

Antibiotiques et biofilm

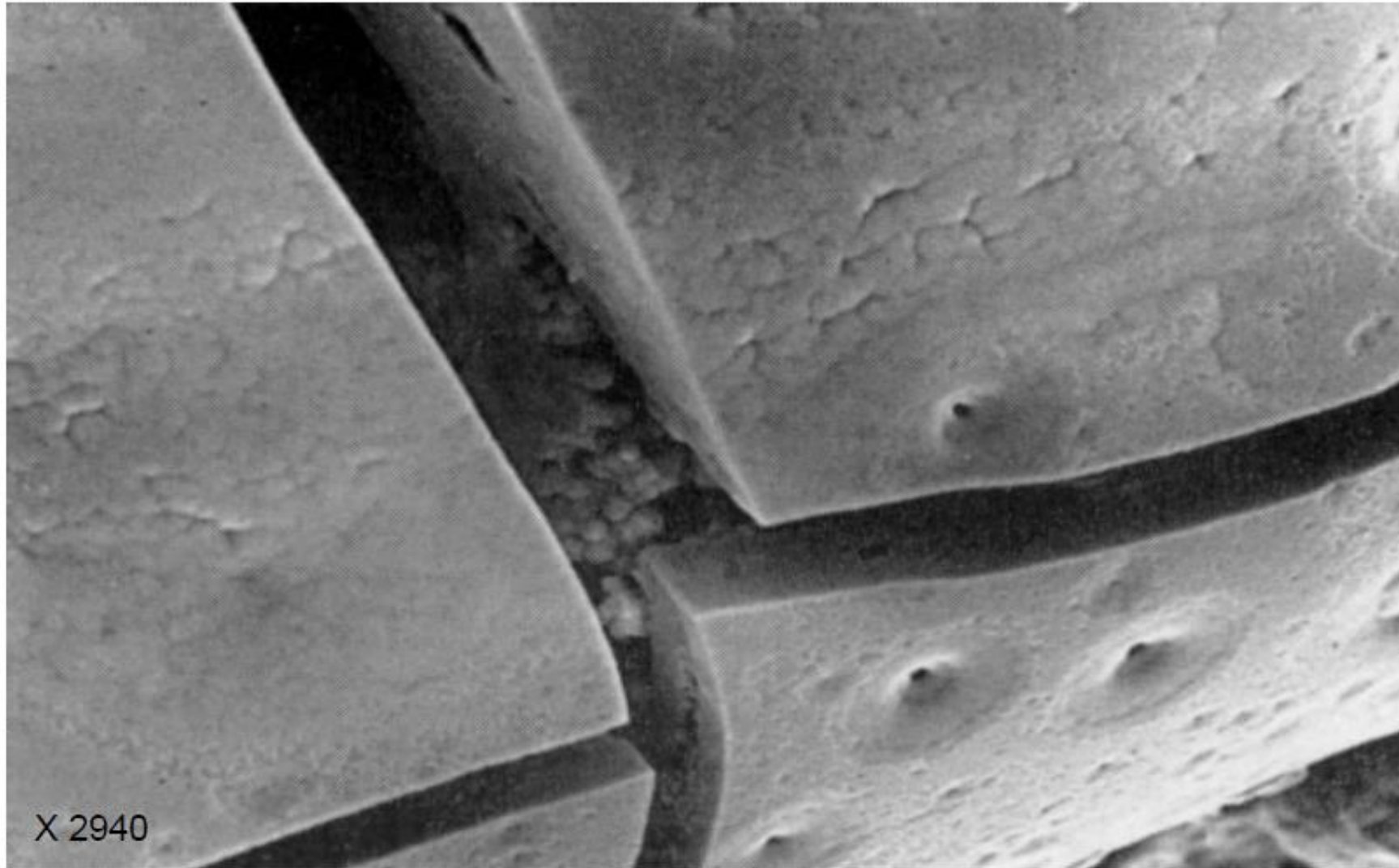
Florent Valour

Service des maladies infectieuses et tropicales – CRIOAc
Hospices Civils de Lyon

CIRI, INSERM U1111 – Faculté de médecine Lyon Sud Charles Mérieux
Université Claude Bernard Lyon 1



