

Infections de prothèse articulaire

Impact clinique des facteurs liés à l'hôte et des mécanismes de persistance bactérienne

Florent Valour

Maladies infectieuses et tropicales – CRIOAc Lyon – Hospices Civils de Lyon

INSERM U1111 – CIRI

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Déclaration de liens d'intérêt avec les industries de santé en rapport avec le thème de la présentation (loi du 04/03/2002) :

Intervenant : Valour Florent

Titre : Coopération virus - autres agents infectieux

- Consultant ou membre d'un conseil scientifique OUI NON
- Conférencier ou auteur/rédacteur rémunéré d'articles ou documents
Sanofi OUI NON
- Prise en charge de frais de voyage, d'hébergement ou d'inscription à des congrès
Sanofi-Pasteur, Pfizer, Astellas, Amgen, Gilead, MSD, Viiv OUI NON
- Investigateur principal d'une recherche ou d'une étude clinique OUI NON

Facteurs liés à l'hôte

Modifiable Host Factors

- BMI - Strong
- Smoking - Strong
- High alcohol intake (alcohol abuse) - Strong
- Low income - Strong
- Malnutrition (low serum albumin) - Strong
- History of DM - Strong
- History of CVD - Moderate
- History of CHF - Strong
- History of cardiac arrhythmia - Strong
- History of PVD - Strong
- Chronic pulmonary disease - Strong
- Chronic obstructive pulmonary disease - Strong
- History of renal disease - Strong
- History of liver disease/cirrhosis - Strong
- History of RA - Strong
- History of cancer/malignancy - Strong
- History of osteonecrosis - Strong
- History of depression - Strong
- History of psychosis - Strong
- History of HIV/AIDS - Strong
- Neurologic disease (hemiplegia, paraplegia) - Moderate
- History of corticosteroid administration - Strong
- History of intra-articular corticosteroid injection - Moderate
- Previous joint surgery - Strong
- Revision arthroplasty - Strong
- Previous joint infection - Moderate
- Frailty - Moderate
- Preoperative anemia - Strong
- ASA grade > 2 - Strong
- Charlson comorbidity index (high) - Strong
- Preoperative hyperglycemia and high HbA_{1c} - Moderate
- Allogeneic blood transfusion - Strong
- Prophylaxis with warfarin or low molecular weight heparin - Moderate

Non-modifiable Host Factors

- Age (>75 years) - Moderate
- Male sex - Strong
- Black race - Strong
- TKA vs. THA - Strong

- BMI, dénutrition
- Tabac et alcool
- Anémie préopératoire
- Comorbidités
 - ID
 - Db déséquilibré
 - PR



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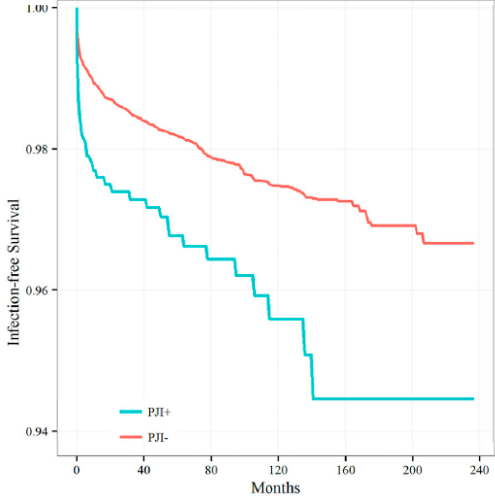


Facteurs génétiques ?

Familial Clustering Identified in Periprosthetic Joint Infection Following Primary Total Joint Arthroplasty

A Population-Based Cohort Study

Mike B. Anderson, MSc, Karen Curtin, PhD, Jathine Wong, BS, Christopher E. Pelt, MD, Christopher L. Peters, MD, and Jeremy M. Gilliland, MD



ATCD PJI 1^e degré
HR = 2,2 (1,2-2,6)

ATCD PJI 1^e/2^e degrés
HR = 1,8 (1,2-2,6)

(après ajustement sur les principaux FR de PJI)

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Facteurs génétiques ?

Genetic susceptibility to prosthetic joint infection following total joint arthroplasty: A systematic review

Xindie Zhou ^a, Mumingjiang Yishake ^b, Jin Li ^d, Lifeng Jiang ^d, Lidong Wu ^d, Ruiping Liu ^{c,*}, Nanwei Xu ^{a,*}

Study and year	Eligible subjects (n)		Genotyping method	Genotype	QAS
	Septic	Aseptic			
Malik_2006	63	150	PCR	OPG-163 OPG-245 OPG + 1181	11
Malik_2007_a	62	144	PCR	RANK + 575 MBL-221 MBL-550	11
Malik_2007_b	62	148	PCR	MBL codon 52 MBL codon 54 MMP1-1 (rs5854) MMP1-3 (rs2397776) MMP1-4 (rs470747) VDR-T, VDR-L	11
Douglas_2008 ^a	286	209	PCR	IL6-174	7
El-Helou_2011	76	208	PCR	TLR2 R753Q	11
Stahelova_2012	89	214	PCR	IL-1B-511 (rs16944), IL-1B + 3962 (rs1143634), TNF-308 (rs1800629), TNF-238 (rs361525), IL6-174 (rs1800795), IL-6nt565 (rs1800797)	10
Malik_2012 ^a	71	150	PCR	OPG-163, OPG-245, OPG + 1181, RANK + 575	7
Navratilova_2012_a	98	253	PCR-SSP	IL-17A (rs2275913), IL-17F (rs763780), IL-4 (rs22432597), IL-12A (rs583911), IL-12B (rs3212227), IL-12B (rs17860508), IL-23R (rs7517847), CXCL1 (rs4074), CXCL5 (rs425535), CXCR2 (rs2230054)	10
Navratilova_2012_b	112	245	PCR-SSP, PCR	MBL2 - 550 (rs11003125), MBL2 - 221 (rs7096206), MBL2 + 54 (rs1800450)	10
Navratilova_2014	98	251	PCR-SSP	OPG-163 (rs3102735)	10
Mrazek_2013	98	252	PCR	TLR2 R753Q (rs5743708), TLR4 D299G (rs4986790), TLR4 T399I (rs4986791)	11

Immunité innée, mannose binding lectine ?

Rôle du matériel

Semin Immunopathol (2011) 33:295–306
DOI 10.1007/s00281-011-0275-7

REVIEW

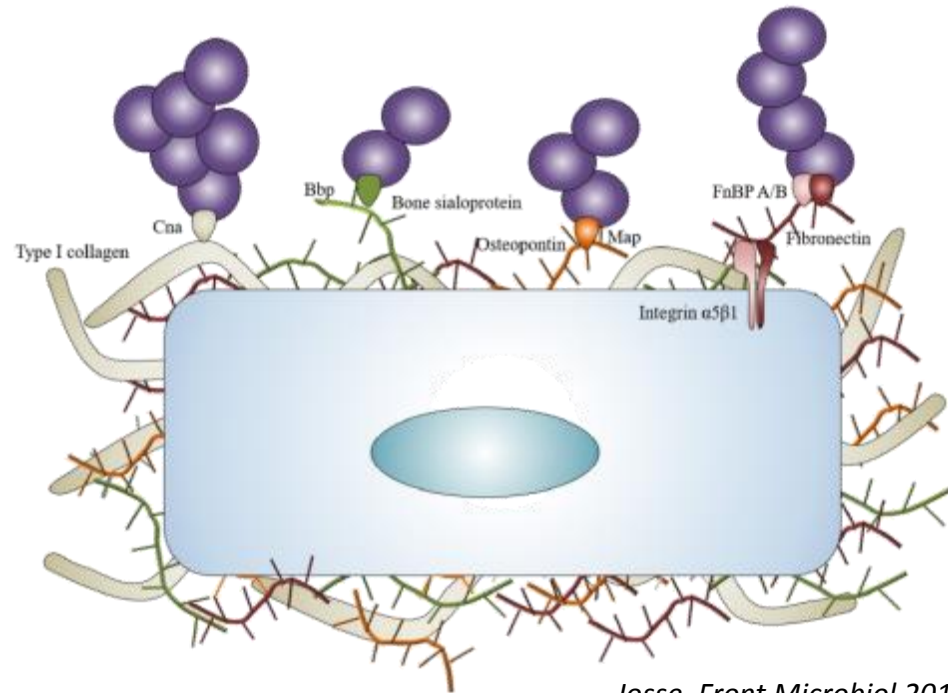
Pathogenesis of implant-associated infection: the role of the host

Werner Zimmerli · Parham Senti

1. Couverture par matrice extracellulaire

Collagène, fibrine, fibrinogène ...

→ Adhésion, initiation formation de biofilm



Rôle du matériel

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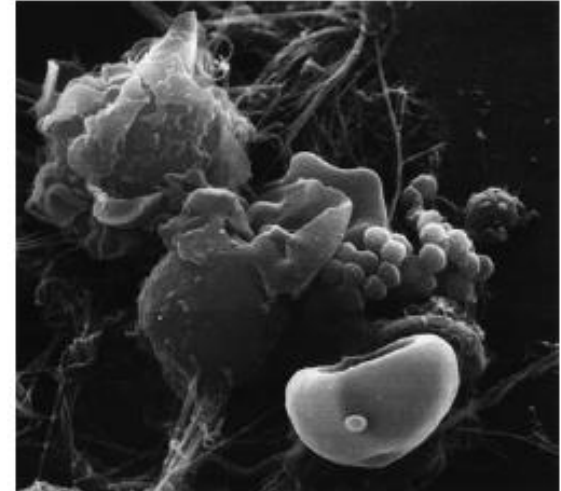
Collagène, fibrine, fibrinogène ...

→ Adhésion, initiation de la formation de biofilm

2. Inhibition locale de l'immunité innée

- inhibition de la phagocytose
- dégranulation des PNN
- mort cellulaire
- activation du complément

→ Diminution +++ de la clairance bactérienne



Pathogenesis of Foreign Body Infection Evidence for a Local Granulocyte Defect

Werner Zimmerli, P. Daniel Lew,
and Francis A. Waldvogel

*Infectious Disease Division, Department of Medicine, University
Hospital, 1211 Geneva 4, Switzerland*

Rôle du matériel

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REVIEW

Pathogenesis of implant-associated infection: the role of the host

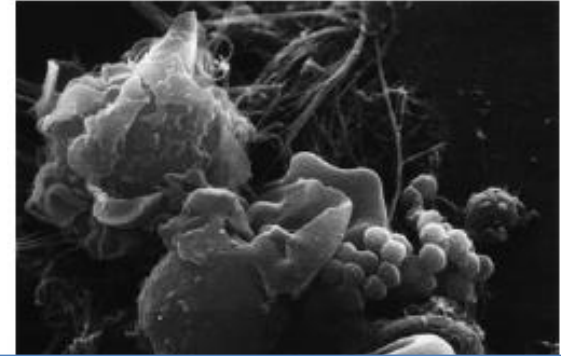
Werner Zimmerli · Parham Senti

1. Couverture par matrice extracellulaire
2. Inhibition locale de l'immunité innée

→ IOA d'INOCULATION

Quantité de *S. aureus* nécessaire
à l'obtention d'une infection
/ 100 000 en présence de matériel

Idem S. epidermidis, P. acnes



THE VIRULENCE OF *STAPHYLOCOCCUS PYOGENES* FOR MAN.
A STUDY OF THE PROBLEMS OF WOUND INFECTION

S. D. ELEK AND P. E. CONEN

*From the Department of Bacteriology, St. George's Hospital Medical School
(University of London), London, S.W.1*

