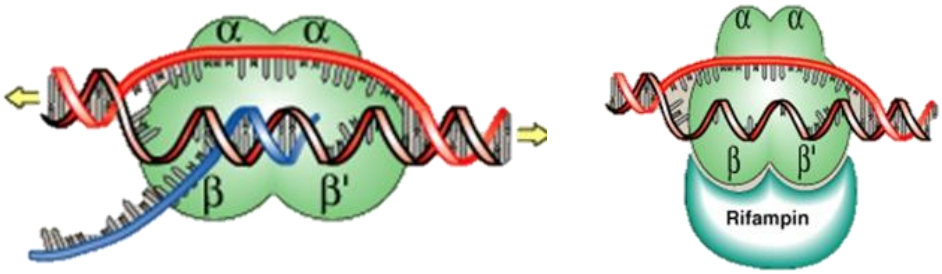
TOLERANCE

< 0.3%

10%

Rifampicine : rappels

Cible : sous-unité B de l'ARN polymérase – Inhibition de la synthèse d'ARN bactérien
Action bactéricide [C]dpdte



Gram+ et intracellulaires

Biodisponibilité > 90% (si prise à jeun : +30%)
Diffusion tissulaire +++ dont osseuse

A UTILISER EN ASSOCIATION

TOLERANCE

< 0.3%

10%

Puissant inducteur enzymatique +++
CYP3A4

Rifampicine et IOA staphylococciques

Rationnel #1 : action anti-staphylococcique

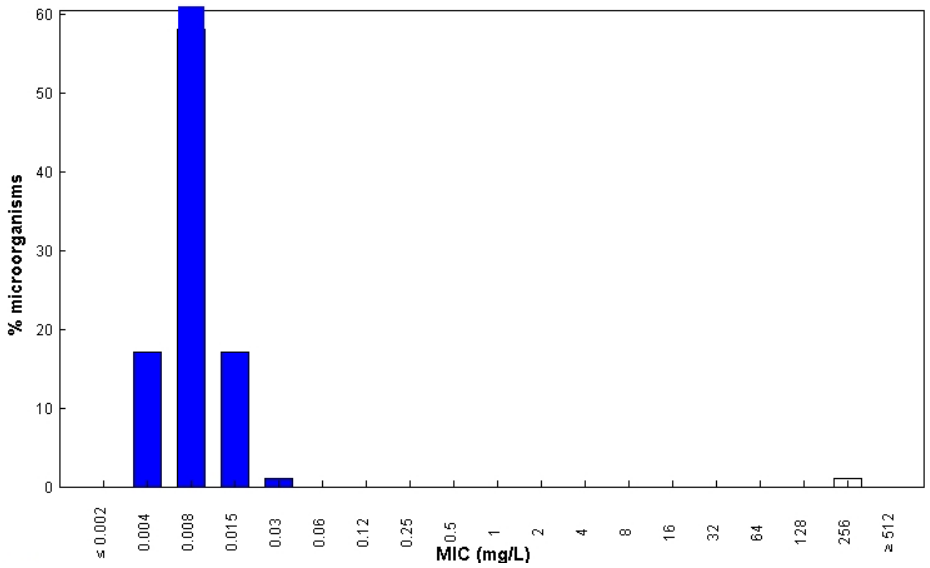
EUCAST

S. aureus

1194 souches

RMP-S (CMI ≤ 0.64 mg/L) : 94.7%

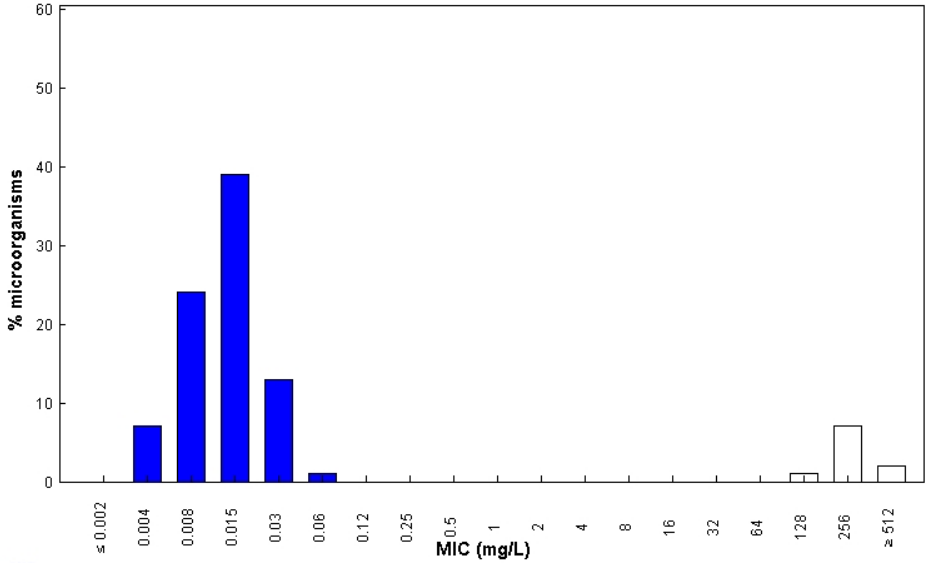
MRSA : 310/317 (97.8%)



SCN

697 souches

RMP-S (CMI ≤ 0.64 mg/L) : 87.5%



Rationnel #2 : action « anti-biofilm »

Minireview – AAC01746-18R – October 27, 2018

The Role of Rifampin against Staphylococcal Biofilm Infections *in Vitro*, in Animal Models, and in Orthopedic Device-Related Infections.

Werner Zimmerli,[1] Parham Sendi[2,3]

Rationnel #2 : action « anti-biofilm »

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 2002, p. 900–903 Vol. 46, No. 3
0066-4804/02/$04.00+0 DOI: 10.1128/AAC.46.3.900–903.2002

Penetration of Rifampin through *Staphylococcus epidermidis* Biofilms

Zhilan Zheng and Philip S. Stewart*

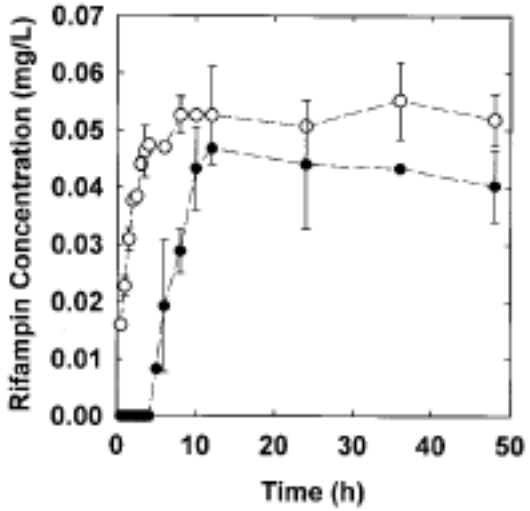


FIG. 1. Penetration of 0.1 μg of rifampin per ml through membrane assemblies with (filled symbols) and without (open symbols) *S. epidermidis* colony biofilms. Error bars indicate the standard errors of the means.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 2006, p. 55–61 Vol. 50, No. 1
0066-4804/06/$08.00+0 doi:10.1128/AAC.50.1.55–61.2006

Multiple Combination Bactericidal Testing of Staphylococcal Biofilms from Implant-Associated Infections

Raphael Saginur,[1,2]* Melissa St. Denis,[2,3] Wendy Ferris,[2,3] Shawn D. Aaron,[1,2] Francis Chan,[2,3] Craig Lee,[1,2] and Karam Ramotar[1,2]

TABLE 5. Number of staphylococcus isolates susceptible to single antibiotics

Drug[a]	*S. epidermidis* (*n* = 17)				MSSA (*n* = 11)				MRSA (*n* = 12)			
	Planktonic		Biofilm		Planktonic		Biofilm		Planktonic		Biofilm	
	Inhibit	Kill	Inhibit	Kill	Inhibit	Kill	Inhibit	Kill	Inhibit	Kill	Inhibit	Kill
LZD	17	0	0	0	11	0	0	0	12	0	1	0
RIF	16	8	1	8	11	3	1	2	10	0	3	5
CFZ	9	1	0	0	11	3	3	0	1	0	0	0
OXA	0	0	0	0	11	2	1	0	0	0	0	0
VAN	17	7	2	0	11	1	2	0	12	1	4	0
GEN	5	4	0	0	4	2	0	0	4	1	0	0
AZM	4	0	0	0	8	0	0	0	1	0	0	0
CIP	0	0	0	0	7	4	1	0	2	1	0	0
FA	14	0	1	1	11	1	0	0	9	0	3	1

Antibiotics	Inhibition of biofilm formation (adhesion)	Biofilm penetration	Bactericidal activity in biofilm
Vancomycin	+	++[16,17]	+[16,17]
Linezolid	+	++[24,29]	+[24]
Daptomycin	+	+++[15]	++[21,24]
Rifampicin	+	+++[8,16,18]	++[16,30]
Moxifloxacin	+	++[31]	++[21,31]
Rifampicin+daptomycin	+	+++[2,30]	+++[28,30]
Rifampicin+vancomycin	+	++[16,18]	++[16,27,32]
Rifampicin+linezolid	+	+++[16,29]	+++[27,32]

Jacqueline JAC 2014

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 2011, p. 1182–1186 Vol. 55, No. 3
0066-4804/11/$12.00 doi:10.1128/AAC.00740-10

Treatment with Linezolid or Vancomycin in Combination with Rifampin Is Effective in an Animal Model of Methicillin-Resistant *Staphylococcus aureus* Foreign Body Osteomyelitis[▽]

Paschalis Vergidis,[1] Mark S. Rouse,[2] Gorane Euba,[1]† Melissa J. Karau,[2] Suzannah M. Schmidt,[2] Jayawant N. Mandrekar,[3] James M. Steckelberg,[1] and Robin Patel[1,2]*

