

Rifampicine dans le traitement des infections non staphylococciques à Gram positif de prothèse ostéo-articulaire

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Conflits potentiels d'intérêt

- BASILEA : orateur, support congrès
- BAYER : orateur, support congrès
- MSD : orateur, support congrès
- NOVARTIS Pharma : orateur, support congrès
- PFIZER : orateur, support congrès
- SANOFI-AVENTIS : orateur, support congrès

Rifampicine

1) Usage en routine en dehors des mycobactéries

- curatif :

spectre utile

. staphylocoques et autres cocci à Gram positif (streptocoques dont le pneumocoque)

. *Legionella pneumophila*

- préventif :

spectre utile

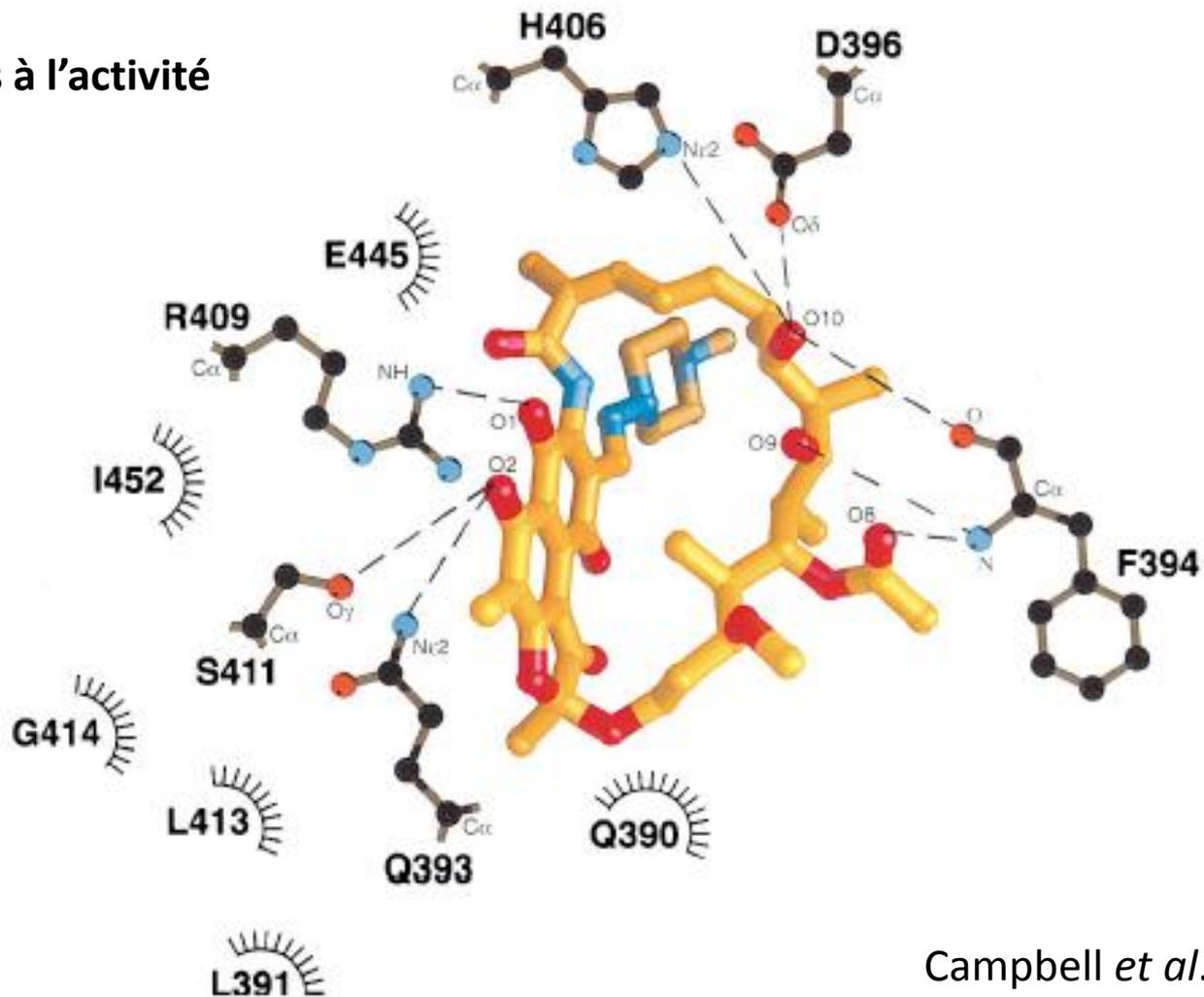
. méningocoque

Mode d'action

- action bactéricide concentration dépendante par fixation à la sous-unité B de l'ARN pol
- souches résistantes naturellement par mutation chromosomique
- **MONOTHERAPIE** proscrite en traitement curatif +++

Mécanisme d'action

5 liaisons H
indispensables à l'activité



Campbell *et al.*, Cell 2001
Korzheva *et al.*, Science 2000

Spectre antibactérien : cocci à Gram positif

- Staphylocoques



- *Staphylococcus aureus*

- CMI : 0,004 – 0,016 µg/mL (>90% sur 1154 isolats)

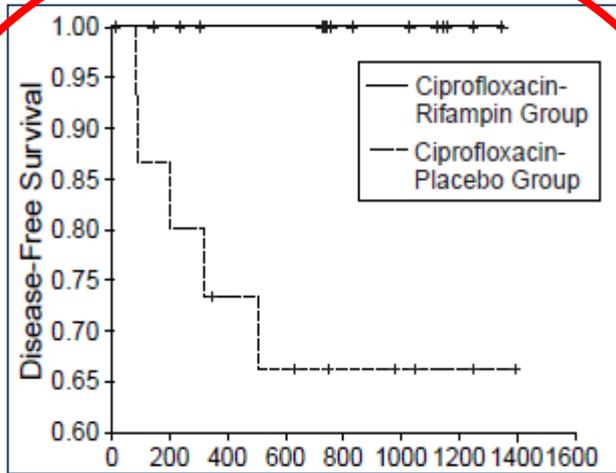
- Staphylocoques à coagulase négative (SCN)

