DESC de maladies infectieuses et tropicales
Thématique n°10 : Infections ostéo-articulaires
Jeudi 13 octobre 2016

Physiopathologie des IOA chroniques

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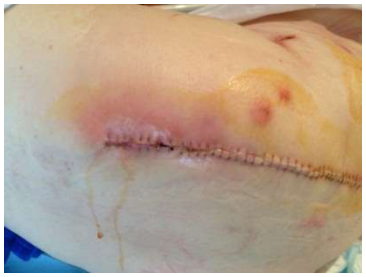
Maladies infectieuses et tropicales
Centre de Référence inter-régional pour la prise en charge des IOA complexes
Hospices Civils de Lyon

INSERM U1111 – Centre International de Recherche en Infectiologie
Université Claude Bernard Lyon 1

Chronicité : importance du concept



Début des symptômes

Diagnostic
Début de prise en charge

3-4 sem

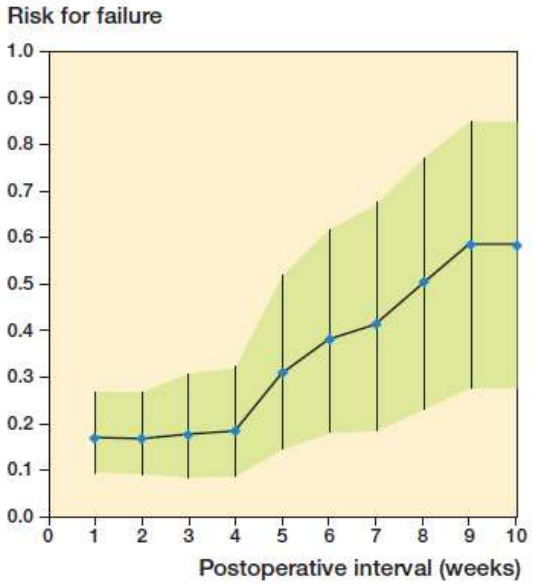
< 3-4 semaines

IOA AIGUE

- Réplication bactérienne +++
- Infection suppurative
- Congestion vasculaire

TRAITEMENT CONSERVATEUR

Risque de récidive



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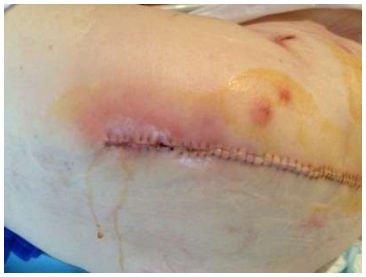

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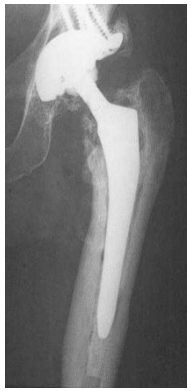
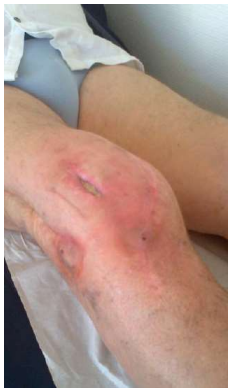




3-4 sem

< 3-4 semaines

IOA AIGUE

- Réplication bactérienne +++
- Infection suppurative
- Congestion vasculaire

TRAITEMENT CONSERVATEUR

Risque de récidive

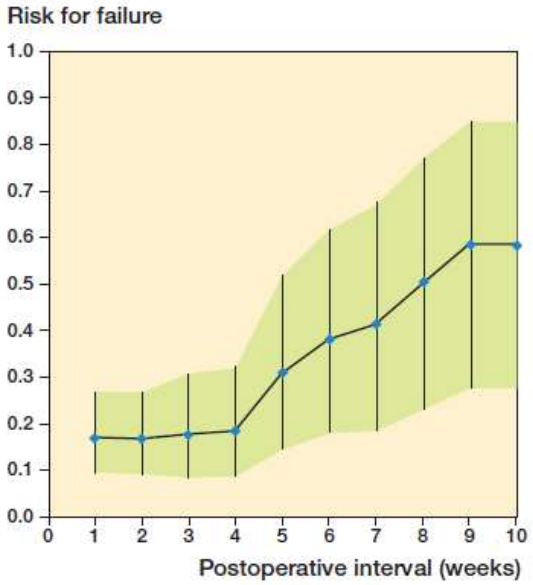
> 3-4 semaines

IOA CHRONIQUE

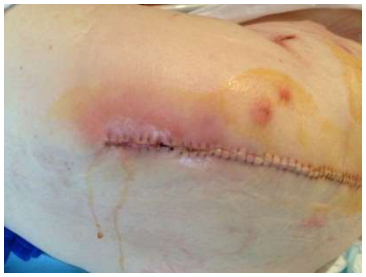
- Tissu osseux ischémique
- Séquestre osseux
- Descellement
- Ralentissement de la croissance bactérienne

ABLATION DES IMPLANTS

Taux élevé d'échec thérapeutique



Chronicité : importance du concept



Début des symptômes

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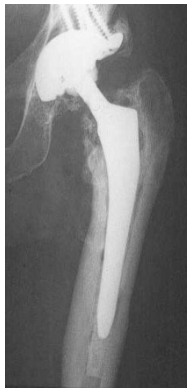
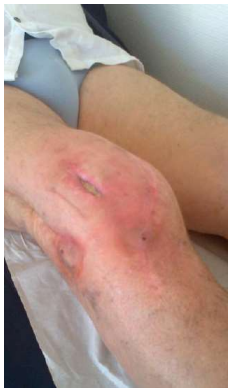
Début de prise en charge





3-4 sem

???

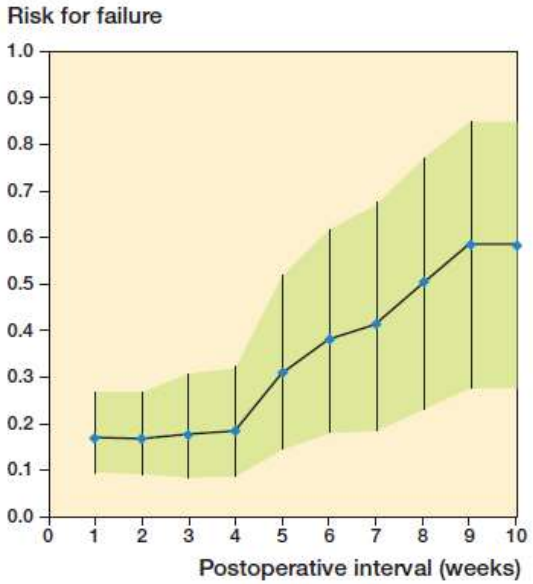
< 3-4 semaines

IOA AIGUE

- Réplication bactérienne +++
- Infection suppurative
- Congestion vasculaire

TRAITEMENT CONSERVATEUR

Risque de récidive



> 3-4 semaines

IOA CHRONIQUE

- Tissu osseux ischémique
- Séquestre osseux
- Descellement
- Ralentissement de la croissance bactérienne

ABLATION DES IMPLANTS

Taux élevé d'échec thérapeutique

Chronicité : bases physiopathologiques

Staphylocoques (50-70% des IOA) → **Formes aiguës – VIRULENCE**

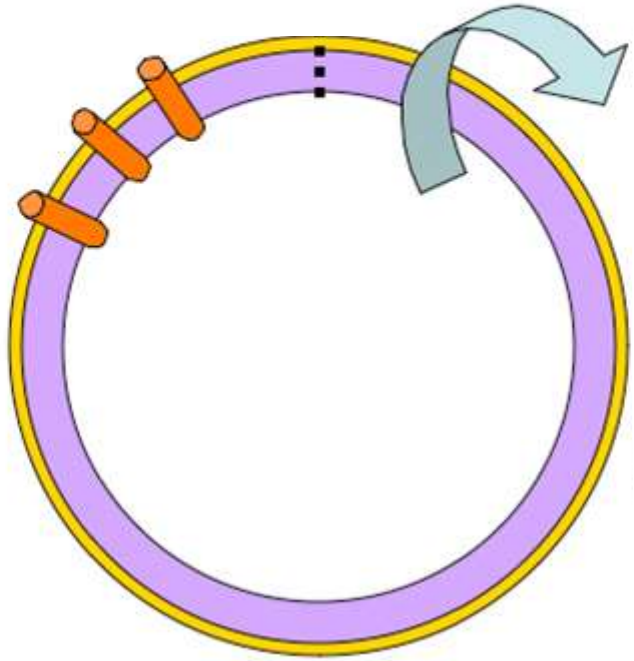
Chronicité : bases physiopathologiques

Staphylocoques (50-70% des IOA) → **Formes aiguës – VIRULENCE**

Facteurs associés à la paroi

Adhésines (MSCRAMMs)
Fibronectin-BPs
Collagen-BP
Bone sialoprotein-BP

Protéine A
binding to Ig and vWF



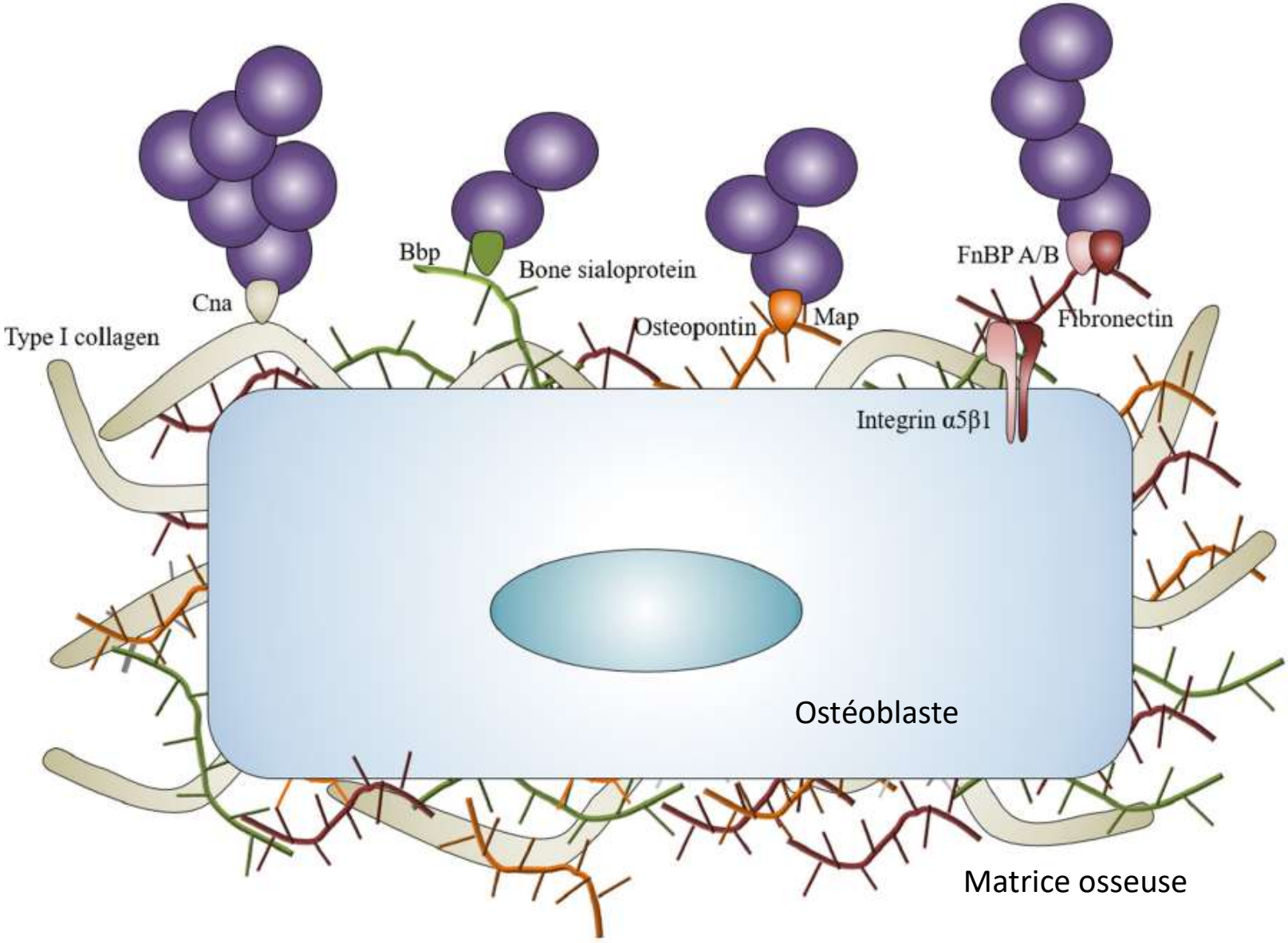
Facteurs de virulence sécrétés

Exotoxines
- Toxines superantigéniques : *TSST-1, SEA, …*
- Hémolysines : *α-toxin, β-toxin …*
- Pore-forming toxins : *PVL …*
- Enzymes : *Staphylokinase, proteases, lipases, …*

Adhésines (SERAMs)
Coagulase, Efb, Emp …

Ferry et al. Curr Infec Dis Rep 2005

FOCUS : Adhésion de *S. aureus* au tissus osseux



Josse, Front Microbiol 2015

Chronicité : bases physiopathologiques

Staphylocoques (50-70% des IOA) → **Formes chroniques, récidives**

PERSISTANCE

Facteurs associés à la paroi

Adhesines (MSCRAMMs)
Fibronectin-BPs
Collagen-BP
Bone sialoprotein-BP

Protéine A
binding to Ig and vWF

Echappement du système immunitaire

Facteurs de virulence sécrétés

Exotoxines
- Toxines superantigéniques : *TSST-1, SEA, …*
- Hémolysines : *α-toxin, β-toxin …*
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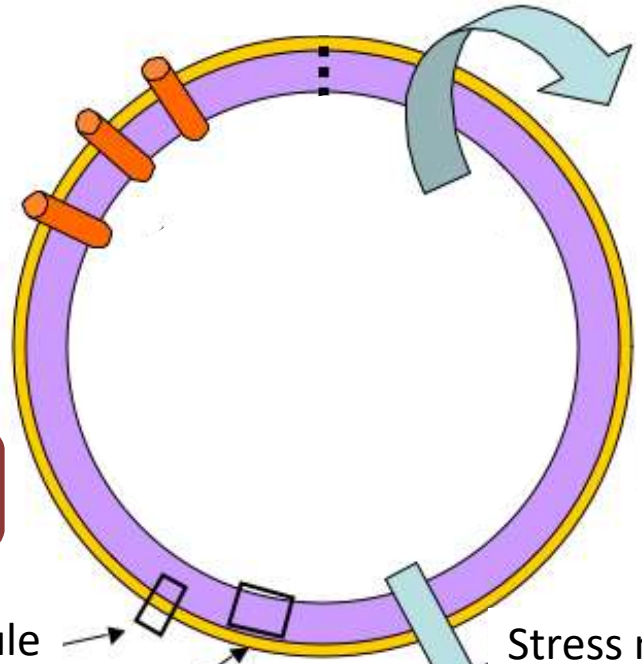
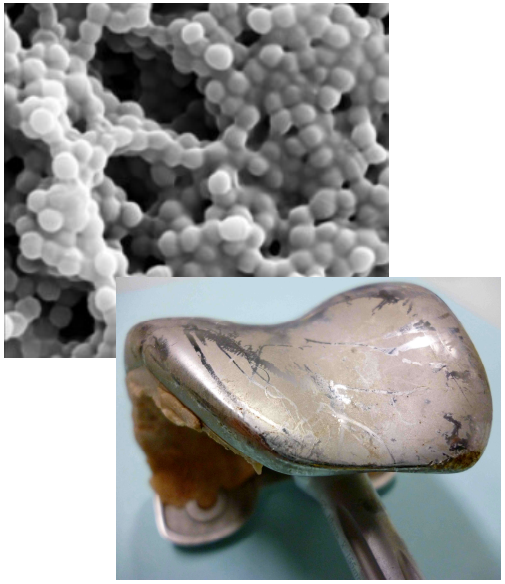


Phénotypes persistants

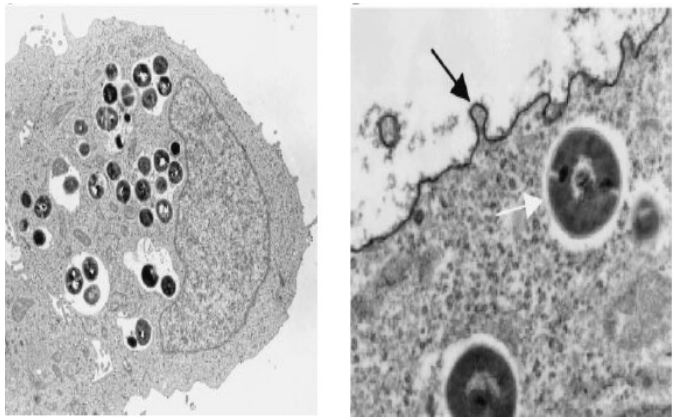
Ferry et al. Curr Infec Dis Rep 2005

Chronicité et persistance
MECANISMES BACTERIENS

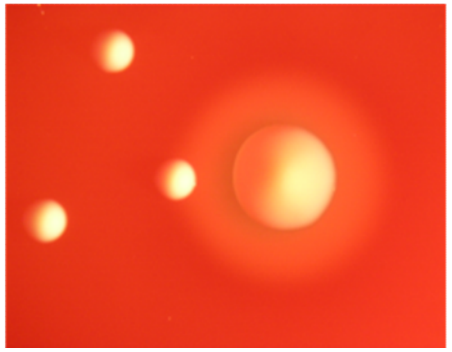
BIOFILM



VIE INTRACELLULAIRE



SMALL COLONY VARIANT (SCV)



Chronicité et persistance
MECANISMES BACTERIENS

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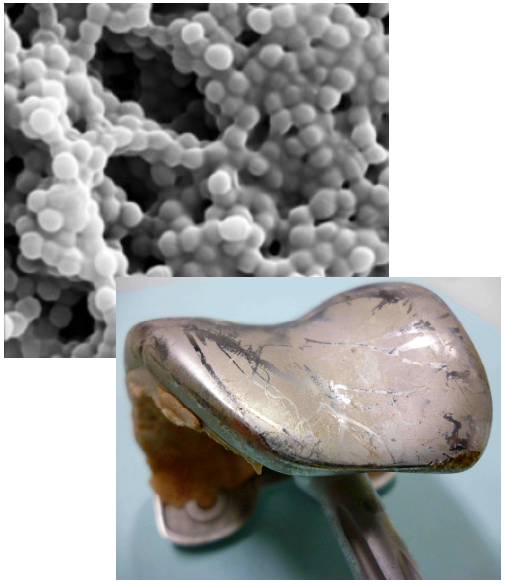

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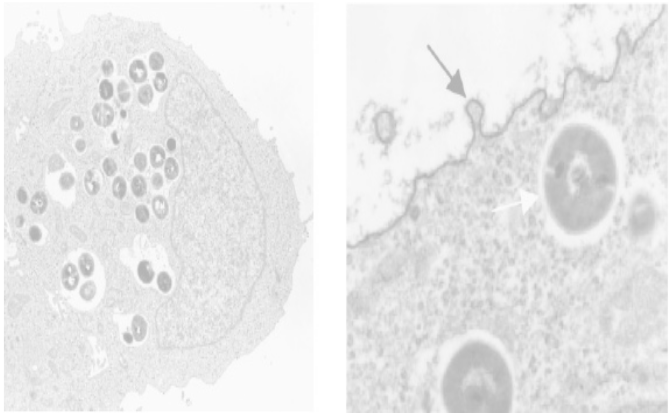

