JNI 20es Journées Nationales d'Infectiologie
Lyon
et la région Auvergne-Rhône-Alpes
du mercredi 5 juin 2019
au vendredi 7 juin 2019

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
Université Claude Bernard Lyon 1
florent.valour@chu-lyon.fr

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	☐ OUI	☑ NON
Sanofi		
Prise en charge de frais de voyage, d'hébergement ou d'inscription à des congrès	☐ OUI	☑ NON
Sanofi-Pasteur, Pfizer, Astellas, Amgen, Gilead, MSD, Viiv		
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 HbA1c – Moderate • Allogenic 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

Second INTERNATIONAL CONSENSUS MEETING (ICM) on MUSCULOSKELETAL INFECTION

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
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• Neurologic disease (hemiplegia, paraplegia) – Moderate
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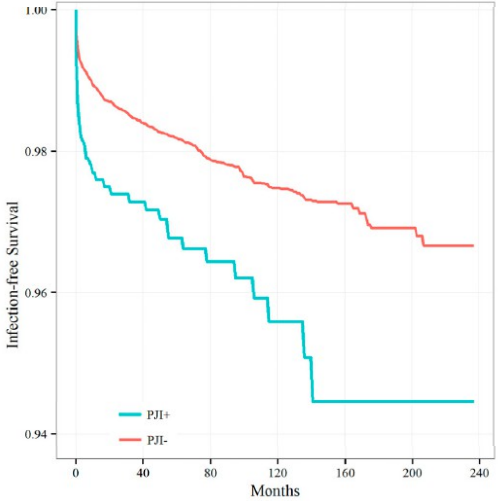
Second INTERNATIONAL CONSENSUS MEETING (ICM) on MUSCULOSKELETAL INFECTION

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. Gililland, MD



ATCD PJI 1e degré
HR = 2,2 (1,2-2,6)

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

(après ajustement sur les principaux FR de PJI)

Facteurs liés à l'hôte

Modifiable Host Factors

- BMI – Strong
- Smoking – Strong
- High alcohol intake (alcohol abuse) – Strong
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- Comorbidités
  - ID
  - Db déséquilibré
  - PR

Second INTERNATIONAL CONSENSUS MEETING (ICM) on MUSCULOSKELETAL INFECTION

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	11
	62	149		OPG-245	
	62	147		OPG + 1181	
	62	144		RANK + 575	
Malik_2007_a	62	145	PCR	MBL-221	11
	61	148		MBL-550	
	62	148		MBL codon 52	
	62	144		MBL codon 54	
Malik_2007_b	62	148	PCR	MMP1-1 (rs5854)	11
	62	148		MMP1-3 (rs2397776)	
	62	147		MMP1-4 (rs470747)	
	63	148		VDR-T, VDR-L	
	63	149		IL6-174	
Douglas_2008[a]	286	209	PCR	TLR9-1486, TLR9-1237	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

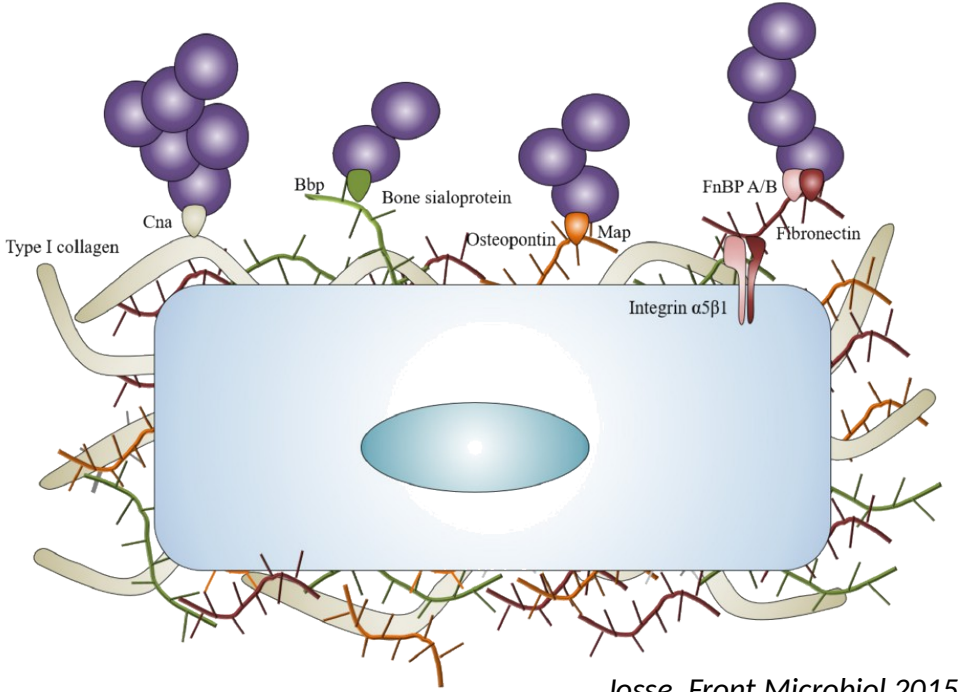
Pathogenesis of implant-associated infection: the role of the host

Werner Zimmerli · Parham Sendi

1. Couverture par matrice extracellulaire

Collagène, fibrine, fibrinogène …

→ Adhésion, initiation formation de biofilm



Josse, Front Microbiol 2015

Rôle du matériel

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REVIEW

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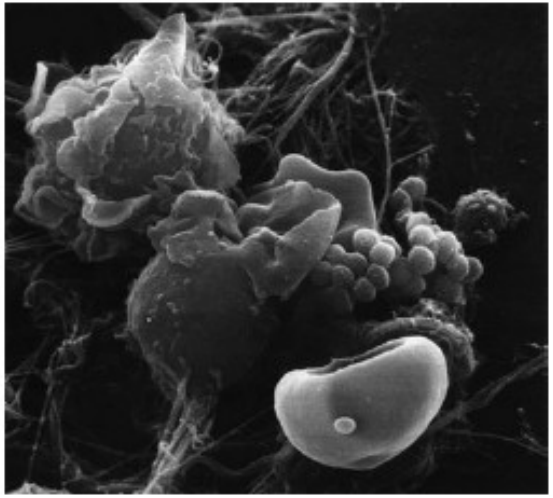


1. Couverture par matrice extracellulaire

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

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 Sendi

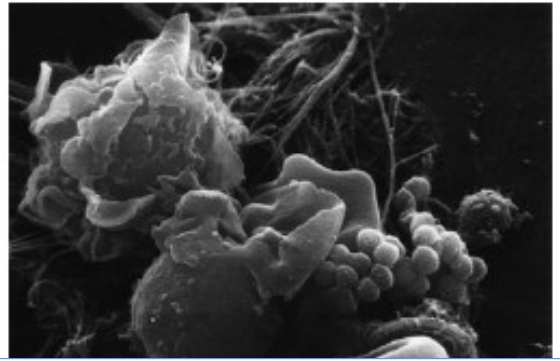
1. Couverture par matrice extracellulaire