- CMI : 0,004 – 0,064 µg/mL (>85% sur 697 isolats)

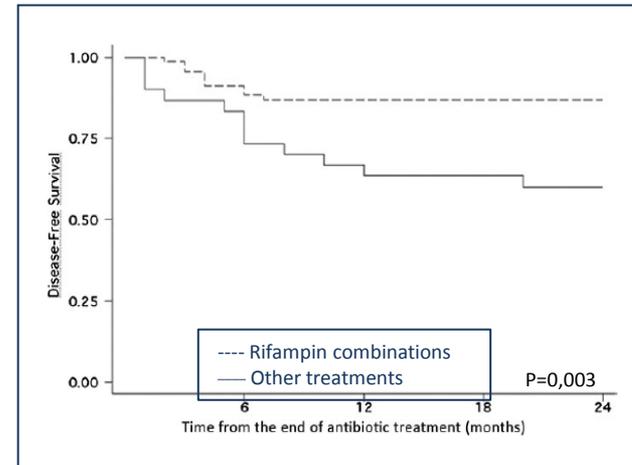
- Fortement bactéricide

- RIF = meilleur anti-staphylocoque contre les formes intracellulaires aux [c] thérapeutiques

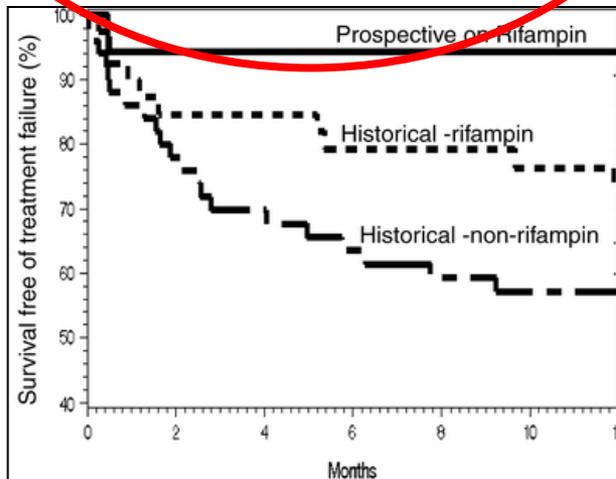
Rifampicine (en association) dans le traitement des IPOA à staphylocoques



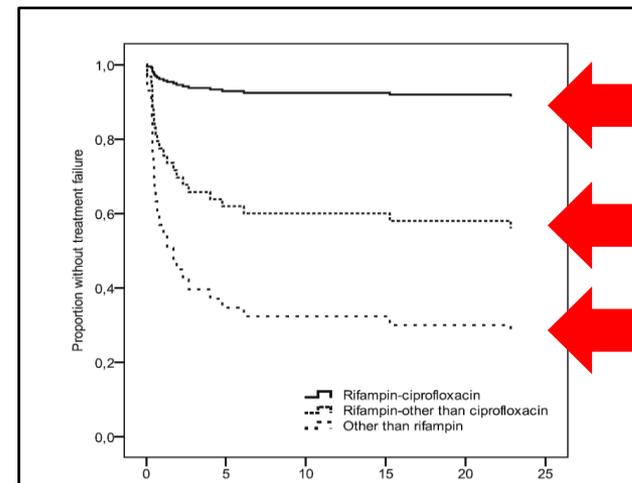
Zimmerli W *et al.* JAMA 1998



Senneville E *et al.* Clin Infect Dis 2011



El Helou OC *et al.* Eur J Clin Microbiol Infect Dis 2010



Puhto AP *et al.* Int Orthop 2015

Concentrations critiques

Micro-organismes	CA-SFM 2017 [c] critiques µg/mL
<i>Staphylococcus</i> spp.	0,06-0,5
<i>Streptococcus pneumoniae</i> , A,B,C,G, autres streptocoques	0,06-0,5
<i>Enterococcus faecalis</i>	1-2
<i>Propionibacterium</i> spp.	-----
corynébactéries	0,06-0,5

Non-staphylococciques

- *Streptococcus* spp.
- *Enterococcus* spp.
- *Propionibacterium* spp.
- (*Corynebacterium* spp.)

Recommandations de la SPILF

Streptocoques	Absence d'allergie à la pénicilline	Si allergie à la pénicilline
Antibiothérapie initiale par voie IV	amoxicilline + gentamicine ¹	clindamycine (si souche érythromycine sensible) + gentamicine ¹ ou céfazoline + gentamicine ¹ ou ceftriaxone + gentamicine ¹
Relais oral	amoxicilline ou clindamycine (si souche érythromycine sensible)	
Entérocoques		
Antibiothérapie initiale par voie IV	amoxicilline + gentamicine ¹ puis amoxicilline ± rifampicine	(vancomycine ² ou teicoplanine) + gentamicine ¹ puis (vancomycine ² ou teicoplanine) + rifampicine
Relais oral	amoxicilline ± rifampicine	Avis spécialisé
Anaérobies à Gram (+) (<i>P. acnes</i> , <i>Peptostreptococcus</i>)	amoxicilline ou céfazoline ou ceftriaxone ou clindamycine (si souche érythromycine sensible)	clindamycine

Recommandations de l'IDSA

Microorganism	Preferred Treatment ^a	Alternative Treatment ^a
<i>Propionibacterium acnes</i>	Penicillin G 20 million units IV q24 h continuously or in 6 divided doses or Ceftriaxone 2 g IV q24 h	Clindamycin 600–900 mg IV q8 h or clindamycin 300–450 mg PO qid or Vancomycin 15 mg/kg IV q12 h
<i>Enterococcus</i> 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
<i>Enterococcus</i> 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
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

Streptococcus spp.

Fiaux et al. *BMC Infectious Diseases* (2016) 16:568
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BMC Infectious Diseases

RESEARCH ARTICLE

Open Access

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



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Streptococcus spp.