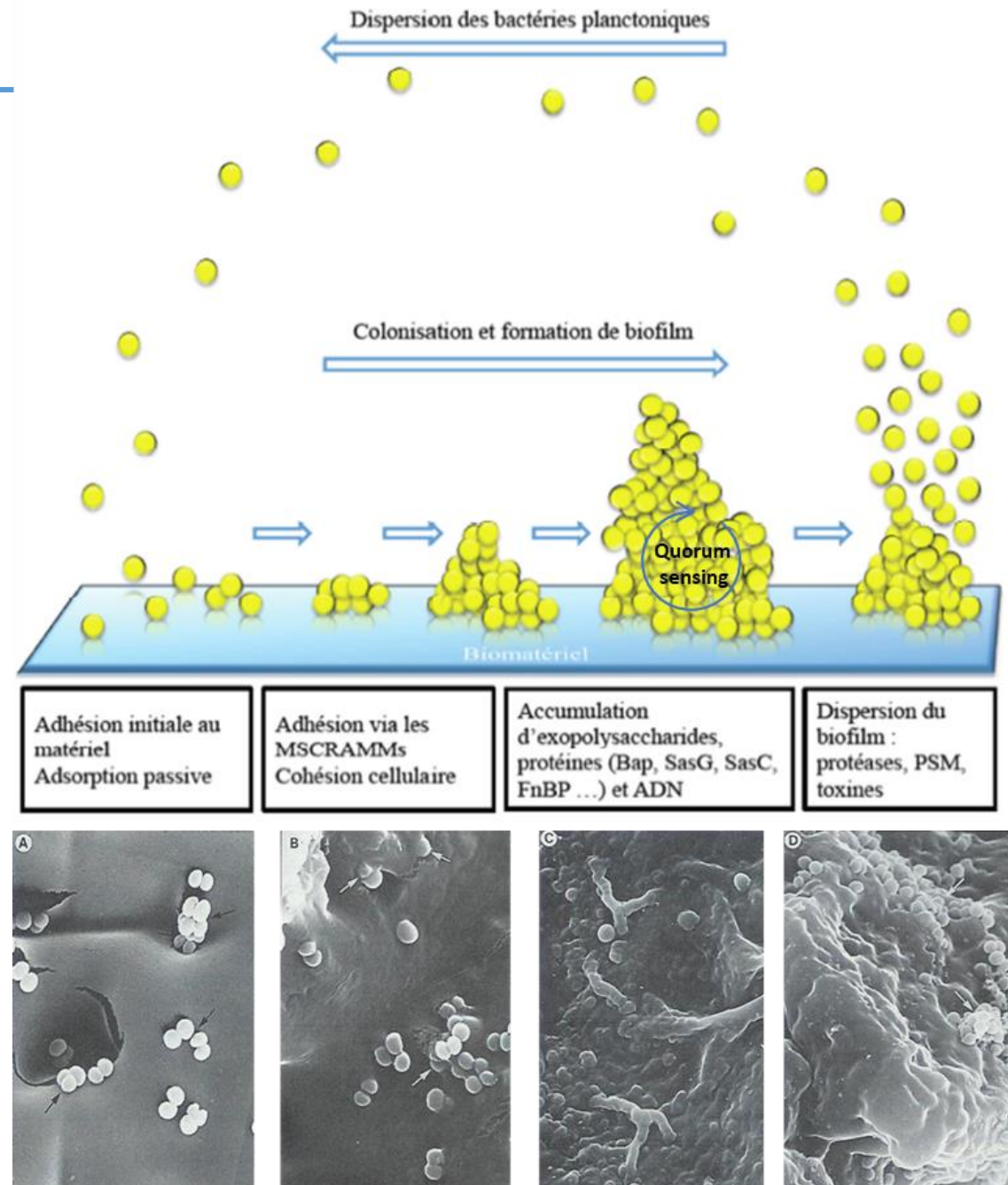
Rappels : le biofilm



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

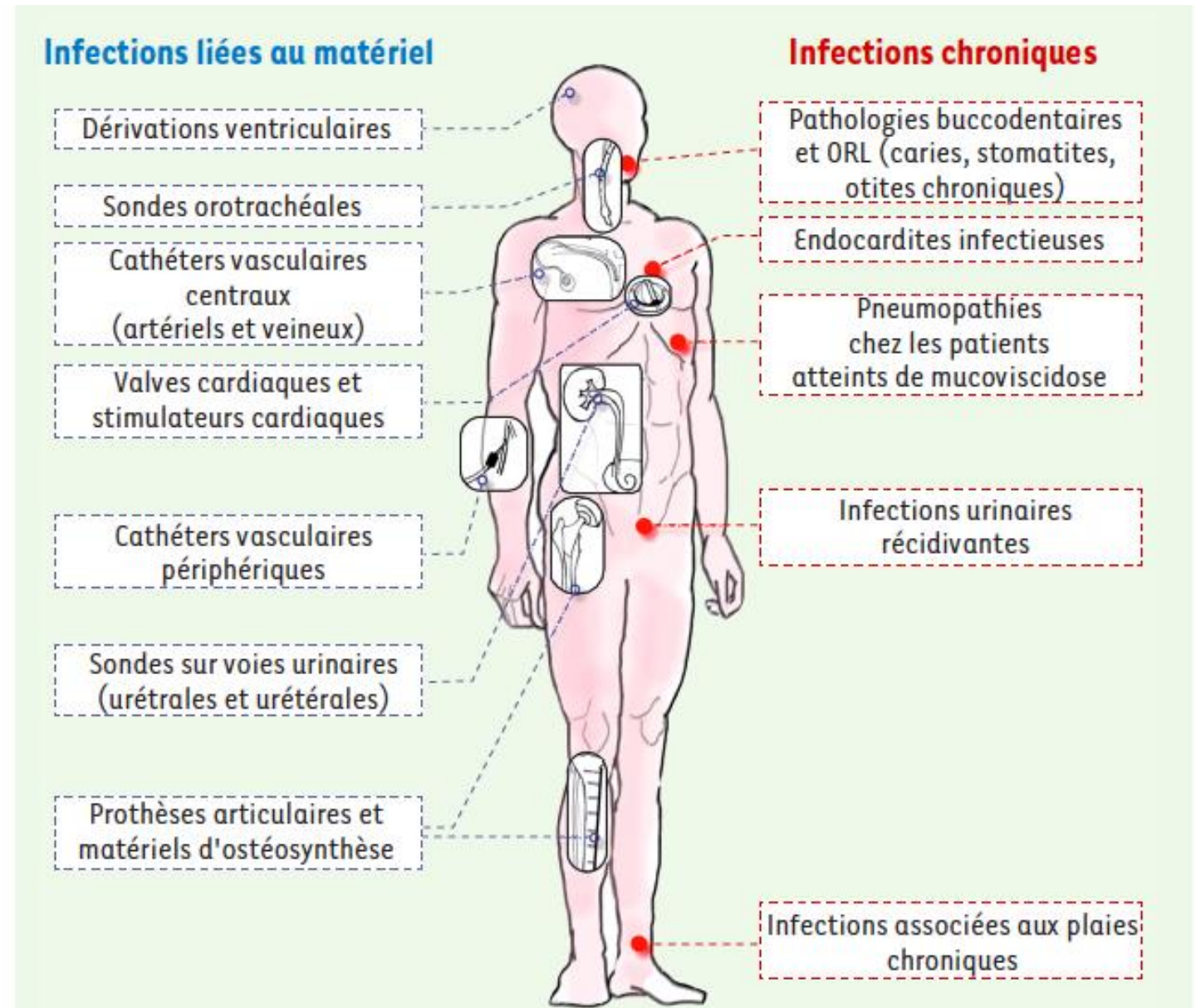
Rappels : le biofilm

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



Rappels : le biofilm

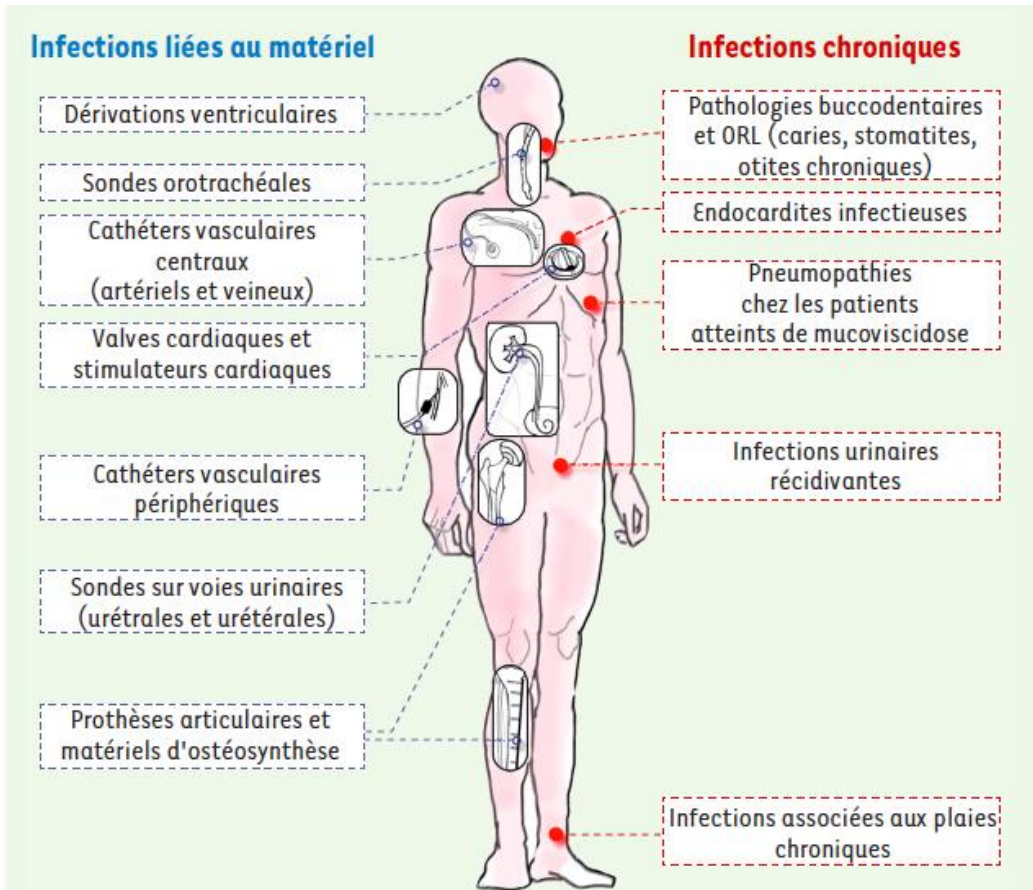
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Implications thérapeutiques

ESCMID GUIDELINES

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

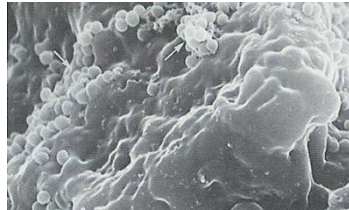


- Aucun test de sensibilité aux antibiotiques des bactéries en biofilm n'est prédictif du succès thérapeutique actuellement
- En cas d'infection sur matériel, éradication par ATB seuls possible uniquement si évolution ≤ 3 (hématogène) à 4 (inoculation) sem
- Importance des ATB « anti-biofilm », notamment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

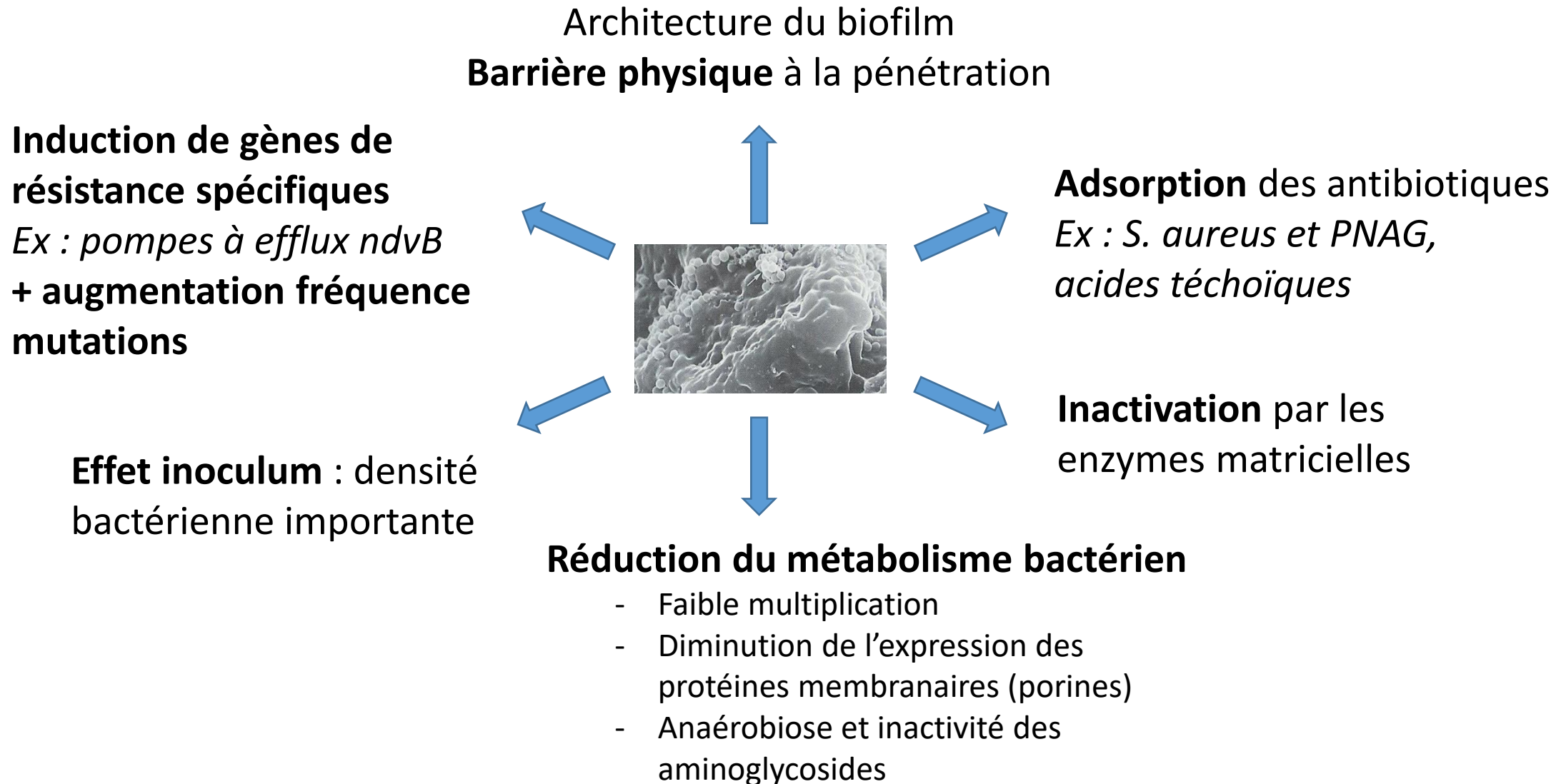
Mécanismes de « tolérance » aux antibiotiques (≠ résistance)