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 I Departme Unive

IOA chronique et persistance bactérienne

Début des symptômes

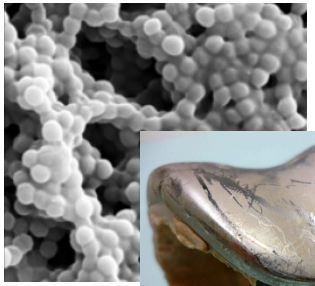
3-4 sem

Diagnostic
Prise en charge

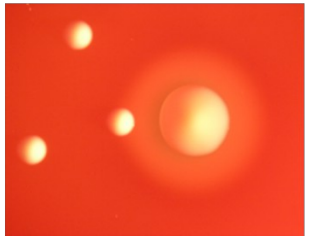
IOA AIGUE

IOA CHRONIQUE

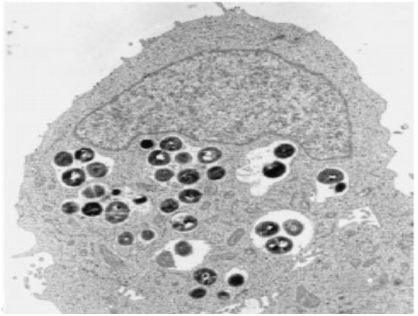
BIOFILM



SMALL COLONY VARIANTS

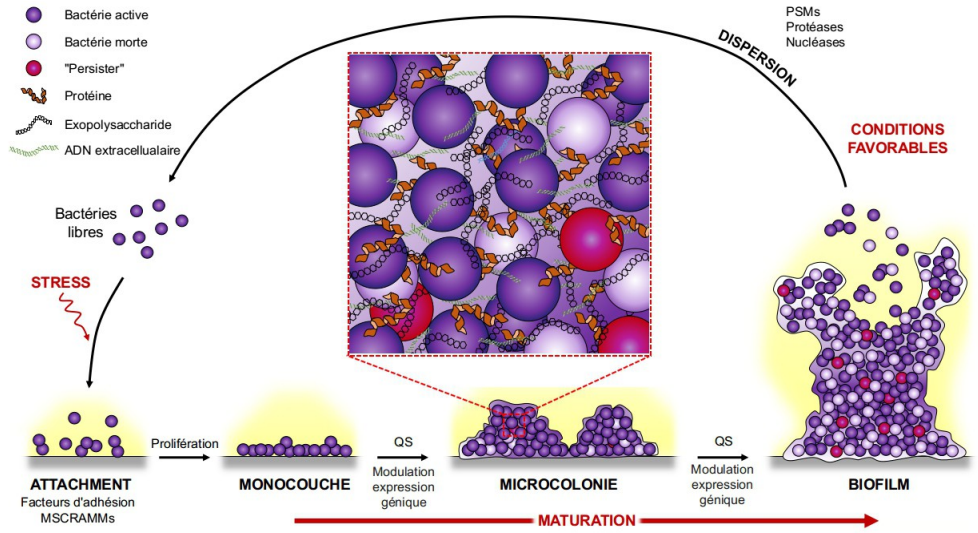


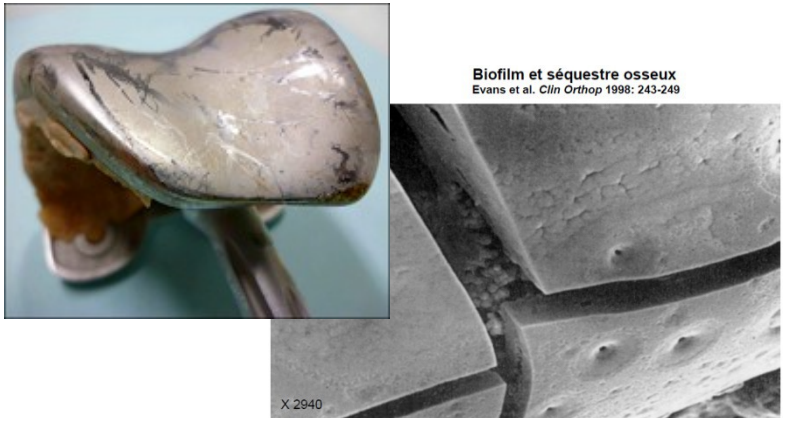
INTRACELLULAIRE

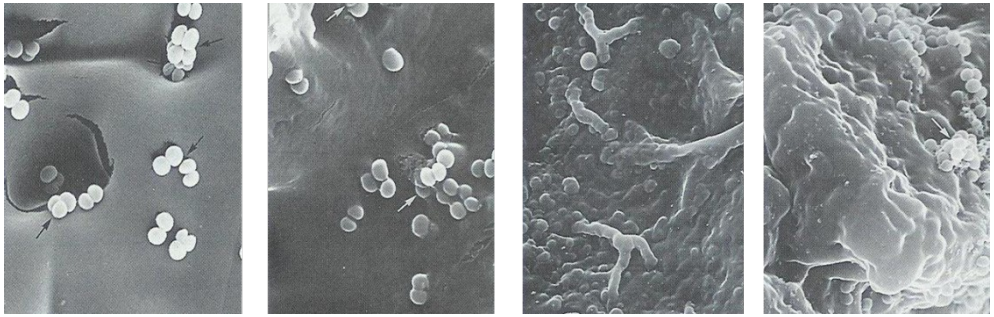


Biofilm

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





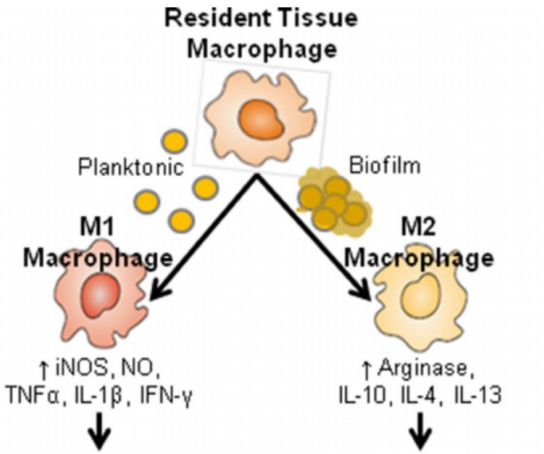


Olson, J Biomed Mater Res 1988 – Costerton, Science 1999 – Arciola, Biomaterials 2012 – Brady, FEMS Immunol Med Microbiol 2008

Biofilm : échappement au système immunitaire

***Staphylococcus aureus* Biofilms Prevent Macrophage Phagocytosis and Attenuate Inflammation In Vivo**

Lance R. Thurlow,*[,1] Mark L. Hanke,* Teresa Fritz,* Amanda Angle,* Amy Aldrich,* Stetson H. Williams,* Ian L. Engebretsen,† Kenneth W. Bayles,* Alexander R. Horswill,‡ and Tammy Kielian*

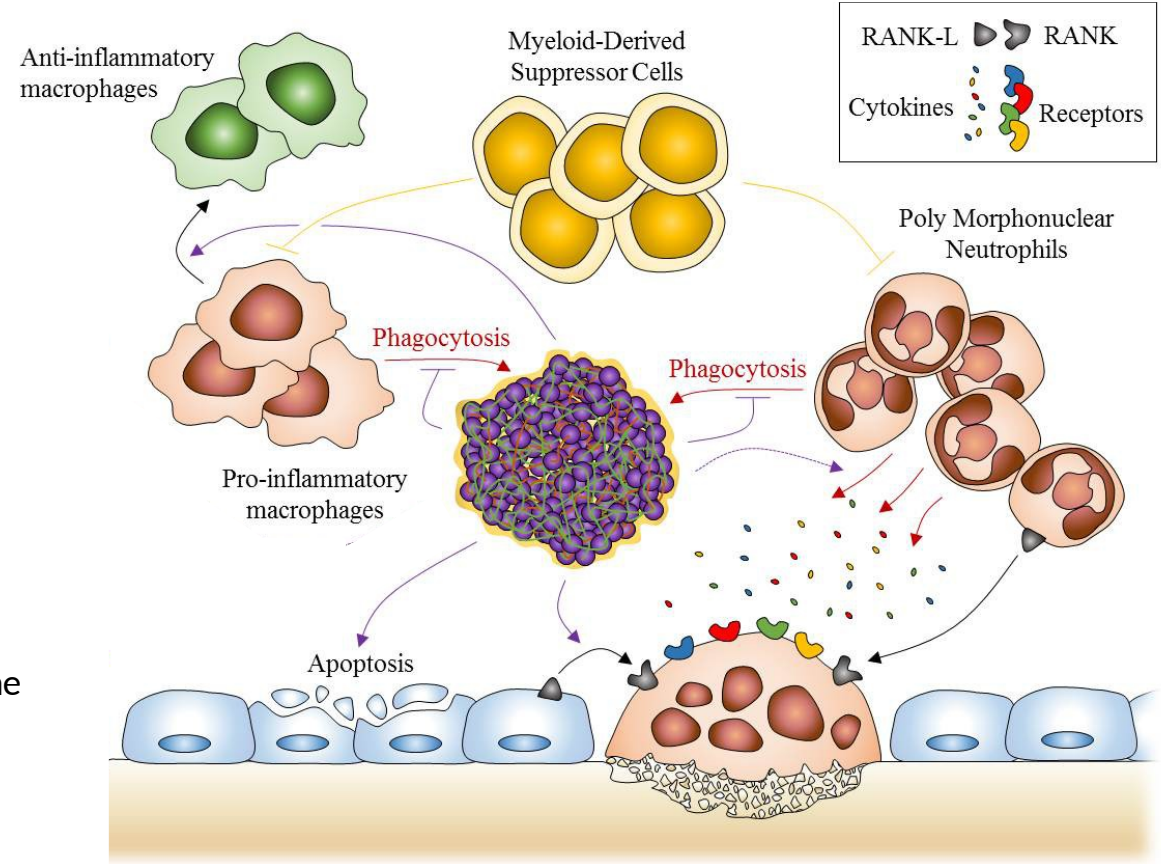


Pro-inflammatoire
Clairance bactérienne

Anti-inflammatoire
Persistance bactérienne

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

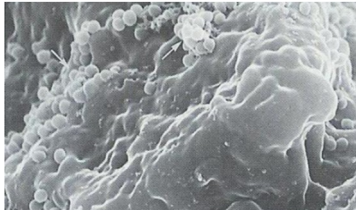


Biofilm : « tolérance » aux antibiotiques

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

Biofilm : « tolérance » aux antibiotiques

Impact : MBEC = 10-1000 x CMI !

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

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

Journal of Antimicrobial Chemotherapy

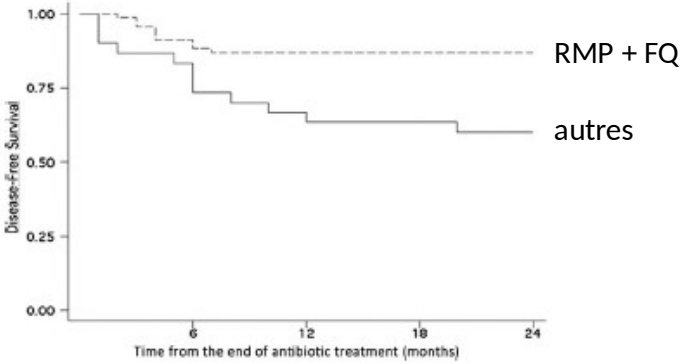
Impact of bacterial biofilm on the treatment of prosthetic joint infections

Cédric Jacqueline* and Jocelyne Caillon

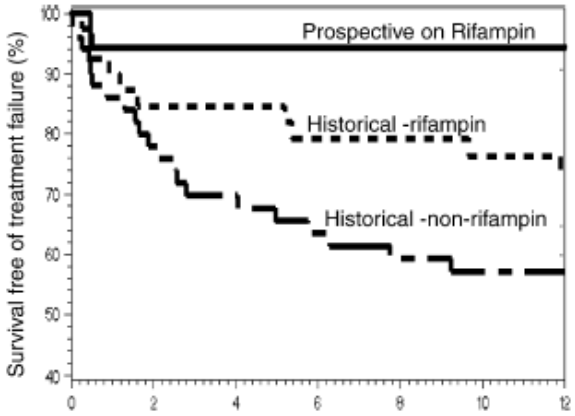
Antibiotics	Inhibition of biofilm formation (adhesion)	Biofilm penetration	Bactericidal activity in biofilm
Vancomycin	+	++	+
Linezolid	+	++	+
Daptomycin	+	+++	++
Rifampicin	+	+++	++
Moxifloxacin	+	++	++
Rifampicin+daptomycin	+	+++	+++
Rifampicin+vancomycin	+	++	++
Rifampicin+linezolid	+	+++	+++