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]*

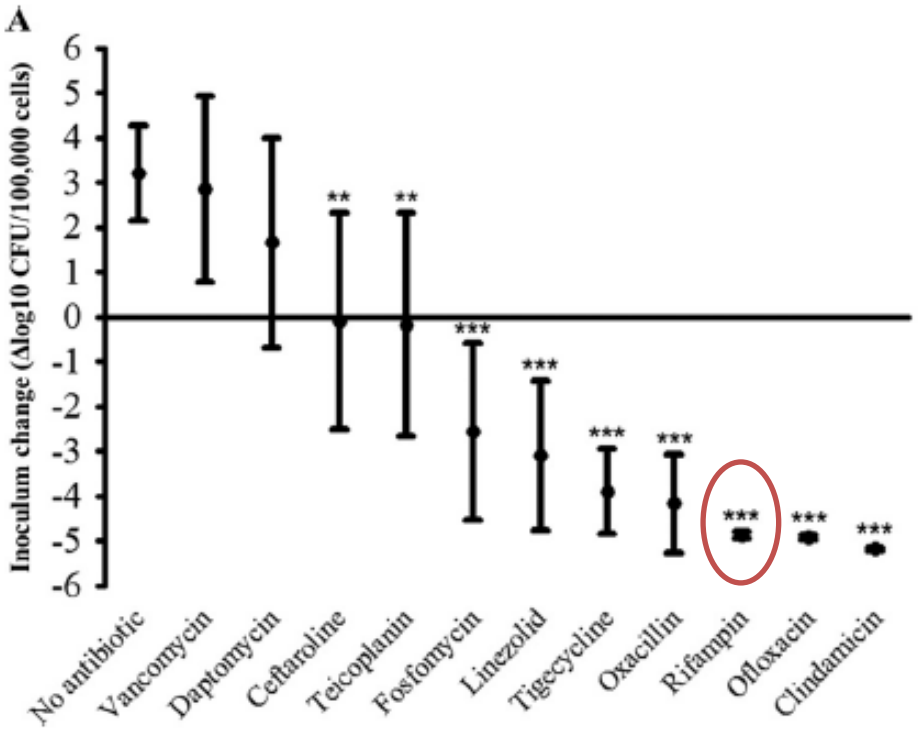
Rationnel #3 : activité intracellulaire

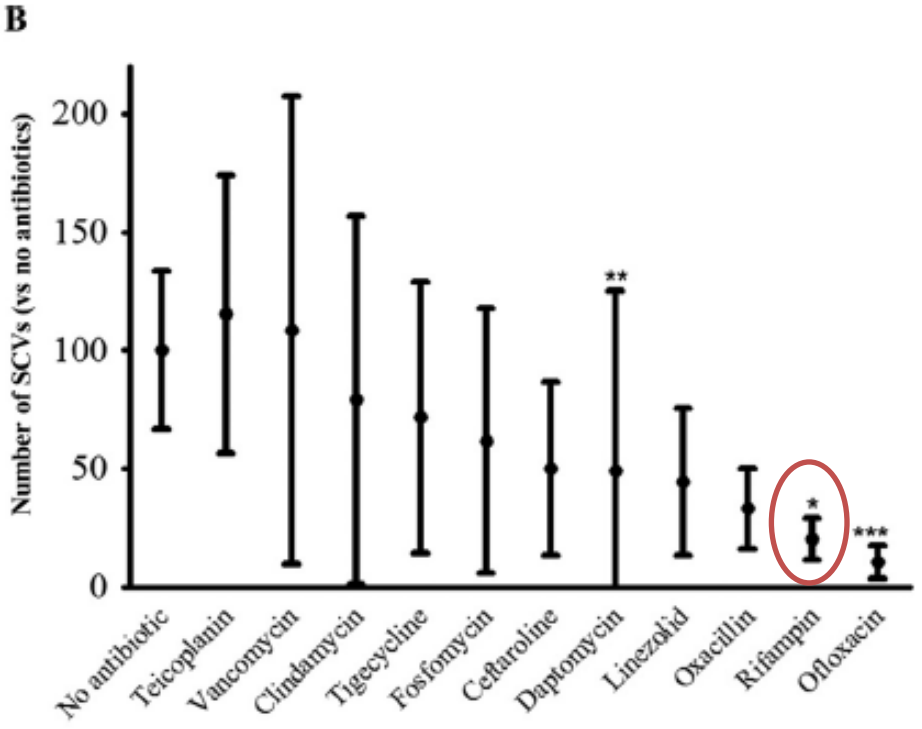
AAC Journals.ASM.org 2015

Antimicrobial Activity against Intraosteoblastic *Staphylococcus aureus*

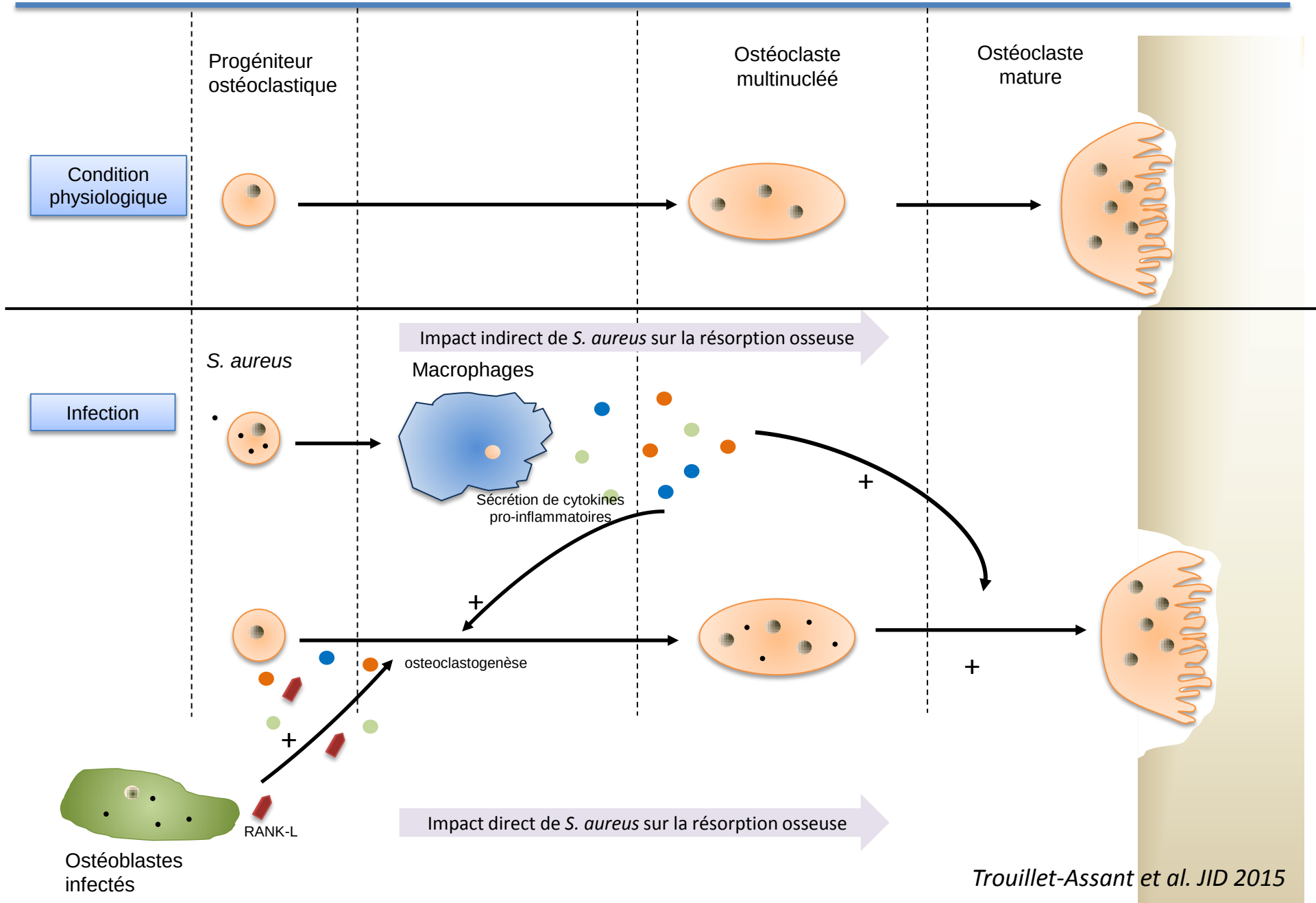
Florent Valour,[a,b] Sophie Trouillet-Assant,[b] Natacha Riffard,[b] Jason Tasse,[b] Sacha Flammier,[b] Jean-Philippe Rasigade,[b,c] Christian Chidiac,[a,b] François Vandenesch,[b,c,d] Tristan Ferry,[a,b] Frédéric Laurent,[b,c,d] on behalf of the Lyon Bone and Joint Infection Study Group

C_{os} = 6 mg/L



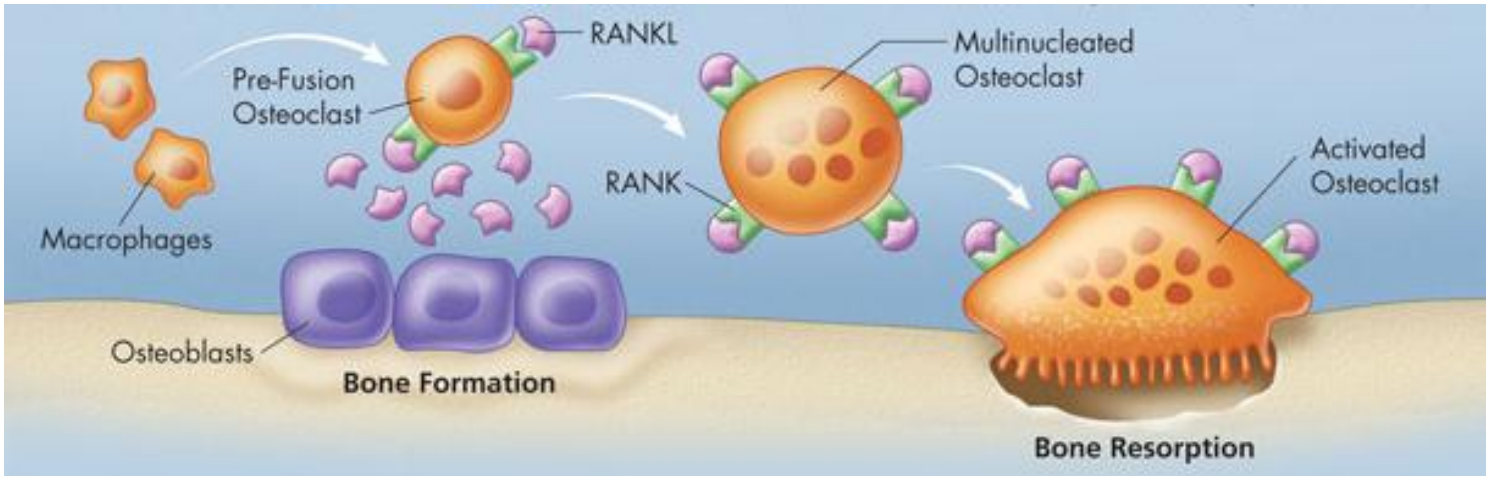


Rationnel #4 : action anti-ostéoclastique



Trouillet-Assant et al. JID 2015

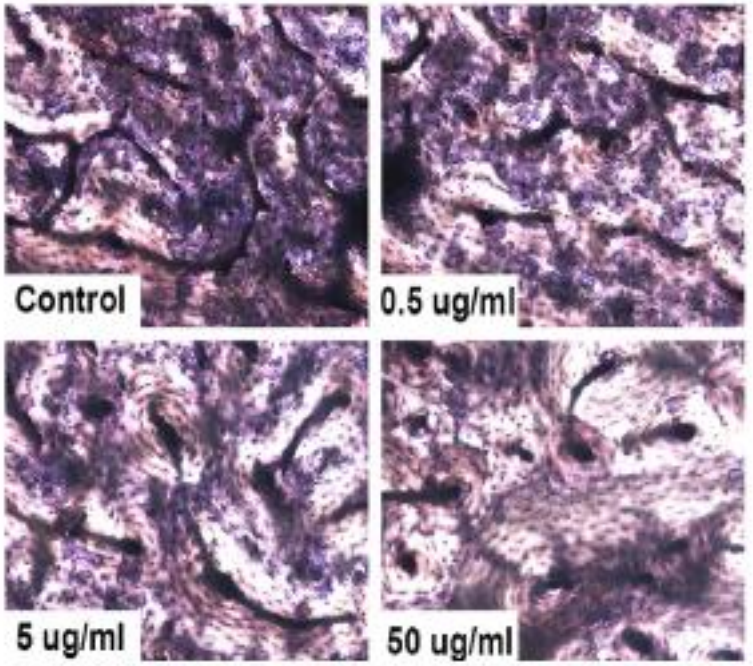
Rationnel #4 : action anti-ostéoclastique



Rifampin suppresses osteoclastogenesis and titanium particle-induced osteolysis via modulating RANKL signaling pathways

Liang Zhu [a, b, 1], Hui Kang [b, 1], Chang-an Guo [a], Wen-shuai Fan [a], Yi-ming Wang [a], Lian-fu Deng [b], Zuo-qin Yan [a, *]

Bioch Bioph Res, 2017



Contexte de descellement aseptique
Particules titane : ↗ ostéoclasie

Rifampicine
- Inhibition de l'ostéoclastogenèse *in vivo*
- Inhibition de la résorption osseuse induite par les particules de titane *in vivo*
- Mécanisme : inhibition du signal transduit par RANK-L

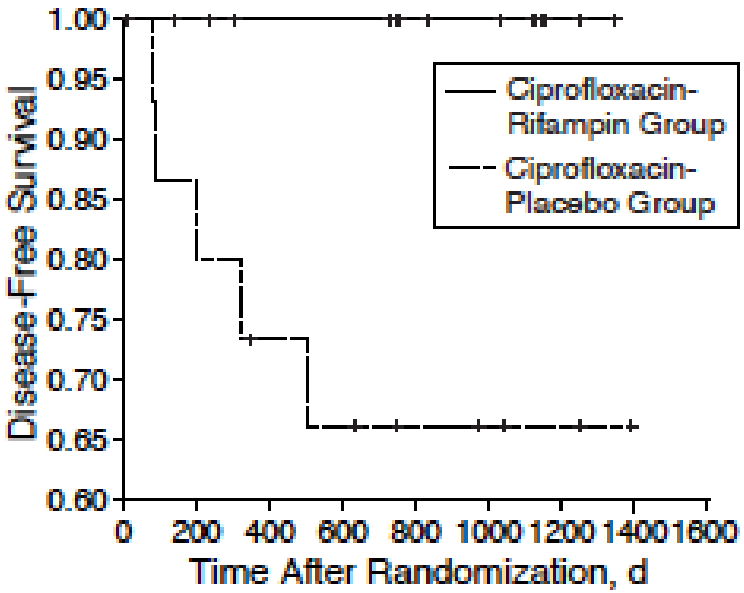
Supériorité clinique

Role of Rifampin for Treatment of Orthopedic Implant–Related Staphylococcal Infections

A Randomized Controlled Trial

Werner Zimmerli, MD; Andreas F. Widmer, MD, MSc; Marianne Blatter, MD; R. Frei, MD; Peter E. Ochsner, MD; for the Foreign-Body Infection (FBI) Study Group

JAMA 1998



Essai clinique randomisé

33 patients, infection aigue sur matériel à SA

Débridement puis

- 2 semaines (péni M ou vanco) IV + (RMP ou placebo)
- Relais cipro + RMP n= 18 cure rate = 100%
  ou cipro + placebo) n= 15 cure rate = 58%

Supériorité clinique

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

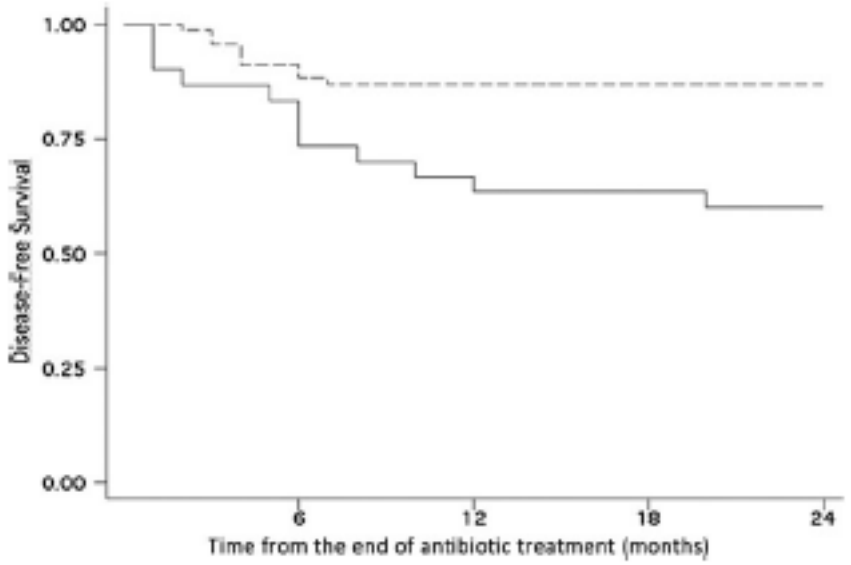
Eric Senneville, Donatienne Joulie, Laurence Legout, Michel Valette, Hervé Dezèque, Eric Beltrand, Bernadette Roselé, Thibaud d'Escrivan, Caroline Loïez, Michèle Caillaux, Yazdan Yazdanpanah, Carlos Maynou, and Henri Migaud

CID 2011

98 patients

Analyse univariée
- ASA score
- ATB empirique correcte
- Rifampicine à la sortie

Analyse multivariée
- ASA score
- Rifampicine + FQ (OR = 0.40)