Received for publication 9 August, 1957

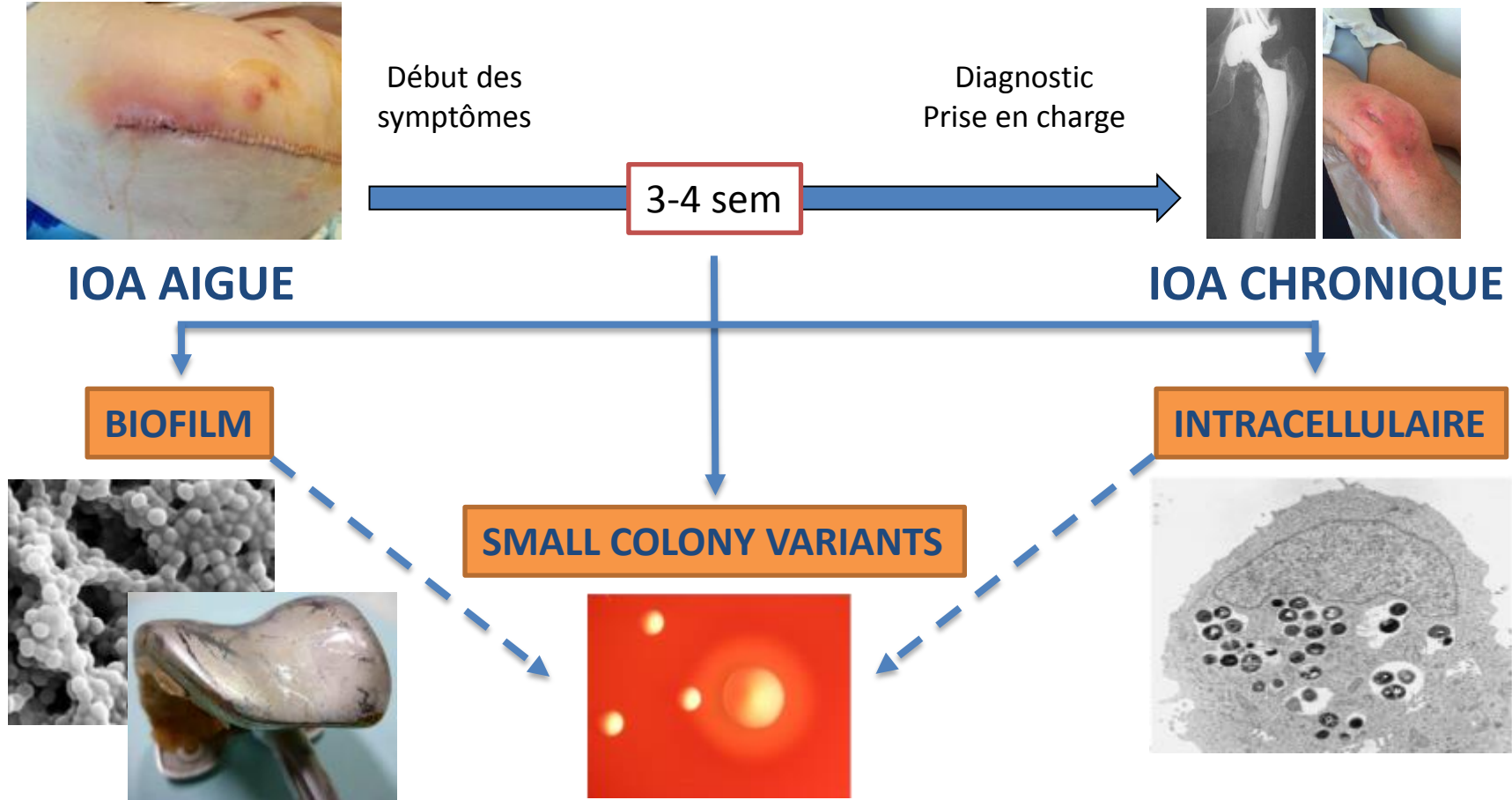
THE JOURNAL OF INFECTIOUS DISEASES • VOL. 146, NO. 4 • OCTOBER 1982
© 1982 by The University of Chicago. All rights reserved. 0022-1899/82/4604-0007\$01.02

**Pathogenesis of Foreign Body Infection: Description and
Characteristics of an Animal Model**

Werner Zimmerli, Francis A. Waldvogel,
Pierre Vaudaux, and Urs E. Nydegger

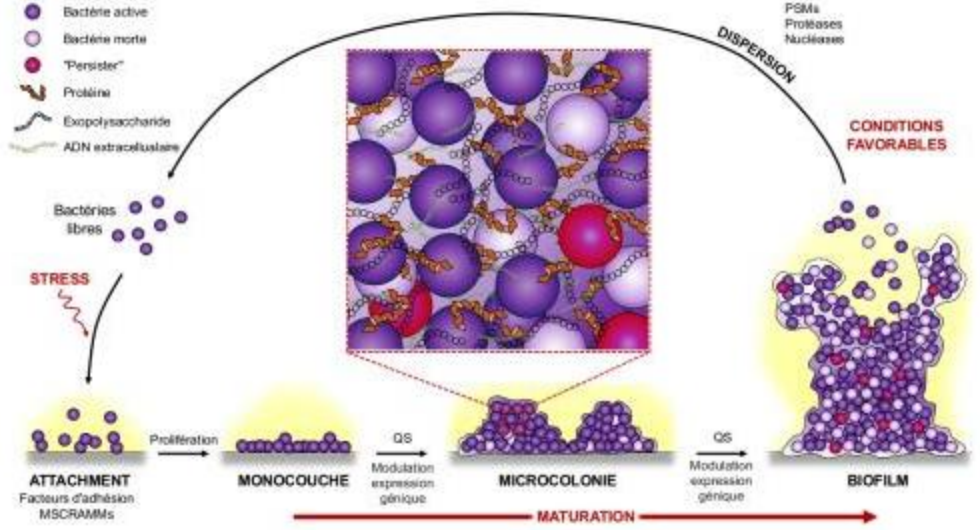
*From the Divisions of
Department
Univer*

IOA chronique et persistance bactérienne

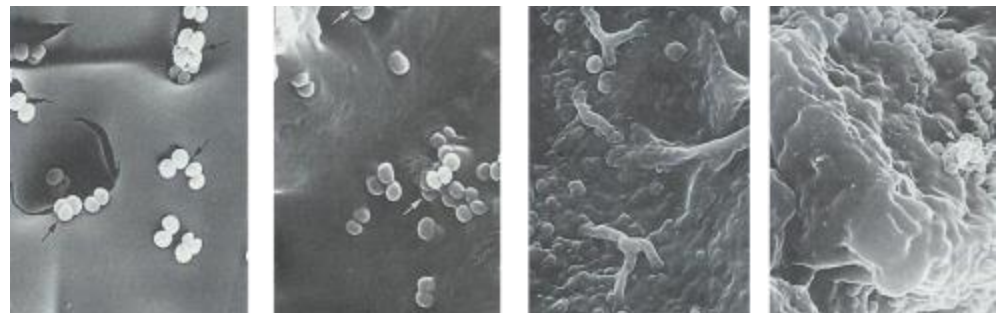
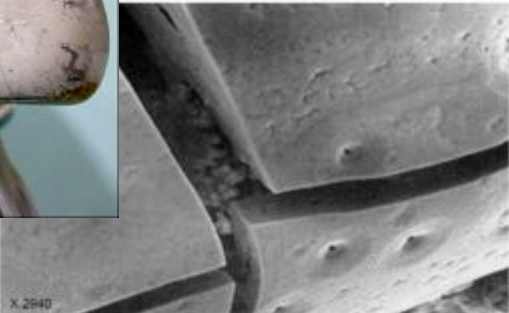


Biofilm

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



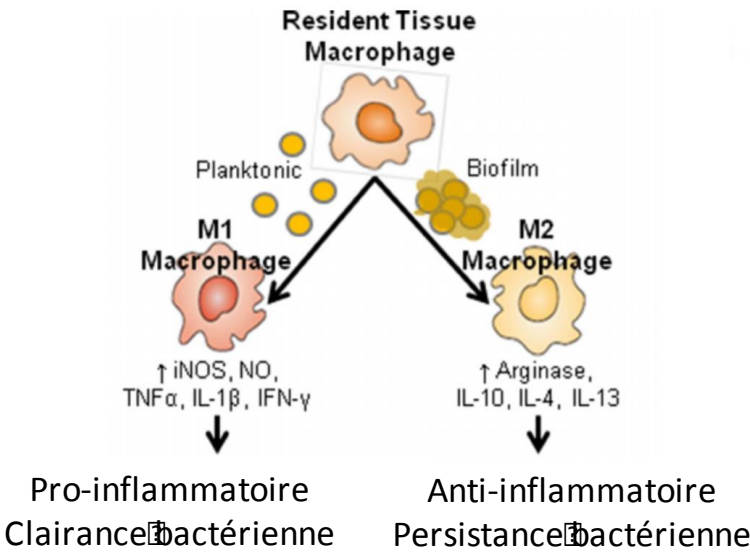
Biofilm et séquestre osseux
Evans et al. Clin Orthop 1998: 243-249



Biofilm : échappement au système immunitaire

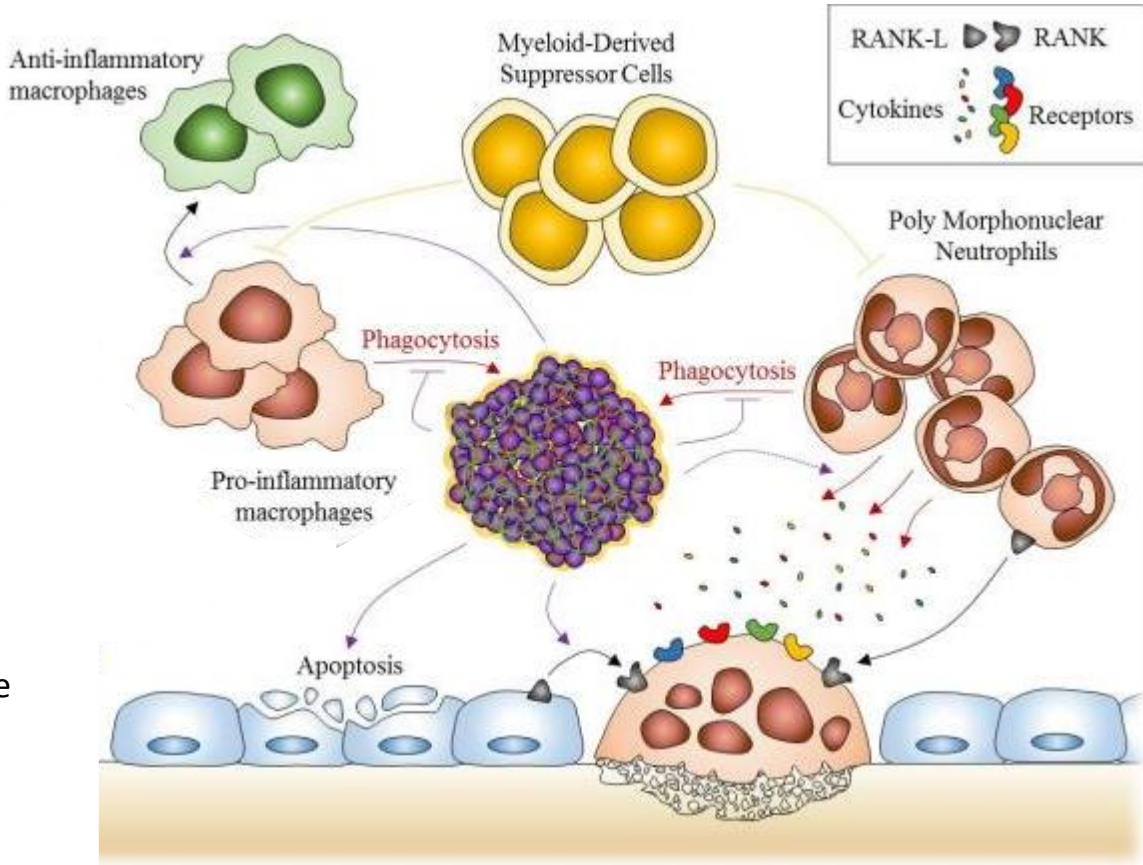
Staphylococcus aureus Biofilms Prevent Macrophage Phagocytosis and Attenuate Inflammation In Vivo

Lance R. Thurlow,^{*†} Mark L. Hanke,^{*†} Teresa Fritz,^{*} Amanda Angle,^{*} Amy Aldrich,^{*} Stetson H. Williams,^{*} Ian L. Engebretsen,[†] Kenneth W. Bayles,^{*} Alexander R. Horswill,[‡] and Tammy Kielian^{*}