SMALL
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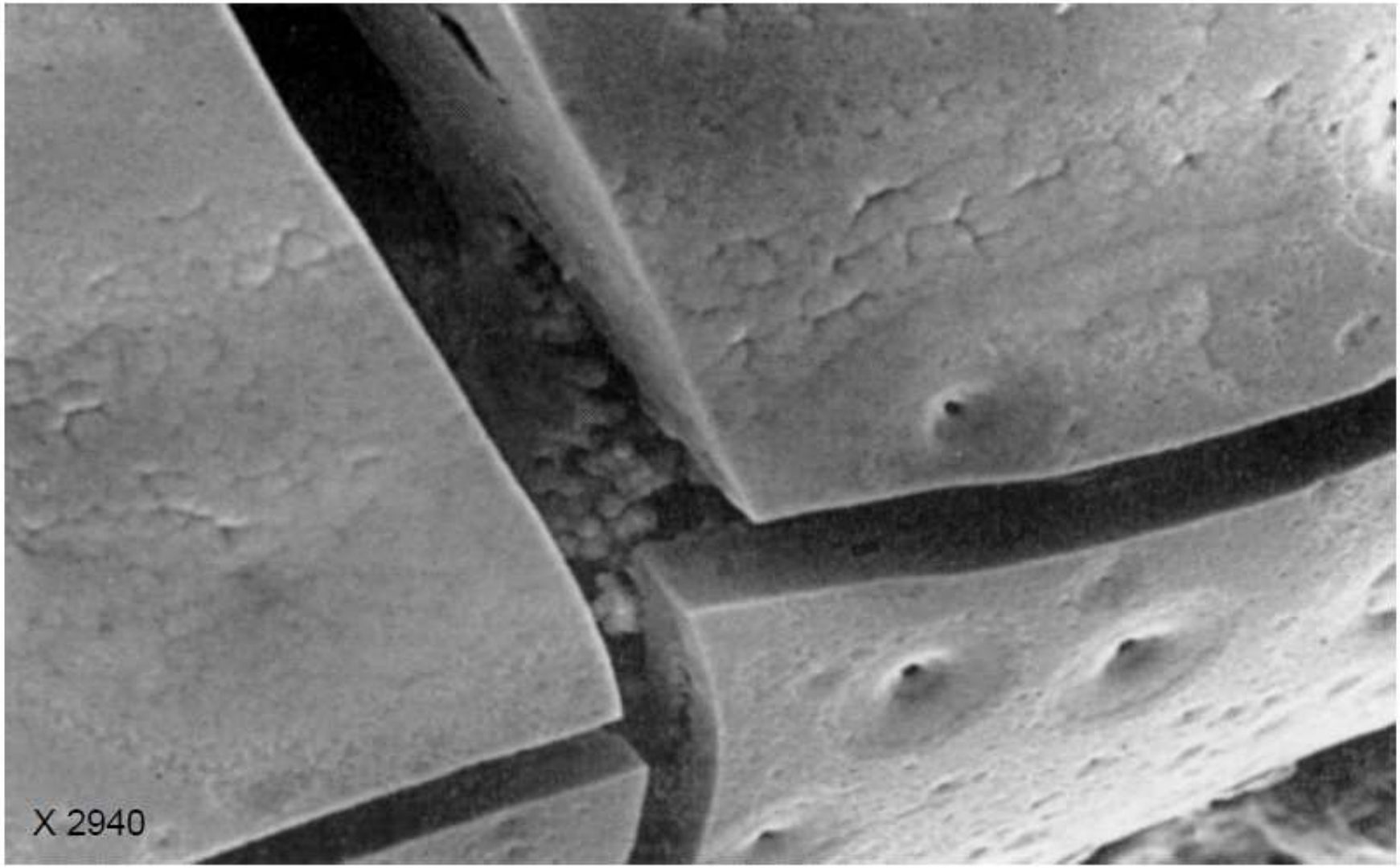
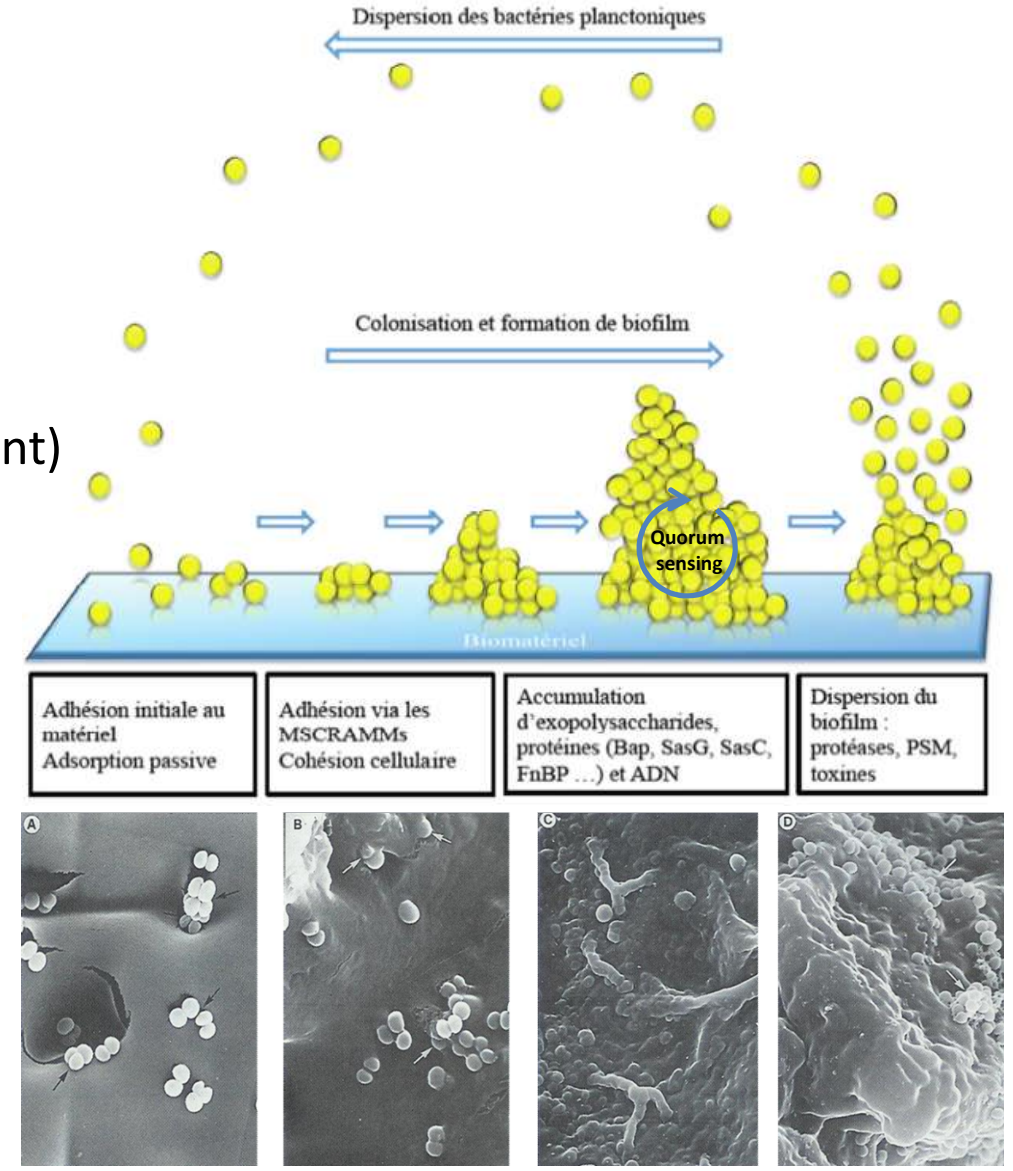
Biofilm



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

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

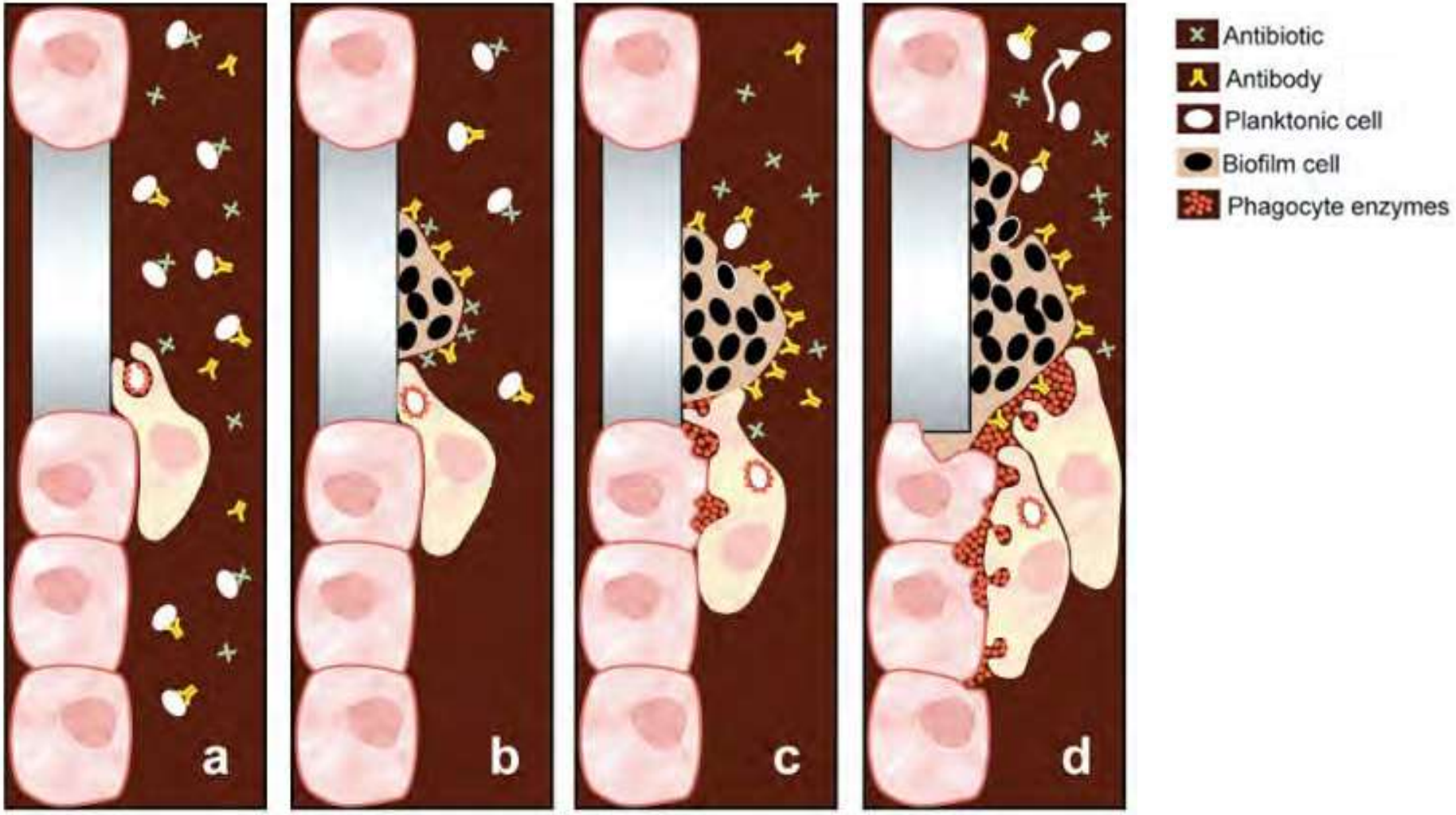
Biofilm

Bactéries planchtoniques

- Accessibles aux phagocytes et anticorps
- Sensibilité aux ATB

Costerton, Science 1999

Biofilm



Bactéries en biofilm

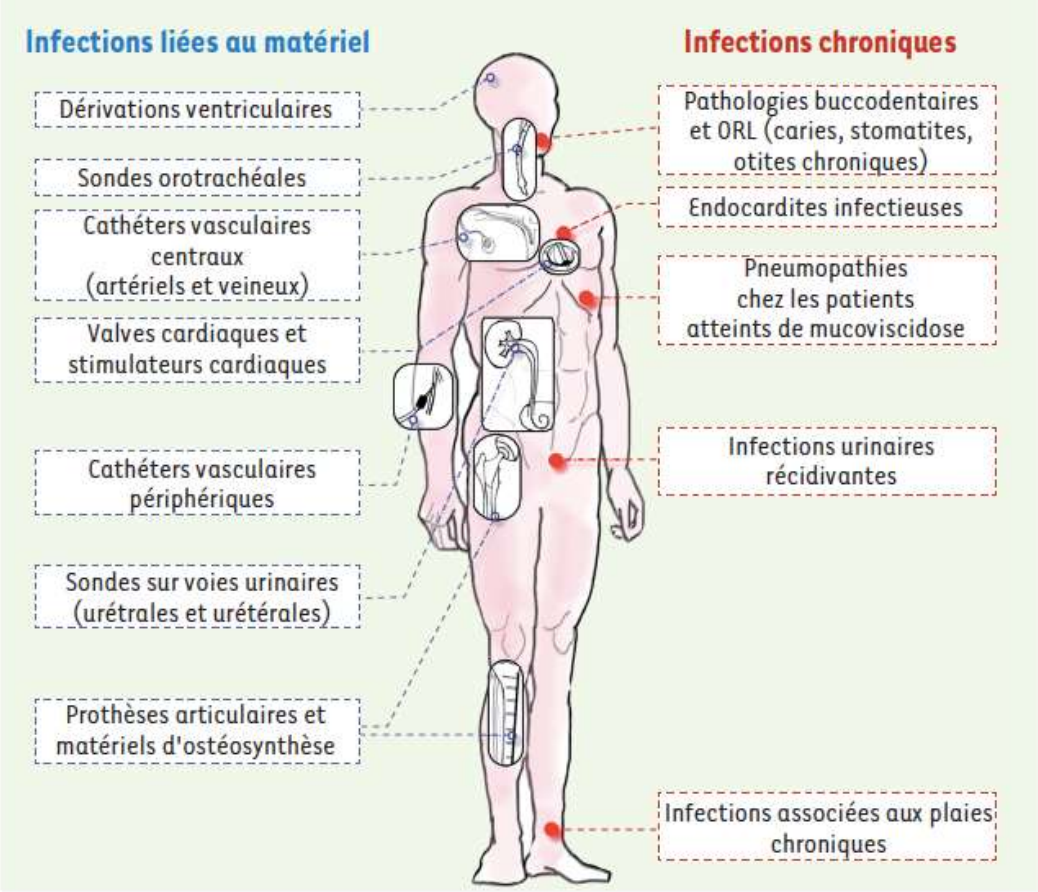
- Phagocytose inefficace, relargage local d'enzymes lysosomales, ostéolyse et descellement
- « Tolérance » aux antibiotiques : diffusion, inactivation, activité réduite

Costerton, Science 1999

FOCUS : Biofilm et thérapeutique

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

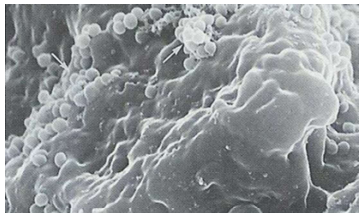
- Importance des ATB « anti-biofilm », notamment en cas de traitement conservateur

FOCUS : Biofilm et thérapeutique

Mécanisme 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***

FOCUS : Biofilm et thérapeutique

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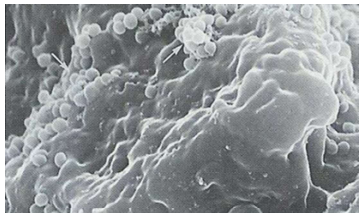

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TABLE 4. Susceptibility of planktonic and biofilm bacteria to selected antibiotics

Reference	Organism	Antibiotic	MIC or MBC of planktonic phenotype (μg/ml)	Concn effective against biofilm phenotype (μg/ml)	
215	*S. aureus* NCTC 8325-4	Vancomycin	2 (MBC)	20[a]	×10
26	*Pseudomonas aeruginosa* ATCC 27853	Imipenem	1 (MIC)	>1,024[b]	×1000
26	*E. coli* ATCC 25922	Ampicillin	2 (MIC)	512[b]	×256
208	*P. pseudomallei*	Ceftazidime	8 (MBC)	800[c]	×100
114	*Streptococcus sanguis* 804	Doxycycline	0.063 (MIC)	3.15[d]	×50

[a] Concentration required for 99% reduction.
[b] Minimal biofilm eradication concentration.
[c] Concentration required for ~99% reduction.
[d] Concentration required for >99.9% reduction.

Donlan, CMR 2002

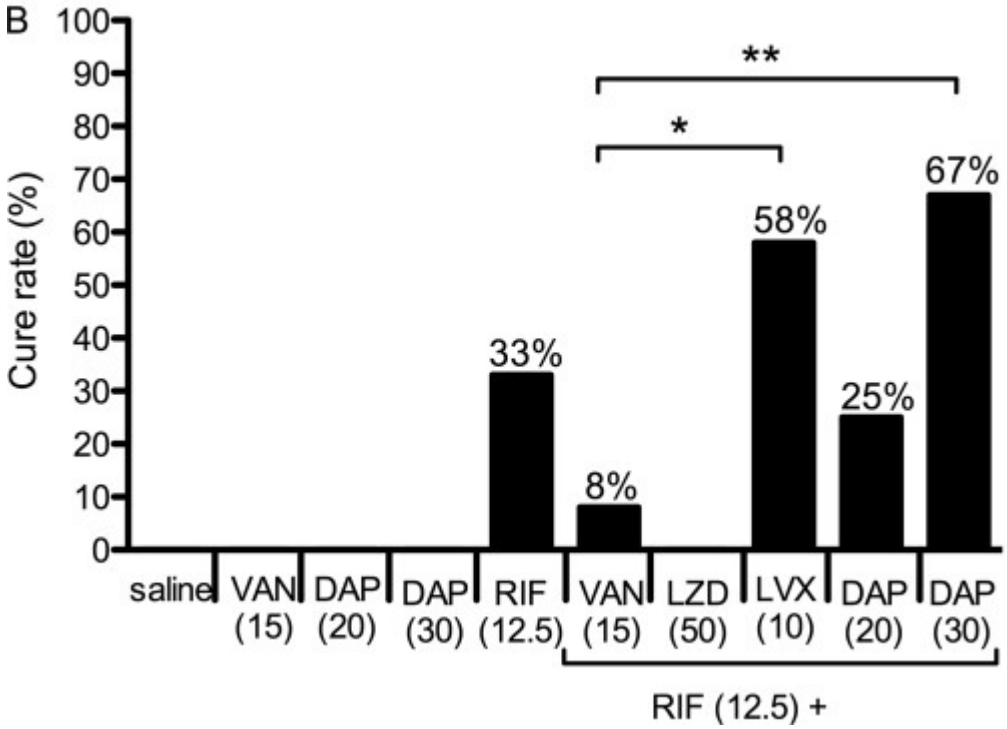
FOCUS : Biofilm et thérapeutique

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

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]*

SARM et DAP-RMP



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)	0/12 (0)
DAP (30) + RIF (12.5)	0/12 (0)	0/12 (0)	0/12 (0)

FOCUS : Biofilm et thérapeutique

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

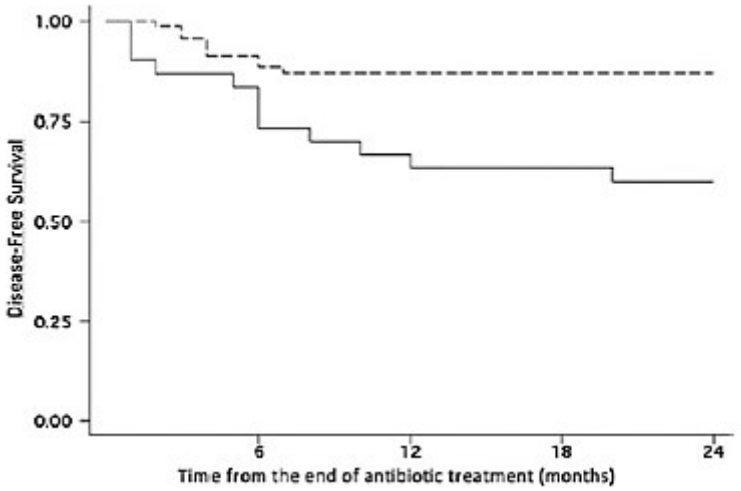
Centre National de Référence des Infections Ostéo-Articulaires Nord-Ouest, Roger Salengro Faculty Hospital of Lille, Lille, France

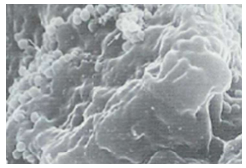
Facteurs protecteurs (univarié)

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

Facteurs protecteurs (multi-varié)

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





FOCUS : Biofilm et thérapeutique

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 1991, p. 741–746 Vol. 35, No. 4
0066-4804/91/040741-06$02.00/0

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]*

BGN et FQ

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

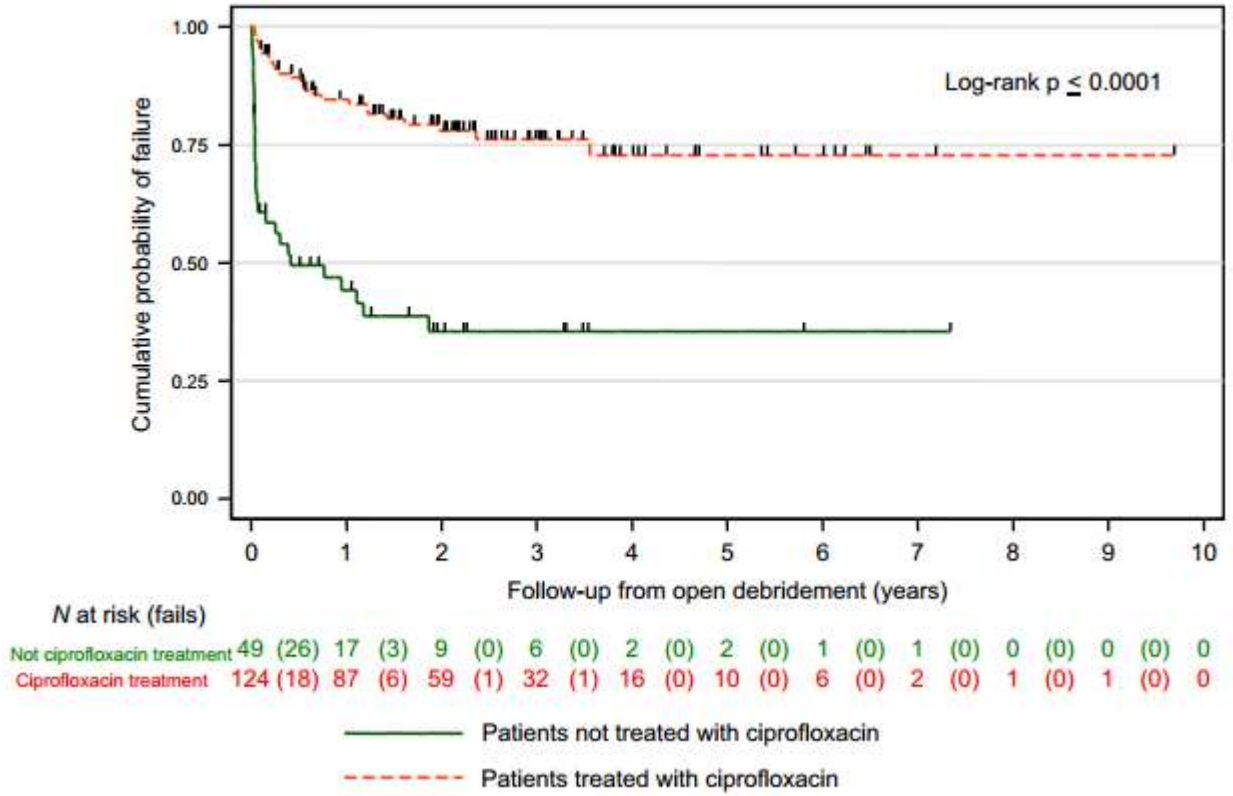
[a] Adherent bacteria were incubated at drug concentrations corresponding to twice the MBC determined in the logarithmic growth phase (see text).