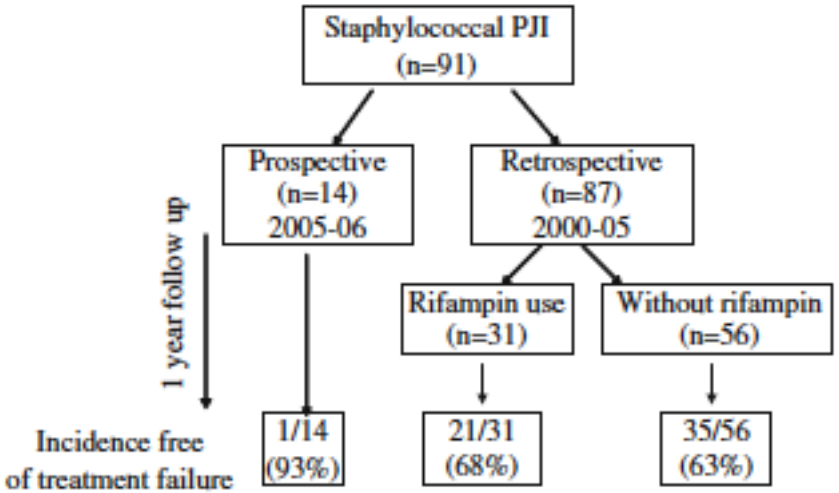
Supériorité clinique

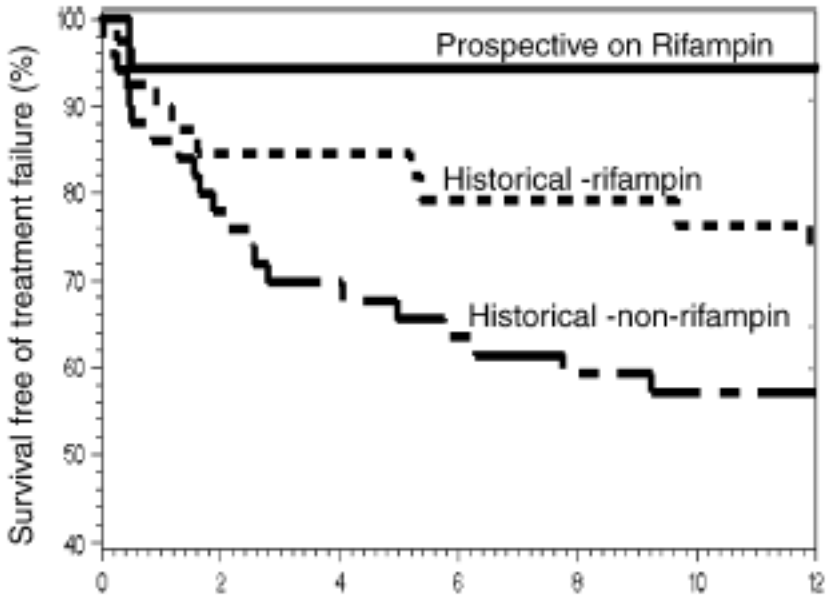
Eur J Clin Microbiol Infect Dis (2010) 29:961–967
DOI 10.1007/s10096-010-0952-9

ARTICLE

Efficacy and safety of rifampin containing regimen for staphylococcal prosthetic joint infections treated with debridement and retention

O. C. El Helou · E. F. Berbari · B. D. Lahr · J. E. Eckel-Passow · R. R. Razonable · I. G. Sia · A. Virk · R. C. Walker · J. M. Steckelberg · W. R. Wilson · A. D. Hanssen · D. R. Osmon





Supériorité clinique

A Large Multicenter Study of Methicillin–Susceptible and Methicillin–Resistant *Staphylococcus aureus* Prosthetic Joint Infections Managed With Implant Retention

Jaime Lora-Tamayo,[1] Oscar Murillo,[1] José Antonio Iribarren,[6] Alex Soriano,[2] Mar Sánchez-Somolinos,[7] Josu Miren Baraia-Etxaburu,[11] Alicia Rico,[8] Julián Palomino,[12] Dolors Rodríguez-Pardo,[3] Juan Pablo Horcajada,[4] Natividad Benito,[5] Alberto Bahamonde,[14] Ana Granados,[15] María Dolores del Toro,[13] Javier Cobo,[11] Melchor Riera,[16] Antonio Ramos,[10] Alfredo Jover-Sáenz,[17] and Javier Ariza,[1] on behalf of the REIPI Group for the Study of Prosthetic Infection

345 MSSA / MRSA (23%) PJI – DAIR

CID 2013

	All Post-Surgical Episodes (n = 244; Failures = 81)				MSSA Post-Surgical Episodes (n = 185; Failures = 60)				MRSA Post-Surgical Episodes (n = 59; Failures = 21)			
	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*	Unadjusted HR (95% CI)	*P*	Adjusted[a] HR (95% CI)	*P*
Sex (male)	.73 (.46–1.17)	NS	–	–	.75 (.43–1.28)	NS	–	–	.72 (.28–1.87)	NS	–	–
Age (years)	1.00 (.98–1.02)	NS	–	–	.99 (.97–1.02)	NS	–	–	1.00 (.96–1.04)	NS	–	–
Diabetes mellitus	1.35 (.80–2.26)	NS	–	–	1.24 (.66–2.34)	NS	–	–	1.51 (.61–3.75)	NS	–	–
Chronic renal impairment	2.87 (1.24–6.63)	.032	–	–	3.24 (.78–13.5)	NS	–	–	2.08 (.70–6.18)	NS	–	–
Rheumatoid arthritis	1.60 (.80–3.19)	NS	–	–	1.70 (.81–3.59)	NS	–	–	1.70 (.23–12.8)	NS	–	–
Immunosuppressive therapy	2.46 (1.13–5.36)	.045	–	–	3.30 (1.41–7.74)	.018	3.40 (1.39–8.37)	.008	1.05 (.14–7.83)	NS	–	–
Revision prosthesis	1.66 (1.01–2.74)	.056	–	–	1.97 (1.08–3.61)	.038	–	–	1.09 (.44–2.69)	NS	–	–
Hip prosthesis	1.08 (.69–1.68)	NS	–	–	.93 (.55–1.59)	NS	–	–	1.26 (.51–3.12)	NS	–	–
Time to infection >90 days[b]	2.19 (1.18–4.05)	.013	–	–	1.84 (.98–3.45)	.089	2.18 (1.04–4.56)	.039	7.48 (2.01–27.8)	.013	–	–
Infection by MRSA	1.32 (.80–2.18)	NS	–	–	–	–	–	–	–	–	–	–
Bacteremia	1.70 (.77–3.73)	NS	–	–	2.21 (.99–4.95)	.078	2.35 (1.04–5.36)	.040	–	–	–	–
Polymicrobial infection	1.47 (.88–2.47)	NS	–	–	1.19 (.64–2.21)	NS	–	–	2.81 (1.07–7.39)	.052	–	–
CRP diagnosis (100 mg/L)	1.28 (1.02–1.60)	.047	1.32 (1.05–1.66)	.018	1.22 (.94–1.59)	NS	–	–	1.95 (1.02–3.75)	.052	–	–
Temperature >37°C	1.30 (.83–2.04)	NS	–	–	1.23 (.73–2.08)	NS	–	–	1.89 (.75–4.75)	NS	–	–
Sinus tract	1.62 (.93–2.82)	.086	–	–	1.49 (.77–2.89)	NS	–	–	2.15 (.78–5.92)	NS	–	–
Abnormal radiography	2.24 (1.31–3.85)	.007	2.22 (1.30–3.81)	.004	1.77 (.92–3.42)	NS	–	–	3.60 (1.37–9.45)	.019	4.49 (1.68–12.0)	.003
Debridement delay >10 days[c]	1.57 (1.01–2.45)	.049	1.68 (1.07–2.64)	.024	1.85 (.91–3.77)	.089	–	–	1.50 (.63–3.58)	NS	–	–
Polyethylene exchange[d]	.57 (.34–.97)	.045	–	–	.70 (.36–1.37)	NS	–	–	.46 (.19–1.13)	.096	–	–
Need ≥2 debridements	3.15 (1.88–5.28)	<.001	3.82 (2.24–6.51)	<.001	4.34 (2.39–7.89)	<.001	5.36 (2.88–9.98)	<.001	1.62 (.54–4.81)	NS	–	–
Rifampin[e]	.55 (.34–0.87)	.011	.52 (.32–.83)	.006	.67 (.39–1.17)	NS	–	–	.27 (.11–.65)	.007	–	–
Levofloxacin + Rifampin[e]	.48 (.27–.88)	.010	–	–	.50 (.27–.92)	.019	.42 (.22–.80)	.008	–	NS	–	–
Vancomycin + Rifampin[e]	.45 (.17–1.24)	.081	–	–	–	–	–	–	.34 (.11–1.01)	.032	.29 (.10–.87)	.027

Supériorité clinique

J Appl Biomater Funct Mater 2014; 12 (3): 129-134
DOI: 10.5301/jabfm.5000209

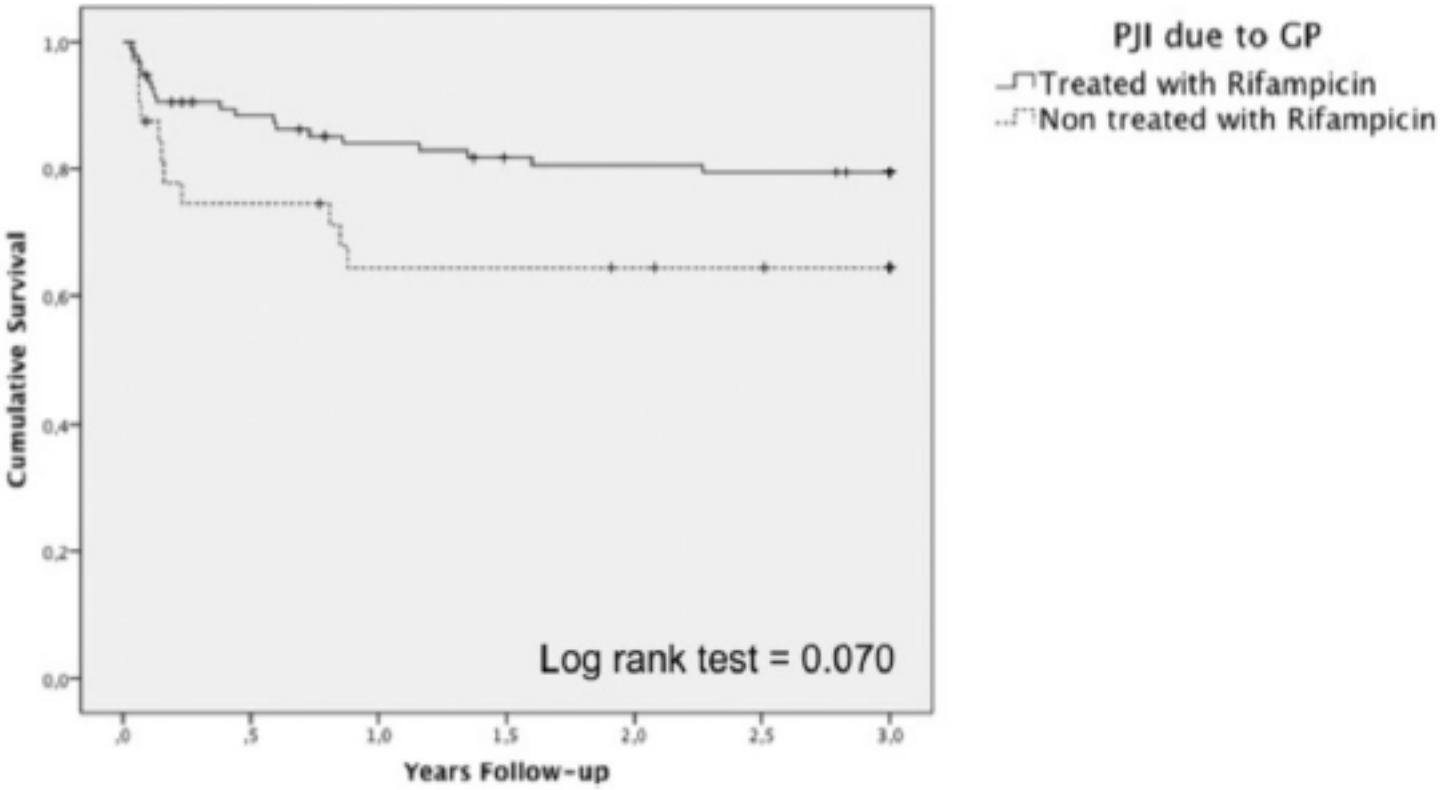
ORIGINAL ARTICLE

Risk factors for failure in early prosthetic joint infection treated with debridement. Influence of etiology and antibiotic treatment

Eduard Tornero[1], Juan C. Martínez-Pastor[1], Guillem Bori[1], Sebastián García-Ramiro[1], Laura Morata[2], Jordi Bosch[3], Josep Mensa[2], Alex Soriano[2]

[1] Department of Orthopedic and Trauma Surgery, Hospital Clínic of Barcelona, Barcelona - Spain
[2] Department of Infectious Diseases, Hospital Clínic of Barcelona, IDIBAPS, Barcelona - Spain
[3] Laboratory of Microbiology, Hospital Clínic of Barcelona, Barcelona - Spain

N=160



Quelle dose ?

SPILF 2008	20 mg/kg/j
IDSA 2013	300-450 mg x 2/j
HAS 2014	300 mg x 2/j 900 mg x 1/j
SEIMC 2017	600 mg x 1/j

Meilleurs prédicteurs d'efficacité : modèle [C]dpdt ➙ Théorie : Cmax / CMI … mais

- AUC / CMI +++
- Auto-induction et saturation du métabolisme hépatique : relation Cmax / dose non linéaire au-delà de 450 mg
- Effet post-antibiotique marqué (y compris intra-biofilm)

Quelle dose ?