Characteristics	No. of episodes (%)	Variables	No. of patients (%)
Joint		Age, years, mean \pm SD	69.1 \pm 13.7
Hip	50 (52.6)	BMI, kg/m ² , mean \pm SD	29.9 \pm 8.1
Knee	45 (47.4)	Sex ratio, Male/Female	0.85, 40/47
Type of infection		Comorbidities	
Early	31 (32.6)	Diabetes mellitus	31 (35.6)
Delayed	25 (26.3)	Rheumatoid polyarthritis	8 (9.1)
Late	39 (41.1)	Chronic renal disease	13 (14.9)
Hematogenous origin of the infection	18 (18.9)	Chronic liver disease	9 (10.3)
Clinical presentation		Malnutrition ^a	25 (28.7)
Pain	78 (82.1)	Neoplasia	7 (8)
Fever	52 (54.7)	Corticosteroids	11 (12.6)
Sinus tract	18 (18.9)	≥ 1 Comorbidity	70 (73.7)
Acute symptoms	21 (22.1)	ASA score ≥ 2	38 (40)
Damaged periprosthetic soft tissue	19 (20)		
Number of previous surgeries			
0	73 (76.9)		
1	21 (22.1)		
≥ 2	1 (1.0)		

Streptococcus spp.

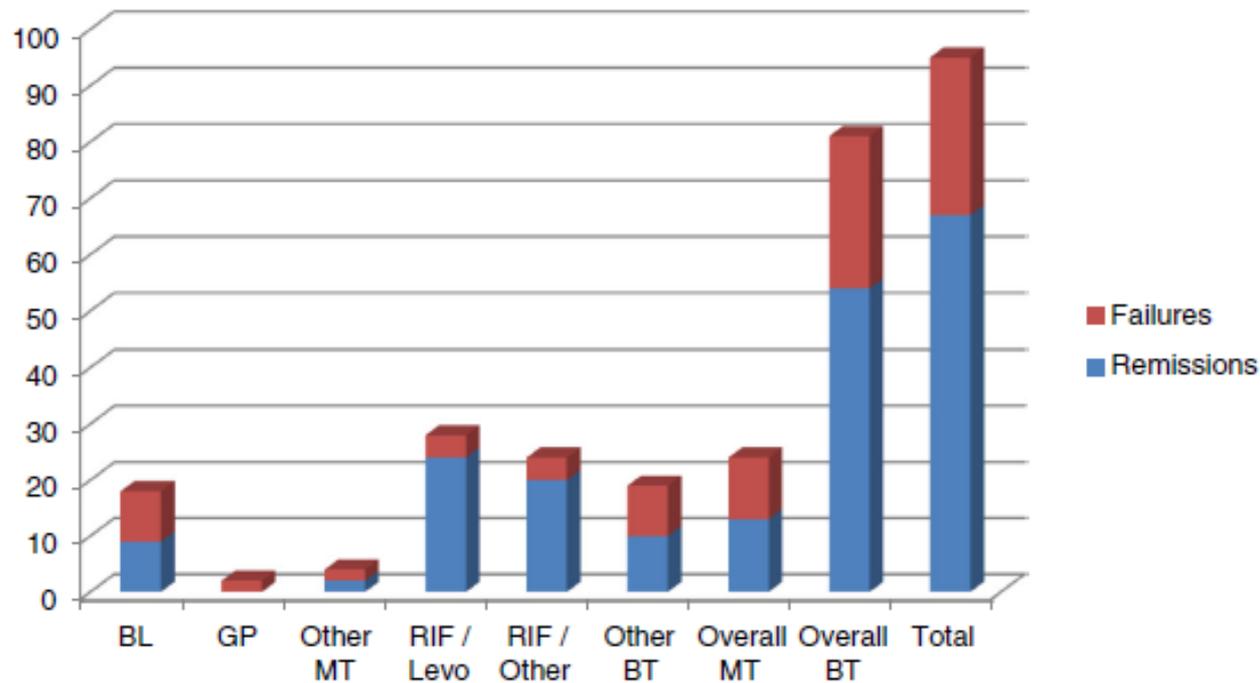


Fig. 1 Proportion of failures/remissions of 95 episodes of streptococcal prosthetic joint infections according to the antibiotic regimen. BL (total = 12): Beta-lactam monotherapy (amoxicillin = 14, ceftriaxone = 4). GP: glycopeptide monotherapy (total = 2, all teicoplanin). Other MT: (monotherapy total = 2, all clindamycin). RIF/Levo (total = 28): rifampicin/levofloxacin combination. RIF/Other (total = 24): rifampicin combinations other than rifampicin-levofloxacin (rifampicin and (i) amoxicillin = 12, (ii) trimethoprim-sulfamethoxazole = 5, (iii) linezolid = 3, (iv) teicoplanin = 2, (v) clindamycin = 1, and (vi) doxycycline = 1). Other BT (bitheraPy total = 19): other bitherapies (clindamycin-levofloxacin = 14, teicoplanin-ceftriaxone = 3, teicoplanin-levofloxacin = 2). Overall MT (total = 24): antibiotic monotherapies all together. Overall BT (total = 71): antibiotic bitherapies all together

Streptococcus spp.

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
<i>S. agalactiae</i> (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

Streptococcus spp.

Type of surgery	Rifampicin combinations, total = 52	Other antibiotic treatments, total = 43	Total	<i>p</i>
DAIR	23/30 (77.7)	9/25 (36)	32/55 (58.2)	.003
1SE	7/8 (87.5)	3/5 (60)	10/13 (76.9)	.25
2SE	10/10 (100)	8/9 (88.9)	18/19 (94.7)	.28
AR	4/4 (100)	3/4 (75)	7/8 (87.5)	.28
Total	44/52 (84.6)	23/43 (53.5)	67/95 (70.5)	.001
Removal	21/22 (95.4)	14/18 (77.8)	35/40 (87.5)	.09

Streptococcus spp.