Microorganism	Antibiotic	Penetration
<i>P. aeruginosa</i>	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
<i>E. coli</i>	Moxalactam	Yes
	Fosfomycin	Yes
	Amoxicillin-clavulanic acid	Yes
	Ciprofloxacin	Yes
<i>K. pneumoniae</i>	Ampicillin	No
	Ciprofloxacin	Yes
<i>S. epidermidis</i>	Rifampin	Yes
	Vancomycin	Yes
	Ciprofloxacin	Yes
	Ofloxacin	Yes
	Clarithromycin	Yes
	Daptomycin	Yes
	Cefotaxime	Reduced
	Oxacillin	Reduced
	Cefotiam	Yes
	Amikacin	Yes
<i>S. aureus</i>	Vancomycin	Yes/reduced
	Cefotaxime	Reduced
	Oxacillin	Reduced
	Ciprofloxacin	Yes
	Amikacin	Yes

Architecture du biofilm
Barrière physique à la pénétration

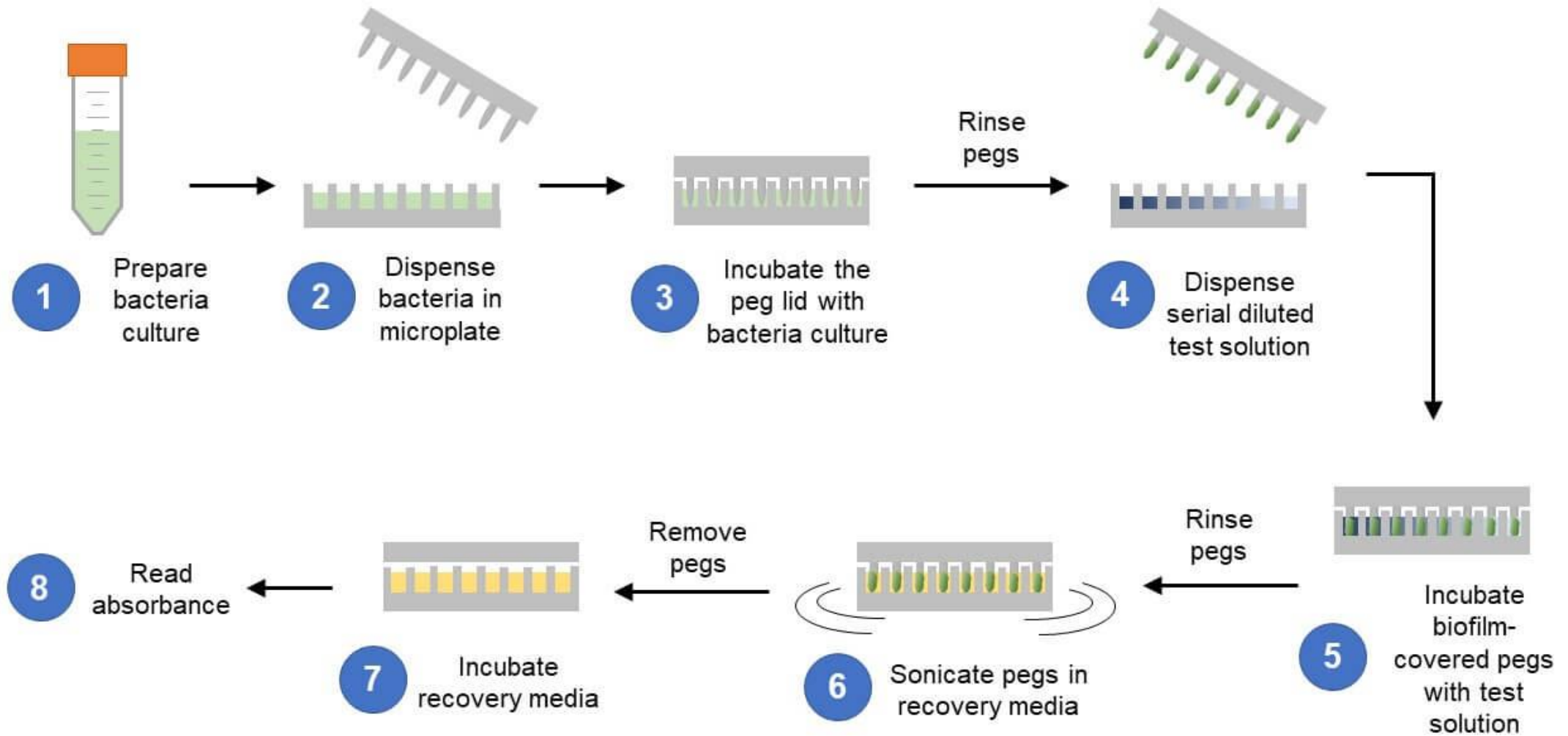


Mécanismes de « tolérance » aux antibiotiques ($\neq$ résistance)



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

MBEC assay



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 ($\mu\text{g/ml}$) NCCLS Assay†	MIC ($\mu\text{g/ml}$) Assay with CBD†	MBEC ($\mu\text{g/ml}$) A_{650} †	MBEC ($\mu\text{g/ml}$) 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 ($\mu\text{g/ml}$) NCCLS assay†	MIC ($\mu\text{g/ml}$) Assay with CBD†	MBEC ($\mu\text{g/ml}$) A_{650} †	MBEC ($\mu\text{g/ml}$) 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