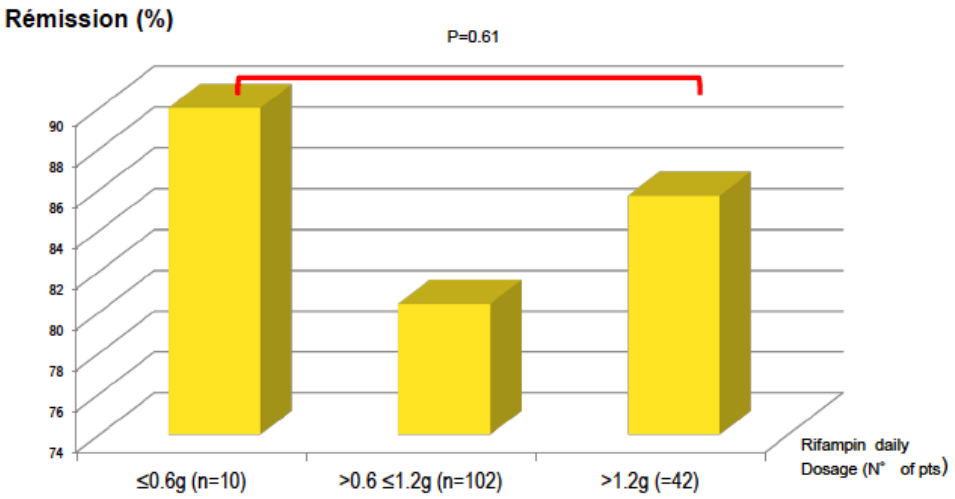
Eur J Clin Microbiol Infect Dis (2015) 34:1675–1682
DOI 10.1007/s10096-015-2404-z

ARTICLE

Influence of daily dosage and frequency of administration of rifampicin–levofloxacin therapy on tolerance and effectiveness in 154 patients treated for prosthetic joint infections

S. Nguyen[1] · O. Robineau[1] · M. Titecat[2] · N. Blondiaux[1] · M. Valette[1] · C. Loiez[2] · E. Beltrand[3] · H. Migaud[4] · E. Senneville[1,5]

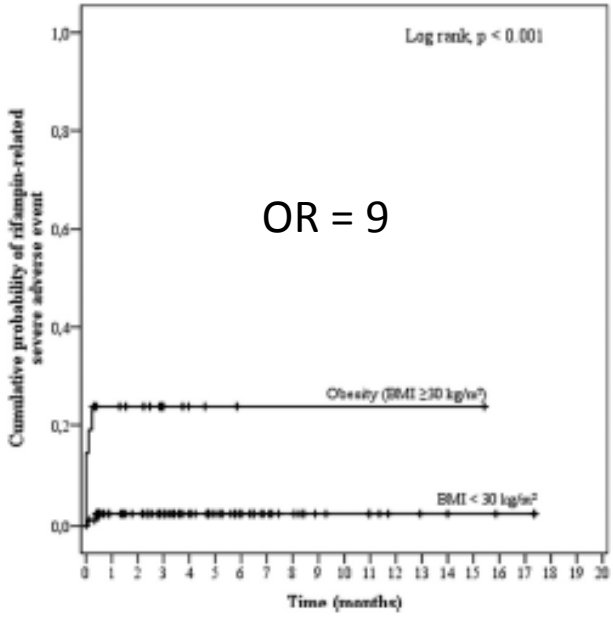
Daily dosing	Intolerance episodes	*p*-Value	Discontinuation	*p*-Value
Rifampicin daily dosage	*n*=48 (31.2)		*n*=29 (18.8)	
. mg:				
≤600 (*n*=10)	1 (10)	0.04	1 (10)	0.65
>600to ≤1,200 (*n*=102)	28 (27.5)		18 (17.6)	
>1,200 (*n*=42)	19 (45.2)		10 (23.8)	
. frequency:				
Once-daily (*n*=11)	3 (27.3)	0.90	3 (27.3)	0.45
Twice-daily (*n*=143)	45 (31.4)		26 (18.2)	



AAC
Journals.ASM.org

Antimicrobial-Related Severe Adverse Events during Treatment of Bone and Joint Infection Due to Methicillin-Susceptible *Staphylococcus aureus*

Florent Valour,[a,b] Judith Karsenty,[a] Anissa Bouaziz,[a] Florence Ader,[a,b] Michel Tod,[c] Sébastien Lustig,[d] Frédéric Laurent,[b,e,f] René Ecochard,[g] Christian Chidiac,[a,b] Tristan Ferry,[a,b] on behalf of the Lyon BJI Study Group



OR = 9

Quelle dose ?

Eur J Clin Microbiol Infect Dis (2015) 34:1675–1682
DOI 10.1007/s10096-015-2404-z

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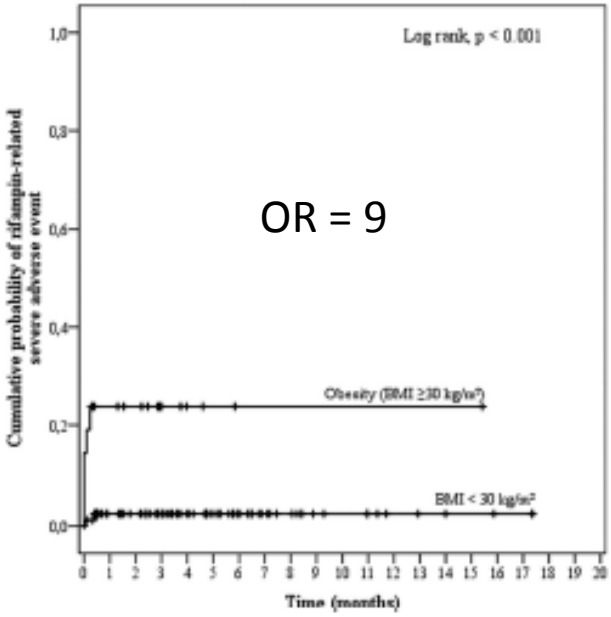
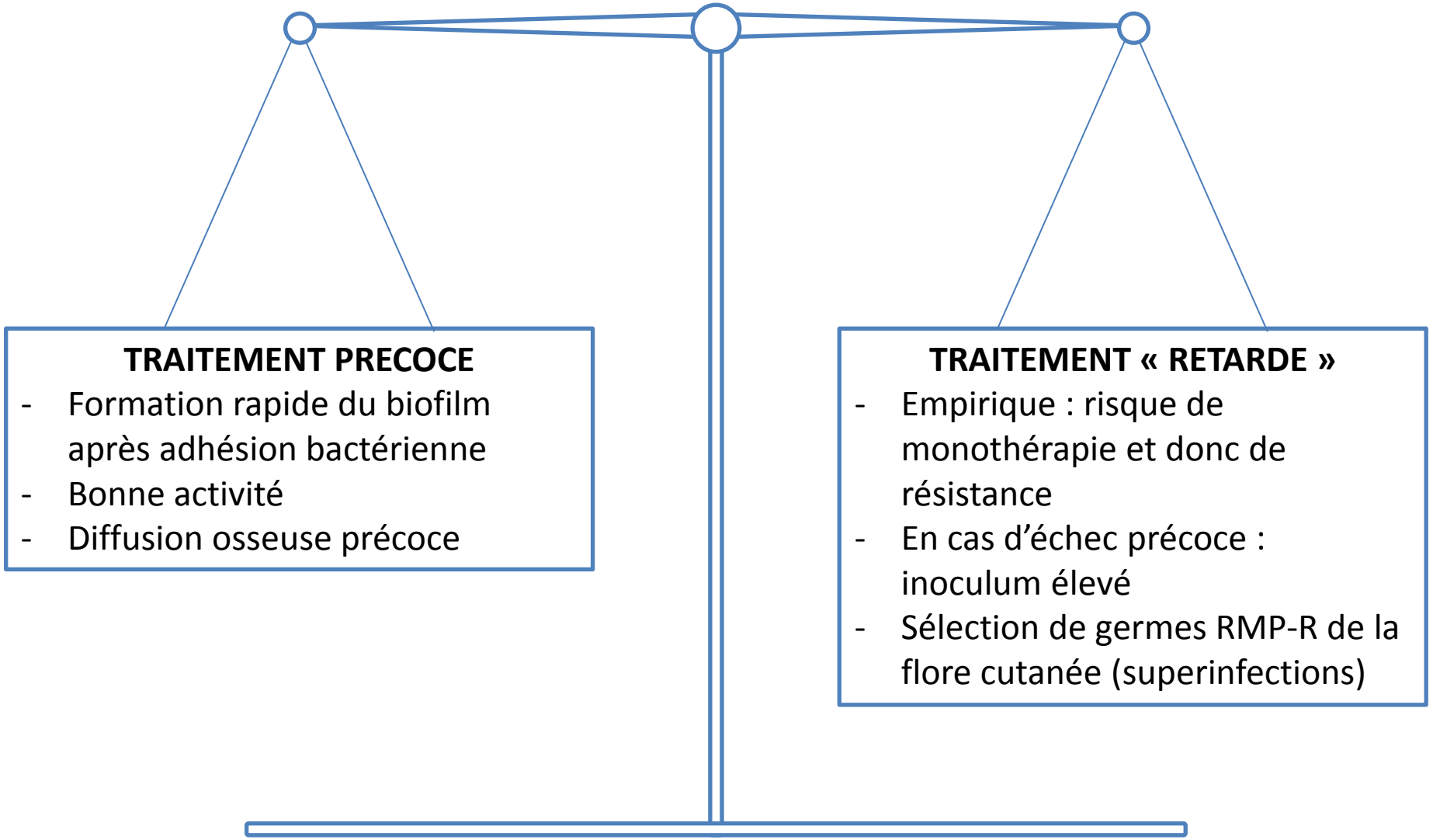


OR = 9

EN PRATIQUE

- 600 mg en 1 ou 2 fois par jour si < 70 kg
- 900 mg en 1 ou 2 fois par jour si > 70 kg ?

Quel timing ? Quelle durée ?



Saginur et al, AAC 2006 – Svensson et al, JAC 1997 – Valentin et al, J Infect 201 – Achermann et al, Infection 2013

Quel timing ? Quelle durée ?

Infection (2013) 41:431–437
DOI 10.1007/s15010-012-0325-7

CLINICAL AND EPIDEMIOLOGICAL STUDY

Factors associated with rifampin resistance in staphylococcal periprosthetic joint infections (PJI): a matched case–control study

Y. Achermann · K. Eigenmann · B. Ledergerber · L. Derksen · P. Rafeiner · M. Clauss · R. Nüesch · C. Zellweger · M. Vogt · W. Zimmerli

48 PJI SCN (38) ou *S. aureus* (10)

Résistance à la rifampicine

- Sexe masculin (OR 3.6)
- ≥ 3 révisions (0R 4.7)
- Fort inoculum (OR 4.9)
  - Chirurgie non optimale
  - < 2 sem de bithérapie IV
- Utilisation inadéquate de la rifampicine (OR 5.4)
  - Monothérapie
  - Utilisation empirique en association avec un ATB à spectre étroit
  - Utilisation avec un ATB per os à faible biodisponibilité
  - Faible dose

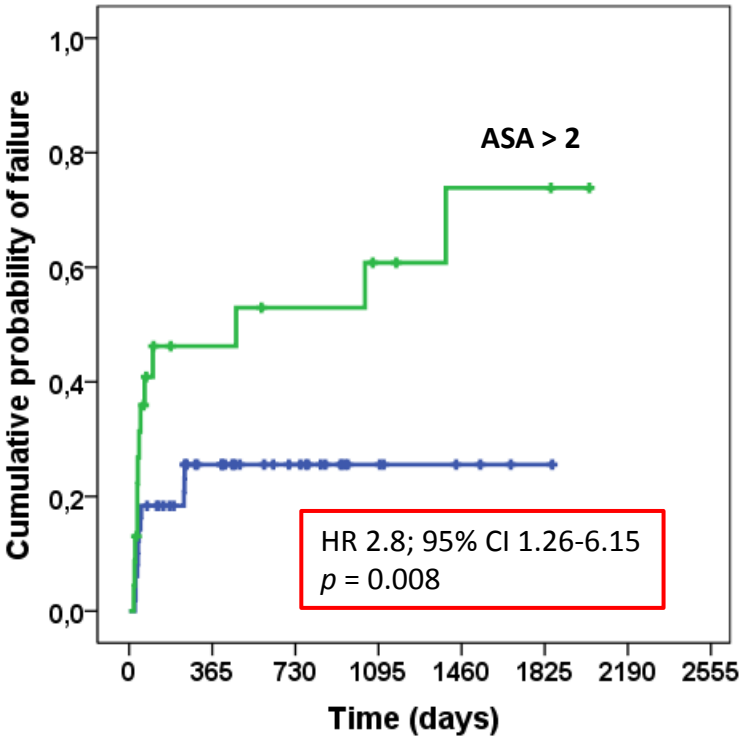
Quel timing ? Quelle durée ?

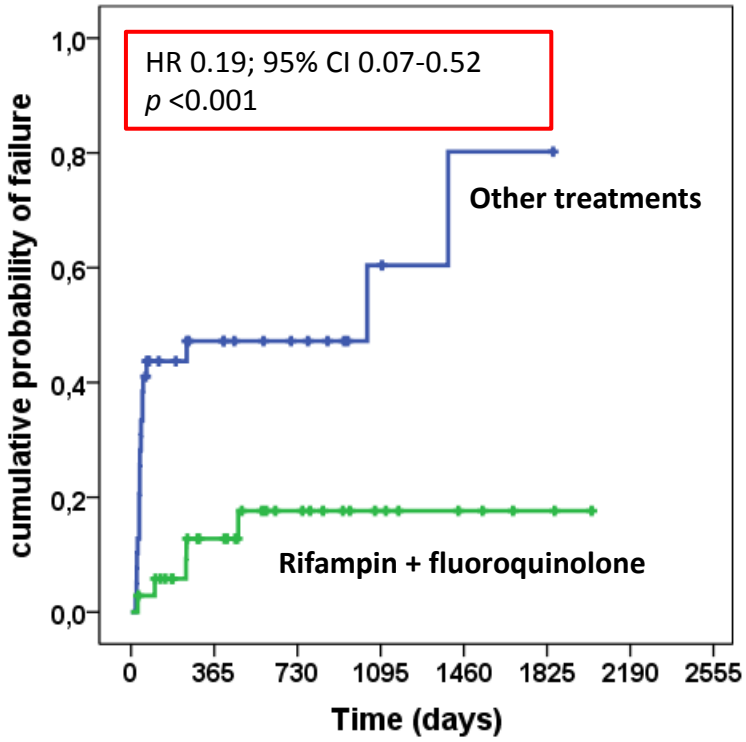
2018

Staphylococcal acute post-operative PJI treated with DAIR and impact of rifampin: a retrospective cohort study in France

A. Becker, C. Triffault-Fillit, E. Forestier, O. Lesens, C. Cazorla, S. Descamps, B. Boyer, C. Chidiac, and T. Ferry on behalf of the IPASTAPH Study Group

Etude de cohorte rétrospective, multicentrique – 79 PJI traitées par DAIR – 21,6% d'échec
74% sous RMP, 44% sous RMP+FQ





Quel timing ? Quelle durée ?