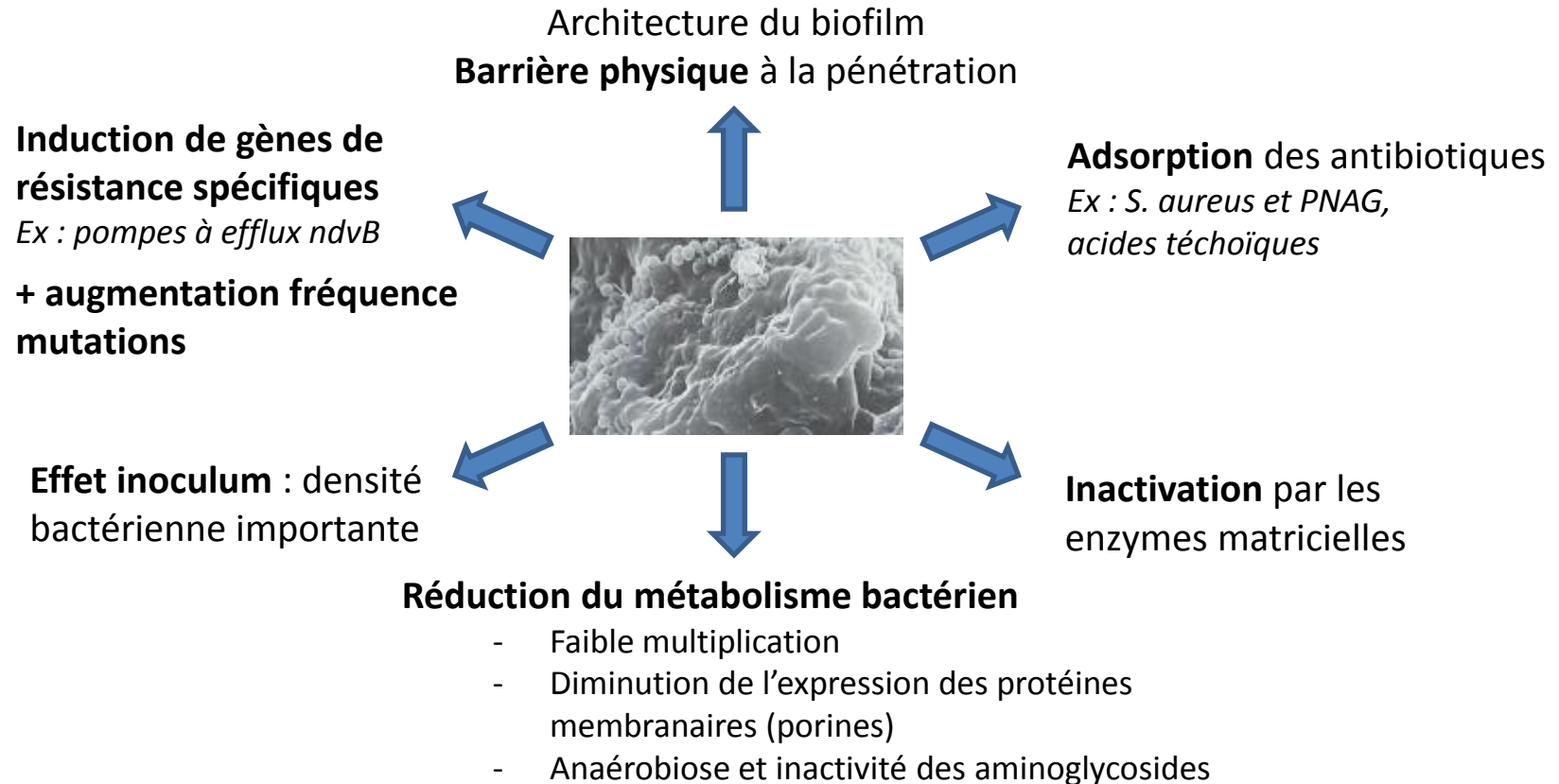


Myeloid-Derived Suppressor Cells Contribute to *Staphylococcus aureus* Orthopedic Biofilm Infection

Cortney E. Heim, Debbie Vidlak, Tyler D. Scherr, Jessica A. Kozel, Melissa Holzapfel, David E. Muirhead, and Tammy Kielian



Biofilm : « tolérance » aux antibiotiques



Biofilm : « tolérance » aux antibiotiques

Impact : MBEC = 10-1000 x CMI !

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

J Antimicrob Chemother 2014; **69** Suppl 1: i37–i40
doi:10.1093/jac/dku254

**Journal of
Antimicrobial
Chemotherapy**

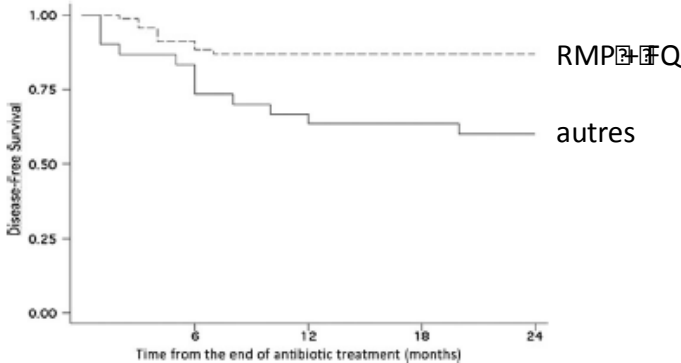
Impact of bacterial biofilm on the treatment of prosthetic joint infections

Cédric Jacqueline* and Jocelyne Caillon

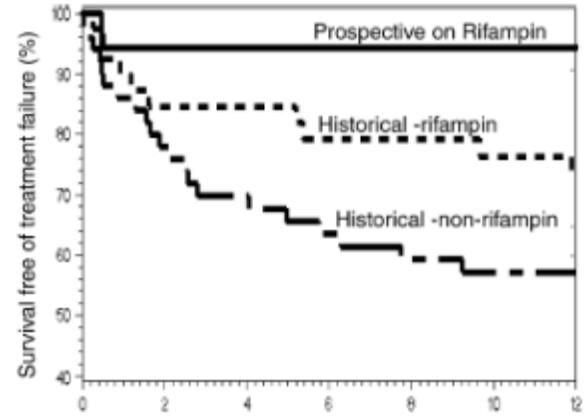
Antibiotics	Inhibition of biofilm formation (adhesion)	Biofilm penetration	Bactericidal activity in biofilm
Vancomycin	+	++	+
Linezolid	+	++	+
Daptomycin	+	+++	++
Rifampicin	+	+++	++
Moxifloxacin	+	++	++
Rifampicin + daptomycin	+	+++	+++
Rifampicin + vancomycin	+	++	++
Rifampicin + linezolid	+	+++	+++

Biofilm : rôle de la rifampicine

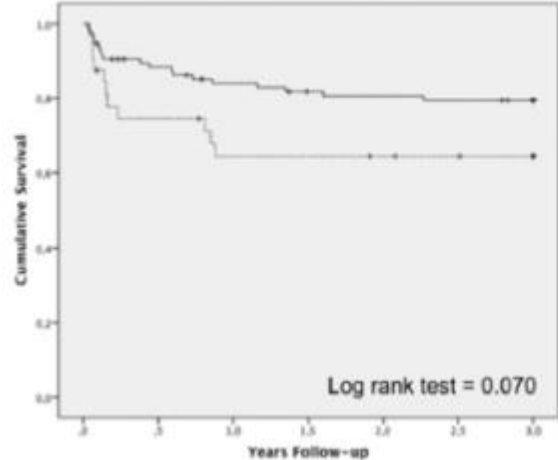
Senneville et al
CID 2011
98 PJI à SA



El Helouet al
EJCMID 2010
91 PJI SA



Tornero al, 2014
160 PJI SA aiguës



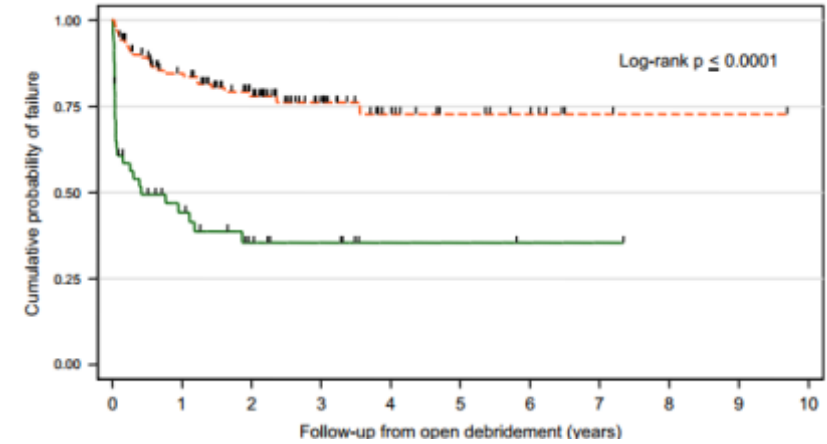
PJI due to GP
 - - - Treated with Rifampicin
 - - - Non treated with Rifampicin

Biofilm : rôle des fluoroquinolones

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. Euba⁷, 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



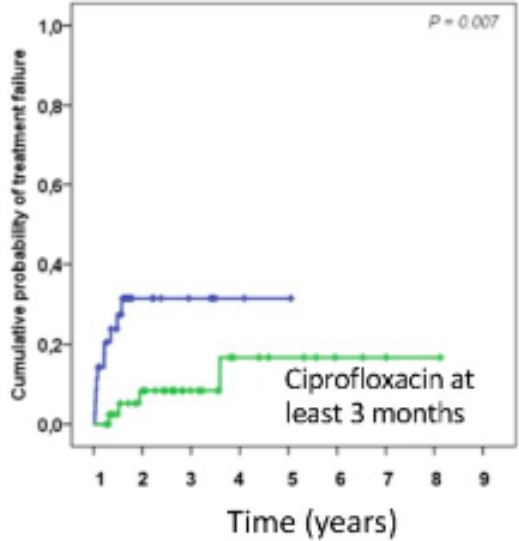
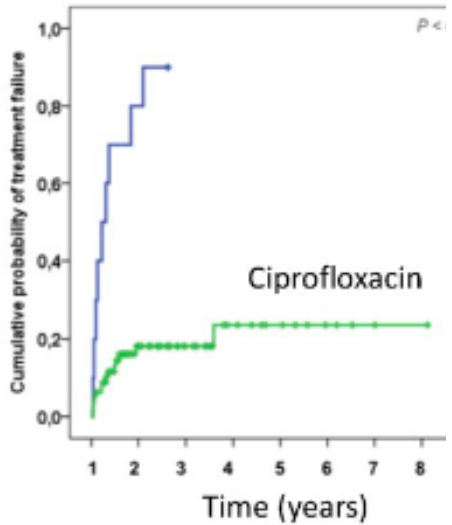
Auditorium Pasteur Jeudi 15h-16h15

Session de communications orales libres

Infections ostéoarticulaires

IOA sur matériel à *Pseudomonas aeruginosa* : expérience d'un centre de référence français

M. Cerioli, C. Batailler, A. Conrad et al, on behalf of the Lyon BJI study group



Réservoir intracellulaire

Van de Velde H.

Etude sur le mécanisme de la virulence du
staphylocoque pyogène.

La Cellule 1894;10:403-60.



THE SURVIVAL OF STAPHYLOCOCCI WITHIN HUMAN LEUKOCYTES*

BY DAVID E. ROGERS, ‡ M.D., AND RALPH TOMPSETT, M.D.