FOCUS : Biofilm et thérapeutique

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



FOCUS : Biofilm et thérapeutique

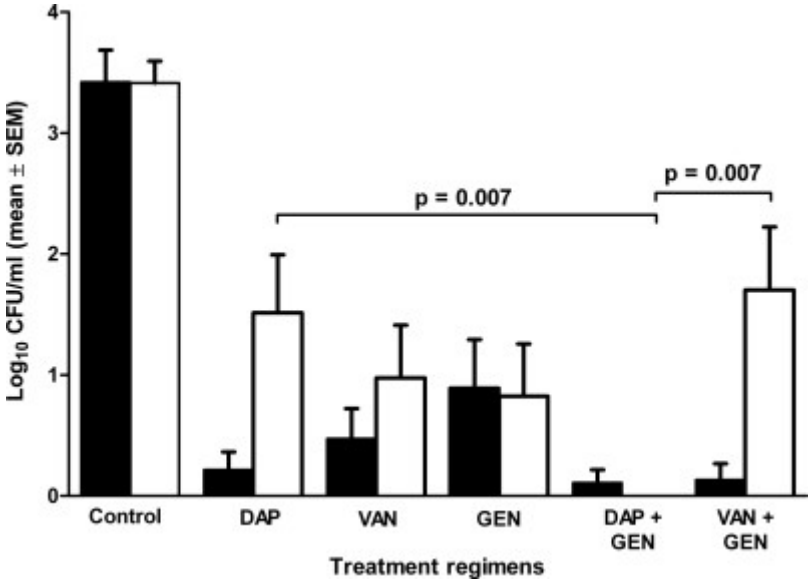
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2011, p. 4821–4827 Vol. 55, No. 10
0066-4804/11/$12.00 doi:10.1128/AAC.00141-11

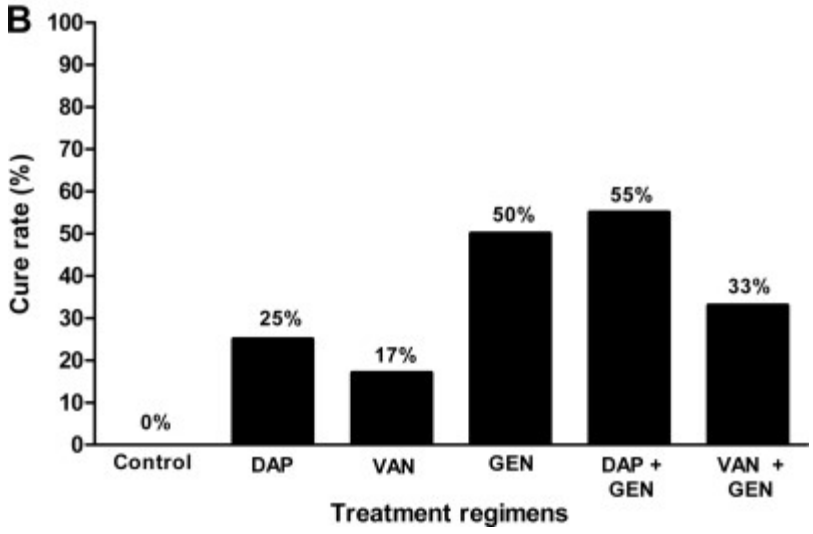
Gentamicin Improves the Activities of Daptomycin and Vancomycin against *Enterococcus faecalis In Vitro* and in an Experimental Foreign-Body Infection Model[▽]

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





Bactéries planctonique : fin de traitement et J5

Cure rate : adherent enc

FOCUS : Biofilm et thérapeutique

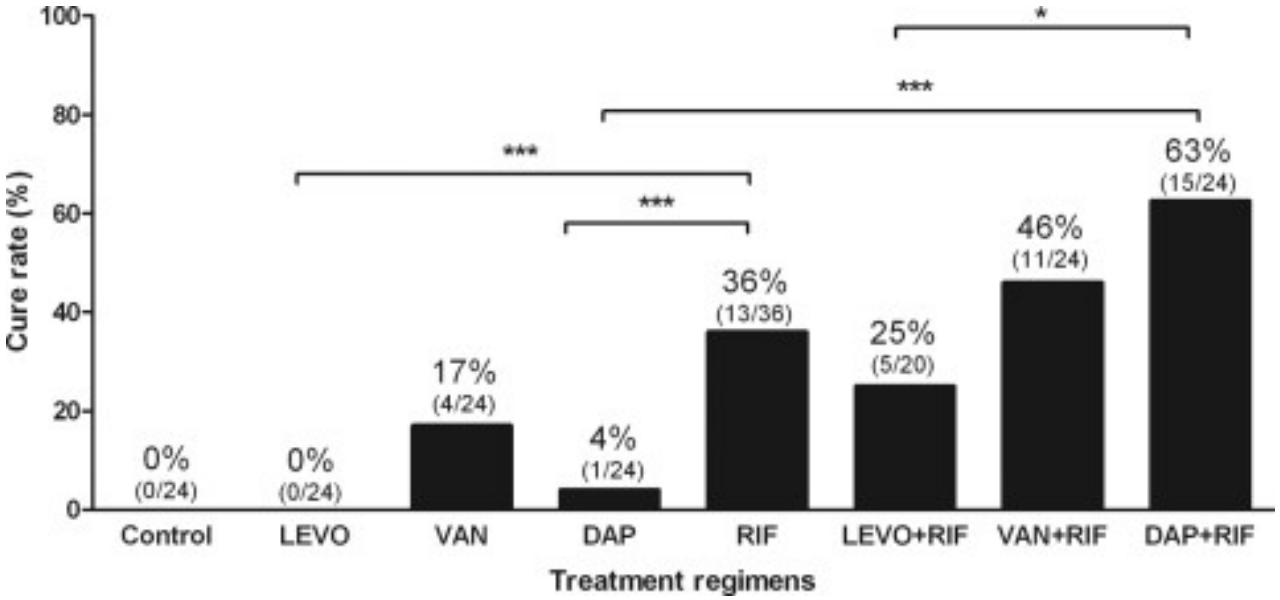
AAC
JournalsASM.org

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]

Propioni et RMP

Pas de données cliniques



Cure rate : adherent enc

FOCUS : Biofilm et thérapeutique

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	+	+++	+++

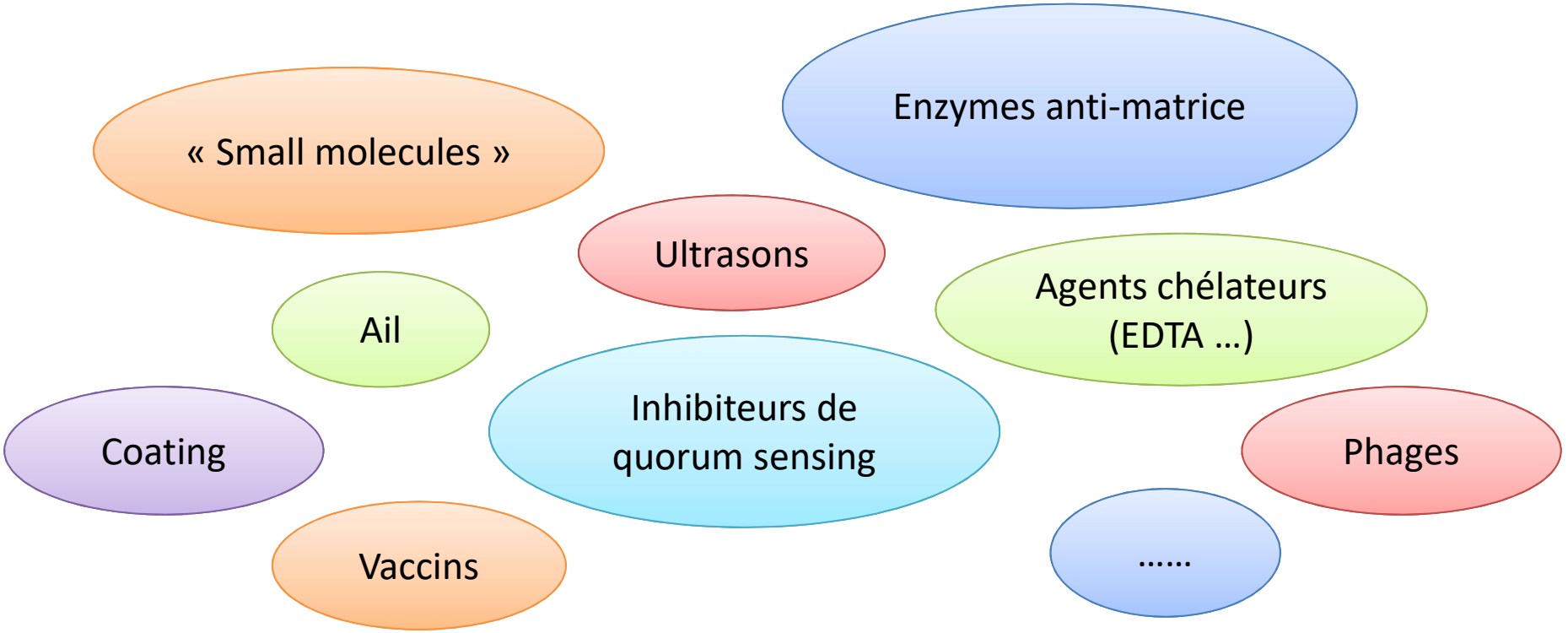
FOCUS : Biofilm et thérapeutique

International Journal of
Molecular Sciences
ISSN 1422-0067
www.mdpi.com/journal/ijms

Review

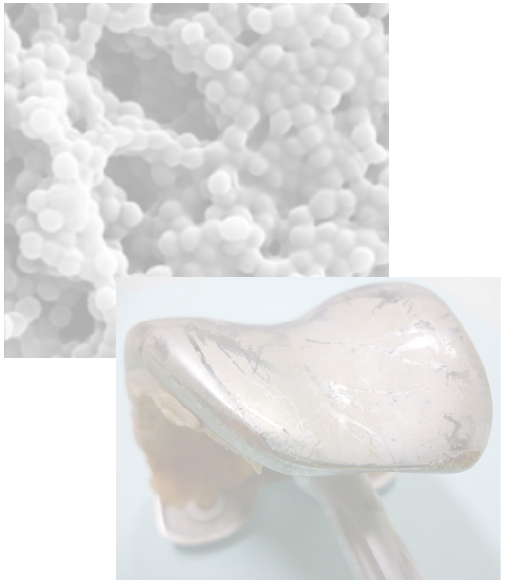
Novel Strategies for the Prevention and Treatment of Biofilm Related Infections

Meng Chen [1], Qingsong Yu [2] and Hongmin Sun [3,*]

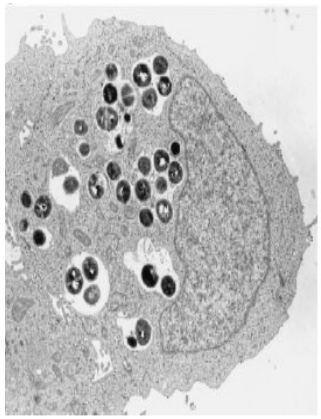


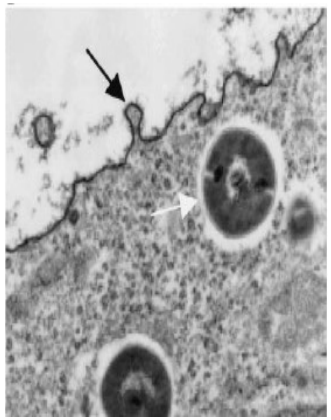
Chronicité et persistance
MECANISMES BACTERIENS

BIOFILM



VIE INTRACELLULAIRE





SMALL
COLONY VARIANT
(SCV)

Vie 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)

Vie intracellulaire

Staphylococcus aureus persistence in non-professional phagocytes

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

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

Décrit avec de nombreux types cellulaires

- Cellules endothéliales
- Cellules épithéliales
- Kératinocytes
- Fibroblastes
- Leucocytes

Vie intracellulaire

Staphylococcus aureus persistence in non-professional phagocytes

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Décrit avec de nombreux types cellulaires

- Cellules endothéliales
- Cellules épithéliales
- Kératinocytes
- Fibroblastes
- Leucocytes
- **…. et ostéoblastes !**

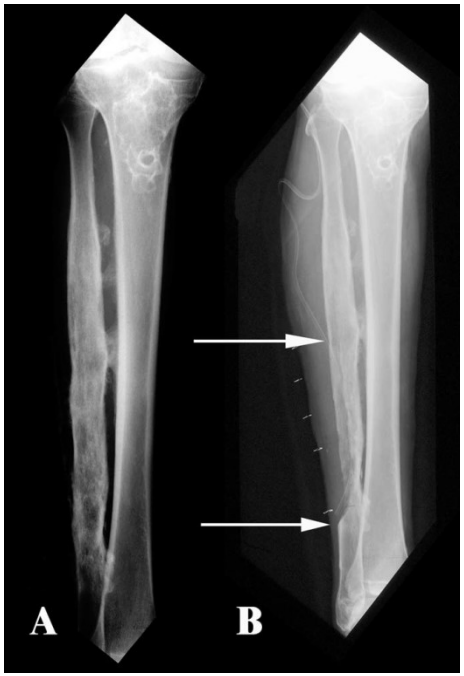
frontiers in Cellular and Infection Microbiology

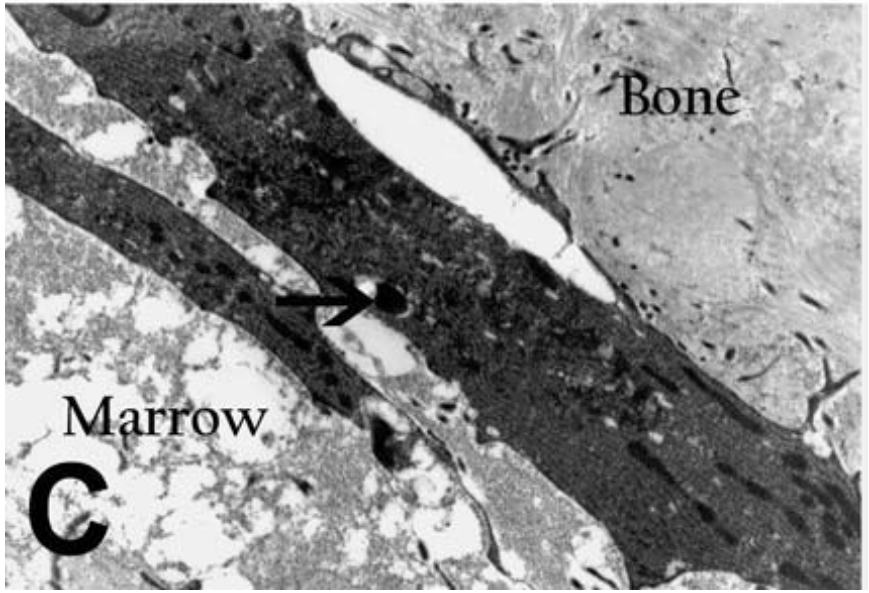
REVIEW
published: 26 November 2015
doi: 10.3389/fcimb.2015.00085

Staphylococcus aureus vs. Osteoblast: Relationship and Consequences in Osteomyelitis

*Jérôme Josse, Frédéric Velard and Sophie C. Gangloff**

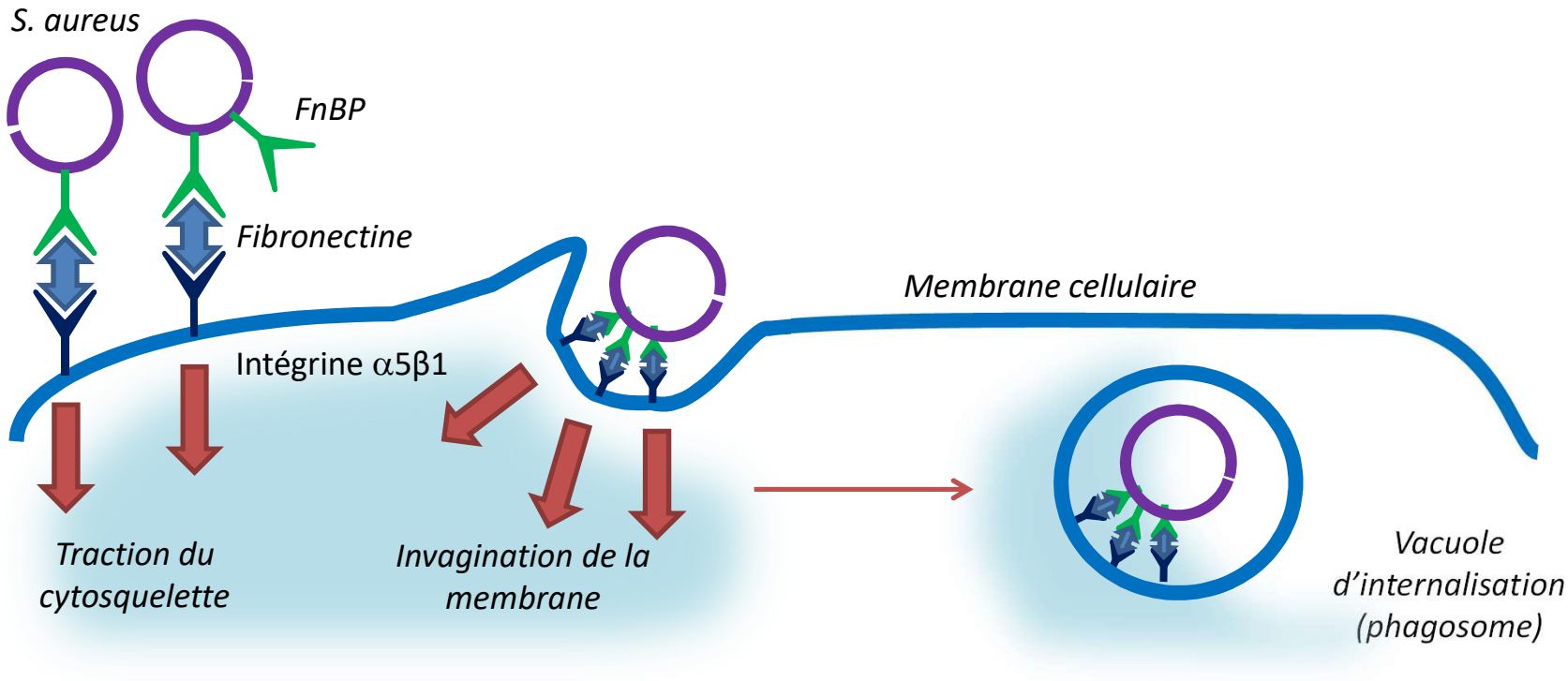
EA 4691 Biomatériaux et inflammation en site osseux, Pôle Santé, Université de Reims Champagne-Ardenne, Reims, France

