Traitement des infections staphylococciques

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Diplôme Universitaire de Thérapeutiques Anti-Infectieuses
Université Grenoble Alpes
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Lecture interprétative de l’antibiogramme

CASFM : liste standard

Pénicilline G

Oxacilline

Céfoxitine

Gentamicine

Erythromycine

Lincosamide

Quinupristine-dalfopristine

Norfloxacine

Fluoroquinolone

Acide fusidique

Cotrimoxazole

Rifampicine

Tétracycline

Fosfomycine

Vancomycine

Téicoplanine

Linézolide

Daptomycine

Résistance à la pénicilline

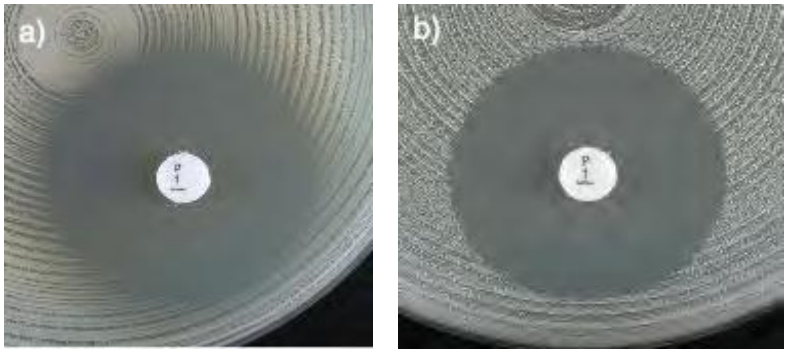
Pénicilline G → Sensibilité naturelle de *S. aureus* aux BL :

Oxacilline
Céfoxitine
Gentamicine
Erythromycine
Lincosamide
Quinupristine-dalfopristine
Norfloxacine
Fluoroquinolone
Acide fusidique
Cotrimoxazole
Rifampicine
Tétracycline
Fosfomycine
Vancomycine
Téicoplanine
Linézolide
Daptomycine

	CMI moyenne
Pénicilline G	**0,008 g/L**
Oxacilline	0,25 g/L
Céfalotine	0,25-0,5 g/L
Cefotaxime	2 g/L
Imipénème	0,12-0,25 g/L

Résistance via pénicillinase
- 75% en communautaire
- 90% en hospitalier

Difficulté de mise en évidence +++



a) Diamètre ≥ 26 mm + bordure floue : souche sensible
b) Diamètre ≥ 26 mm + bordure nette : souche résistante

Résistance à la méticilline

Pénicilline G

Oxacilline → Pénicilline M résistant à l'hydrolyse par Pase

SA**MS**

Résistance via modification de cible : gène *mecA* / PLP2a

SA**RM**

→ résistance à l'ensemble des BL (sauf « C5G »)

→ Multi-résistance souvent associée

Céfoxitine

Gentamicine

Erythromycine

Lincosamide

Quinupristine-dalfopristine

Norfloxacine

Fluoroquinolone

Acide fusidique

Cotrimoxazole

Rifampicine

Tétracycline

Fosfomycine

Vancomycine

Téicoplanine

Linézolide

Daptomycine

Environ 15% (versus > 30% en 2000)

Principalement hospitalier en France et en Europe (≠ USA)

- CA-MRSA USA : 60%, USA300, PVL+
- CA-MRSA France : < 5%, ST80 PVL+ surtout

Macrolides – Lincosamides – Synergistines

Pénicilline G
Oxacilline
Céfoxitine
Gentamicine
Erythromycine
Lincosamide
Quinupristine-dalfopristine
Norfloxacine
Fluoroquinolone
Acide fusidique
Cotrimoxazole
Rifampicine
Tétracycline
Fosfomycine
Vancomycine
Téicoplanine
Linézolide
Daptomycine

	Efflux *msr*	**Modification de cible** *erm* (MLS_B) inductible	constitutif
Macrolide	R	R	R
Lincosamide	S	S	R
Synergistine	S	S_A	S_A

Mécanismes de résistance multiples

1. **Modification de cible : gène erm**
   Constitutif : phénotype « MLS_B »
   - perte de la synergie des 2 sous-unités de la pristi
   Inductible : phénotype « M »
   - résistance apparente qu'aux macrolides
   - induction possible de type MLS_B
2. **Efflux :** résistance isolée aux macrolides
3. **Inactivation :** résistance isolée aux lincosamides
   Sensibilité apparente de la clindamycine

Lecture interprétative de l'antibiogramme : *S. aureus*

Pénicilline G
Oxacilline
Céfoxitine
Gentamicine
Erythromycine
Lincosamide
Quinupristine-dalfopristine
Norfloxacine
Fluoroquinolone
Acide fusidique
Cotrimoxazole
Rifampicine
Tétracycline
Fosfomycine
Vancomycine
Téicoplanine
Linézolide
Daptomycine

S. aureus : vanco-S = téico-S (généralement …)
SCN : téico-R / vanco-S possibles (*S. epidermidis* : 40% (?))

Lecture interprétative de l'antibiogramme : *S. aureus*

Pénicilline G
Oxacilline
Céfoxitine
Gentamicine
Erythromycine
Lincosamide
Quinupristine-dalfopristine
Norfloxacine
Fluoroquinolone → « I » / sensible à « fortes posologies »
Acide fusidique
Cotrimoxazole
Rifampicine
Tétracycline
Fosfomycine
Vancomycine
Téicoplanine
Linézolide
Daptomycine

Lecture interprétative de l'antibiogramme : *S. aureus*

Pénicilline G
Oxacilline
Céfoxitine
Gentamicine
Erythromycine
Lincosamide
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Norfloxacine
Fluoroquinolone
Acide fusidique
Cotrimoxazole
Rifampicine
Tétracycline
Fosfomycine
Vancomycine
Téicoplanine
Linézolide → Résistance exceptionnelle chez *S. aureus* (0,05%)
Clones épidémiques de SCN +++ (1,4%)
Daptomycine

Bactériémie : succès et limites des stratégies actuelles

Patient de 73 ans, autonome à domicile
Diabétique de type 2, HTA, PTG gauche
Admis aux urgences pour fièvre depuis 24h
Hémocultures positives en 14h à cocci+ en amas (4 flacons)
Aucun signe de gravité

Quelle antibiothérapie probabiliste débutez-vous ?

A. céfazoline
B. daptomycine
C. oxa/cloxacilline
D. vancomycine
E. autre

Patient de 73 ans, autonome à domicile
Diabétique de type 2, HTA, PTG gauche
Admis aux urgences pour fièvre depuis 24h
Hémocultures positives en 14h à cocci+ en amas (4 flacons)
Aucun signe de gravité

Quelle antibiothérapie probabiliste débutez-vous ?

A. céfazoline
B. daptomycine
C. oxa/cloxacilline
D. vancomycine
E. autre

Staphylococcus aureus

Oxacilline	S
Kanamycine	S
Gentamicine	S
Erythromycine	S
Clindamycine	S
Pristinamycine	S
Tétracycline	S
Lévofloxacine	SFP
Cotrimoxazole	S
Nitrofurantoïne	S
Rifampicine	S
Fosfomycine	S
Acide fusidique	S
Vancomycine	S
Daptomycine	S
Linézolide	S

Patient de 73 ans, autonome à domicile
Diabétique de type 2, HTA, PTG gauche
Admis aux urgences pour fièvre depuis 24h
Hémocultures positives en 14h à cocci+ en amas (4 flacons)
Aucun signe de gravité

Quelle antibiothérapie probabiliste débutez-vous ?

A. ceftaroline
B. daptomycine
C. linézolide
D. vancomycine
E. autre

Staphylococcus aureus

Oxacilline	**R**
Kanamycine	S
Gentamicine	S
Erythromycine	**R**
Clindamycine	**R**
Pristinamycine	S
Tétracycline	S
Lévofloxacine	SFP
Cotrimoxazole	S
Nitrofurantoïne	S
Rifampicine	S
Fosfomycine	S
Acide fusidique	S
Vancomycine	S
Daptomycine	S
Linézolide	S

Patient de 73 ans, autonome à domicile
Diabétique de type 2, HTA, PTG gauche
Admis aux urgences pour fièvre depuis 24h
Hémocultures positives en 14h à cocci+ en amas (4 flacons)
Aucun signe de gravité

Quelle durée de traitement ?

A. 3 jours
B. 5 jours
C. 7 jours
D. 10 jours
E. 14 jours

Faites-vous un relais per os ?

A. oui
B. non

Staphylococcus aureus

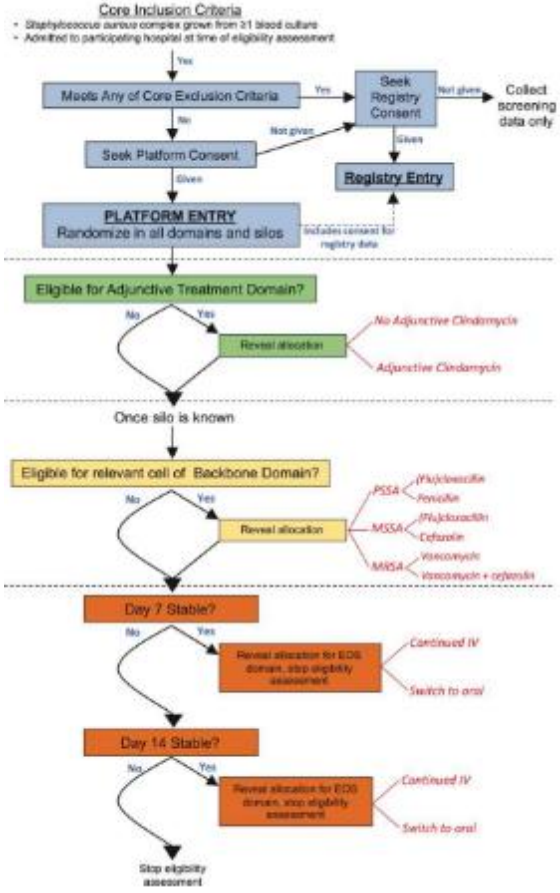
Oxacilline	**R**
Kanamycine	S
Gentamicine	S
Erythromycine	**R**
Clindamycine	**R**
Pristinamycine	S
Tétracycline	S
Lévofloxacine	SFP
Cotrimoxazole	S
Nitrofurantoïne	S
Rifampicine	S
Fosfomycine	S
Acide fusidique	S
Vancomycine	S
Daptomycine	S
Linézolide	S

Bactériémie à staphylocoque : SNAP trial plateform

The *Staphylococcus aureus* Network Adaptive Platform Trial Protocol: New Tools for an Old Foe

Steven Y. C. Tong,[1] Jocelyn Mora,[1] Asha C. Bowen,[2,3] Matthew P. Cheng,[4] Nick Daneman,[5] Anna L. Goodman,[6,7] George S. Heriot,[1] Todd C. Lee,[8] Roger J. Lewis,[9,10,11] David C. Lye,[12,13,14,15] Robert K. Mahar,[16,17] Julie Marsh,[18] Anna McGlothlin,[9] Zoe McQuilten,[19,20] Susan C. Morpeth,[21] David L. Paterson,[22] David J. Price,[1,16] Jason A. Roberts,[23,24] J. Owen Robinson,[25,26,27,28] Sebastiaan J. van Hal,[29,30] Genevieve Walls,[21] Steve A. Webb,[31] Lyn Whiteway,[32] Dafna Yahav,[33] and Joshua S. Davis[34]; for the *Staphylococcus aureus* Network Adaptive Platform (SNAP) Study Group

Silo	Domain		
	Backbone antibiotic	Adjunctive antibiotic	Early oral switch
PSSA	(Flu)cloxacillin vs penicillin	No clindamycin vs clindamycin	Continued IV vs early oral switch at either day 7 (uncomplicated disease) or day 14 (complicated disease)
MSSA	(Flu)cloxacillin vs cefazolin		
MRSA	(Vancomycin/ daptomycin) vs (Vancomycin/ daptomycin) + cefazolin		



Bactériémie à staphylocoque méti-S

GOLD STANDARD : pénicilline M <u>en IV</u> à forte dose

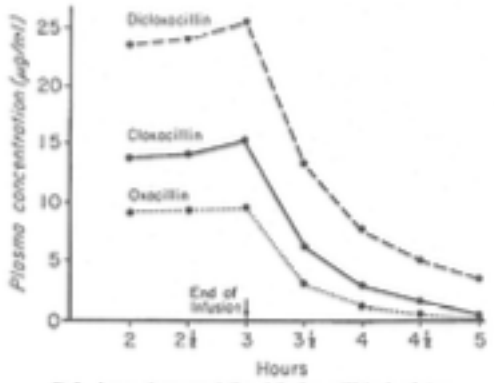
Oxacilline (BRISTOPEN®) ou Cloxacilline (ORBENINE®)

150-200 mg/kg

14 j

Meilleure stabilité (diffuseur)
Moins veinotoxique
Adaptation rénale moindre

Meilleure profil PK/PD ?
Pas de données SNC



Bactériémie à staphylocoque méti-S

GOLD STANDARD : pénicilline M en IV à forte dose

Oxacilline (BRISTOPEN®) ou Cloxacilline (ORBENINE®)
150-200 mg/kg
14 j

ALTERNATIVES
Glycopeptides ? Autres béta-lactamines ? Autres ?

Bactériémie à staphylocoque méti-S

The Empirical Combination of Vancomycin and a β-Lactam for Staphylococcal Bacteremia

Kevin W. McConeghy,[1] Susan C. Bleasdale,[2] and Keith A. Rodvold[1,2]

[1]Department of Pharmacy Practice, College of Pharmacy, and [2]Department of Medicine, University of Illinois at Chicago

Table 1. Summary of Published Studies Evaluating Empirical Therapy for Methicillin-Susceptible *Staphylococcus aureus* Bacteremia

Study	Year	Design	Study Size, No.	Outcome	Vancomycin vs β-Lactam	Result[a]
Vancomycin therapy vs β-lactam therapy[b]						
Chang et al [19]	2003	Prospective cohort	505	Bacteriologic failure[c]	19% vs 0%	OR, 6.5 (1.0–53)
Khatib et al [20]	2006	Prospective cohort	120	Overall mortality	27% vs 12%	HR, 2.3 (1.1–4.9)
Stryjewski et al [21][d]	2007	Prospective cohort	123	Treatment failure	31% vs 13%	OR, 3.5 (1.2–13)
Lodise et al [6][e]	2007	Retrospective cohort	84	Infection-related mortality	39% vs 11%	OR, 6.5 (1.4–29)
Kim et al [22]	2008	Retrospective case-control	27	Infection-related mortality	37% vs 11%	OR, 3.3 (1.2–9.5)
Schweizer et al [23]						HR, 4.8 (2.1–11)[f]
Chan et al [24]						HR, 1.6 (1.2–2.2)[f]
Vancomycin therap						
Lodise et al [6][e]						NS
Schweizer et al [2						HR, 3.2 (1–10)
Vancomycin therap						
Khatib et al [25]						$P = .03$
Lodise et al [6][e]	2007	Retrospective cohort	84	Infection-related mortality	41% vs 11%	Not reported

BACTERIEMIE A MSSA TRAITEE PAR VANCOMYCINE *versus* BELA-LACTAMINE

=

MORTALITE x 3-6

Bactériémie à staphylocoque méti-S

Are all beta-lactams similarly effective in the treatment of methicillin-sensitive *Staphylococcus aureus* bacteraemia?

Clin Microb Infect 2011

M. Paul[1,2], N. Zemer-Wassercug[1], O. Talker[1], Y. Lishtzinsky[1], B. Lev[3], Z. Samra[3,2], L. Leibovici[4,2] and J. Bishara[1,2]

TABLE 2. Multivariable logistic regression analysis for 30-day mortality: empirical antibiotic treatment[a]

Variable[b]	OR, 95% CI *n* = 541 patients, deaths = 202	p-value
Empirical antibiotic treatment		
Oxacillin/cefazolin	Reference	
Cefuroxime	1.98 (0.98–4.01)	0.058
Ceftriaxone/cefotaxime	2.24 (1.23–4.08)	0.008
Beta-lactam-beta-lactamase	2.68 (1.23–5.85)	0.013
Other beta-lactams	0.81 (0.35–1.9)	0.629
Age (per 1 year increment)	1.04 (1.02–1.06)	<0.001
Female sex	1.69 (1.08–2.63)	0.021
Poor functional capacity (bedridden)	1.73 (1.02–2.93)	0.041
Malignancy	1.89 (1.15–3.09)	0.012
Shock at onset	5.61 (2.75–11.45)	<0.001
Urea (per 1 mg/dL increment)	1.01 (1.007–1.016)	<0.001
Albumin (per 1 mg/dL increment)	0.54 (0.38–0.78)	0.001
Thrombocytes (per 1 K/μL increment)	0.996 (0.994–0.998)	<0.001
Mechanical ventilation	Not retained in final model	0.078
Skin/soft tissue source of infection		0.111

FACTEURS DE RISQUE DE MORTALITE :

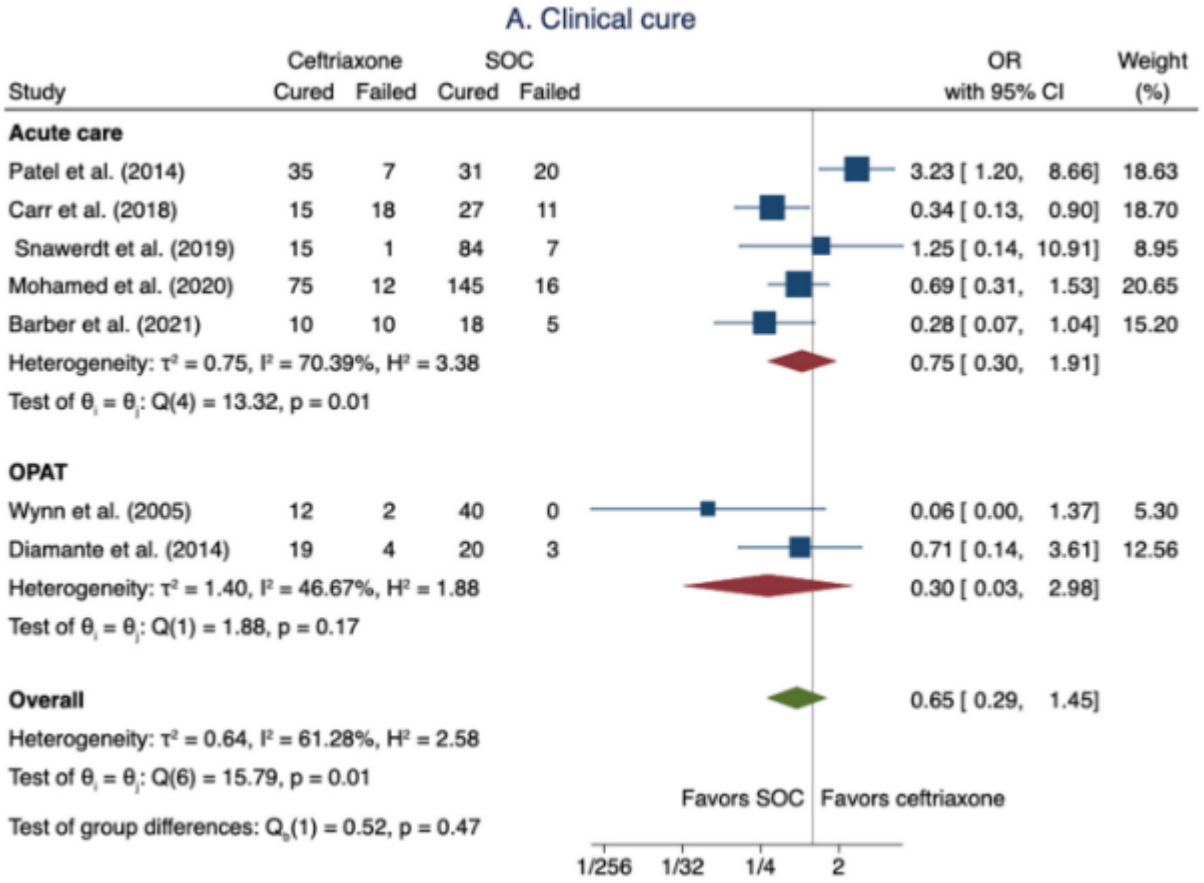
- C3G injectables
- Amox - Ac clav
- Pipé - Tazobactam

Bactériémie à staphylocoque méti-S : C3G or not ?

Antibiotics 2022

Effectiveness and Safety of Ceftriaxone Compared to Standard of Care for Treatment of Bloodstream Infections Due to Methicillin-Susceptible *Staphylococcus aureus*: A Systematic Review and Meta-Analysis

Yazed Saleh Alsowaida [1,2,3,*], Gregorio Benitez [2], Khalid Bin Saleh [4], Thamer A. Almangour [5], Fadi Shehadeh [1,2,6] and Eleftherios Mylonakis [1,2,*]



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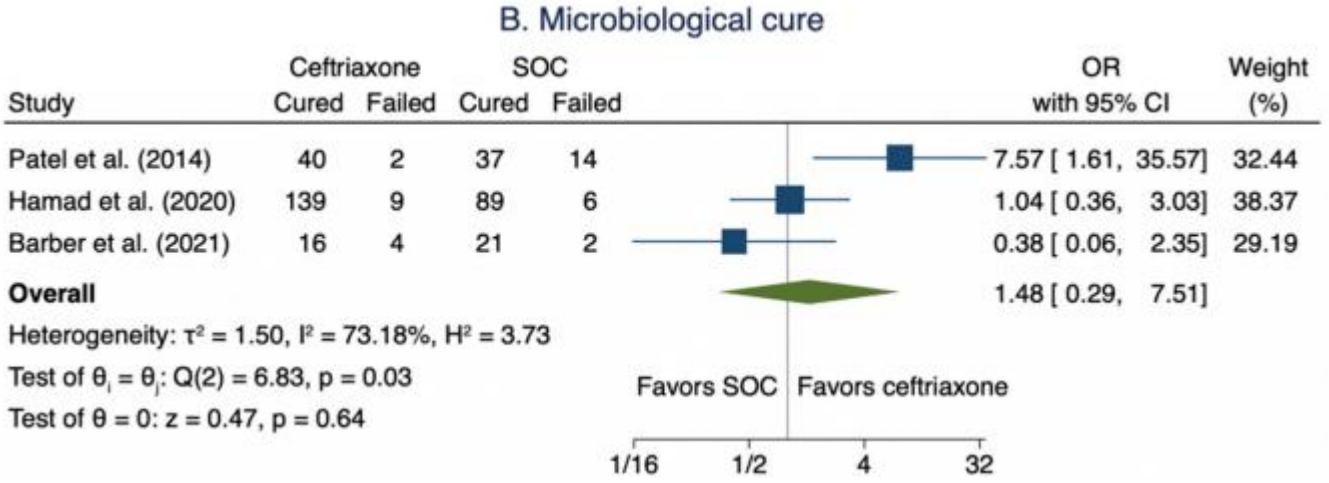
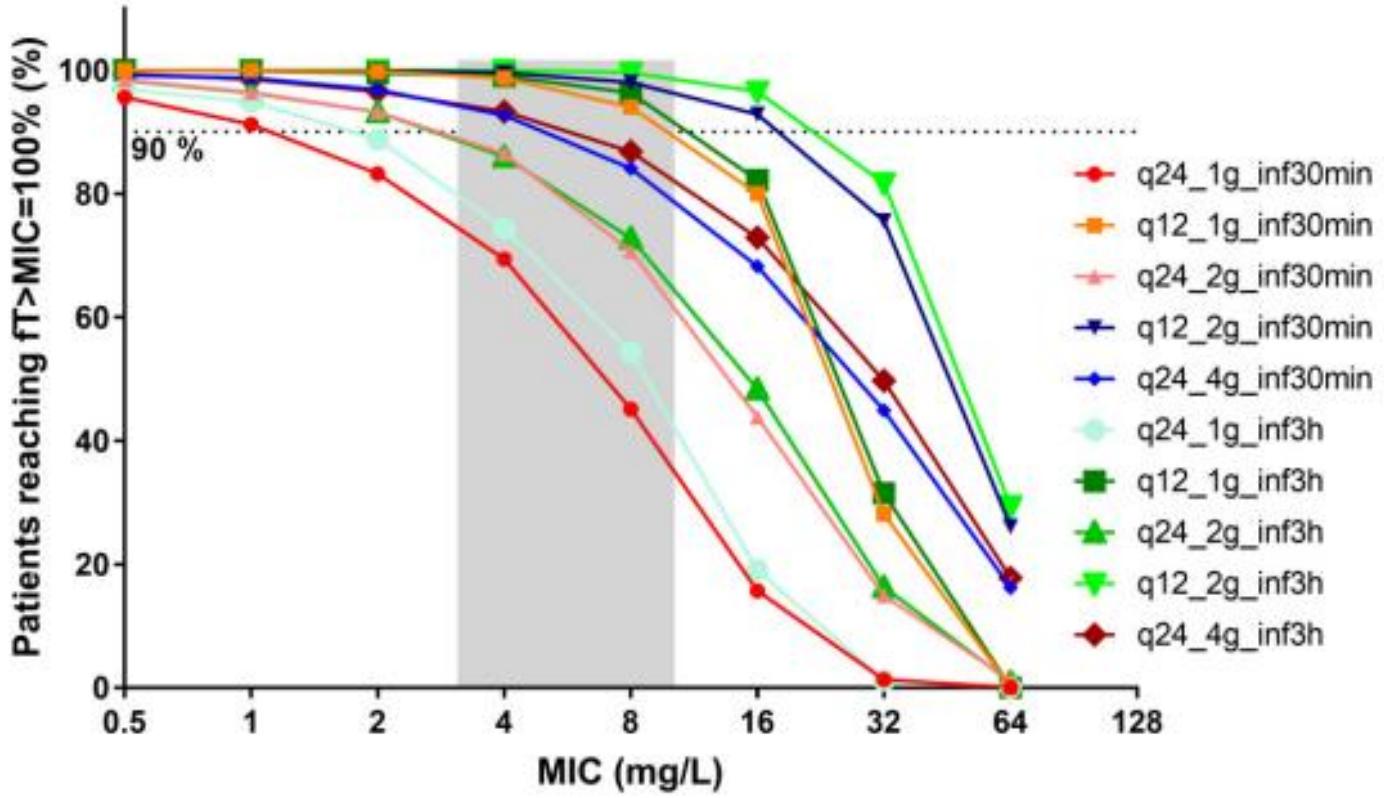


Bactériémie à staphylocoque méti-S : C3G or not ?

