DES-C « Pathologie Infectieuse et Tropicale » - Du 4 au 8 Octobre 2021

Séminaire 2 – Thématique N° 2 – Principaux antibactériens II – Utilisation, pharmacologie

Antibiotiques et biofilm

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Service des maladies infectieuses et tropicales – CRIOAc
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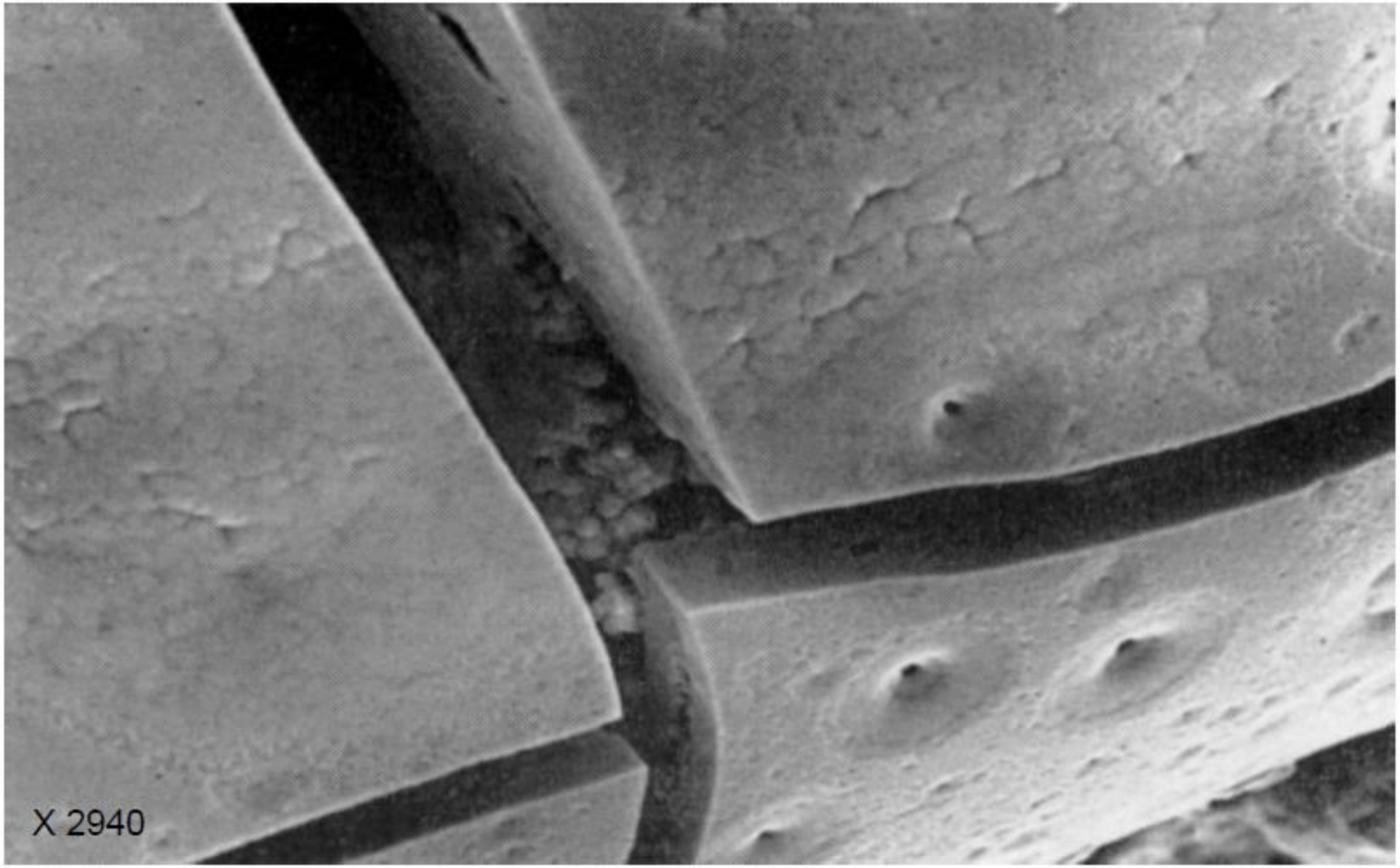
CIRI, INSERM U1111 – Faculté de médecine Lyon Sud Charles Mérieux
Université Claude Bernard Lyon 1

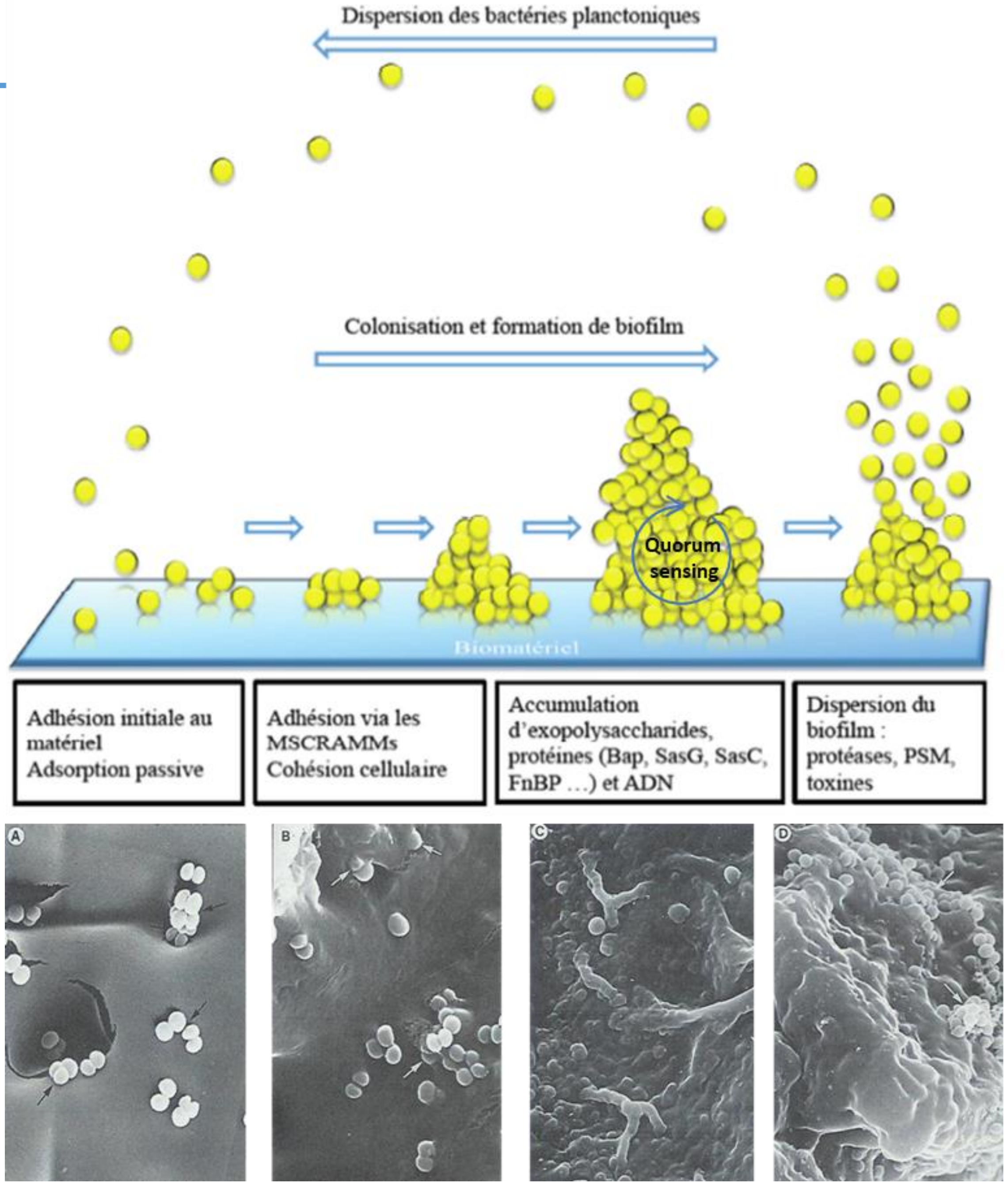
Rappels : le biofilm



Biofilm et séquestre osseux
Evans et al. *Clin Orthop* 1998: 243-249

Rappels : le biofilm

- **Adhésion**
  Adhésines
- **Multiplication**
- **Cohésion**
  PNAG (*ica*), FnBP, ADN …
- **Maturation**
- **Coordination : « quorum sensing »**
  (densité bactérienne, environnement)



Olson, J Biomed Mater Res 1988 – Costerton, Science 1999 – Arciola, Biomaterials 2012 – Brady, FEMS Immunol Med Microbiol 2008