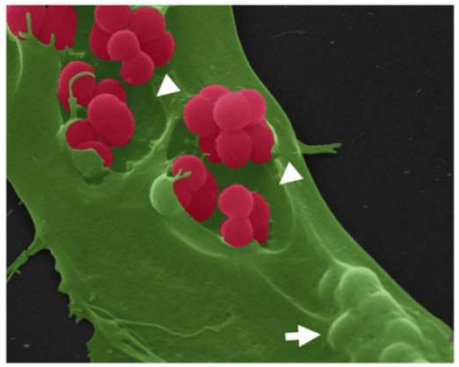




Bosse, 2005
Ostéite chronique
ME

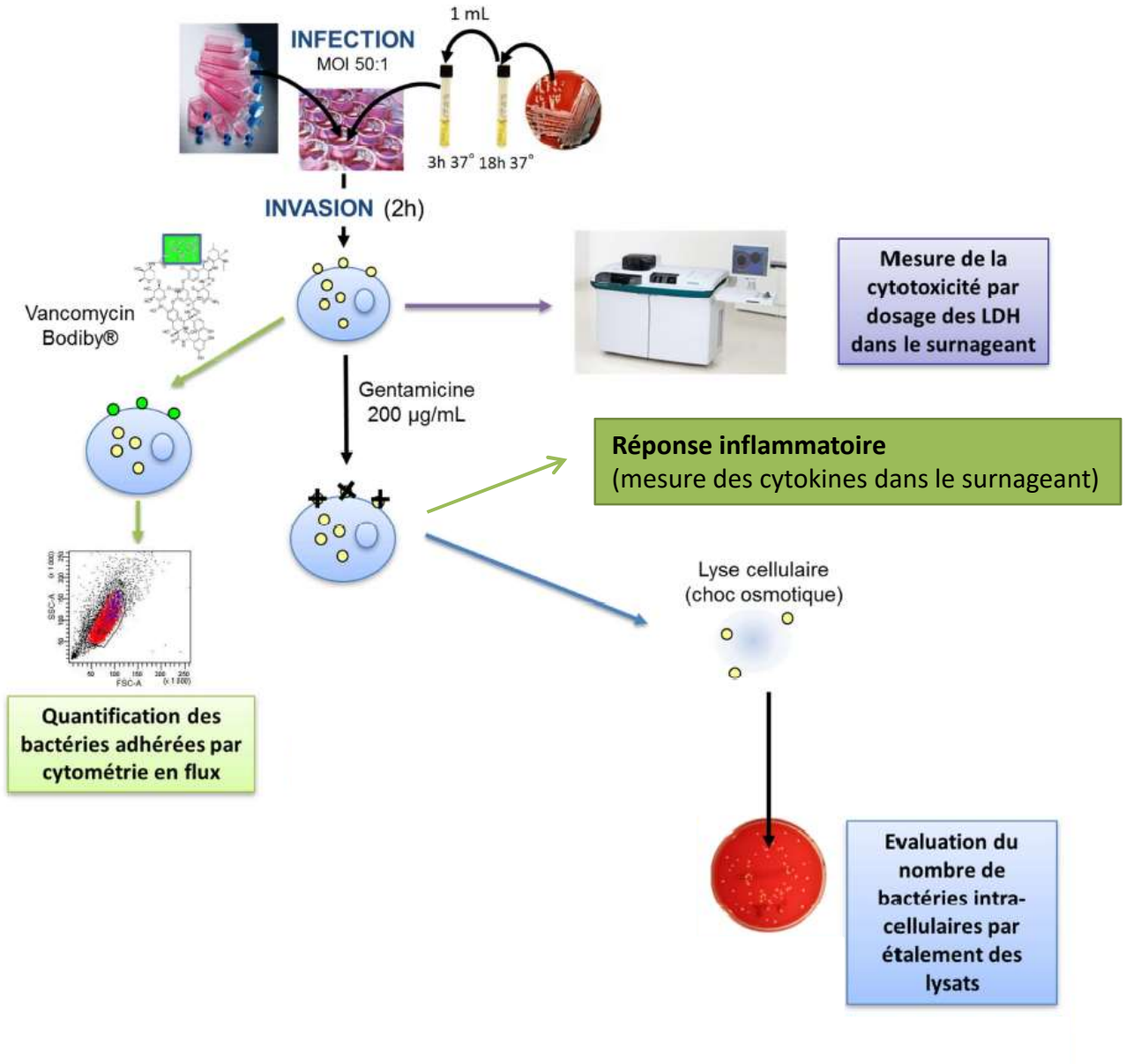
Interactions avec les ostéoBlastes

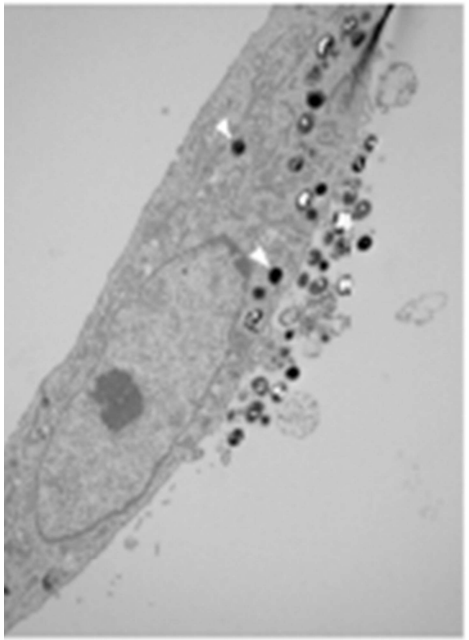


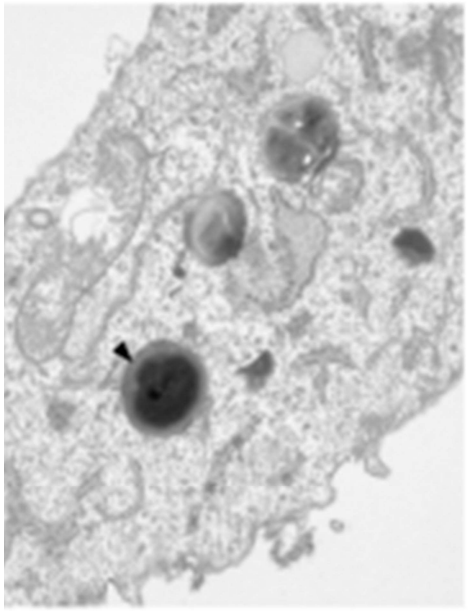


Microscopie électronique
Hoffmann *et al.*, Eur J Cell Biol 2011

Interactions avec les ostéoBlastes







Interactions avec les ostéoBlastes : MRSA

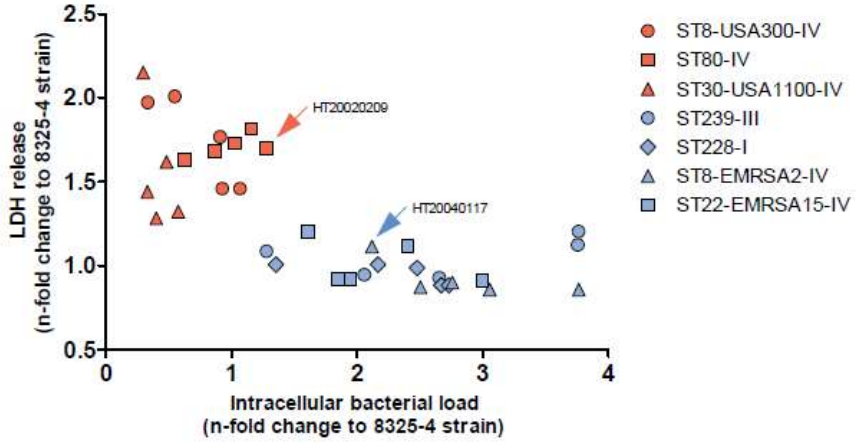
May 2013 | Volume 8 | Issue 5 | e63176 PLOS ONE

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)
- Infections post-opératoires
- Sur matériel
- Indolentes : chronicisation, récidive
- **Faible cytotoxicité**
- **Survie intracellulaire +++**

CA-MRSA (n=20)
- Ostéomyélites (enfants) +++
- Progression rapide, inflammation majeure, destruction osseuse, dommages tissulaires
- **Cytotoxicité +++**
- **Faible survie intracellulaire**
- Dommages tissulaires (rôle de la PVL)



Interactions avec les ostéoBlastes : MSSA

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

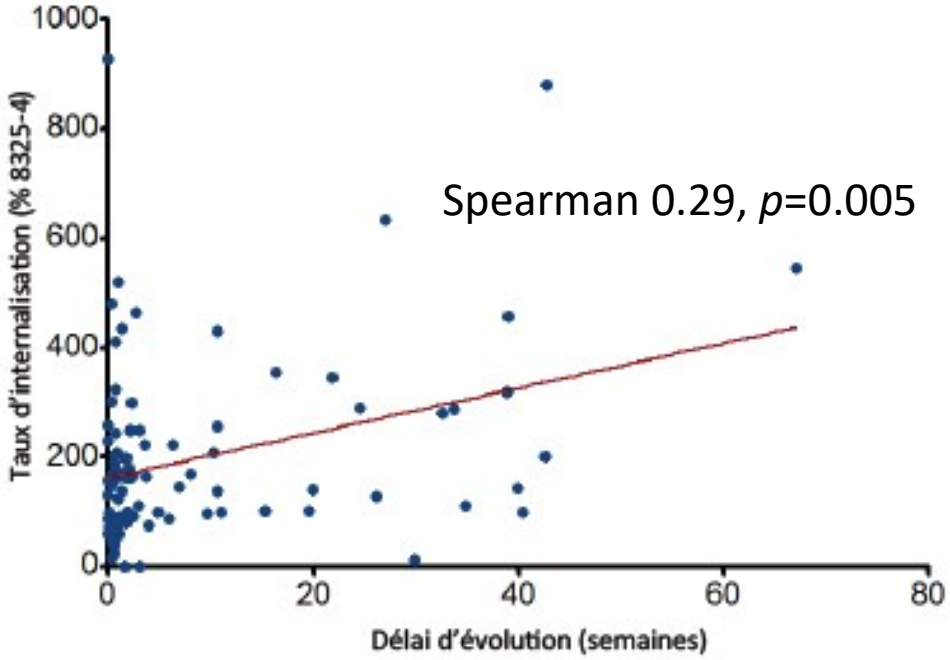
Clin Microbiol Infect 2015; **21**: 568.e1–568.e11

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

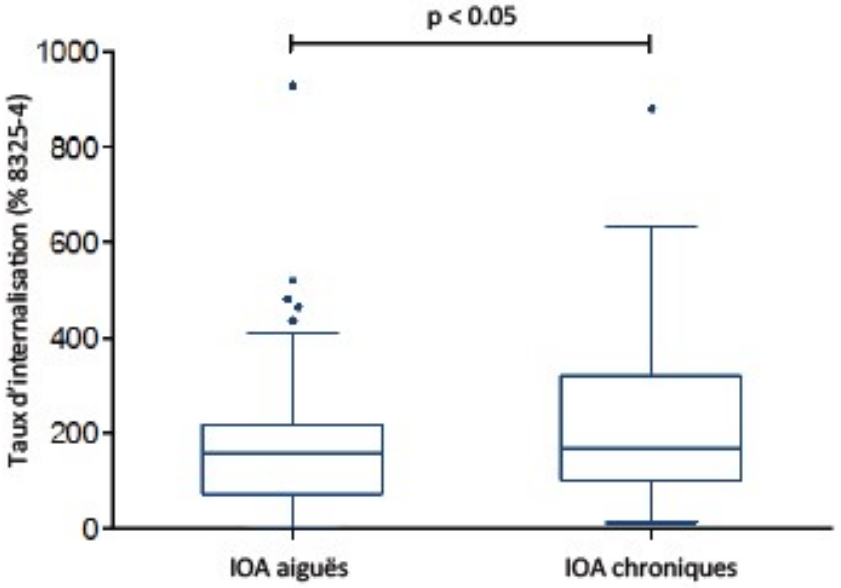
95 couples patient-souche inclus

IOA aiguës	IOA chroniques
n=64	n=31

Délai d'évolution > 4 semaines



Spearman 0.29, *p*=0.005



Interactions avec les ostéoBlastes : SCN

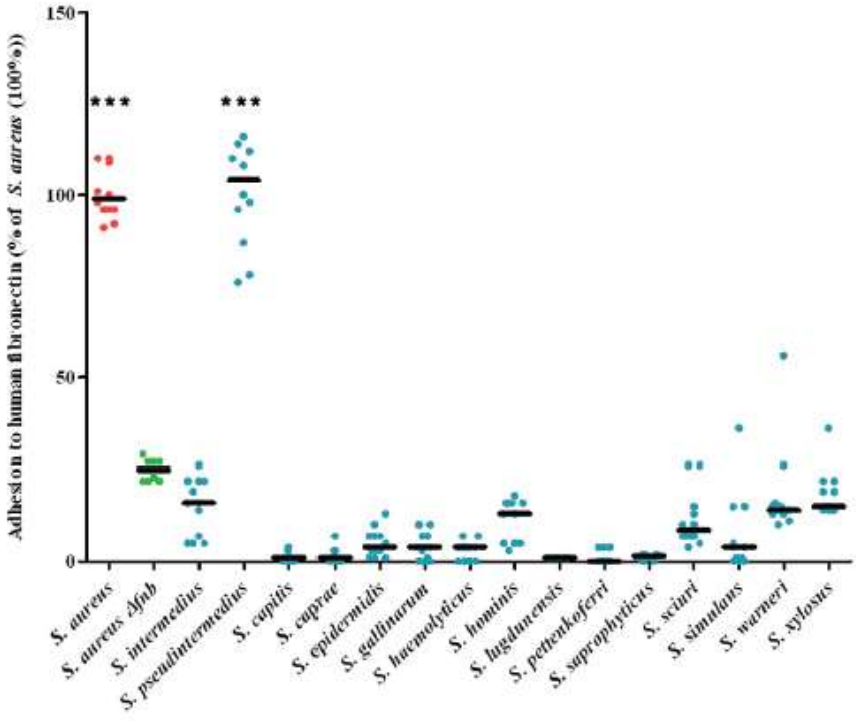
frontiers in Microbiology July 2016 | Volume 7 | Article 1063

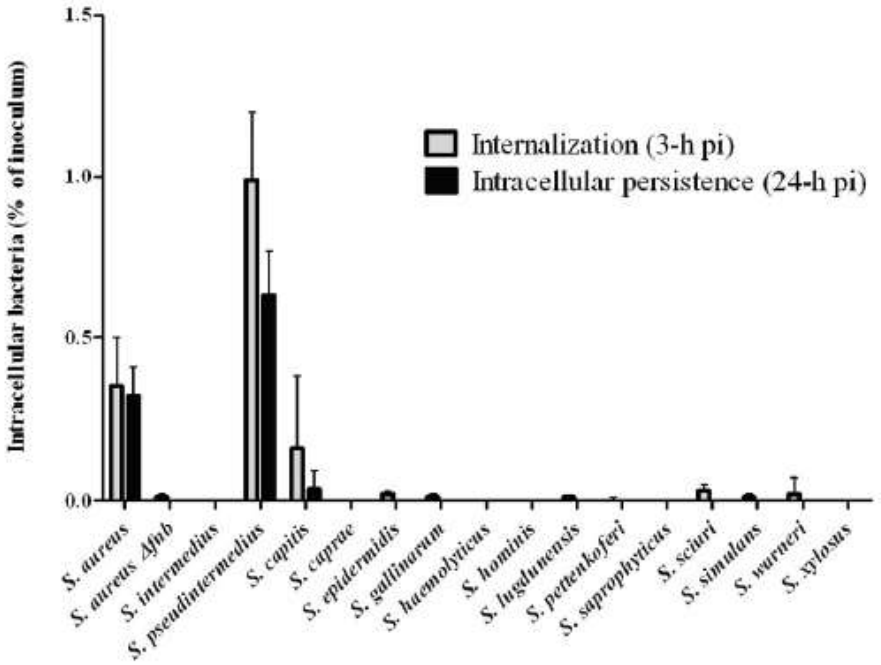
Pathophysiological Mechanisms of *Staphylococcus* Non-*aureus* Bone and Joint Infection: Interspecies Homogeneity and Specific Behavior of *S. pseudintermedius*

Yousef Maali[1,2], Patricia Martins-Simões[1,2], Florent Valour[1,3], Daniel Bouvard[4,5], Jean-Philippe Rasigade[1,6], Michele Bes[6], Marisa Haenni[7], Tristan Ferry[1,3], Frédéric Laurent[1,2,6†] and Sophie Trouillet-Assant[1,2†]*

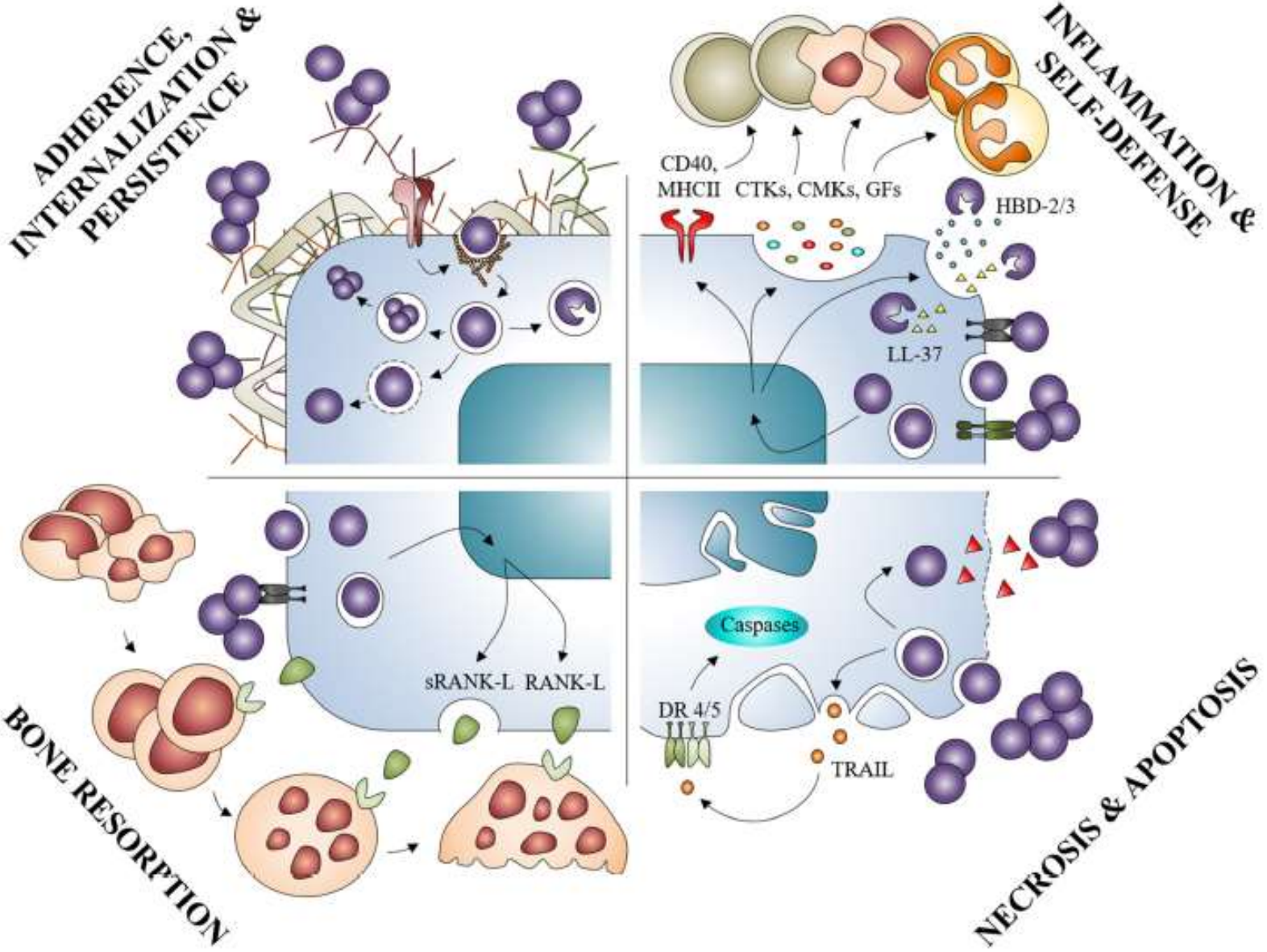
Evaluation de l'adhésion et internalisation dans les ostéoblastes de 16 espèces de SCN (souches cliniques responsables d'IOA)

Faible capacité d'internalisation et de persistance des SCN à l'exception de *S. pseudintermedius*





Interactions avec les ostéoBlastes

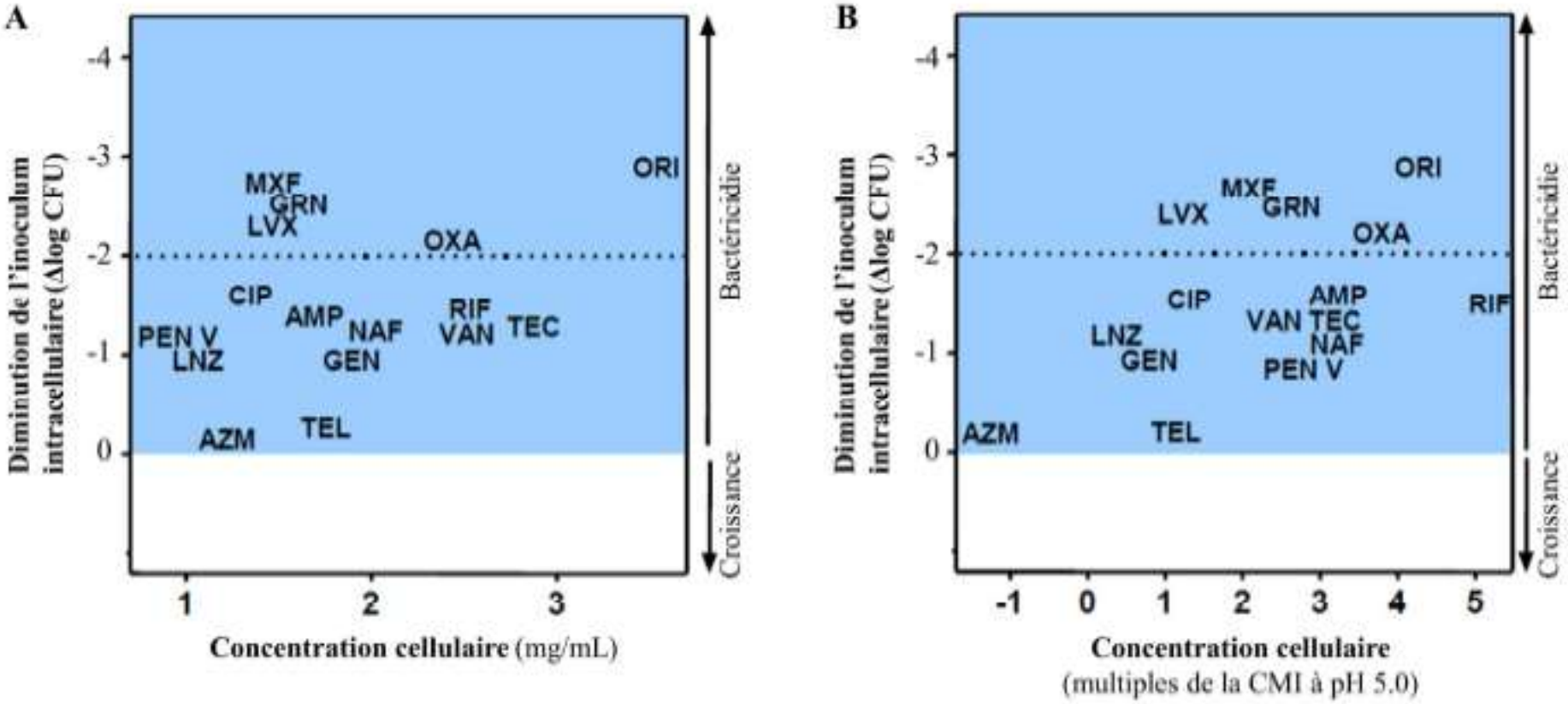


Josse, Front Microbiol 2015

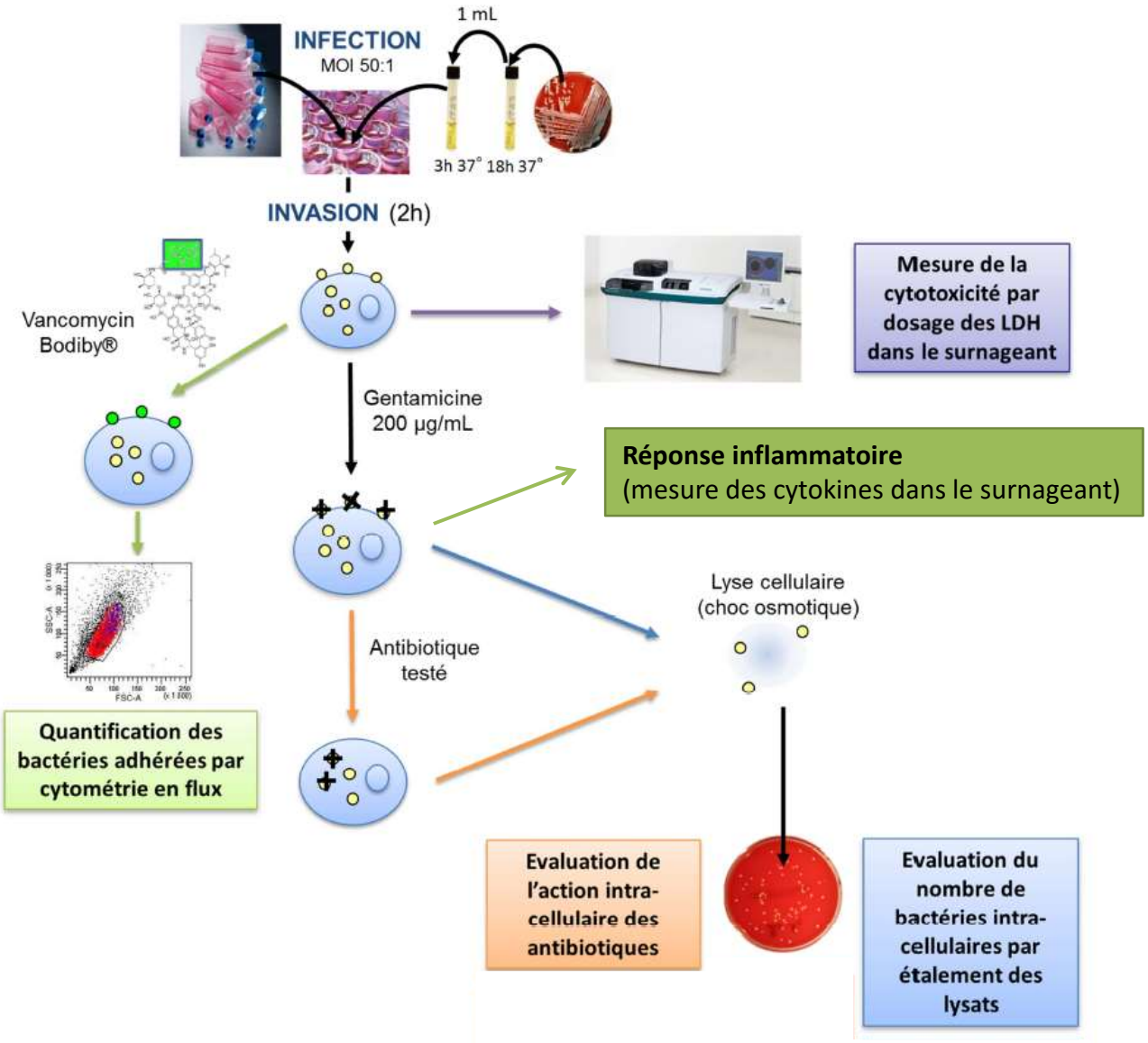
FOCUS : réservoir intracellulaire et thérapeutique