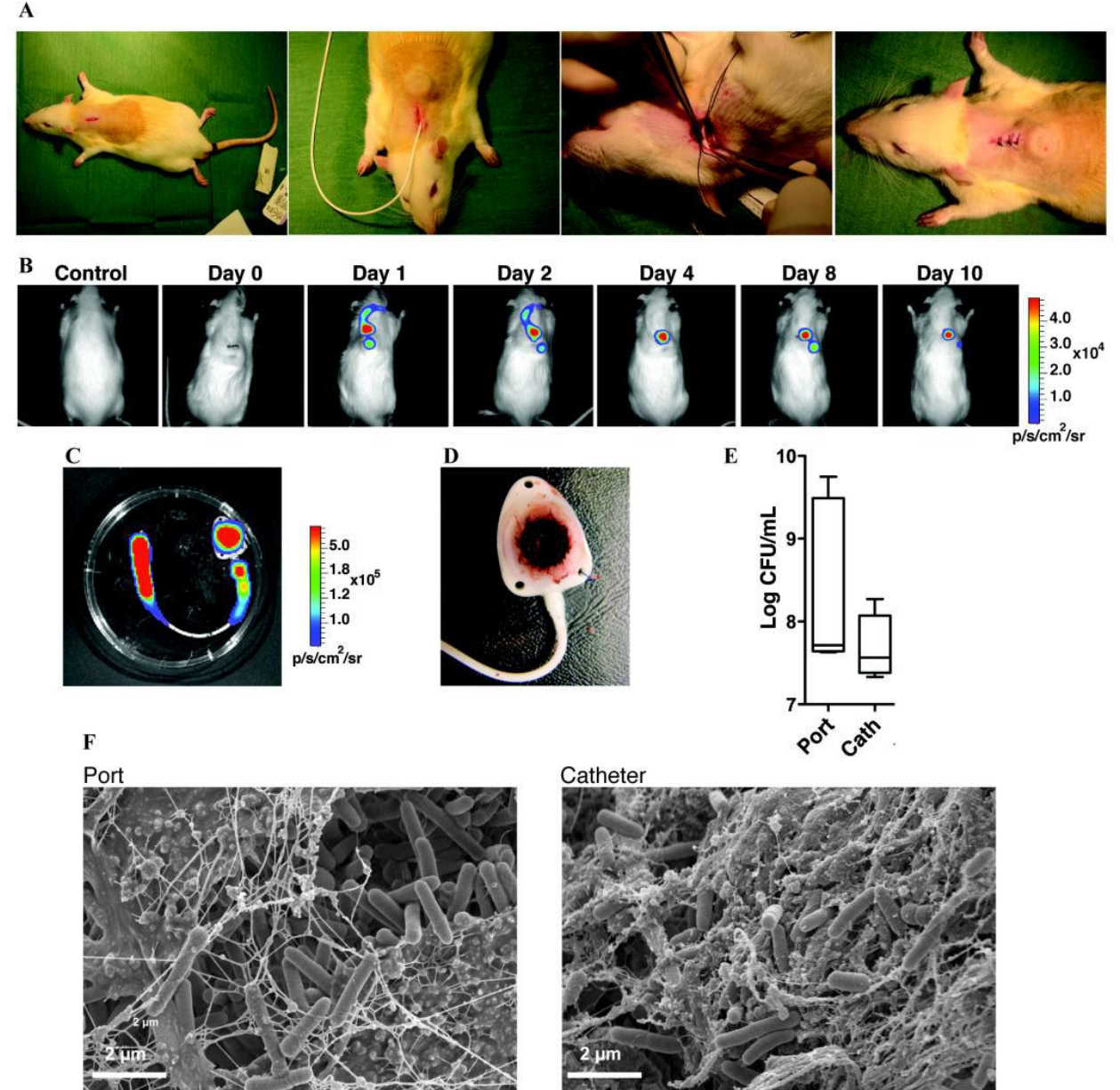
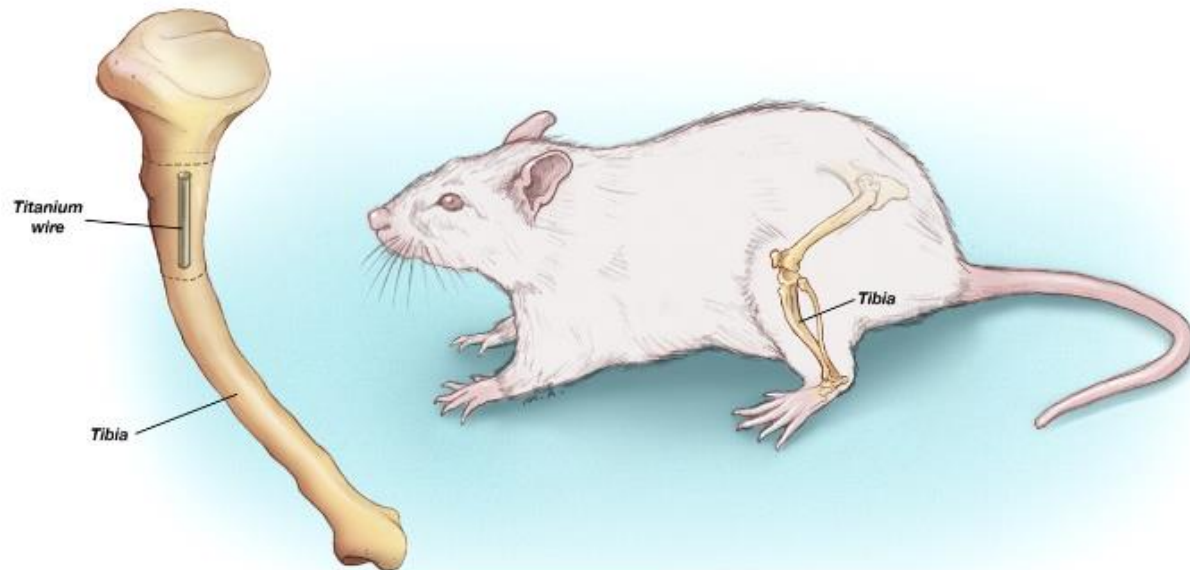
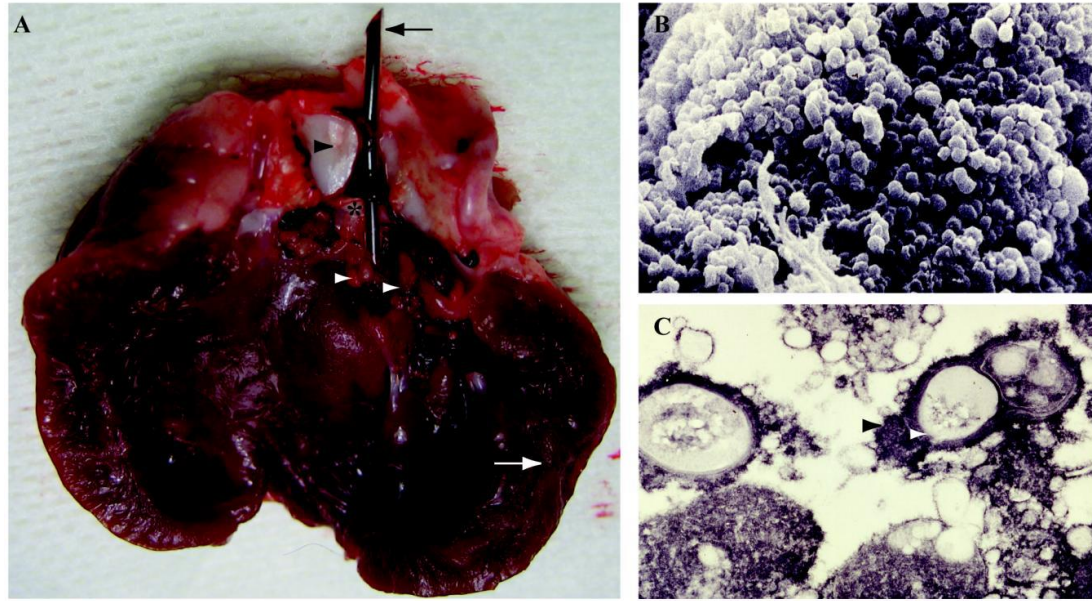
Minimum bactericidal concentrations of prosthetic hip isolates grown on polymethylmethacrylate

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)
<i>P. acnes</i> 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%
<i>S. epidermidis</i> 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*



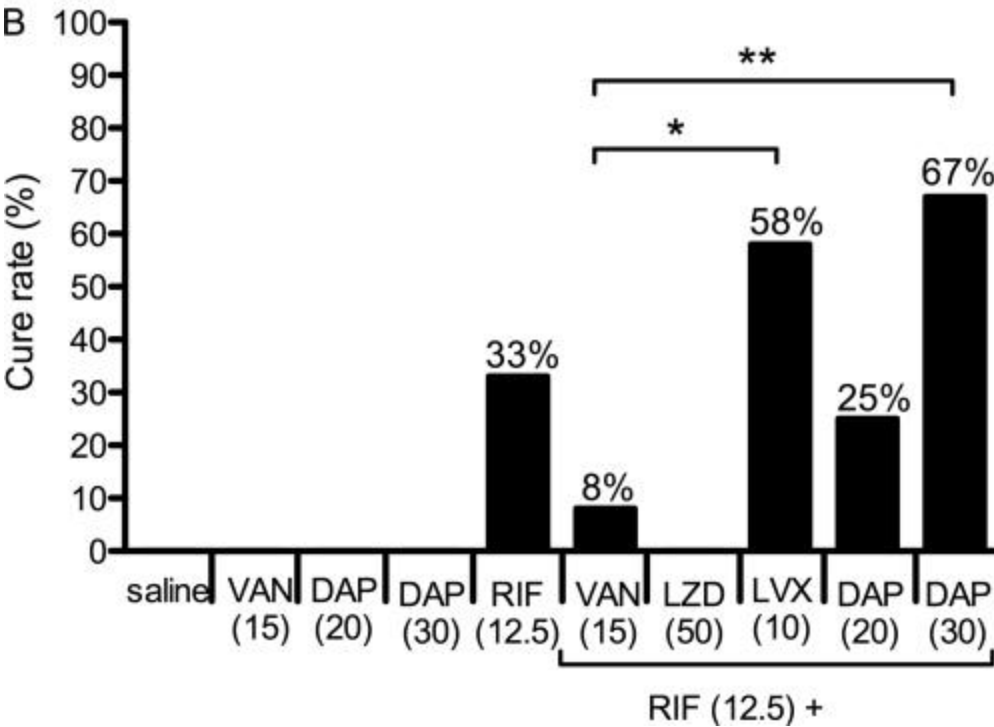
Staphylococcus aureus

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2009, p. 2719–2724
0066-4804/09/\$08.00+0 doi:10.1128/AAC.00047-09
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Vol. 53, No. 7