Rappels : le biofilm

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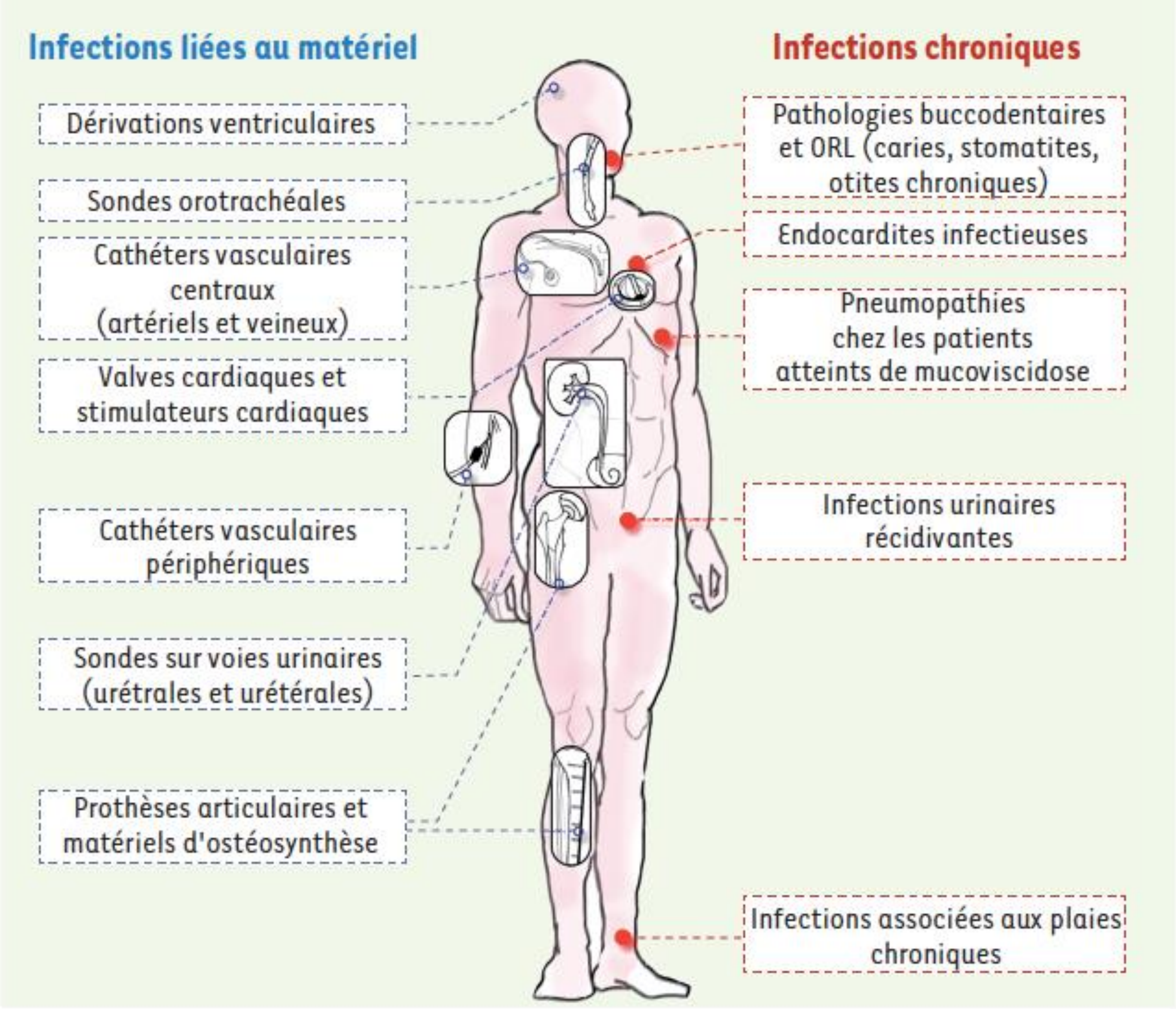
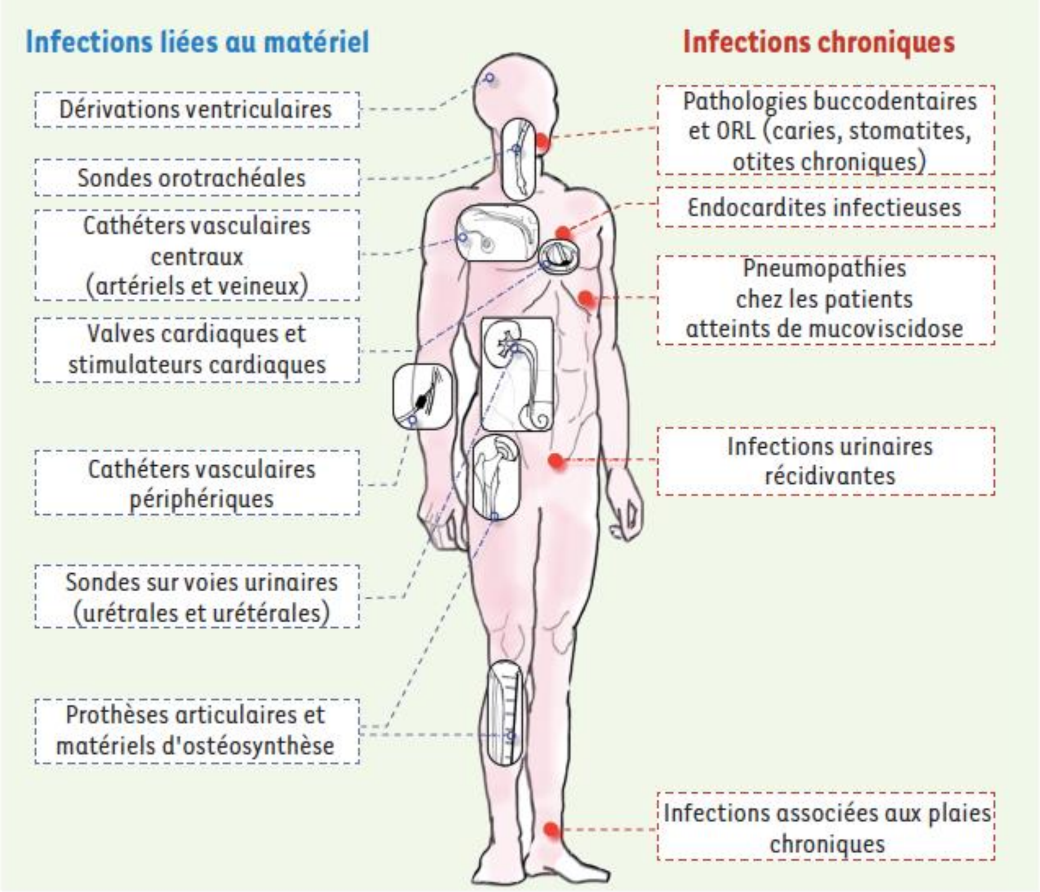


Olson, J Biomed Mater Res 1988 – Costerton, Science 1999 – Arciola, Biomaterials 2012 – Brady, FEMS Immunol Med Microbiol 2008

Implications thérapeutiques

ESCMID GUIDELINES

ESCMID* guideline for the diagnosis and treatment of biofilm infections 2014



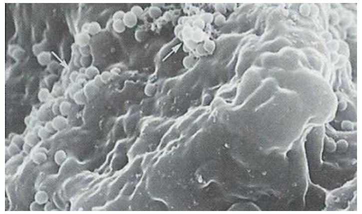
- Aucun test de sensibilité aux antibiotiques des bactéries en biofilm n'est prédictif du succès thérapeutique actuellement
- En cas d'infection sur matériel, éradication par ATB seuls possible uniquement si évolution ≤ 3 (hématogène) à 4 (inoculation) sem
- Importance des ATB « anti-biofilm », notamment en cas de traitement conservateur

Mécanismes de « tolérance » aux antibiotiques (≠ résistance)

Microorganism	Antibiotic	Penetration
P. aeruginosa	Piperacillin	Reduced/yes
	Imipenem	Yes
	Ofloxacin	Yes
	Ciprofloxacin	Yes
	Levofloxacin	Yes
	Sparfloxacin	Yes
	Gentamicin	Reduced
	Amikacin	Reduced
	Tobramycin	Reduced
	Amoxicillin-clavulanic acid	Yes
	Fosfomycin	Yes
	Clarithromycin	Yes
E. coli	Moxalactam	Yes
	Fosfomycin	Yes
	Amoxicillin-clavulanic acid	Yes
	Ciprofloxacin	Yes
K. pneumoniae	Ampicillin	No
	Ciprofloxacin	Yes
S. epidermidis	Rifampin	Yes
	Vancomycin	Yes
	Ciprofloxacin	Yes
	Ofloxacin	Yes
	Clarithromycin	Yes
	Daptomycin	Yes
	Cefotaxime	Reduced
	Oxacillin	Reduced
	Cefotiam	Yes
	Amikacin	Yes
S. aureus	Vancomycin	Yes/reduced
	Cefotaxime	Reduced
	Oxacillin	Reduced
	Ciprofloxacin	Yes
	Amikacin	Yes

Architecture du biofilm

Barrière physique à la pénétration

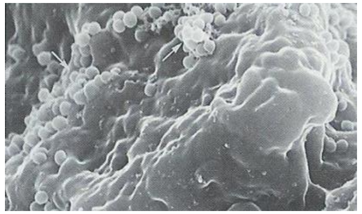


Stewart, Lancet 2001 – Cremet, DMID 2013 – Richards, Chembiochim 2009 – ***Olsen, Eur J Microbiol Infect Dis 2015***

Mécanismes de « tolérance » aux antibiotiques (≠ résistance)

Architecture du biofilm
Barrière physique à la pénétration

Induction de gènes de résistance spécifiques
Ex : pompes à efflux ndvB
+ augmentation fréquence mutations



Adsorption des antibiotiques
Ex : S. aureus et PNAG, acides téchoïques

Effet inoculum : densité bactérienne importante

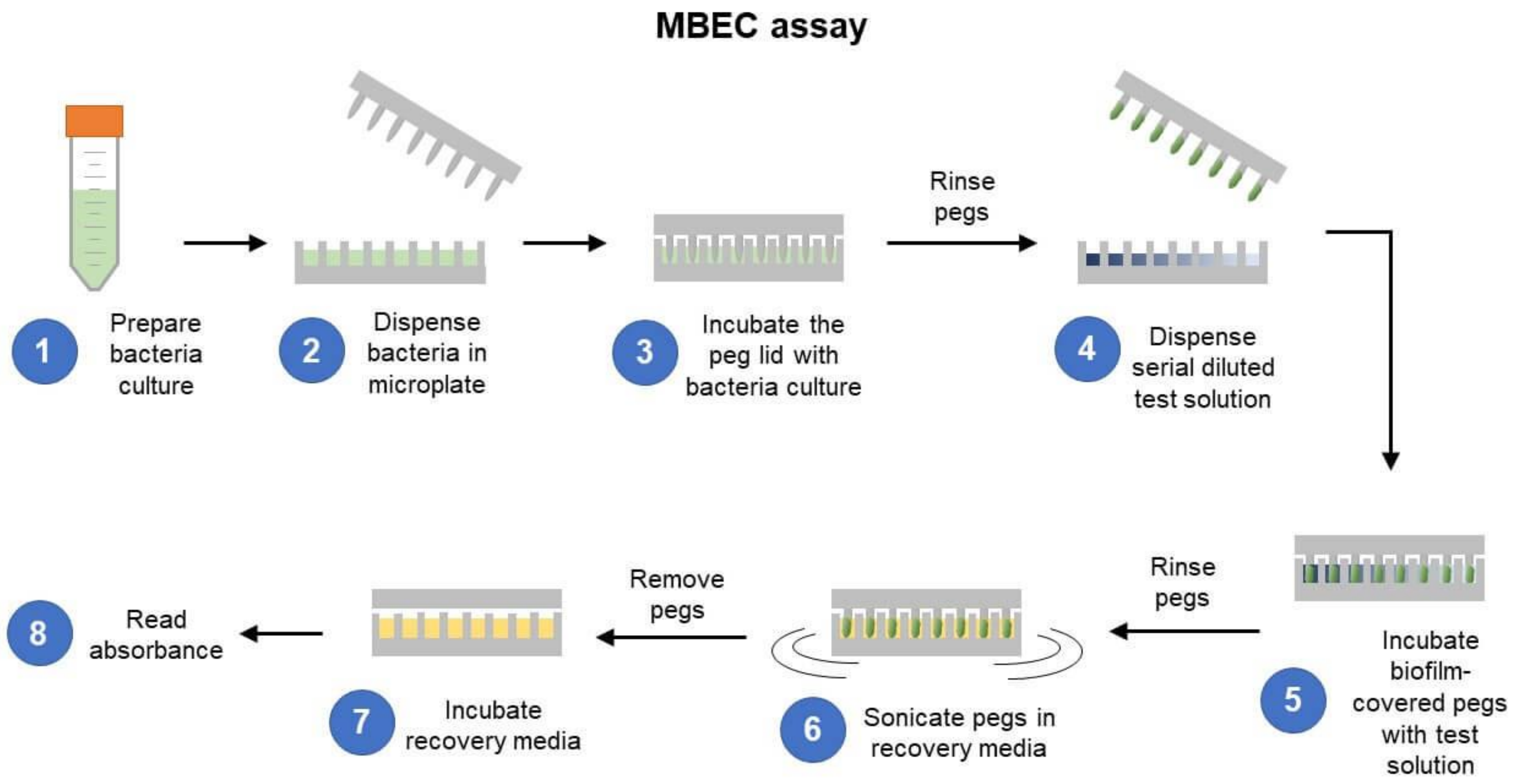
Inactivation par les enzymes matricielles