Ceftriaxone and methicillin-susceptible *staphylococcus aureus*: a perspective from pharmacokinetics/pharmacodynamics studies

Joao Paulo Telles, Rodrigo Cuiabano Paes Leme, Michel Leandro Campos, Carmen Ito, Larissa Bail, Keite da Silva Nogueira & Felipe Francisco Tuon



Bactériémie à staphylocoque méti-S : céfazoline

Cefazolin vs. antistaphylococcal penicillins for the treatment of methicillin-susceptible *Staphylococcus aureus* bacteraemia: a systematic review and meta-analysis

Connor Prosty [1, 2, *], Dean Noutsios [1], Todd C. Lee [2, 3, 4], Nick Daneman [5, 6], Joshua S. Davis [7, 8, 9], Nynke G.L. Jager [10], Nesrin Ghanem-Zoubi [11], Anna L. Goodman [12], Achim J. Kaasch [13], Ilse Kouijzer [14], Brendan J. McMullan [15], Emily G. McDonald [2, 4, 16], Steven Y.C. Tong [17, 18], Sean W.X. Ong [5, 6, 17, 18], on behalf of Staphylococcus aureus Network Adaptive Platform MSSA/PSSA domain specific working group

Figure 1. 30-Day All-Cause Mortality

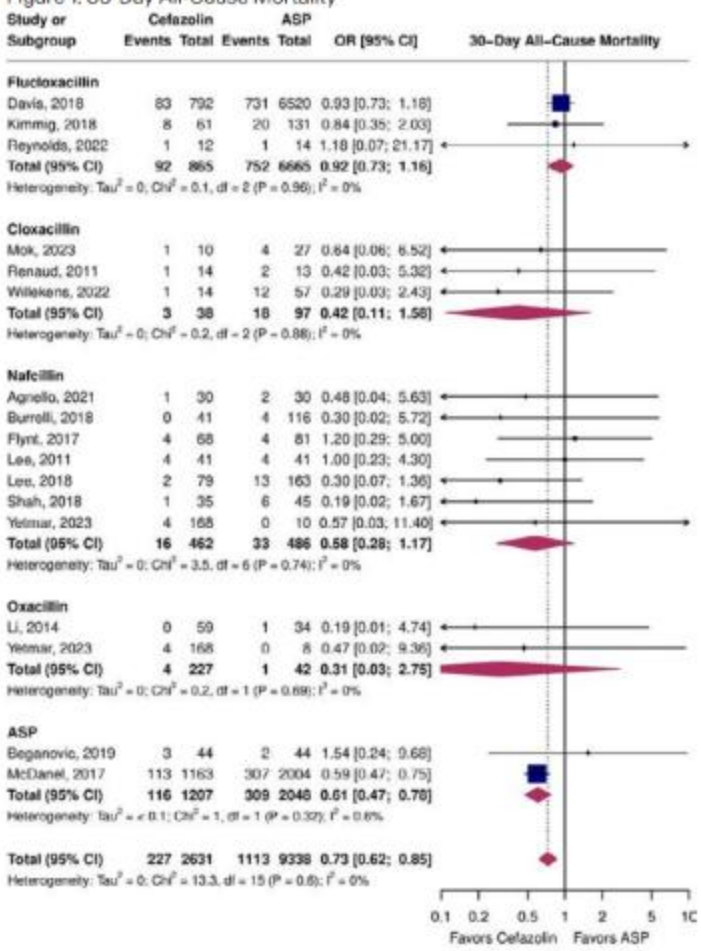
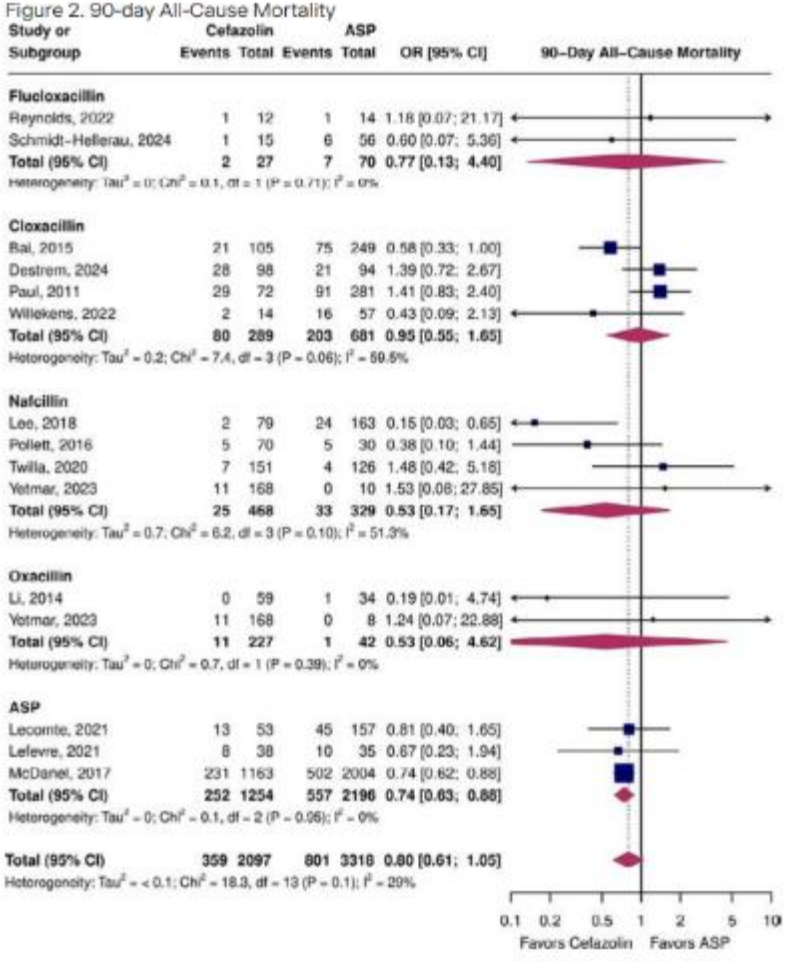


Figure 2. 90-day All-Cause Mortality



Bactériémie à staphylocoque méti-S : céfazoline

SNAP
Staphylococcus aureus Network Adaptive Platform

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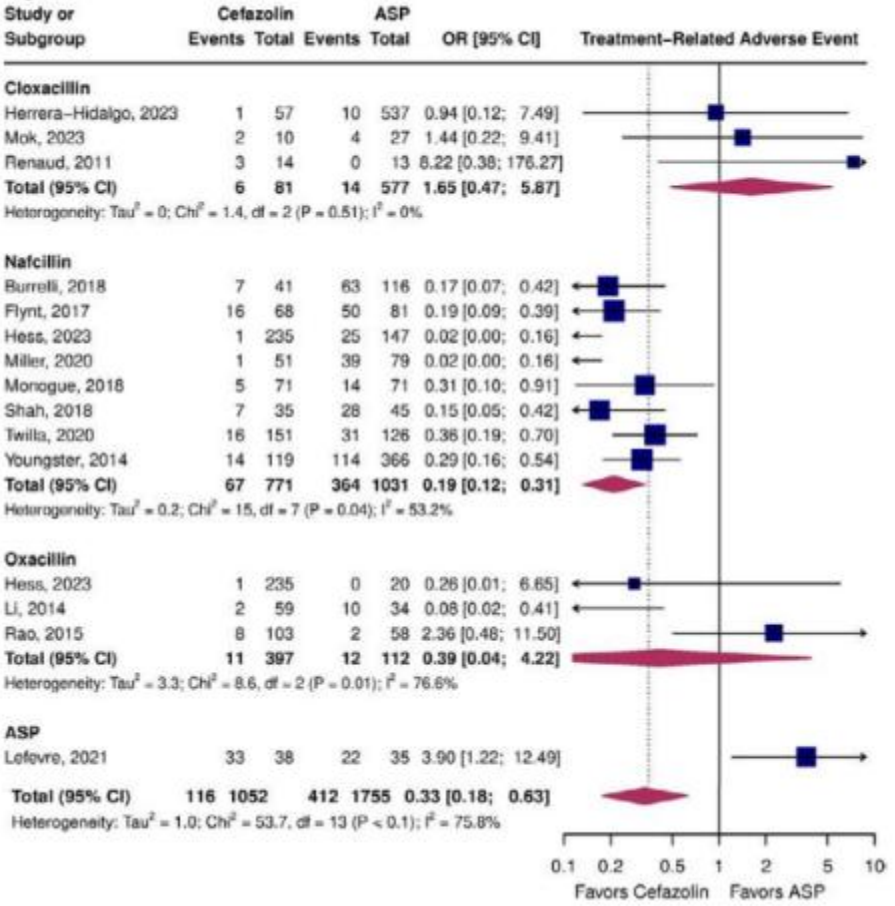
Figure 3. Treatment-Related Adverse Events



Bactériémie à staphylocoque méti-S : céfazoline

Cefazolin versus (flu)cloxacillin for the treatment of penicillin-resistant, methicillin-susceptible *Staphylococcus aureus* bacteraemia: a randomised controlled trial within the S. aureus network adaptive platform (SNAP)

S. Aureus Network Adaptive Platform Trial Group[1]

[1]University of Melbourne - Melbourne (Australia)

Presenting author email: josh.davis@newcastle.edu.au

1341 MSSA bacteremia (92 sites, 8 countries) : 671 cefazolin / 670 (flu)cloxacillin
Closed for increased AKI incidence in the (flu)cloxacillin group

	cefazolin	(flu)cloxa	aOR (CrI)
90-day all-cause mortality	15,0%	17,0%	0,81 (0,59-1,12)
AKI	14,0%	19,7%	0,67 (0,50-0,90)

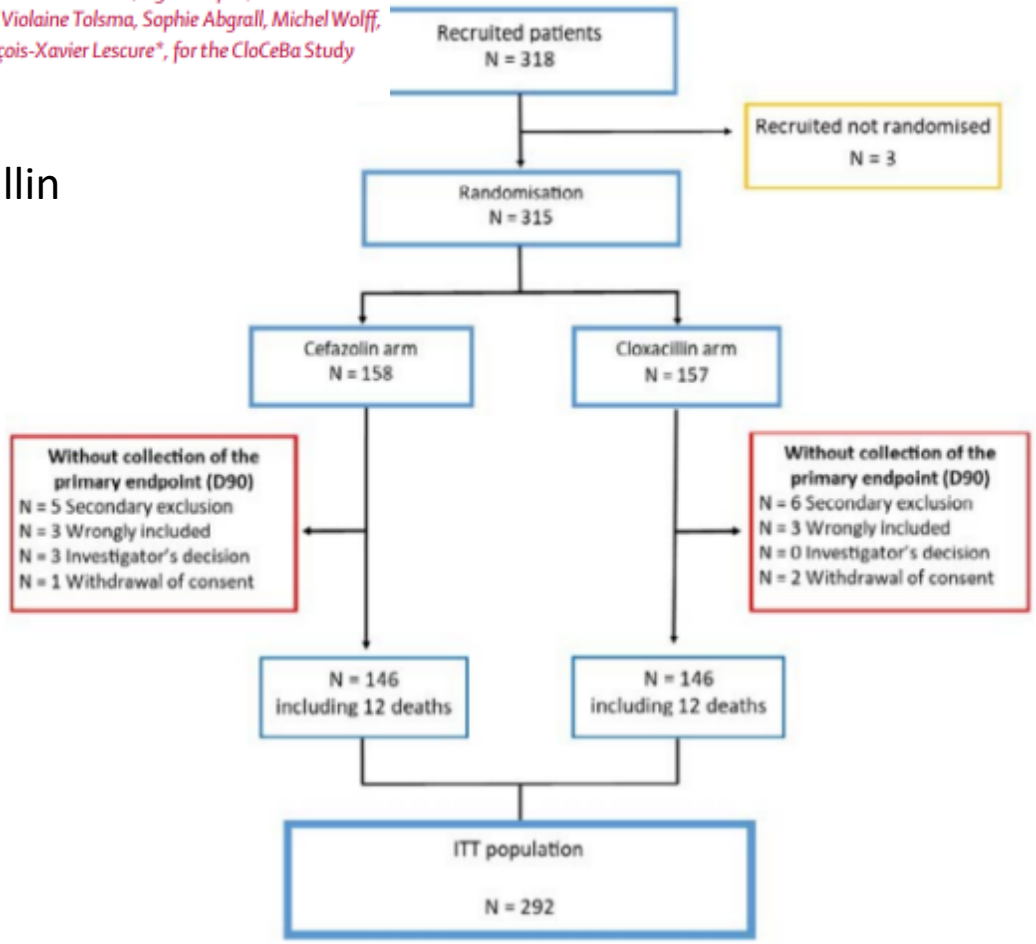
Posterior probabilities non-inferiority: 0.992
superiority: 0.898

Bactériémie à staphylocoque méti-S : céfazoline

Cloxacillin versus cefazolin for meticillin-susceptible *Staphylococcus aureus* bacteraemia (CloCeBa): a prospective, open-label, multicentre, non-inferiority, randomised clinical trial

Charles Burdet, Nadia Saïdani, Céline Dupieux, Adrien Lemaignen, Etienne Canouï, Laure Surgers, Marc Olivier Vareil, Agnès Lefort, Raphaël Lepeule, Nathan Peiffer-Smadja, Alexandre Charmillon, Vincent Le Moing, David Boutoille, Violaine Tolsma, Sophie Abgrall, Michel Wolff, Pierre Tattevin, Marina Esposito-Farèse, François Vandenesch, Xavier Duval, Sarah Tubiana*, François-Xavier Lescure*, for the CloCeBa Study Group†*

315 MSSA bacteremia : cefazolin / cloxacillin



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315 MSSA bacteremia : cefazolin / cloxacillin

	cefazolin	cloxa	p-value
90-day all-cause mortality	8,2%	8,2%	1,00
Bacteriological success D3	93,2%	91,8%	0,66
Relapse D90	0,7%	1,4%	>0,99
Clinical success D90	80,6%	79,9%	0,88
Severe AE	34,2%	43,8%	0,093

Non-inferiority: difference 0.008 (95%CI, -0.111; 0.095)

Bactériémie à staphylocoque méti-S : céfazoline

Cefazolin in the treatment of central nervous system infections: A narrative review and recommendation

Kayla Antosz[1,2] | Sarah Battle[2,3] | Jack Chang[4,5] | Marc H. Scheetz[4,5] | Majdi Al-Hasan[2,3] | P. Brandon Bookstaver[1,2]

Beta-lactam	Vd[a]	Protein binding	CSF % relative to serum
Ampicillin	0.33 L/kg	18%	13-35% (inflamed)
Penicillin G	0.35 L/kg	46%–58%	2–10% (inflamed)
Nafcillin	0.5–1.5 L/kg	90%–94%	1-20% (inflamed), ~0.1-3% (uninflamed)
Oxacillin	0.4 L/kg	90%–94%	~1-3% (inflamed)
Cefazolin	0.19 L/kg	73%–87%	3-11% (inflamed), 1-3% (uninflamed)
Cefuroxime	0.3–1.1 L/kg	33%–35%	11-33% (inflamed)
Ceftriaxone	0.08–0.2 L/kg	85%–95%	1.5-13% (inflamed), 1.5% (uninflamed)
Cefepime	0.26 L/kg	20%	4–34% (inflamed)
Ceftaroline	0.26–0.30 L/kg	20%	2–7% (inflamed)
Piperacillin/ tazobactam	0.24 L/kg	26%–33%	~22% (piperacillin, inflamed)
Ampicillin/ sulbactam	0.25 L/kg	38%	–
Ertapenem	0.12 L/kg	85%–95%	4–7% (inflamed), 2.4% (uninflamed)
Meropenem	0.21–0.28 L/kg	2%	~9% (inflamed)

Données cliniques limitées

Données PK/PD suggère une utilisation possible
à dose plus élevées : 2g/6h (ou 8-10 g IVSE)
avec suivi PK (objectif > 2 mg/L)

Bactériémie à staphylocoque méti-S : effet inoculum

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2009, p. 3437–3441 Vol. 53, No. 8
0066-4804/09/$08.00+0 doi:10.1128/AAC.00317-09

Inoculum Effect with Cefazolin among Clinical Isolates of Methicillin-Susceptible *Staphylococcus aureus*: Frequency and Possible Cause of Cefazolin Treatment Failure▽

Esteban C. Nannini,[1] Martin E. Stryjewski,[2,3] Kavindra V. Singh,[5] Agathe Bourgogne,[5] Tom H. Rude,[4] G. Ralph Corey,[4] Vance G. Fowler, Jr.,[4] and Barbara E. Murray[5,6]*

TABLE 2. Correlation between cefazolin MIC and inoculum size for 98 strains

Inoculum size	% of strains inhibited at cefazolin concn (μg/ml)							
	≤1	2	4	8	16[a]	32	64	≥128
Low	100	0	0	0	0	0	0	0
Standard	89	5	6	0	0	0	0	0
Intermediate	33	50	8	2	2	1	3	0
High	23	12	20	24	5	9	3	2

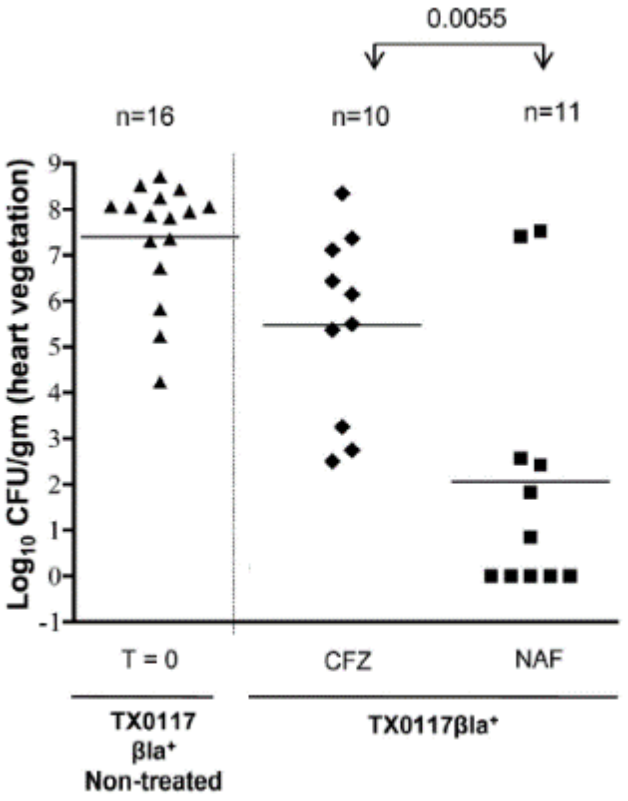
[a] CLSI breakpoint for nonsusceptibility.

***BlaZ* type A**

AAC September 2013 Volume 57 Number 9

In Vivo Effects of Cefazolin, Daptomycin, and Nafcillin in Experimental Endocarditis with a Methicillin-Susceptible *Staphylococcus aureus* Strain Showing an Inoculum Effect against Cefazolin

Esteban C. Nannini,[a] Kavindra V. Singh,[b] Cesar A. Arias,[b,c] Barbara E. Murray[b,d]



Relapse of Type A β-Lactamase–Producing *Staphylococcus aureus* Native Valve Endocarditis during Cefazolin Therapy: Revisiting the Issue

Clinical Infectious Diseases 2003; 37:1194–8

Esteban C. Nannini,[1,2] Kavindra V. Singh,[1,2] and Barbara E. Murray[1,2,3]
[1]Center for the Study of Emerging and Re-emerging Pathogens, [2]Division of Infectious Diseases, Department of Internal Medicine, and [3]Department of Microbiology and Molecular Genetics, University of Texas Medical School, Houston

Bactériémie à staphylocoque méti-S : effet inoculum

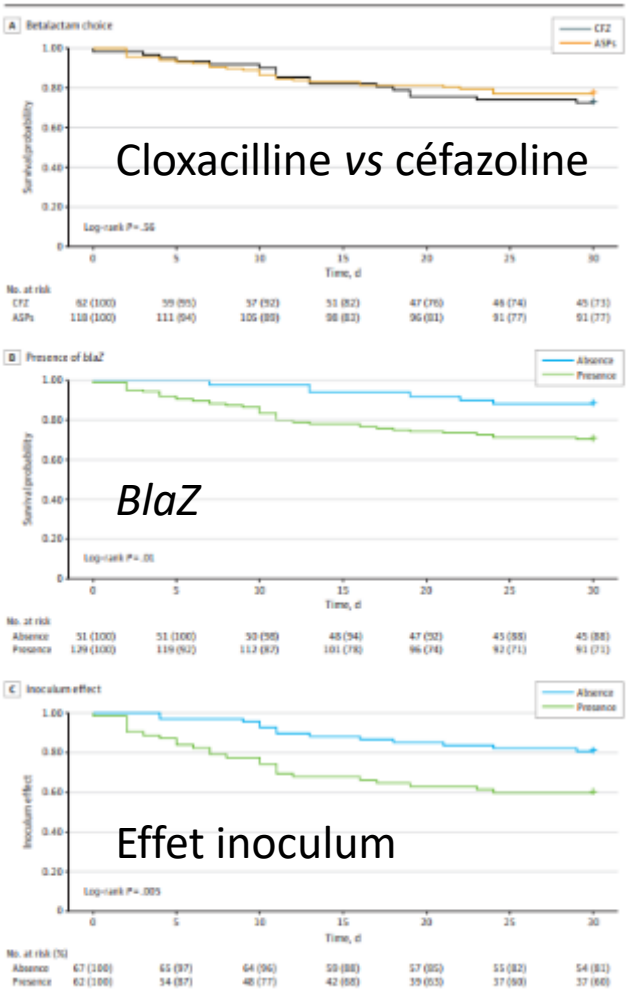
β-Lactam Inoculum Effect in Methicillin-Susceptible *Staphylococcus aureus* Infective Endocarditis

Baptiste Jean, MD; Maelys Crolle, PharmD; Candice Pollani, PharmD; Adèle Le Guilloux; Guillaume Martin-Blondel, PhD; Pierre Tattevin, PhD; Audrey Le Bot, MD; David Luque Paz, MD; François Guérin, PhD; Vincent Cattoir, PhD; Laurence Armand-Lefevre, PhD; Signara Gueye; François-Xavier Lescure, PhD; Xavier Duval, PhD; Clémence Massip, PhD; Pierre Delobel, PhD