Modèle d'infection de monocytes – macrophages humains

S. Lemaire, PM Tulkens - Université Catholique de Louvain



FOCUS : réservoir intracellulaire et thérapeutique

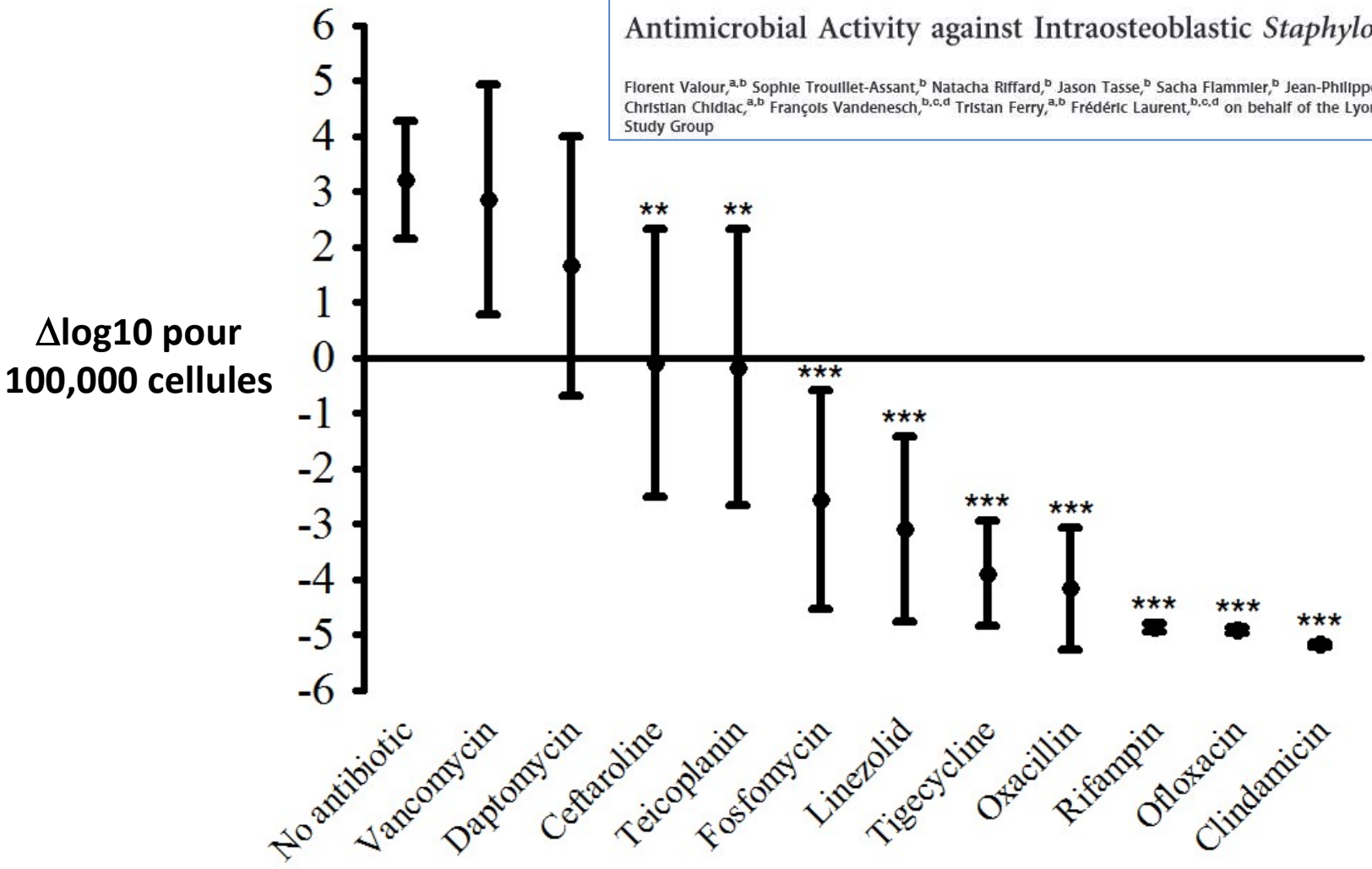


FOCUS : réservoir intracellulaire et thérapeutique

AAC
Journals.ASM.org

Antimicrobial Activity against Intraosteoblastic *Staphylococcus aureus*

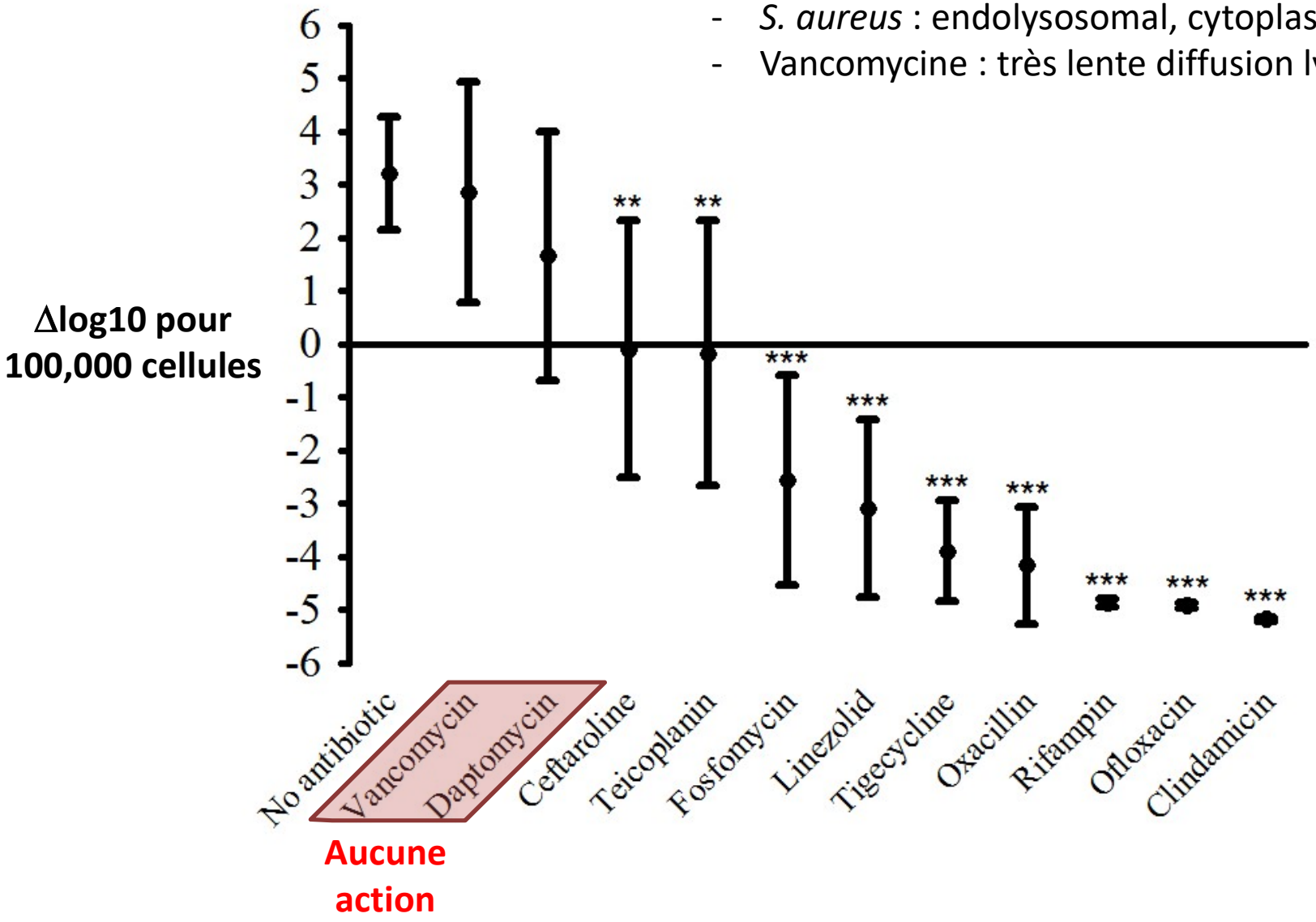
Florent Valour,[a,b] Sophie Trouillet-Assant,[b] Natacha Riffard,[b] Jason Tasse,[b] Sacha Flammier,[b] Jean-Philippe Rasigade,[b,c] Christian Chidiac,[a,b] François Vandenesch,[b,c,d] Tristan Ferry,[a,b] Frédéric Laurent,[b,c,d] on behalf of the Lyon Bone and Joint Infection Study Group



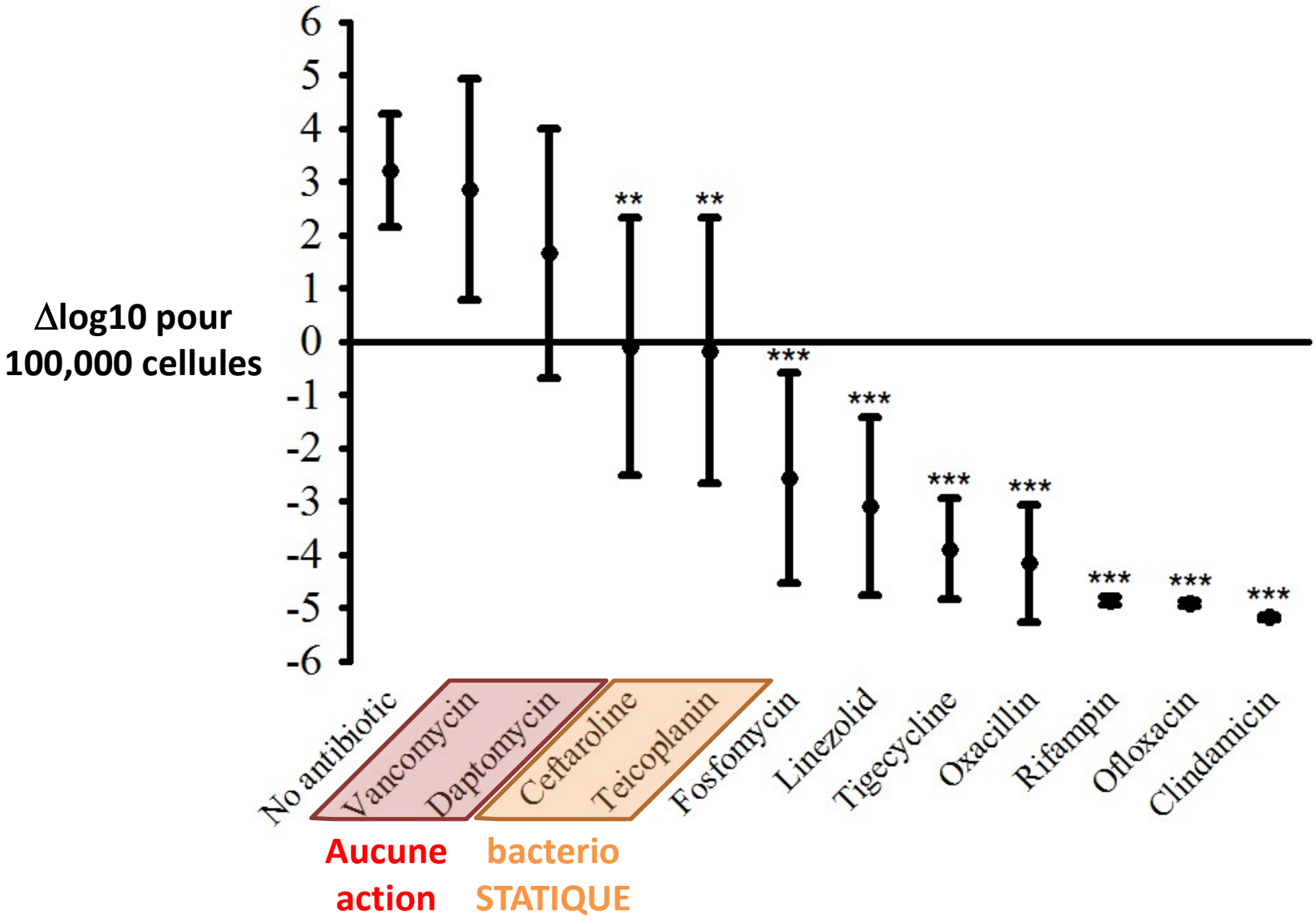
FOCUS : réservoir intracellulaire et thérapeutique

Importance de la localisation intra-cellulaire

- *S. aureus* : endolysosomal, cytoplasme (30%)
- Vancomycine : très lente diffusion lysosomale



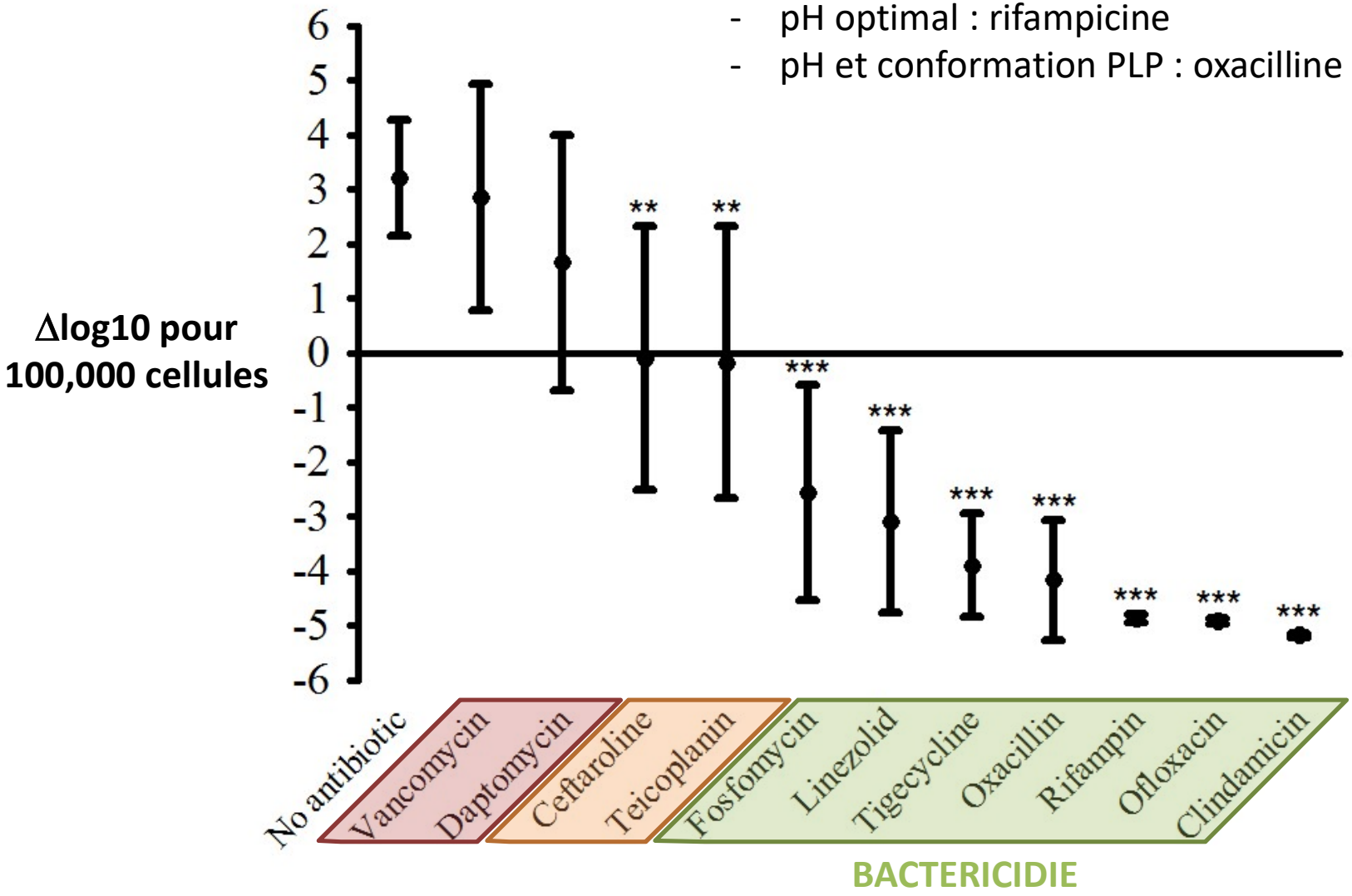
FOCUS : réservoir intracellulaire et thérapeutique



FOCUS : réservoir intracellulaire et thérapeutique

Importance des conditions physico-chimiques

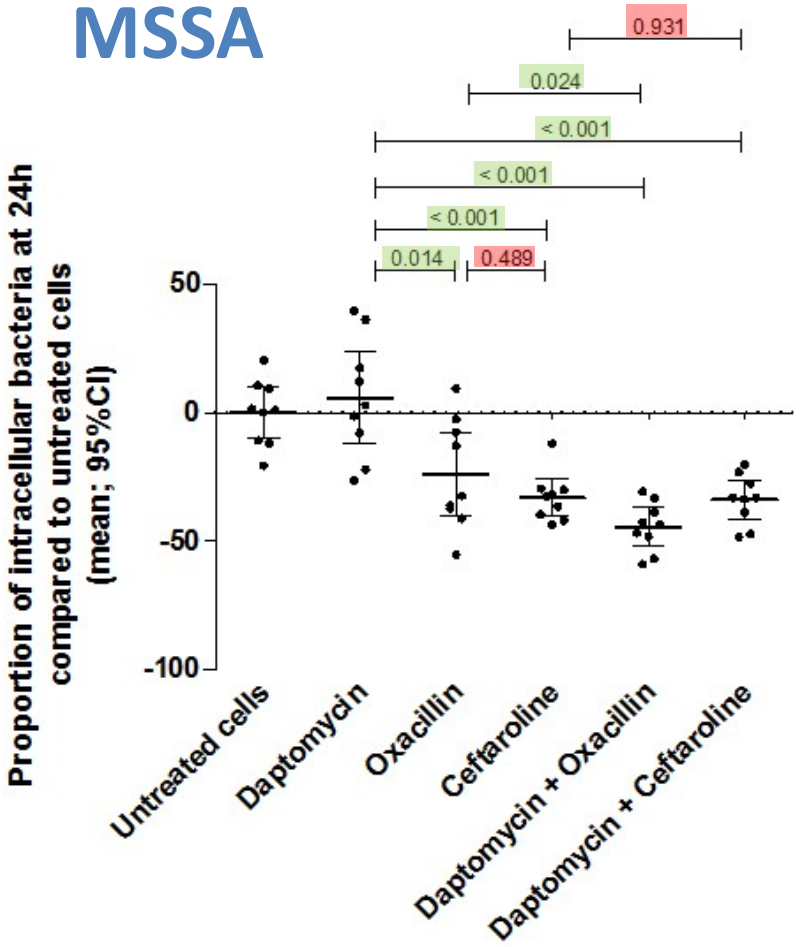
- pH optimal : rifampicine
- pH et conformation PLP : oxacilline