Biofilm : rôle de la rifampicine

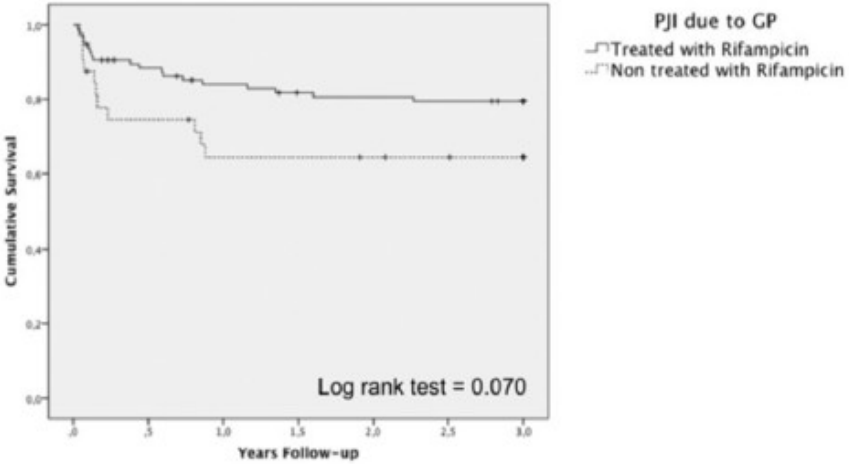
Senneville et al
CID 2011
98 PJI à SA



El Helouet al
EJCMID 2010
91 PJI SA



Tornero al, 2014
160 PJI SA aiguës

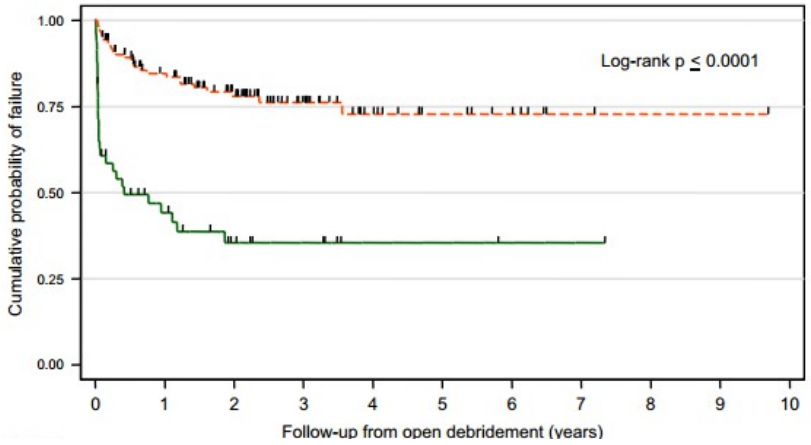


Biofilm : rôle des fluoroquinolones

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



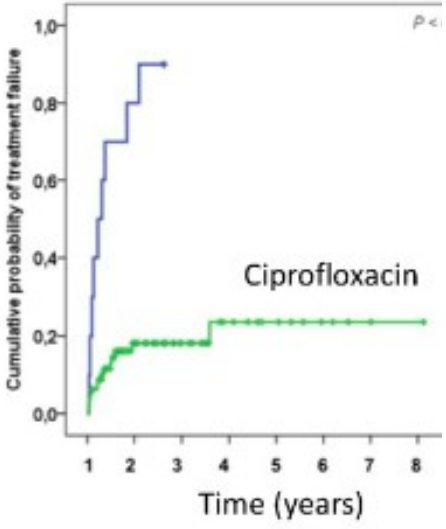
Auditorium Pasteur Jeudi 15h-16h15

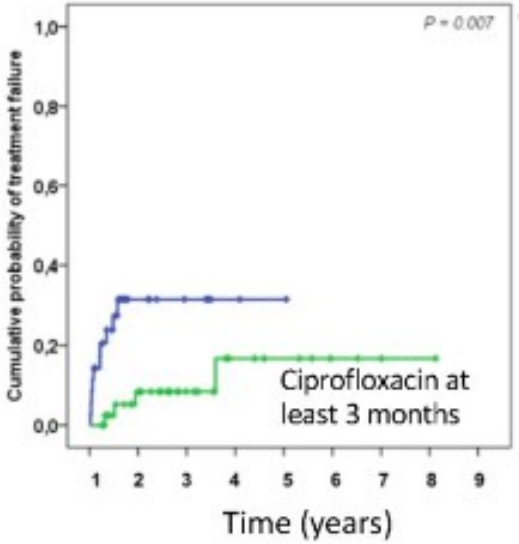
Session de communications orales libres

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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Plates 8 to 10

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Staphylococcus aureus persistence in non-professional phagocytes

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

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

- Cellules endothéliales
- Cellules épithéliales
- Kératinocytes
- Fibroblastes

Réservoir intracellulaire

Van de Velde H.
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Plates 8 to 10

(Received for publication, October 10, 1951)

Mini Review

Interaction of staphylococci with bone

John A. Wright, Sean P. Nair*

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

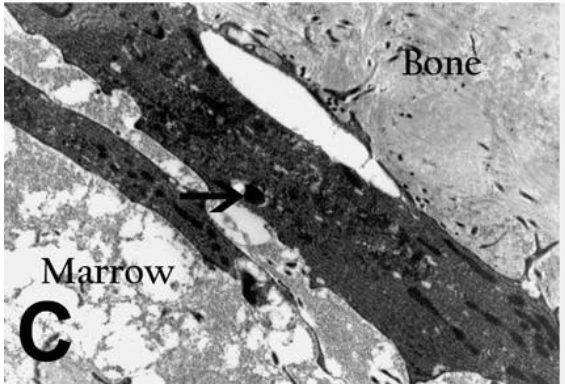
Staphylococcus aureus persistence in non-professional phagocytes

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

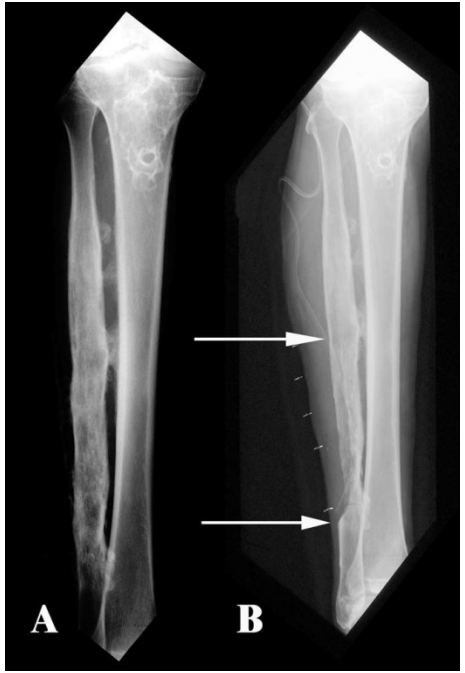
International Journal of Medical Microbiology 304 (2014) 170–176

- Cellules endothéliales
- Cellules épithéliales
- Kératinocytes
- Fibroblastes

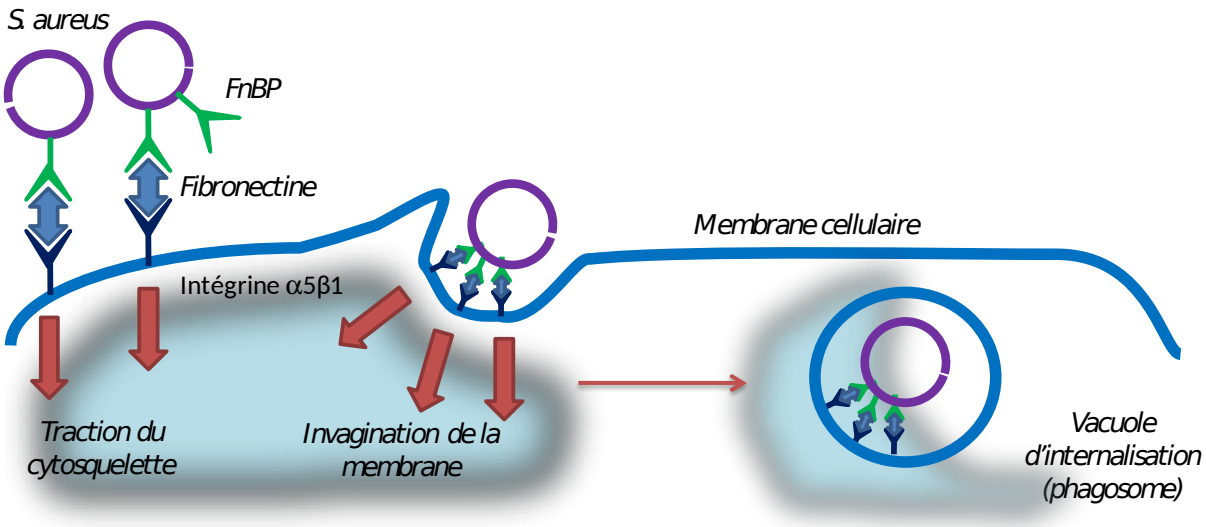
… et les **cellules osseuses**

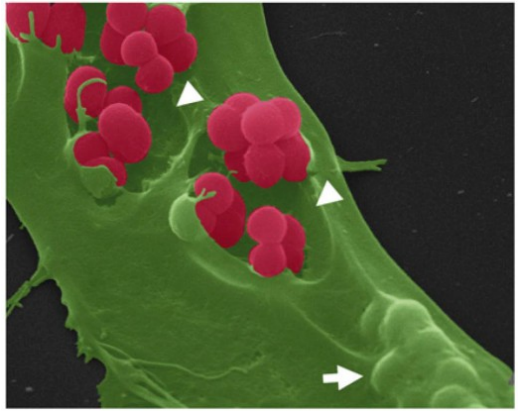


Bosse, 2005

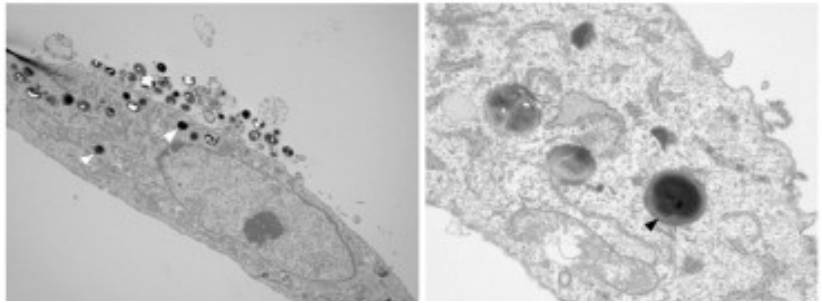


Réservoir intracellulaire : ostéoBlastes

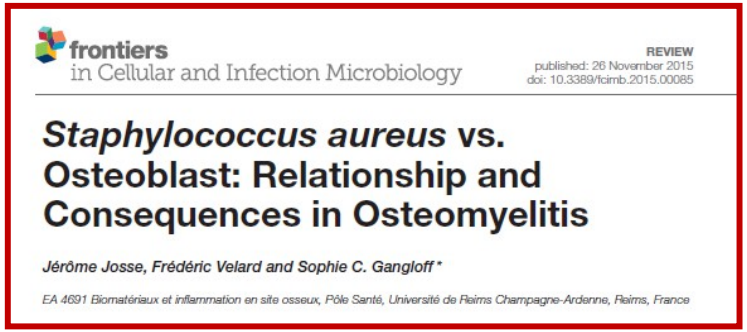




Hoffmann *et al.*
Eur J Cell Biol 2011



Photographies, Céline Dupieux



frontiers in Cellular and Infection Microbiology

REVIEW
published: 26 November 2015
doi: 10.3389/fcimb.2015.00085

Staphylococcus aureus vs. Osteoblast: Relationship and Consequences in Osteomyelitis