*(From the Department of Medicine, New York Hospital-Cornell
Medical Center, New York)*

PLATES 8 TO 10

(Received for publication, October 10, 1951)

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Staphylococcus aureus persistence in non-professional phagocytes

Bettina Löffler*, Lorena Tuchscher, Silke Niemann, Georg Peters

International Journal of Medical Microbiology 304 (2014) 170–176

- Cellules endothéliales
- Cellules épithéliales
- Kératinocytes
- Fibroblastes

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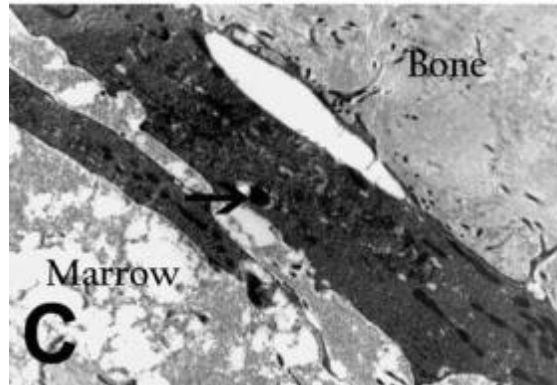
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... et les **cellules osseuses**

Bosse, 2005



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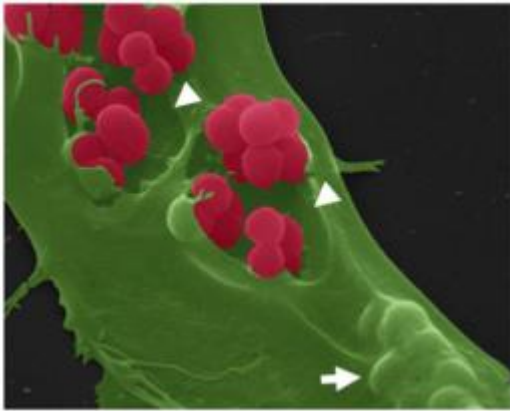
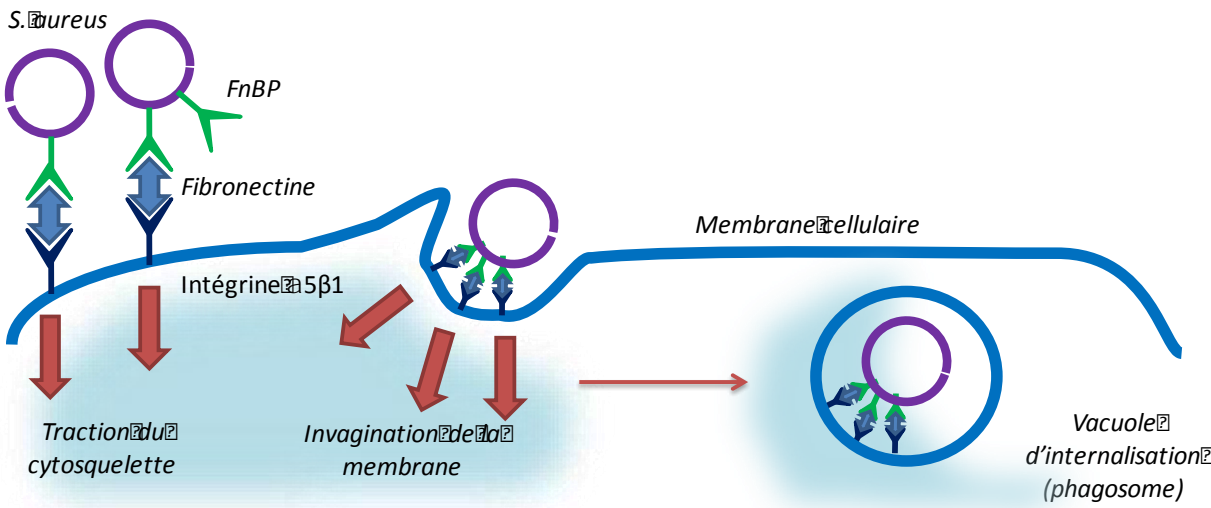
Mini Review

Interaction of staphylococci with bone

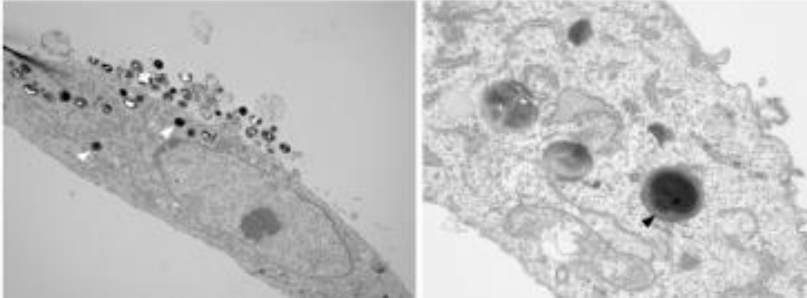
John A. Wright, Sean P. Nair*

International Journal of Medical Microbiology 300 (2010) 193-204

Réservoir intracellulaire : ostéo_Blastes



Hoffmann et al.
 Eur J Cell Biol 2011



Photographies, Céline Dupieux

frontiers
 in Cellular and Infection Microbiology

REVIEW
 published: 25 November 2010
 doi: 10.3389/fcimb.2010.00065

Staphylococcus aureus vs. Osteoblast: Relationship and Consequences in Osteomyelitis

Jérôme Josse, Frédéric Velard and Sophie C. Gangloff*

EA 4037 Biomatériaux et inflammation en site osseux, Pôle Santé, Université de Reims Champagne-Ardenne, Reims, France

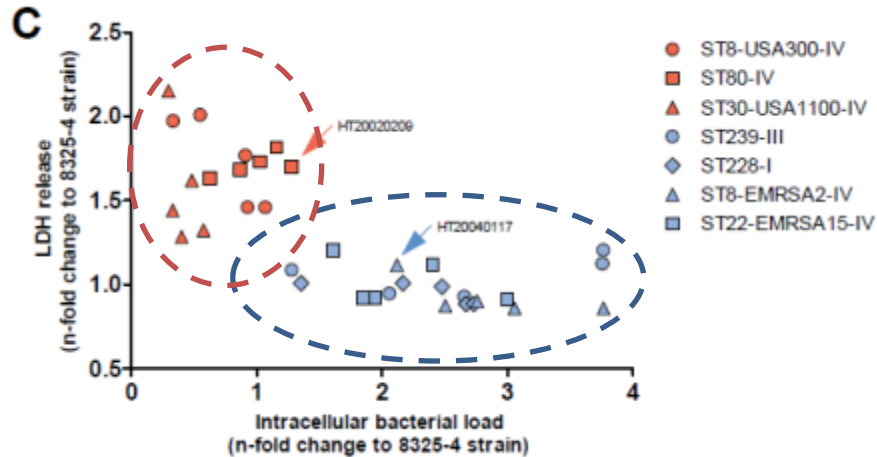
Réservoir intracellulaire : ostéoBlastes

May 2013 | Volume 8 | Issue 5 | e62176



PSMs of Hypervirulent *Staphylococcus aureus* Act as Intracellular Toxins That Kill Infected Osteoblasts

Jean-Philippe Rasigade^{1,2,3*}, Sophie Trouillet-Assant¹, Tristan Ferry¹, Binh An Diep⁴, Anaïs Sapin³, Yannick Lhoste³, Jérémy Ranfaing¹, Cédric Badiou¹, Yvonne Benito², Michèle Bes², Florence Couzon¹, Sylvestre Tigaud³, Gérard Lina^{1,2}, Jérôme Etienne^{1,2}, François Vandenesch^{1,2}, Frédéric Laurent^{1,2,3}



HA-MRSA (n=15)

- ISO / matériel
- Indolentes, chroniques, récidivantes
- **Faible cytotoxicité**
- **Survie intracellulaire +++**

CA-MRSA (n=20)

- Ostéomyélites +++
- Progression rapide, inflammation majeure, destruction osseuse, dommages tissulaires
- **Cytotoxicité +++**
- **Faible survie intracellulaire**
- Dommages tissulaires (rôle de la PVL)

Réservoir intracellulaire : ostéoBlastes

May 2013 | Volume 8 | Issue 5 | e62176



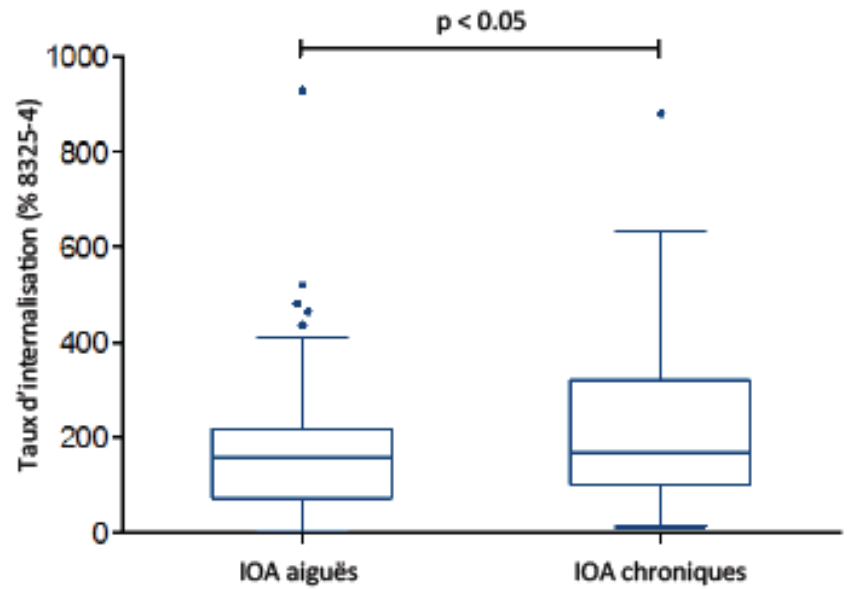
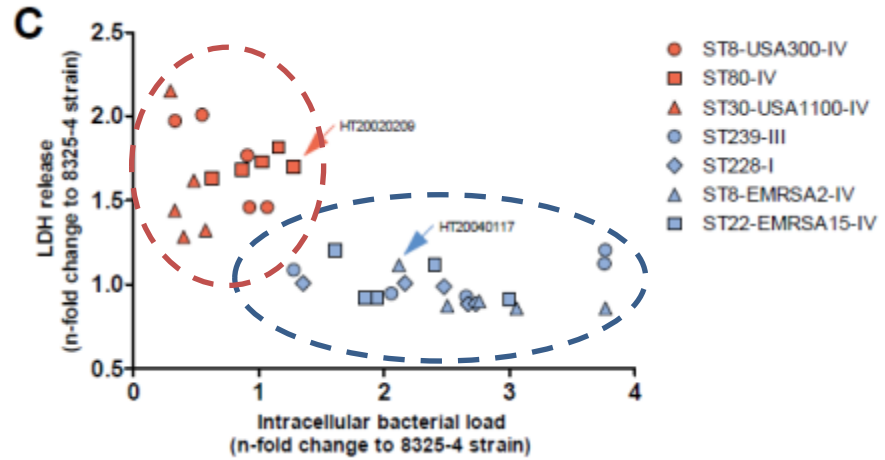
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Delta-toxin production deficiency in *Staphylococcus aureus*: a diagnostic marker of bone and joint infection chronicity linked with osteoblast invasion and biofilm formation

Clin Microbiol Infect 2015; 21: 568.e1–568.e11

F. Valour^{1,2,3,4}, J.-P. Rasigade^{2,3,4}, S. Trouillet-Assant³, J. Gagnaire², A. Bouaziz¹, J. Karsenty¹, C. Lacour², M. Bes^{2,3}, S. Lustig^{3,4,5}, T. Béné⁶, C. Chidiac^{1,3,4}, J. Etienne^{2,3,4}, F. Vandenesch^{2,3,4}, T. Ferry^{1,3,4} and F. Laurent^{2,3,4}, on behalf of the Lyon BJI Study Group