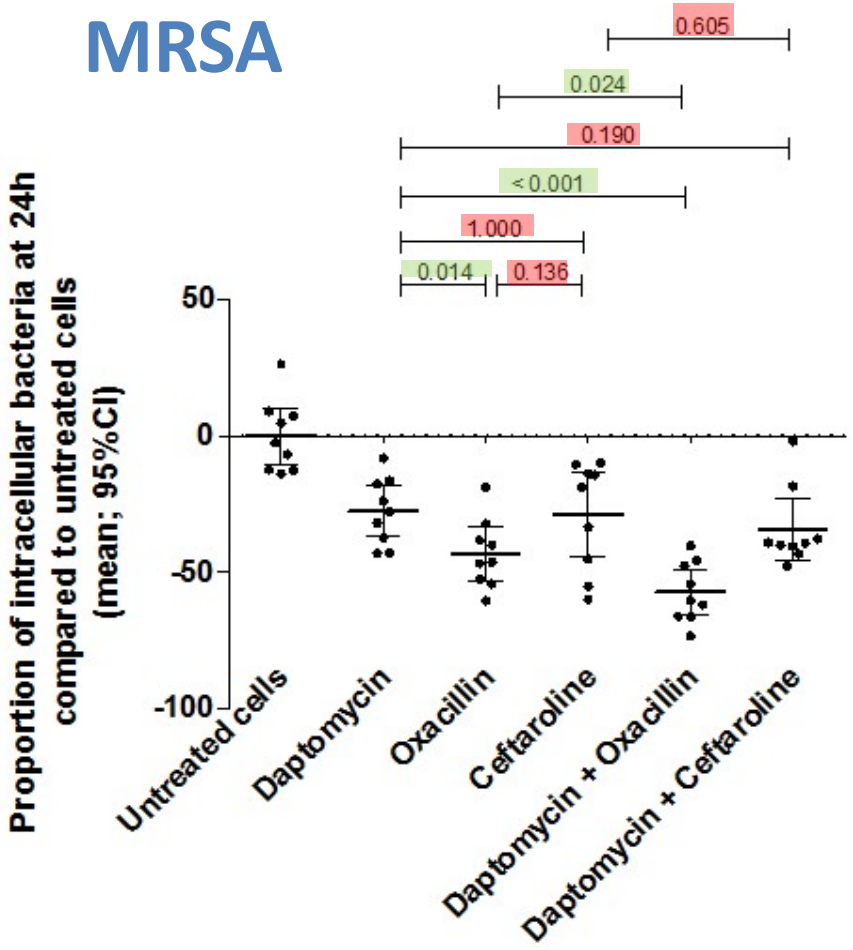
Carryn et al. Infect Dis Clin North Am 2003 – Lemaire et al. AAC 2007, 2008 et 2009 – Sandberg et al. AAC 2009

FOCUS : réservoir intracellulaire et thérapeutique

MSSA

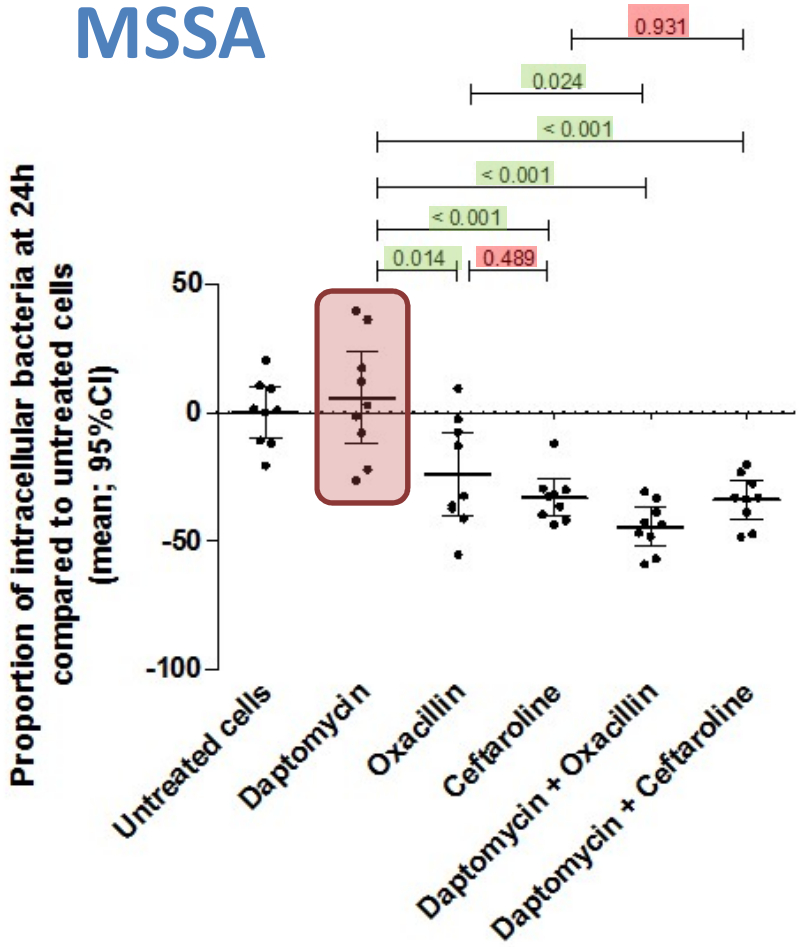


MRSA

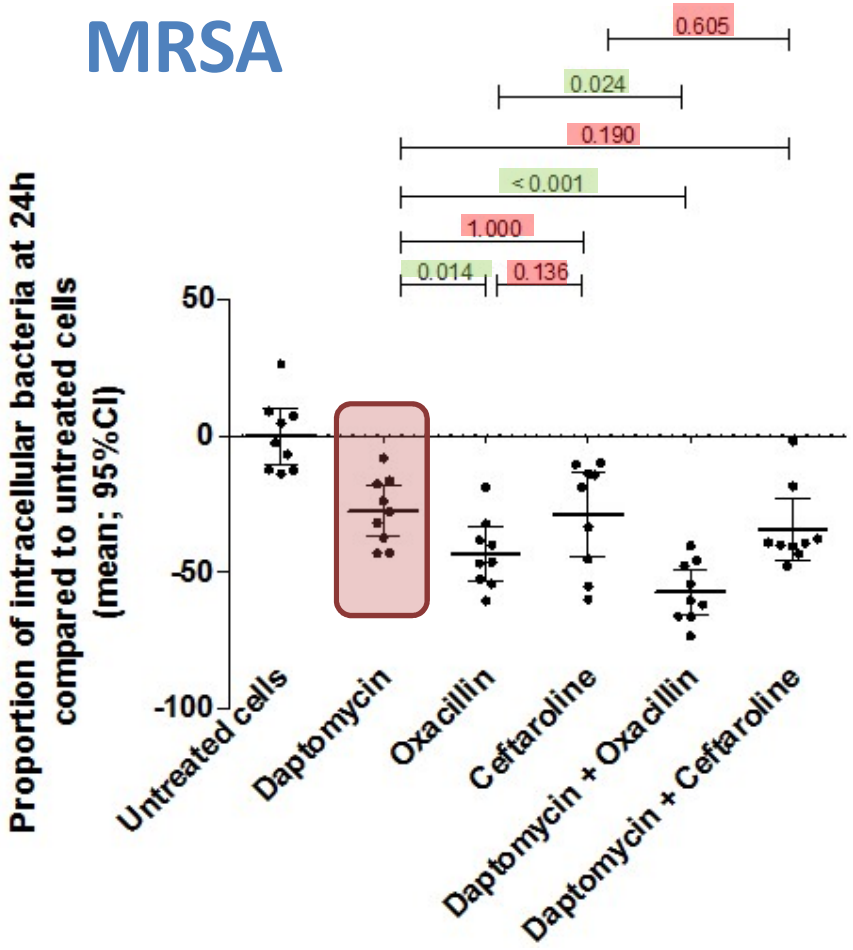


FOCUS : réservoir intracellulaire et thérapeutique

MSSA



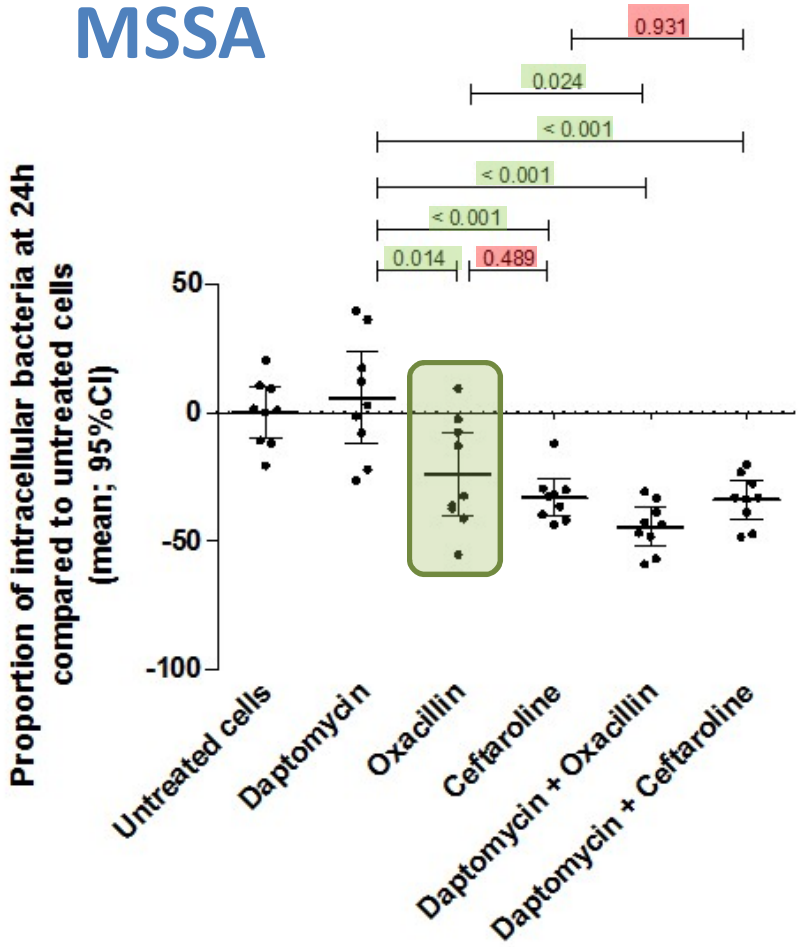
MRSA



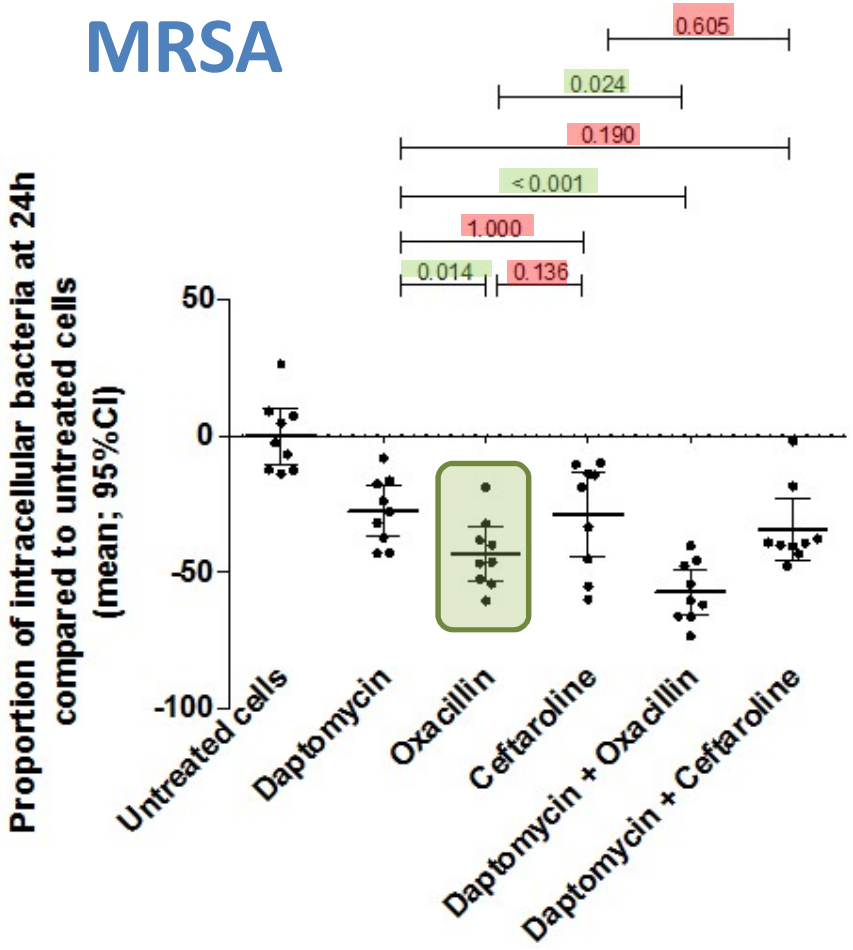
→ **Confirmation of the weak intraosteoblastic activity of daptomycin against MSSA/MRSA**

FOCUS : réservoir intracellulaire et thérapeutique

MSSA



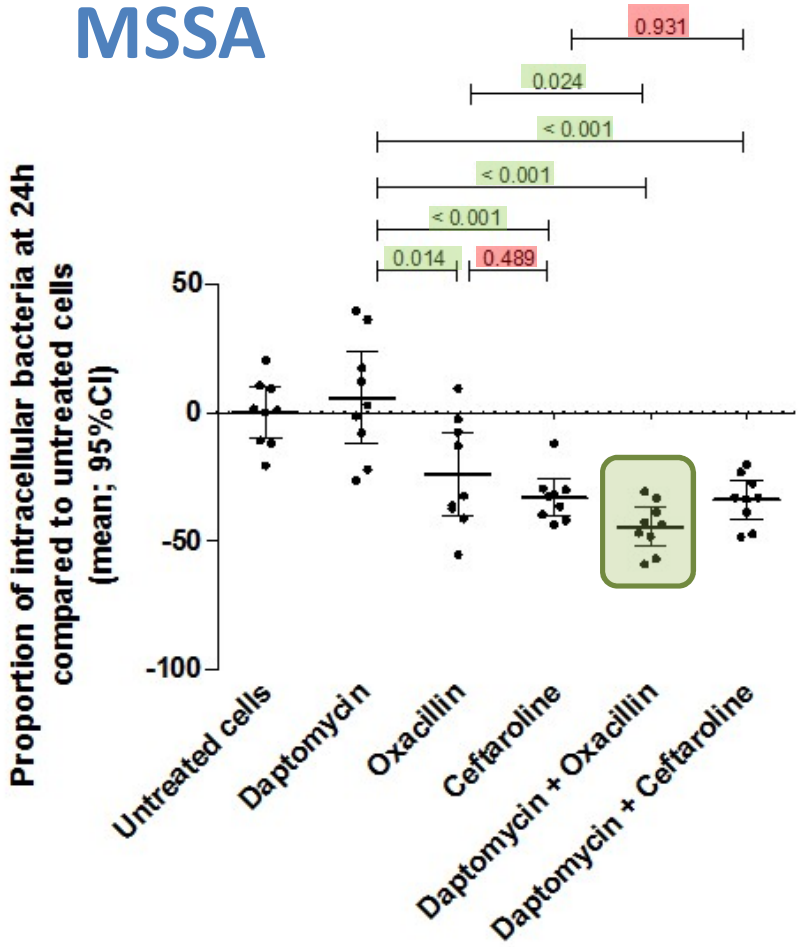
MRSA



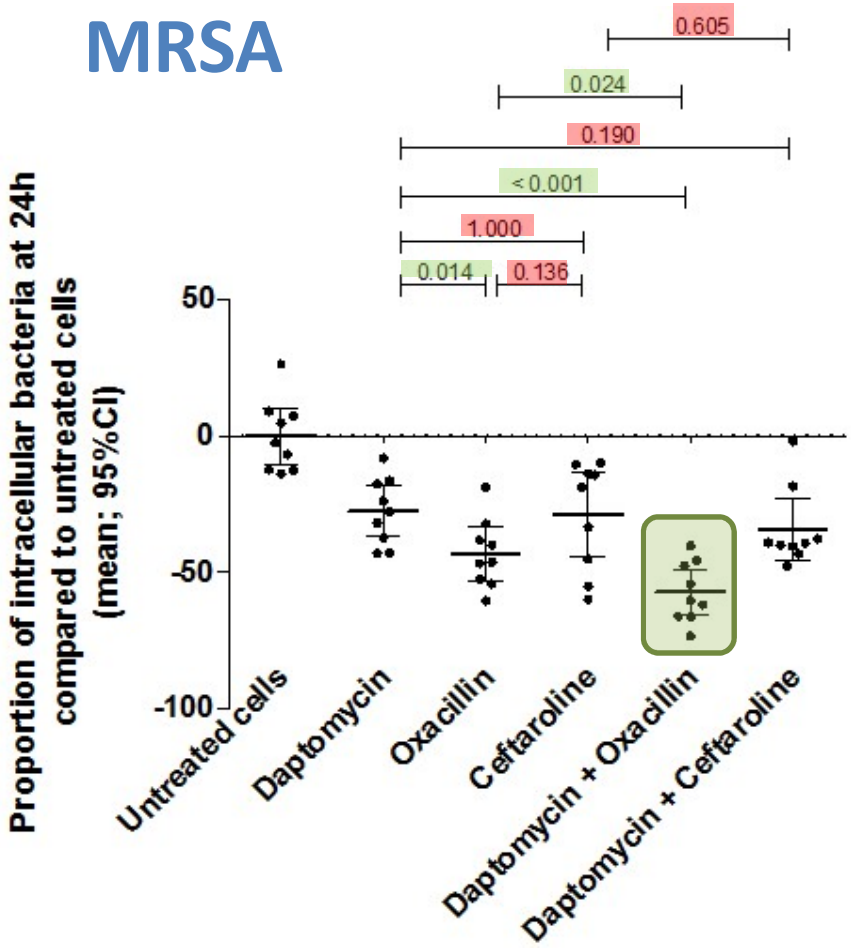
→ **Acceptable efficacy of oxacillin against intracellular *S. aureus* <u>INCLUDING MRSA</u>**

FOCUS : réservoir intracellulaire et thérapeutique

MSSA



MRSA



→ **Superiority of the daptomycin-oxacillin combination compared to each molecule alone not observed for the daptomycin-ceftarolin combination**

FOCUS : réservoir intracellulaire et thérapeutique

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**

FOCUS : réservoir intracellulaire et thérapeutique

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

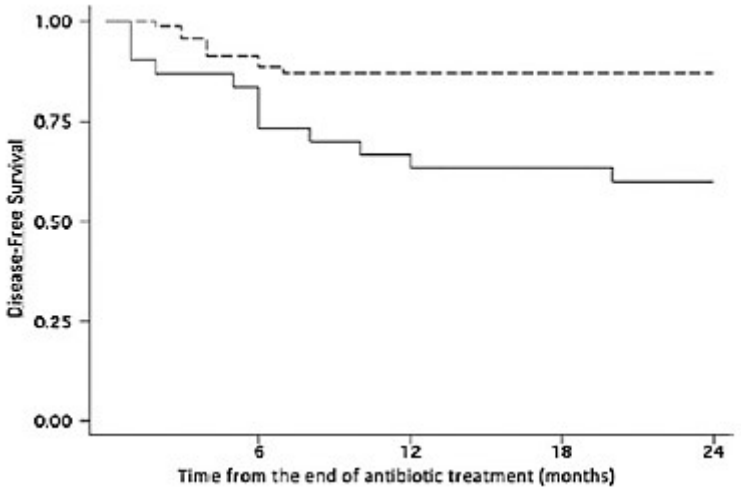
Centre National de Référence des Infections Ostéo-Articulaires Nord-Ouest, Roger Salengro Faculty Hospital of Lille, Lille, France

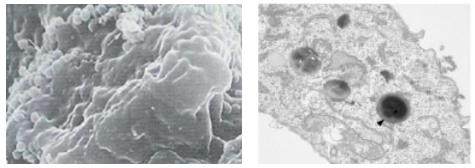
Facteurs protecteurs (univarié)

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

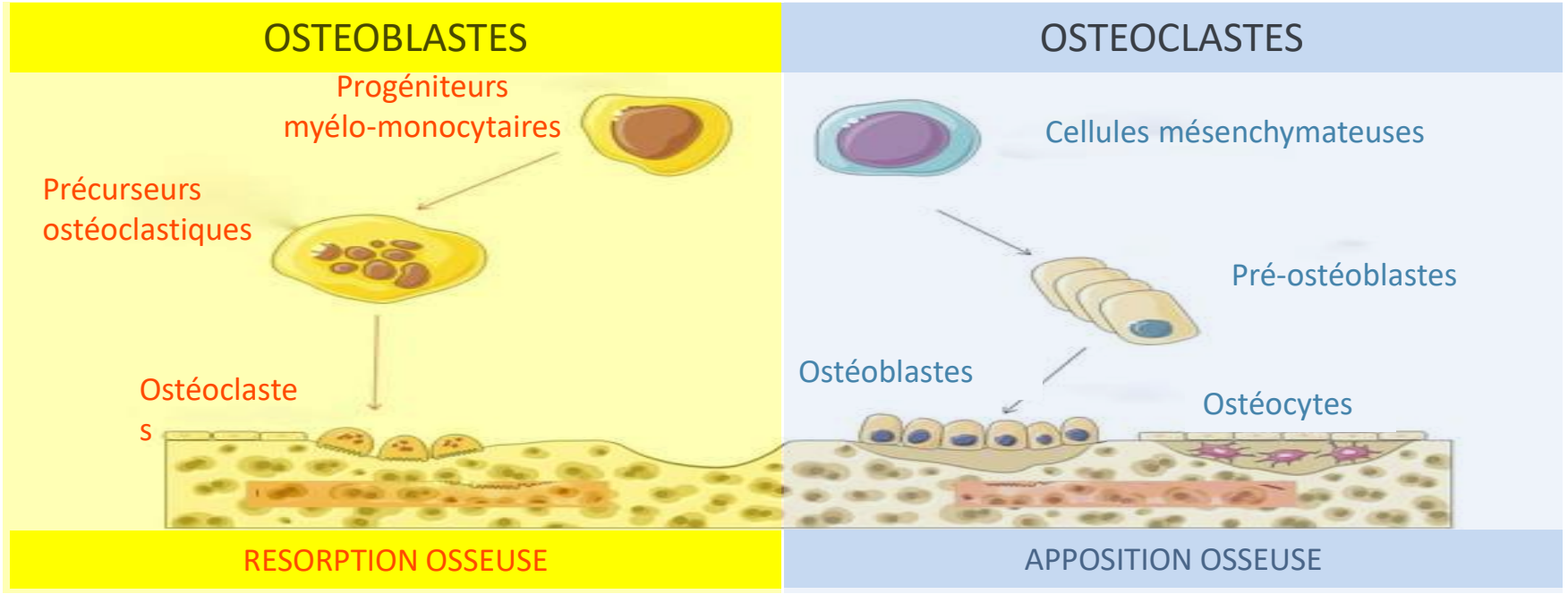
Facteurs protecteurs (multi-varié)