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		Adherent bacteria ^c after treatment (day 12)
	During treatment (day 6)	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
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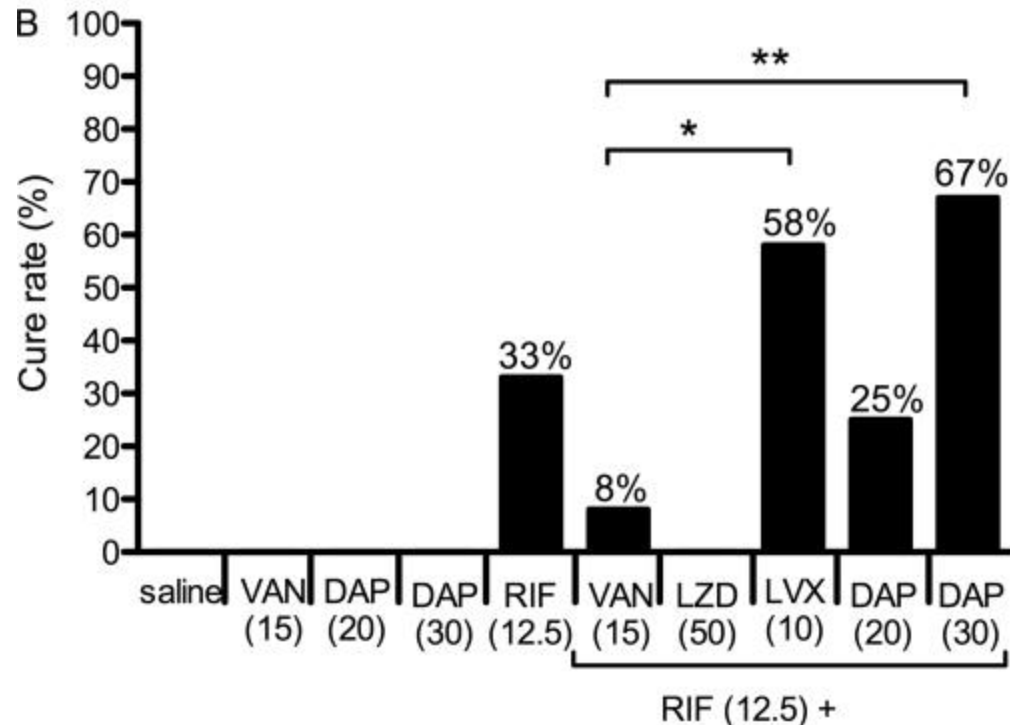
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Outcome and Predictors of Treatment Failure in Total Hip/Knee Prosthetic Joint Infections Due to *Staphylococcus aureus*

Eric Senneville, Donatienne Joulie, Laurence Legout, Michel Valette, Hervé Dezègue, Eric Beltrand, Bernadette Roseló, Thibaud d'Escrivan, Caroline Loiez, 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



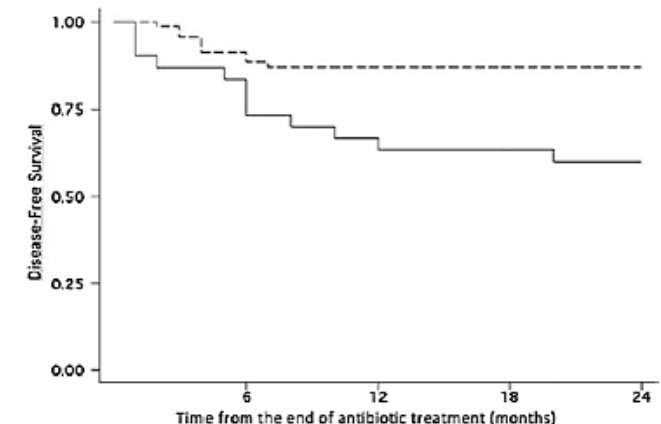
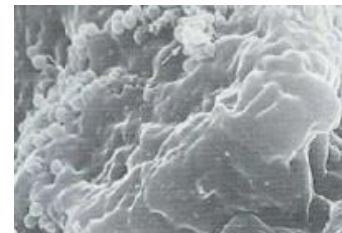
Cure rate of adherent MRSA in explanted cages

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**



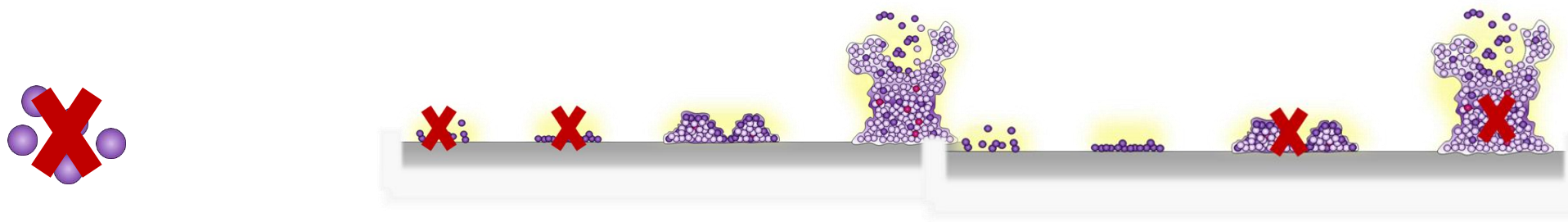
Staphylococcus aureus

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 Josse¹, Jason Tasse¹, Sébastien Lustig^{2,4,5}, Tristan Ferry^{1,2,4,6}, Alan Diot¹, 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
0066-4804/91/040741-06\$02.00/0
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Vol. 35, No. 4

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*}

Modèle cage / cochon d'Inde

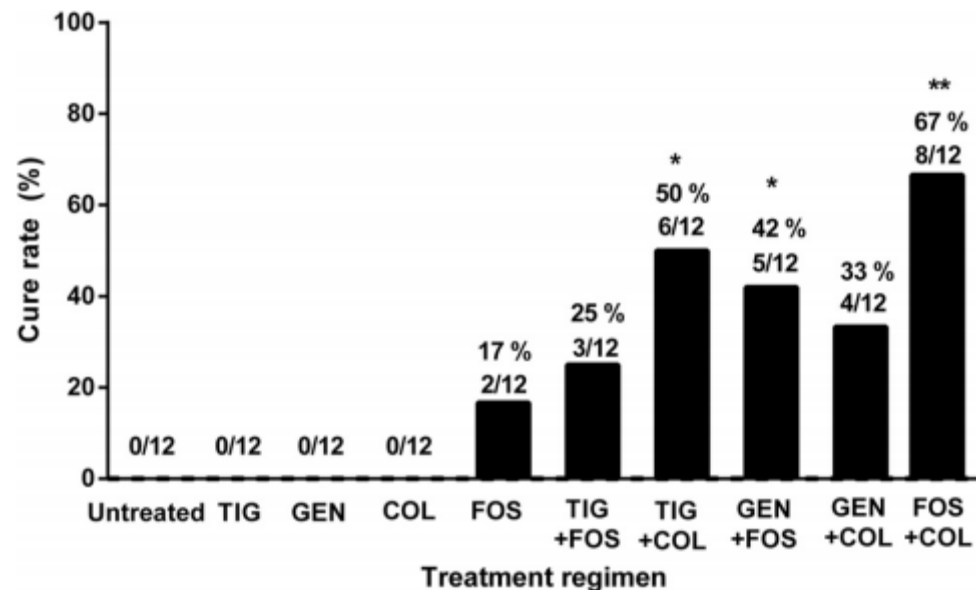
TABLE 6. Killing of glass-adherent *E. coli* ATCC 25922

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).