- Étude rétrospective multicentrique internationale 2003-2012
- Uniquement lavage-synovectomie
- 444 patients évaluable (âge médian 72 ans, 50% M)
- *S. agalactiae* (34%)
- 52% d'origine hématogène
- Antibiothérapie : β -lactams, 37% des patients ont reçu la rifampicine
- Évolution : échec chez 187 patients (42,1%) en moyenne 62 jours après l'intervention
- Suivi médian des patients sans échec = 802 jours

Paramètres associés à l'échec

	Early failure (n=444, 55 failures) ^a				Late Failure (n=389, 71 failures) ^b				Failure After Therapy (N=318, 61 failures) ^c			
	OR (CI95%)	p	aOR (95%CI)	p	HR (95%CI)	p	aHR (CI95%)	p	HR (95%CI)	p	aHR (CI95%)	p
Sex (female)	1.19 (0.68-2.10)	0.540			0.50 (0.31-0.81)	0.004	0.51 (0.30-0.85)	0.009	1.16 (0.69-1.92)	0.572		
Age (per year)	1.03 (0.99-1.01)	0.076	1.04 (1.00-1.07)	0.027	1.00 (0.98-1.02)	0.995			0.99 (0.97-1.01)	0.348		
Rheumatoid arthritis	2.98 (1.35-6.56)	0.007	3.33 (1.40-7.93)	0.007	2.95 (1.55-5.62)	0.004	-	-	1.19 (0.37-3.81)	0.772		
Immunosuppressant therapy	1.49 (0.66-3.66)	0.343			2.76 (1.56-4.89)	0.002	2.64 (1.46-4.79)	0.001	1.51 (0.65-3.51)	0.363		
Renal chronic disease	1.67 (0.73-3.81)	0.223			1.99 (1.05-3.79)	0.053	-	-	1.17 (0.47-2.91)	0.746		
Prosthesis location (knee)	1.04 (0.86-1.26)	0.677			0.98 (0.83-1.14)	0.753			1.18 (0.98-1.41)	0.073	-	-
Revision prosthesis	1.53 (0.83-2.81)	0.173			1.78 (1.09-2.91)	0.027	1.77 (1.07-2.93)	0.027	1.56 (0.90-2.70)	0.129		
Chronic post-surgical inf.	1.212 (0.97-1.23)	0.091	1.41 (1.10-1.81)	0.007	1.12 (0.92-1.37)	0.256			1.47 (1.22-1.77)	<0.001	2.24 (1.24-4.05)	0.008
Sinus tract	0.75 (0.31-1.84)	0.529			1.05 (0.54-2.06)	0.881			1.61 (0.84-3.11)	0.175		
Bacteremia	2.17 (1.20-3.92)	0.011	2.23 (1.80-4.20)	0.014	1.24 (0.74-2.06)	0.420			1.23 (0.70-2.19)	0.478		
Rx signs of infection	1.16 (0.98-1.39)	0.091	-	-	0.77 (0.40-1.48)	0.421			2.21 (1.14-4.30)	0.025	-	-
Infection by <i>S. pyogenes</i>	3.10 (1.41-6.85)	0.005	3.31 (1.41-7.77)	0.006	0.60 (0.19-1.92)	0.357			1.11 (0.45-2.78)	0.821		
Infection by <i>S. viridans</i>	0.71 (0.32-1.57)	0.401			1.60 (0.94-2.70)	0.094	-	-	1.01 (0.51-1.98)	0.987		
Polymicrobial infection	0.95 (0.41-2.20)	0.896			1.33 (0.71-2.47)	0.385			1.23 (0.61-2.49)	0.579		
Time to debridement (>7 days) [†]	0.96 (0.54-1.72)	0.899			1.60 (1.00-2.54) [†]	0.050	1.70 (1.05-2.75)	0.033	1.33 (0.80-2.20)	0.281		
Exchange of polyethylene	0.56 (0.31-1.02)	0.059	-	-	0.75 (0.46-1.21)	0.234			0.45 (0.26-0.77)	0.033	0.44 (0.26-0.76)	0.003
Need for ≥ 2 debridements	1.16 (0.57-2.36)	0.683			2.26 (1.63-4.36)	<0.001	2.45 (1.45-4.15)	0.001	0.60 (0.26-1.40)	0.206		
Antimicrobial therapy [‡]												
B-lactams (without Rifampin)	-	-			1.41 (0.88-2.27)	0.155			0.62 (0.37-1.03)	0.061	0.48 (0.28-0.84)	0.010
β-lactams + Rifampin	-	-			0.89 (0.47-1.70)	0.724			0.42 (0.18-0.98)	0.025	0.34 (0.12-0.96)	0.041
Quinolones + Rifampin	-	-			0.19 (0.03-1.36)	0.082	0.21 (0.03-1.54)	0.125	1.03 (0.45-2.40)	0.940		
Glycopeptides Without Rifampin	-	-			3.97 (2.08-7.58)	<0.001	2.82 (1.43-5.53)	0.003	4.25 (1.32-13.7)	0.015	-	-
Duration of therapy > 120 days	-	-			-	-			0.54 (0.29-0.90)	0.046	-	-

Enterococcus spp.