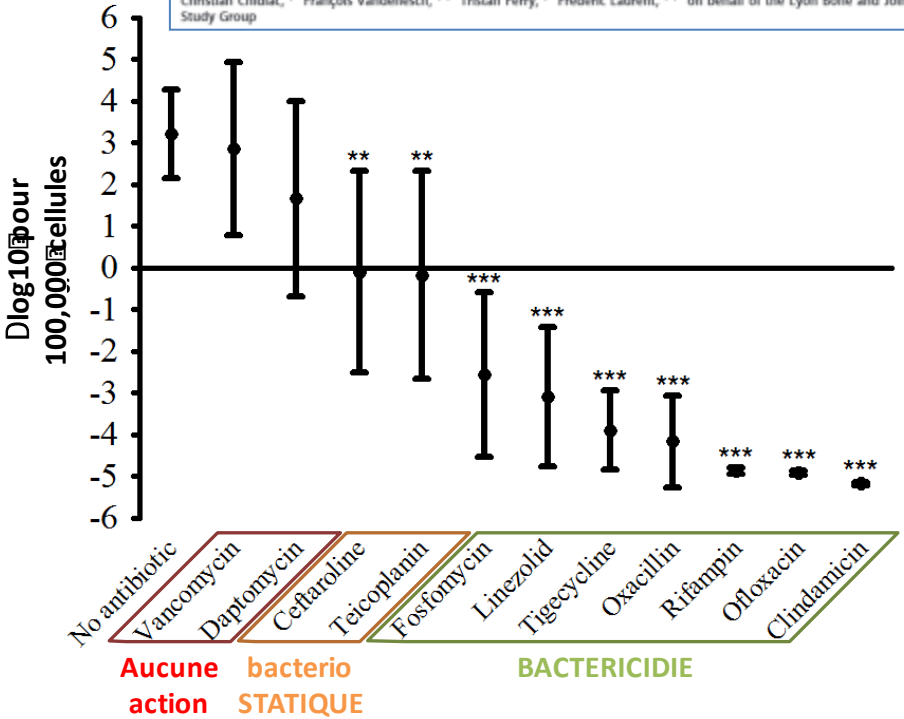


Réservoir intracellulaire : ostéo_Blastes



Antimicrobial Activity against Intraosteoblastic *Staphylococcus aureus*

Florent Valour,^{A,B} Sophie Trouillet-Assant,^D Natacha Riffard,^D Jason Tasse,^D Sacha Flammier,^D 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

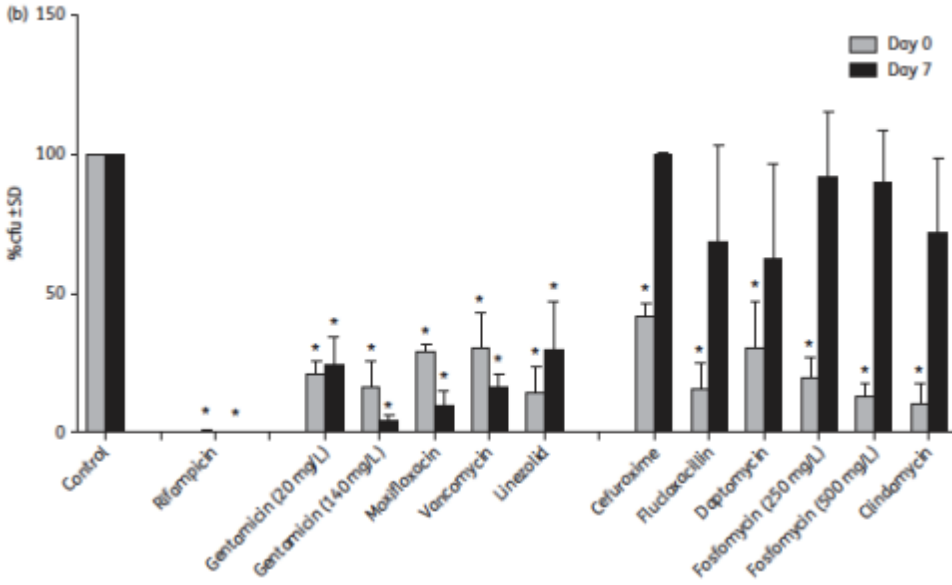


Journal of Antimicrobial Chemotherapy

J Antimicrob Chemother 2016; 71: 438-448
doi:10.1093/jac/dkv371 Advance Access publication 20 November 2015

Staphylococcus aureus develops increased resistance to antibiotics by forming dynamic small colony variants during chronic osteomyelitis

L. Tuchscher^{1,2}, C. A. Kreis², V. Hoerr^{1,2}, L. Flint⁴, M. Hochmeister⁴, J. Geraci⁵, S. Bremer-Streck⁵, M. Kiehntopf⁶, E. Medina⁴, M. Kribus⁷, M. Raschke¹, M. Pietz⁸, G. Peters⁴ and B. Löffler^{1,3}

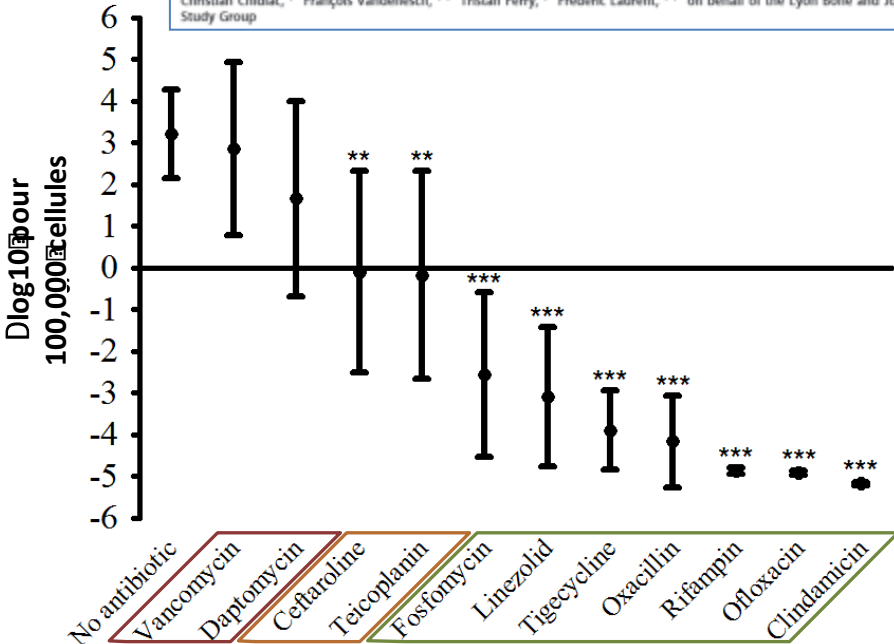


Réservoir intracellulaire : ostéoBlastes

AAC
Journal of Antimicrobial Chemotherapy

Antimicrobial Activity against Intraosteoblastic *Staphylococcus aureus*

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Aucune bacterio action STATIQUE

BACTERICIDIE

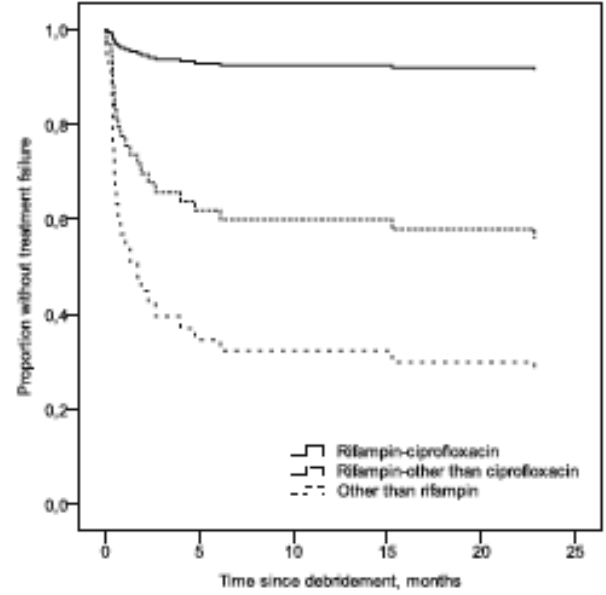
International Orthopaedics (SICOT) (2015) 39:1785-1791
DOI 10.1007/s00264-015-2819-2

ORIGINAL PAPER

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

Ari-Pekka Puhua¹ · Teija Puhua² · Tuukka Niemi¹ · Paul Ottosson³ · Johana Leppänen¹ · Hanna Syrjä¹

113 PJI aigus
66 SA et SCN



RMP + FQ

RMP sans FQ

Pas de RMP

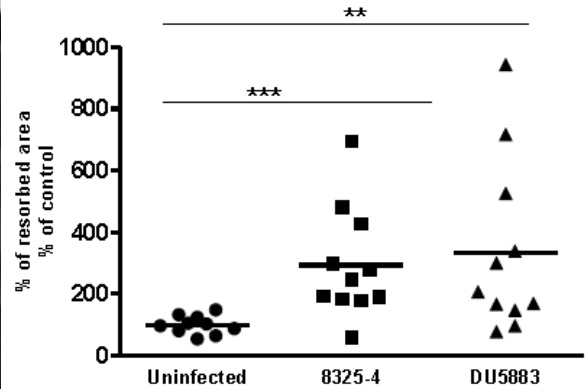
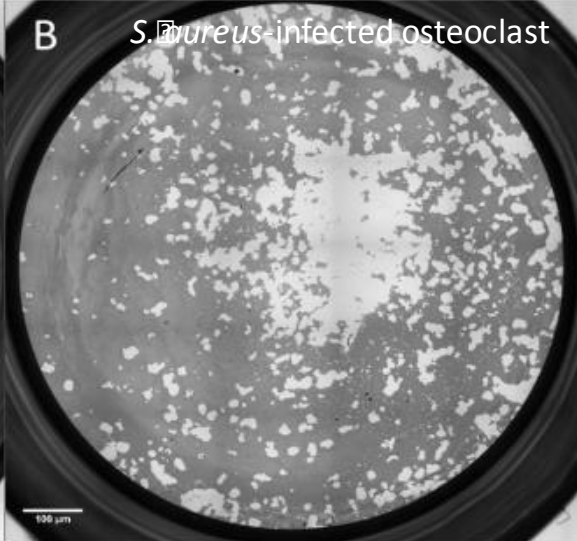
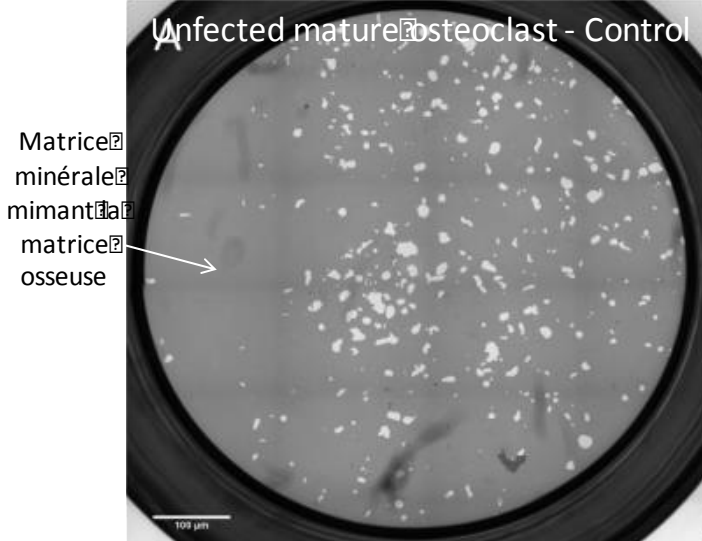
Fig. 3 Survival curves for staphylococcal prosthetic joint infections (PJIs) based on antibiotic treatment group