Réduction du métabolisme bactérien

- Faible multiplication
- Diminution de l'expression des protéines membranaires (porines)
- Anaérobiose et inactivité des aminoglycosides

Stewart, Lancet 2001 – Cremet, DMID 2013 – Richards, Chembiochim 2009 – __Olsen, Eur J Microbiol Infect Dis 2015__

Sensibilité des bactéries en biofilm aux antibiotiques *in vitro* : MBEC



Sensibilité des bactéries en biofilm aux antibiotiques *in vitro* : MBEC

Role of Biofilms in Antimicrobial Resistance

RODNEY M. DONLAN *ASAIO Journal 2000*

Table 2. Antibiotic Susceptibility of *P. aeruginosa* ATCC 27853 as a Planktonic Population (MIC) and as a Biofilm Population (MBEC) as Derived by the NCCLS Assay and an Assay with the CBD*

Antibiotic	MIC (µg/ml) NCCLS Assay†	MIC (µg/ml) Assay with CBD†	MBEC (µg/ml) A_{650}†	MBEC (µg/ml) 0 CFU/peg‡
Amikacin	2	4	16	16
Aztreonam	2	4	>1,024	>1,024
Ceftazidime	1	2	>1,024	>1,024
Ciprofloxacin	0.25	0.25	4	4
Gentamicin	2	4	128	128
Imipenem	1	4	>1,024	>1,024
Piperacillin	2	16	>1,024	>1,024
Tobramycin	0.5	1	2	2

Table 3. Antibiotic Susceptibility of *S. aureus* ATCC 29213 as a Planktonic Population (MIC) and as a Biofilm Population (MBEC) Derived by the NCCLS Assay and an Assay with the CBD*

Antibiotic	MIC (µg/ml) NCCLS assay†	MIC (µg/ml) Assay with CBD†	MBEC (µg/ml) A_{650}†	MBEC (µg/ml) 0 CFU/peg‡
Cefazolin	0.5	0.5	>1,024	>1,024
Ciprofloxacin	0.25	0.5	512	512
Clindamycin	0.12	0.25	128	256
Gentamicin	0.5	0.5	2	2
Oxacillin	0.12	0.25	>1,024	>1,024
Penicillin	1	4	128	128
Vancomycin	1	1	>1,024	>1,024

Sensibilité des bactéries en biofilm aux antibiotiques *in vitro* : MBEC

Table 2
Minimum bactericidal concentrations of prosthetic hip isolates grown on polymethylmethacrylate

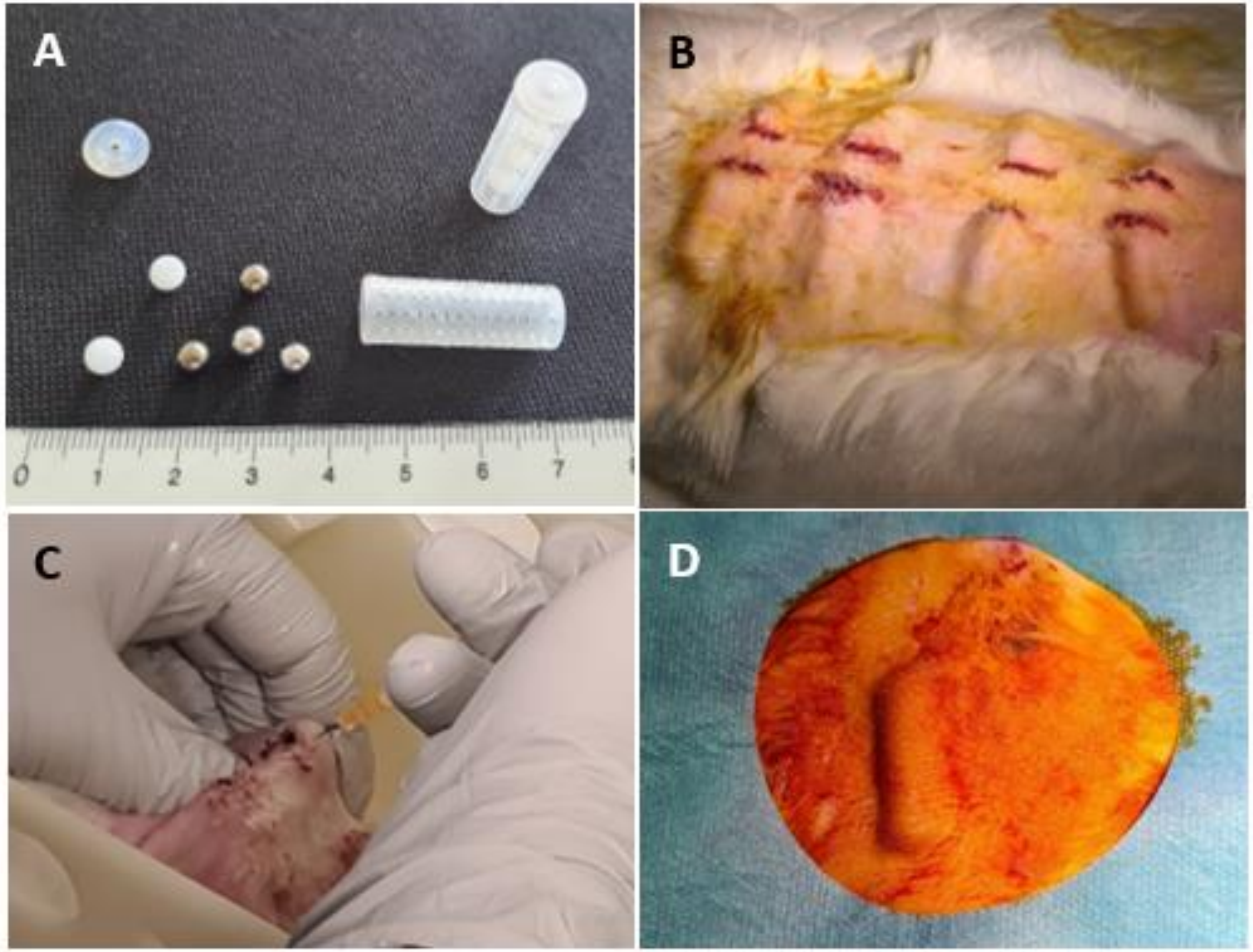
Strain	Gentamicin		Cefamandole		Vancomycin		Ciprofloxacin	
	PMBC[a] (µg/ml)	SMBC[b] (µg/ml)	PMBC (µg/ml)	SMBC (µg/ml)	PMBC (µg/ml)	SMBC (µg/ml)	PMBC (µg/ml)	SMBC (µg/ml)
P. acnes strains								
HJ 1	32	32	1	> 1024	32	> 1024	8	512
HJ 2	32	32	<0.5	512	8	512	16	512
HJ 3	32	32	<0.5	> 1024	16	> 1024	16	256
HJ 4	16	32	<0.5	> 1024	32	> 1024	16	512
L671	32	128	4	> 1024	8	> 1024	16	512
L149	16	64	2	> 1024	8	> 1024	4	1024
L1958	32	64	1	256	1	> 1024	8	512
CK77	32	32	1	> 1024	32	> 1024	4	512

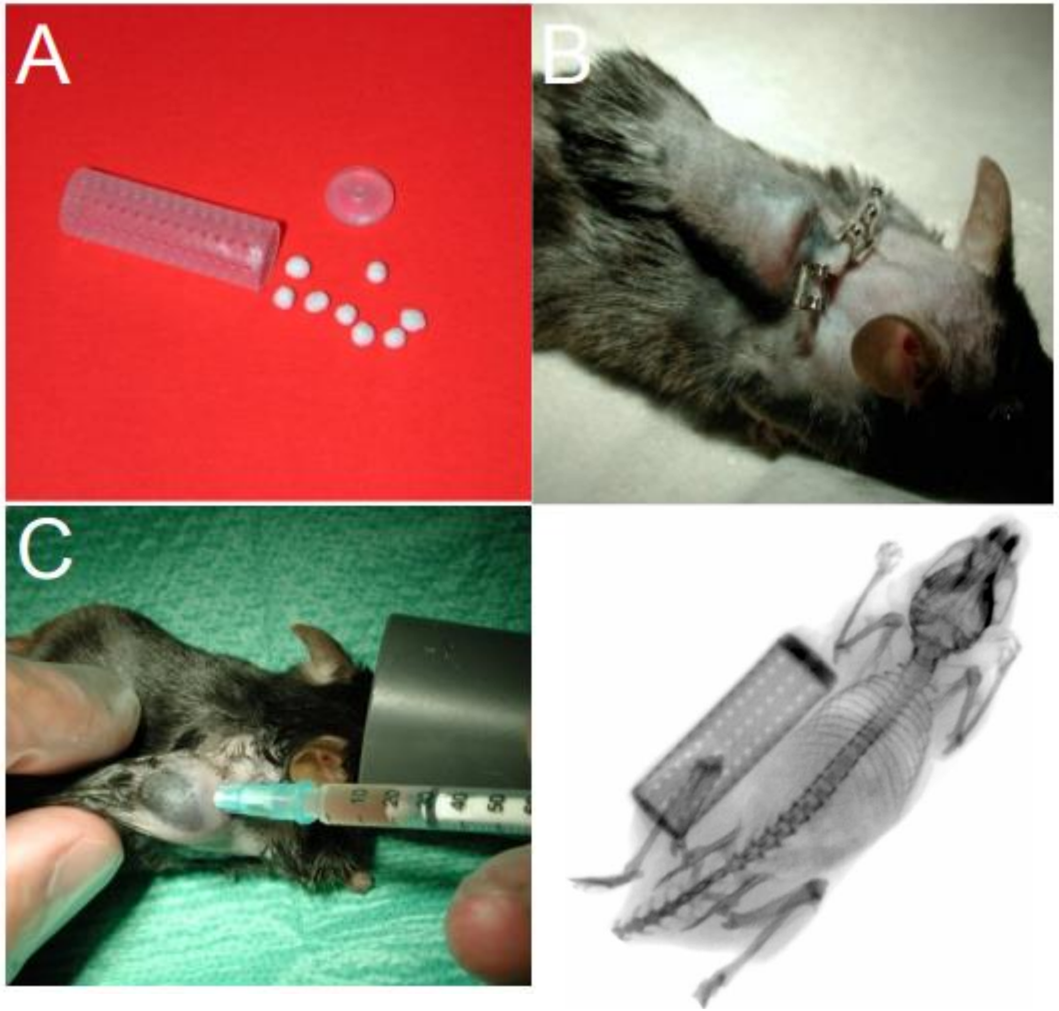
TABLE 2. Antimicrobial susceptibilities of staphylococcal species isolated from orthopedic implants