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

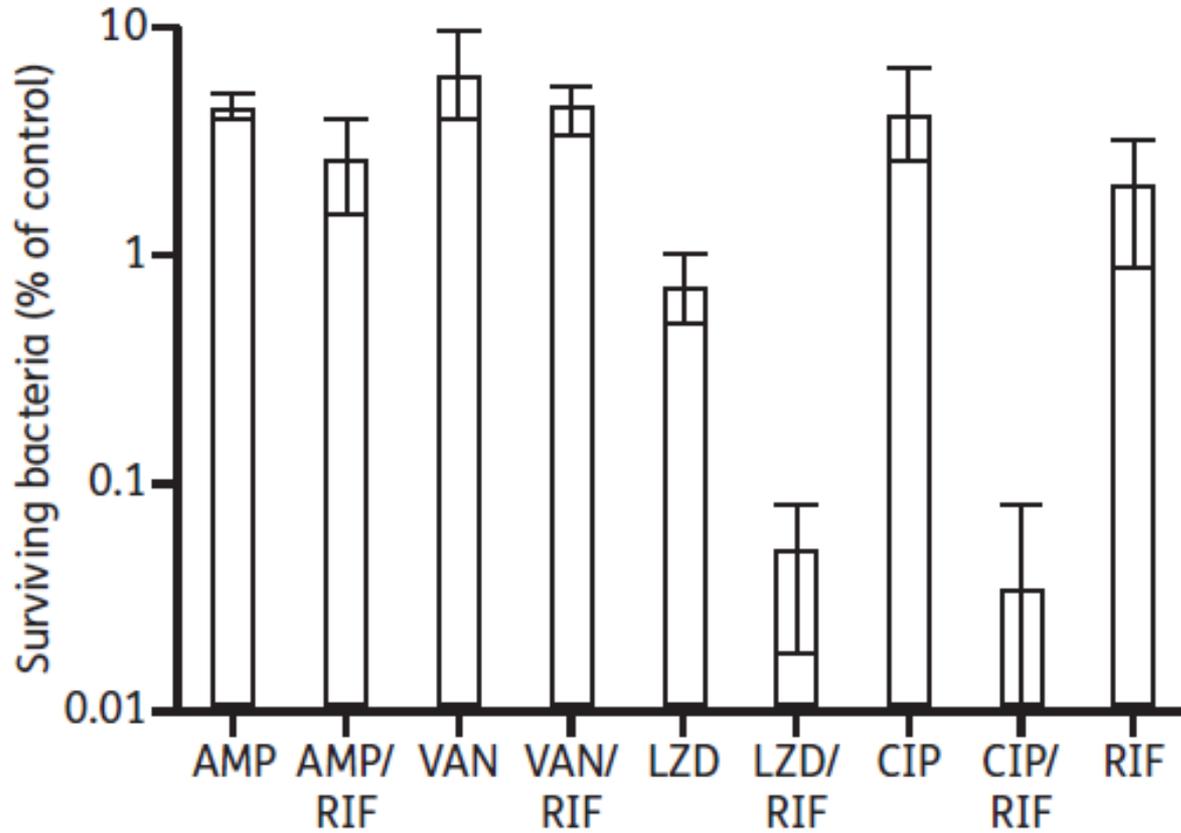
Journal of
Antimicrobial
Chemotherapy

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

Anna Holmberg*, Matthias Mörgelin and Magnus Rasmussen

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)

Enterococcus spp.



***Enterococcus* spp.**

Antibiotic/ combination	cfu reduction (log), median (range)	Rifampicin resistance (cfu/ bead), median (range)
Rifampicin	0.76 (0.75–0.77)	1.2×10^7 (9.9×10^6 – 1.8×10^7)
Ampicillin/rifampicin	0.73 (0.5–1.1)	2.0×10^7 (1.2×10^7 – 2.6×10^7)
Linezolid/rifampicin	2.78 (2.56–3.0)	1.2×10^3 (8.8×10^2 – 1.8×10^3)
Ciprofloxacin/ rifampicin	3.2 (2.67–3.4)	5×10^2 (4×10^2 – 7×10^2)

Bacterial epidemiology of osteoarticular infections in a referent center: 10-year study



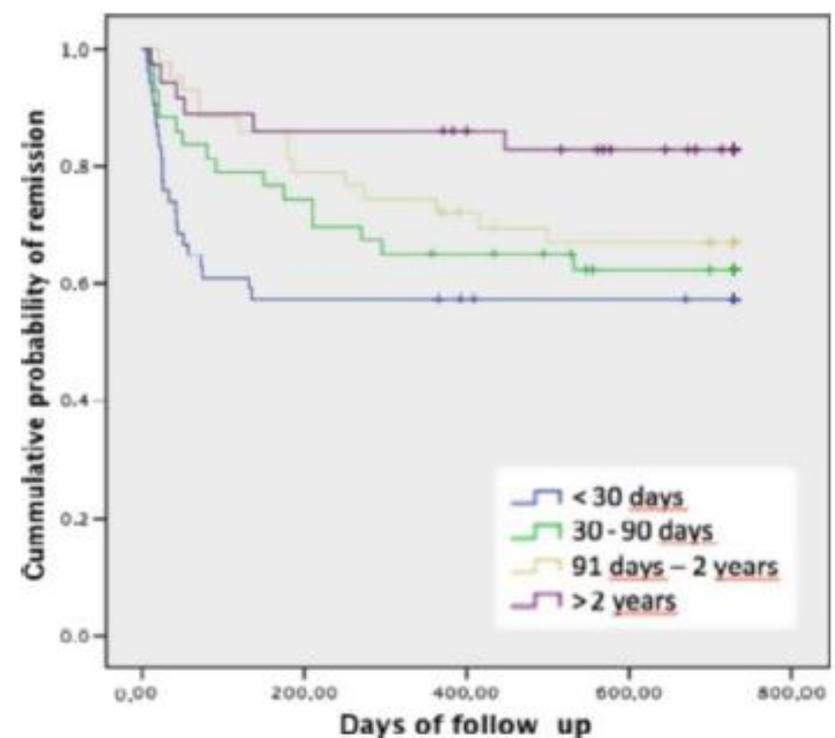
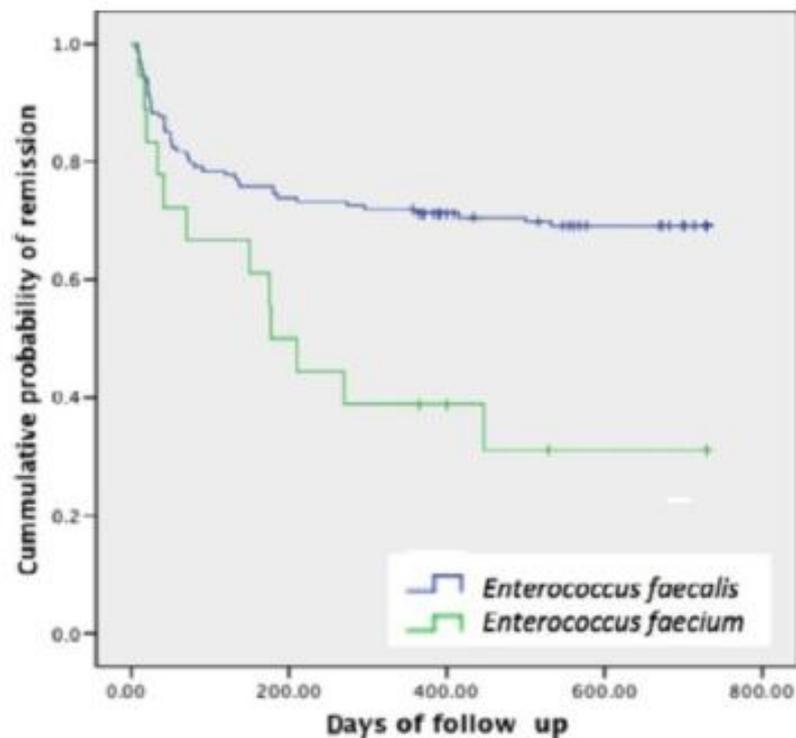
M. Titécat^{a,e}, E. Senneville^{b,d,e,1}, F. Wallet^{a,e}, H. Dezèque^{c,d,e,1}, H. Migaud^{c,d,e,1}, R.-J. Courcol^{a,e}, C. Loïez^{a,e,*}