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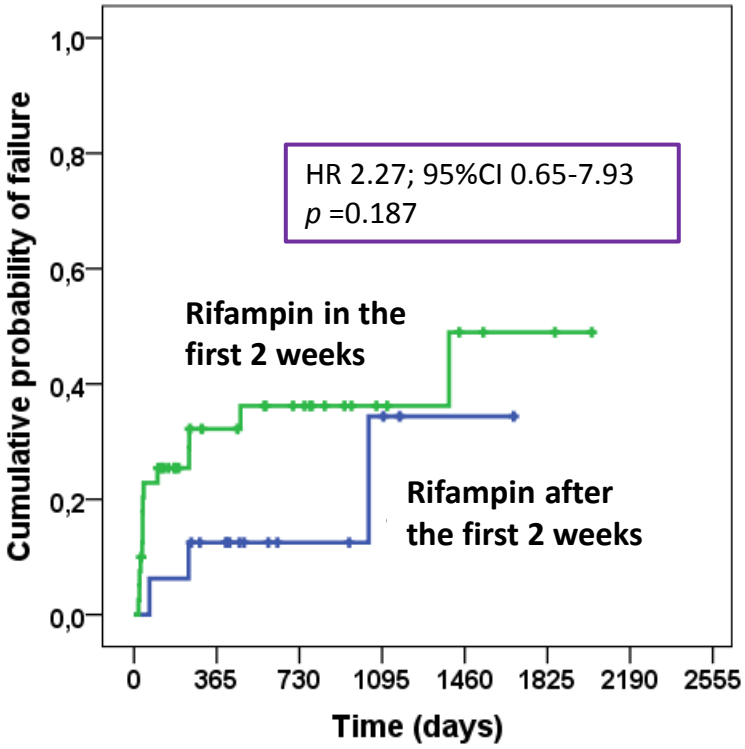
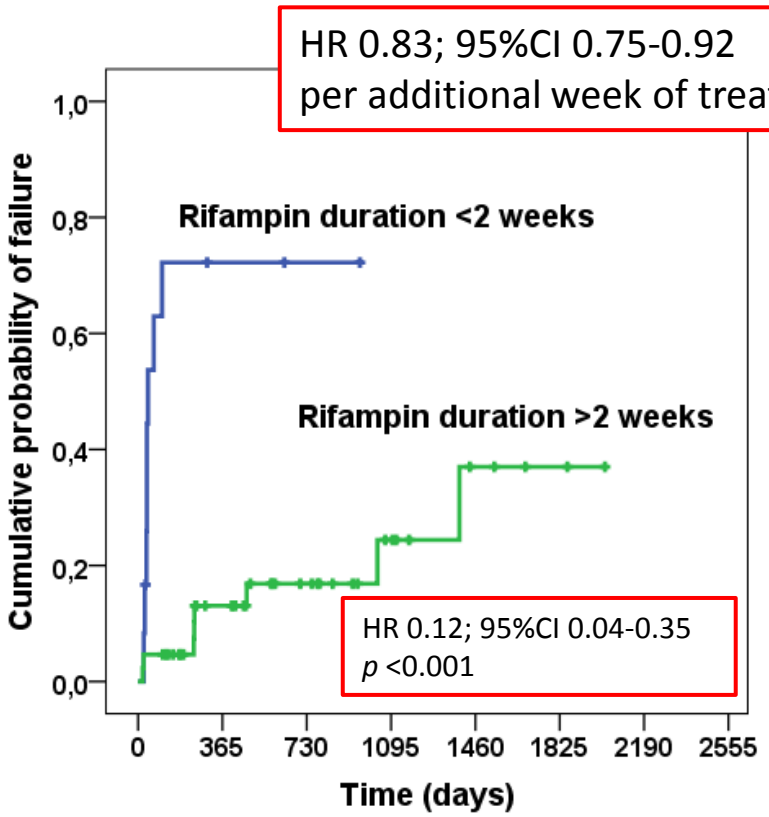




Quel timing ? Quelle durée ?

European Journal of Clinical Microbiology & Infectious Diseases
https://doi.org/10.1007/s10096-018-3330-7

ORIGINAL ARTICLE

Should we expand the indications for the DAIR (debridement, antibiotic therapy, and implant retention) procedure for *Staphylococcus aureus* prosthetic joint infections? A multicenter retrospective study

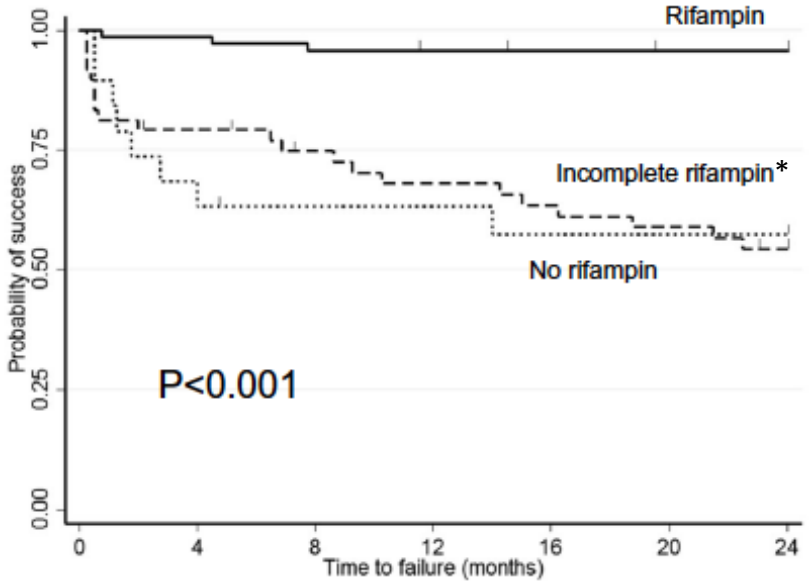
O. Lesens[1,2] · T. Ferry[3] · E. Forestier[4] · E. Botelho-Nevers[5] · P. Pavese[6] · E. Piet[7] · B. Pereira[8] · E. Montbarbon[9] · B. Boyer[10] · S. Lustig[3] · S. Descamps[11,12] · on behalf of the Auvergne-Rhône-Alpes Bone and Joint Infections Study Group

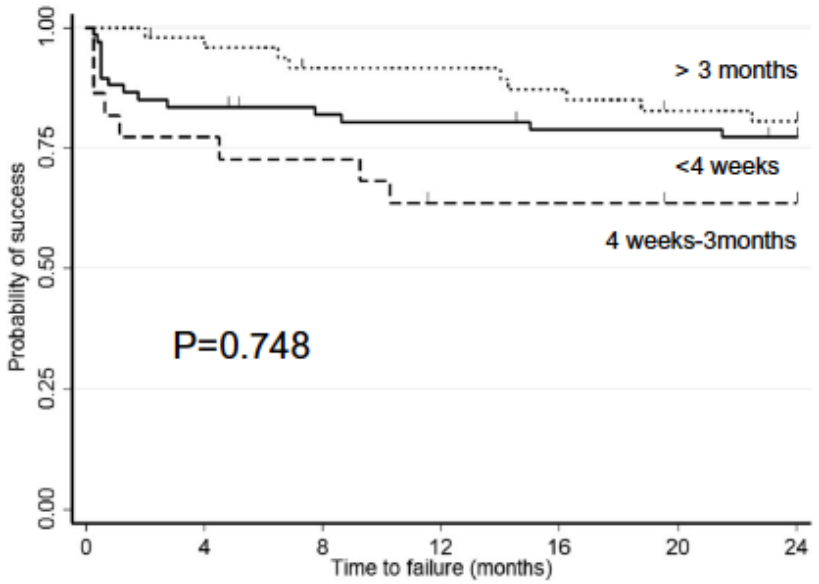
137 SA PJI (SARM 20%) traitées par DAIR
RMP : 65%
Succès à 2 ans : 76%

	Onset of infection < 3 months $n = 89$		All patients $n = 137$	
Variables	HR [95% CI]	p	HR [95% CI]	p
Incomplete rifampin regimen*	0.5 [0.16–1.6]	0.248	0.5 [0.2–1.28]	0.151
Complete rifampin regimen	0.16 [0.03–0.82]	0.028	0.08 [0.018–0.36]	0.001
Treatment duration	0.76 [0.66–0.89]	0.001	0.78 [0.69–0.88]	< 0.001
Active smoking	3.29 [0.8–13.41]	0.097	3.6 [1.09–11.84]	0.036
Early acute	0.25 [0.09–0.7]	0.009	–	–

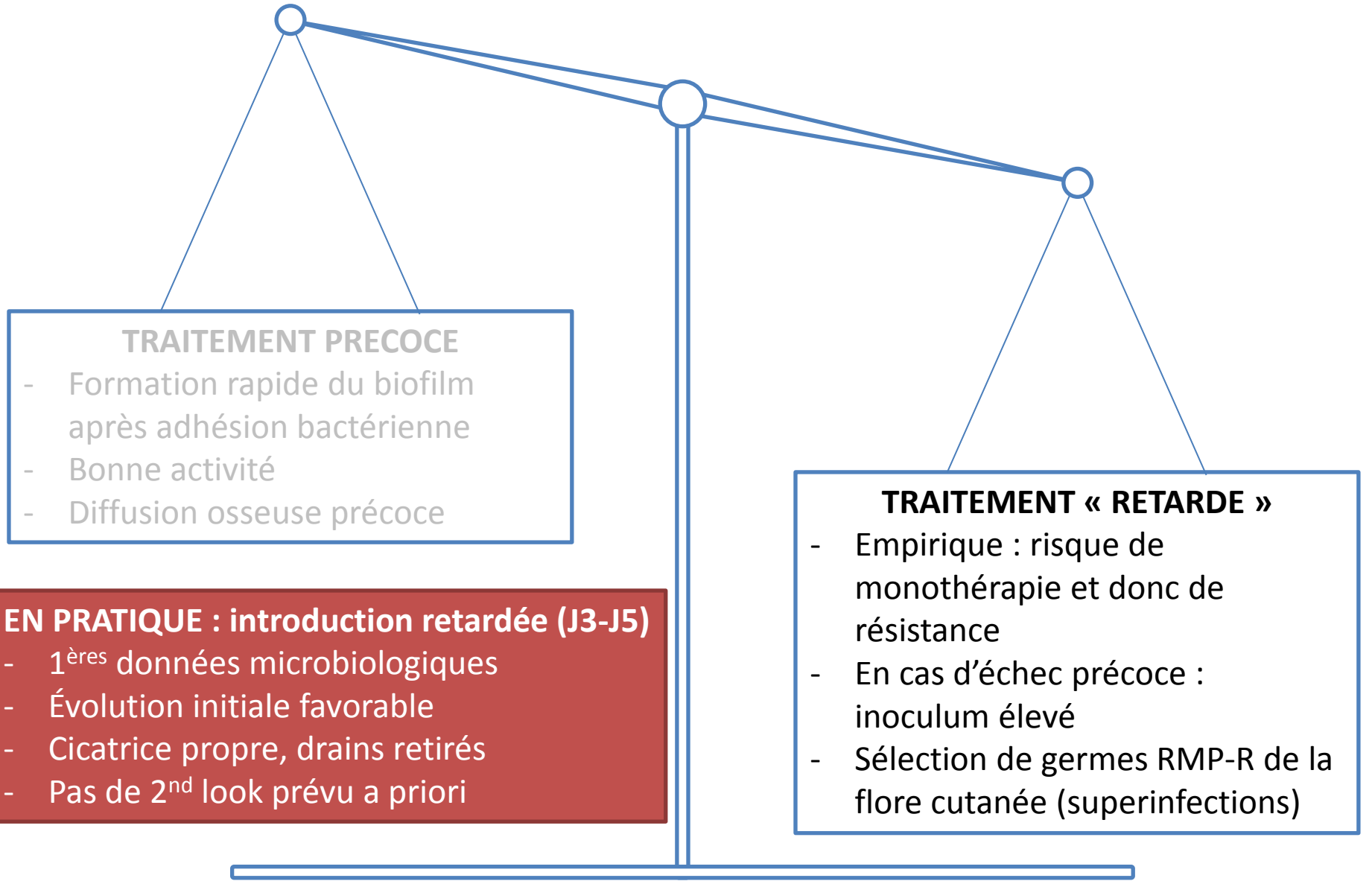
Courbe ROC :
durée optimale RMP de 10.5 sem

* < 3 sem





Quel timing ? Quelle durée ?



TRAITEMENT PRECOCE

- Formation rapide du biofilm après adhésion bactérienne
- Bonne activité
- Diffusion osseuse précoce

EN PRATIQUE : introduction retardée (J3-J5)

- 1ères données microbiologiques
- Évolution initiale favorable
- Cicatrice propre, drains retirés
- Pas de 2nd look prévu a priori

TRAITEMENT « RETARDE »

- Empirique : risque de monothérapie et donc de résistance
- En cas d'échec précoce : inoculum élevé
- Sélection de germes RMP-R de la flore cutanée (superinfections)

Saginur et al, AAC 2006 – Svensson et al, JAC 1997 – Valentin et al, J Infect 201 – Achermann et al, Infection 2013

Quel compagnon ?