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 Tufin,^a Bertrand Betrisey,^a Olivier Borens,^c Andrej Trampuz^{a,d}



Bacilles Gram négatif

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 1991, p. 741-746
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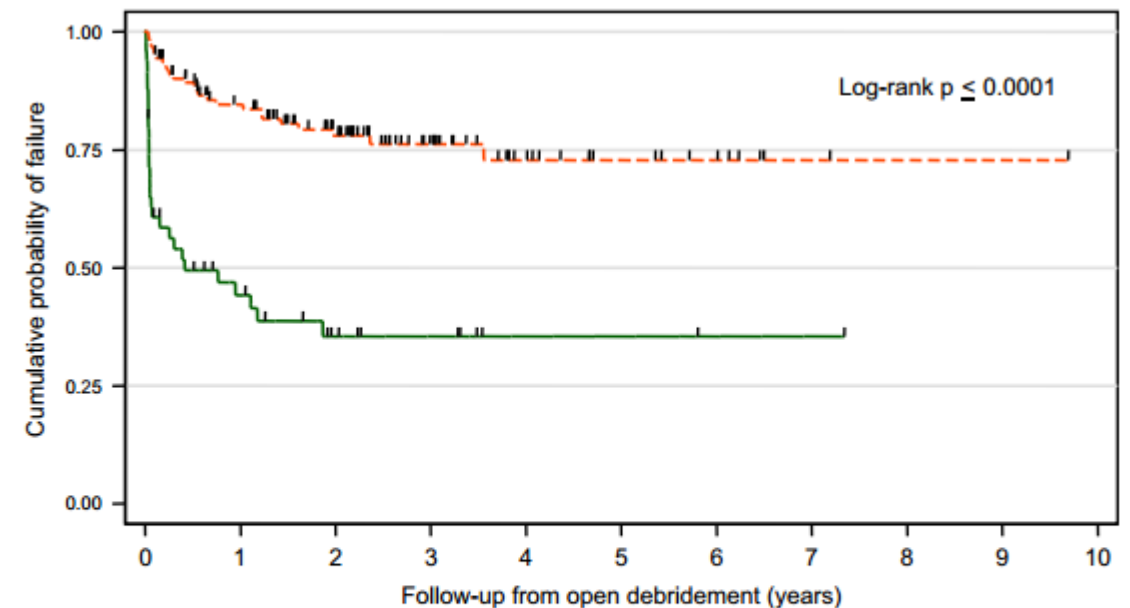
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Gram-negative prosthetic joint infection: outcome of a debridement, antibiotics and implant retention approach. A large multicentre study

D. Rodríguez-Pardo¹, C. Pigrau¹, J. Lora-Tamayo², A. Soriano³, M. D. del Toro⁴, J. Cobo⁵, J. Palomino⁶, G. Euba², M. Riera⁷, M. Sánchez-Somolinos⁸, N. Benito⁹, M. Fernández-Sampedro¹⁰, L. Sorli¹¹, L. Guio¹², J. A. Iribarren¹³, J. M. Baraia-Etxaburu¹⁴, A. Ramos¹⁵, A. Bahamonde¹⁶, X. Flores-Sánchez¹⁷, P. S. Corona¹⁷ and J. Ariza² 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)

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
0066-4804/11/\$12.00 doi:10.1128/AAC.00141-11
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Vol. 55, No. 10

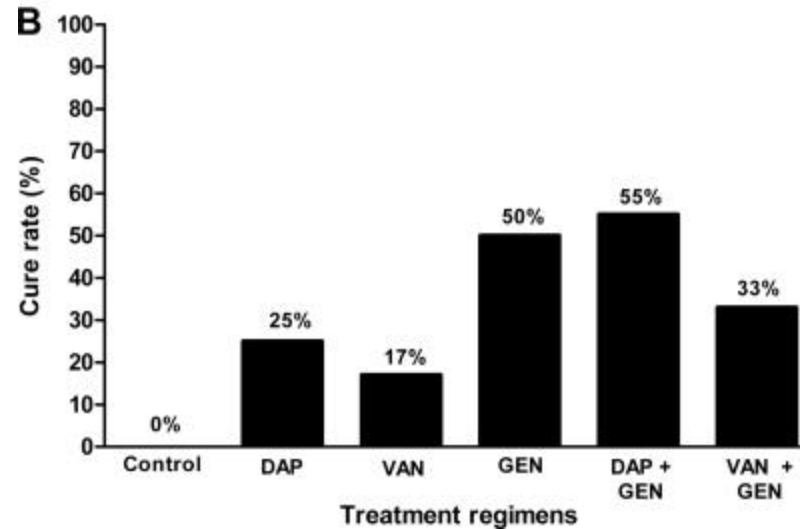
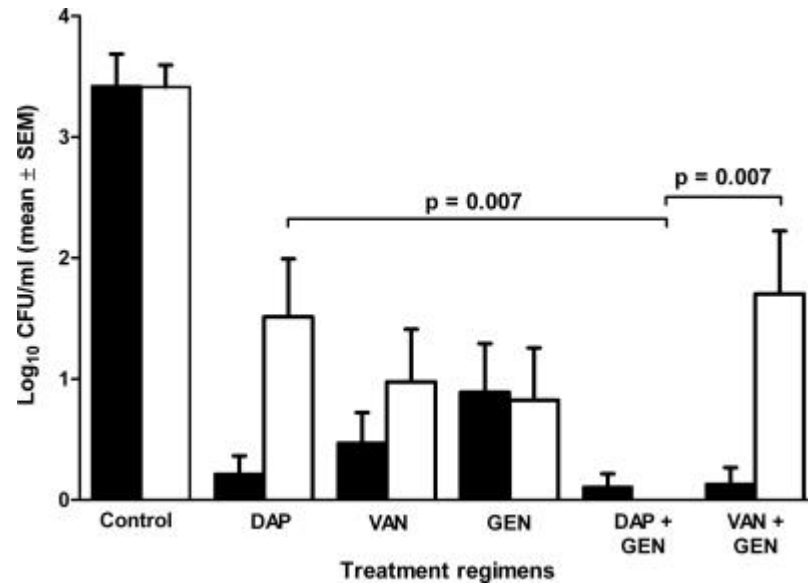
Gentamicin Improves the Activities of Daptomycin and Vancomycin against *Enterococcus faecalis* In Vitro and in an Experimental Foreign-Body Infection Model[▽]

Ulrika Furustrand Tabin,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

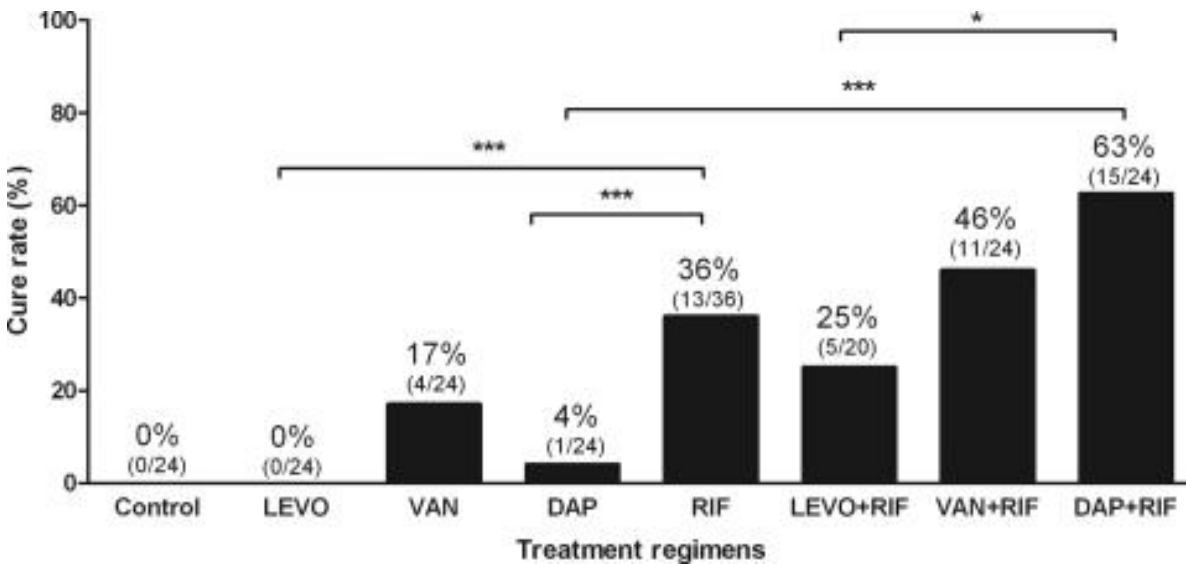
Cutibacterium acnes



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

Ulrika Furustrand Tabin,^a Stéphane Corvec,^{a,b} Bertrand Betrisey,^a Werner Zimmerli,^c and Andrej Trampuz^a

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cure rates of adherent bacteria from explanted cages