	2002	2008	2009	2010	2011	Mean % (±SD)
<i>Staphylococcus aureus</i>						
Methicillin	27.9	21.1	21.1	23.7	20.6	22.9 (±3.1)
Levofloxacin	27	22.2	23	31.8	17.7	24.3 (±3.1)
Rifampicin	13.1	6.6	5.3	2.6	1	5.7 (±3.1)
Vancomycin	0	0	0	0	0	0.0 (±0.0)
Teicoplanin	0	0	0	0	0	0.0 (±0.0)
Linezolid	NT	0	0	0	0	0.0 (±0.0)
CoNS						
Methicillin	30.4	44.3	54.4	49.8	43.9	44.6 (±9.0)
Levofloxacin	20.3	32.5	41.2	24.5	34.1	30.5 (±8.2)
Rifampicin	13	18.3	18.5	20.2	18.5	17.7 (±2.7)
Vancomycin	0.4	0	0	0	2.3	0.5 (±1.0)
Teicoplanin	3.7	14.9	21.3	7.4	22	13.9 (±8.2)
Linezolid	NT	1.2	2	1	3.5	1.9 (±1.1)
<i>Enterococcus spp.</i>						
Amoxicillin	22.3	8.6	15.6	12.5	3.1	12.4 (±7.2)
High-concentration gentamicin	13.9	17.4	12.5	25	9.4	15.6 (±6.0)
Levofloxacin	NT	31.8	32.2	29.2	31.3	31.1 (±1.3)
Rifampicin	NT	5	16.6	17.4	6.5	11.4 (±6.5)
Vancomycin	2.8	0	0	4.2	6.2	2.6 (±2.7)
Teicoplanin	0	0	0	0	0	0.0 (±0.0)
Linezolid	NT	0	0	0	0	0.0 (±0.0)

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

Clin Microbiol Infect 2014;

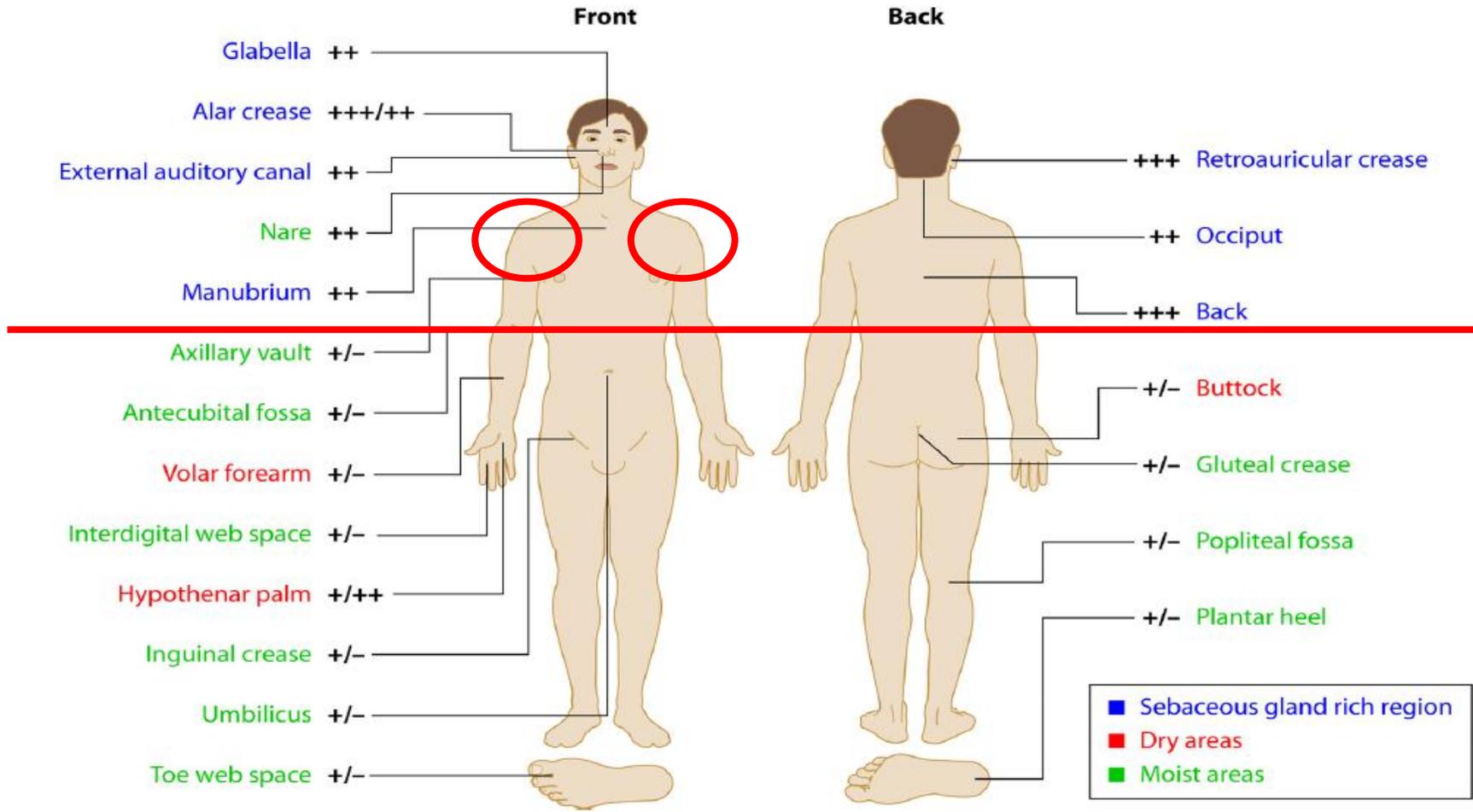
E. Tornero¹, E. Senneville², G. Euba³, S. Petersdorf⁴, D. Rodriguez-Pardo⁵, B. Lakatos⁶, M. C. Ferrari⁷, M. Pilaes⁸, A. Bahamonde⁹, R. Trebse¹⁰, N. Benito¹¹, L. Sorli¹², M. D. del Toro¹³, J. M. Baraiaetxaburu¹⁴, A. Ramos¹⁵, M. Riera¹⁶, A. Jover-Sáenz¹⁷, J. Palomino¹⁸, J. Ariza³ and A. Soriano¹ on behalf of the European Society Group of Infections on Artificial Implants (ESGIAI)