Jérôme Josse, Frédéric Velard and Sophie C. Gangloff*

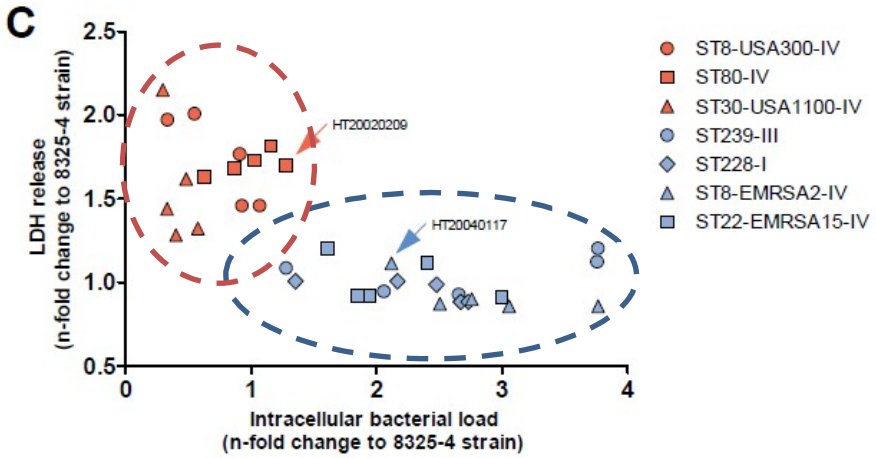
EA 4691 Biomatériaux et inflammation en site osseux, Pôle Santé, Université de Reims Champagne-Ardenne, Reims, France

Réservoir intracellulaire : ostéoBlastes

May 2013 | Volume 8 | Issue 5 | e63176 PLOS | ONE

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

Jean-Philippe Rasigade[1,2,3]*, Sophie Trouillet-Assant[1], Tristan Ferry[1], Binh An Diep[4], Anaïs Sapin[3], Yannick Lhoste[3], Jérémy Ranfaing[1], Cédric Badiou[1], Yvonne Benito[2], Michèle Bes[2], Florence Couzon[1], Sylvestre Tigaud[3], 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

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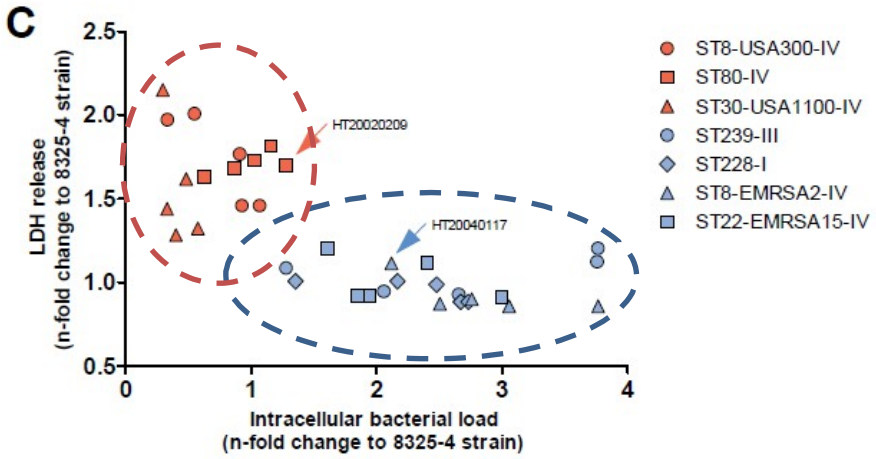
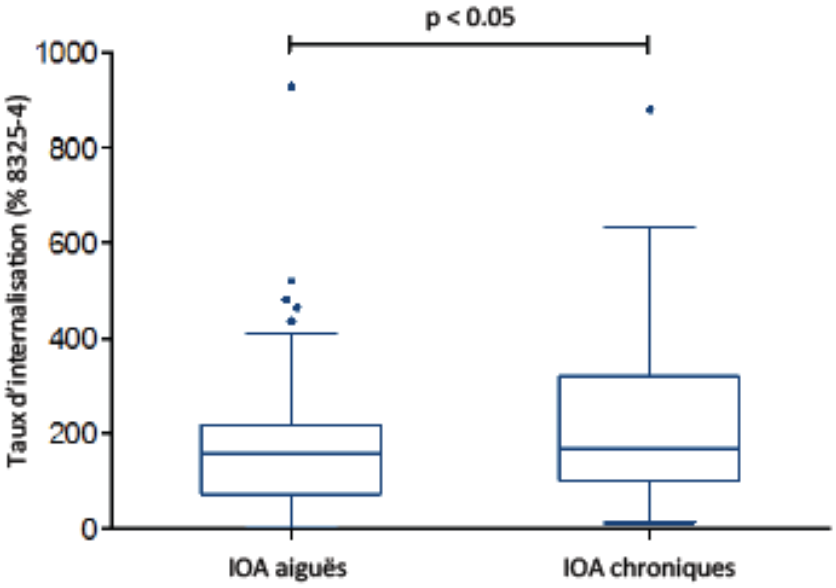
Delta-toxin production deficiency in *Staphylococcus aureus*: a diagnostic marker of bone and joint infection chronicity linked with osteoblast invasion and biofilm formation

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

F. Valour[1,2,3,4], J.-P. Rasigade[2,3,4], S. Trouillet-Assant[3], J. Gagnaire[2], A. Bouaziz[1], J. Karsenty[1], C. Lacour[2], M. Bes[2,3], S. Lustig[3,4,5], T. Bénet[6], 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



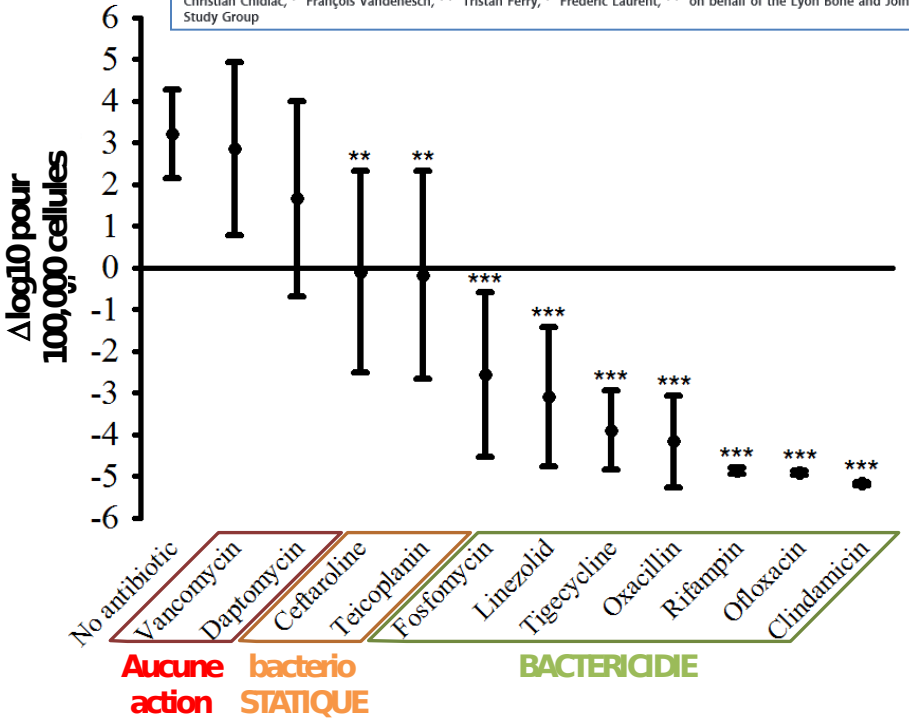


Réservoir intracellulaire : ostéoBlastes

AAC
Journals.ASM.org

Antimicrobial Activity against Intraosteoblastic *Staphylococcus aureus*

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

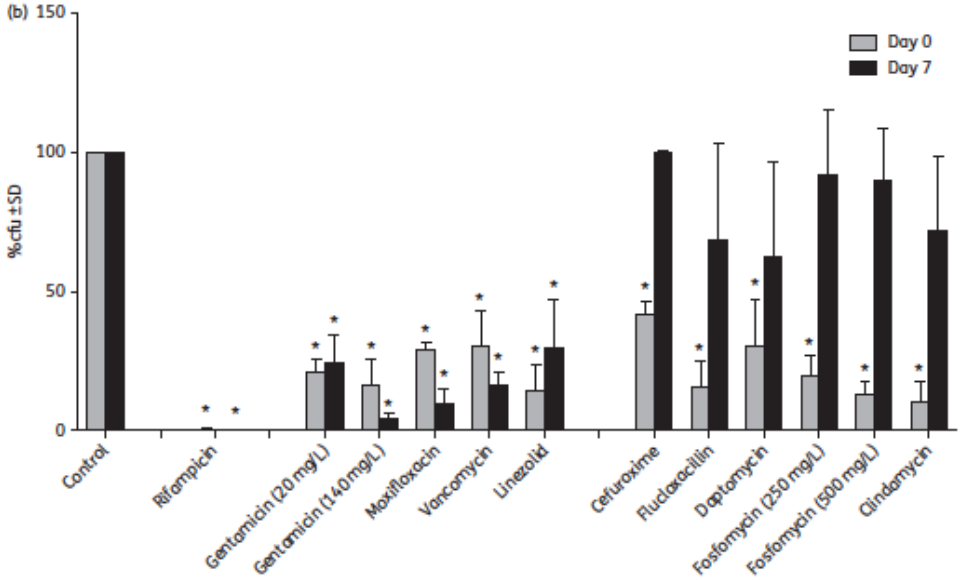


J Antimicrob Chemother 2016; **71**: 438–448
doi:10.1093/jac/dkv371 Advance Access publication 20 November 2015