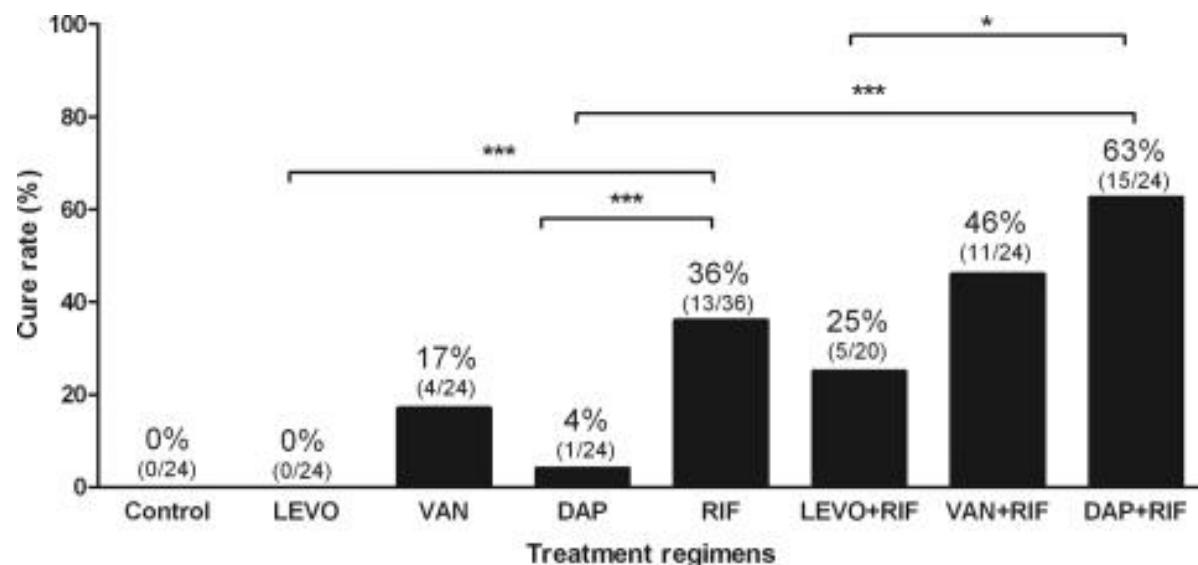
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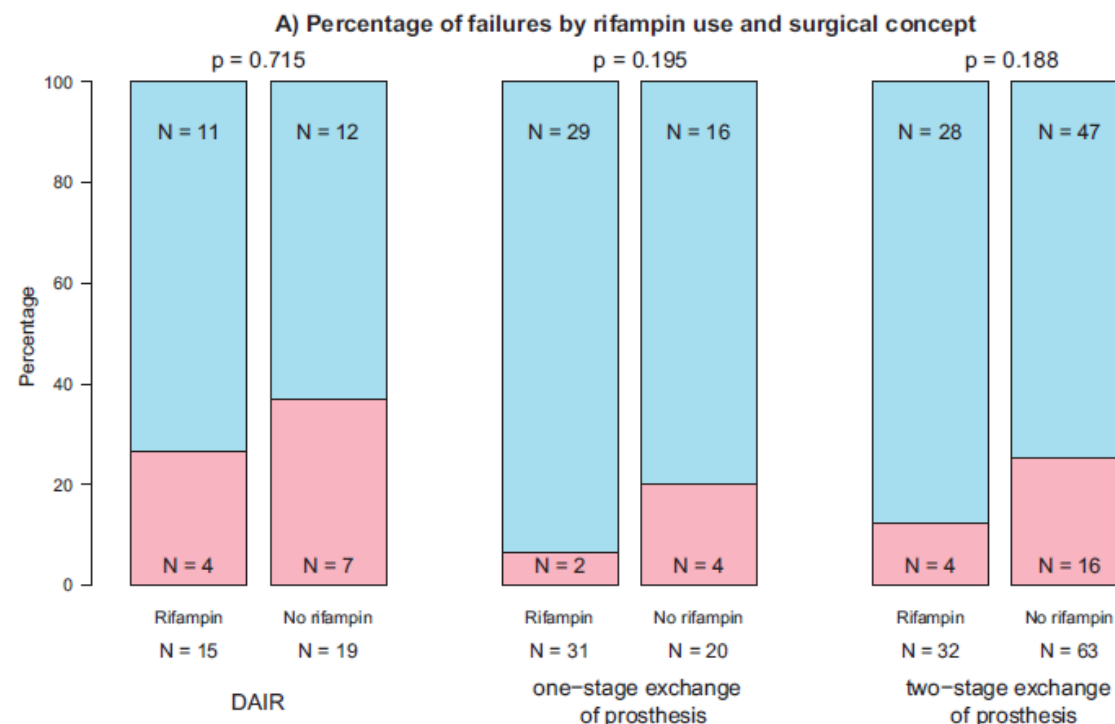
The Impact of Surgical Strategy and Rifampin on Treatment Outcome in *Cutibacterium* Periprosthetic Joint Infections

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Etude rétrospective multicentrique – n=187

81 (43%) patients sous rifampicine

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



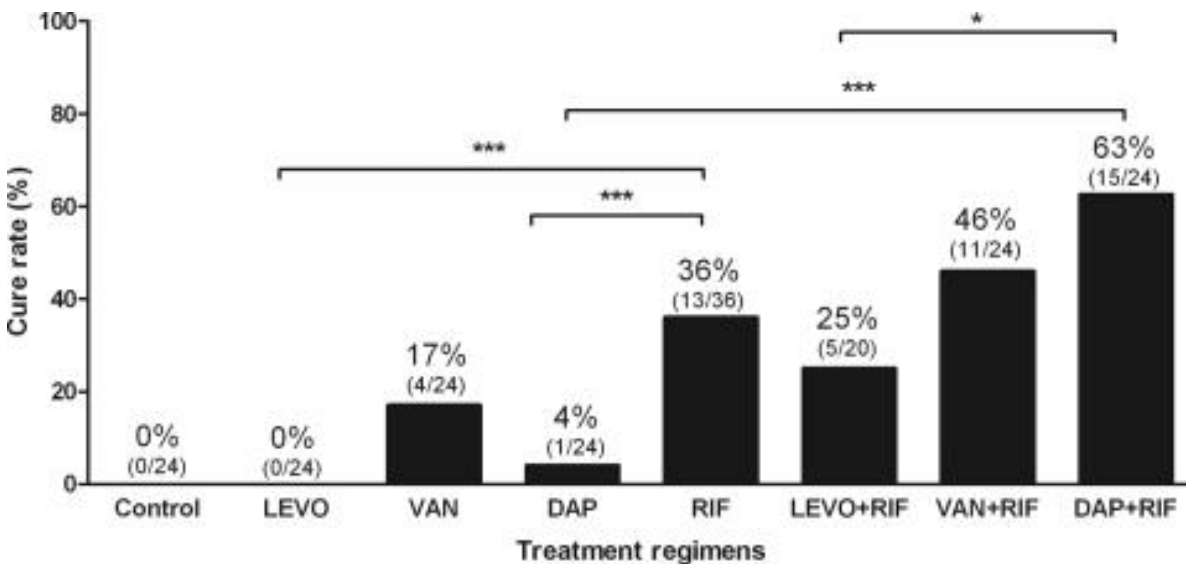
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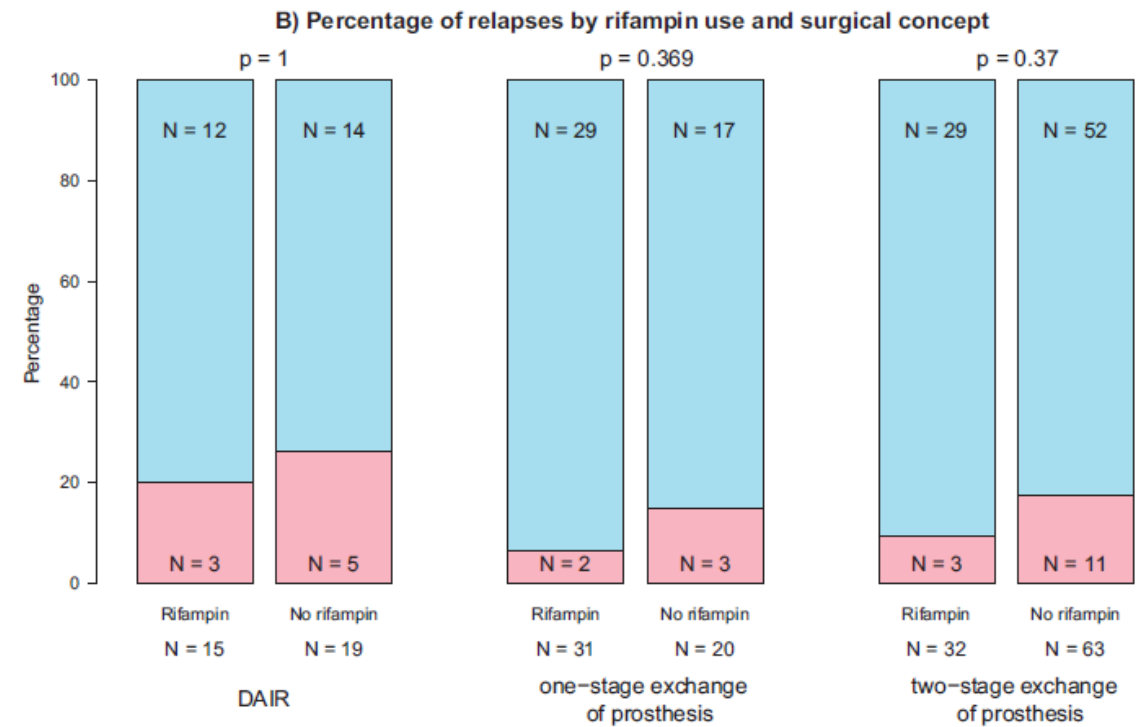
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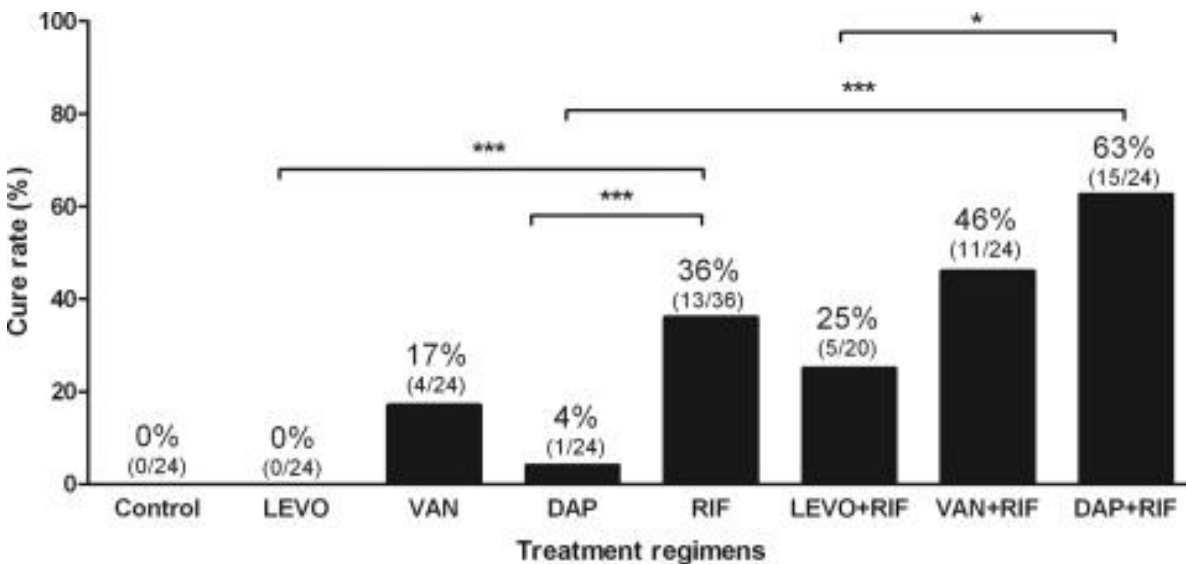
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Modèle cage / cochon d'Inde