Isolate (no. of strains tested)	Test agent	MIC (µg/ml)			MBC (µg/ml)		
		Range	50%	90%	Range	50%	90%
S. epidermidis (17)	Gentamicin	<0.5–512	16	256	1–>1,024	128	>1,024
	Cefamandole	<0.5–64	4	32	1–512	16	64
	Cefotaxime	<0.5–32	4	16	4–>1,024	128	512
	Erythromycin	<0.5–>1,024	>1,024	>1,024	2–>1,024	>1,024	>1,024
	Vancomycin	1–2	2	2	8–64	16	64
	Ciprofloxacin	0.25–1	0.5	1	0.5–64	16	32
	Fusidic acid	<0.125–16	0.5	16	1–>256	>256	>256

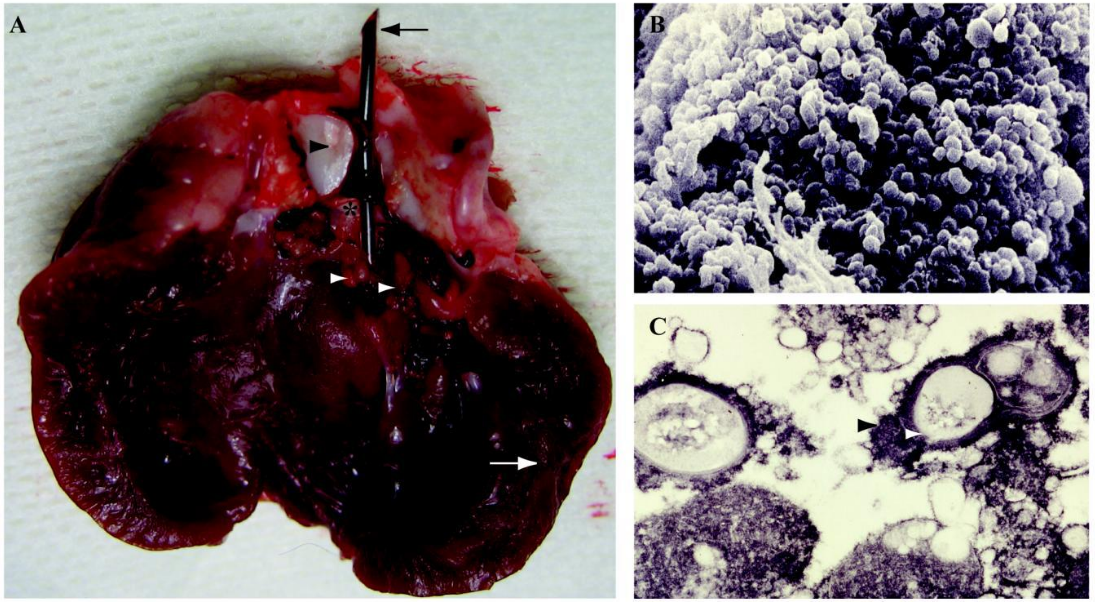
Sensibilité des bactéries en biofilm aux antibiotiques *in vivo*

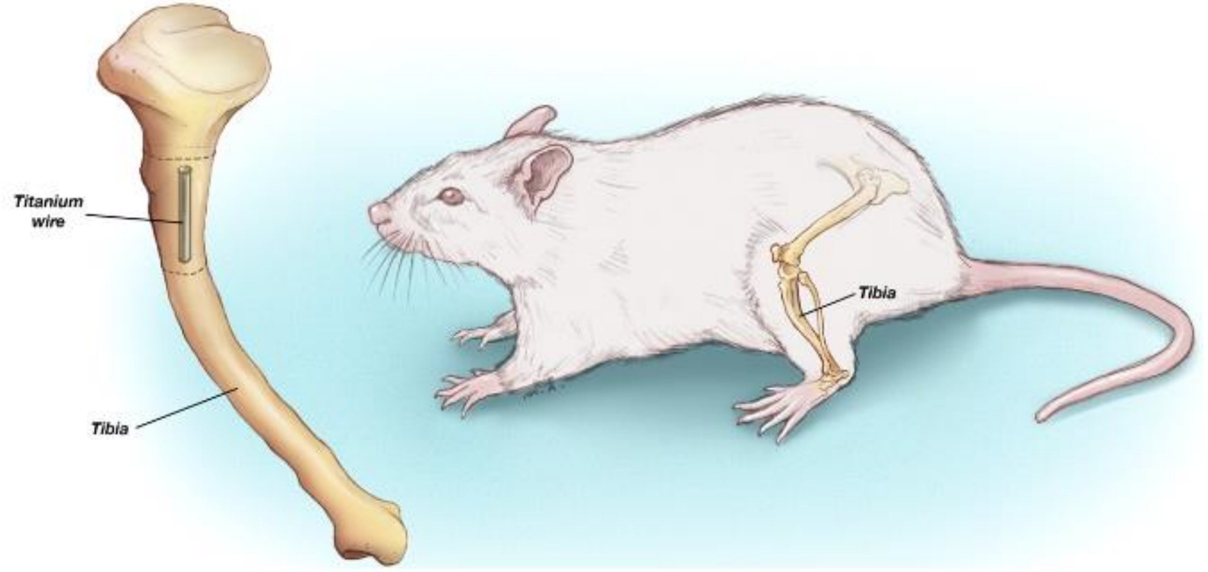
TISSUE-CAGE MODEL

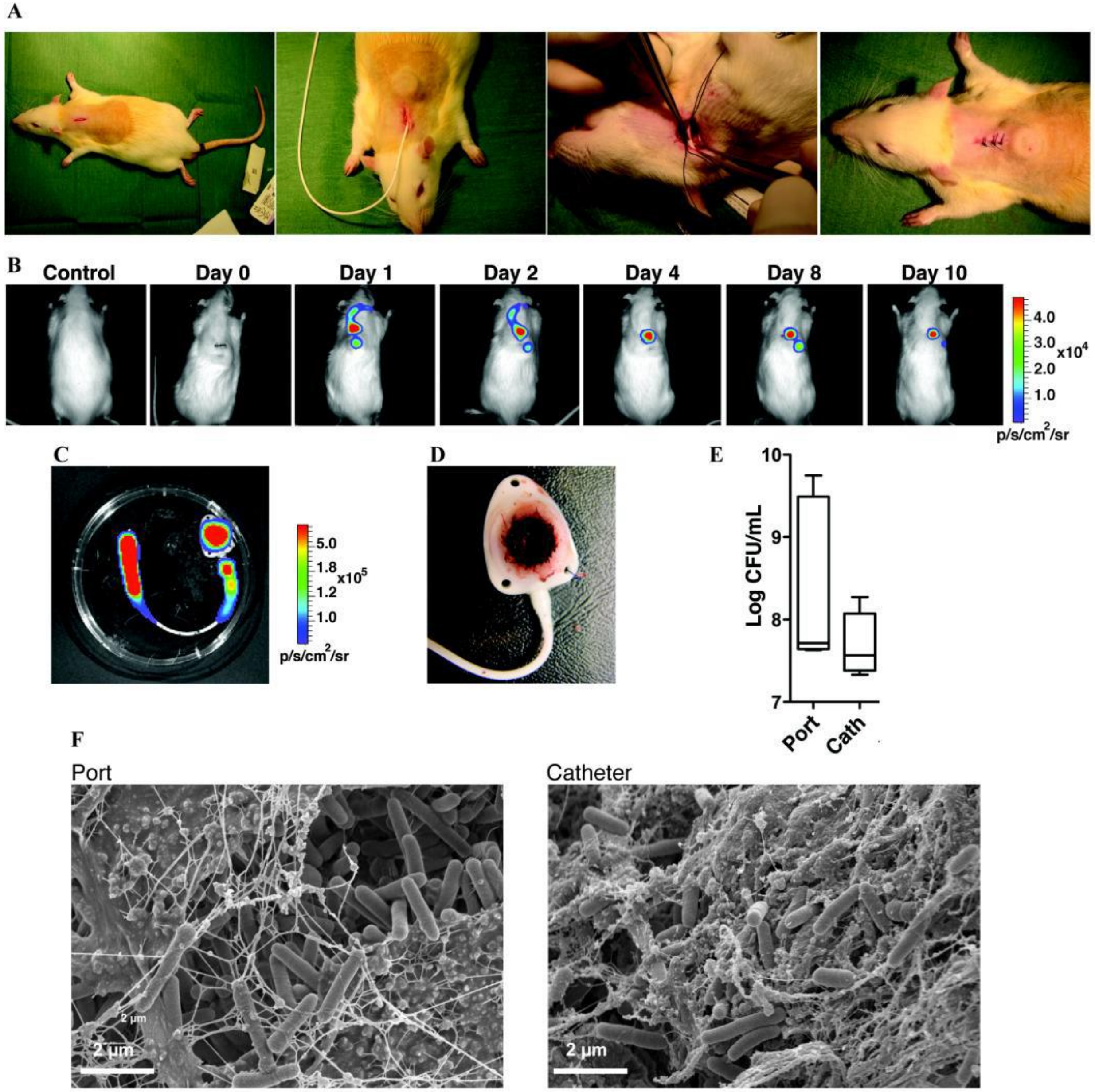




Sensibilité des bactéries en biofilm aux antibiotiques *in vivo*







Staphylococcus aureus

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2009, p. 2719–2724 Vol. 53, No. 7
0066-4804/09/$08.00+0 doi:10.1128/AAC.00047-09
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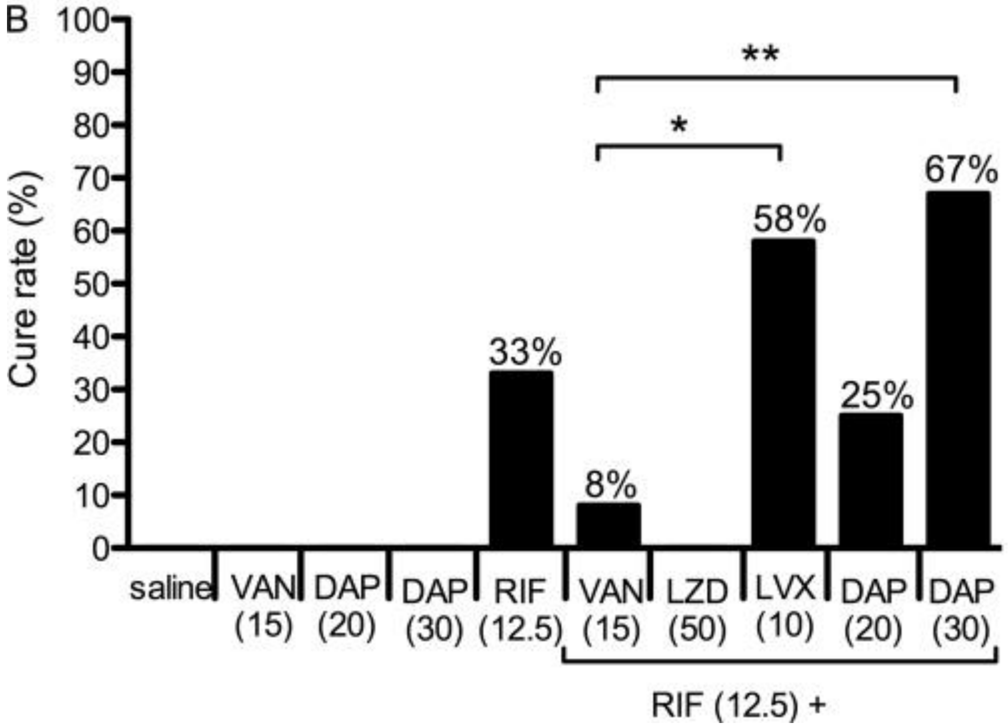
Efficacy of Daptomycin in Implant-Associated Infection Due to Methicillin-Resistant *Staphylococcus aureus*: Importance of Combination with Rifampin[∇]