Journal of Antimicrobial Chemotherapy

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

L. Tuchscherr[1]*†, C. A. Kreis[2]†, V. Hoerr[1,3]†, L. Flint[4], M. Hachmeister[4], J. Geraci[1], S. Bremer-Streck[5], M. Kiehntopf[5], E. Medina[6], M. Kribus[7], M. Raschke[2], M. Pletz[8], G. Peters[4] and B. Löffler[1,9]



Réservoir intracellulaire : ostéoBlastes

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Antimicrobial Activity against Intraosteoblastic *Staphylococcus aureus*

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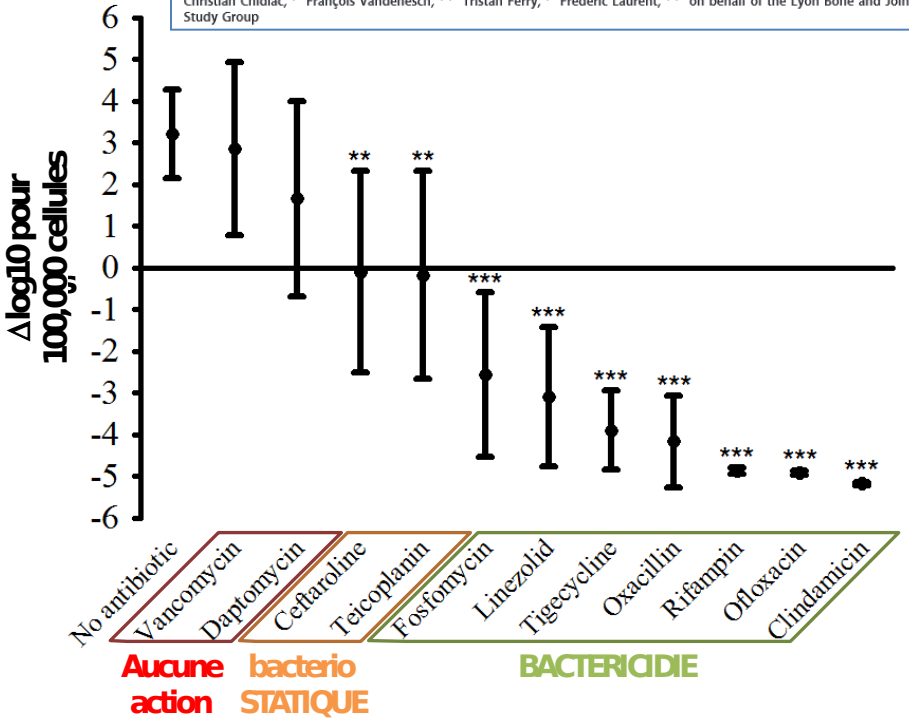


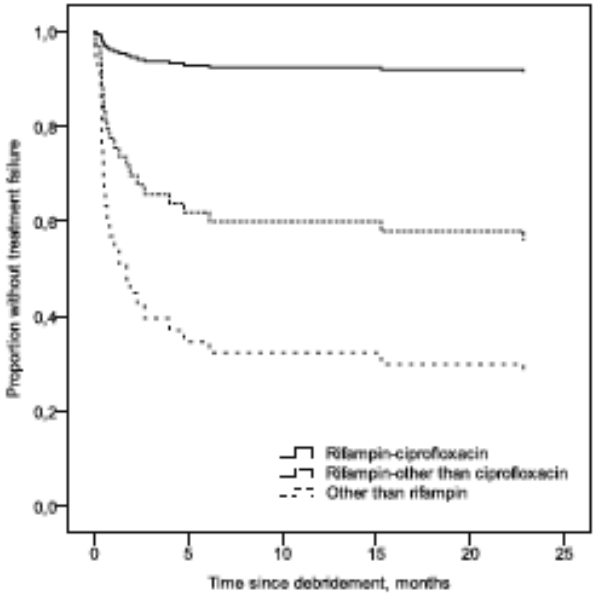
International Orthopaedics (SICOT) (2015) 39:1785–1791
DOI 10.1007/s00264-015-2819-2

ORIGINAL PAPER

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

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

113 PJI aiguës
66 SA et SCN



RMP + FQ

RMP sans FQ

Pas de RMP

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

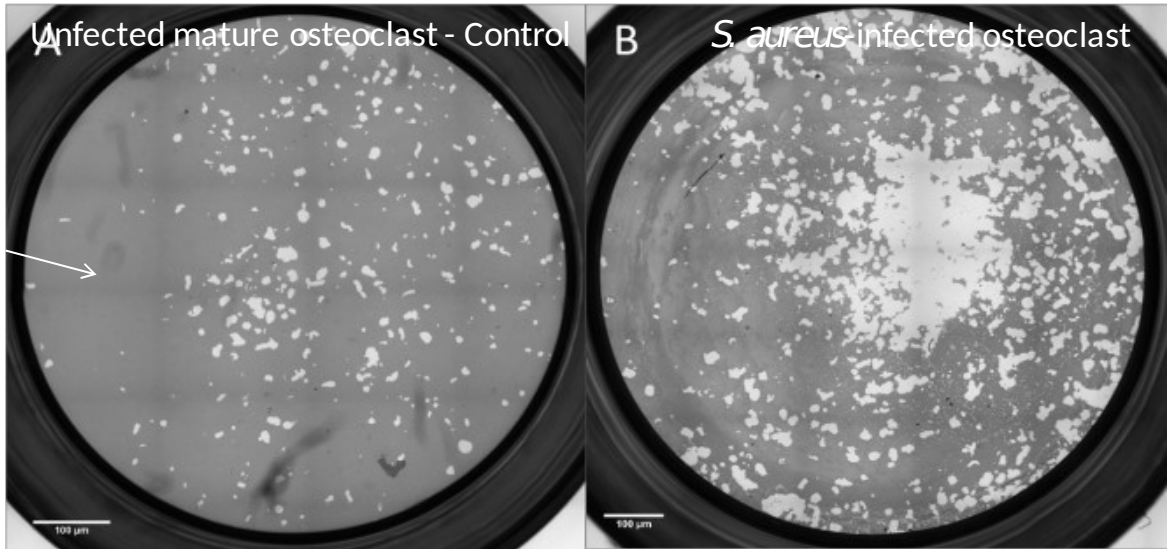
Réservoir intracellulaire : ostéoClastes

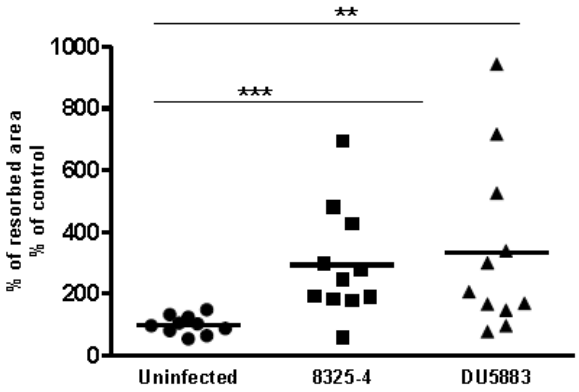
Dual Impact of Live *Staphylococcus aureus* on the Osteoclast Lineage, Leading to Increased Bone Resorption

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 Flammier,[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]

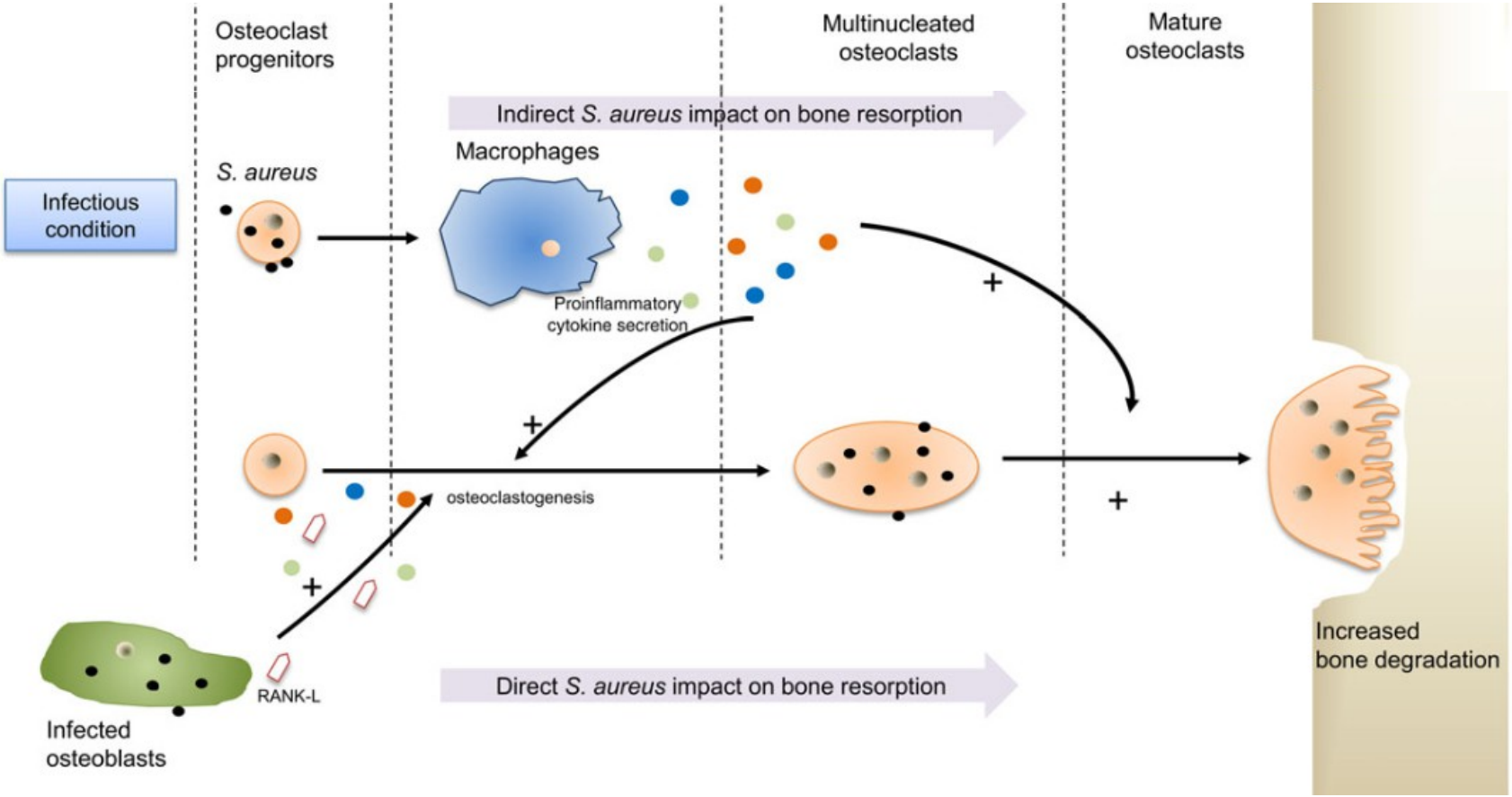
Augmentation de la résorption osseuse par les OC matures