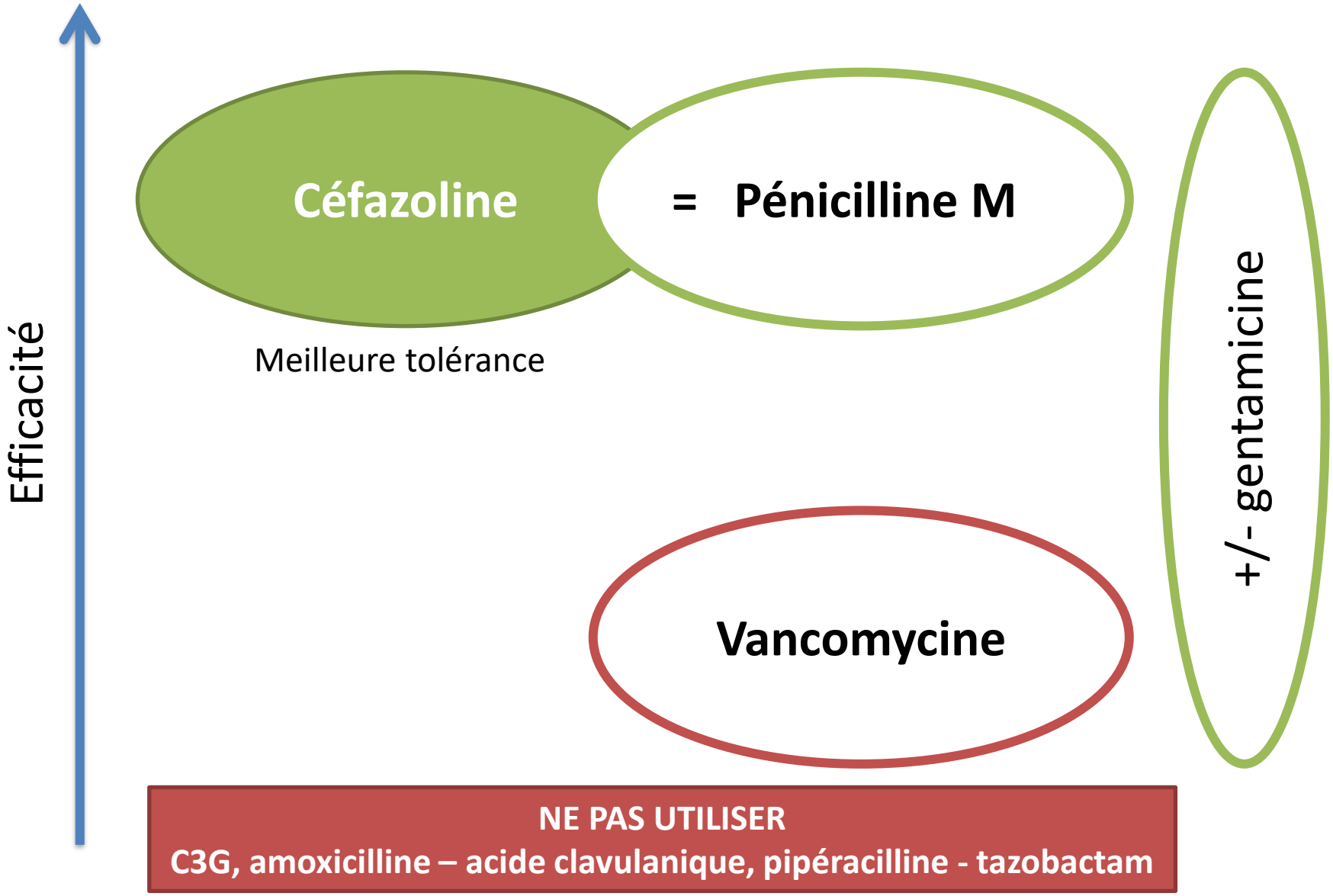
108 EI du cœur gauche à SASM

Effet inoculum
- Céfazoline : 19,0%
- Oxacilline : 38,0%

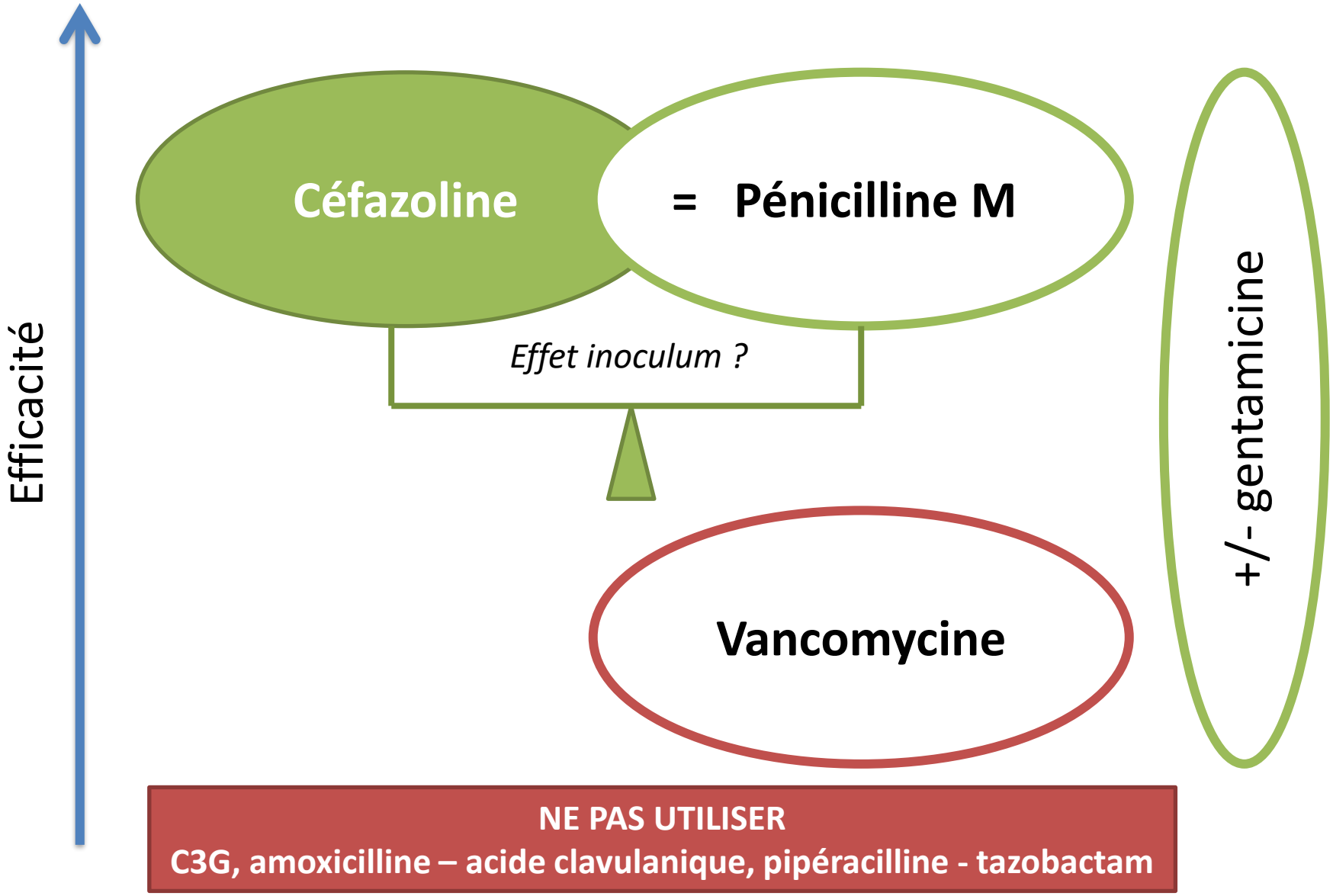
Effet inoculum indépendamment associé à la mortalité : HR, 2.84; 95% CI, 1.28-6.30; P = .01



Bactériémie à staphylocoque méti-S



Bactériémie à staphylocoque méti-S



Bactériémie à staphylocoque péni-S : pénicilline G ?

Benzylpenicillin versus (flu)cloxacillin for the treatment of penicillin-susceptible *Staphylococcus aureus* bacteraemia: a randomised controlled trial of the *S. aureus* network adaptive platform (SNAP)

S. Aureus Network Adaptive Platform Trial Group[1]

[1]University of Melbourne - Melbourne (Australia)

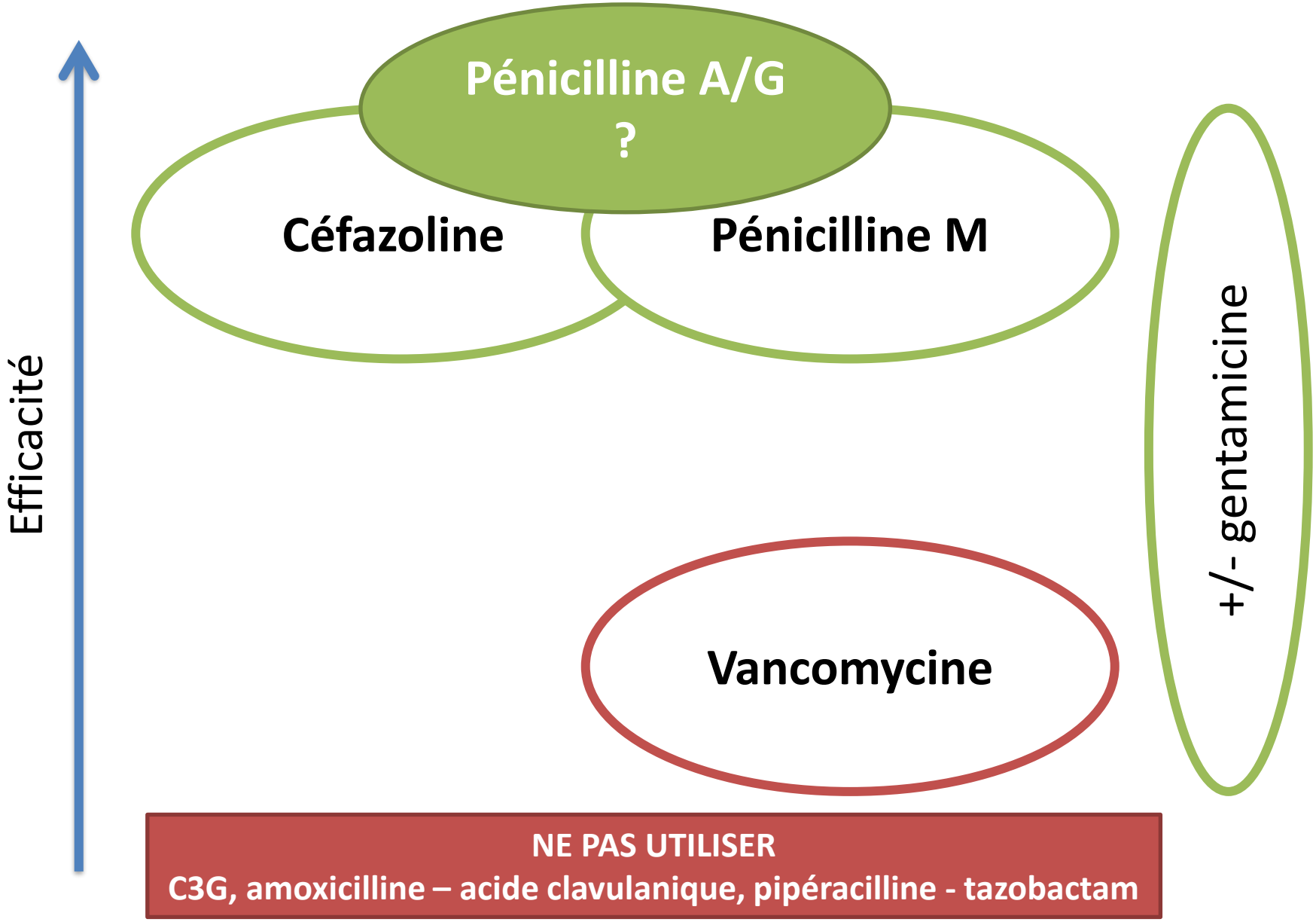
Presenting author email: steven.tong@unimelb.edu.au

281 PSSA bacteremia : 156 benzylpenicillin / 125 (flu)cloxacillin
Closed for increased AKI incidence in the (flu)cloxacillin group of the cefazo/cloxa trial

	benzylpenicillin	(flu)cloxa	aOR (CrI)
90-day all-cause mortality	13,8%	21,5%	0,67 (0,35-1,28)
AKI	11,1%	21,8%	0,50 (0,26-0,94)

Posterior probabilities non-inferiority: 0.961
superiority: 0.889

Bactériémie à staphylocoque péni-S



Bactériémie à staphylocoque méti-S : bithérapies ?

SOC +	Type d'études	Population	Remarques	PMID
Rifampicine	RCT	MRSA, MSSA	Pas de bénéfice	1929035 29249276
Aminoside	Observationnelles RCT	MRSA, MSSA	1 jours de moins Toxicité +++	Multiples
Daptomycine	RCT	MSSA	Pas de bénéfice	32667982
Céfazo - erta	Observationnelles	MSSA persistant	Négativation bactériémie	31773134 35493130

Bactériémie à staphylocoque méti-S : bithérapies ?

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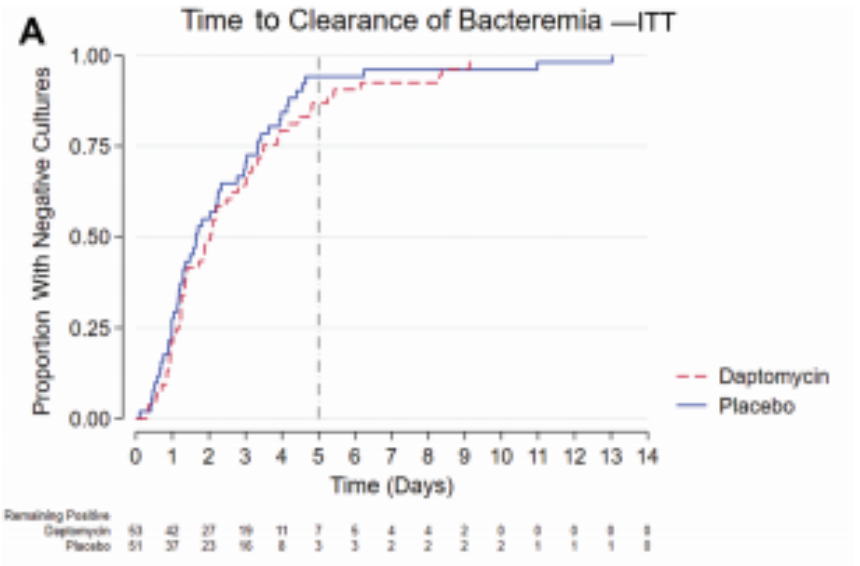
Adjunctive Daptomycin in the Treatment of Methicillin-susceptible *Staphylococcus aureus* Bacteremia: A Randomized, Controlled Trial

Matthew P. Cheng,[1,a] Alexander Lowandi,[2,a,©] Guillaume Butler-Laporte,[2,a,©] Samuel De l'Étoile-Morel,[2] Katryn Paquette,[3] and Todd C. Lee[2,4,5]

115 bactériémies à MSSA / céfazo ou cloxa
+ 5 jrs daptomycine 6 mg/kg ou placebo
Randomisation 47h après H+



Bactériémie à staphylocoque méti-S : bithérapies ?

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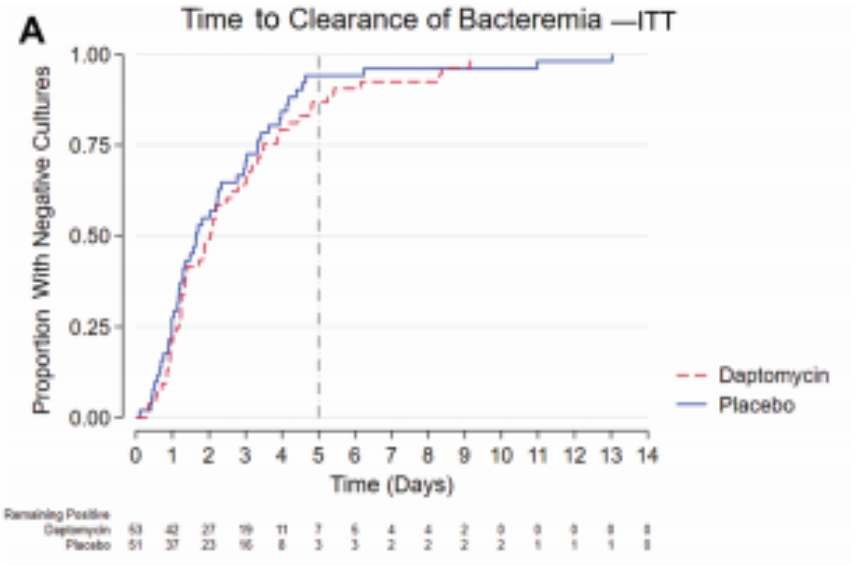
115 bactériémies à MSSA / céfazo ou cloxa
+ **5 jrs** daptomycine **6 mg/kg** ou placebo
Randomisation **47h après H+**

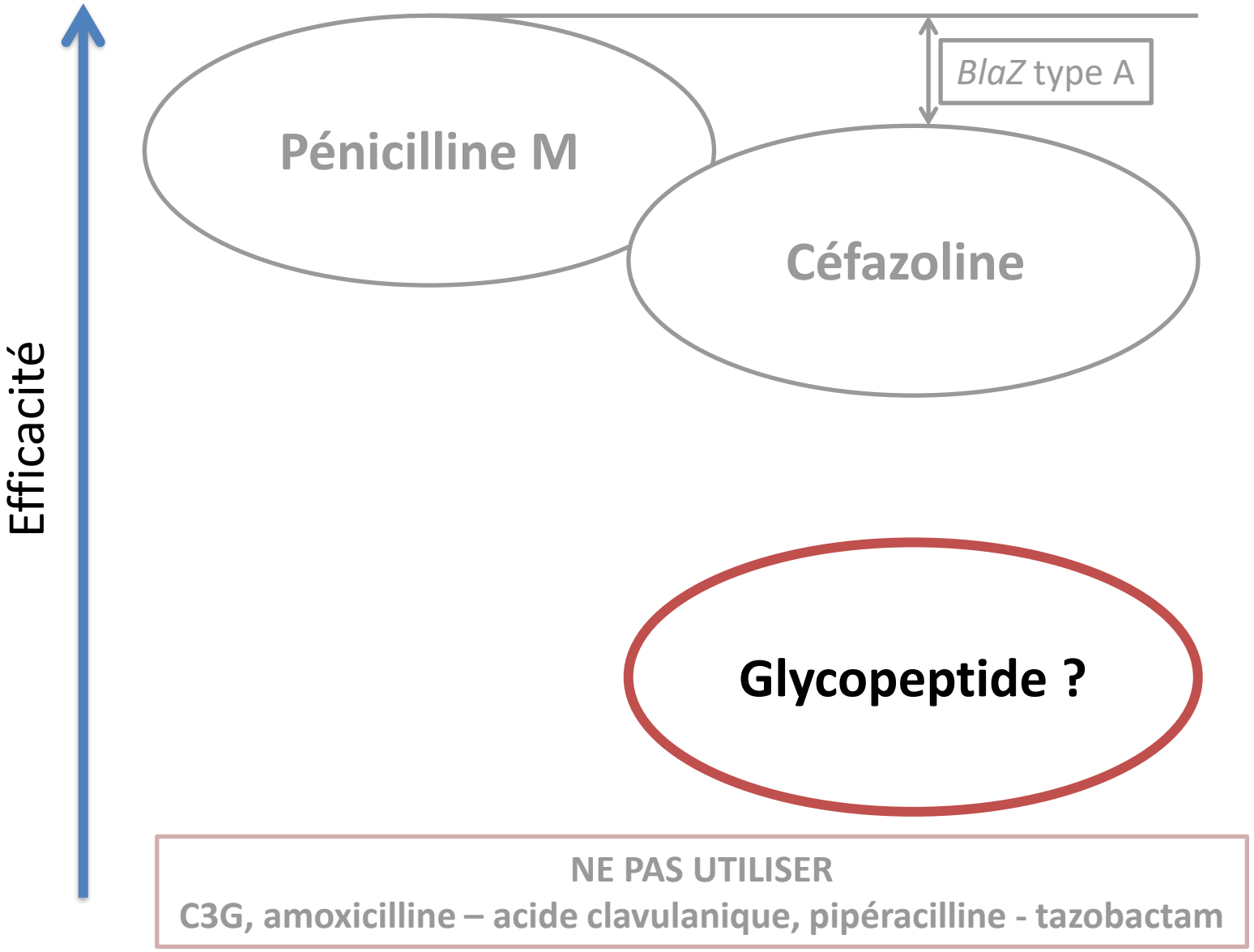


Bactériémie à staphylocoque méti-S : bithérapies ?

SOC +	Type d'études	Population	Re	D
Rifampicine	RCT	MRSA, MSSA		1929035 29249276
Aminoside	Observationnelles RCT		jours de moins Toxicité +++	Multiples
Daptomycine	RCT		Pas de bénéfice	32667982
Céfazo - erta		MSSA persistant	Négativation bactériémie	31773134 35493130

RESCUE THERAPY

Bactériémie à staphylocoque méti-R



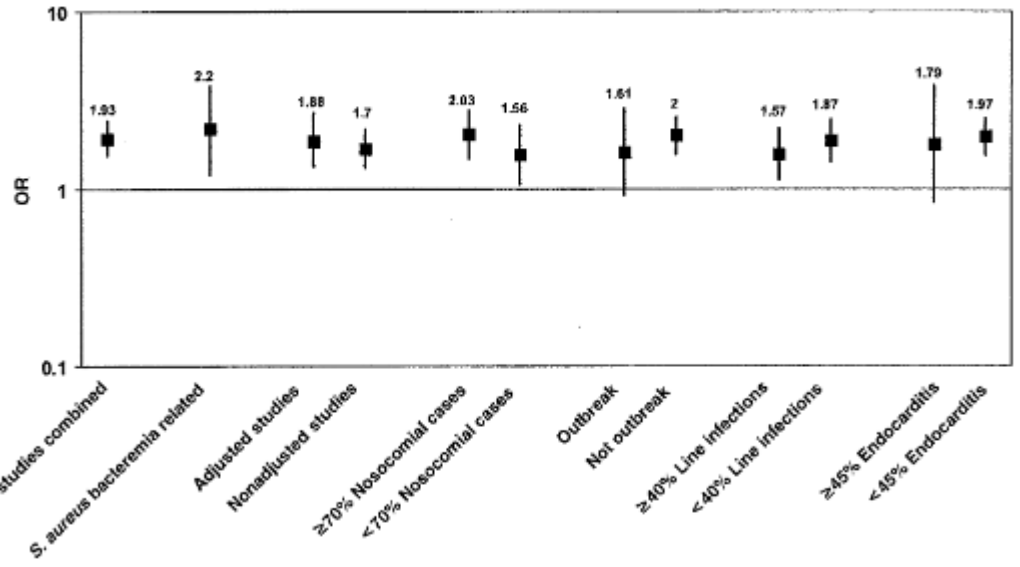
Bactériémie à *S. aureus* méti-R : glycopeptides

	VANCOMYCINE	TEICOPLANINE
Posologie	20-30 mg/kg puis 20-30 mg/kg/j TR cible 15-20 (sf SNC : 25-30)	9-12 mg/kg/12h pdt 48h puis 9-12 mg/kg/24h TR cible 20-25 mg/L
Voie	IVL > 1h ou IVSE (VVC)	IV, IM (ou SC)
Spectre	Cocci +	> Entérocoques SCN : 30-40% de résistance
Toxicité	Rénale, red man, hémato	Néphrotoxicité moindre

Bactériémie à *S. aureus* méti-R : glycopeptides

Comparison of Mortality Associated with Methicillin-Resistant and Methicillin-Susceptible *Staphylococcus aureus* Bacteremia: A Meta-analysis

Sara E. Cosgrove,[1] George Sakoulas,[1] Eli N. Perencevich,[1] Mitchell J. Schwaber,[1] Adolf W. Karchmer,[1] and Yehuda Carmeli[1,2]



SARM plus virulent ???

Vancomycine non optimal ?