cure rates of adherent bacteria from explanted cages

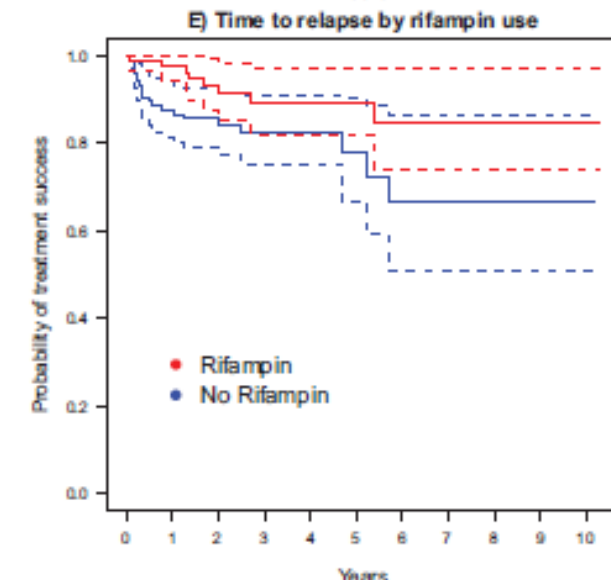
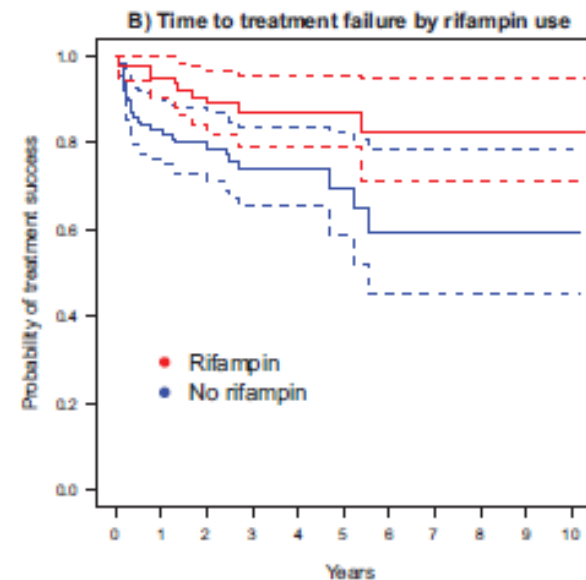
The Impact of Surgical Strategy and Rifampin on Treatment Outcome in *Cutibacterium* Periprosthetic Joint Infections

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,^{9,*} 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 (ESGII)

Etude rétrospective multicentrique – n=187

81 (43%) patients sous rifampicine

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

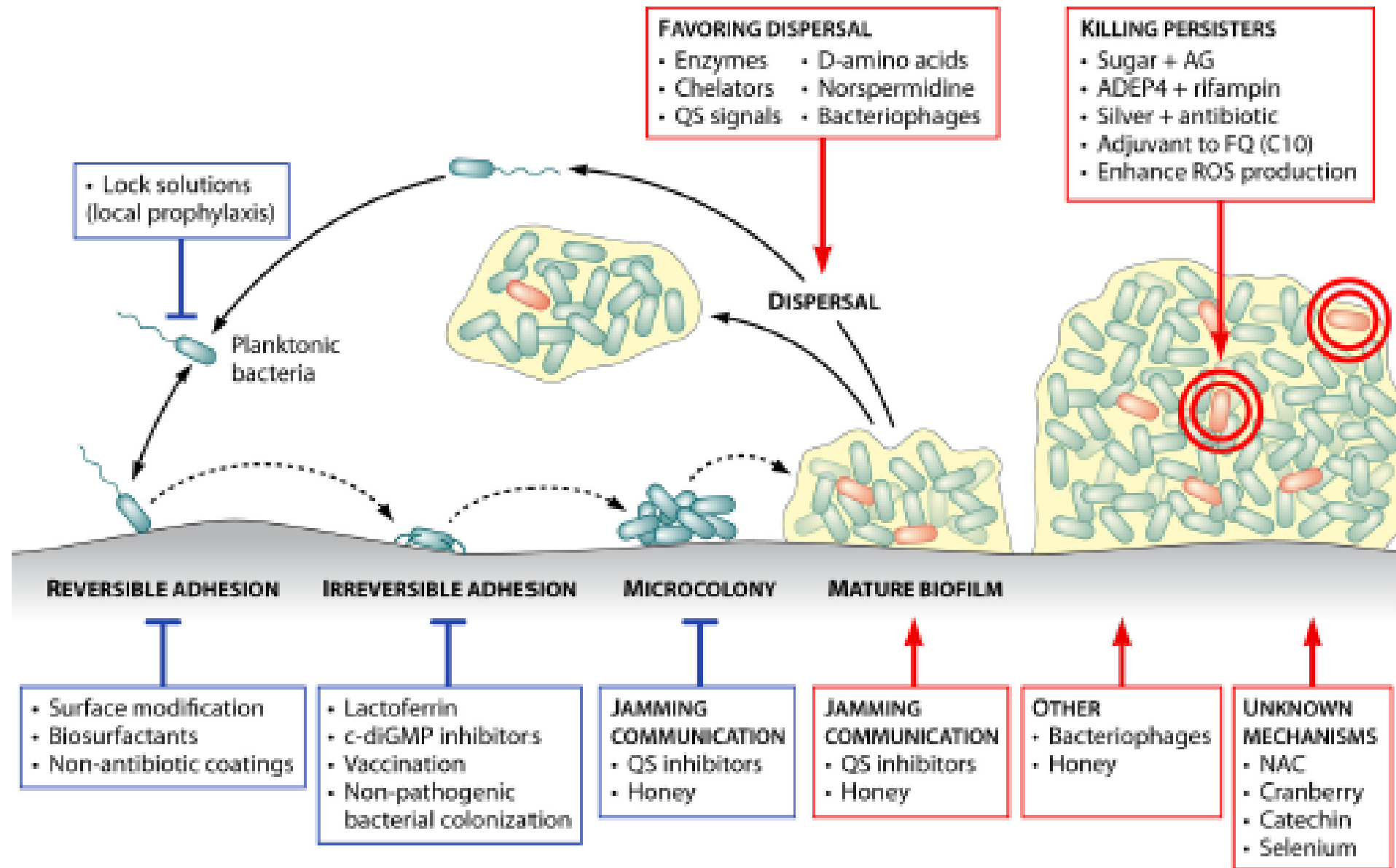


Impact of bacterial biofilm on the treatment of prosthetic joint infections

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



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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Impact of bacterial biofilm on the treatment of prosthetic joint infections

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