FLUOROQUINOLONES

International Orthopaedics (SICOT) (2015) 39:1785–1791
DOI 10.1007/s00264-015-2819-2

ORIGINAL PAPER

Predictors of treatment outcome in prosthetic joint infections treated with prosthesis retention

Ari-Pekka Puhto[1] · Teija Puhto[2] · Tuukka Niinimäki[1] · Pasi Ohtonen[3] · Juhana Leppilahti[1] · Hannu Syrjälä[2]

113 PJI aiguës
66 SA et SCN

- RMP + ciprofloxacine (n=23)
- RMP + autres que FQ (n=29) : HR 6
- Pas de RMP (n=14) : HR 14.4

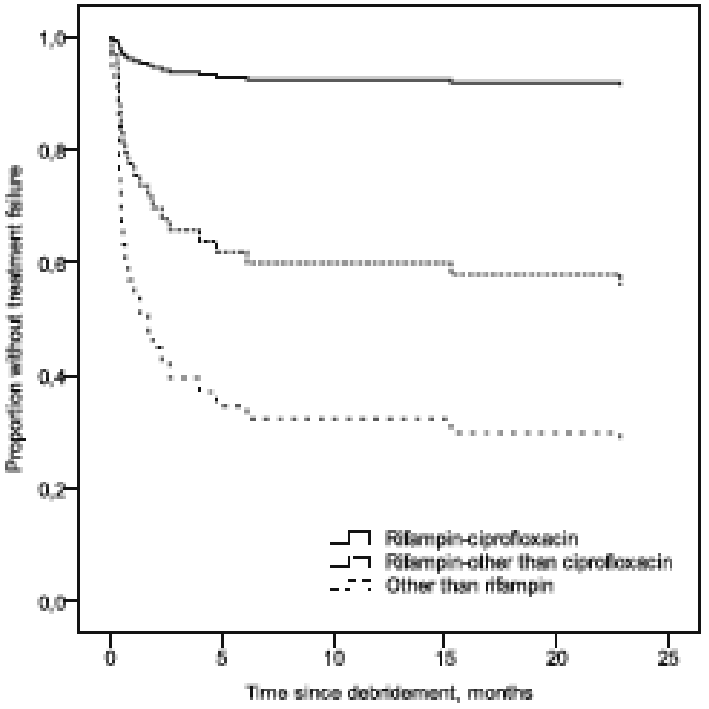


Fig. 3 Survival curves for staphylococcal prosthetic joint infections (PJIs) based on antibiotic treatment group

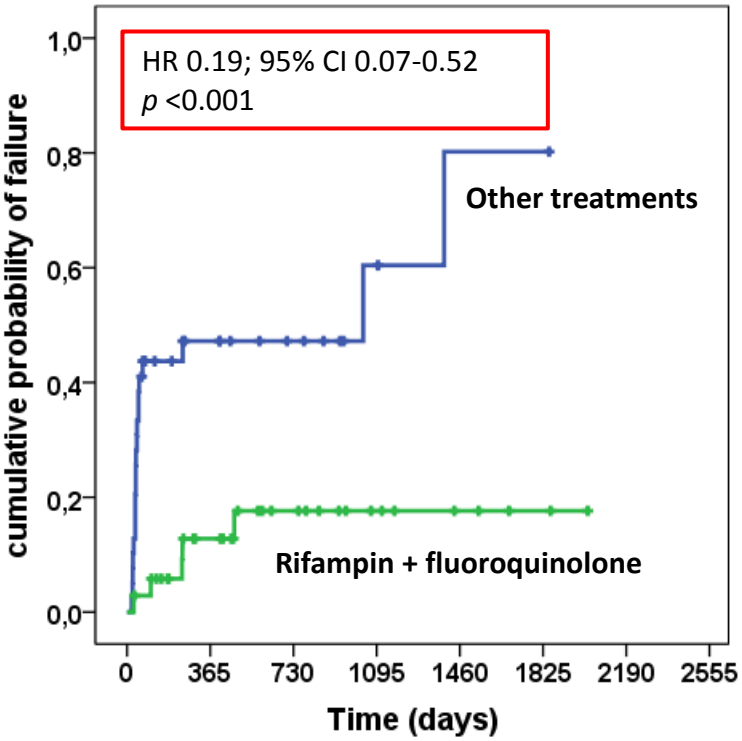
Quel compagnon ?

FLUOROQUINOLONES

2018

Staphylococcal acute post-operative PJI treated with DAIR and impact of rifampin: a retrospective cohort study in France

A. Becker, C. Triffault-Fillit, E. Forestier, O. Lesens, C. Cazorla, S. Descamps, B. Boyer, C. Chidiac, and T. Ferry on behalf of the IPASTAPH Study Group



Quel compagnon ?

FLUOROQUINOLONES

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 1993, p. 1214–1218 Vol. 37, No. 6
0066-4804/93/061214-05$02.00/0

Oral Rifampin plus Ofloxacin for Treatment of *Staphylococcus*-Infected Orthopedic Implants

MICHEL DRANCOURT,[1] ANDREAS STEIN,[1] JEAN NOEL ARGENSON,[2] ARNOLD ZANNIER,[1] GEORGES CURVALE,[3] AND DIDIER RAOULT[1]*

Moxifloxacin plus rifampin as an alternative for levofloxacin plus rifampin in the treatment of a prosthetic joint infection with *Staphylococcus aureus*

Marjan Wouthuyzen-Bakker [a,*], Eduard Tornero [b], Laura Morata [c], Prashant V. Nannan Panday [d], Paul C. Jutte [e], Guillem Bori [f], Greetje A. Kampinga [g], Alex Soriano [c]

Molécule	Dose PO (mg)	Pos. /j	C_{max} (mg/l)	BD orale (%)	t1/2 (h)	Vd (l/kg)	E. rénale (%)
Norfloxacine	400	2 x	1.6	50%	4-5	1.5	25-40
Pefloxacine	400	2 x	4.6	>90%	10	1.5-2.0	30-60
Ciprofloxacine	500	2 x	1.5	60-80%	3-5	2.5-5.0	30-50
Ofloxacine	400	2 x	3.1	85-95%	5-7	1.2	70-85
Levofloxacine	500	1 x	8.7	>90%	6-8	0.5	85-90
Moxifloxacine	400	1 x	3.6	90%	10	2	20-30

LEVOFLOXACINE

- 1 prise par jour
- CMI plus basses
- Diffusion tissulaire élevée

RECOMMENDED ORAL COMPANION DRUGS : CIPROFLOXACINE (AI) or LEVOFLOXACINE (AII)

Quel compagnon ?

DAPTOMYCINE

Nombreuses études animales
Supériorité daptomycine à forte dose (8-10 mg/kg) + RMP

Saleh-Mghir et al, AAC 2011 – Garrigos et al, AAC 2010
El Haj et al, IJAA 2015 – Stewart et al, AAC 2009

High doses of daptomycin (10 mg/kg/d) plus rifampin for the treatment of staphylococcal prosthetic joint infection managed with implant retention: a comparative study

Jaime Lora-Tamayo [a,*], Jorge Parra-Ruiz [b], Dolors Rodríguez-Pardo [c], José Barberán [d], Alba Ribera [a], Eduardo Tornero [e], Carles Pigrau [c], José Mensa [f], Javier Ariza [a], Alex Soriano [f]

Cas-témoins historique

18 PJI aiguës post-opératoires à SA FQ-R traitées par DAIR et dapto (10 mg/kg/j) – RMP
44 contrôles : PJI à SA FQ-R traitées par RMP + autre

- Outcome clinique et microbiologique similaire
- Echec clinique sous traitement inférieur dans le groupe DPT-RMP (22 *vs* 73%)

Quel compagnon ?

LINEZOLIDE

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[3], 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]

94 patients, LNZ > 4 sem
RMP protecteur / anémie : 9% vs 44%
Pas de différence d'outcome

Infect Dis Ther (2014) 3:235–243
DOI 10.1007/s40121-014-0032-z

ORIGINAL RESEARCH

A Retrospective Review of the Clinical Experience of Linezolid with or Without Rifampicin in Prosthetic Joint Infections Treated with Debridement and Implant Retention

Laura Morata · Eric Senneville · Louis Bernard · Sophie Nguyen · Rodolphe Buzelé · Jérome Druon · Eduard Tomero · Josep Mensa · Alex Soriano

Characteristics	Receiving rifampicin (n = 22)	Not receiving rifampicin (n = 17)	P
Outcome (%)			
Remission	14 (64)	14 (82)	0.28
Relapse	6 (27)	2 (12)	
New infection	2 (9)	1 (6)	

Decreased serum linezolid concentrations in two patients receiving linezolid and rifampicin due to bone infections

Irma Hoyo, Juan Martínez-Pastor, Sebastian Garcia-Ramiro, Consuelo Climent, Mercé Brunet, Marta Cuesta, Josep Mensa & Alex Soriano

Quel compagnon ?

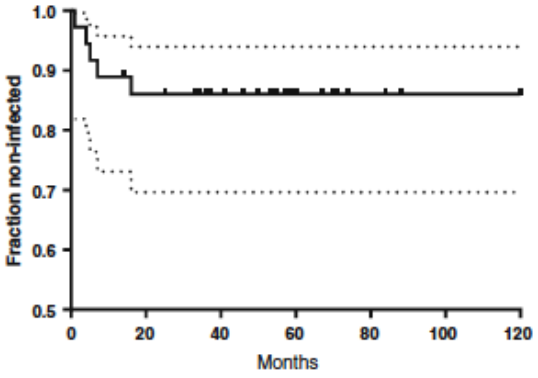
CLINDAMYCINE

	Clinda	Clinda + RMP	*p*-value	Association outcome	Ref
Cmin (mg/L)	1.52	0.46	0.034	non évalué, cure 92%	Zeller et al, AAC 2010
Cmin (mg/L)	4.7 +/- 1.2	0.79 +/- 0.3	0.001	NON	Curis et al, Infect 2015
Cmax (mg/L)	10.2 +/- 1.8	3.48 +/- 1.1	0.001	NON	Bernard et al, J Infect 2015

Clindamycin-rifampin combination therapy for staphylococcal periprosthetic joint infections: a retrospective observational study

Borg Leijtens[1*], Joris B. W. Elbers[1], Patrick D. Sturm[2], Bart Jan Kullberg[3] and Berend W. Schreurs[1]

BMC Infect dis 2017



36 patients
86% cure rate
14% effets IIR

Eur J Clin Microbiol Infect Dis (2017) 36:2513–2518
DOI 10.1007/s10096-017-3094-5

ORIGINAL ARTICLE

Efficacy and safety of clindamycin-based treatment for bone and joint infections: a cohort study

J. Courjon[1,2] · E. Demonchy[1] · E. Cua[1] · E. Bernard[1] · P.-M. Roger[1,2]

196 BJI, 80 ODI

Antibiotic regimen		Success (%),	Failure (%),	*p-value*	AOR
Clindamycin + fluroquinolones	81.6%	44 (40)	2 (9)	**0.012**	5.35 [1.16–24.55]
Clindamycin + rifampicin	**81.4%**	22 (25)	5 (23)	0.804	
Clindamycin + others[b]	71.4%	15 (13)	6 (27)	0.138	
Clindamycin + amoxicillin	72.7%	8 (7)	3 (14)	0.562	
Clindamycin alone	71.4%	15 (13)	6 (27)	0.105	

Quel compagnon ?

ACIDE FUSIDIQUE

Outcome of Debridement and Retention in Prosthetic Joint Infections by Methicillin-Resistant Staphylococci, with Special Reference to Rifampin and Fusidic Acid Combination Therapy

T. N. Peel,[a,b] K. L. Buising,[a] M. M. Dowsey,[b,c] C. A. Aboltins,[a] J. R. Daffy,[a] P. A. Stanley,[a] P. F. M. Choong[b,c]

AAC 2012

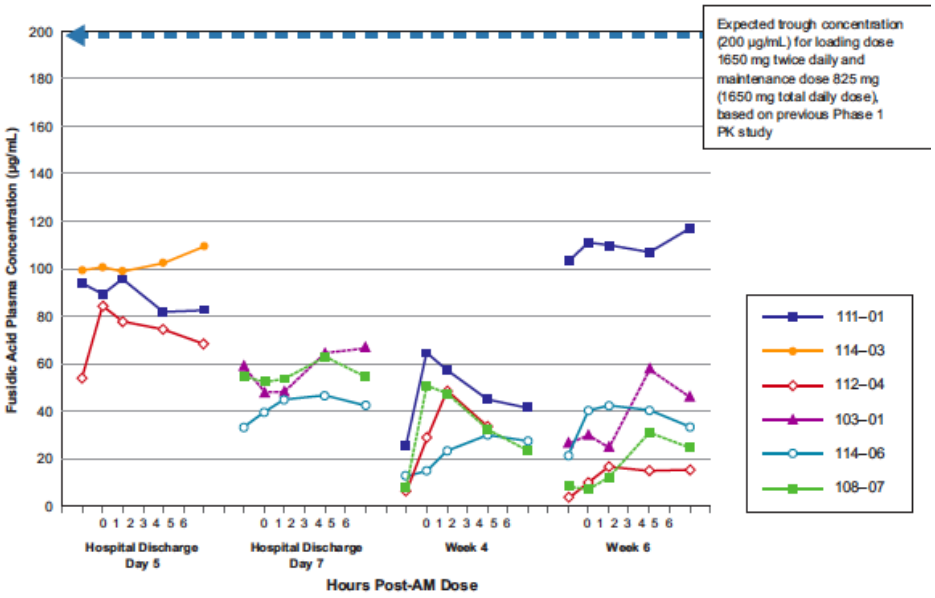
43 patients, dont 38 sous RMP - FUCI
9 échecs, dont 8 sous RMP - FUCI
4 échecs avec persistance du MRSA/MRCoNS
3 acquisition de résistance à RMP et FUCI

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

Richard Pushkin,[1] Maria D. Iglesias-Ussel,[1,2] Kara Keedy,[1] Chris MacLauchlin,[1] Diane R. Mould,[3] Richard Berkowitz,[4] Stephan Kreuzer,[5] Rabih Darouiche,[6] David Oldach,[1] and Prabha Fernandes[1]

CID 2016

14 patients randomisés, 6 RMP-FUCI
[C] FUCI -45% à S6
3 échecs dans le groupe RMP-FUCI
(1 effet secondaires, 2 persistances infection)



British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2017) **83** 1039–1047 1039

Population pharmacokinetics of rifampicin in adult patients with osteoarticular infections: interaction with fusidic acid

Amélie Marsot[1,2], Amelie Ménard[3], Julien Dupouey[1,2], Cedric Muziotti[1], Romain Guilhaumou[1,2] and Olivier Blin[1,2]

Elévation des [C] de RMP
parfois supra-toxiques

Quel compagnon ?

- Absence d'antagonisme
- Bonne diffusion tissulaire
- Mode d'action différent
- Faible interaction avec la rifampicine

EN PRATIQUE : RIFAMPICINE + …

1e choix :
- CIPROFLOXACINE (A-I) ou LEVOFLOXACINE (A-II)

2e choix :
- COTRIMOXAZOLE (A-II)
- DOXYCYCLINE (B-III)
- BETA-LACTAMINE anti-staphylococcique (C-III)

Pas d'acide fusidique
Pas de clindamycine ?