Bactériémie à *S. aureus* méti-R

The Clinical Significance of Vancomycin Minimum Inhibitory Concentration in *Staphylococcus aureus* Infections: A Systematic Review and Meta-analysis

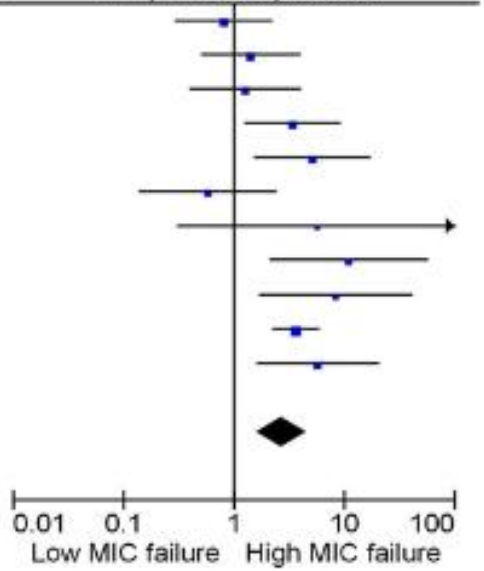
S. J. van Hal,[1,2] T. P. Lodise,[3] and D. L. Paterson[4]

Clin Infect Dis 2012

Study or Subgroup	High MIC≥1.5µg/mL Events	Total	Low MIC<1.5µg/mL Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bae et al (12)	14	37	12	28	10.9%	0.81 [0.30, 2.21]
Choi et al (15)	12	34	10	36	10.8%	1.42 [0.51, 3.91]
Ferry et al (17)	9	24	9	28	9.7%	1.27 [0.40, 3.98]
Hidayat et al (21)	20	51	7	44	11.0%	3.41 [1.27, 9.12]
Hsu et al (25)	17	45	4	38	9.3%	5.16 [1.56, 17.11]
Lalueza et al (32)	3	13	17	50	7.7%	0.58 [0.14, 2.40]
Lodise et al (36)	6	66	0	26	2.7%	5.69 [0.31, 104.78]
Moise et al (41)	11	14	5	20	6.5%	11.00 [2.16, 56.09]
Moise-Broder et al (42)	23	25	22	38	6.8%	8.36 [1.72, 40.68]
Takesue et al (53)	34	97	85	662	15.9%	3.66 [2.28, 5.89]
Yoon et al (58)	14	18	17	45	8.8%	5.76 [1.63, 20.41]
Total (95% CI)		**424**		**1015**	**100.0%**	**2.69 [1.60, 4.51]**
Total events	163		188			

Heterogeneity: Tau² = 0.38; Chi² = 22.59, df = 10 (P = 0.01); I² = 56%

Test for overall effect: Z = 3.75 (P = 0.0002)

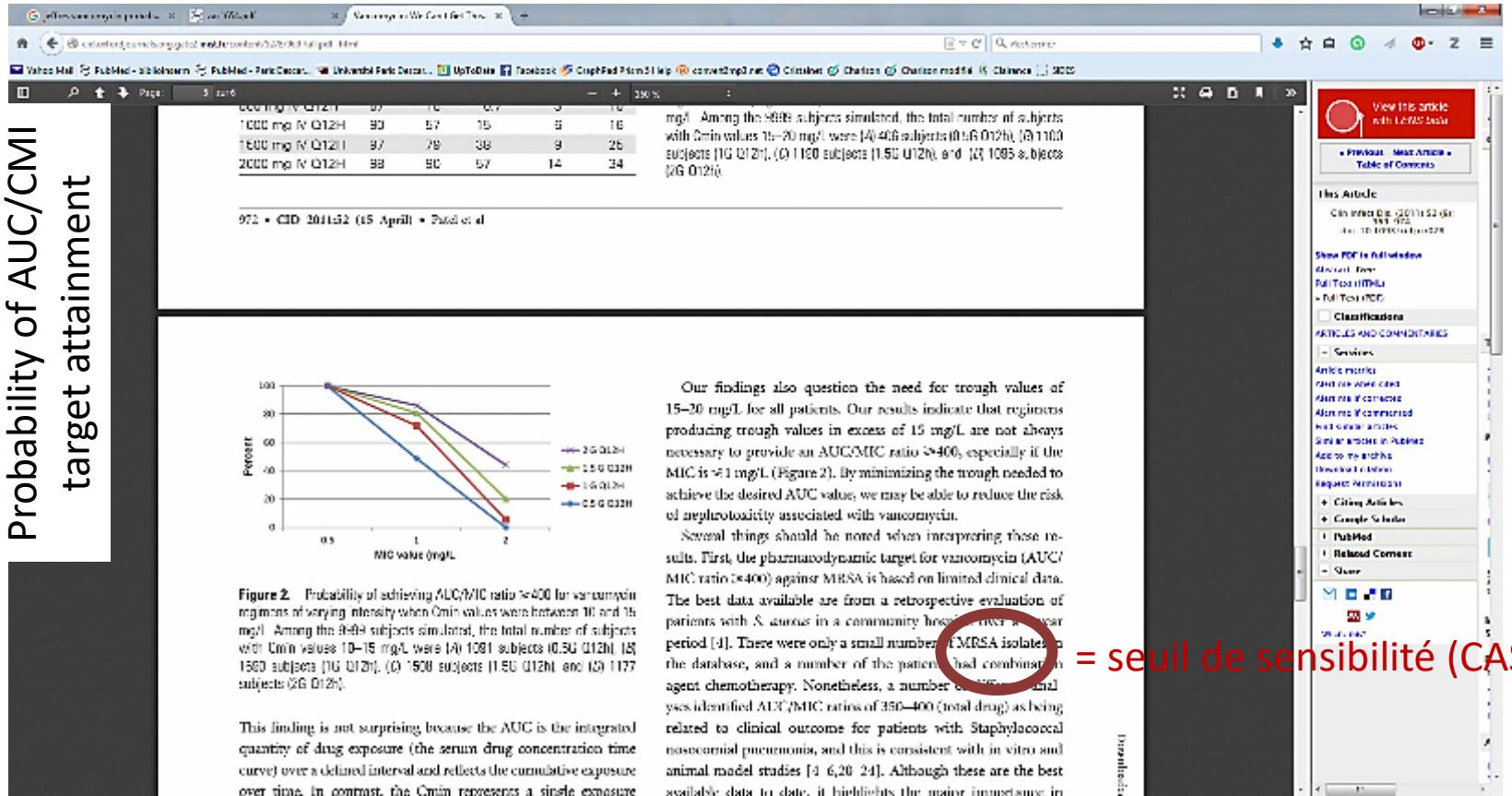


Bactériémie à *S. aureus* méti-R

Vancomycin: We Can't Get There From Here

Nimish Patel,[1] Manjunath P. Pai,[1] Keith A. Rodvold,[5] Ben Lomaestro,[3,4] George L. Drusano,[2] and Thomas P. Lodise[1,2]

[1]Albany College of Pharmacy and Health Sciences, [2]Ordway Research Institute, [3]Albany Medical Center Hospital; [4]Albany Medical College, Albany, New York; and [5]University of Illinois at Chicago, Chicago, Illinois



= seuil de sensibilité (CASFM)

Bactériémie à *S. aureus* méti-R : glycopeptides

Infect Drug Resist. 2018; 11: 1073–1081.
Published online 2018 Aug 6. doi: 10.2147/IDR.S159447
PMCID: PMC6084090
PMID: 30122964

Clinical outcomes after initial treatment of methicillin-resistant *Staphylococcus aureus* infections

Nobuaki Shime,[1,2] Nobuyuki Saito,[3] Miya Bokui,[4] Naoki Sakane,[5] Mitsuhiro Kamimura,[6] Tsutomu Shinohara,[7] Tadashi Kosaka,[8] Hisashi Ishikura,[9] and Atsuko Kobayashi[10]

245 infections à SARM

Variable	All patients (n=245)	Anti-MRSA pharmaceuticals			
		Vancomycin (n=174)	Linezolid (n=38)	Daptomycin (n=11)	Teicoplanin (n=22)
Age, years	71 (61–79)	71 (60–78)	74 (65–79)	70 (65–74)	65 (53–82)
Men	176 (71.8)	121 (69.5)	26 (68.4)	11 (100)	18 (81.8)
APACHE II	12 (8–20)	11 (8–19)	15 (9–23)	11 (7–12)	12 (8–16)
Charlson score	3 (1–4)	3 (1–5)	2 (1–4)	2 (0–3)	2 (0–3)
History of					
Diabetes mellitus*	90 (36.7)	75 (43.1)	6 (15.8)	3 (27.3)	6 (27.3)
End-stage renal disease	43 (17.6)	34 (19.5)	5 (13.2)	1 (9.1)	3 (13.6)
Cancer	67 (27.3)	40 (23.0)	16 (42.1)	4 (36.4)	6 (27.3)
Liver disease	23 (9.4)	16 (9.2)	4 (10.5)	2 (18.2)	0
Infectious source					
Bacteraemia[a]	69 (28.2)	56 (32.2)	6 (15)	2 (18.2)	5 (22.7)
Lung*	105 (42.9)	72 (41.4)	29 (76.3)	1 (9.1)	3 (13.6)
Skin and soft tissue*	73 (29.8)	50 (28.7)	5 (13.2)	7 (63.6)	11 (50.0)
Bone and joint	21 (8.6)	14 (8.0)	2 (5.3)	2 (18.2)	3 (13.6)
Others[b]	38 (13.5)	28 (16.1)	5 (13.2)	1 (9.1)	4 (18.2)
SOFA score					
Day 0*	2 (0–6)	2 (0–6)	4 (2–7)	2 (1–7)	0 (0–3)
Days 2–3 (n=244)	2 (0–5)	2 (0–5)	3 (1–6)	1 (0–6)	0 (0–4)
Days 5–7 (n=243)	2 (0–4)	1 (0–4)	3 (0–5)	1 (0–2)	0 (0–3)
Intensive care unit admission*	83 (33.9)	55 (31.6)	20 (52.6)	7 (63.6)	1 (4.5)
Mechanical ventilation*	58 (23.7)	38 (21.8)	13 (34.2)	6 (54.5)	1 (4.5)
Days of initial therapy	11 (7–16)	12 (7–17)	8 (7–13)	11 (8–17)	10 (6–13)
Change in MRSA therapy*	66 (26.9)	38 (21.8)	3 (7.8)	3 (27.2)	6 (27.2)
Change or discontinuation of antimicrobial for adverse effect	17 (6.9)	11 (6.4)	5 (13.2)	0	1 (4.5)
Newly acquired renal dysfunction	35 (14.3)	30 (17.2)	3 (7.9)	0	2 (9.1)
30-day mortality, %	12.2	14.4	7.9	9.1	4.5

Bactériémie à *S. aureus* méti-R : glycopeptides

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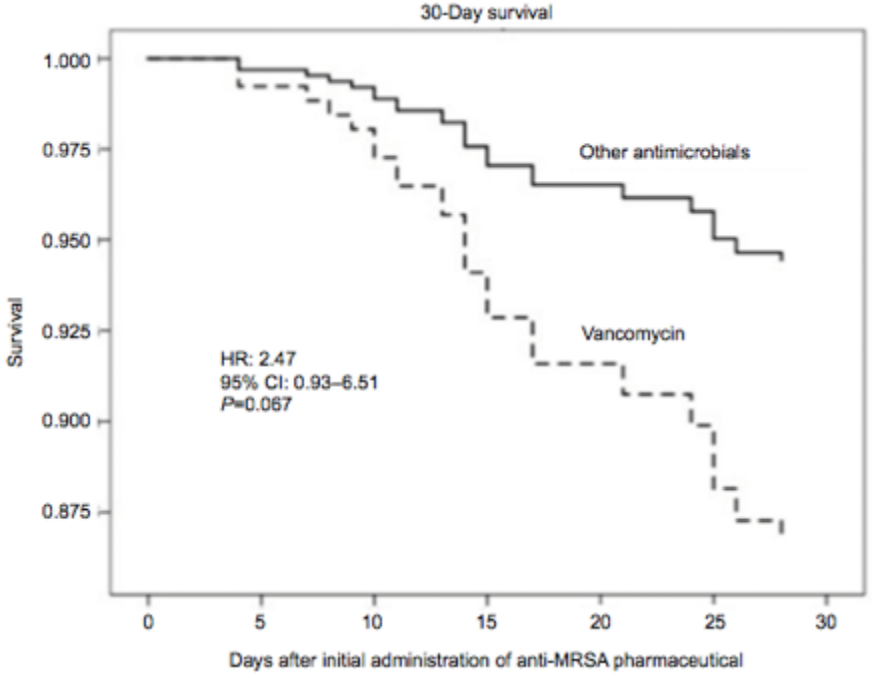
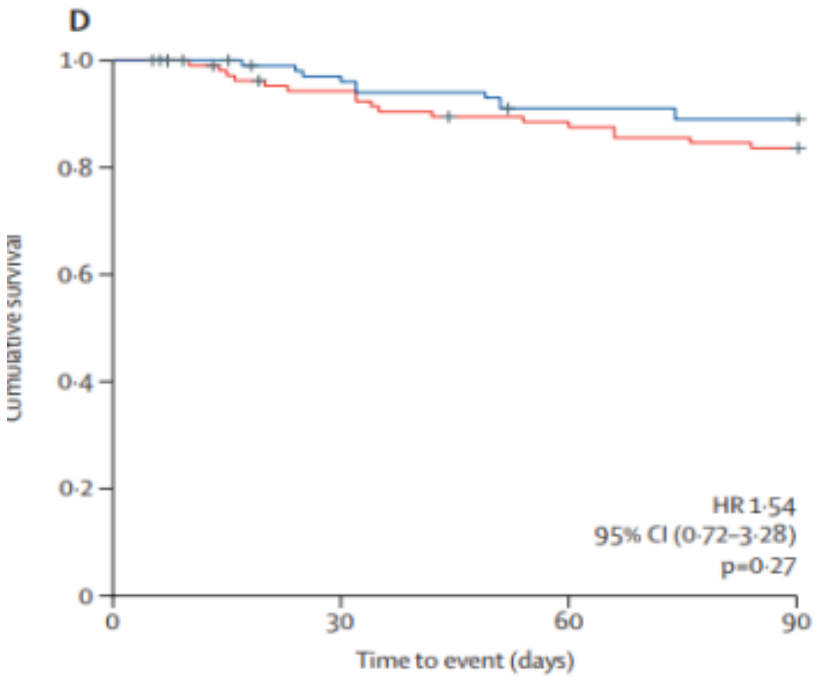


Variable	Cox model					
	Unadjusted			Adjusted		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Vancomycin versus non-vancomycin						
30-day mortality	2.28	0.88–5.93	0.09	2.47	0.93–6.51	0.06
Newly acquired renal dysfunction	2.65	1.02–6.83	0.04	1.99	0.76–5.18	0.15

Bactériémie à staphylocoque : relais per os ?

Efficacy and safety of an early oral switch in low-risk *Staphylococcus aureus* bloodstream infection (SABATO): an international, open-label, parallel-group, randomised, controlled, non-inferiority trial

*Achim J Kaasch, Luis Eduardo López-Cortés, Jesús Rodríguez-Baño, José Miguel Cisneros, M Dolores Navarro, Gerd Fätkenheuer, Norma Jung, Siegbert Rieg, Raphaël Lepeule, Laetitia Coutte, Louis Bernard, Adrien Lemaignen, Katrin Kösters, Colin R MacKenzie, Alex Soriano, Stefan Hagel, Bruno Fantin, Matthieu Lafaurie, Jean-Philippe Talarmin, Aurélien Dinh, Thomas Guimard, David Boutoille, Tobias Welte, Stefan Reuter, Jan Kluytmans, María Luisa Martín, Emmanuel Forestier, Hartmut Stocker, Virginie Vitrat, Pierre Tattevin, Anna Rommerskirchen, Marion Noret, Anne Adams, Winfried V Kern, Martin Hellmich, Harald Seifert, for the SABATO study group**



Essai ouvert randomisé

5 à 7 jours d'ATB IV puis relais PO
versus 14 jours IV

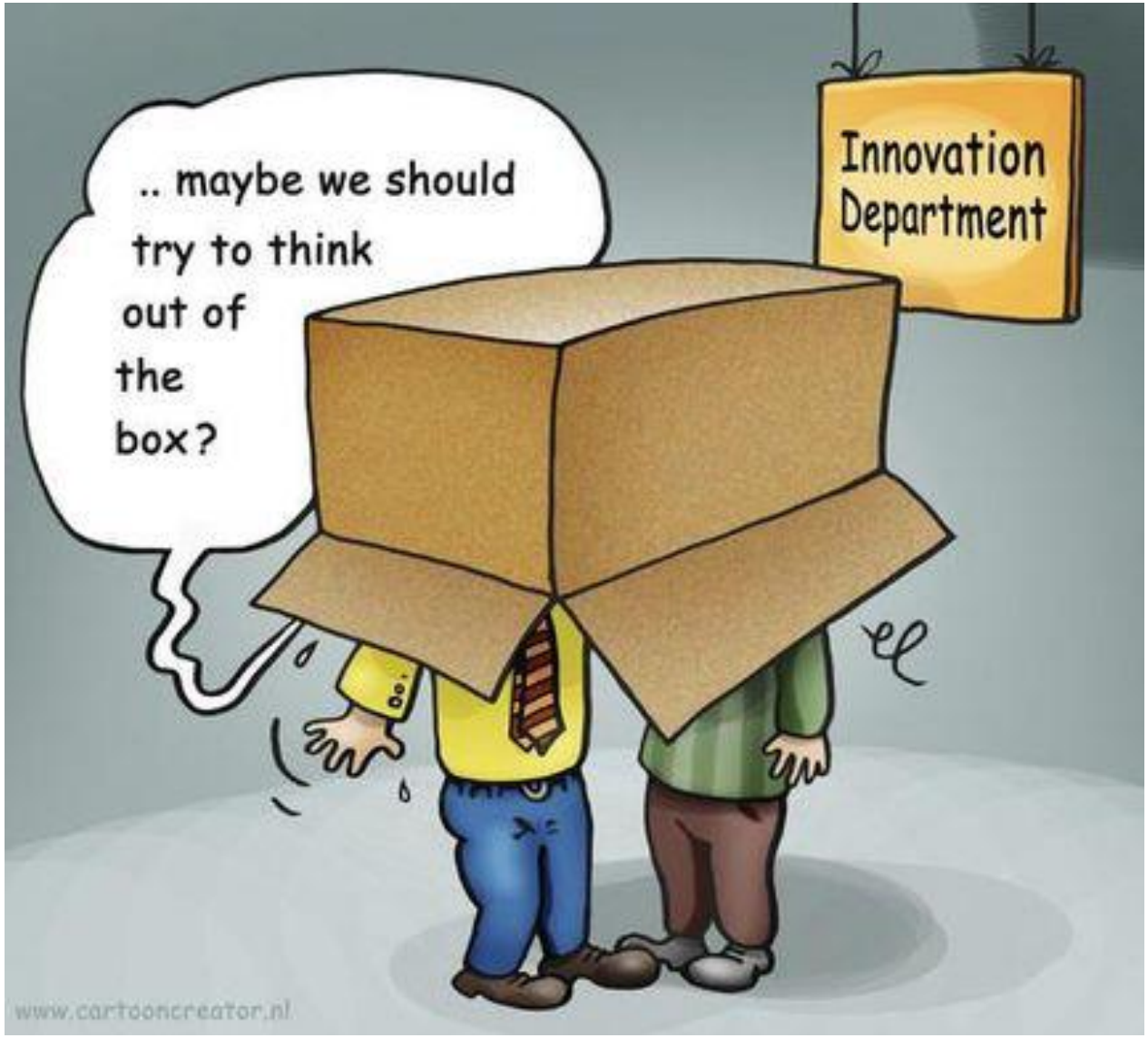
Exclusion

- Bactériémie compliquée (foyer profond, choc septique, bactériémie >72h)
- Ablation de cathéter non réalisée dans les 4j
- ATCD d'infection à S. aureus dans les 3 mois, toxicomanie IV, immunosuppression, prothèse cardiaque ou vasculaire ; PM ou prothèse articulaire

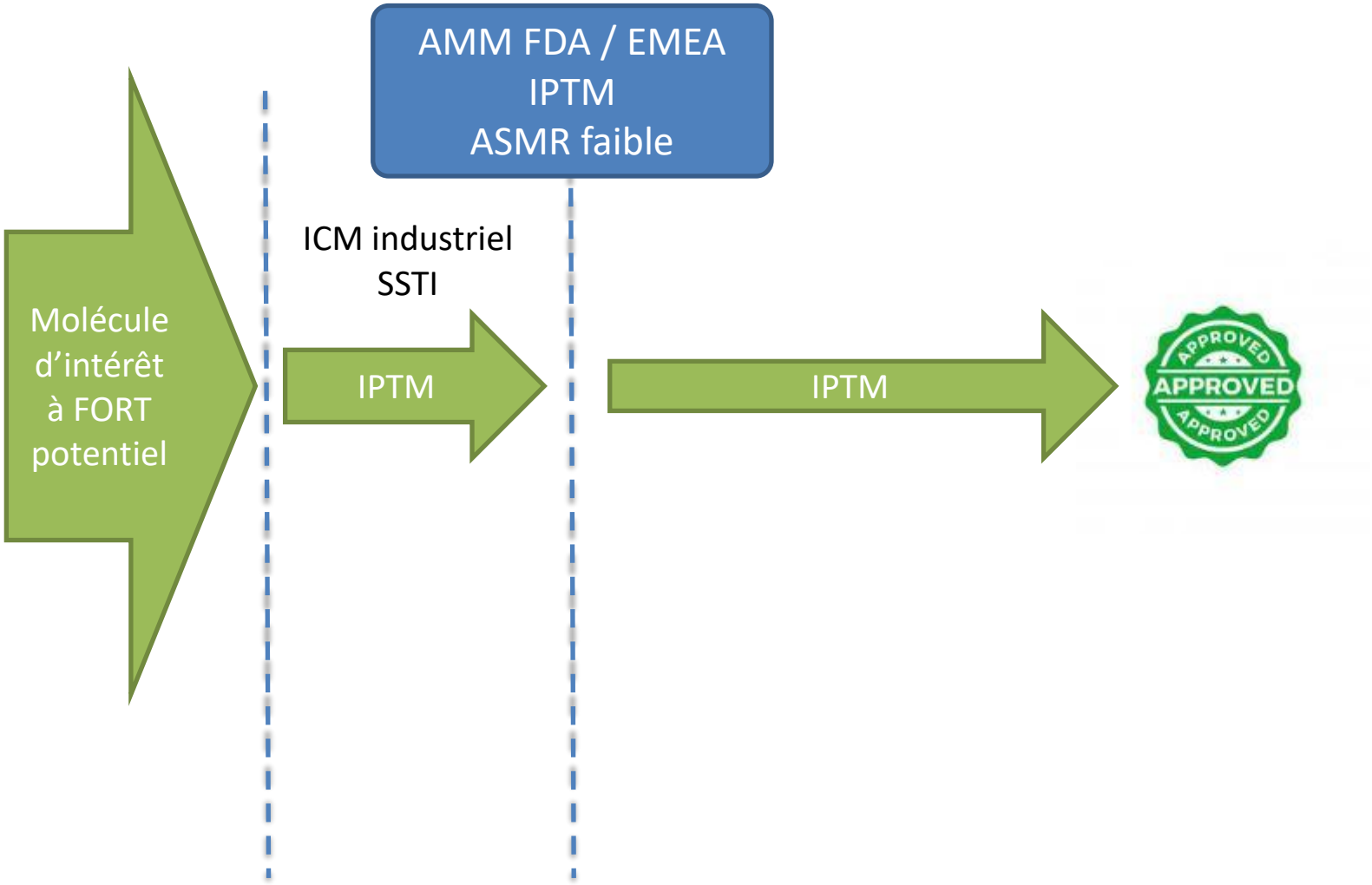
5063 patients screenés, 213 inclus

« Nouveaux » anti-staphylococciques

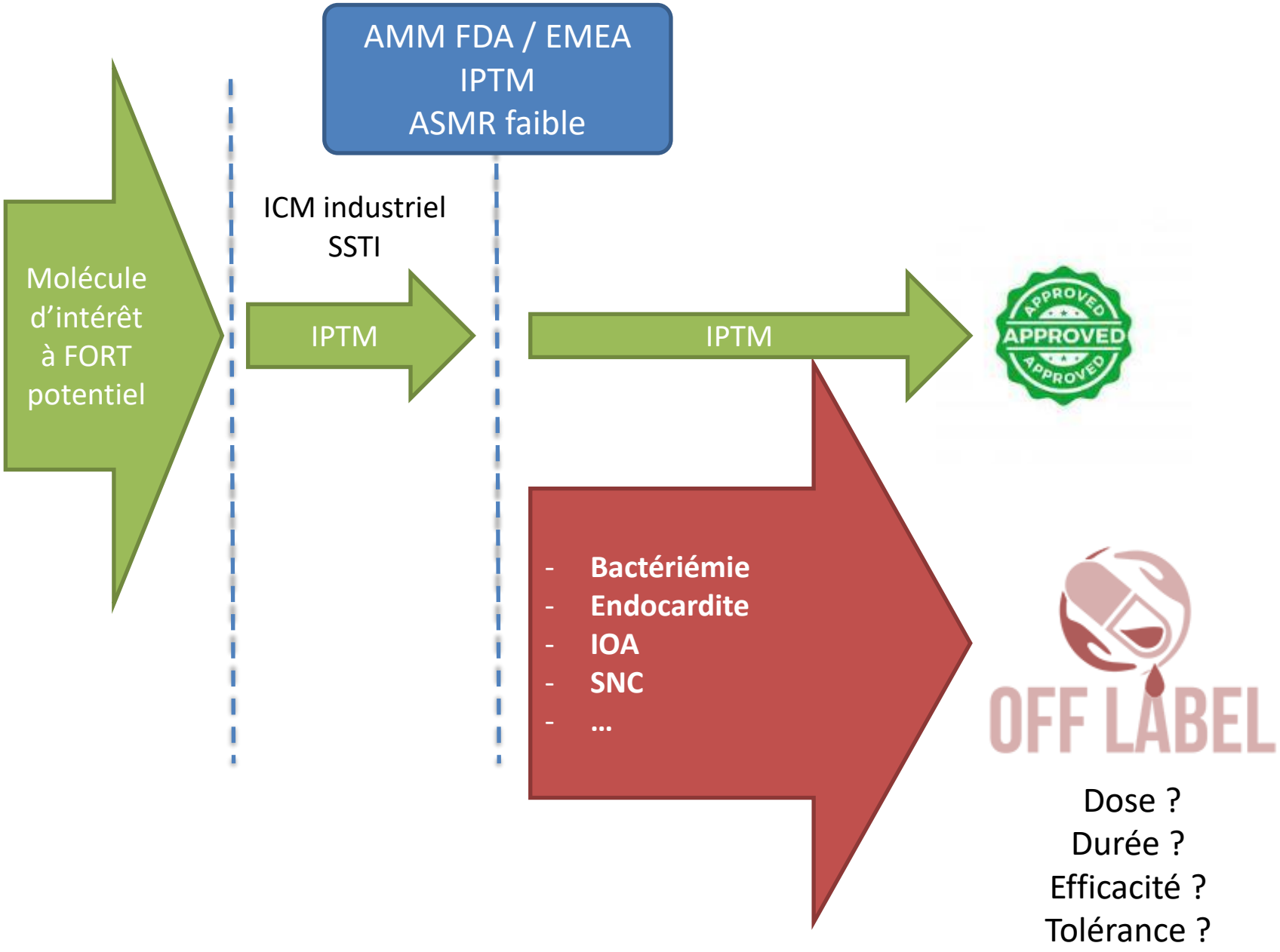
A garder en tête …



A garder en tête … (1)