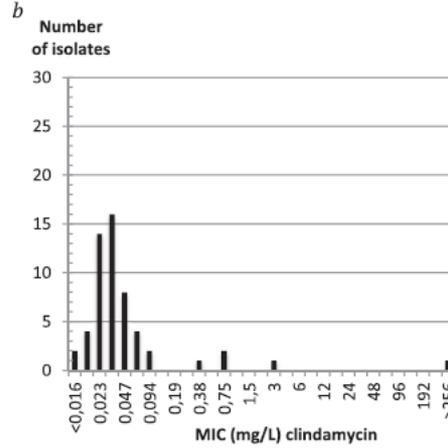
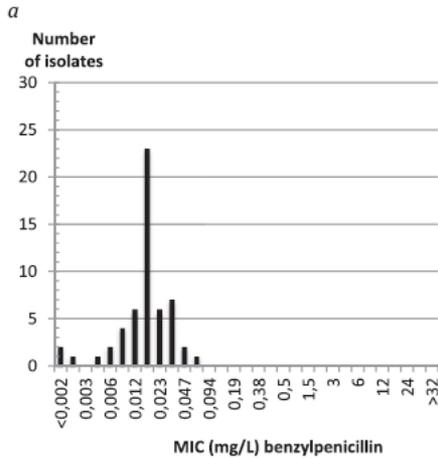
Enterococcus spp.

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

Propionibacterium spp.



Propionibacterium spp.



Propionibacterium spp.

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%)

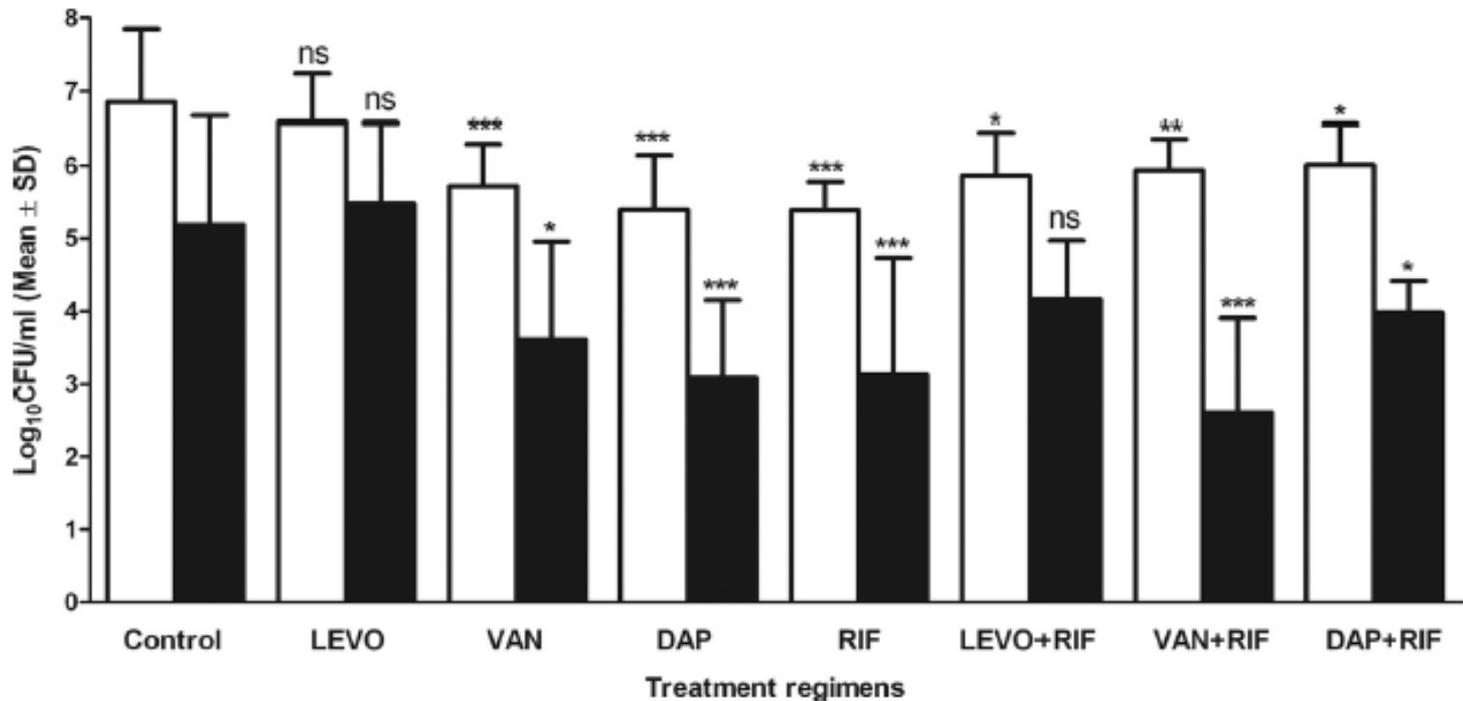
Propionibacterium spp.