Matrice minérale mimant la matrice osseuse





Réservoir intracellulaire : ostéoClastes

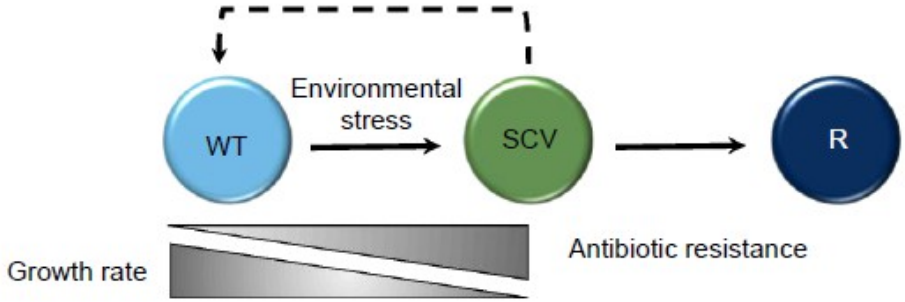


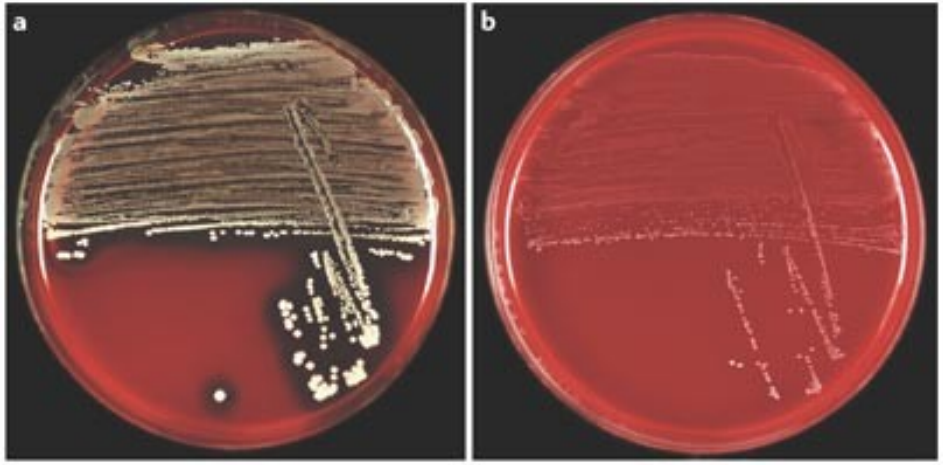
Small colony variants

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





Proctor, Nat Rev Microbiol 2006 – Proctor, CID 1995 – Tuchscherr, JID 2010 – Tuchscherr, JAC 2016

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] Kerryl E. Greenwood-Quaintance,[b] Tad M. Mabry,[c] Arlen D. Hanssen,[c] Robin Patel[a,b,d]

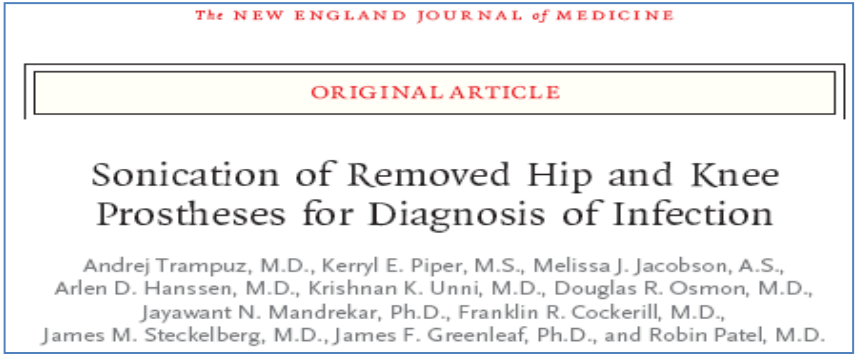
mBio September/October 2014 Volume 5 Issue 5 e01910-14

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]		
	Yes (n = 38)	No (n = 75)	P value
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

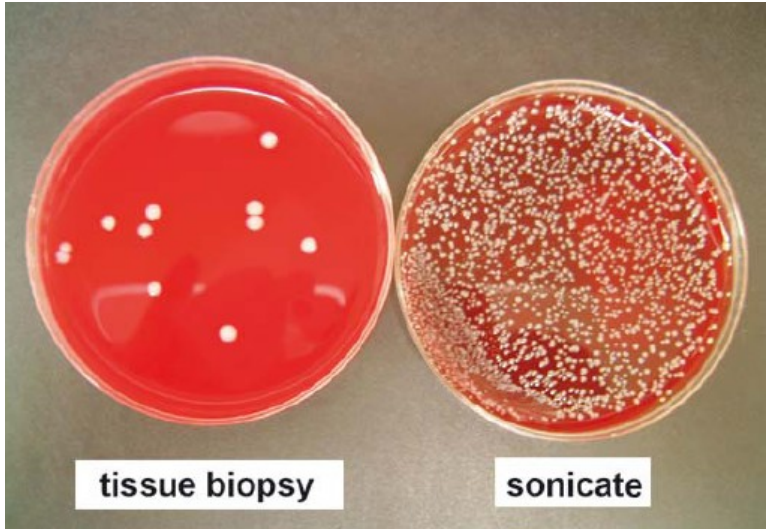
Small colony variants : diagnostic


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sonication of Removed Hip and Knee Prostheses for Diagnosis of Infection

Andrej Trampuz, M.D., Kerryl 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

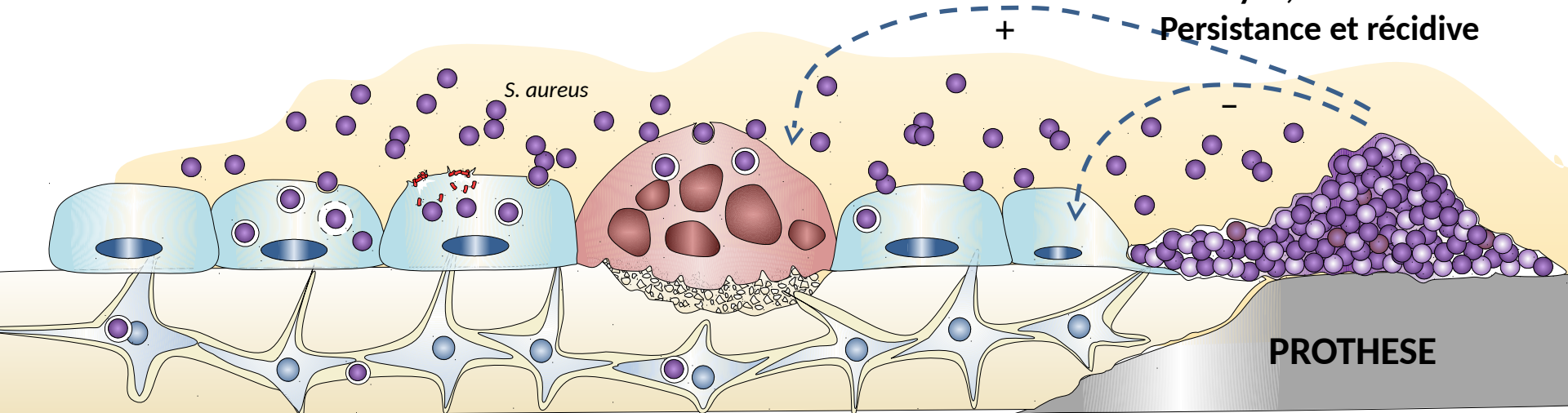
- *S. aureus*
- *S. epidermidis*
- *P. aeruginosa*
- *S. gallolyticus*
- *P. acnes*
- *S. sanguinis*

Conclusions

SURVIE DANS LES OSTEOBLASTES
↓
Réservoir intracellulaire
Inactivité des ATB
Emergence « persisters »
↓
Persistance et récidive

INFECTION DES OSTEOCLASTES
↓
Augmentation résorption
↓
Ostéolyse
Descellement

BIOFILM
↓
Apoptose OB, stimulation OC
Inhibition phagocytose
Réservoir, tolérance ATB
Emergence « persisters »
↓
Ostéolyse, descellement
Persistance et récidive