Réservoir intracellulaire : ostéoClastes

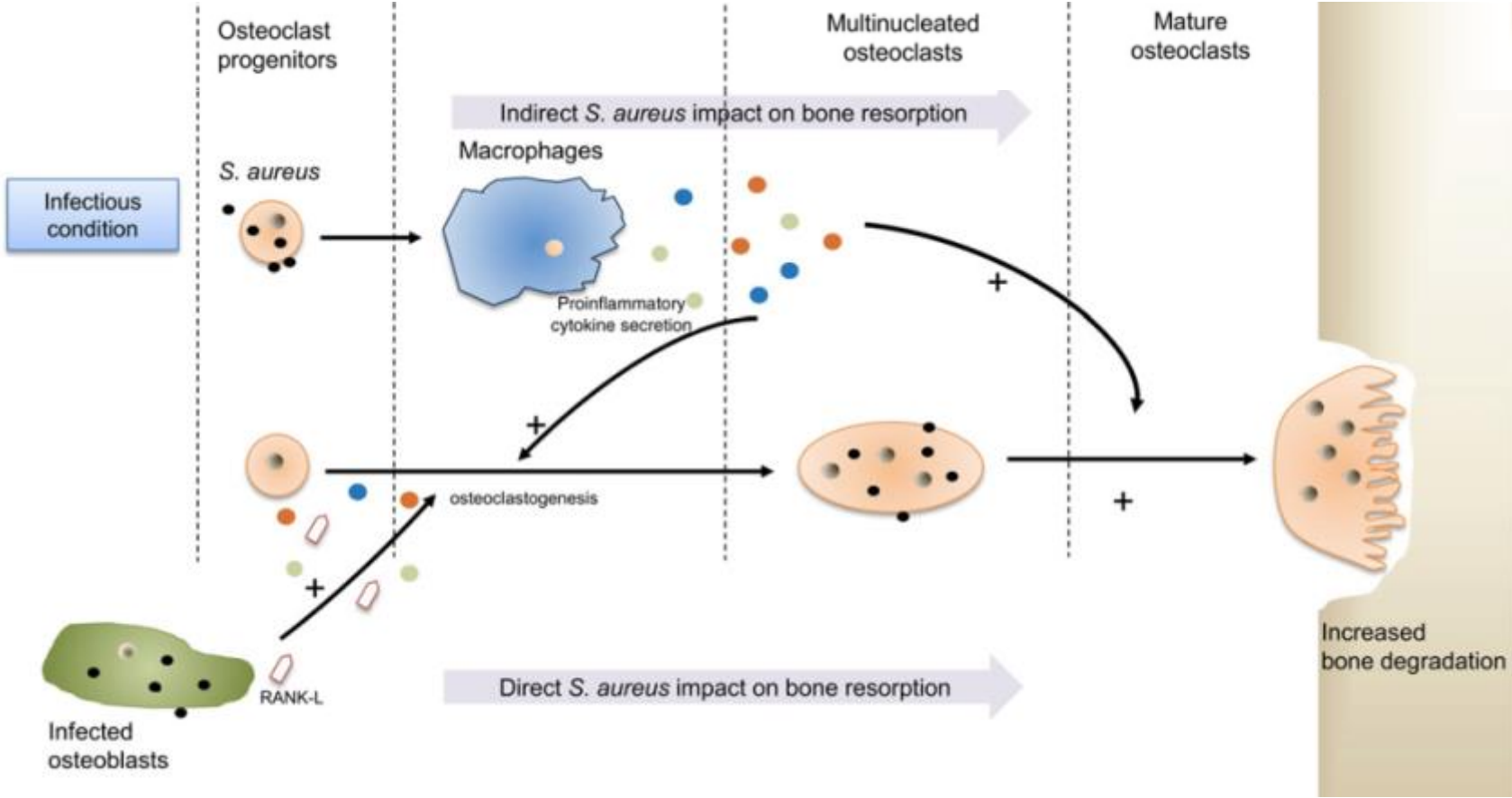
Dual Impact of Live *Staphylococcus aureus* on the Osteoclast Lineage, Leading to Increased Bone Resorption

Augmentation de la résorption osseuse par les OC matures

Sophie Trouillet-Assant,^{1,2,3,4,5,6} Marlène Gallet,^{4,5,6,7} Pauline Nauroy,^{4,5,6,7} Jean-Philippe Rasigade,^{1,2,3,4,5,6}
 Sacha Flamnier,^{1,2,3,4,5,6} Peggy Parroche,^{2,3,4,5,6} Jacqueline Marvel,^{2,3,4,5,6} Tristan Ferry,^{1,2,3,4,5,6} Francois Vandenesch,^{1,2,3,4,5,6}
 Pierre Jurdic,^{4,5,6,7} and Frederic Laurent^{1,2,3,4,5,6}



Réservoir intracellulaire : ostéoClastes

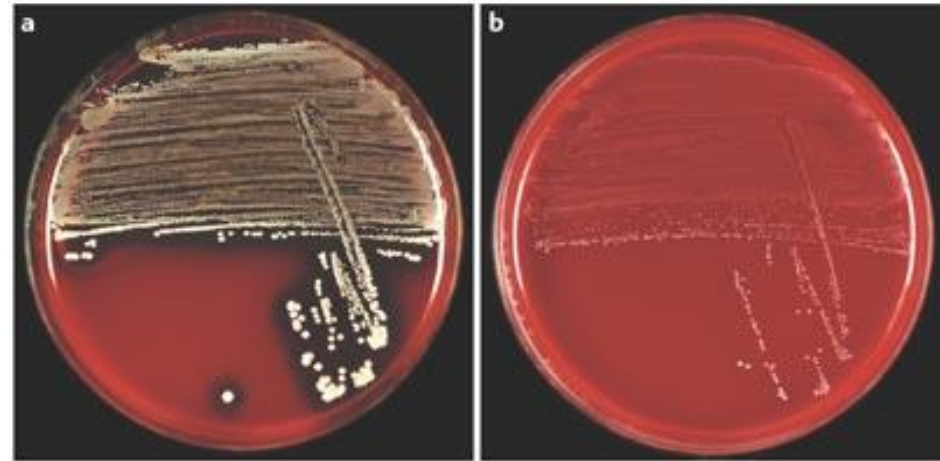
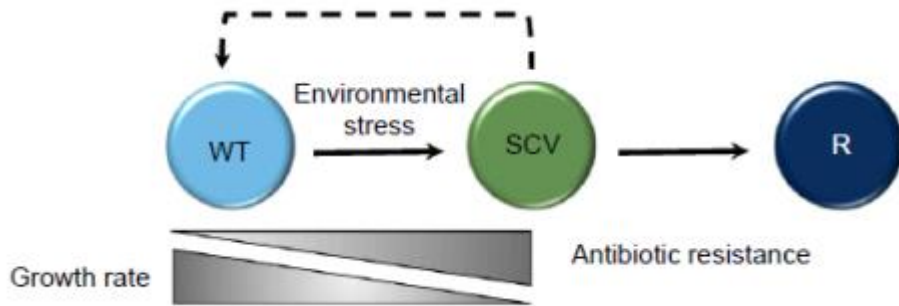


Small colony variants

Modifications phénotypiques réversibles

Adaptation à un environnement hostile : os, biofilm, intracellulaire

- Croissance lente (temps de doublement x 10)
- Petites colonies atypiques
- Résistance accrue aux antibiotiques
- Adhérence +++
- Survie intracellulaire +++
- Révertant



Small colony variants : chronicité

Clinical Characteristics and Outcomes of Prosthetic Joint Infection Caused by Small Colony Variant Staphylococci

Aaron J. Tande,^{a,b} Douglas R. Osmon,^a Kerryll E. Greenwood-Quaintance,^b Tad M. Mabry,^c Arlen D. Hanssen,^c Robin Patel^{a,b,d}

mBio September/October 2014 Volume 5 Issue 5 e01910-14

Retrospective series of 113 patients with staphylococcal PJI, with prospective testing of archived sonicate fluid samples

38 subjects (34%) with SCVs and 75 (66%) with only normal-phenotype (NP) bacteria

Characteristic ^d	SCV ^b		P value
	Yes (n = 38)	No (n = 75)	
Orthopedic history			
Joint age in days, median (range)	1,295 (216–13,712)	646 (23–11,883)	0.007
Prior arthroplasty revision	32 (84.2)	52 (70.3)	0.17
Time since last surgery in days, median (range)	743 (31–10,030)	306 (20–8,686)	<0.0001
Cemented arthroplasty	33 (86.8)	60 (80.0)	0.44
Antibiotic-loaded cement in place ^a	8 (44.4)	16 (39.0)	0.78
Aminoglycoside in cement ^a	7 (38.9)	8 (19.5)	0.19
PJI history			
Sinus tract	11 (28.9)	19 (25.3)	0.82
Duration of PJI symptoms in days, median (range)	491 (14–2,306)	165 (2–1,656)	0.0003
Prior surgery for this PJI	23 (60.5)	28 (37.3)	0.03
Cumulative antibiotic days in prior 6 mo, median (range)	66 (0–180)	13 (0–180)	0.37
Receiving 120 or more days of antibiotics in prior 6 mo	16 (42.1)	17 (22.7)	0.048

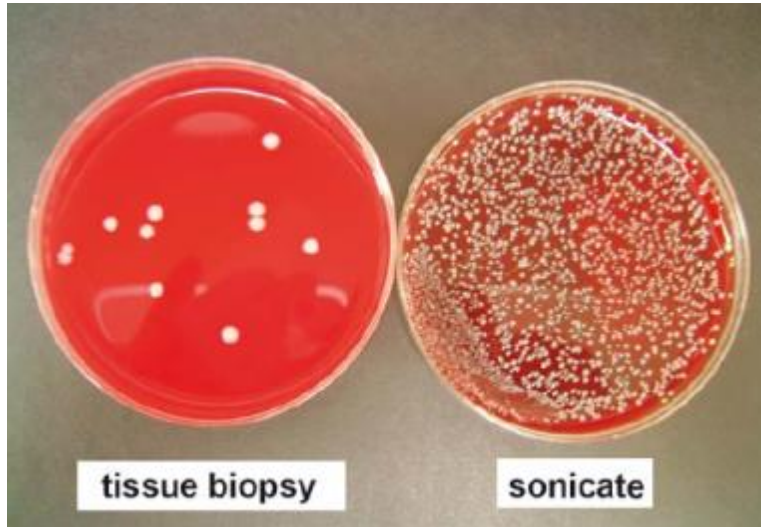
Small colony variants : diagnostic

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sonication of Removed Hip and Knee Prostheses for Diagnosis of Infection

Andrej Trampuz, M.D., Kerry E. Piper, M.S., Melissa J. Jacobson, A.S., Arlen D. Hanssen, M.D., Krishnan K. Unni, M.D., Douglas R. Osmon, M.D., Jayawant N. Mandrekar, Ph.D., Franklin R. Cockerill, M.D., James M. Steckelberg, M.D., James F. Greenleaf, Ph.D., and Robin Patel, M.D.



17 suspicion de sepsis, 9 cultures +
6 avec SCV

S. aureus

S. epidermidis

P. aeruginosa

S. gallolyticus

P. acnes

S. sanguinis

Conclusions

SURVIE DANS LES OSTEOBLASTES



Réservoir intracellulaire
Inactivité des ATB
Emergence « persisters »



Persistence et récurrence

INFECTION DES OSTEOCLASTES



Augmentation résorption



Ostéolyse
Descellement

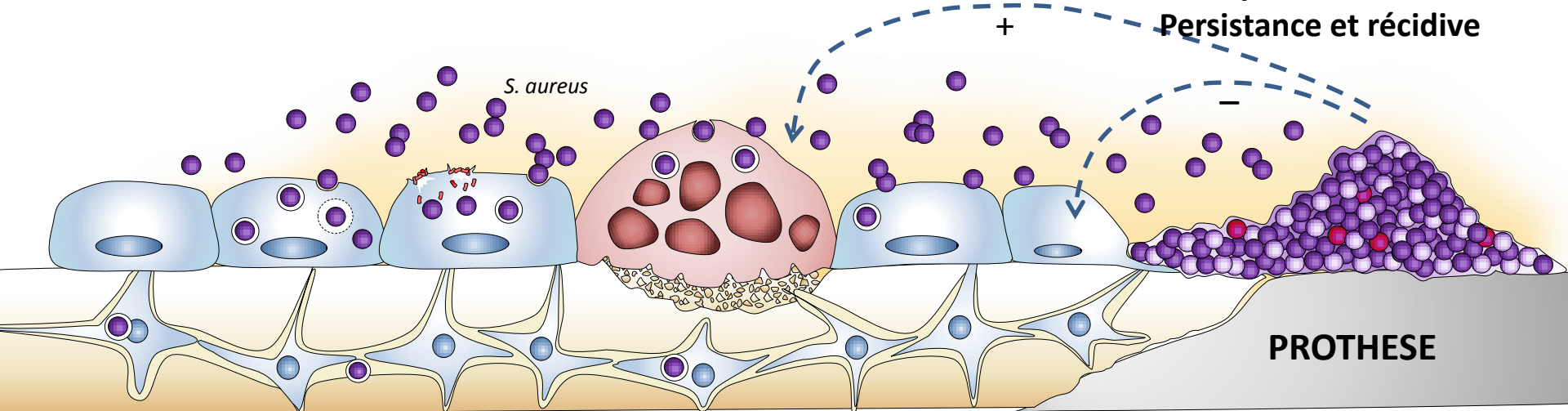
BIOFILM



Apoptose OB, stimulation OC
Inhibition phagocytose
Réservoir, tolérance ATB
Emergence « persisters »