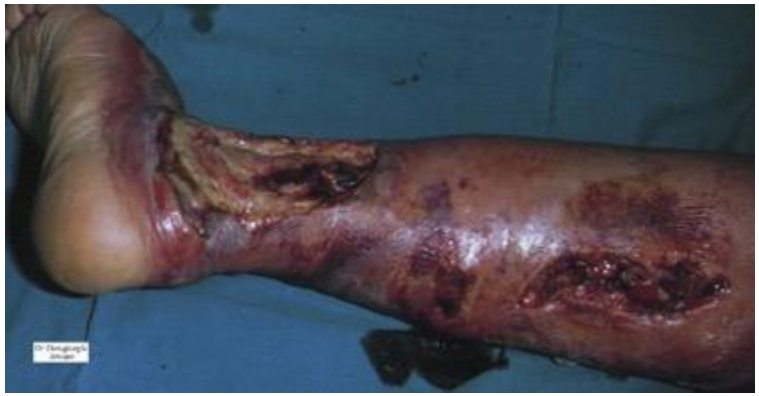


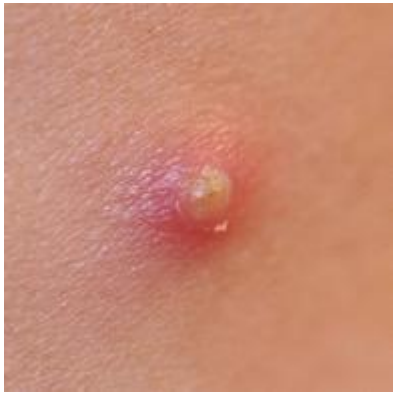
A garder en tête … (1)



A garder en tête … (2)

Infections « compliquées » de la peau et des tissus mous



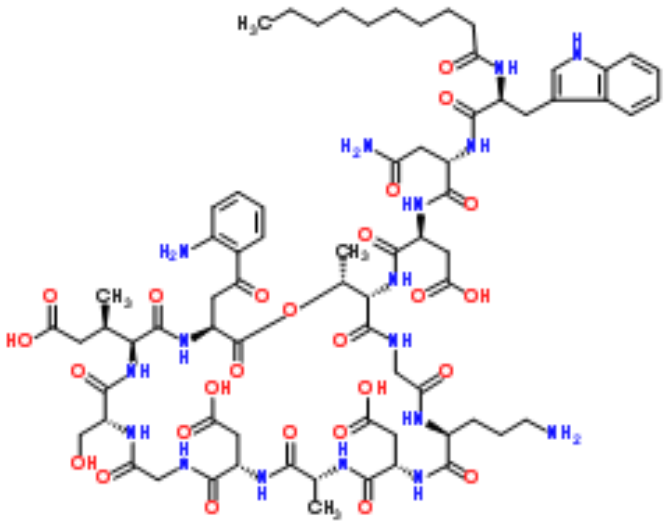


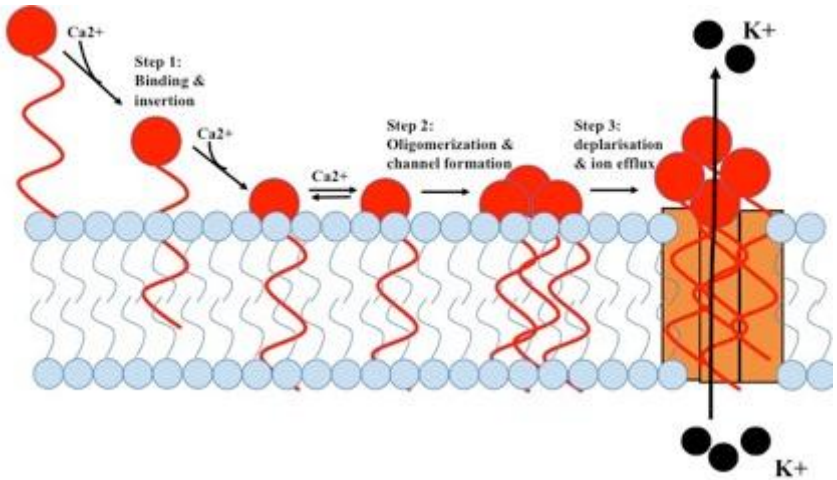
Age
Comorbidités
Bactériémie
Chirurgie
Documentation
Comparateur

A garder en tête … (3)

Daptomycine (CUBICIN®)

- **Classe :** lipopeptide
- **Cible :** membrane
- **Action :** bactéricidie rapide
- **Spectre :** cocci + dont SARM, ERV (CMI +++)
- **Biodisponibilité :** IV
- **Diffusion :** inact / surfactant
  Faible diffusion LCR
- **Posologie :** selon indication, 1/j
- **Adaptation :** 1/48h si DFG < 30
- **Coût :** 125 € / j (hospitalier)

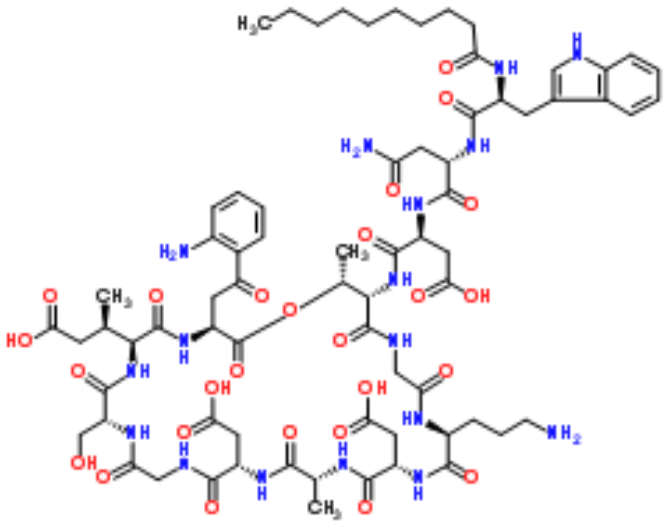


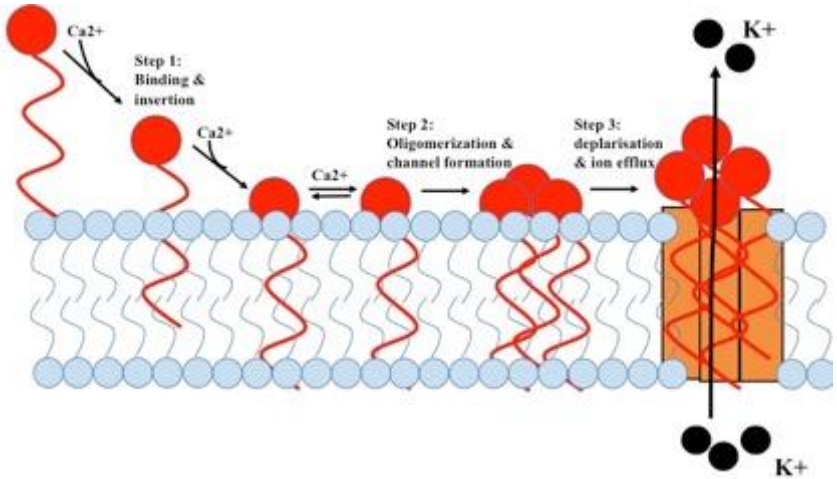


Daptomycine (CUBICIN®)

- **Classe :** lipopeptide
- **Cible :** membrane
- **Action :** bactéricidie rapide
- **Spectre :** cocci + dont SARM, ERV (CMI +++)
- **Biodisponibilité :** IV
- **Diffusion :** inact / surfactant
  Faible diffusion LCR
- **Posologie :** selon indication, 1/j
- **Adaptation :** 1/48h si DFG < 30
- **Coût :** [illegible] € / j (hospitalier)

Générique !!





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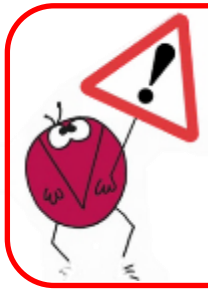
- **Adaptation :** 1/48h si DFG < 30
- **Coût :** 125 € / j (hospitalier)



- **Rhabdomyolyse +++**
ARRET DES STATINES, CPK
- **PNP éosinophiles**
- neuropathie périphérique
- IRA (rare)

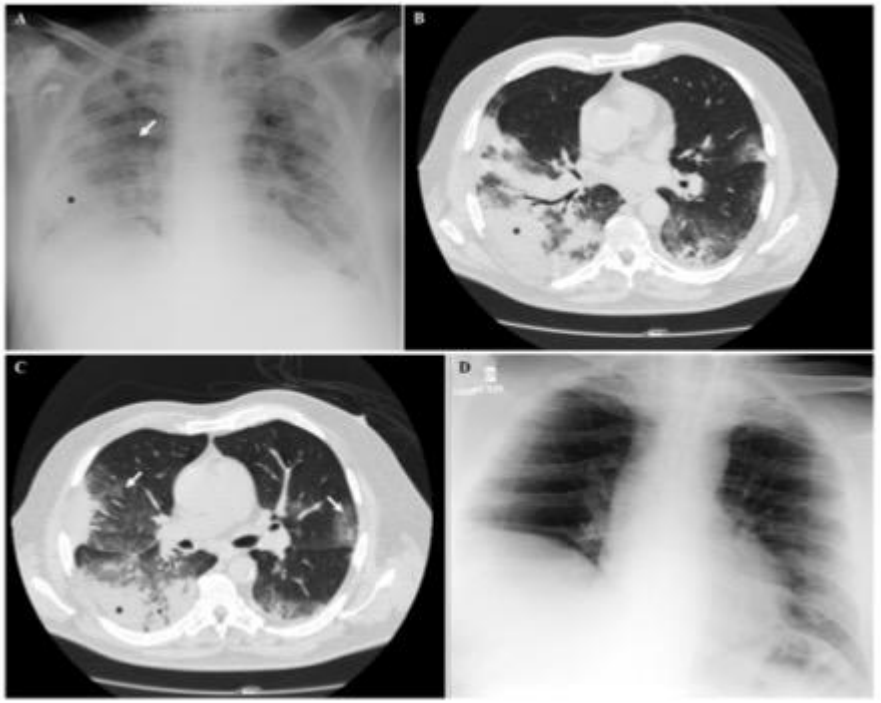
Seventeen Cases of Daptomycin-Induced Eosinophilic Pneumonia in a Cohort of Patients Treated for Bone and Joint Infections: Proposal for a New Algorithm

Truong-Thanh Phan, Romain Garreau, Fabien Craighero, Vincent Cottin, Benoit Ben Said, Sylvain Goutelle, and Tristan Ferry on behalf of the Lyon Bone and Joint Infection Study Group

Int J Infect Dis. 2015 Aug;37:95-6. doi: 10.1016/j.ijid.2015.06.010. Epub 2015 Jun 24.

Daptomycin-induced eosinophilic pneumonia.

Roux S[1], Ferry T[1], Chidiac C[1], Valour F[2].



Daptomycine (CUBICIN®)

APPROVED

Infections « compliquées » PTM

4-6 mg/kg/j

50 ans, peu de comorbidités

Critères d'exclusion

- Nécessité de chirurgie
- Bactériémies

Documentation : 12%
SARM : 18.5%

Optimisation vanco ?

The Safety and Efficacy of Daptomycin for the Treatment of Complicated Skin and Skin-Structure Infections

Robert D. Arbeit,[1,a] Dennis Maki,[2] Francis P. Tally,[1] Edward Campanaro,[1] Barry I. Eisenstein,[1] and the Daptomycin 98-01 and 99-01 Investigators
[1]Cubist Pharmaceuticals, Lexington, Massachusetts; and [2]University of Wisconsin Medical School, Madison

Clinical Infectious Diseases 2004; 38:1673–81

Daptomycine (CUBICIN®)

APPROVED

Infections « compliquées » PTM

4-6 mg/kg/j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[1]Cubist Pharmaceuticals, Lexington, Massachusetts; and [2]University of Wisconsin Medical School, Madison

Clinical Infectious Diseases 2004; 38:1673–81

EI du cœur droit

6 mg/kg/j


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 17, 2006 VOL. 355 NO. 7

Daptomycin versus Standard Therapy for Bacteremia and Endocarditis Caused by *Staphylococcus aureus*

Vance G. Fowler, Jr., M.D., M.H.S., Helen W. Boucher, M.D., G. Ralph Corey, M.D., Elias Abrutyn, M.D., Adolf W. Karchmer, M.D., Mark E. Rupp, M.D., Donald P. Levine, M.D., Henry F. Chambers, M.D.,

236 patients, SARM 40%, EI 22%

Daptomycine (6 mg/kg/j)

VERSUS vanco 1g/12h puis selon TR
ou péni M (2g/4h)
+ genta

NON INFERIORITE (toute bactériémie et MRSA, EI)

Daptomycine (CUBICIN®)

APPROVED

Infections « compliquées » PTM

4-6 mg/kg/j

EI du cœur droit

Bactériémie / EI ou SSTI

6 mg/kg/j

The Safety and Efficacy of Daptomycin for the Treatment of Complicated Skin and Skin-Structure Infections

Robert D. Arbeit,[1,a] Dennis Maki,[2] Francis P. Tally,[1] Edward Campanaro,[1] Barry I. Eisenstein,[1] and the Daptomycin 98-01 and 99-01 Investigators

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Daptomycine (CUBICIN®)

APPROVED

Infections « compliquées » PTM

4-6 mg/kg/j

EI du cœur droit

Bactériémie / EI ou SSTI

6 mg/kg/j

OFF-LABEL

EI forte dose 8-10 mg/kg

IOA > 6 mg/kg

Alternative à la vancomycine +++

- Allergie
- Insuffisance rénale / sujet âgé
- Abord veineux
- Echec
- CMI > 1 mg/L

The Safety and Efficacy of Daptomycin for the Treatment of Complicated Skin and Skin-Structure Infections

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AAC

High-Dose Daptomycin Therapy for Left-Sided Infective Endocarditis: a Prospective Study from the International Collaboration on Endocarditis

Manuela Carugati,[a,d] Arnold S. Bayer,[b] José M. Miró,[c] Lawrence P. Park,[d] Armenio C. Guimarães,[e] Athanasios Skoutelis,[f] Claudio Q. Fortes,[g] Emanuele Durante-Mangoni,[h] Margaret M. Hannan,[i] Francisco Nacinovich,[j] Nuria Fernández-Hidalgo,[k] Paolo Grossi,[l] Ru-San Tan,[m] Thomas Holland,[d] Vance G. Fowler, Jr.,[d] Ralph G. Corey,[d] Vivian H. Chu,[d] on behalf of the International Collaboration on Endocarditis

Daptomycin > 6 mg/kg/day in Patients with Complex Bone and Joint Infection: Prospective Cohort Study in a Regional Reference Center

S. Roux,[1, 2] F. Valour,[1, 2, 3] J. Karsenty,[1, 2, 3] MC Gagnieu,[1] T. Perpoint,[1] S. Lustig,[1, 2] B. Martha,[4] F. Laurent,[1, 2, 3] C. Chidiac,[1, 2, 3] T. Ferry,[1, 2, 3] on behalf of the Lyon BJI Study group

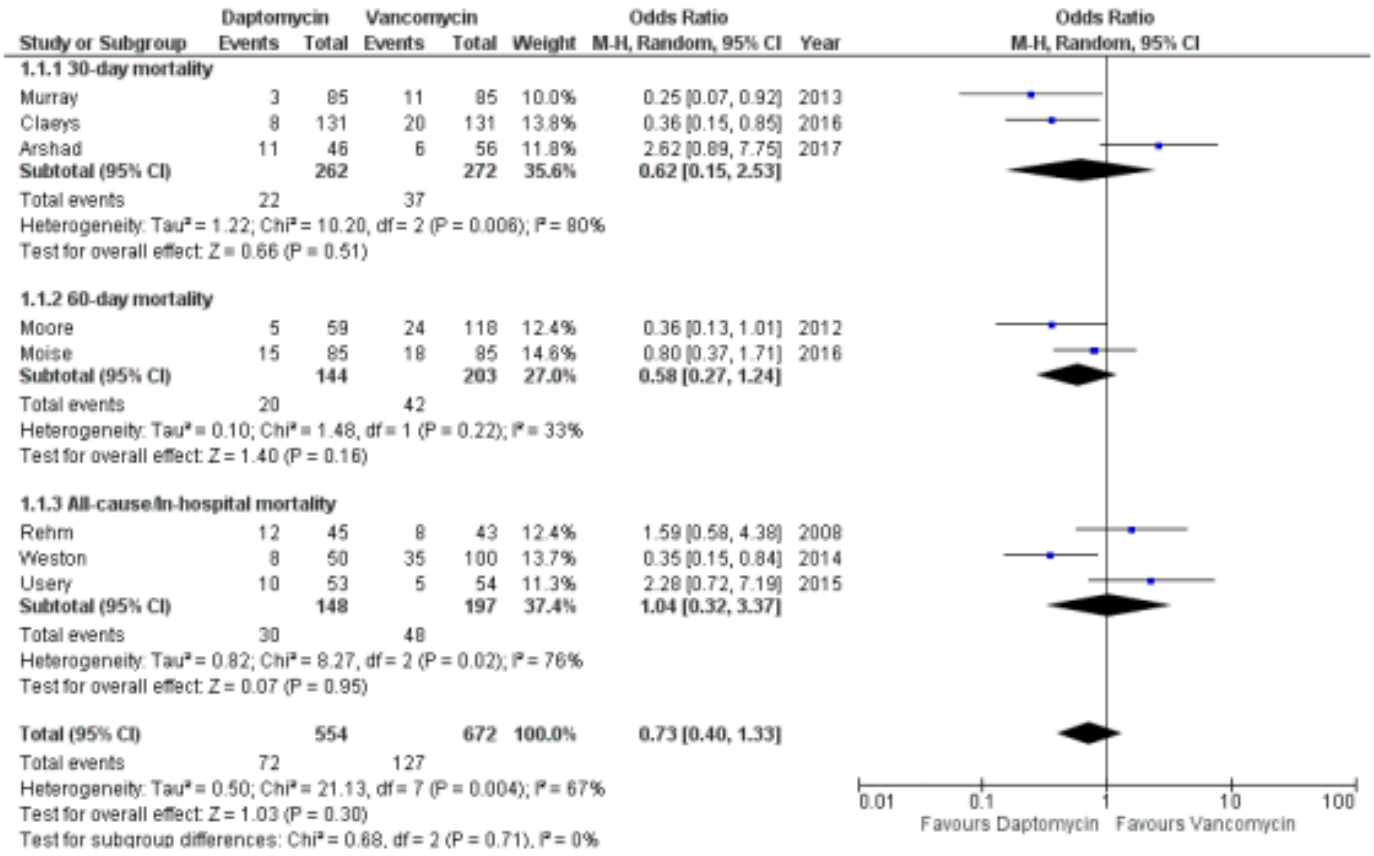
Daptomycine vs. Vancomycine

Review

Daptomycin versus Vancomycin for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infection with or without Endocarditis: A Systematic Review and Meta-Analysis

Alberto Enrico Maraolo [1,*], Agnese Giaccone [2], Ivan Gentile [2], Annalisa Saracino [3] and Davide Fiore Bavaro [3]

MORTALITE



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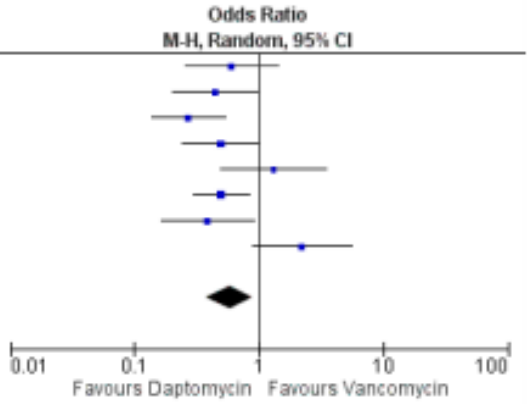
ECHEC CLINIQUE

Study or Subgroup	Daptomycin Events	Daptomycin Total	Vancomycin Events	Vancomycin Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Rehm	25	45	29	43	11.4%	0.60 [0.25, 1.44]	2008
Moore	10	59	37	118	12.4%	0.45 [0.20, 0.98]	2012
Murray	17	85	41	85	13.9%	0.27 [0.14, 0.53]	2013
Weston	17	50	51	100	13.5%	0.49 [0.24, 1.00]	2014
Usery	11	53	9	54	10.1%	1.31 [0.49, 3.48]	2015
Moise	38	131	59	131	16.4%	0.50 [0.30, 0.83]	2016
Claeys	9	85	20	85	11.5%	0.38 [0.16, 0.90]	2016
Arshad	15	46	10	56	10.7%	2.23 [0.89, 5.59]	2017
Total (95% CI)		**554**		**672**	**100.0%**	**0.58 [0.38, 0.89]**	
Total events	142		256				

Heterogeneity: Tau² = 0.22; Chi² = 17.35, df = 7 (P = 0.02); I² = 60%

Test for overall effect: Z = 2.52 (P = 0.01)

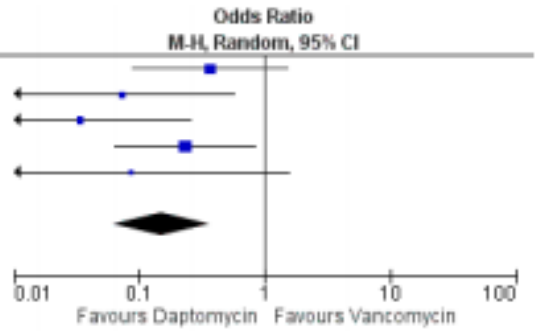


EFFETS SECONDAIRES

Study or Subgroup	Daptomycin Events	Daptomycin Total	Vancomycin Events	Vancomycin Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Rehm	3	45	7	43	28.0%	0.37 [0.09, 1.53]	2008
Moore	1	59	13	68	15.5%	0.07 [0.01, 0.58]	2012
Murray	1	85	22	85	16.0%	0.03 [0.00, 0.26]	2013
Claeys	3	131	12	131	32.1%	0.23 [0.06, 0.84]	2016
Moise	0	85	5	85	8.4%	0.09 [0.00, 1.57]	2016
Total (95% CI)		**405**		**412**	**100.0%**	**0.15 [0.06, 0.36]**	
Total events	8		59				

Heterogeneity: Tau² = 0.20; Chi² = 4.96, df = 4 (P = 0.29); I² = 19%

Test for overall effect: Z = 4.22 (P < 0.0001)



Daptomycine vs. Vancomycine

Systematic Review

Efficacy and Safety of Daptomycin versus Vancomycin for Bacteremia Caused by Methicillin-Resistant *Staphylococcus aureus* with Vancomycin Minimum Inhibitory Concentration > 1 µg/mL: A Systematic Review and Meta-Analysis

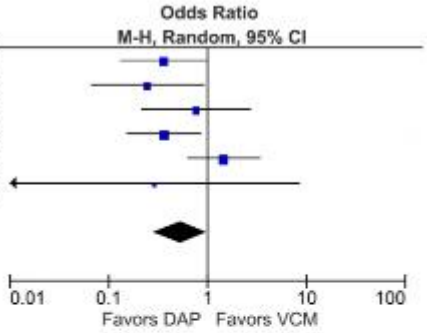
Masaru Samura [1,†], Yuki Kitahiro [1,†], Sho Tashiro [1], Hiromu Moriyama [1], Yuna Hamamura [1], Isamu Takahata [1], Rina Kawabe [1], Yuki Enoki [1,*], Kazuaki Taguchi [1], Yoshio Takesue [2,3] and Kazuaki Matsumoto [1]

MORTALITE

(A)

Study or Subgroup	DAP Events	DAP Total	VCM Events	VCM Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Moore 2012	5	59	24	118	19.8%	0.36 [0.13, 1.01]	2012
Murray 2013	3	85	11	85	14.5%	0.25 [0.07, 0.92]	2013
Cheng 2013	4	26	10	52	15.2%	0.76 [0.21, 2.72]	2013
Claeys 2016	8	131	20	131	23.5%	0.36 [0.15, 0.85]	2016
Moise 2016	15	85	11	85	23.9%	1.44 [0.62, 3.35]	2016
Kalimuddin 2018	0	7	1	7	3.1%	0.29 [0.01, 8.39]	2018
Total (95% CI)		**393**		**478**	**100.0%**	**0.53 [0.29, 0.98]**	
Total events	35		77				