Rifampicine et IOA non staphylococciques

IOA streptococciques

Outcome of patients with streptococcal prosthetic joint infections with special reference to rifampicin combinations

E. Riaux[1], M. Titecat[2], O. Robineau[3], J. Loza-Tamayo[4], Y. El Samad[5], M. Etienne[1], N. Frebourg[6], N. Blondiaux[7], B. Brunschweiler[8], F. Dujardin[9], E. Beltrand[10], C. Loiez[2], V. Cattoir[11], J P. Canarelli[8], C. Hulet[12], M. Valette[3], S. Nguyen[3], F. Caron[1], H. Migaud[13], and E. Senneville[3,14*] on behalf of the G4 bone and joint infection study group (G4BJIS)

Table 3 Outcome of 95 episodes of streptococcal prosthetic joint infections; univariate analysis

Variables	Remission ($n = 67$)	Failure ($n = 28$)	p
Age > 70 years	35 (36.8 %)	11 (39.3 %)	.25
≥1 comorbidity	46 (68.7 %)	24 (85.7 %)	.09
Total hip arthroplasty	40 (42.1 %)	10 (35.7 %)	.03
Type of infection (early/delayed/late)	20 (29.8 %)/18 (26.9 %)/29 (43.3 %)	11 (39.3 %)/7 (25 %)/10 (35.7 %)	.19
Fever	35 (36.8 %)	17 (60.7 %)	.45
CRP in mg/L, mean value ± SD	154.6 ± 121.9	207.2 ± 148.3	.09
S. agalactiae (group B streptococci)	27 (28.4 %)	10 (35.7 %)	.68
Antibiotic treatment prior to admission	18 (18.9 %)	8 (28.6 %)	.86
Sinus tract	15 (15.8 %)	3 (10.7 %)	.18
Concomitant bacteremia at the time of diagnosis	11 (16.4 %)	8 (28.6 %)	.18
DAIR	32 (33.7 %)	23 (82.1 %)	.002
Primary arthroplasty	53 (79.1 %)	20 (71.4 %)	.42
Hematogenous origin	10 (14.9 %)	8 (28.6 %)	.12
Rifampicin based combinations	44 (46.3 %)	8 (28.6 %)	.001
Rifampicin + levofloxacin	24 (25.2 %)	4 (14.3 %)	.04

IOA streptococciques

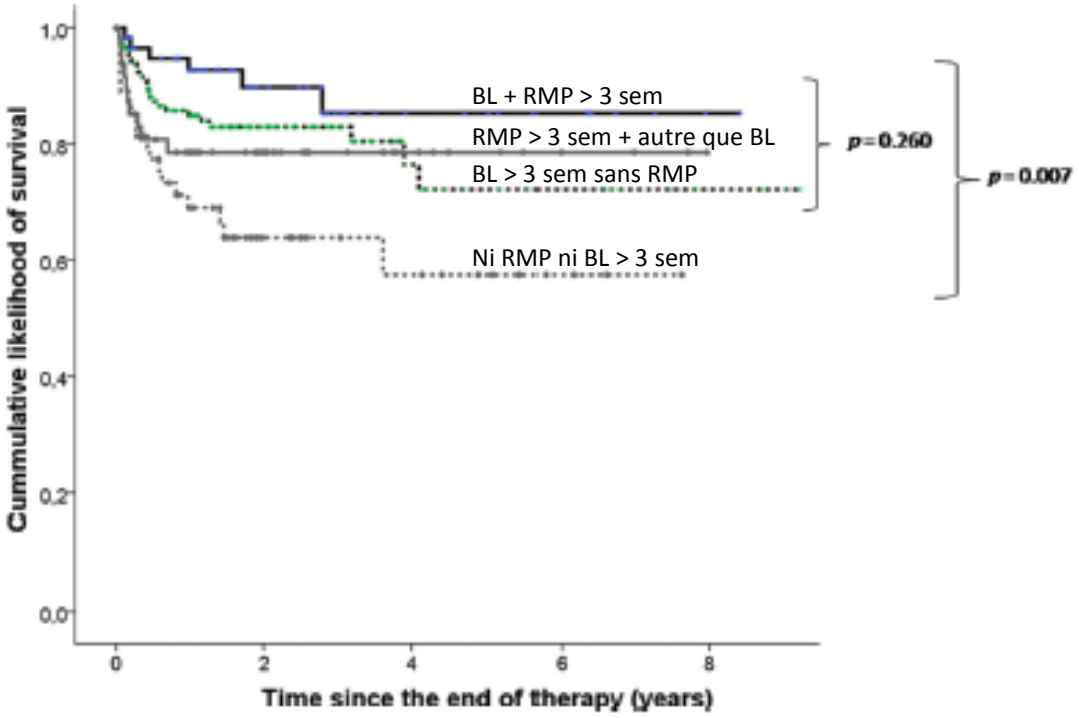
The Not-So-Good Prognosis of Streptococcal Periprosthetic Joint Infection Managed by Implant Retention: The Results of a Large Multicenter Study

Jaime Lora-Tamayo,[1,2] Éric Senneville,[3] Alba Ribera,[2,4,5] Louis Bernard,[6,7] Michel Dupon,[8] Valérie Zeller,[9] Ho Kwong Li,[5] Cédric Arvieux,[7,10] Martin Clauss,[11] Ilker Uçkay,[12] Dace Vigante,[13] Tristan Ferry,[14] José Antonio Iribarren,[15] Trisha N. Peel,[16] Parham Sendi,[17] Nina Gorišek Miksić,[18] Dolors Rodríguez-Pardo,[2,19] María Dolores del Toro,[2,20] Marta Fernández-Sampedro,[2,21] Ulrike Dapunt,[22] Kaisa Huotari,[23] Joshua S. Davis,[24] Julián Palomino,[2,20] Danielle Neut,[25] Benjamin M. Clark,[26] Thomas Gottlieb,[27] Rihard Trebše,[28] Alex Soriano,[2,29,30] Alberto Bahamonde,[31] Laura Guío,[2,32] Alicia Rico,[33] Mauro J. C. Salles,[34] M. José G. Pais,[35] Natividad Benito,[2,36] Melchor Riera,[2,37] Lucía Gómez,[38] Craig A. Aboltins,[39] Jaime Esteban,[40] Juan Pablo Horcajada,[41] Karina O'Connell,[42] Matteo Ferrari,[43] Gábor Skaliczki,[44] Rafael San Juan,[1,2] Javier Cobo,[2,45] Mar Sánchez-Somolinos,[2,46] Antonio Ramos,[47] Efthymia Giannitsioti,[48] Alfredo Jover-Sáenz,[49] Josu Mirena Baraia-Etxaburu,[50] José María Barbero,[51] Peter F. M. Choong,[52] Nathalie Asseray,[7,53] Séverine Ansart,[7,54] Gwenäel Le Moal,[7,55] Werner Zimmerli,[11] and Javier Ariza[2,4]; for the Group of Investigators for Streptococcal Prosthetic Joint Infection*

462 PJI
34% *S. agalactiae*
Beta-lactamines +++
37% rifampicine

Echec (42.1%)
- PR
- Infection post-opératoire tardive
- Bactériémie

Succès
- Changement des pièces mobiles
- **Rifampicine (0.98 / jour dans les 30 premiers jours)**
- **Béta-lactamine > 3 sem en monothérapie (0.48) ou avec RMP (0.34)**



IOA streptococciques

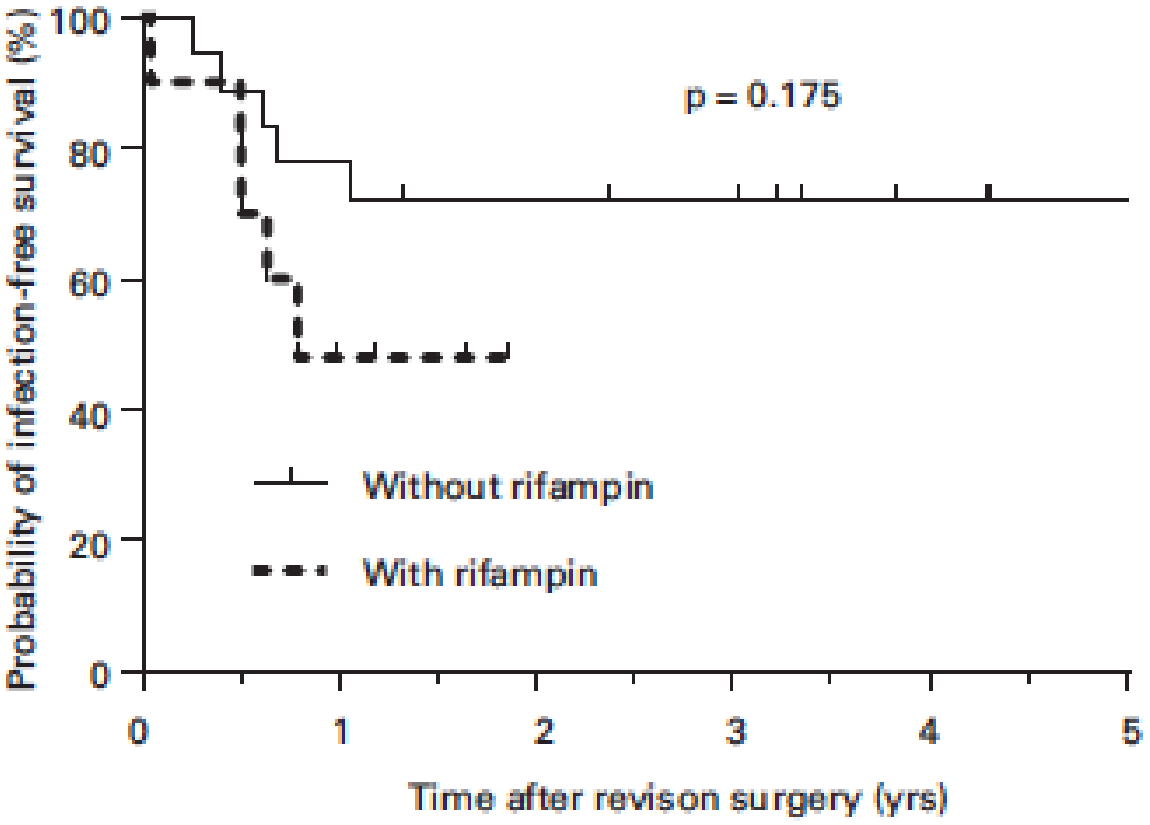
THE BONE & JOINT JOURNAL

■ ARTHROPLASTY

High failure rates in treatment of streptococcal periprosthetic joint infection

RESULTS FROM A SEVEN-YEAR RETROSPECTIVE COHORT STUDY

D. Akgün,
A. Trampuz,
C. Perka,
N. Renz



30 patients
40% *S. agalactiae*
10% RMP-based

IOA à entérocoque

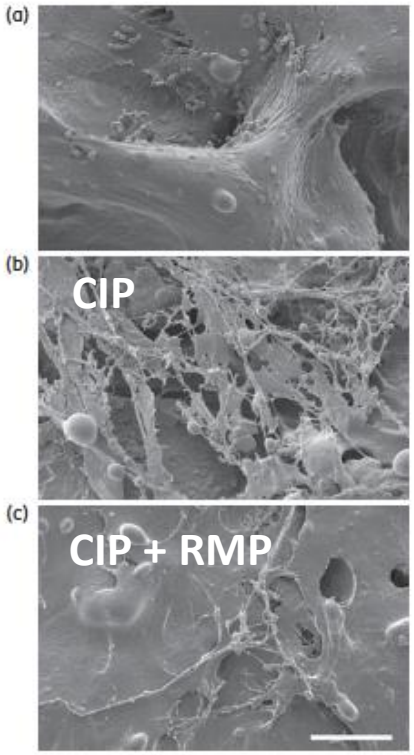
J Antimicrob Chemother 2012; **67**: 433–439
doi:10.1093/jac/dkr477 Advance Access publication 22 November 2011

Journal of Antimicrobial Chemotherapy

Effectiveness of ciprofloxacin or linezolid in combination with rifampicin against *Enterococcus faecalis* in biofilms

Anna Holmberg*, Matthias Mörgelin and Magnus Rasmussen

Bonne action anti-biofilm
+ LNZ ou CIP



Antibiotic/combination	MIC (mg/L), median (range)	MBEC (mg/L), mode (range)
Ampicillin	0.5 (0.25–2)	256 (128–512)
Ampicillin/rifampicin		↓ 64 (32–256)
Vancomycin	2 (2–4)	256 (256–512)
Vancomycin/rifampicin		↓ 64 (32–256)
Linezolid	1 (0.5–2)	128 (64–256)
Linezolid/rifampicin		↓ 64 (32–64)
Ciprofloxacin	2 (1–>16)	256 (256)
Ciprofloxacin/rifampicin		↓ 32 (16–32)
Rifampicin	1 (0.5–8)	128 (64–128)

IOA à entérocoque

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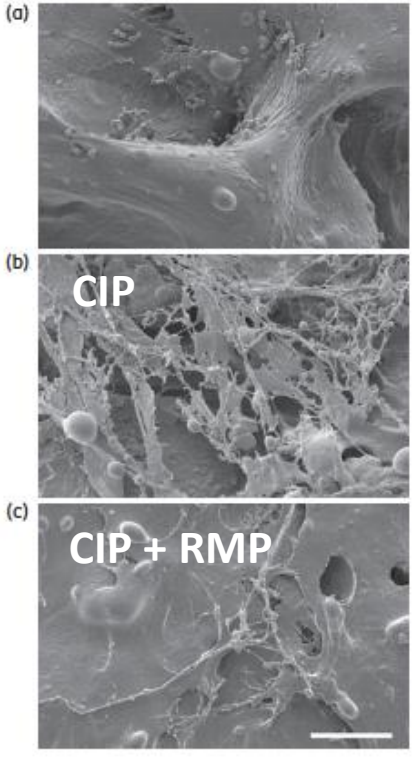