Ostéolyse, descellement
Persistence et récurrence



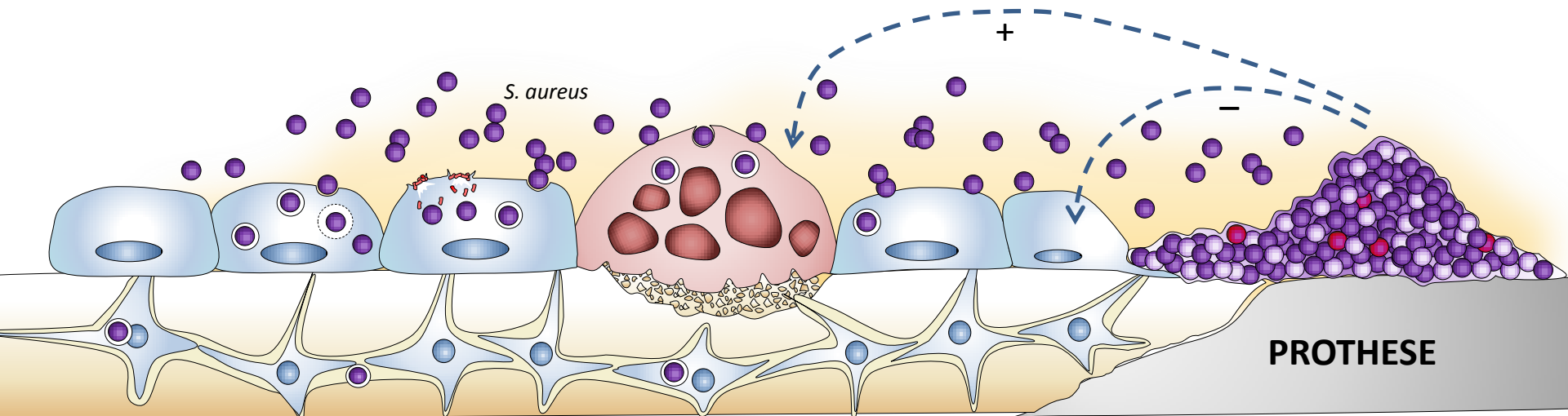
Conclusions

Importance du débridement

Molécules « anti-biofilm » : rifampicine, daptomycine, fluoroquinolones

Activité intracellulaire : rifampicine, fluoroquinolones

Thérapeutiques ciblées



Remerciements : Lyon BJI study group

Coordinator: Tristan Ferry

Infectious Diseases Specialists – Tristan Ferry, Florent Valour, Thomas Perpoint, Florence Ader, Sandrine Roux, Patrick Miaillhes, Claire Triffault-Philit, Agathe Becker, Anne Conrad, Marielle Perry, Cécile Pouderoux, Marie-Elodie Langlois, Johanna Lippman, Evelyne Braun, Christian Chidiac

Surgeons – Sébastien Lustig, Elvire Servien, Cécile Batailler, Romain Gaillard, Stanislas Gunst, Julien Roger, Charles Fiquet, Michel Henri Fessy, Anthony Viste, Philippe Chaudier, Jean Luc Besse, Lucie Louboutin , Gaël Gaudin , Tanguy Ledru, Adrien Van Haecke, Quentin Ode , Marcelle Mercier, Florie Alech-tournier, Sébastien Martres, Franck Trouillet, Philippe Céruse, Carine Fuchsmann, Cédric Barrey, Emmanuel Jouanneau, Brice Gérenton, Ana Velicanu, Ali Mojallal, Fabien Boucher

Anesthesiologists – Frédéric Aubrun, Mikhail Dziadzko, Caroline Macabéo

Microbiologists – Frederic Laurent, Céline Dupieux, Laetitia Berraud, Camille Kolenda, Jérôme Josse

Nuclear Medicine – Isabelle Morelec, Marc Janier, Francesco Giammarile

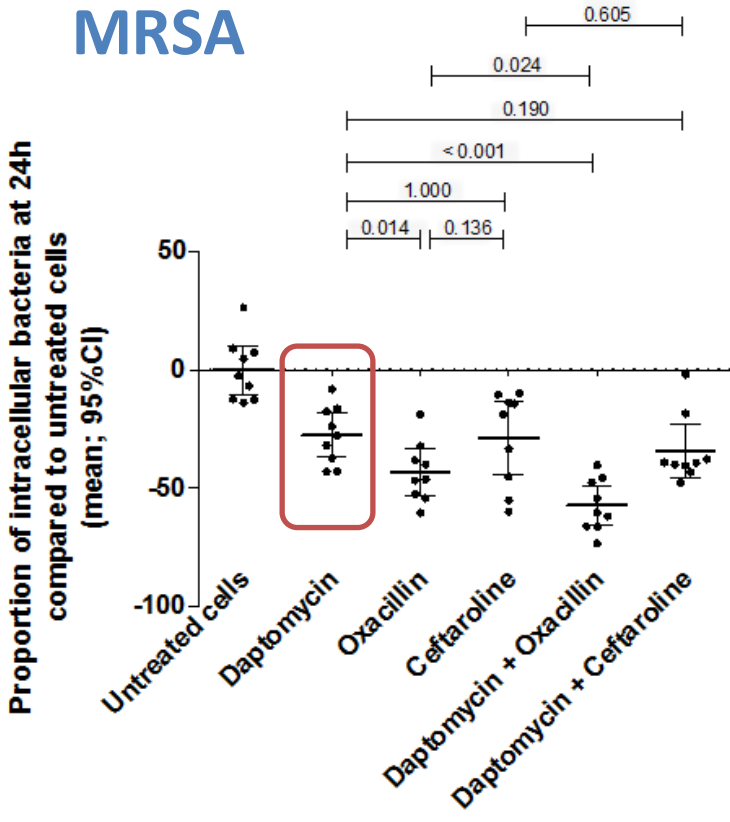
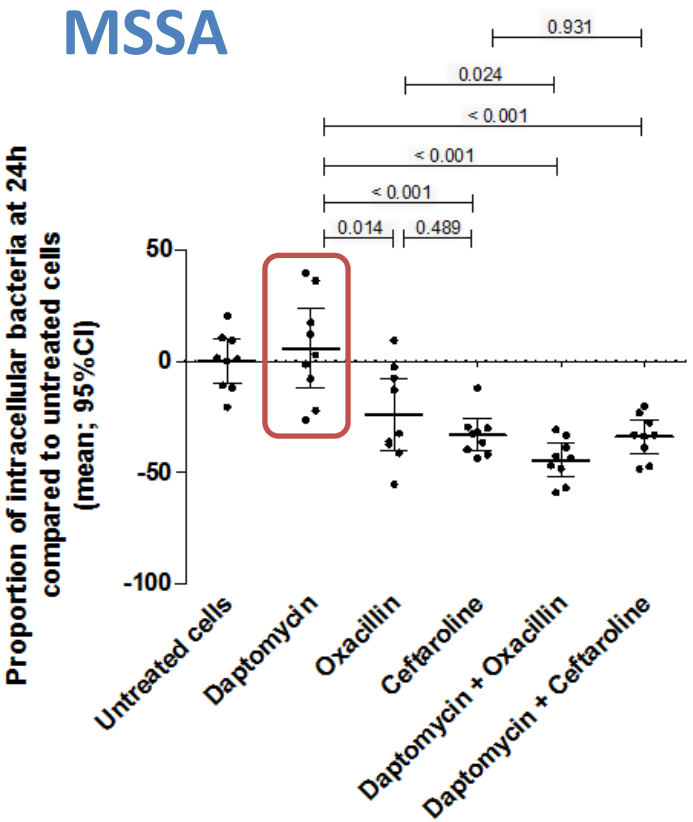
PK/PD specialists – Michel Tod, Marie-Claude Gagnieu, Sylvain Goutelle

Clinical Research Assistant – Eugénie Mabrut

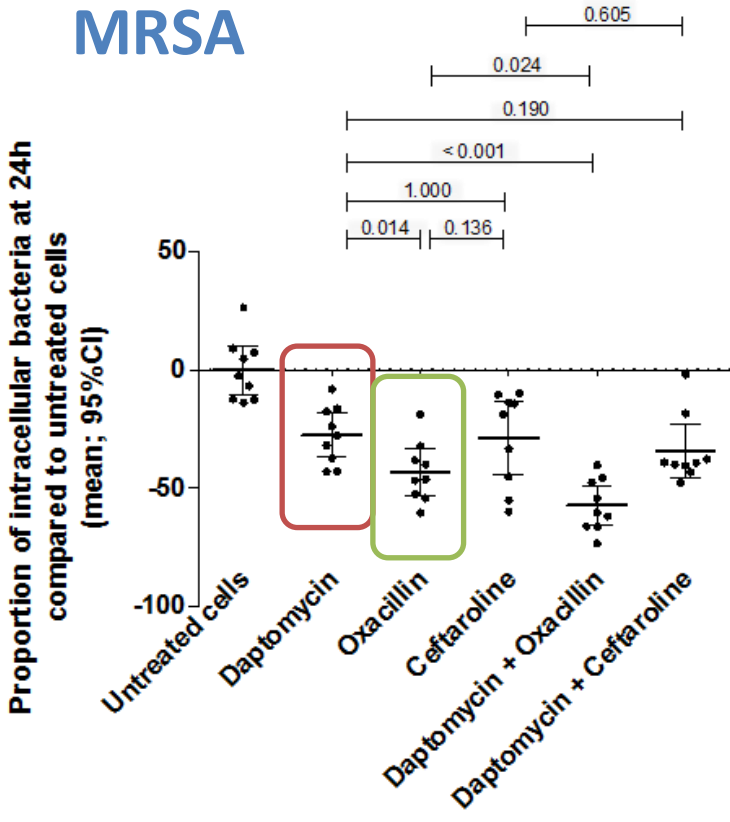
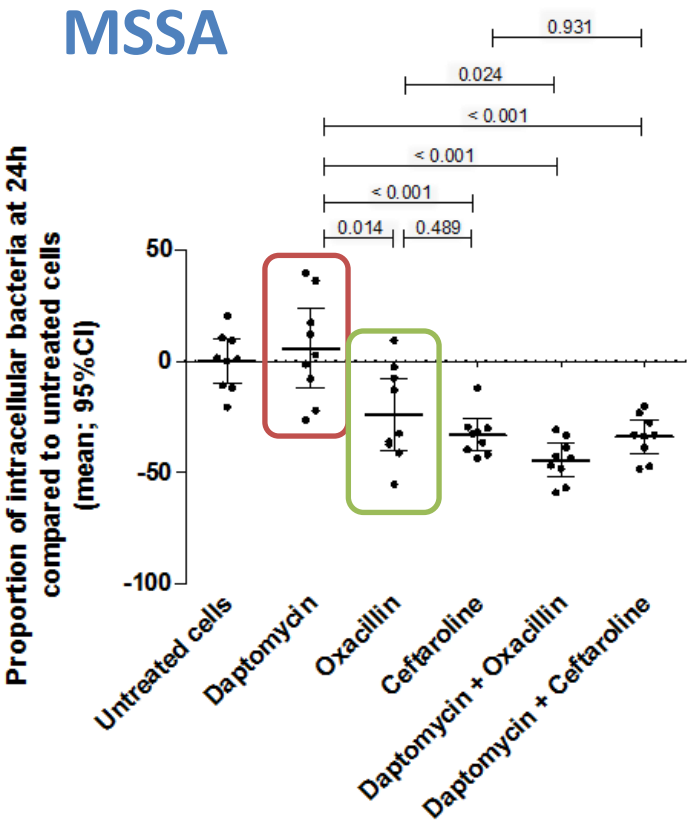