Heterogeneity: Tau² = 0.23; Chi² = 8.42, df = 5 (P = 0.13); I² = 41%
Test for overall effect: Z = 2.03 (P = 0.04)

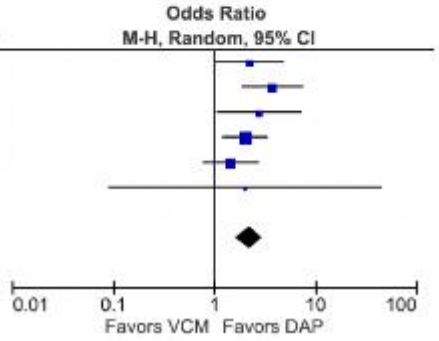


ECHECS CLINIQUES

(B)

Study or Subgroup	DAP Events	DAP Total	VCM Events	VCM Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Moore 2012	49	59	81	118	14.5%	2.24 [1.02, 4.90]	2012
Murray 2013	68	85	44	85	19.2%	3.73 [1.89, 7.36]	2013
Cheng 2013	16	26	19	52	9.4%	2.78 [1.05, 7.34]	2013
Claeys 2016	93	131	72	131	34.0%	2.01 [1.20, 3.34]	2016
Moise 2016	59	85	52	85	22.0%	1.44 [0.76, 2.72]	2016
Cubist 2018	6	7	3	4	0.9%	2.00 [0.09, 44.35]	2018
Total (95% CI)		**393**		**475**	**100.0%**	**2.20 [1.63, 2.96]**	
Total events	291		271				

Heterogeneity: Tau² = 0.00; Chi² = 4.37, df = 5 (P = 0.50); I² = 0%
Test for overall effect: Z = 5.19 (P < 0.00001)



Daptomycine vs. Bétalactamines

Clinical Outcomes of Daptomycin Versus Anti-Staphylococcal Beta-Lactams in Definitive Treatment of Methicillin-susceptible *Staphylococcus aureus* Bloodstream Infections

Sydney Agnello[a], Lynn C Wardlow[b], Erica Reed[b], Jessica M Smith[b], Kelci Coe[a], Shandra R Day[a,*]

Cohorte rétrospective, 89 patients

- 29 / daptomycine
- 30 / céfazoline
- 30 / nafcilline

	CEF (n = 30)	NAF (n = 30)	ASBL (n = 60)	DAP (n = 29)	*P*-value (ASBL vs. DAP)
Primary outcome					
Composite of the following	1 (3)	2 (7)	3 (5)	3 (10)	0.39
Clinical failure	0 (0)	0 (0)	0 (0)	1 (3)	0.33
MSSA recurrence	1 (3)	0 (0)	1 (2)	1 (3)	0.55
MSSA persistence	0 (0)	0 (0)	0 (0)	1 (3)	0.32
Inpatient infection-related mortality	0 (0)	2 (7)	2 (3)	0 (0)	1
Secondary outcomes					
Duration of MSSA bacteraemia (days)	2 (2.0,4)	3 (24)	2.5 (2–4)	2 (1–4)	0.74
Infection-related LOS (days)	11 (8–18)	8.5 (7–14)	9 (7–15.5)	18 (15–22)	< 0.0001
Hospital LOS (days)	13 (9–27)	9.5 (7–17)	11.5 (8–19)	20 (16–28)	0.0007
Infection-related 90-day readmission	2 (7)	2 (7)	4 (7)	3 (10)	0.68
30-day all-cause mortality	1 (3)	2 (7)	3 (5)	1 (3)	1
ADE requiring therapy change	0 (0)	0 (0)	0 (0)	0 (0)	

NS

Daptomycine (CUBICIN®)

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus Aureus* Infections in Adults and Children

Catherine Liu,[1] Arnold Bayer,[2,3] Sara E. Cosgrove,[5] Robert S. Daum,[7] Scot
Sheldon L. Kaplan,[10] Adolf W. Karchmer,[11] Donald P. Levine,[12] Barbara E.
A. Talan,[4,5] and Henry F. Chambers[1,2]

Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications

A Scientific Statement for Healthcare Professionals From the American Heart Association

Diagnosis and Management of Prosthetic Joint Infection: Clinical Practice Guidelines by the Infectious Diseases Society of America[a]

merli,[4] James M. Steckelberg,[1]

ELSEVIER

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Review

Medical treatment of prosthetic vascular graft infections: Review of the literature and proposals of a Working Group

M. Revest[a,b], F. Camou[c], E. Senneville[d], J. Caillon[e], F. Laurent[f], B. Calvet[g], P. Feugier[h], M. Batt[i], C. Chidiac[j,*], Groupe de Réflexion sur les Infections de Prothèses vasculaires (GRIP)[1]

Daptomycine (CUBICIN®)

High rate of decreasing daptomycin susceptibility during the treatment of persistent *Staphylococcus aureus* bacteremia

Sharma M and col

2008; 27:433

Emergence de résistance sous traitement

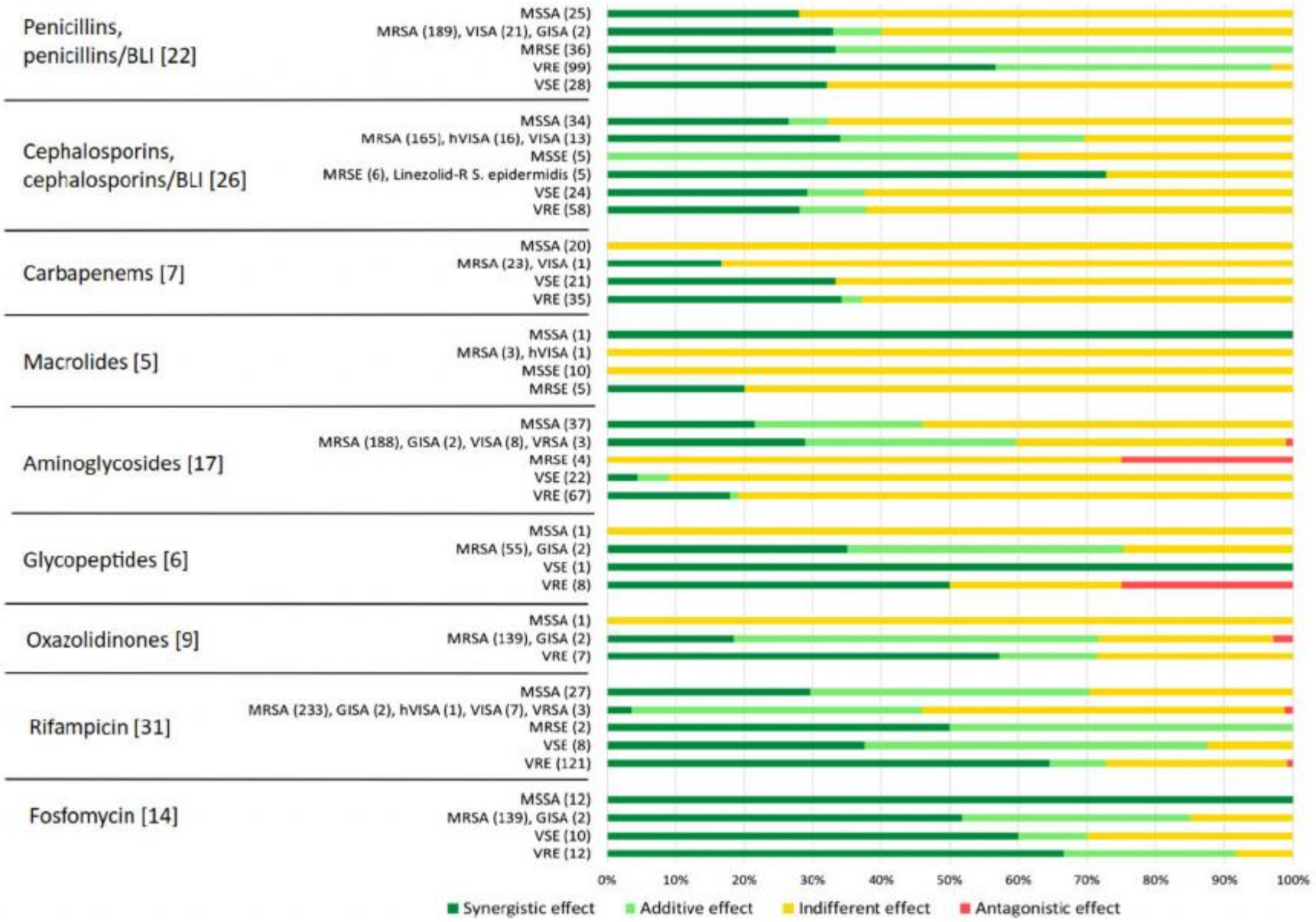
- Traitement prolongé
- Pré-exposition à la vancomycine

10 bactériémies persistantes / 74 patients traités par daptomycine
4 augmentation de CMI / 10

Case	(SCC*mec*)	DAP (day)	DAP dose mg/kg[a]	Pre-therapy MIC (µg/ml)	Post-therapy MIC (µg/ml) day					
					2–4	5–8	9–12	13–14	15–20	≥21
1	II	10	4; 6	ND[b]		0.125				
2	II	27	4	0.5	0.5	2	4	4	4	4
3	NA[c] (MSSA)	4	6	0.125		0.125				
4	II	18	5	0.25	0.25					
5	II	15	4; 6	ND		2		2	2	2
6	II	UD[d]	6	0.25						0.25
7	II	27	5	0.25						2
8	NT[e]	28	5	ND	0.5			2		2
9	IVa	26	4; 6	0.25	0.5		2	2		
10	II	13	5	0.5	0.5	1	2	2	2	

Daptomycin synergistic properties from *in vitro* and *in vivo* studies: a systematic review

Roberta Maria Antonello[1]*, Diana Canetti[2] and Niccolò Riccardi[3]



Daptomycine (CUBICIN®)

Clinical Therapeutics/Volume 36, Number 10, 2014

Daptomycin in Combination With Other Antibiotics for the Treatment of Complicated Methicillin-Resistant *Staphylococcus aureus* Bacteremia

Abhay Dhand, MD[1]; and George Sakoulas, MD[2]

Daptomycine + β-lactamines

- Augmentation surface d'action dapto
- y compris sur SARM
- Limite émergence de dapto-R
- Oxacilline, ceftaroline
- Données cliniques limitées (≈ 50 pts)

Adjuvant β-Lactam Therapy Combined with Vancomycin or Daptomycin for Methicillin-Resistant *Staphylococcus aureus* Bacteremia: a Systematic Review and Meta-analysis

Chunjiang Wang,[a] Chao Ye,[b] Linglong Liao,[c] Zhaohui Wang,[b] Ying Hu,[b] Chao Deng,[d] Liang Liu[e]

What do beta-lactams add to vancomycin or daptomycin in the treatment of patients with methicillin-resistant *Staphylococcus aureus* bacteraemia? A review

Laura García Aragonés , José Javier Blanch Sancho , Juan Carlos Segura Luque , Fernando Mateos Rodríguez , Elisa Martínez Alfaro , Julián Solís García del Pozo

- Meilleur succès microbiologique
- Durée de bactériémie réduite
- Pas d'impact sur la mortalité
- Alerte sur le risque de colite à CD+

Daptomycine (CUBICIN®)

Clinical Therapeutics/Volume 36, Number 10, 2014

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Abhay Dhand, MD[1]; and George Sakoulas, MD[2]

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- Augmentation surface d'action dapto
- y compris sur SARM
- Limite émergence de dapto-R
- Oxacilline, ceftaroline
- Données cliniques limitées (≈ 50 pts)

Daptomycine + fosfomycine

- Augmentation surface d'action dapto
- Modèle animal (IOA)
- Case reports (4)
- ECR (IDweek 2018)
  - Moins de bactériémie persistante
  - Moins de complications

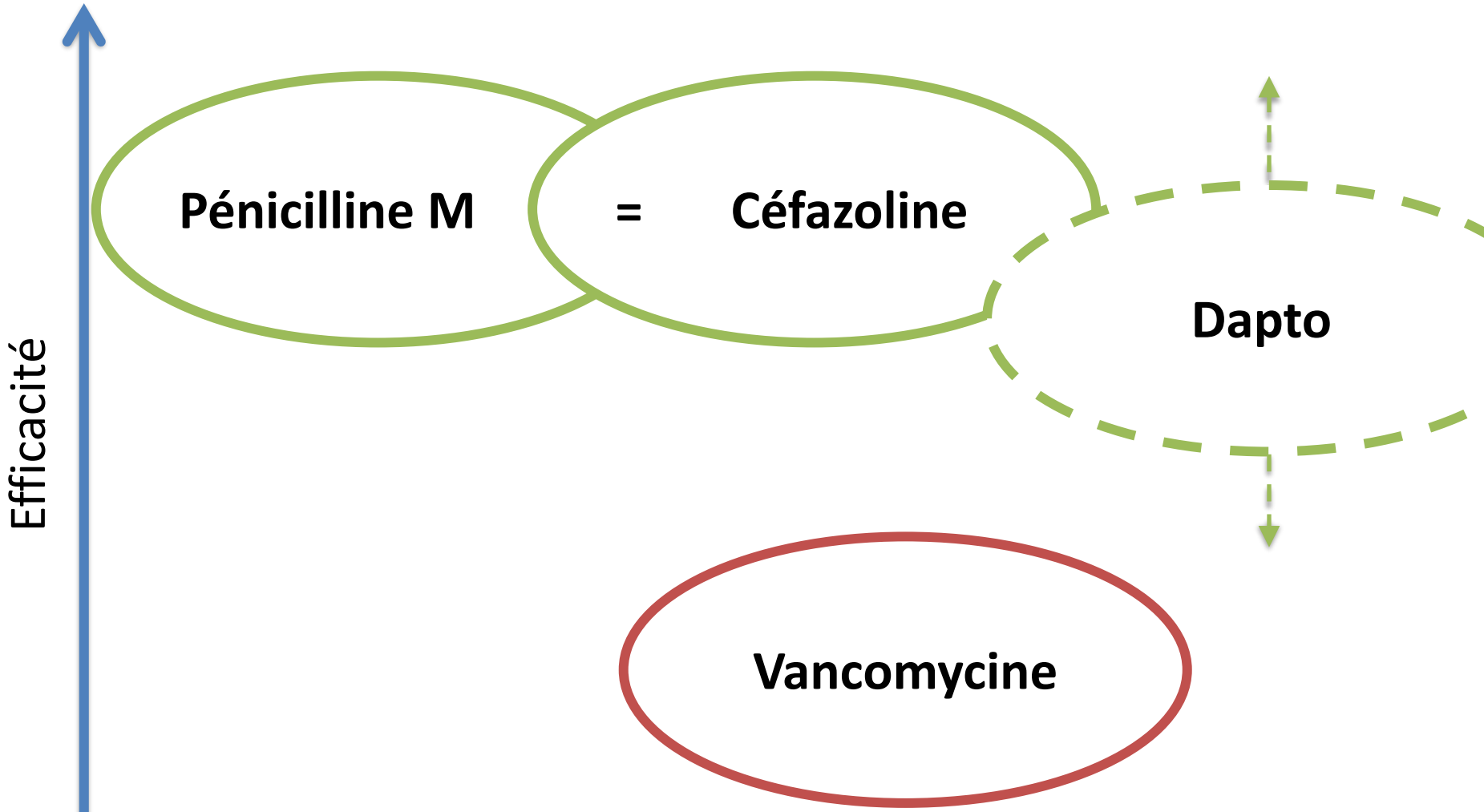
Daptomycine + rifampicine

- Synergie controversée
- Données cliniques : IOA surtout (environ 50 pts)

Daptomycine + cotrimoxazole

- Augmentation surface d'action dapto
- Données cliniques (environ 30 pts)

Bactériémie à staphylocoque

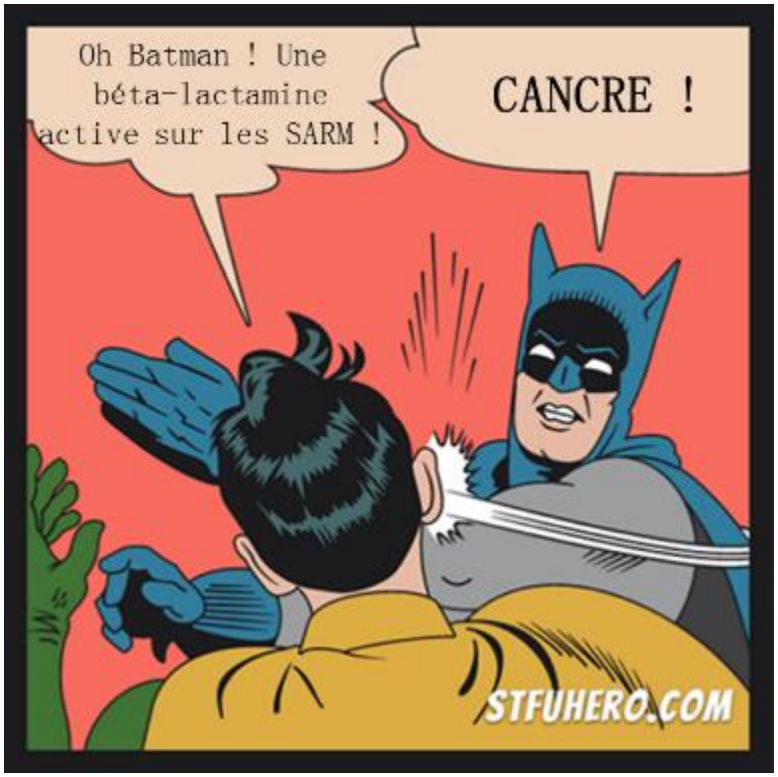


NE PAS UTILISER

C3G, amoxicilline – acide clavulanique, pipéracilline - tazobactam

Ceftaroline (ZINFORO®) – Ceftobiprole (MABELIO®)

- **Classe :** C5G ?
- **Cible :** paroi (PLP)
- **Action :** bactéricide
- **Spectre :** C2G anti-SARM
- **Biodisponibilité :** IV
- **Diffusion :** bonne
- **Posologie :** 600 mg/12h et 500 mg/8h
- **Adaptation :** selon DFG
- **Coût :** 180-200 € / j (hospitalier)



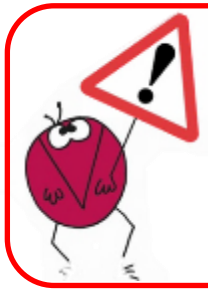
Ceftaroline (ZINFORO®) – Ceftobiprole (MABELIO®)

- **Classe :** C5G ?
- **Cible :** paroi (PLP)
- **Action :** bactéricide
- **Spectre :** C2G anti-SARM
- **Biodisponibilité :** IV
- **Diffusion :** bonne
- **Posologie :** 600 mg/12h et 500 mg/8h
- **Adaptation :** selon DFG
- **Coût :** 180-200 € / j (hospitalier)

High Incidence of Discontinuations Due to Adverse Events in Patients Treated with Ceftaroline

Rupali Jain,[1,2,*] Jeannie D. Chan,[2,3] Lisa Rogers,[1] Timothy H. Dellit,[4,5] John B. Lynch,[4,5] and Paul S. Pottinger[5,6]

(Pharmacotherapy 2014;34(7):758–763) doi: 10.1002/phar.1435



- Allergie
- Hématotoxicité ?

Neutropenia Associated with Long Term Ceftaroline Use

Katherine W. LaVie, M.D.,[a,*] Scott W. Anderson, M.D.,[a,*] Hollis R. O'Neal Jr., M.D., M.Sc.,[c#] Todd W. Rice, M.D., M.Sc.,[d] Tatiana C. Saavedra, M.D.[b] ,Catherine S. O'Neal, M.D. [b]

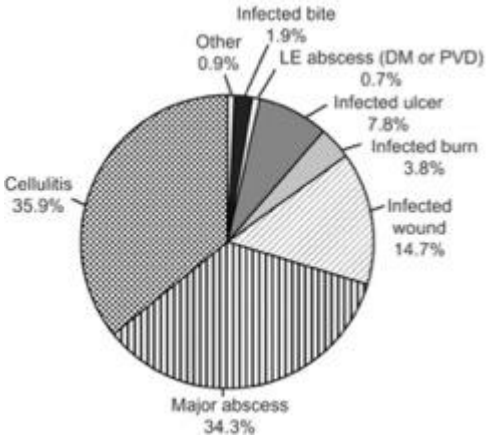
AAC Accepted Manuscript Posted Online 26 October 2015
Antimicrob. Agents Chemother. doi:10.1128/AAC.01471-15

39 patients, durée médiane 27 jours
NEUTROPENIE : 18%

Ceftaroline (ZINFORO®)

APPROVED

Infections « compliquées » PTM



Bactériémie 4%
Chirurgie 14%

Integrated Analysis of CANVAS 1 and 2: Phase 3, Multicenter, Randomized, Double-Blind Studies to Evaluate the Safety and Efficacy of Ceftaroline versus Vancomycin plus Aztreonam in Complicated Skin and Skin-Structure Infection

G. Ralph Corey,[1] Mark Wilcox,[4] George H. Talbot,[2*] H. David Friedland,[2] Tanya Baculik,[2] Gary W. Witherell,[2] Ian Critchley,[2] Anita F. Das,[3] and Dirk Thye[2]

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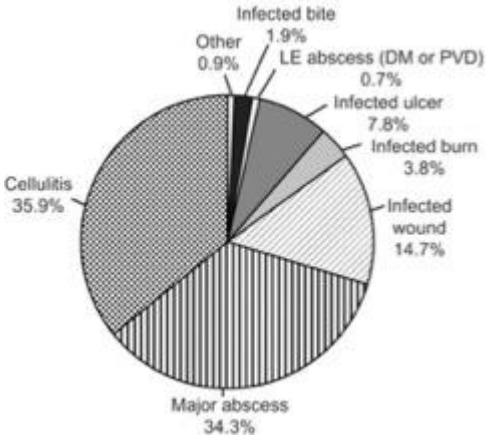
Clinical Infectious Diseases 2010; 51(6):641–650

Ceftaroline (ZINFORO®)

APPROVED

Infections « compliquées » PTM



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Clinical Infectious Diseases 2010; 51(6):641–650

Pneumopathies

J Antimicrob Chemother 2011; 66 Suppl 3: iii53 – iii59
doi:10.1093/jac/dkr099

Journal of Antimicrobial Chemotherapy

Integrated safety summary of FOCUS 1 and FOCUS 2 trials: Phase III randomized, double-blind studies evaluating ceftaroline fosamil for the treatment of patients with community-acquired pneumonia

Douglas R. Rank[1]*, H. David Friedland[1] and Joseph B. Laudano[2]

Peu de données :

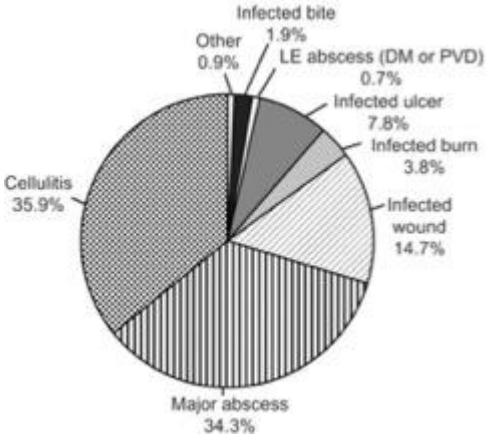
- Infections graves ?
- Immunodéprimés ?
- SARM, PSDP ?

stratégie thérapeutique	Dans le traitement des PAC La ceftaroline n'a pas démontré d'intérêt dans les pneumopathies communautaires en raison : - de l'absence de données d'efficacité en cas de pneumopathies à staphylocoque et à *S. pneumoniae* non sensibles à la pénicilline, - d'un risque de sélection de résistance du à son spectre trop large. En conséquence, la ceftaroline n'a pas de place dans les PAC compte tenu de l'existence d'alternatives thérapeutiques plus simples d'emploi et de spectre plus étroit.
Recommandations	**La Commission donne un avis :** - **favorable à l'inscription sur la liste des spécialités agréées à l'usage des collectivités dans l'indication « traitement des infections compliquées de la peau et des tissus mous »** - **défavorable à l'inscription sur la liste des spécialités agréées à l'usage des collectivités dans l'indication « pneumonies aiguë communautaire ».**

Ceftaroline (ZINFORO®)

APPROVED

Infections « compliquées » PTM



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OFF-LABEL

Bactériémies

48 patients, 63% de SARM

	SSTI	PNP
Succès clinique	52%	67%
si SARM	50%	63%

Ceftaroline Fosamil for the Treatment of *Staphylococcus aureus* Bacteremia Secondary to Acute Bacterial Skin and Skin Structure Infections or Community-Acquired Bacterial Pneumonia

Jose A. Vazquez, MD, FACP, FIDSA, Christy R. Maggiore, PharmD, BCPS,† Phillip Cole, MD,‡ Alexander Smith, MS,‡ Alena Jandourek, MD,‡ and H. David Friedland, MD, MBA‡*

Clinical Therapeutics/Volume 36, Number 10, 2014

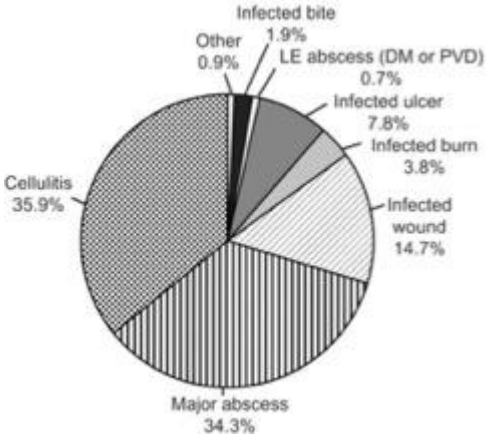
Original Research

Antimicrobial Salvage Therapy for Persistent Staphylococcal Bacteremia Using Daptomycin Plus Ceftaroline

Ceftaroline (ZINFORO®)

APPROVED

Infections « compliquées » PTM



Bactériémie 4%
Chirurgie 14%

Pneumopathies

OFF-LABEL

Bactériémies

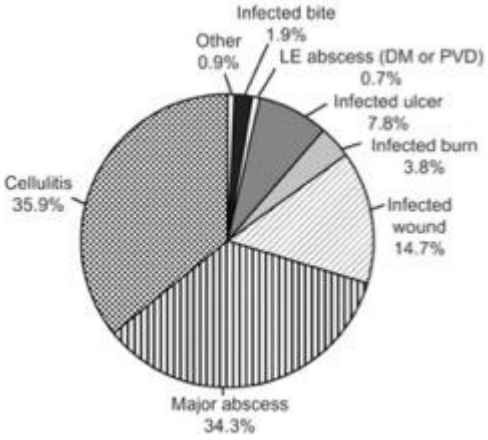
+ DAPTOMYCINE ?