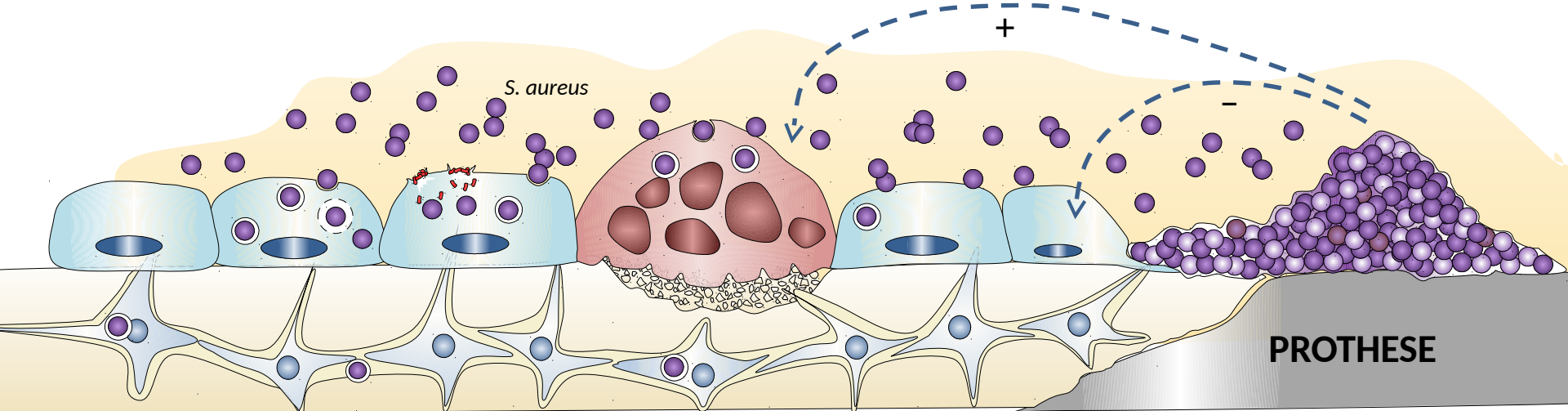
Conclusions

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 Miailhes, 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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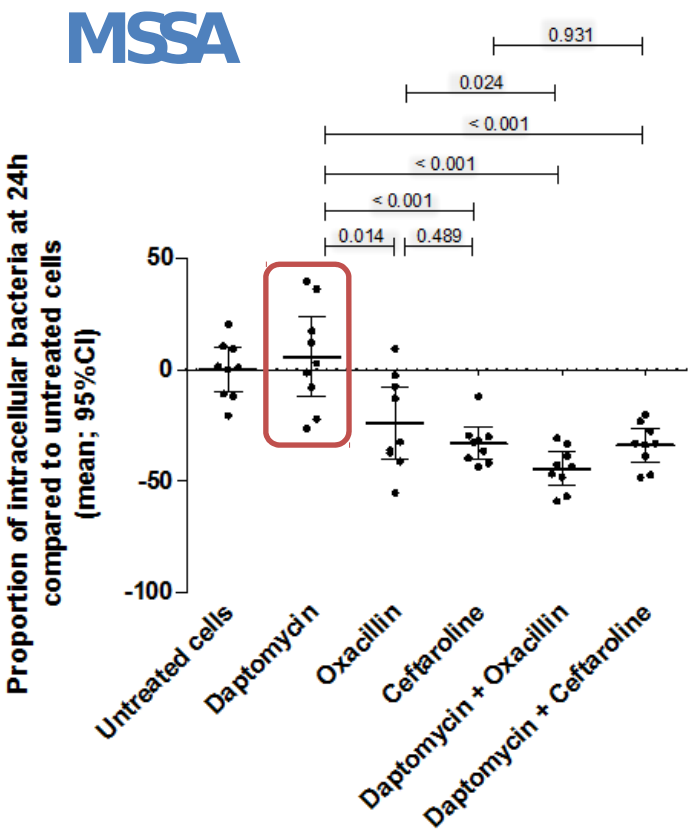
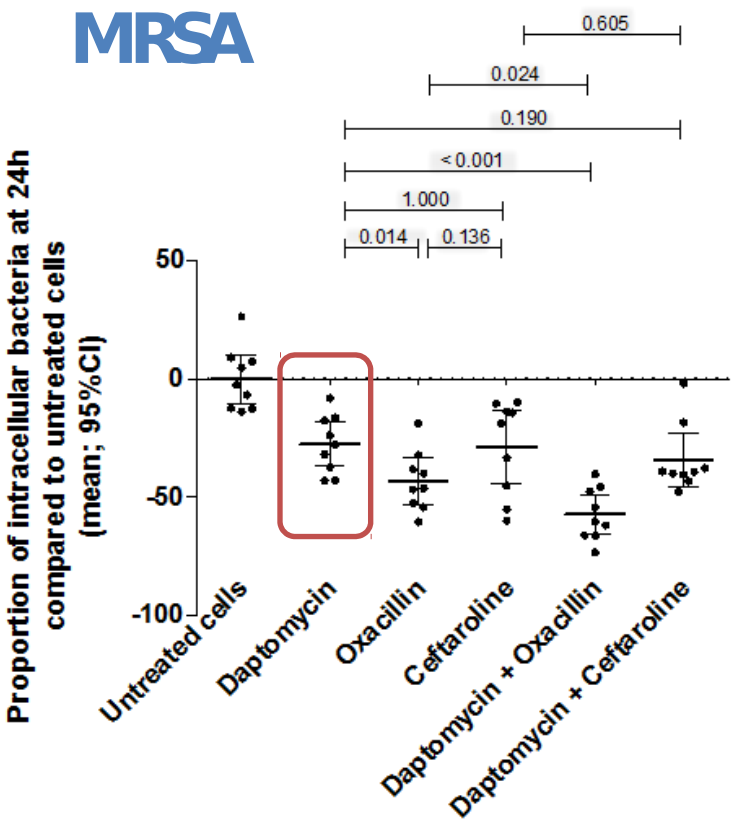
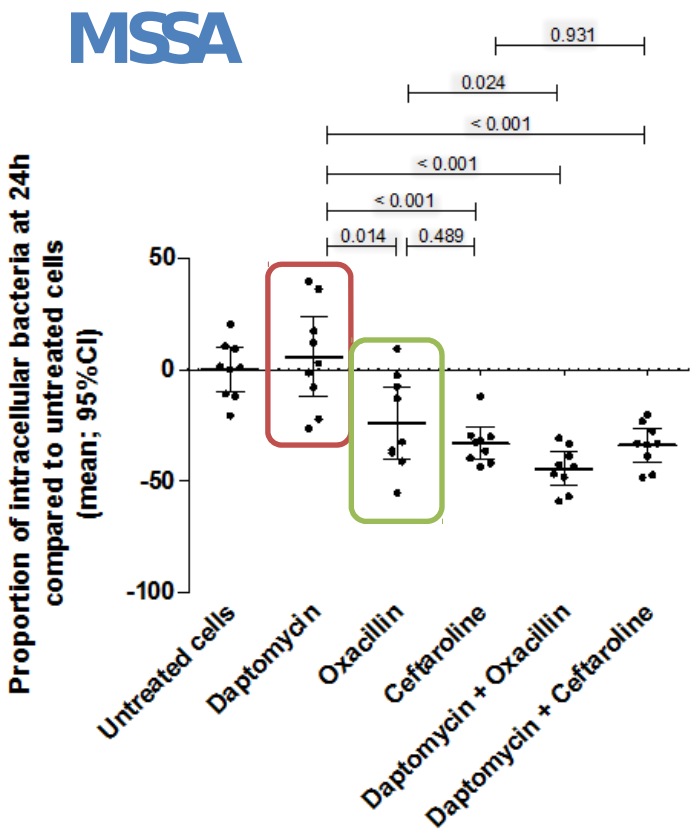
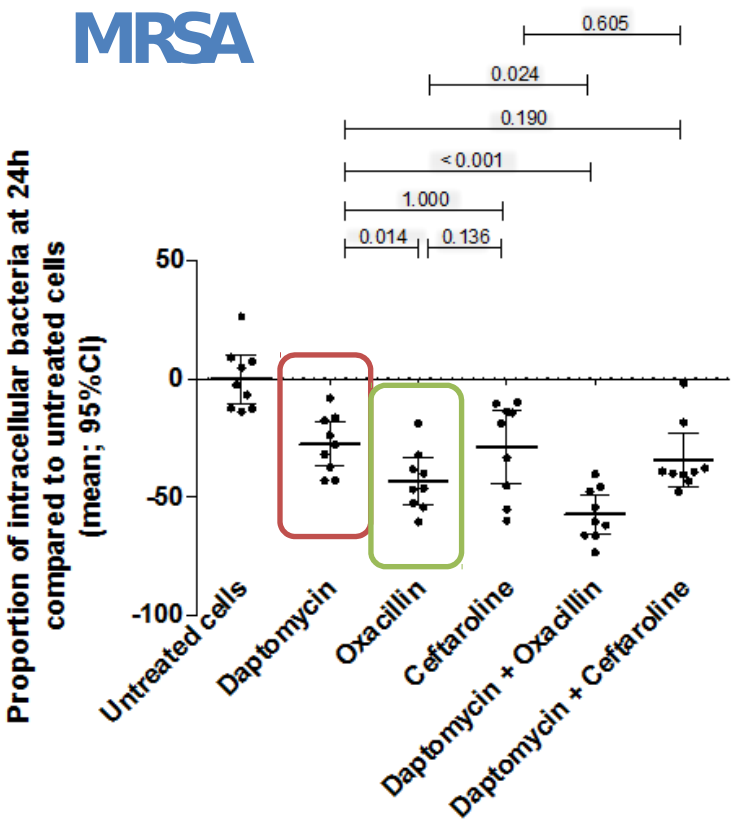
Réservoir intracellulaire : ostéoBlastes