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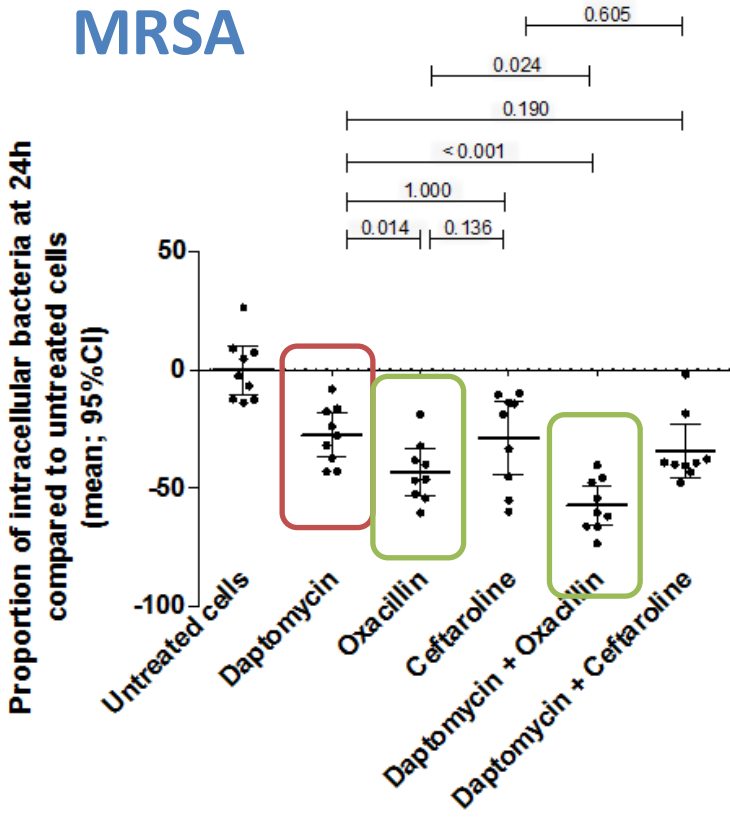
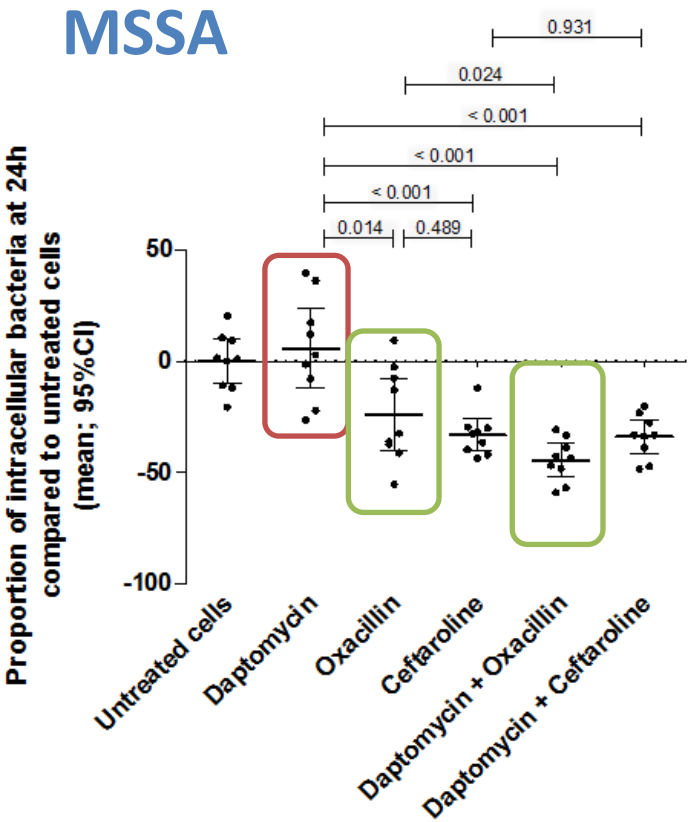
Réservoir intracellulaire : ostéoBlastes



Réservoir intracellulaire : ostéoBlastes



Réservoir intracellulaire : ostéo_Blastes



Réservoir intracellulaire : ostéoBlastes

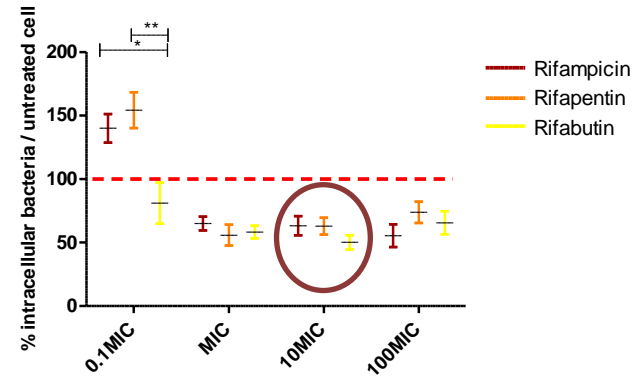
Impact du pH intralysosomal

	SASM			SARM		
	pH 7	pH 5	<i>p</i> -value	pH 7	pH 5	<i>p</i> -value
Daptomycin	0,25	1,83	0,002	0,29	2,00	0,002
Oxacillin	0,50	0,06	0,047	106,70	0,35	0,001
Ceftaroline	4,00	0,08	0,059	8,00	0,062	0,047

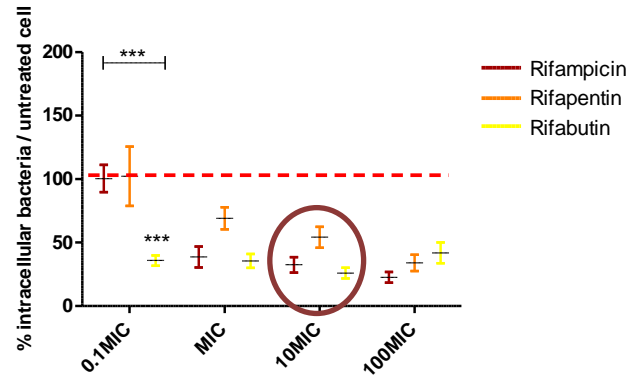
- Intracellular restauration of oxacillin activity against MRSA is (at least partly) due to a major decrease in MICs at the intralysosomal acidic pH
- Intracellular weak activity of daptomycin might be partly due to its decrease in activity at acidic pH

Réservoir intracellulaire : ostéoBlastes

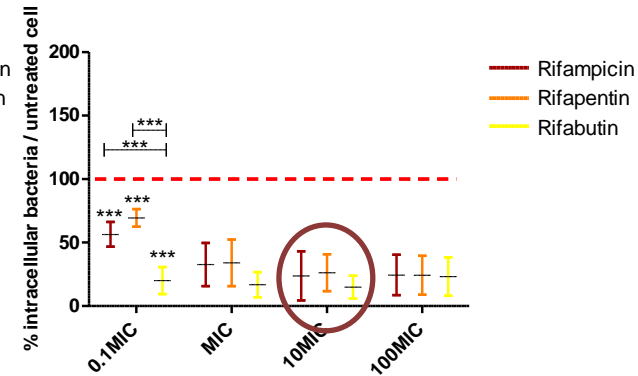
6850 strain



Clinical strain n°1



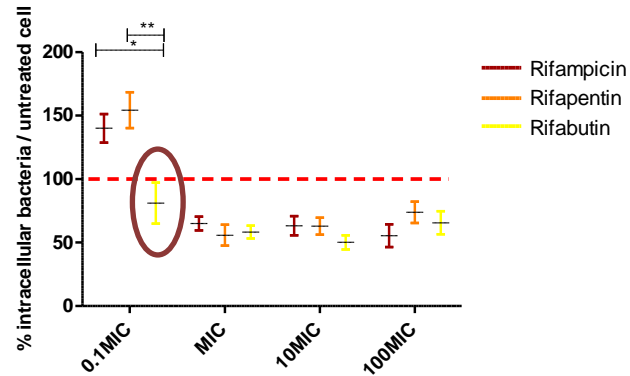
Clinical strain n°2



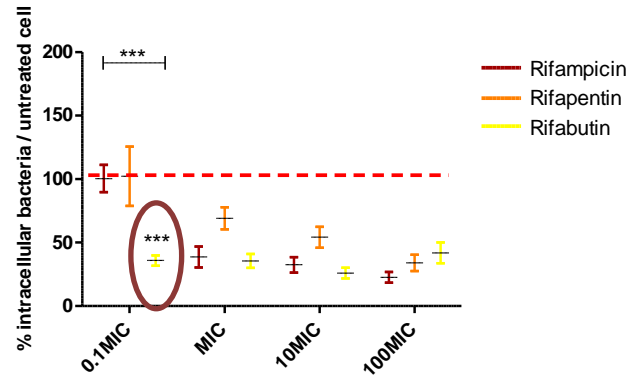
→ Bonne activité intracellulaire des 3 rifamycines à concentration osseuse

Réservoir intracellulaire : ostéoBlastes

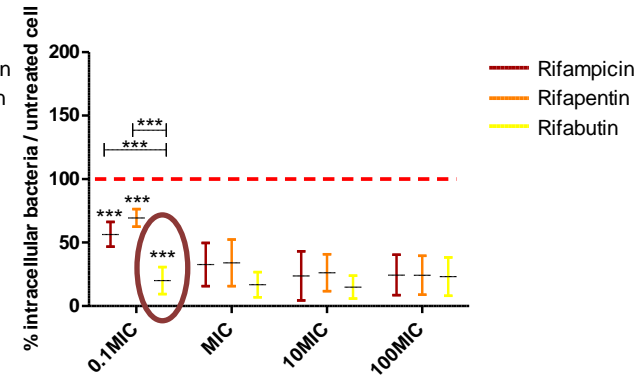
6850 strain



Clinical strain n°1



Clinical strain n°2



- Bonne activité intracellulaire des 3 rifamycines à concentration osseuse
- Meilleure activité de la rifabutine à faible concentration (dès 0,1 CMI)
- Maintien de l'activité de la rifampicine et de la rifabutine à J7 (vs rifapentine)

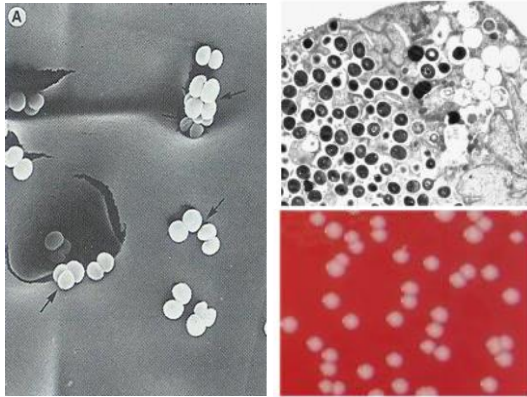
Conclusions

Adaptation bactérienne

IOA aiguë



IOA chronique



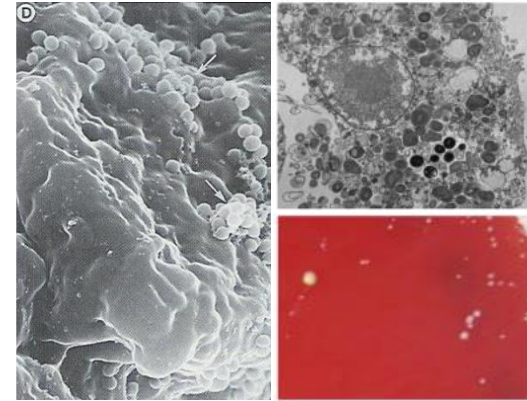
↑ Toxines

↓ Adhésines

Biofilm

Persistence
intracellulaire

SCVs



↓ Toxines

↑ Adhésines

Agression tissulaire

Réponse immunitaire / inflammatoire

- Destruction cellulaire
- Invasion et destruction tissulaire

↓ Inflammation, dommages tissulaires

- Échappement au système immunitaire
- « Tolérance » aux ATB : débridement, RMP, FQ
- Thérapeutiques ciblées