Study	Patients (DAP+CPT)	Outcome
Johnson *et al.* IJAA 2021	60 (30)	OR ttt failure 0.23 (0.06-0.89)
McCreary et al. OFID 2020	171 (58)	vs SOC, † 6,8% vs 14,2%
Nichols *et al.* 2021	286 (66)	NS
Zasowski *et al.* AAC 2017*	126 (28)	69.7 and 64.9% treatment failure

Ceftaroline (ZINFORO®)

APPROVED

Infections « compliquées » PTM



Bactériémie 4%
Chirurgie 14%

Pneumopathies

OFF-LABEL

Bactériémies

Clinical Data on Daptomycin plus Ceftaroline versus Standard of Care Monotherapy in the Treatment of Methicillin-Resistant *Staphylococcus aureus* Bacteremia

Matthew Geriak,[a] Fadi Haddad,[b] Khulood Rizvi,[c] Warren Rose,[d] Ravina Kullar,[e] Kerry LaPlante,[f] Marie Yu,[b] Logan Vasina,[a] Krista Ouellette,[a] Marcus Zervos,[c] Victor Nizet,[f] George Sakoulas[a,g]

+ DAPTOMYCINE ?

40 patients with + MRSA Blood Culture
Identified By Verigene
Confirmed By Standard Microbiology Testing (MicroScan)

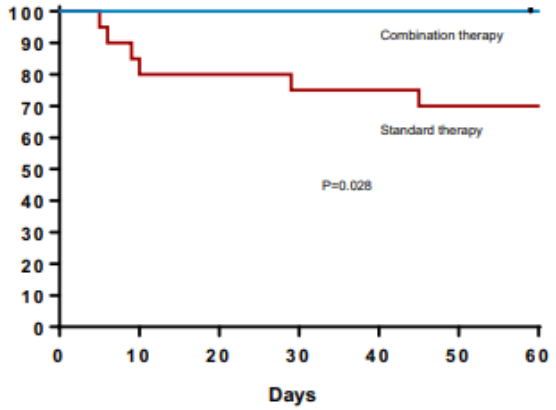
↓

Randomization Within 72 hrs

↙ ↘

17 Patients
Combination Therapy
Daptomycin + Ceftaroline

23 Patients
Standard Monotherapy
Vancomycin n=21; Daptomycin n= 2



Ceftaroline (ZINFORO®)

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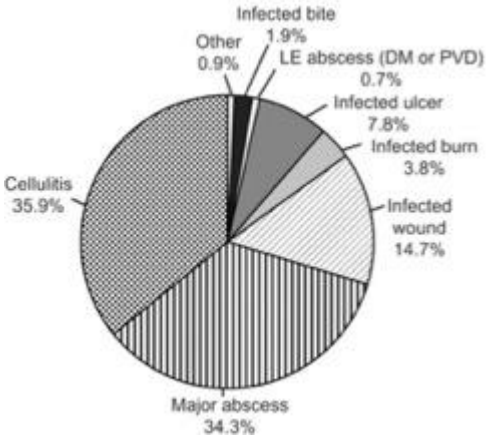
Infections « compliquées » PTM



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Douglas R. Rank[1]*, H. David Friedland[1] and Joseph B. Laudano[2]

OFF-LABEL

Bactériémies ?

EI ? IOA ? SNC ?

Ceftaroline-Fosamil Efficacy against Methicillin-Resistant *Staphylococcus aureus* in a Rabbit Prosthetic Joint Infection Model

Laure Gatin,[a] Azzam Saleh-Mghir,[a] Jason Tasse,[b] Idir Ghout,[c] Frédéric Laurent,[b] Anne-Claude Crémieux[a]

EA 3647, Faculté de Médecine Paris-Île-de-France Ouest, Université Versailles Saint-Quentin en Yvelines, Hôpital Raymond Poincaré, Garches, France[a]; Laboratoire de Bactériologie, Hôpital de la Croix Rousse, Centre National de Référence des Staphylocoques, INSERM Unité 851, Faculté de Médecine Lyon-Est, Lyon, France[b]; URC Paris-Ouest Laboratoire de Biostatistiques, Hôpital Ambroise Paré, Boulogne-Billancourt, France[c]

Antimicrobial Agents and Chemotherapy p. 6496–6500 November 2014 Volume 58 Number 11

J Antimicrob Chemother 2014
doi:10.1093/jac/dku085
Advance Access publication 28 March 2014

Salvage treatment of methicillin-resistant staphylococcal endocarditis with ceftaroline: a multicentre observational study

Pierre Tattevin[1,2]*, David Boutoille[2,3], Virginie Vitrat[4], Nicolas Van Grunderbeeck[5], Matthieu Revest[1,2], Mathieu Dupont[6], Serge Alfandari[7] and Jean-Paul Stahl[8]

Ceftobiprole (MABELIO®)

APPROVED

PAC (non remboursé)

A randomised, double-blind trial comparing ceftobiprole medocaril with ceftriaxone with or without linezolid for the treatment of patients with community-acquired pneumonia requiring hospitalisation

Susan C. Nicholson[a,*], Tobias Welte[b], Thomas M. File Jr[c], Richard S. Strauss[d], Bart Michiels[e], Pratibha Kaul[f], Dainius Balis[g], Deborah Arbit[g], Karen Amsler[g], Gary J. Noel[g,h]

PNP nosocomiales hors PAVM

A Phase 3 Randomized Double-Blind Comparison of Ceftobiprole Medocaril Versus Ceftazidime Plus Linezolid for the Treatment of Hospital-Acquired Pneumonia

Clin Infect Dis 2014

g Chuang,[3] Zsuszanna Marjanek,[4] Alex J. Pareigis,[5] Gilmar Reis,[6] Xin Zhou,[10] Mikaël Souley,[11] and Marc Engelhardt[12]

SMR	• le service médical rendu par MABELIO 500mg est : - <u>modéré</u> dans l'indication « traitement chez l'adulte, des pneumonies nosocomiales à l'exclusion des pneumonies acquises sous ventilation mécanique » - <u>insuffisant</u> dans l'indication « traitement chez l'adulte des pneumonies communautaires »
ASMR	• En l'état actuel des données, MABELIO n'apporte pas d'amélioration du service médical rendu (ASMR V, inexistante) par rapport aux thérapeutiques utilisées dans la prise en charge actuelle des pneumonies nosocomiales à l'exclusion des pneumonies acquises sous ventilation mécanique. • Pneumonies communautaires : sans objet
Place dans la stratégie thérapeutique	• Dans le traitement des pneumonies nosocomiales à l'exclusion des pneumonies acquises sous ventilation mécanique, la place de MABELIO est à l'heure actuelle difficile à préciser du fait de la documentation insuffisante de son efficacité clinique. Dans l'indication de l'AMM, MABELIO serait plus particulièrement réservé aux patients requérant un traitement par voie intra-veineuse, en cas d'infections à bactéries multi-résistantes (*Staphylococcus aureus* méti-R, *Streptococcus pneumoniae* péni-R) sensibles au ceftobiprole et lorsqu'il n'existe aucune alternative thérapeutique ou lorsque les autres alternatives thérapeutiques ne peuvent être utilisées. • Dans le traitement des pneumonies communautaires, le ceftobiprole n'a pas de place au regard des alternatives thérapeutiques existantes plus simples d'emploi et de spectre plus étroit, d'autant plus qu'il manque des données sur l'efficacité dans les pneumonies communautaires à SARM et vis-à-vis des souches de *S. pneumoniae* non sensibles à la pénicilline.

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PNP nosocomiales hors PAVM

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OFF-LABEL

Infections « compliquées » PTM

The efficacy and safety of ceftobiprole in the treatment of complicated skin and skin structure infections: evidence from 2 clinical trials

Stanley C. Deresinski*

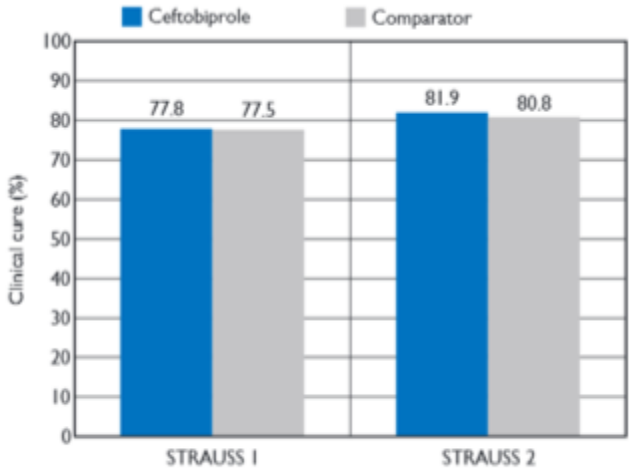

Figure 1 Clinical cure rates for the intent-to-treat population.
(Data from Noel GJ, Straus RS, Amsler K, et al. *Antimicrob Agents Chemother* 2008; 52:37–44;[24] and Noel GJ, Bush K, Bagchi P, et al. *Clin Infect Dis* 2008;46:647–655.[26])

vs VANCO (1)
vs VANCO-CEFTA (2)

Cellulitis < 20%

Ceftobiprole (MABELIO®)

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Stanley C. Deresinski*

Bactériémies ? EI ? IOA ? SNC ?

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 2005, p. 884–888 Vol. 49, No. 3
0066-4804/05/$08.00+0 doi:10.1128/AAC.49.3.884–888.2005

Evaluation of Ceftobiprole in a Rabbit Model of Aortic Valve Endocarditis Due to Methicillin-Resistant and Vancomycin-Intermediate *Staphylococcus aureus*

Henry F. Chambers*

AAC

Evaluation of Ceftobiprole Activity against a Variety of Gram-Negative Pathogens, Including *Escherichia coli*, *Haemophilus influenzae* (β-Lactamase Positive and β-Lactamase Negative), and *Klebsiella pneumoniae*, in a Rabbit Meningitis Model

A. Stucki,[a] M. Cottagnoud,[b] F. Acosta,[b] U. Egerman,[c] J. Läuffer,[d] and P. Cottagnoud[a]

AAC

Ceftobiprole Efficacy *In Vitro* against Panton-Valentine Leukocidin Production and *In Vivo* against Community-Associated Methicillin-Resistant *Staphylococcus aureus* Osteomyelitis in Rabbits

Azzam Saleh-Mghir,[a,b] Oana Dumitrescu,[c] Aurélien Dinh,[a,b] Yassine Boutrad,[a,b] Laurent Massias,[d] Émilie Martin,[c] François Vandenesch,[c] Jérôme Etienne,[c] Gérard Lina,[c] and Anne Claude Crémieux[a,b]

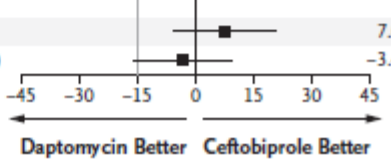
Ceftobiprole (MABELIO®)

Ceftobiprole for Treatment of Complicated *Staphylococcus aureus* Bacteremia

T.L. Holland, S.E. Cosgrove, S.B. Doernberg, T.C. Jenkins, N.A. Turner, H.W. Boucher, O. Pavlov, I. Titov, S. Kosulnykov, B. Atanasov, I. Poromanski, M. Makhviladze, A. Anderzhanova, M.E. Stryjewski, M. Assadi Gehr, M. Engelhardt, K. Hamed, D. Ionescu, M. Jones, M. Saulay, J. Smart, H. Seifert, and V.G. Fowler, Jr., for the ERADICATE Study Group*

RCT ceftobiprole vs daptomycine
n=387

Subgroup	Ceftobiprole	Daptomycin	Percentage-Point Difference (95% CI)
	no. of patients/total no. (%)		
All patients	132/189 (69.8)	136/198 (68.7)	2.0 (–7.1 to 11.1)
Age at written informed consent			
18 to <65 yr	98/131 (74.8)	101/135 (74.8)	0.6 (–9.8 to 10.9)
≥65 yr	34/58 (59)	35/63 (56)	6.9 (–10.5 to 24.3)
Sex			
Male	93/128 (72.7)	92/140 (65.7)	8.0 (–2.8 to 18.8)
Female	39/61 (64)	44/58 (76)	–11.3 (–27.7 to 5.1)
Baseline category of complicated *S. aureus* bacteremia			
Soft-tissue infection	81/116 (69.8)	80/121 (66.1)	4.5 (–7.3 to 16.3)
S. aureus bacteremia excluding soft-tissue infection	51/73 (70)	56/77 (73)	–1.7 (–15.9 to 12.6)
Osteoarticular infection	23/32 (72)	24/35 (69)	2.9 (–19.7 to 25.6)
Abdominal abscess	18/26 (69)	22/29 (76)	–9.7 (–33.3 to 13.9)
Hemodialysis	13/24 (54)	15/25 (60)	–4.6 (–32.5 to 23.3)
Persistent *S. aureus* bacteremia	8/16 (50)	8/16 (50)	–0.0 (–35.9 to 35.9)
Infective endocarditis on right side of heart	10/15 (67)	7/10 (70)	–6.6 (–40.1 to 27.0)
Baseline *S. aureus* infection			
Methicillin-susceptible	100/141 (70.9)	97/146 (66.4)	4.8 (–5.9 to 15.5)
Methicillin-resistant	31/45 (69)	38/49 (78)	–8.3 (–25.3 to 8.6)
Previous antibiotic use			
Yes	92/139 (66.2)	85/134 (63.4)	2.9 (–8.4 to 14.2)
No	40/50 (80)	51/64 (80)	–0.2 (–15.0 to 14.6)
Trial cohort			
Cohort 1	68/97 (70)	62/96 (65)	7.6 (–5.6 to 20.8)
Cohort 2	64/92 (70)	74/102 (72.5)	–3.4 (–16.1 to 9.3)



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T.L. Holland, S.E. Cosgrove, S.B. Doernberg, T.C. Jenkins, N.A. Turner, H.W. Boucher, O. Pavlov, I. Titov, S. Kosulnykov, B. Atanasov, I. Poromanski, M. Makhviladze, A. Anderzhanova, M.E. Stryjewski, M. Assadi Gehr, M. Engelhardt, K. Hamed, D. Ionescu, M. Jones, M. Saulay, J. Smart, H. Seifert, and V.G. Fowler, Jr., for the ERADICATE Study Group*

RCT ceftobiprole vs daptomycine
n=387

Table 1. Characteristics of the Patients at Baseline (Modified Intention-to-Treat Population).*

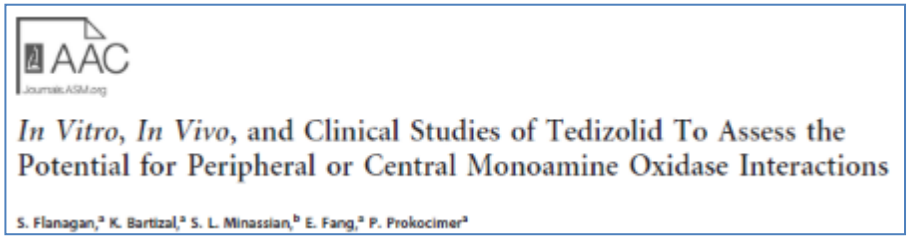
Characteristic	Ceftobiprole (N=189)	Daptomycin (N=198)	Overall (N=387)
Age — yr			
Median	57.0	58.0	58.0
Range	20–89	19–91	19–91
Median duration of administration of ceftobiprole or daptomycin (IQR) — days	21 (21–25)	21 (21–23)	21 (21–24)
Receipt of daptomycin at a daily dose >7 mg/kg — no. (%)	NA	22 (11.1)	
Categories of complicated *S. aureus* bacteremia — no. (%)‖			
Any complicated *S. aureus* bacteremia	189 (100.0)	198 (100.0)	387 (100.0)
Soft-tissue infections**	116 (61.4)	121 (61.1)	237 (61.2)
Osteoarticular infections††	32 (16.9)	35 (17.7)	67 (17.3)
Abdominal abscesses‡‡	26 (13.8)	29 (14.6)	55 (14.2)
Hemodialysis-associated *S. aureus* bacteremia§§	24 (12.7)	25 (12.6)	49 (12.7)
Persistent *S. aureus* bacteremia¶¶	16 (8.5)	16 (8.1)	32 (8.3)
Infective endocarditis on right side of heart	15 (7.9)	10 (5.1)	25 (6.5)

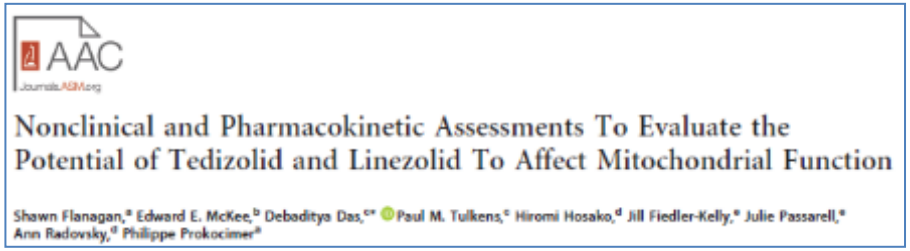
Tédizolide (SIVEXTRO®)

- **Classe :** oxazolidinone
- **Cible :** synthèse protéique
- **Spectre :** cocci+
- **Biodisponibilité :** IV = per os
- **Diffusion : ?**
- **Posologie :** 200 mg/24h
- **Adaptation :** non
- **Coût : 200 euros/j**

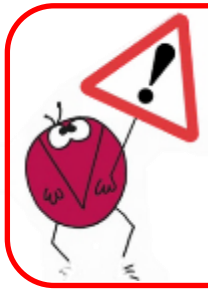
Tédizolide (SIVEXTRO®)

- **Classe :** oxazolidinone
- **Cible :** synthèse protéique
- **Spectre :** cocci+
- **Biodisponibilité :** IV = per os
- **Diffusion : ?**
- **Posologie :** 200 mg/24h
- **Adaptation :** non
- **Coût : 200 euros/j**





Plus forte inhibition des protéines mitochondriales mais liaison moins prolongée (effet cumulatif)
9 mois de ttt (rat) : moins d'EI neuro et hémato



- Hématotoxicité ?
- Neurotoxicité moindre que le LNZ ?

Tédizolide (SIVEXTRO®)

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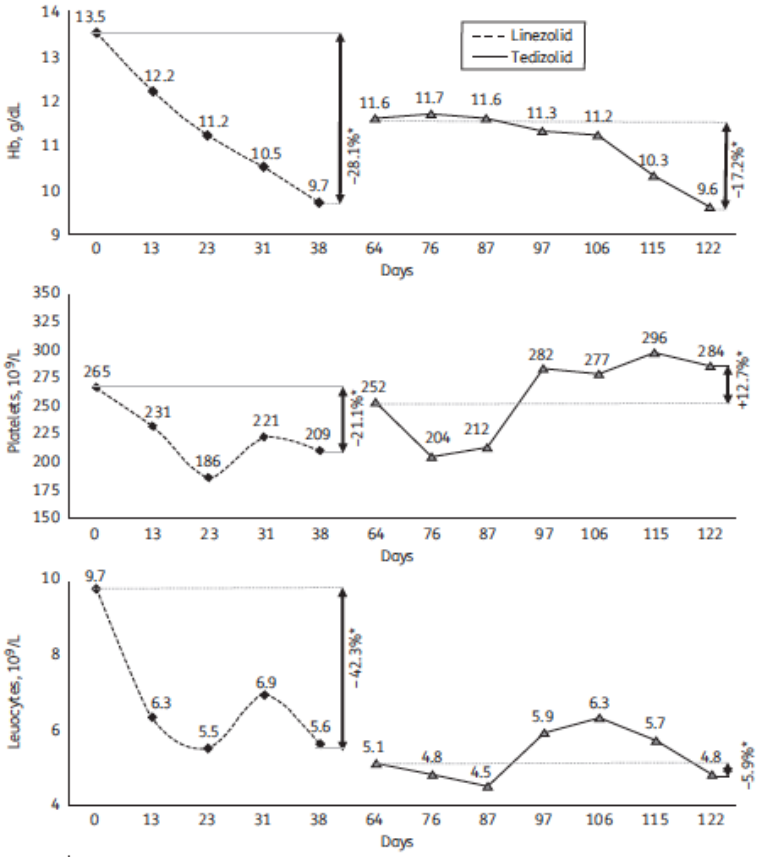
- **Cible :** synthèse protéique
- **Spectre :** cocci+
- **Biodisponibilité :** IV = per os
- **Diffusion : ?**
- **Posologie :** 200 mg/24h
- **Adaptation :** non
- **Coût : 200 euros/j**

J Antimicrob Chemother
doi:10.1093/jac/dkw484

Prolonged use of tedizolid in a pulmonary non-tuberculous mycobacterial infection after linezolid-induced toxicity

Jose R. Yuste[1,2]*, Juan Bertó[3], Jose L. Del Pozo[1,4] and Jose Leiva[4]

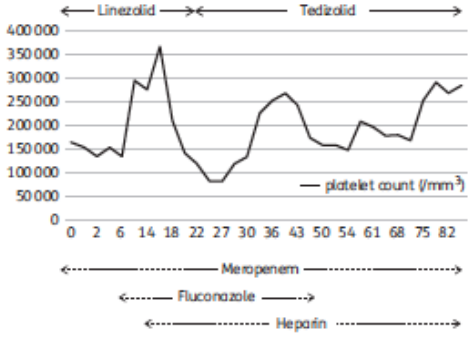


J Antimicrob Chemother
doi:10.1093/jac/dkx097

Correction of myelotoxicity after switch of linezolid to tedizolid for prolonged treatments

L. Khatchatourian[1], A. Le Bourgeois[2], N. Asseray[1], C. Biron[1], M. Lefebvre[1], D. Navas[3], M. Grégoire[4], B. Gaborit[1], F. Raffi[1] and D. Boutoille[1]*

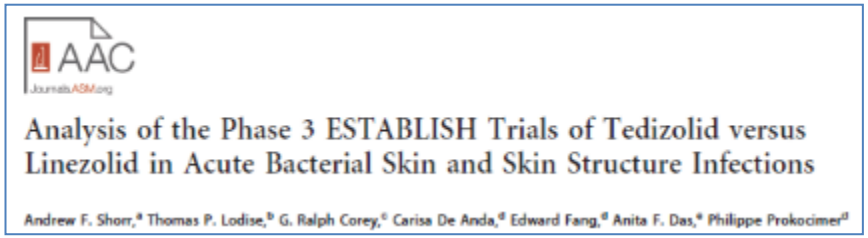
[1]*Infectious Diseases Department, University Hospital of Nantes, Nantes, France;* [2]*Clinical Haematology Department, University Hospital of Nantes, Nantes, France;* [3]*Clinical Pharmacology Department, University Hospital of Nantes, Nantes, France;* [4]*Pharmacy, University Hospital of Nantes, Nantes, France*



Tédizolide (SIVEXTRO®)

APPROVED

Infections « aiguës » PTM



2 RCT, 1 333 patients

Tedizolide 6 jours versus linézolide 10 jours
Cure rate > 85%, non infériorité

Age : 44 ans (10% > 65 ans)
Diabète : 10%

Fièvre : 23%
Bactériémie : 2%

Troubles digestifs +++

Tédizolide (SIVEXTRO®)

APPROVED

Infections « aiguës » PTM

AAC

Analysis of the Phase 3 ESTABLISH Trials of Tedizolid versus Linezolid in Acute Bacterial Skin and Skin Structure Infections

Andrew F. Shorr,[a] Thomas P. Lodise,[b] G. Ralph Corey,[c] Carisa De Anda,[d] Edward Fang,[d] Anita F. Das,[e] Philippe Prokocimer[d]

2 RCT, 1 333 patients

Tedizolide 6 jours versus linézolide 10 jours
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Age : 44 ans (10% > 65 ans)
Diabète : 10%

Fièvre : 23%
Bactériémie : 2%

Troubles digestifs +++

Quid des durées de traitements ?