Parameter	Value ($\mu\text{g/ml}$) ^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	571	4	2	8	4,096	5,333	128
MBEC	16	64	512	512	128	32	64

Furustrand U *et al.* AAC 2012

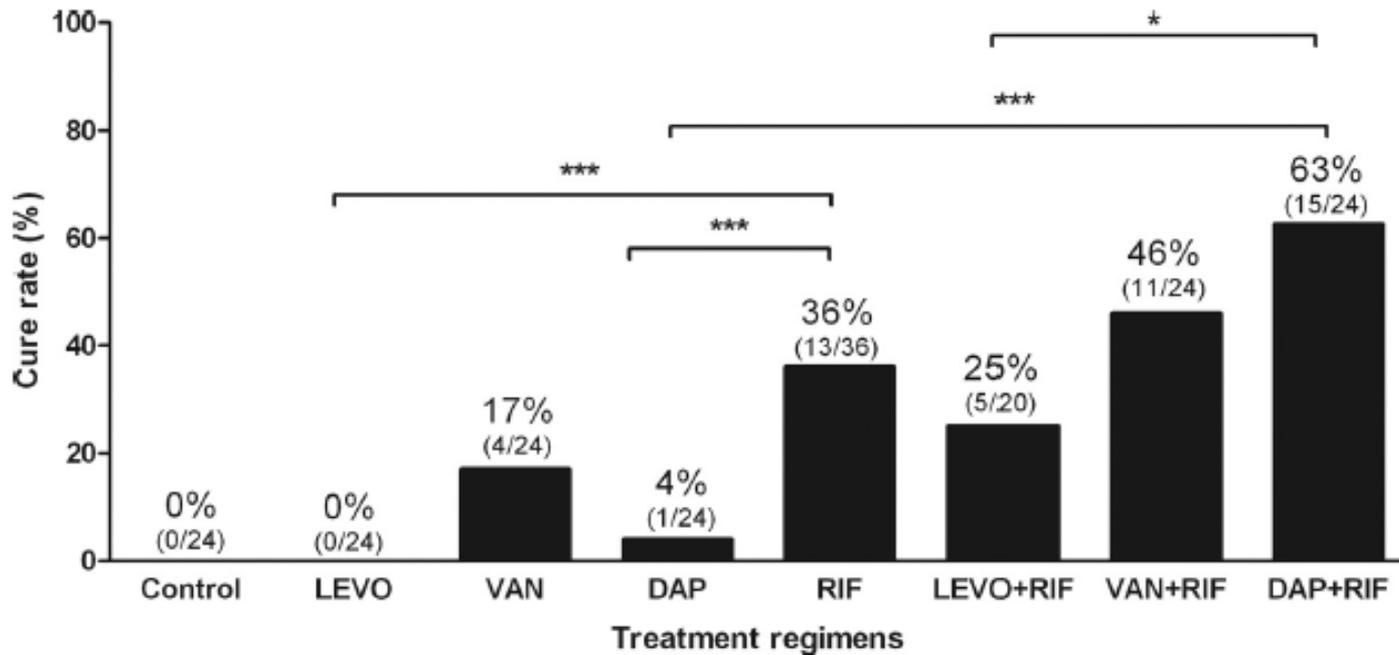
Propionibacterium spp.

Modèle animal; cage sous-cutanée; évaluation J5 traitement



Propionibacterium spp.

Modèle animal; cage sous-cutanée; évaluation J5 traitement



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Propionibacterium spp.

- 24 cas d'IPTE à *P. acnes*
- Toutes les souches sensibles à BL, FQ, Vancomycine, Rifampicine (6% Clinda-R)

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)

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

Étude rétrospective

60 patients IPOA PTH/G/E à *P. acnes*

Influence du traitement avec Rifampicine sur l'évolution de l'infection

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

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Characteristic	Rifampicin (n = 39)	No rifampicin (n = 21)	Total group (n = 60)	p-value
Surgical treatment				0.5
Debridement and prosthesis retention	5	1	6	
1-stage revision (partial revision)	25 (5)	16 (5)	41 (10)	
2-stage revision	9	4	13	
Antibiotic treatment (daily doses)				
→ Clindamycin 600 mg x 3 and rifampicin 450 mg x 2	33	–	33	
→ Teicoplanin 400 mg x 1 i.v. and rifampicin 450 mg x 2	6	–	6	
Clindamycin 600 mg x 3	–	16	16	
Amoxicillin 500 mg x 4	–	1	1	
Ciprofloxacin 750 mg x 2 and clindamycin 600 mg x 3	–	1	1	
Doxycycline 200 mg x 1	–	1	1	
Linezolid 600 mg x 2	–	1	1	
Teicoplanin 400 mg x 1 i.v.	–	1	1	

Conclusions

Bactérie	Intérêt de la Rifampicine
staphylocoques	Avec FQ +++
streptocoques	++ (avec FQ?)
entérocoques	+
<i>Propionibacterium</i> spp.	+/-
corynébactéries	???