Anne-Kathrin John,[1] Daniela Baldoni,[1] Manuel Haschke,[2] Katharina Rentsch,[3] Patrick Schaerli,[4] Werner Zimmerli,[5] and Andrej Trampuz[1,6]*



Cure rate of adherent MRSA in explanted cages

TABLE 3. Rates of emergence of rifampin resistance in cage fluid during and after treatment (planktonic bacteria) and in culture from explanted cages (adherent bacteria)

Treatment (dose)[a]	Planktonic bacteria[b] During treatment (day 6)	Planktonic bacteria[b] After treatment (day 12)	Adherent bacteria[c] after treatment (day 12)
RIF (12.5)	2/12 (17)	2/12 (17)	3/12 (25)
VAN (15) + RIF (12.5)	4/12 (33)	5/12 (42)	7/12 (58)
LZD (50) + RIF (12.5)	0/12 (0)	0/12 (0)	1/12 (8)
LVX (10) + RIF (12.5)	0/12 (0)	0/12 (0)	0/12 (0)
DAP (20) + RIF (12.5)	0/12 (0)	0/12 (0)	2/12 (17)
DAP (30) + RIF (12.5)	0/12 (0)	0/12 (0)	0/12 (0)

Staphylococcus aureus

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2009, p. 2719–2724 Vol. 53, No. 7
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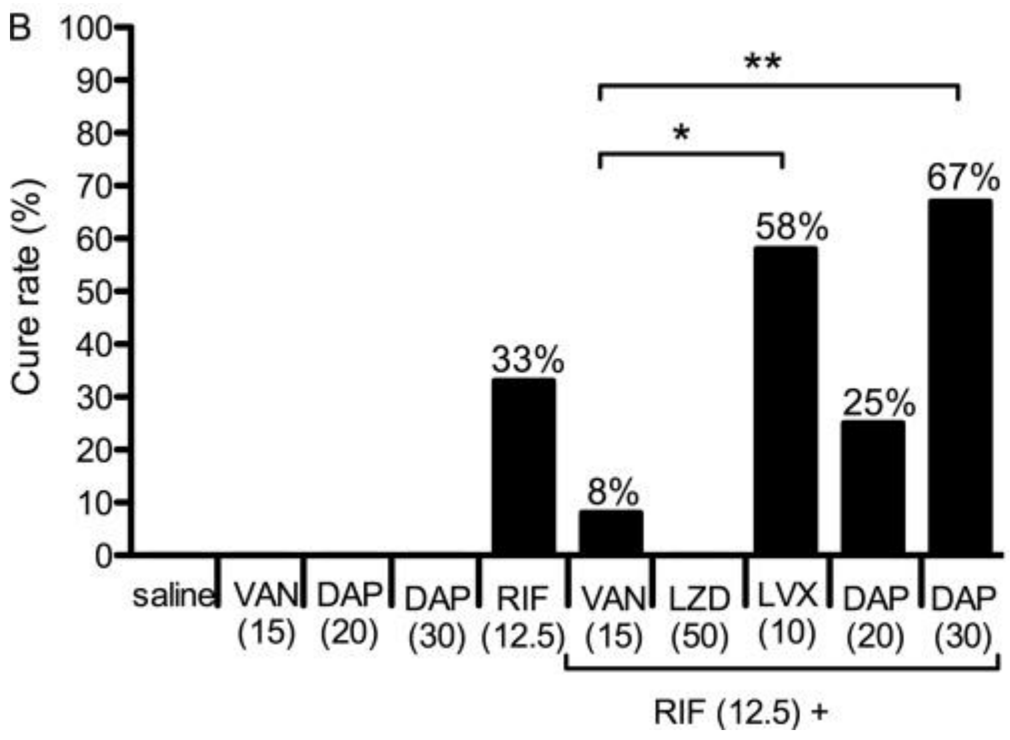
Outcome and Predictors of Treatment Failure in Total Hip/Knee Prosthetic Joint Infections Due to *Staphylococcus aureus*

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



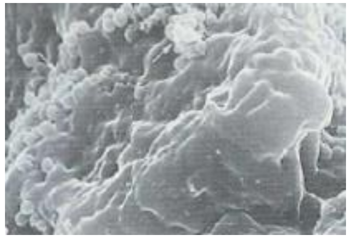
Cure rate of adherent MRSA in explanted cages

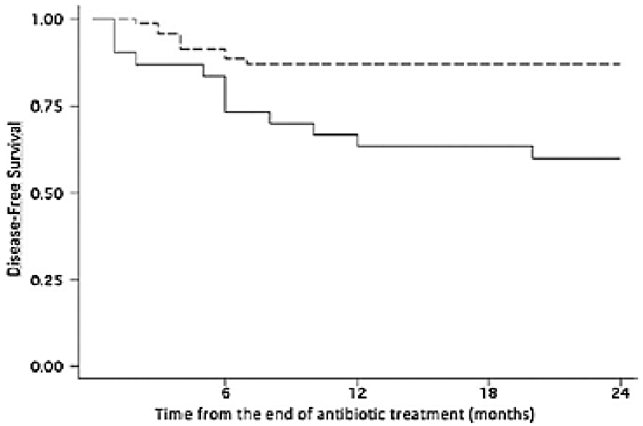
Facteurs protecteurs (univarié)

- ASA score ≤ 2
- ATB empirique post-opératoire adéquate
- Combinaison à base de rifampicine

Facteurs protecteurs (multi-varié)

- ASA score ≤ 2
- **Rifampicine – FQ**





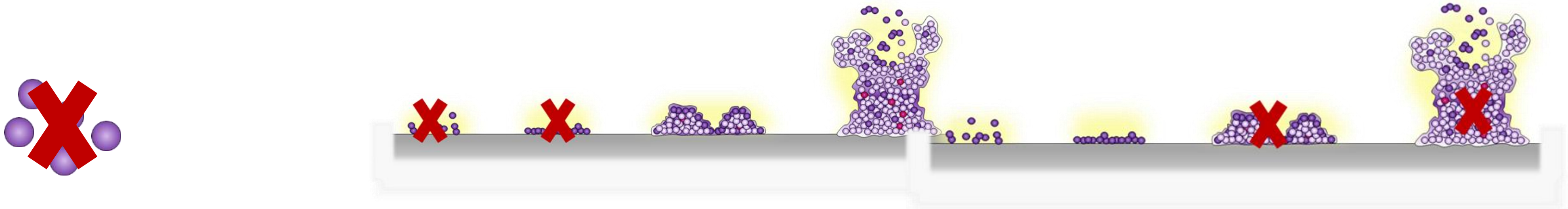
Staphylococcus aureus

J Antimicrob Chemother 2020; **75**: 1466–1473
doi:10.1093/jac/dkaa061 Advance Access publication 3 March 2020

Journal of Antimicrobial Chemotherapy

Antibiofilm and intraosteoblastic activities of rifamycins against *Staphylococcus aureus*: promising *in vitro* profile of rifabutin

Lélia Abad[1–3], Jérôme Josse[1], Jason Tasse[1], Sébastien Lustig[2,4,5], Tristan Ferry[1,2,4,6], Alan Diot[1], Frédéric Laurent[1–4]*† and Florent Valour[1,2,4,6]†



Isolate	MIC (mg/L)			bMIC (mg/L)			$MBEC_{90}$ (mg/L)		
	rifampicin	rifapentine	rifabutin	rifampicin	rifapentine	rifabutin	rifampicin	rifapentine	rifabutin
6850	0.016	0.062	0.031	0.05	0.1	0.05	50	0.39	0.19
Clinical isolate 1	0.008	0.031	0.031	0.0125	0.0125	0.025	3.125	0.78	0.19
Clinical isolate 2	0.031	0.062	0.062	0.025	0.05	0.05	>100	0.19	0.78

Bacilles Gram négatif

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 1991, p. 741–746 Vol. 35, No. 4
0066-4804/91/040741-06$02.00/0
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Killing of Nongrowing and Adherent *Escherichia coli* Determines Drug Efficacy in Device-Related Infections

ANDREAS F. WIDMER,[1]† ADRIAN WIESTNER,[1] RENO FREI,[2] AND WERNER ZIMMERLI[1]*

Activities of Fosfomycin, Tigecycline, Colistin, and Gentamicin against Extended-Spectrum-β-Lactamase-Producing *Escherichia coli* in a Foreign-Body Infection Model

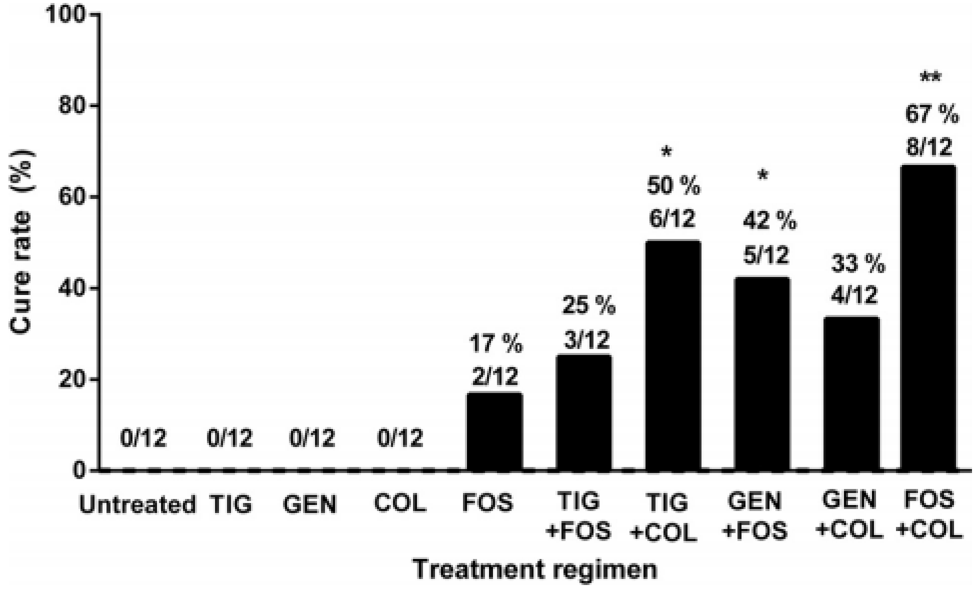
Stéphane Corvec,[a,b] Ulrika Furustrand Tafin,[a] Bertrand Betrisey,[a] Olivier Borens,[c] Andrej Trampuz[a,d]

Modèle cage / cochon d'Inde

TABLE 6. Killing of glass-adherent *E. coli* ATCC 25922

Drug	CFU/slide (mean ± SE)		% Killing	Log killing
	Controls	After treatment[a]		
Co-trimoxazole	153 ± 19	576 ± 129	0	0
Aztreonam	241 ± 17	14 ± 7	94.3	1.25
Fleroxacin	338 ± 10	39 ± 20	88.4	0.93
Ciprofloxacin	531 ± 56	0 ± 0	>99.9	>3

[a] Adherent bacteria were incubated at drug concentrations corresponding to twice the MBC determined in the logarithmic growth phase (see text).