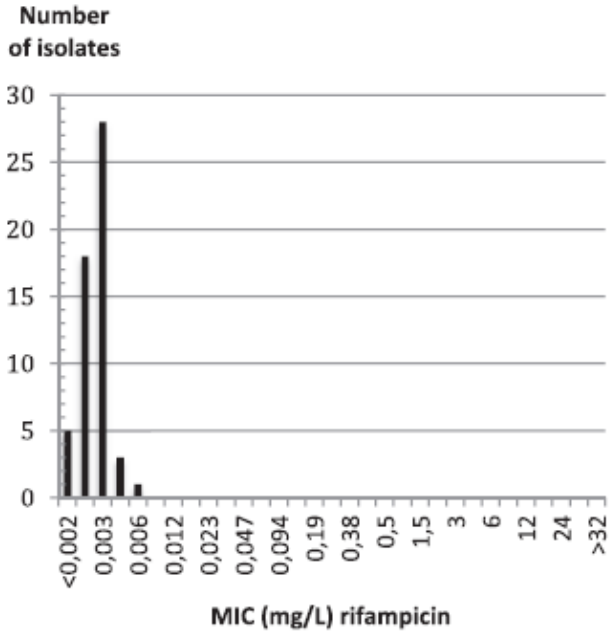
Characteristics of prosthetic joint infections due to *Enterococcus* sp. and predictors of failure: a multi-national study

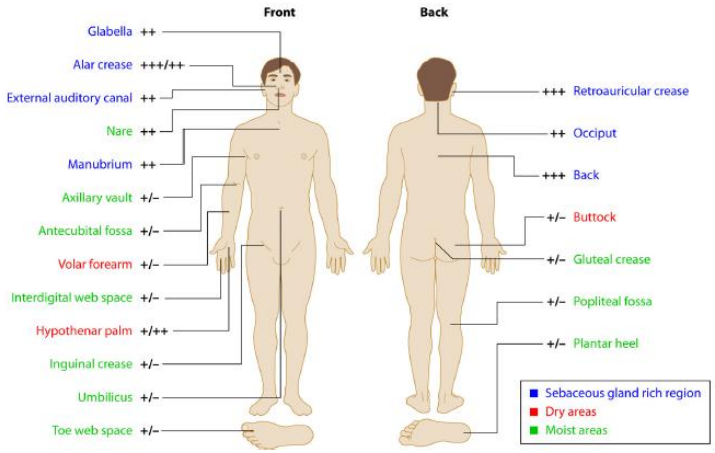
E. Tornero[1], E. Senneville[2], G. Euba[3], S. Petersdorf[4], D. Rodriguez-Pardo[5], B. Lakatos[6], M. C. Ferrari[7], M. Pilares[8], A. Bahamonde[9], R. Trebse[10], N. Benito[11], L. Sorli[12], M. D. del Toro[13], J. M. Baraiaetxaburu[14], A. Ramos[15], M. Riera[16], A. Jover-Sáenz[17], J. Palomino[18], J. Ariza[3] and A. Soriano[1] on behalf of the European Society Group of Infections on Artificial Implants (ESGIAI)

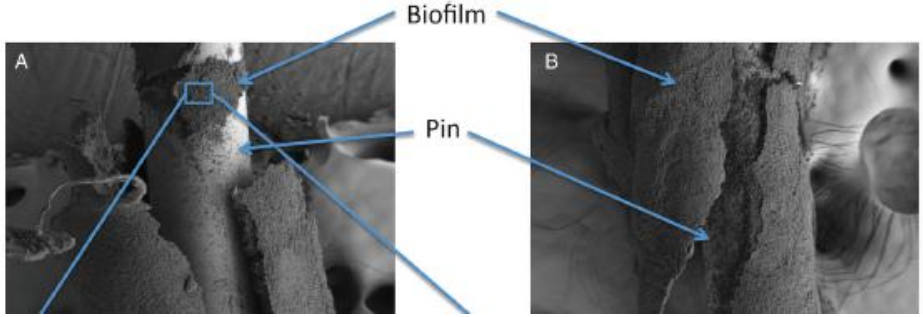
Age of implant at the moment of infection	Type of antibiotic	Remission (%)	Failure (%)	p value
≤30 days	Vancomycin	9 (36)	16 (64)	0.41
	Ampicillin	6 (40)	9 (60)	1
	Rifampin[a,b]	12 (60)	8 (40)	0.04
	Aminoglycoside[a]	3 (30)	7 (70)	0.49
	Linezolid	4 (80)	1 (20)	0.15
	Daptomycin	0	1	1
>30 days	Vancomycin	37 (65)	20 (35)	0.60
	Ampicillin	30 (67)	15 (33)	0.49
	Rifampin[a]	35 (58)	25 (42)	0.31
	Aminoglycoside[a]	20 (54)	17 (46)	0.20
	Linezolid	6 (46)	7 (54)	0.22
	Daptomycin	3 (43)	4 (57)	0.42

IOA à *Cutibacterium* (ex-*Propionibacterium*) *acnes*

- Cause fréquente de PJI (épaule)
- Sensibilité à la RMP







- Sécrétion d'adhésines, formation de biofilm
- Sensibilité diminuée des souches en biofilm
- MBEC RMP la plus faible *in vitro*

Parameter	Value (μg/ml)[a]						
	Rifampin	Daptomycin	Levofloxacin	Vancomycin	Clindamycin	Penicillin G	Ceftriaxone
MIC	0.007	1	1	1	0.125	0.03	0.25
MBC	4	4	2	8	512	16	32
MBC/MIC ratio	57	4	2	8	4,096	5,333	128
MBEC	16	64	512	512	128	32	64

Furustrand et al. AAC 2012

… mais pas de synergie *in vitro* (planctonique)

Antimicrobial combination	Number (%) of isolates			
	Synergism	Additive	Indifference	Antagonism
RI+PG	0	23 (42%)	32 (58%)	0
RI+CM	0	0	55 (100%)	0
RI+MZ	0	13 (24%)	41 (75%)	1 (2%)
RI+FU	0	8 (15%)	44 (80%)	3 (5%)
RI+DC	0	4 (7%)	49 (89%)	2 (4%)
RI+MX	0	10 (18%)	44 (80%)	1 (2%)
RI+LZ	0	7 (13%)	46 (87%)	2 (4%)

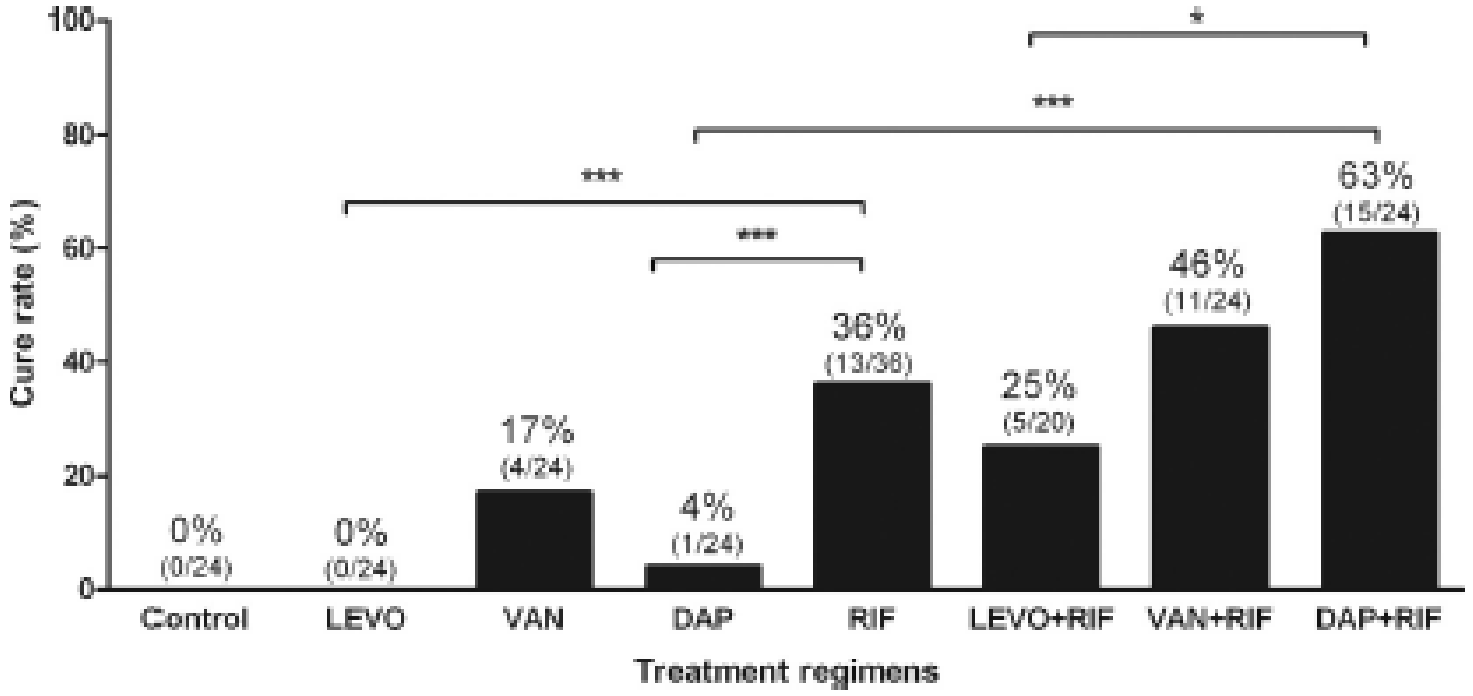
Khassebaf et al. Anaerobe 2014

IOA à *Cutibacterium* (ex-*Propionibacterium*) *acnes*

AAC Journals.ASM.org *2012*

Role of Rifampin against *Propionibacterium acnes* Biofilm *In Vitro* and in an Experimental Foreign-Body Infection Model

Ulrika Furustrand Tafin,[a] Stéphane Corvec,[a,b] Bertrand Betrisey,[a] Werner Zimmerli,[c] and Andrej Trampuz[a]



Pas d'évaluation BL + RMP

IOA à *Cutibacterium* (ex-*Propionibacterium*) *acnes*

Characteristics and Treatment Outcomes of *Propionibacterium acnes* Prosthetic Shoulder Infections in Adults

Damani A. Piggott,[1,4] Yvonne M. Higgins,[1] Michael T. Melia,[1] Brandon Ellis,[5] Karen C. Carroll,[1,2] Edward G. McFarland,[3] and Paul G. Auwaerter[1,5]

OFID 2015

Etude rétrospective
24 PJI épaule
15 sous RMP

Treatment	Total Treated No. (%)	Favorable Outcome[a] No. (%)
Type of treatment*		
Antibiotic therapy only	7 (29)[b]	4 (67)
Antibiotic therapy + surgery	14 (58)	10 (71)
Surgical type*		
1-stage exchange	4 (27)[c]	3 (75)
2-stage exchange	7 (47)	6 (86)
Rifampin therapy*		
Yes	15 (71)[d]	11 (73)
No	5 (24)	3 (60)

P=0.61

mais 40% d'arrêt prématuré de RMP / effets secondaires

IOA à *Cutibacterium* (ex-*Propionibacterium*) *acnes*

60 *Acta Orthopaedica* 2016; 87 (1): 60–66

Treatment of prosthetic joint infections due to *Propionibacterium*

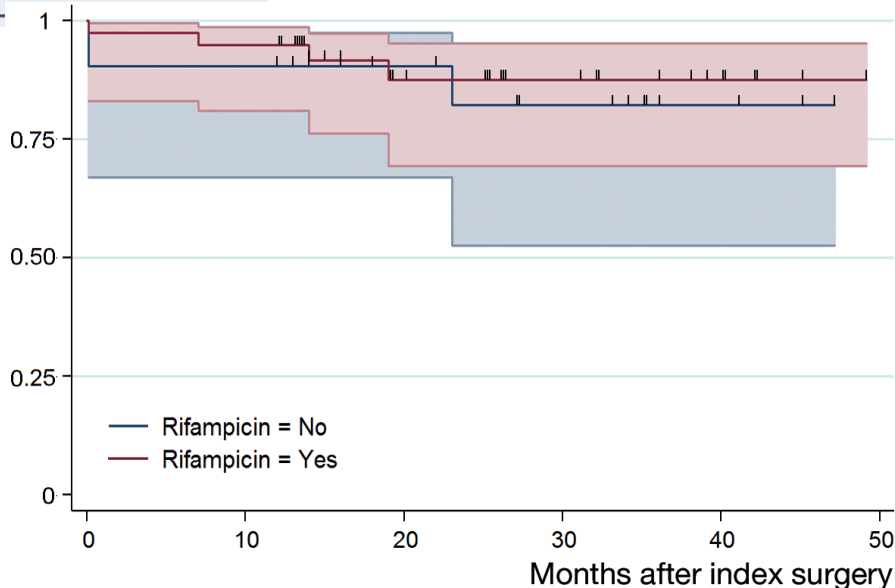
Similar results in 60 patients treated with and without rifampicin

Anouk M E JACOBS [1], Miranda L VAN HOOFF [2], Jacques F MEIS [3,4], Fidel VOS [5], and Jon H M GOOSEN [1]

Etude rétrospective
60 patients avec PJI
39 sous RMP + clinda (n=33)
+ téico (n=6)

vs.21 sans RMP

Characteristic	Rifampicin (n = 39)	No rifampicin (n = 21)	Total group (n = 60)	p-value
Failures				
1-year follow-up	2/39	2/21	4/60	0.7
2-year follow-up	4/23	3/13	7/36	0.6
Survival, median (range), months	19 (0.1–49)	23 (0.2–47)	21 (0.1–49)	0.9
Type of failure				
Relapse [a]	2	2	4	0.4
Reinfection [b]	2	1	3	0.5



IOA à corynébactéries

Take-home messages

Synthèse

IOA à *S. aureus* / matériel traitées par DAIR … avec FQ

- ✓ SENSIBILITE *IN VITRO*
- ✓ DIFFUSION TISSULAIRE
- ✓ ACTION « ANTI-BIOFILM » (et intracellulaire)
- ✓ TOLERANCE
- ✓ ETUDES CLINIQUES

SCN

POSOLOGIE OPTIMALE

TIMING

IOA sans MATERIEL

Autres Gram +

Remerciements : Lyon BJI study group

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Pharmacologie – *Michel Tod, Marie-Claude Gagnieu, Sylvain Goutelle*

Attaché de recherche clinique – *Eugénie Mabrut*

Hospices Civils de Lyon

CRIOAc LYON

STAPHYLOCOQUES Centre National de Référence

ciri Centre International de Recherche en Infectiologie

UCBL