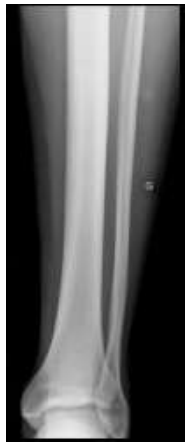
- ASA score ≤ 2
- **Rifampicine – fluoroquinolone**

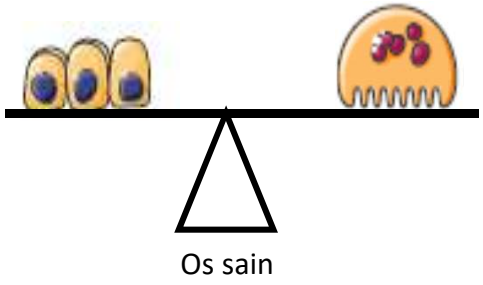




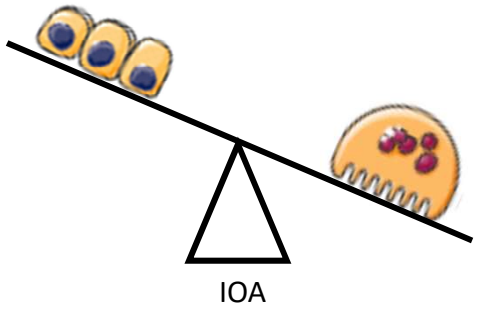
Interaction avec les ostéoClastes



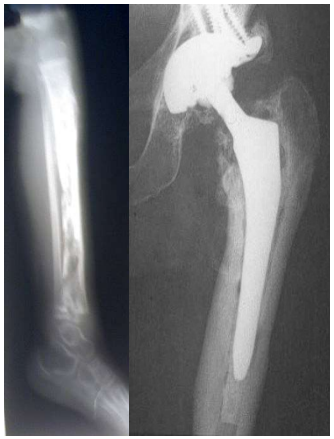




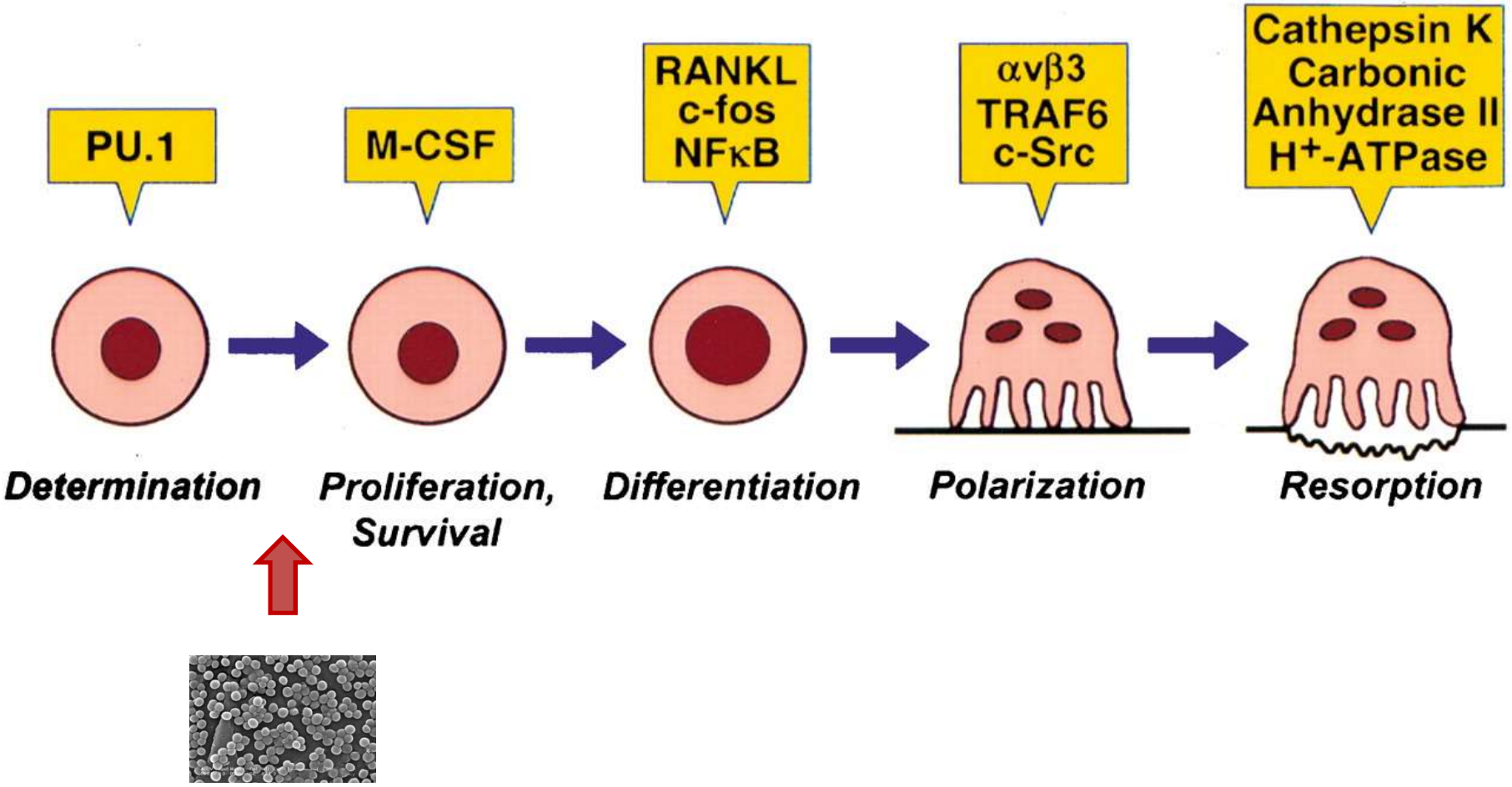
Equilibre OB / OC



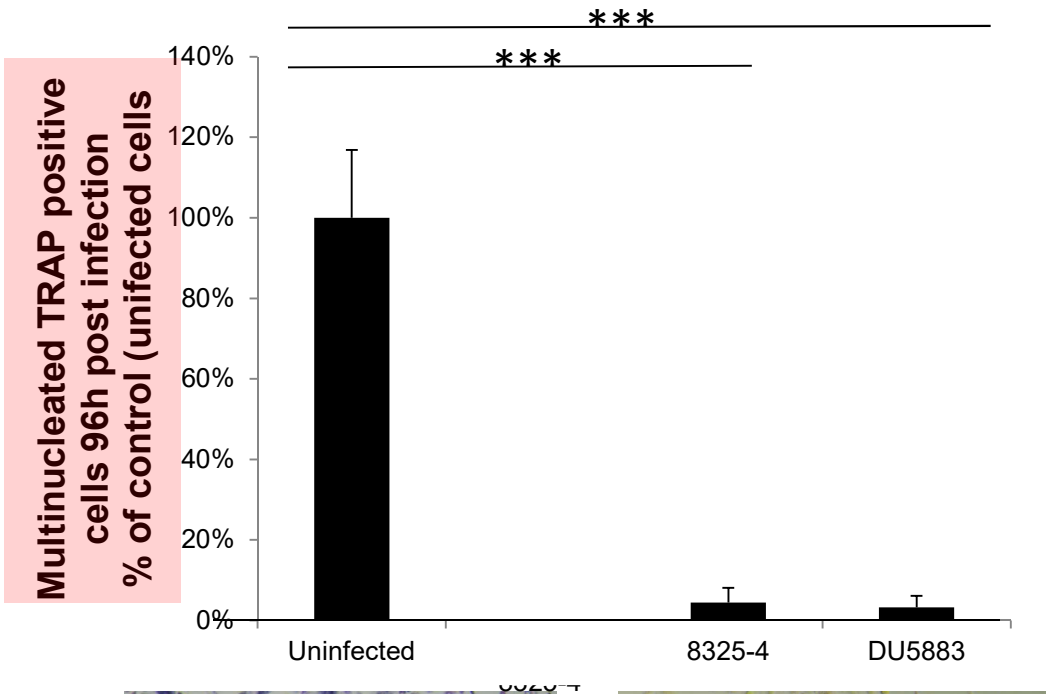
Ostéolyse progressive
- Descellement prothétique
- Séquestres



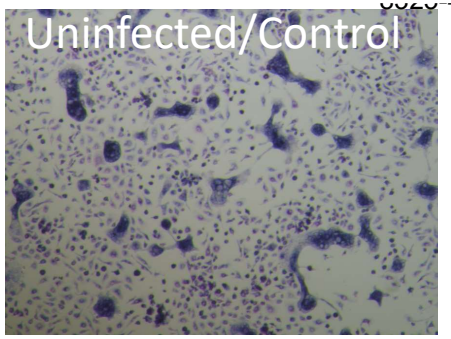
Interaction avec les ostéoClastes

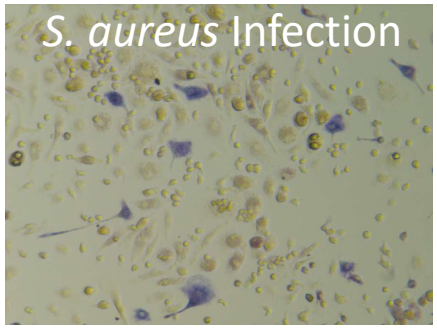


Interaction avec les ostéoClastes



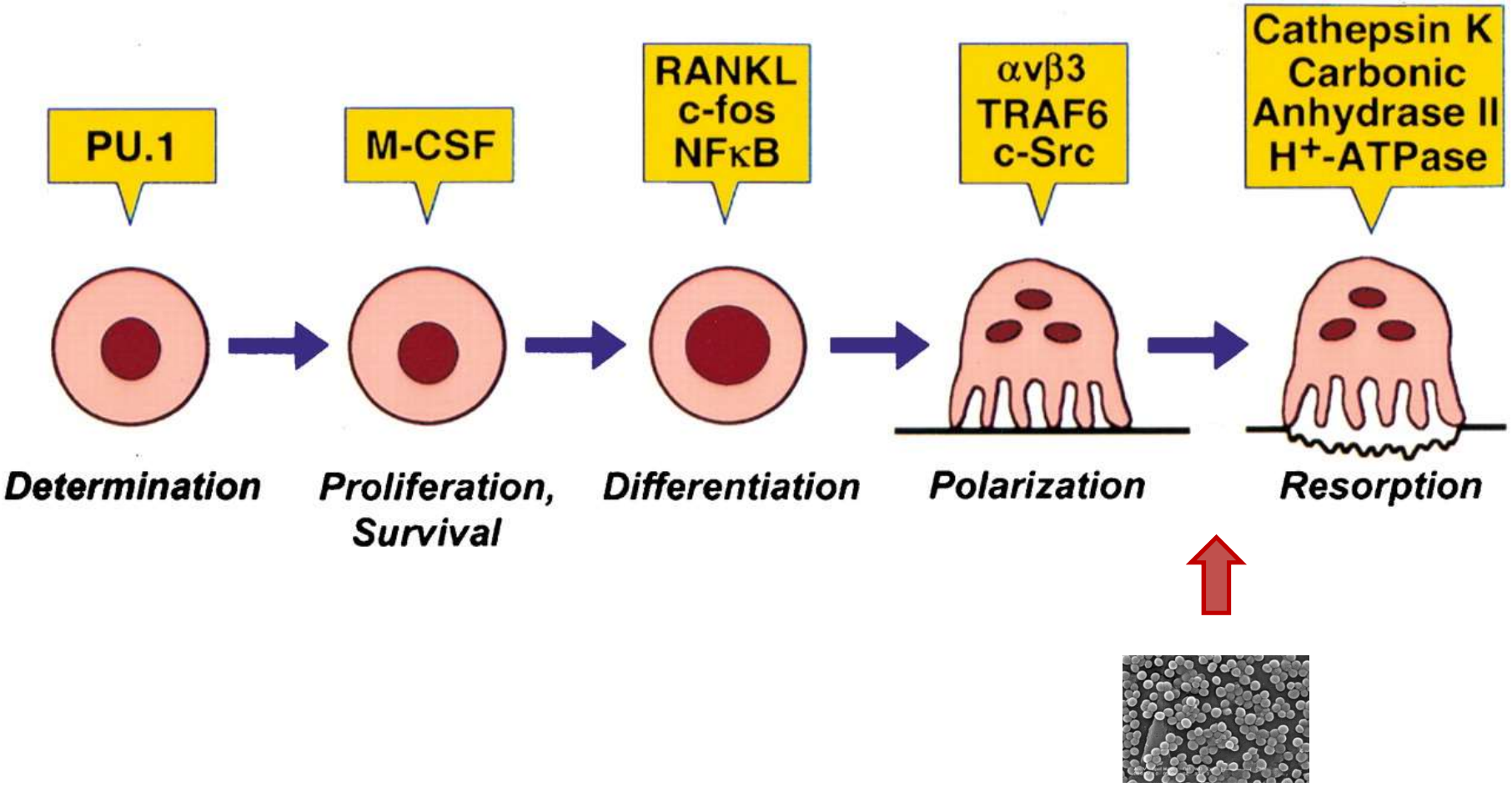
Infection par *S. aureus*
Inhibition de l'ostéoclastogenèse





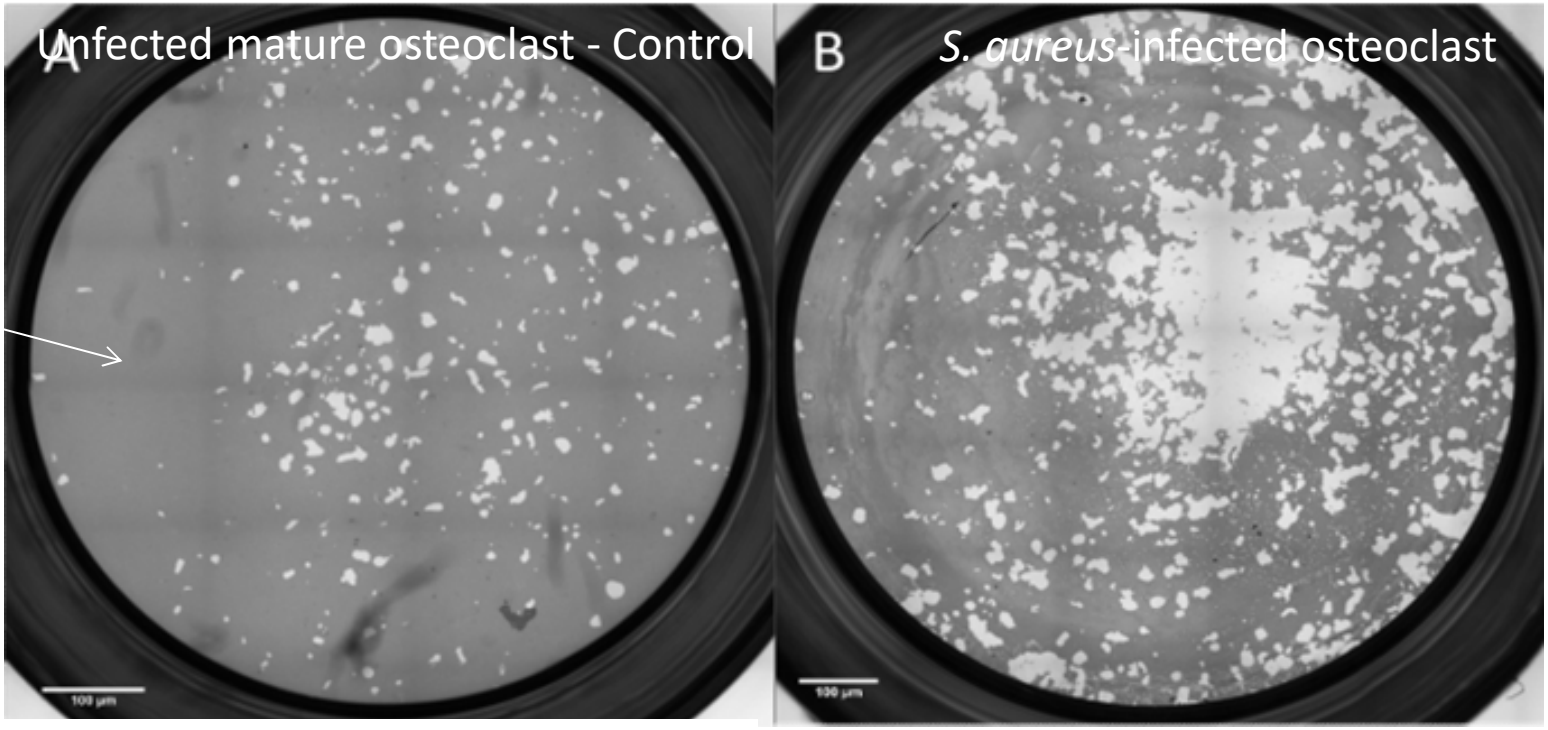
- Typage cytométrique = **macrophages**
- **Relargage de cytokines pro-inflammatoires**
- Surnageant = **boost de la résorption osseuse** par des ostéoclastes non infectés

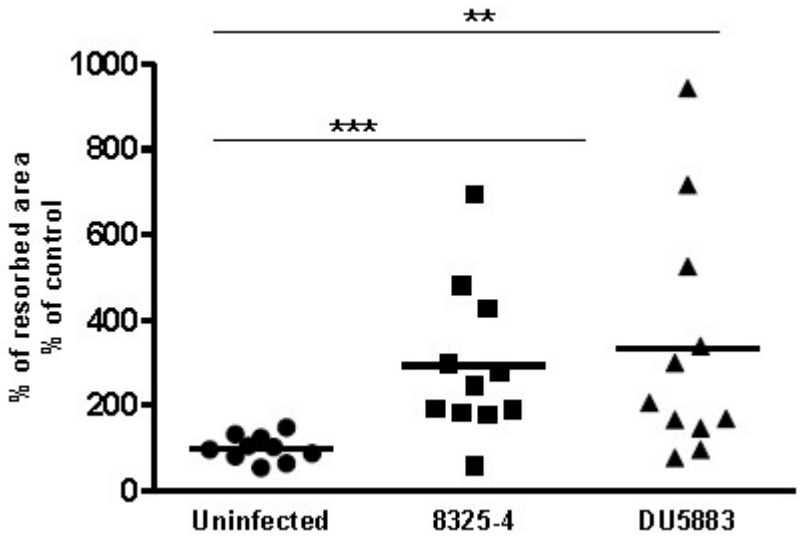
Interaction avec les ostéoClastes



Interaction avec les ostéoClastes

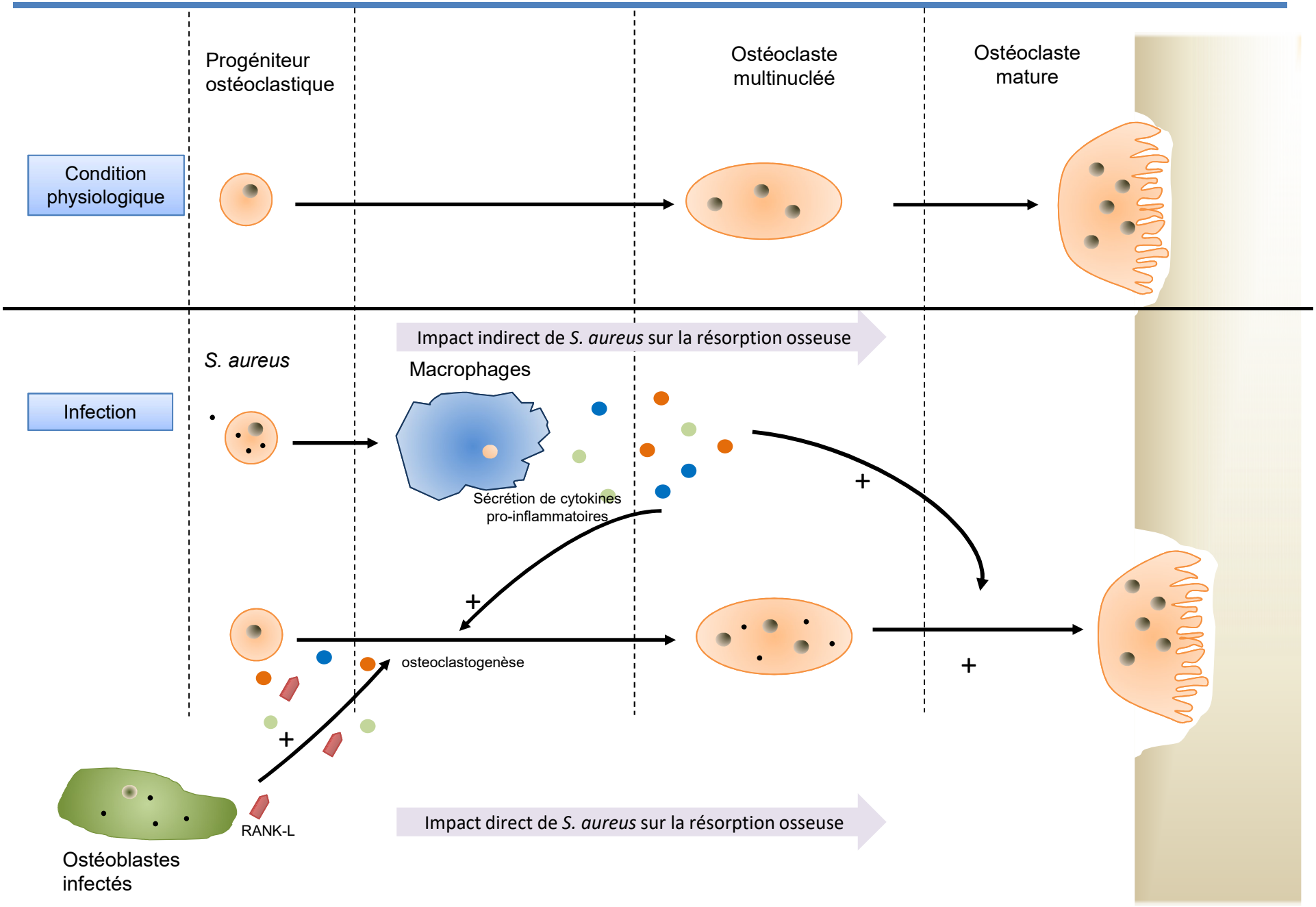
Matrice minérale mimant la matrice osseuse