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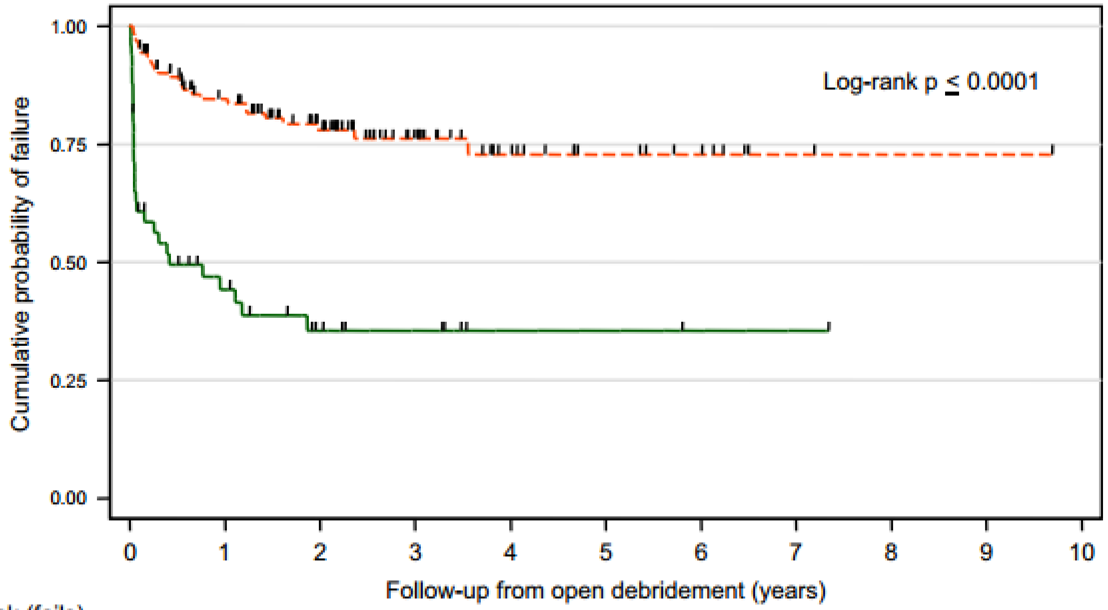
Gram-negative prosthetic joint infection: outcome of a debridement, antibiotics and implant retention approach. A large multicentre study

D. Rodríguez-Pardo[1], C. Pigrau[1], J. Lora-Tamayo[2], A. Soriano[3], M. D. del Toro[4], J. Cobo[5], J. Palomino[6], G. Euba[2], M. Riera[7], M. Sánchez-Somolinos[8], N. Benito[9], M. Fernández-Sampedro[10], L. Sorli[11], L. Guio[12], J. A. Iribarren[13], J. M. Baraia-Etxaburu[14], A. Ramos[15], A. Bahamonde[16], X. Flores-Sánchez[17], P. S. Corona[17] and J. Ariza[2] on behalf of the REIPI Group for the Study of Prosthetic Infection*

Clinical Microbiology and Infection, Volume 20 Number 11, November 2014



N at risk (fails)

	0		1		2		3		4		5		6		7		8		9		10
Not ciprofloxacin treatment	49	(26)	17	(3)	9	(0)	6	(0)	2	(0)	2	(0)	1	(0)	1	(0)	0	(0)	0	(0)	0
Ciprofloxacin treatment	124	(18)	87	(6)	59	(1)	32	(1)	16	(0)	10	(0)	6	(0)	2	(0)	1	(0)	1	(0)	0

Patients not treated with ciprofloxacin
Patients treated with ciprofloxacin

Enterococcus faecalis

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2011, p. 4821–4827 Vol. 55, No. 10
0066-4804/11/$12.00 doi:10.1128/AAC.00141-11
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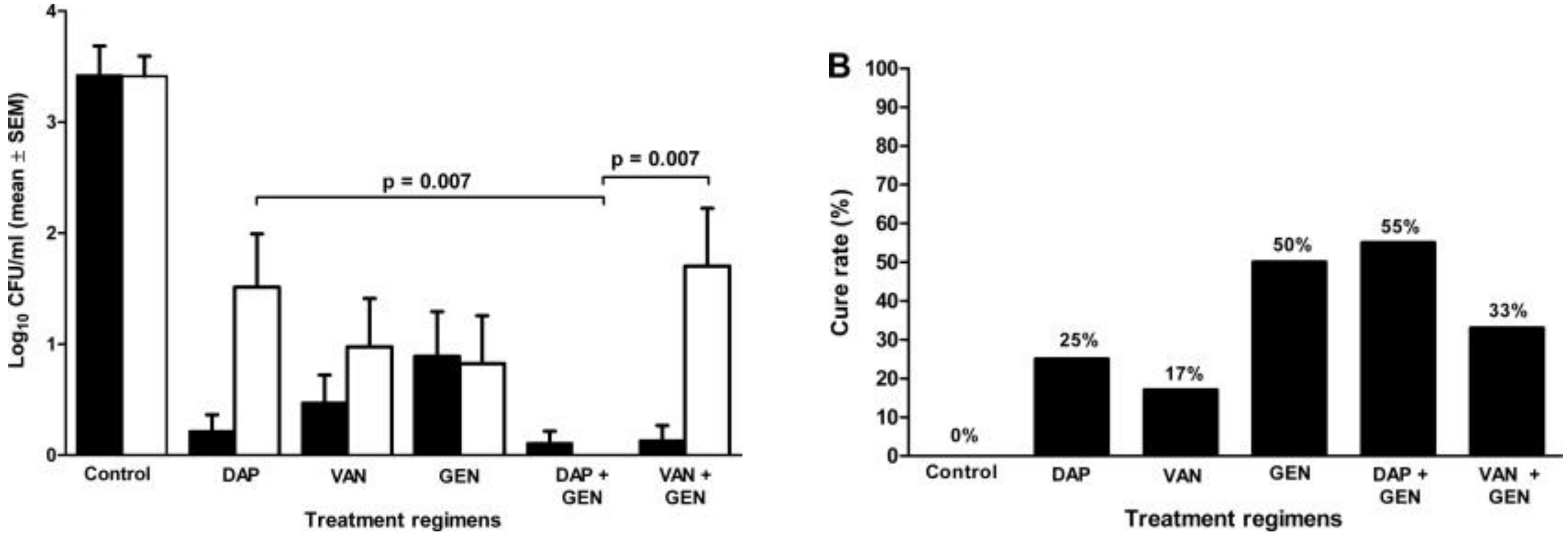
Gentamicin Improves the Activities of Daptomycin and Vancomycin against *Enterococcus faecalis In Vitro* and in an Experimental Foreign-Body Infection Model▽

Ulrika Furustrand Tafin,[1] Ivana Majic,[2] Cyrine Belkhodja Zalila,[1] Bertrand Betrisey,[1] Stéphane Corvec,[1,3] Werner Zimmerli,[4] and Andrej Trampuz[1,2]*

ENC et DAP-GEN

Pas de données cliniques

Modèle cage / cochon d'Inde



Bactéries planctonique : fin de traitement et J5

Cure rate : adherent enc

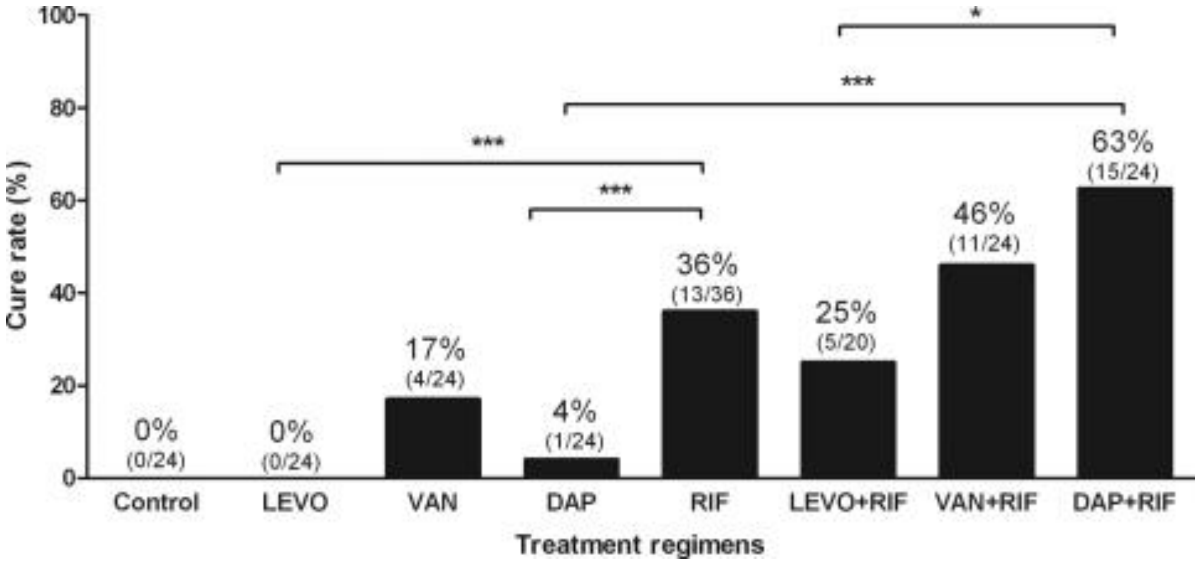
Cutibacterium acnes

AAC
Journals.ASM.org

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]