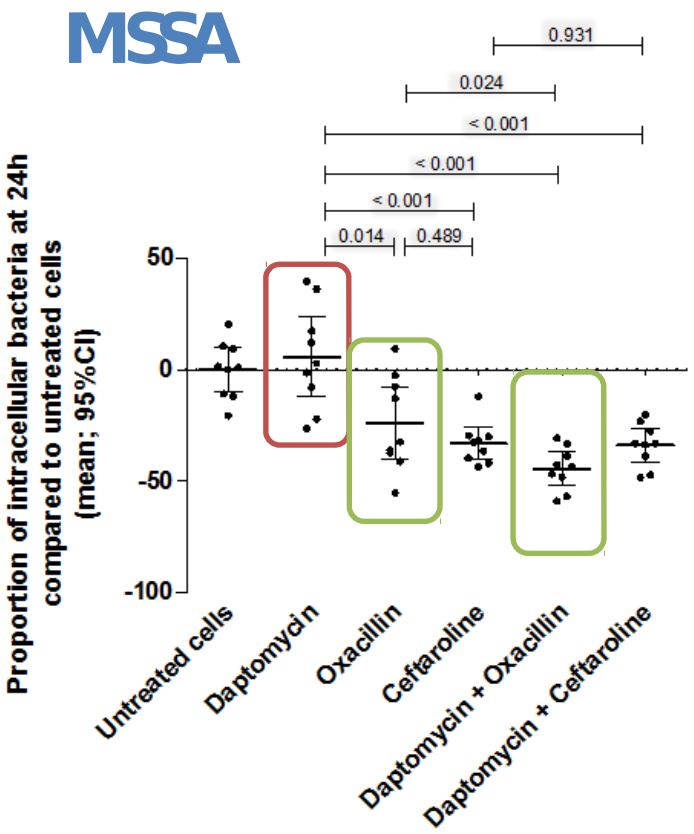


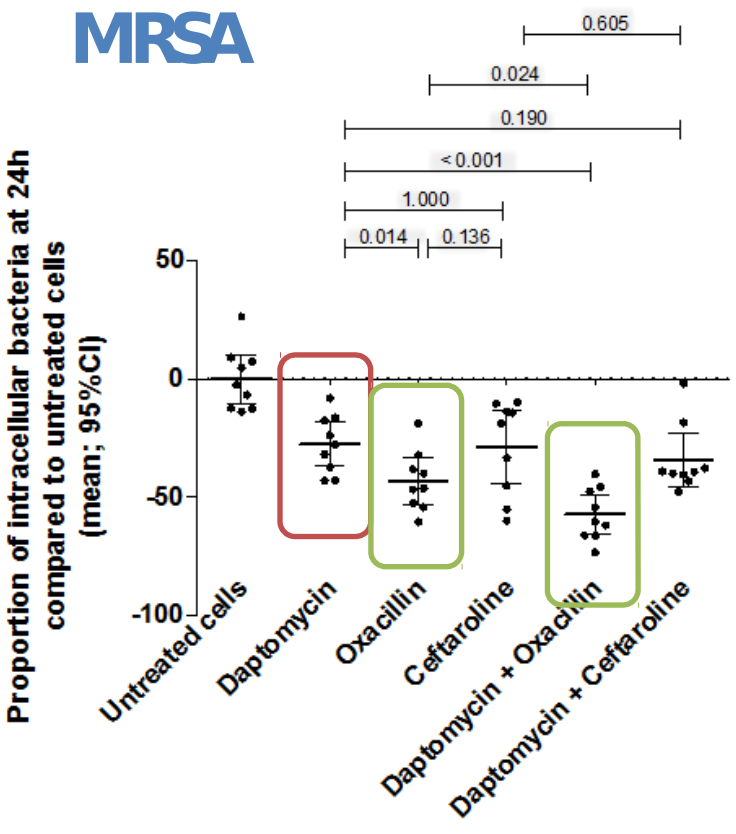
Réservoir intracellulaire : ostéoBlastes





Réservoir intracellulaire : ostéoBlastes





Réservoir intracellulaire : ostéoBlastes

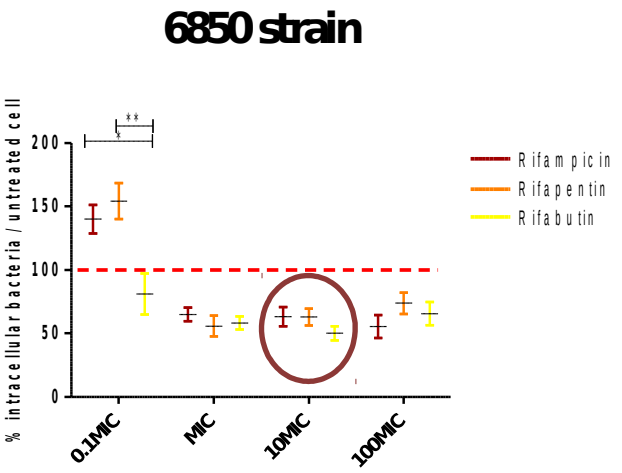
Impact du pH intralysosomal

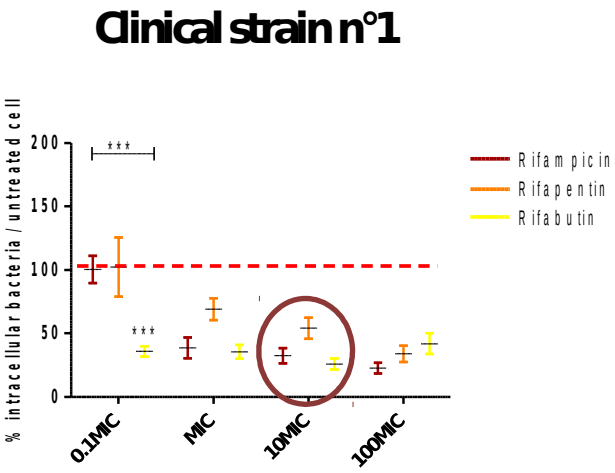
	SASM			SARM		
	pH 7	**pH 5**	*p*-value	**pH 7**	**pH 5**	*p*-value
Daptomycin	0,25	1,83	0,002	0,29	2,00	0,002
Oxacillin	0,50	0,06	0,047	106,70	0,35	0,001
Ceftaroline	4,00	0,08	0,059	8,00	0,062	0,047

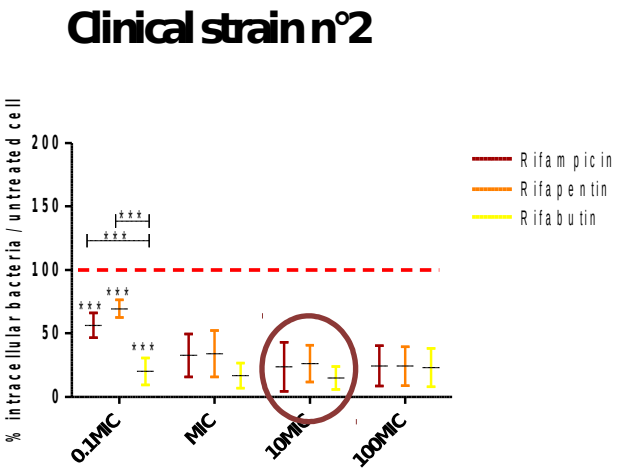
→ **Intracellular restauration of oxacillin activity against MRSA is (at least partly) due to a major decrease in MICs at the intralysosomal acidic pH**

→ **Intracellular weak activity of daptomycin might be partly due to its decrease in activity at acidic pH**

Réservoir intracellulaire : ostéoBlastes

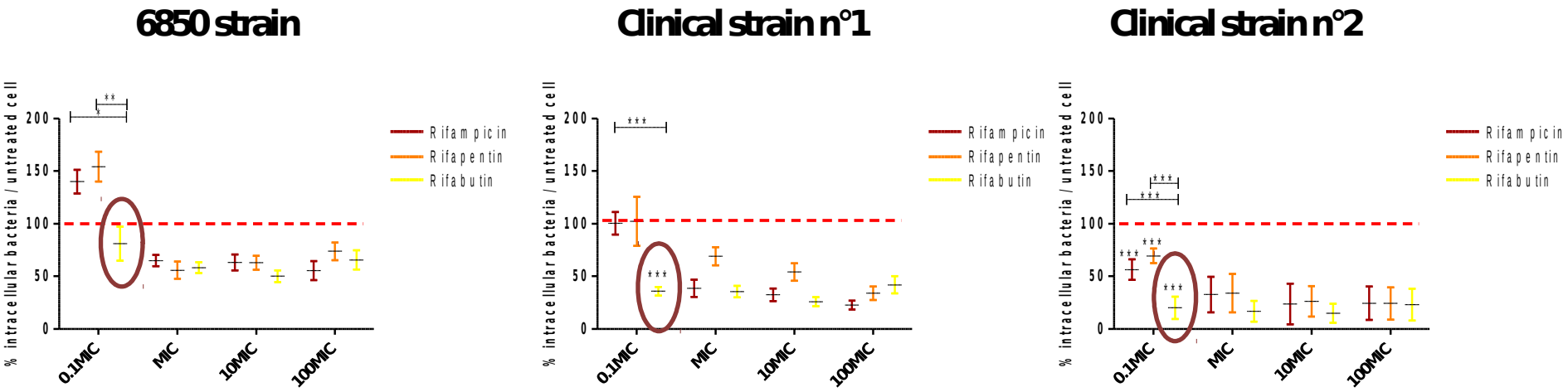






→ **Bonne activité intracellulaire des 3 rifamycines à concentration osseuse**

Réservoir intracellulaire : ostéoBlastes

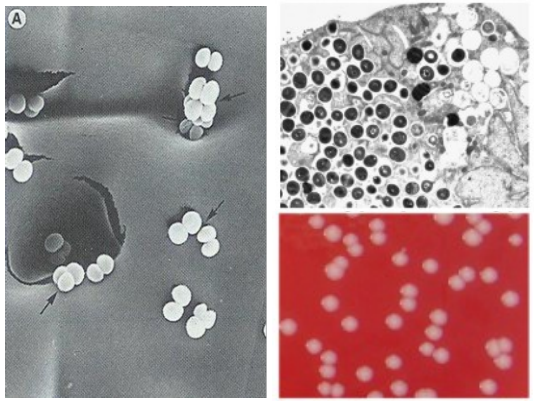


→ Bonne activité intracellulaire des 3 rifamycines à concentration osseuse
→ Meilleure activité de la rifabutine à faible concentration (dès 0,1 CMI)
→ Maintien de l'activité de la rifampicine et de la rifabutine à J7 (vs rifapentine)

Conclusions

Adaptation bactérienne

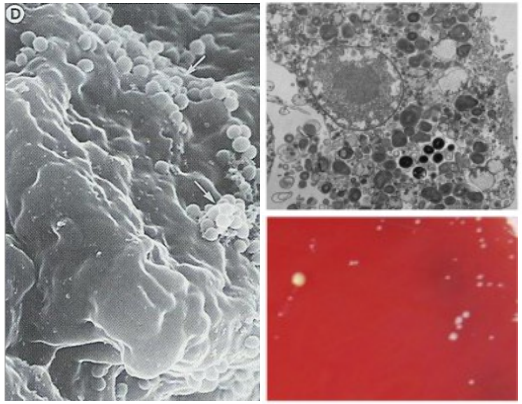
IOA aiguë → **IOA chronique**



Biofilm

Persistance intracellulaire

SCVs



↑ Toxines ↓ Adhésines

↓ 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