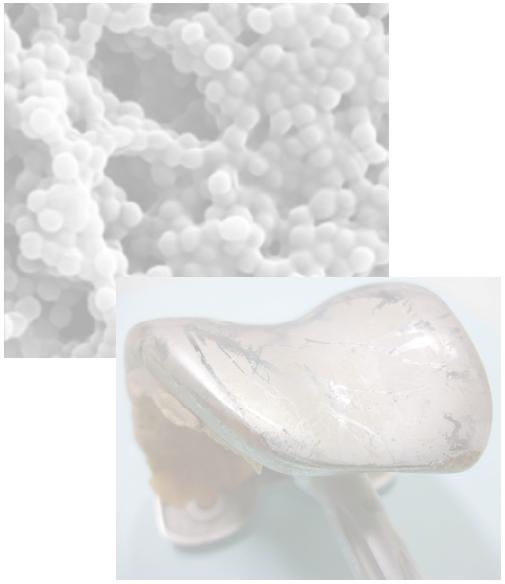
Infection par *S. aureus*
Augmentation de la résorption osseuse par les OC matures

Interaction avec les ostéoClastes

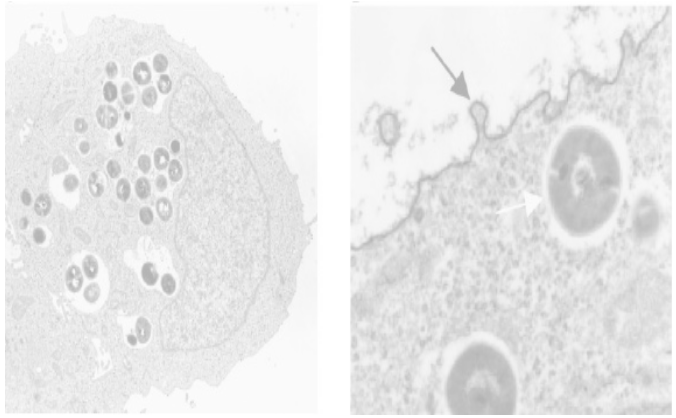


Chronicité et persistance
MECANISMES BACTERIENS

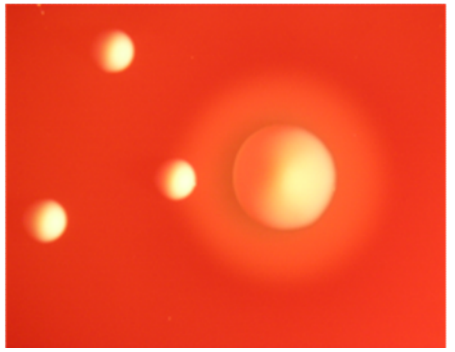
BIOFILM



VIE INTRACELLULAIRE



SMALL COLONY VARIANT (SCV)



Small colony variants (SCVs)

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 +++

Research Article December 16, 2010 EMBO Molecular Medicine

***Staphylococcus aureus* phenotype switching: an effective bacterial strategy to escape host immune response and establish a chronic infection**

*Lorena Tuchscherr[1], Eva Medina[2], Muzaffar Hussain[1], Wolfgang Völker[3], Vanessa Heitmann[1], Silke Niemann[1], Dirk Holzinger[4,5], Johannes Roth[4,5], Richard A. Proctor[6], Karsten Becker[1], Georg Peters[1,4], Bettina Löffler[1,4]**

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

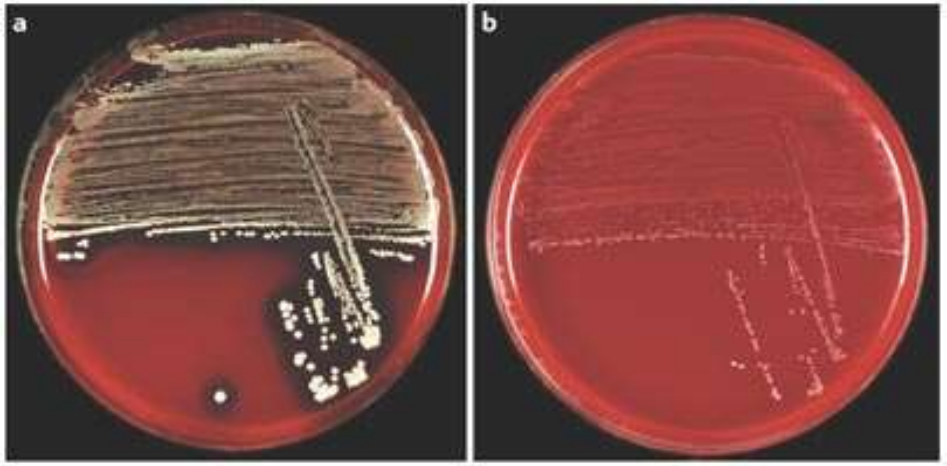
***Staphylococcus aureus* develops increased resistance to antibiotics by forming dynamic small colony variants during chronic osteomyelitis**

L. 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]

Staphylococcus aureus Small Colony Variants in Prosthetic Joint Infection

Parham Sendi,[1] Markus Rohrbach,[2] Peter Graber,[1] Reno Frei,[3] Peter E. Ochsner,[2] and Werner Zimmerli[3]
[1]Unit of Infectious Diseases, Basel University Medical Clinic Liestal and [2]Clinic of Orthopedic Surgery, Kantonsspital, Liestal, and [3]Microbiology Laboratory, University Hospital Basel, Basel, Switzerland

Sendi et al. *Clin Infect Dis*. 2006



Décrits dans de nombreuses situations cliniques
(IOA, infections / matériel, mucoviscidose …)

… et chez de nombreuses espèces
(staphylocoques, *Pseudomonas*, *E. coli*, *P. acnes* …)

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

Small colony variants

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
Serum WBC in 10^9 cells/liter, median (range)	7.4 (4.5–11.7)	7.9 (3–23.3)	0.13
Serum ESR in mm/h, median (range)	46 (5–111)	43 (3–123)	0.54
Serum CRP in mg/liter, median (range)	23 (5–222)	44 (3–269)	0.2
Preoperative SF aspirate	26 (68.4)	51 (68.0)	
SF WBC in cells/μl, median (range)	28,574 (8,175–155,000)	44,275 (629–1,071,472)	0.13
SF neutrophil %, median (range)	88 (79–98)	91 (51–100)	0.84

Small colony variants

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

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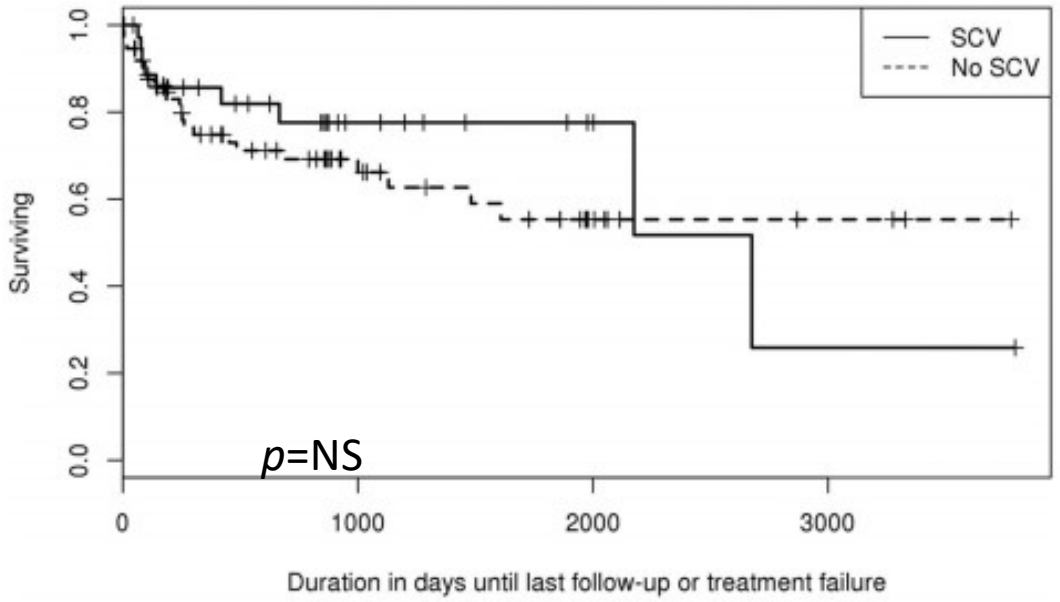


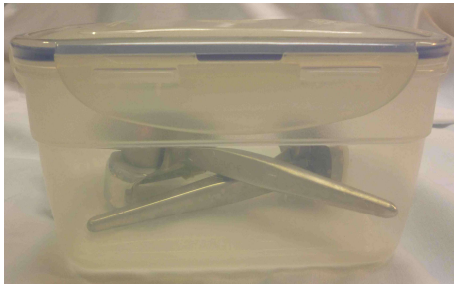
Treatment failure predicitve factor = *S. aureus* (HR, 4.03; 95%CI, 1.80-9.04)

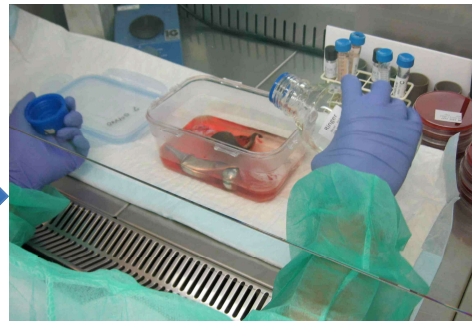
SCVs associés à la chronicité sans impact sur le pronostic

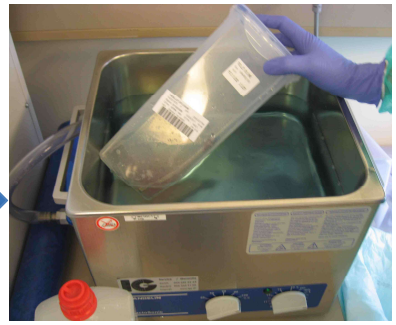
FOCUS : SCVs, biofilm et diagnostic

Intérêt de la sonication

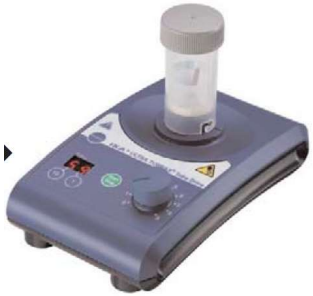
Prothèses explantées

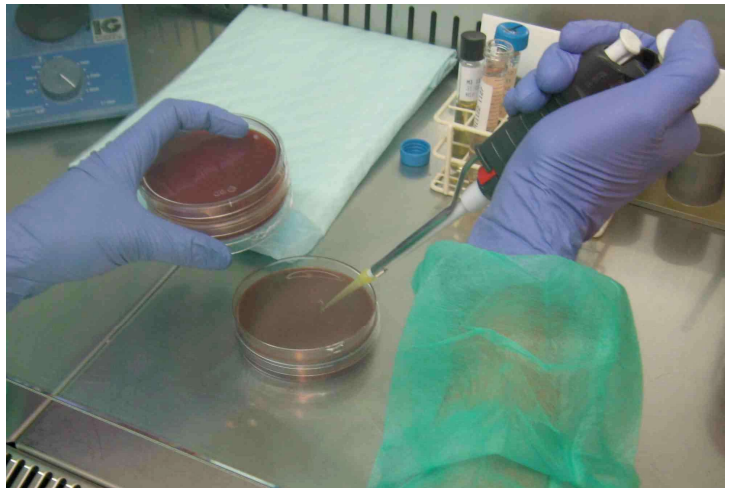






Culture bactérienne classique
(1-10 prélèvements
per-opératoires)





FOCUS : SCVs, biofilm et diagnostic

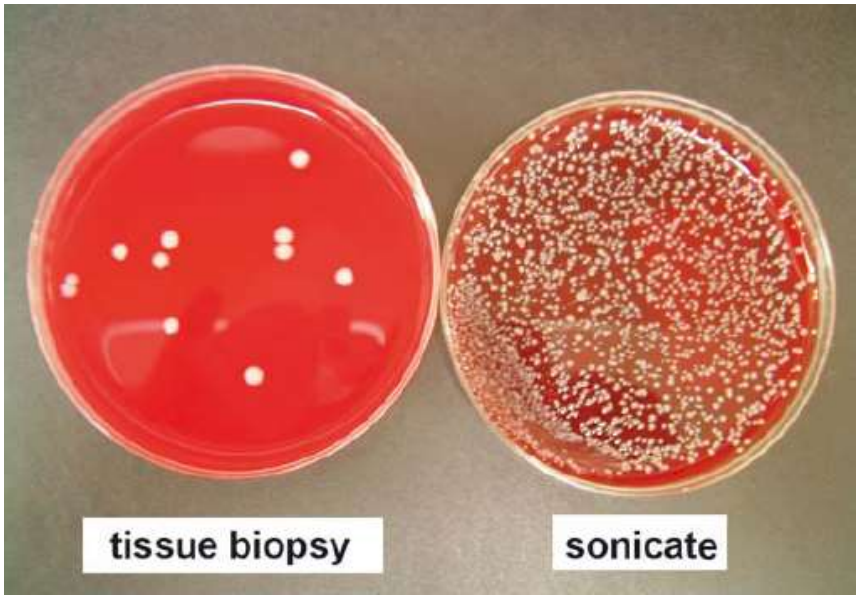
Intérêt de la sonication

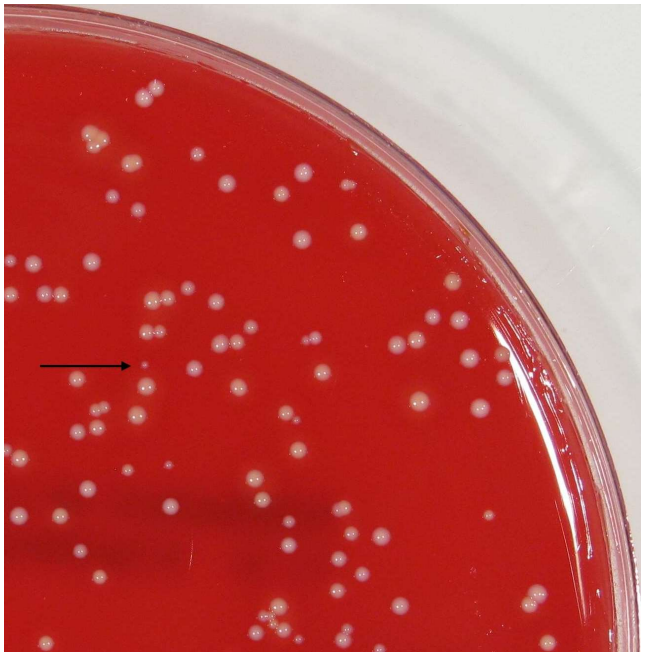
The NEW ENGLAND JOURNAL of MEDICINE

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.



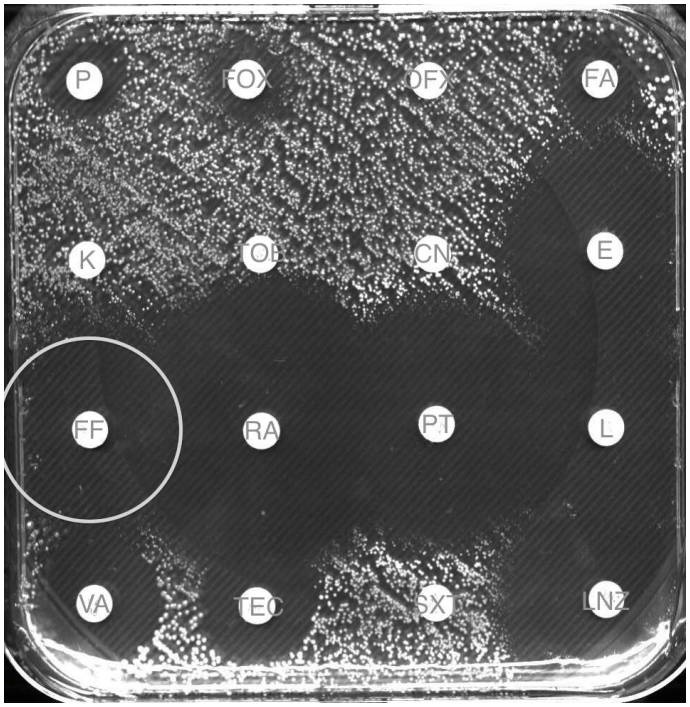


Culture de sonicat

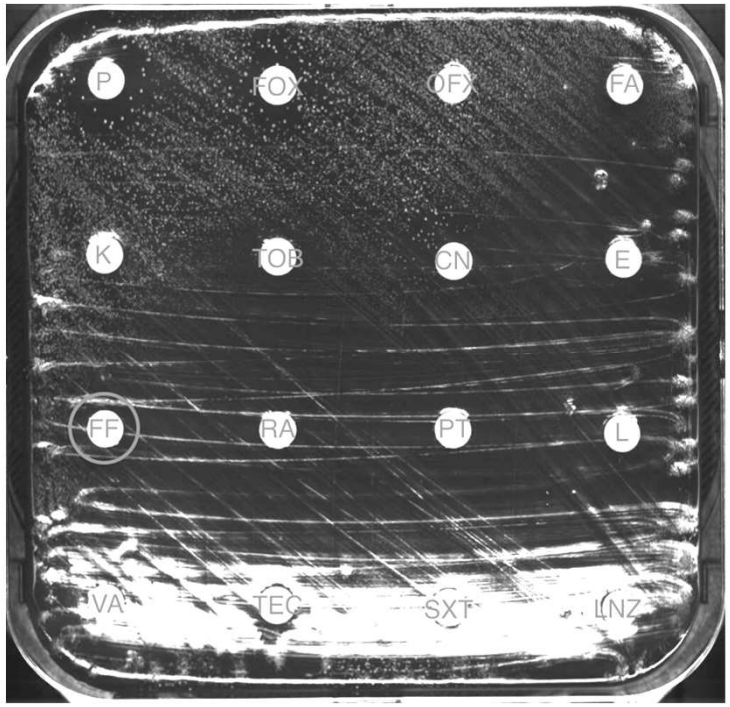
17 suspicion de sepsis, 9 cultures +
6 avec SCV

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

FOCUS : SCVs et thérapeutique



S. epidermidis



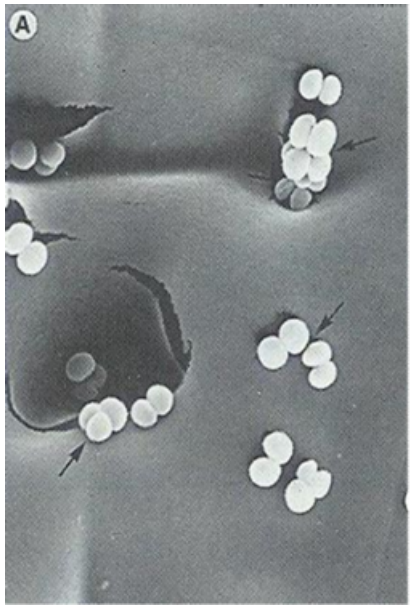
S. epidermidis de phénotype SCV

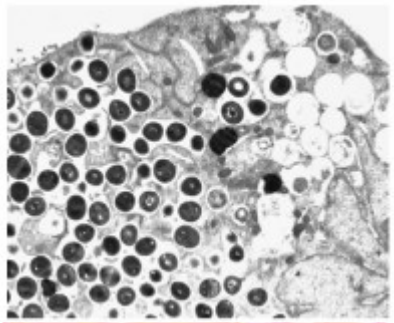
Take-home messages

Synthèse

Adaptation bactérienne

IOA aiguë → **IOA chronique**

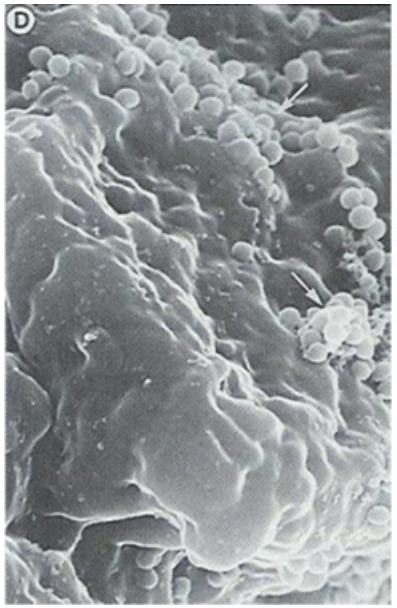


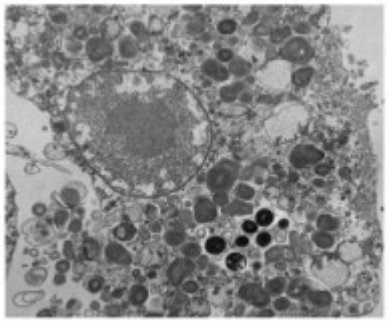


Biofilm

Persistance intracellulaire

SCVs





↑ Toxines ↓ Adhésines

Agression tissulaire
Réponse immunitaire / inflammatoire
- Destruction cellulaire
- Invasion et destruction tissulaire

↓ Toxines ↑ Adhésines

↓ Inflammation, dommages tissulaires
- Échappement au système immunitaire
- « Tolérance » aux antibiotiques

DEBRIDEMENT, ABLATION MATERIEL
CHOIX DES ANTIBIOTIQUES : rmp, fq, dap
THERAPEUTIQUES CIBLEES ?

Remerciements : Lyon BJI study group

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Attaché de recherche clinique – *Eugénie Mabrut*

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