Modèle cage / cochon d'Inde



cure rates of adherent bacteria from explanted cages

Cutibacterium acnes

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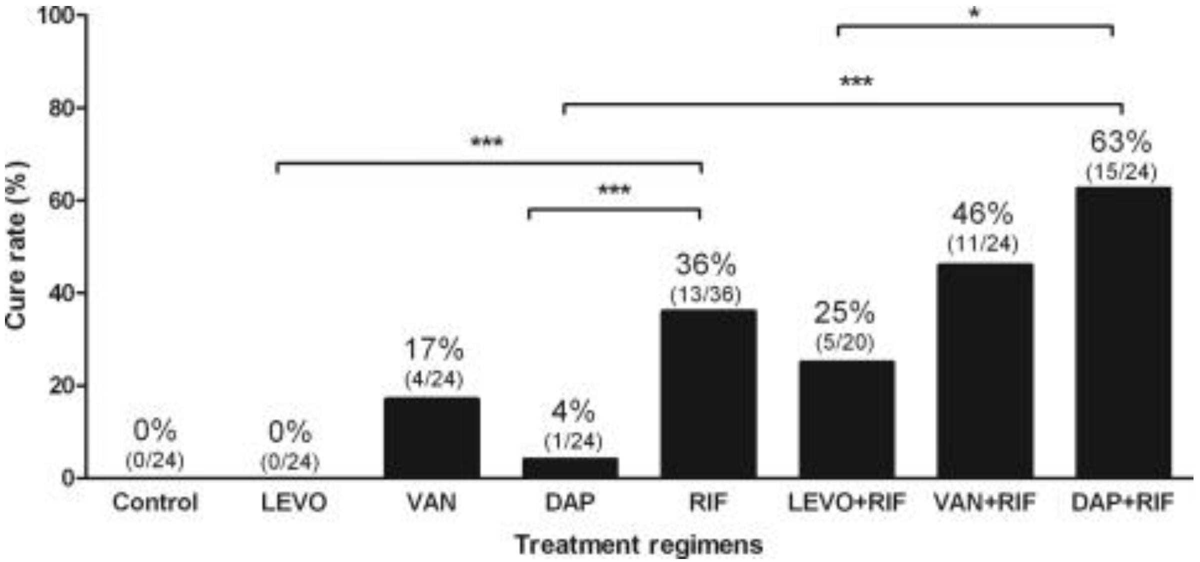
Role of Rifampin against *Propionibacterium acnes* Biofilm *In Vitro* and in an Experimental Foreign-Body Infection Model

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

The Impact of Surgical Strategy and Rifampin on Treatment Outcome in *Cutibacterium* Periprosthetic Joint Infections

Katharina Kusejko,[1] Álvaro Auñón,[2,*] Bernhard Jost,[3,*] Benito Natividad,[4,*] Carol Strahm,[5,*] Christine Thurnheer,[6,*] Daniel Pablo-Marcos,[7,*] Dorsaf Slama,[8,*] Giulia Scanferla,[5,*] Ilker Uckay,[9,*] Isabelle Waldmann,[1,*] Jaime Esteban,[2,*] Jaime Lora-Tamayo,[10,*] Martin Clauss,[11,*] Marta Fernandez-Sampedro,[7,*] Marjan Wouthuyzen-Bakker,[12,*] Matteo Carlo Ferrari,[13,*] Natalie Gassmann,[1,*] Parham Sendi,[14,*] Philipp Jent,[6,*] Philippe C. Morand,[15,*] Prakhar Vijayvargiya,[16,*] Rihard Trebše,[17,*] Robin Patel,[16,*] Roger D. Kouyos,[1,18,*] Stéphane Corvec,[19,*] Tobias Siegfried Kramer,[20,*] Vincent A. Stadelmann,[21,*] and Yvonne Achermann,[1]; on behalf of the ESCMID Study Group for Implant-Associated Infections (ESGIAI)

Modèle cage / cochon d'Inde

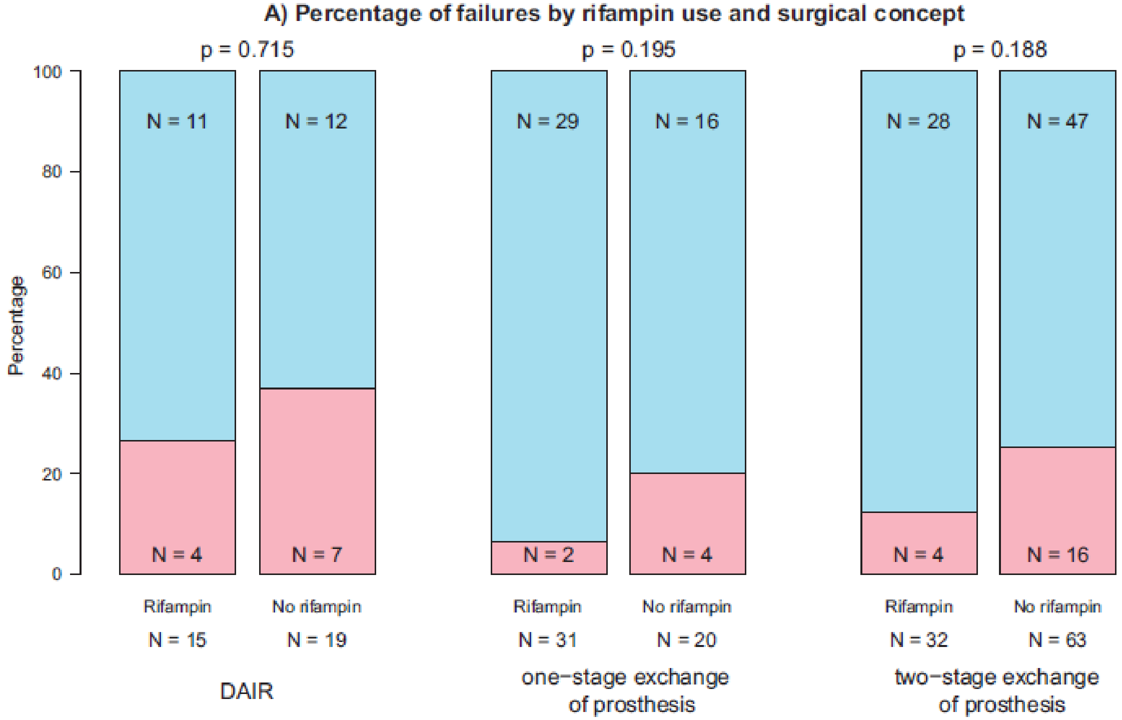


cure rates of adherent bacteria from explanted cages

Etude rétrospective multicentrique – n=187

81 (43%) patients sous rifampicine

20% d'échec – FR = DAIR et traitement < 6 sem



Cutibacterium acnes

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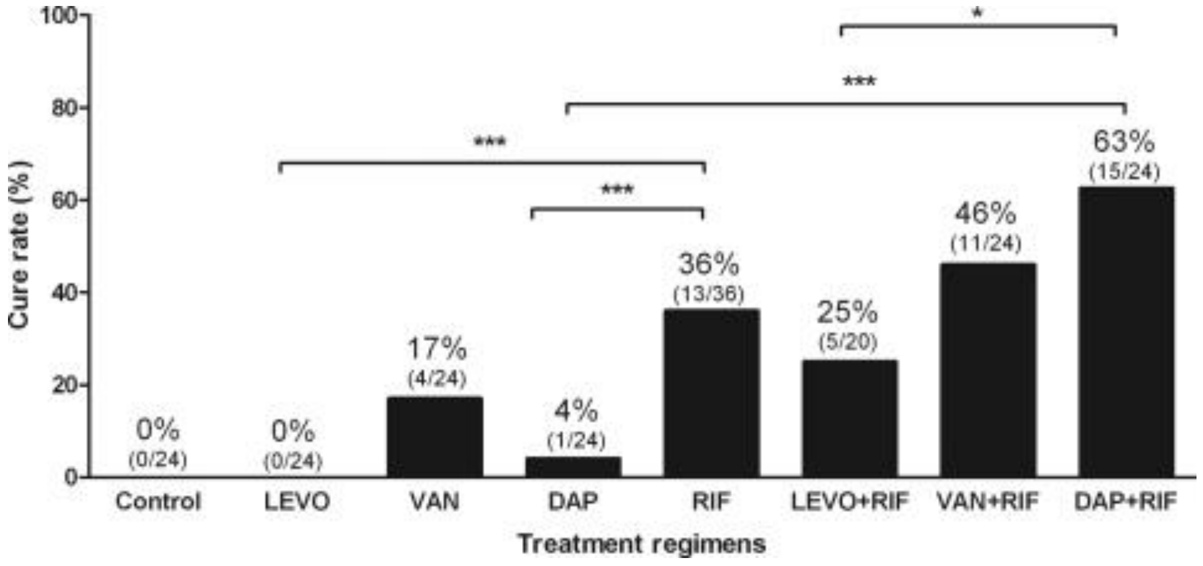
Role of Rifampin against *Propionibacterium acnes* Biofilm *In Vitro* and in an Experimental Foreign-Body Infection Model

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

Modèle cage / cochon d'Inde



cure rates of adherent bacteria from explanted cages

The Impact of Surgical Strategy and Rifampin on Treatment Outcome in *Cutibacterium* Periprosthetic Joint Infections

Katharina Kusejko,[1] Álvaro Auñón,[2,*] Bernhard Jost,[3,*] Benito Natividad,[4,*] Carol Strahm,[5,*] Christine Thurnheer,[6,*] Daniel Pablo-Marcos,[7,*] Dorsaf Slama,[8,*] Giulia Scanferla,[5,*] Ilker Uckay,[9,*] Isabelle Waldmann,[1,*] Jaime Esteban,[2,*] Jaime Lora-Tamayo,[10,*] Martin Clauss,[11,*] Marta Fernandez-Sampedro,[7,*] Marjan Wouthuyzen-Bakker,[12,*] Matteo Carlo Ferrari,[13,*] Natalie Gassmann,[1,*] Parham Sendi,[14,*] Philipp Jent,[6,*] Philippe C. Morand,[15,*] Prakhar Vijayvargiya,[16,*] Rihard Trebše,[17,*] Robin Patel,[16,*] Roger D. Kouyos,[1,18,*] Stéphane Corvec,[19,*] Tobias Siegfried Kramer,[20,*] Vincent A. Stadelmann,[21,*] and Yvonne Achermann,[1]; on behalf of the ESCMID Study Group for Implant-Associated Infections (ESGIAI)

Etude rétrospective multicentrique – n=187

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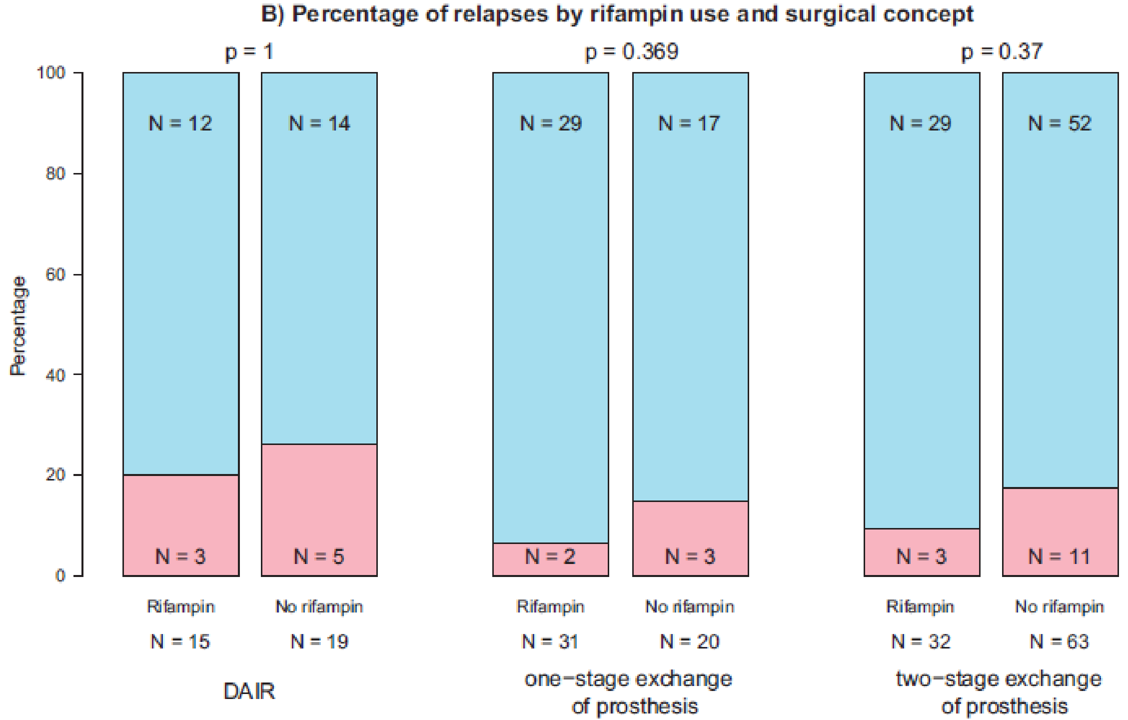

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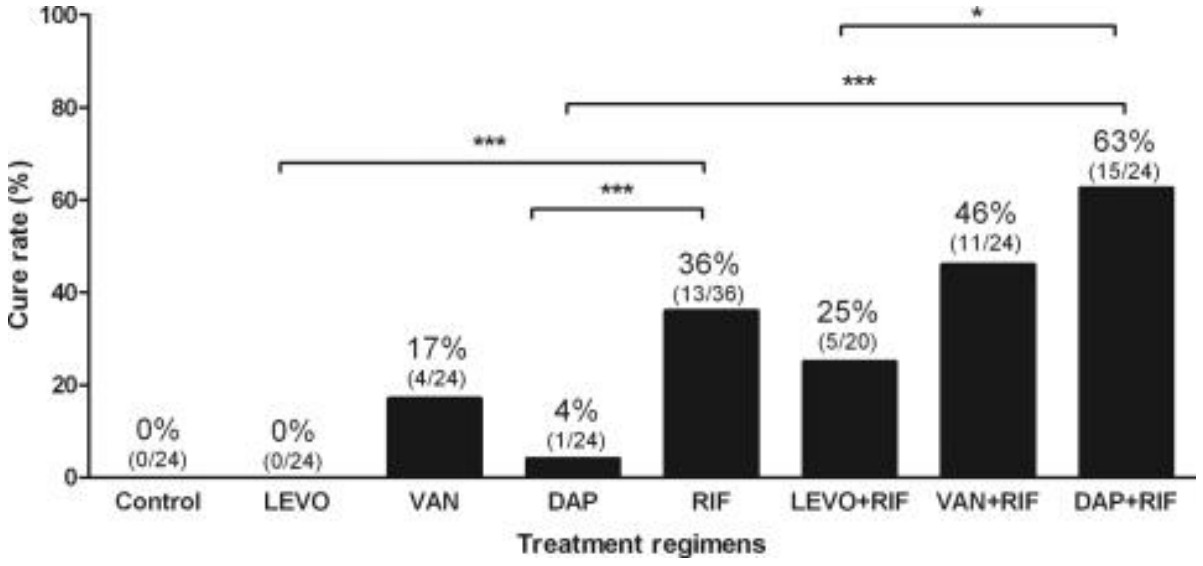

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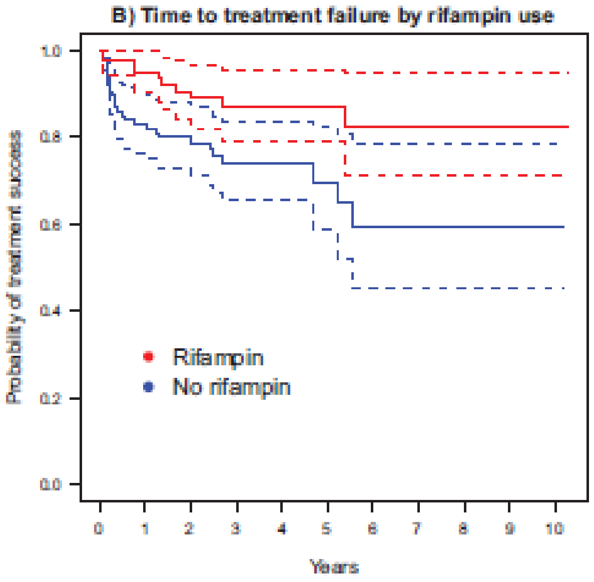

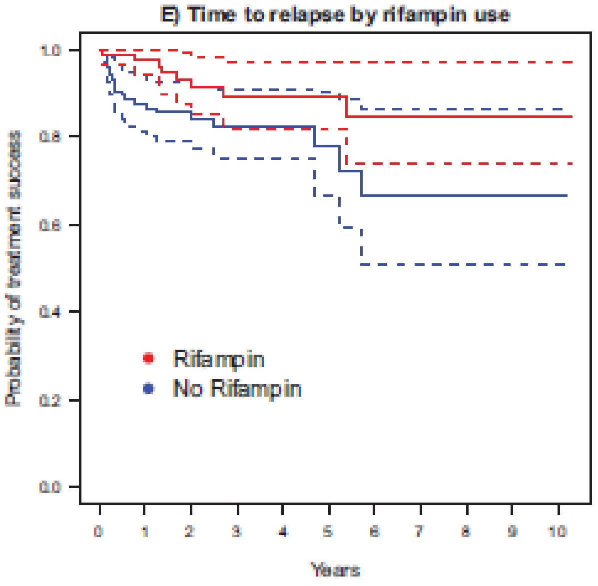

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doi:10.1093/jac/dku254

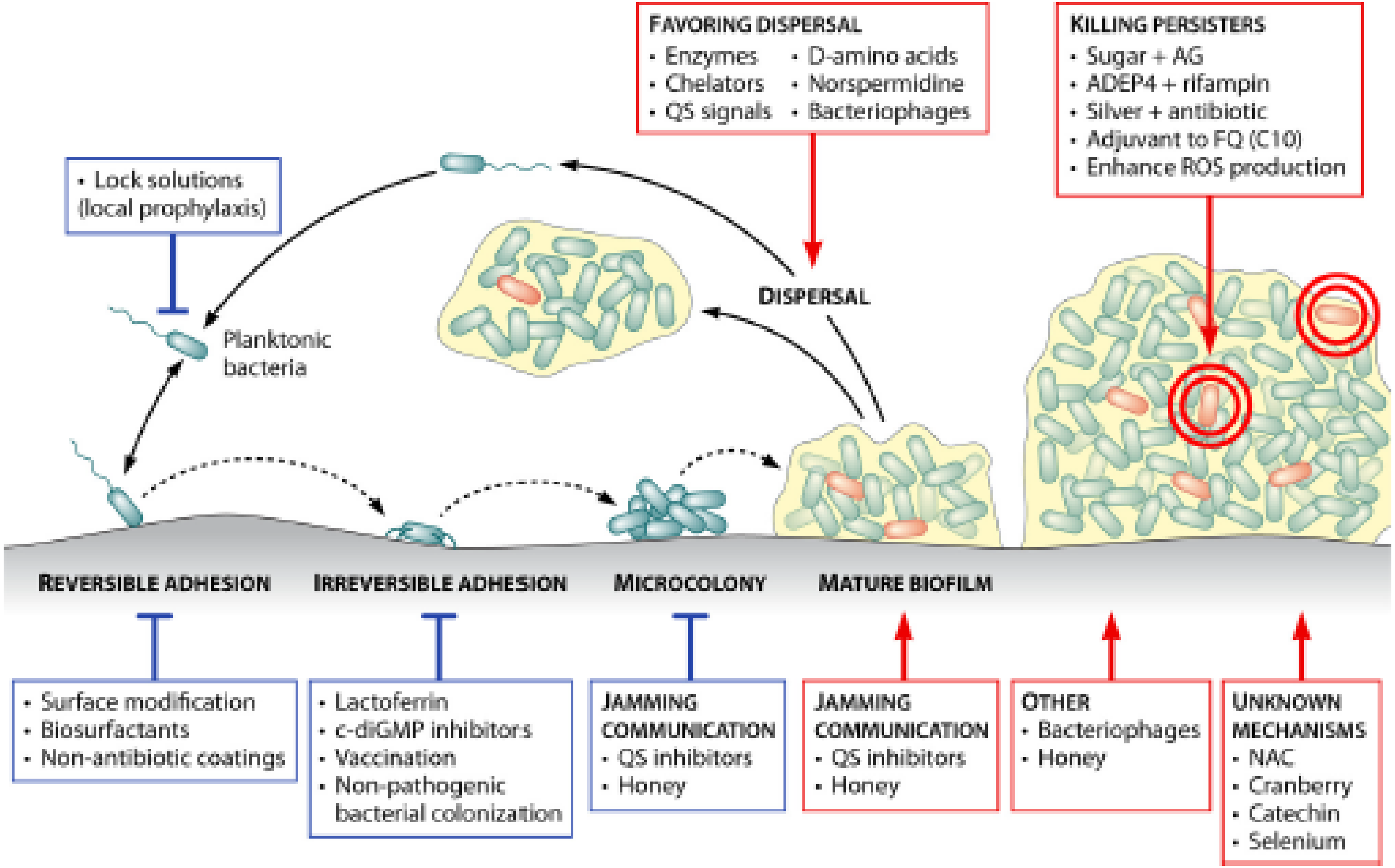
Journal of Antimicrobial Chemotherapy

Impact of bacterial biofilm on the treatment of prosthetic joint infections

Cédric Jacqueline* and Jocelyne Caillon

Antibiotics	Inhibition of biofilm formation (adhesion)	Biofilm penetration	Bactericidal activity in biofilm
Vancomycin	+	++	+
Linezolid	+	++	+
Daptomycin	+	+++	++
Rifampicin	+	+++	++
Moxifloxacin	+	++	++
Rifampicin+daptomycin	+	+++	+++
Rifampicin+vancomycin	+	++	++
Rifampicin+linezolid	+	+++	+++

« Nouvelles » stratégies



Lebeaux et al, MMBR 2014 – Chen et al, IJMS 2014

Biofilm-Related Infections: Bridging the Gap between Clinical Management and Fundamental Aspects of Recalcitrance toward Antibiotics

David Lebeaux,[a,b] Jean-Marc Ghigo,[a] Christophe Beloin[a]

ESCMID GUIDELINES

ESCMID* guideline for the diagnosis and treatment of biofilm infections 2014

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