La principale information apportée par ces essais serait-elle que 6 jours de traitement sont suffisants dans les infections cutanées ?!

Tédizolide (SIVEXTRO®)

APPROVED

Infections « aiguës » PTM

2 RCT, 1 333 patients

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OFF-LABEL

Bactériémies et EI ?

NON efficacité à la dose approuvée
(équivalent 200 mg/j)
Equivalence de doses 2-3 fois supérieures ?

Antimicrobial Agents and Chemotherapy

Comparative Efficacies of Tedizolid Phosphate, Linezolid, and Vancomycin in a Murine Model of Subcutaneous Catheter-Related Biofilm Infection Due to Methicillin-Susceptible and -Resistant *Staphylococcus aureus*

Arnold S. Bayer,[a,b] Wessam Abdelhady,[a] Liang Li,[a] Rochelle Gonzales,[a] Yan Q. Xiong[a,b]

AAC

Comparative Efficacies of Tedizolid Phosphate, Vancomycin, and Daptomycin in a Rabbit Model of Methicillin-Resistant *Staphylococcus aureus* Endocarditis

Liana C. Chan,[a,b] Li Basuino,[a] Etyene C. Diep,[a] Henry F. Chambers[a]

Division of Infectious Diseases, San Francisco General Hospital, San Francisco, California, USA[a]; Division of Molecular Medicine, Harbor-UCLA Medical Center, Torrance, California, USA[b]

Tédizolide (SIVEXTRO®)

APPROVED

Infections « aiguës » PTM

2 RCT, 1 333 patients

Tedizolide 6 jours versus linézolide 10 jours
Cure rate > 85%, non infériorité

AAC

Analysis of the Phase 3 ESTABLISH Trials of Tedizolid versus Linezolid in Acute Bacterial Skin and Skin Structure Infections

Andrew F. Shorr,[a] Thomas P. Lodise,[b] G. Ralph Corey,[c] Carisa De Anda,[d] Edward Fang,[d] Anita F. Das,[e] Philippe Prokocimer[d]

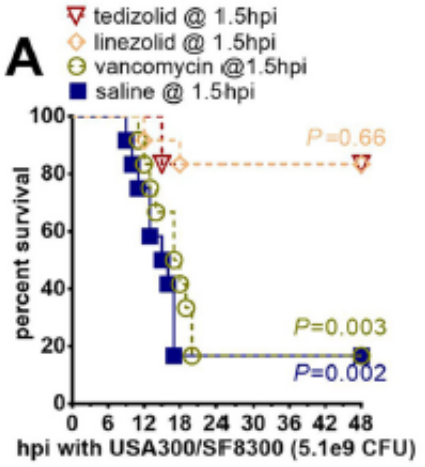
OFF-LABEL

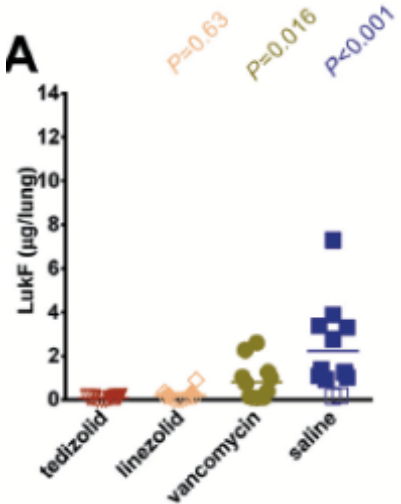
Bactériémies et EI ?

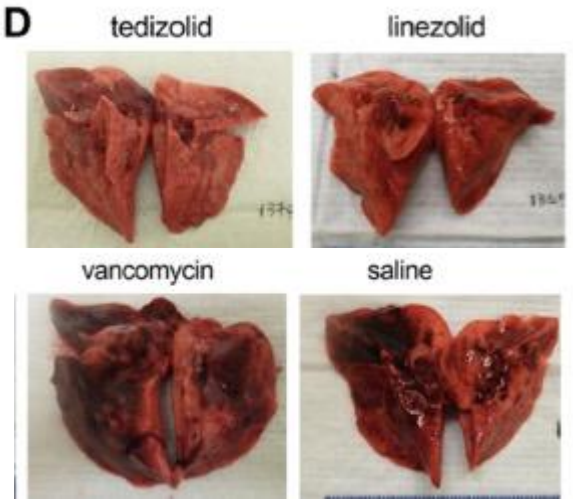
Pneumonie nécrosante

Effects of Tedizolid Phosphate on Survival Outcomes and Suppression of Production of Staphylococcal Toxins in a Rabbit Model of Methicillin-Resistant *Staphylococcus aureus* Necrotizing Pneumonia

Vien T. M. Le,[a] Hoan N. Le,[a] Marcos Gabriel Pinheiro,[a] Kenneth J. Hahn,[a] Mary L. Dinh,[a] Kajal B. Larson,[b] Shawn D. Flanagan,[b] Cedric Badiou,[c,d] Gerard Lina,[c,d] Christine Tkaczyk,[e] Bret R. Sellman,[e] Binh An Diep[a]







Tédizolide (SIVEXTRO®)

APPROVED

Infections « aiguës » PTM

2 RCT, 1 333 patients

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Analysis of the Phase 3 ESTABLISH Trials of Tedizolid versus Linezolid in Acute Bacterial Skin and Skin Structure Infections

Andrew F. Shorr,[a] Thomas P. Lodise,[b] G. Ralph Corey,[c] Carisa De Anda,[d] Edward Fang,[d] Anita F. Das,[e] Philippe Prokocimer[d]

OFF-LABEL

Bactériémies et EI ?

Pneumonie nécrosante

IOA

In vitro activity of tedizolid against staphylococci isolated from prosthetic joint infections☆

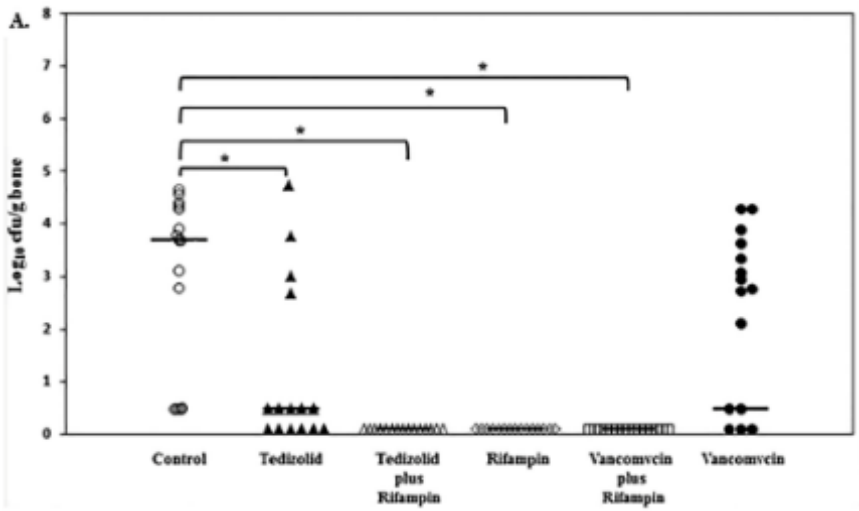
Suzannah M. Schmidt-Malan [b], Kerryl E. Greenwood Quaintance [b], Melissa J. Karau [b], Robin Patel [a,b,*]

Tolerance of Prolonged Oral Tedizolid for Prosthetic Joint Infections: Results of a Multicentre Prospective Study

Eric Senneville [1,2,3,*], Aurélien Dinh [4,5], Tristan Ferry [6,7], Eric Beltrand [3,8], Nicolas Blondiaux [3,9] and Olivier Robineau [1,2,3]

Activity of Tedizolid in Methicillin-Resistant *Staphylococcus epidermidis* Experimental Foreign Body-Associated Osteomyelitis

Kyung-Hwa Park,[a,d] Kerryl E. Greenwood-Quaintance,[a] Audrey N. Schuetz,[a] Jayawant N. Mandrekar,[c] Robin Patel[a,b]



Tédizolide (SIVEXTRO®)

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Infections « aiguës » PTM

2 RCT, 1 333 patients

Tedizolide 6 jours versus linézolide 10 jours
Cure rate > 85%, non infériorité

OFF-LABEL

Bactériémies et EI ?

Pneumonie nécrosante

IOA

Mycobactéries, dont TB MDR

J Antimicrob Chemother 2017; 72 Suppl 2: ii30–ii35
doi:10.1093/jac/dkx305

Journal of Antimicrobial Chemotherapy

Tedizolid is highly bactericidal in the treatment of pulmonary *Mycobacterium avium* complex disease

Devyani Deshpande, Shashikant Srivastava, Jotam G. Pasipanodya, Pooi S. Lee and Tawanda Gumbo*

Center for Infectious Diseases Research and Experimental Therapeutics, Baylor Research Institute, Baylor University Medical Center, Dallas, TX, USA

Intracellular activity of tedizolid phosphate and ACH-702 versus *Mycobacterium tuberculosis* infected macrophages

Carmen A Molina-Torres[1*], Alejandra Barba-Marines[1], Orestes Valles-Guerra[1], Jorge Ocampo-Candiani[1], Norma Cavazos-Rocha[4], Michael J Pucci[2], Jorge Castro-Garza[3] and Lucio Vera-Cabrera[1]

Antimicrobial Agents and Chemotherapy

Contribution of Oxazolidinones to the Efficacy of Novel Regimens Containing Bedaquiline and Pretomanid in a Mouse Model of Tuberculosis

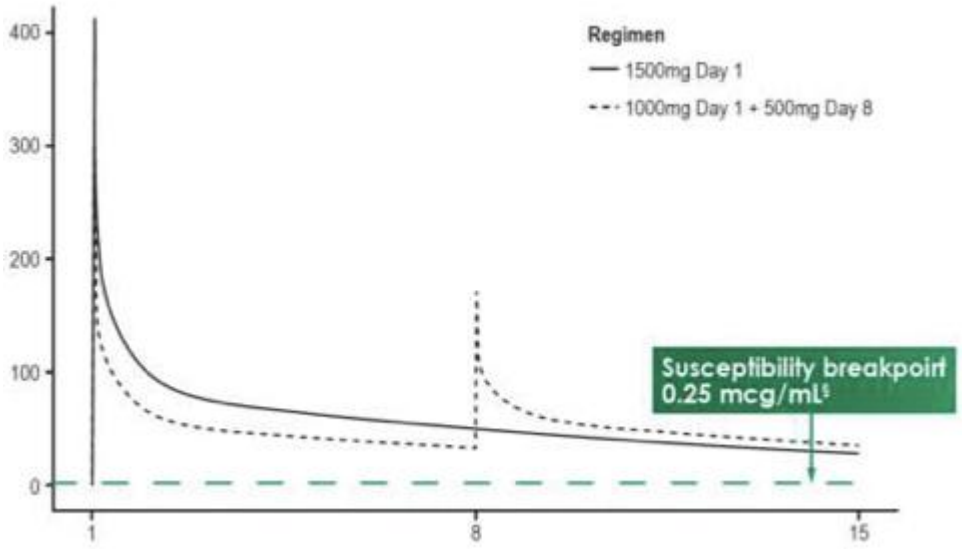
Rokeya Tasneen,[a] Fabrice Betoudji,[a] Sandeep Tyagi,[a] Si-Yang Li,[a] Kathy Williams,[a] Paul J. Converse,[a] Véronique Dartois,[b] Tian Carl M. Mendel,[a] Khisimuzi E. Mdluli,[a] Eric L. Nuermberger[a,c]

Tedizolid vs Linezolid for the Treatment of Nontuberculous Mycobacteria Infections in Solid Organ Transplant Recipients

Yi Kee Poon,[1] Ricardo M. La Hoz,[2] Linda S. Hynan,[3] James Sanders,[1,2] and Marguerite L. Monogue[1,2]

Dalbavancine (XYDALBA®)

- **Classe :** lipoglycopeptide (proche téicoplanine)
- **Cible :** synthèse peptidoglycane, bactéricidie lente
- **Spectre :** cocci+ (sauf *E. faecium*)
- **Biodisponibilité :** IV (30 min)
- **Diffusion : ?**
- **½ vie : 372h (15 jours)**
- **Posologie :** 1500 mg
  - 1500 mg J0
  - 1000 mg J0, 500 mg J8
- **Adaptation :** DFG < 30
  (1g à J0 ou 750 mg J0 / 375 mg J8)
- **Principale toxicité :** hépatique
- **Coût : 2 100 euros**



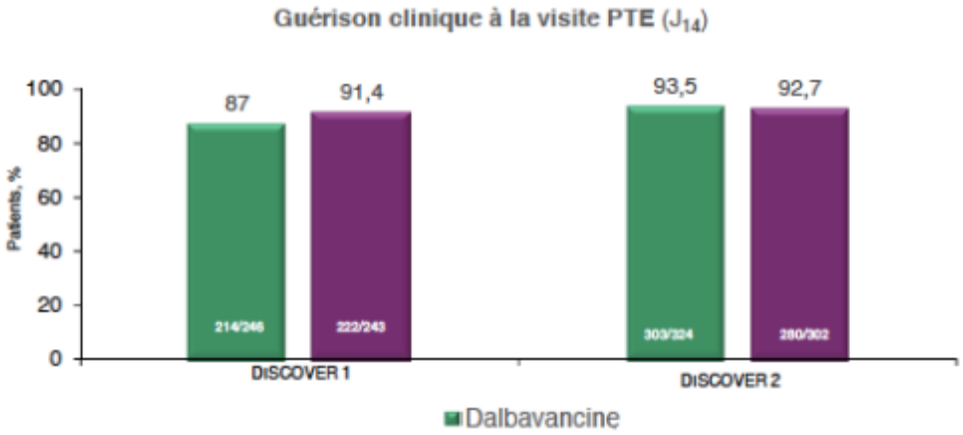
Dalbavancine (XYDALBA®)

APPROVED

Infections « aiguës » PTM

DISCOVER 1 (n=573) et 2 (n=739)
1g J0 + 500 mg J8
+ 1 essai 1g/500mg vs 1500mg

NON INFERIORITE




The NEW ENGLAND JOURNAL of MEDICINE

JUNE 5, 2014

Once-Weekly Dalbavancin versus Daily Conventional Therapy for Skin Infection

Helen W. Boucher, M.D., Mark Wilcox, M.D., George H. Talbot, M.D., Sailaja Puttagunta, M.D., Anita F. Das, Ph.D., and Michael W. Dunne, M.D.

A Randomized Clinical Trial of Single Dose vs Weekly Dalbavancin for Treatment of Acute Bacterial Skin and Skin Structure Infection

MW Dunne, S Puttagunta, P Giordano, D Krievins, M Zelasky, and J Baldassarre

Clin Infect Dis. 2016 Mar 1;62(5):545-51

Age moyen : 50 ans
Diabète : 12%
Ambulatoire : 25%
Bactériémie : 40 patients / grpe
Critères de jugement principal : Arrêt extension et fièvre (≠ guérison)

Dalbavancine (XYDALBA®)

APPROVED

Infections « aiguës » PTM

DISCOVER 1 (n=573) et 2 (n=739)

+ 1 essai dose unique J0 1500 mg versus 1g J0 + 500 mg J8

Eur J Clin Microbiol Infect Dis (2017) 36:607–610
DOI 10.1007/s10096-016-2845-z

ORIGINAL ARTICLE

Dalbavancin reduces biofilms of methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus epidermidis* (MRSE)

D. Knoll[1] · S. Tobudic[1] · S. C. Cheng[2] · B. R. Bellamy[3] · F. Thalhammer[1]

OFF-LABEL

IOA

Quelle dose ?

Case report 1g J0 puis 500 mg/sem

… en fait probablement moins :

J Antimicrob Chemother 2016; 71: 460–463
doi:10.1093/jac/dkv357 Advance Access publication 30 October 2015

Journal of Antimicrobial Chemotherapy

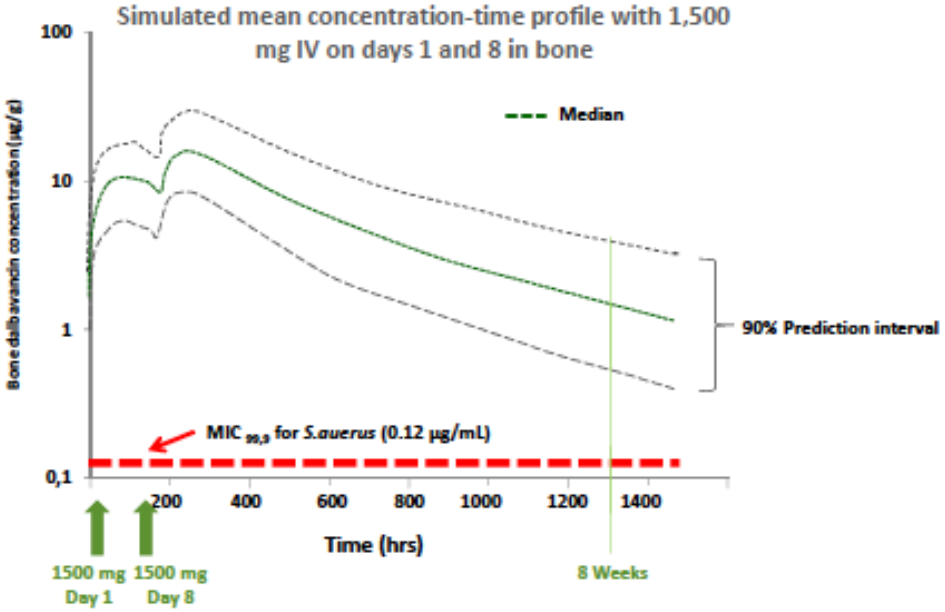
Efficacy of dalbavancin in the treatment of MRSA rat sternal osteomyelitis with mediastinitis

Yoav Barnea[1†], Anat Lerner[2†], Asaf Aizic[1], Shiri Navon-Venezia[4], Eleanor Rachi[1], Michael W. Dunne[5], Sailaja Puttagunta[5] and Yehuda Carmeli[2*]

AAC Journals.ASM.org

Extended-Duration Dosing and Distribution of Dalbavancin into Bone and Articular Tissue

Michael W. Dunne,[a] Sailaja Puttagunta,[a] Craig R. Sprenger,[a,c] Chris Rubino,[b] Scott Van Wart,[b] James Baldassarre[a]



Dalbavancine (XYDALBA®)

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Infections « aiguës » PTM

DISCOVER 1 (n=573) et 2 (n=739)

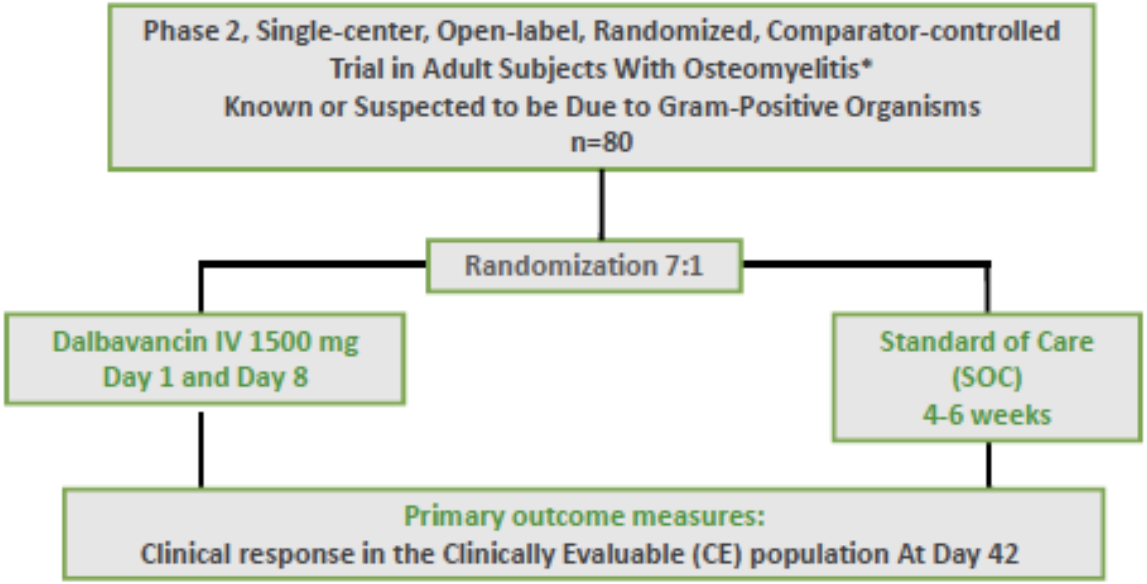
+ 1 essai dose unique J0 1500 mg
versus 1g J0 + 500 mg J8

OFF-LABEL

IOA

Dalbavancin for the Treatment of Osteomyelitis in Adult Patients: A Randomized Clinical Trial of Efficacy and Safety

Urania Rappo,[1,*] Sailaja Puttagunta,[1,**] Vadym Shevchenko,[2] Alona Shevchenko,[2] Alona Jandourek,[1,3] Pedro L. Gonzalez,[1] Amy Suen,[1] Veronica Mas Casullo,[1] David Melnick,[1,4] Rosa Miceli,[1] Milan Kovacevic,[1] Gertjan De Bock,[1,5] and Michael W. Dunne[1,*]



Dalbavancine (XYDALBA®)

APPROVED

Infections « aiguës » PTM

DISCOVER 1 (n=573) et 2 (n=739)

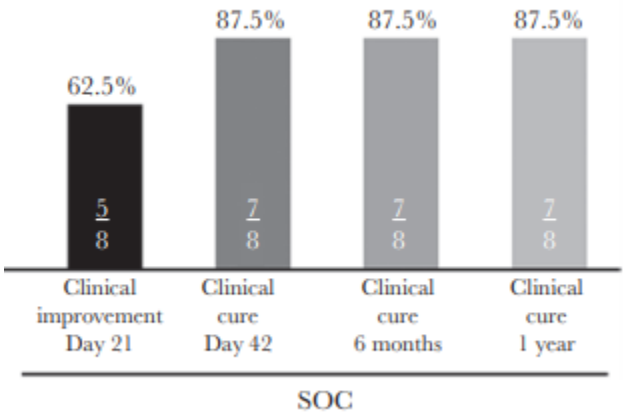
+ 1 essai dose unique J0 1500 mg
versus 1g J0 + 500 mg J8

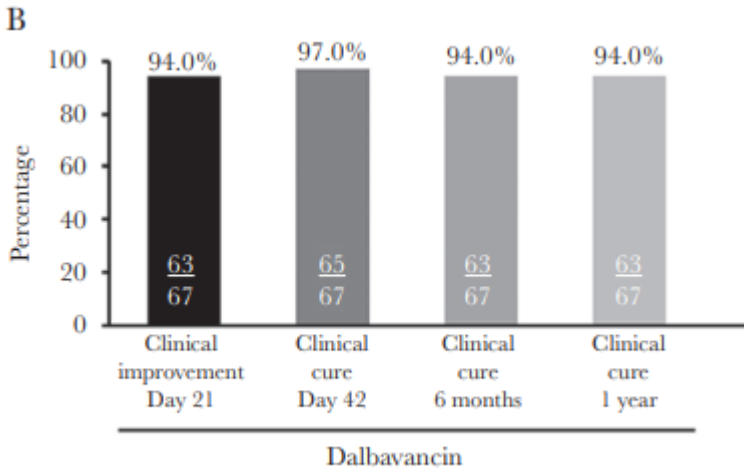
OFF-LABEL

IOA

Dalbavancin for the Treatment of Osteomyelitis in Adult Patients: A Randomized Clinical Trial of Efficacy and Safety

Urania Rappo,[1,*] Sailaja Puttagunta,[1,**] Vadym Shevchenko,[2] Alona Shevchenko,[2] Alona Jandourek,[1,3] Pedro L. Gonzalez,[1] Amy Suen,[1] Veronica Mas Casullo,[1] David Melnick,[1,4] Rosa Miceli,[1] Milan Kovacevic,[1] Gertjan De Bock,[1,5] and Michael W. Dunne[1,*]





Dalbavancine (XYDALBA®)

APPROVED

Infections « aiguës » PTM

DISCOVER 1 (n=573) et 2 (n=739)

+ 1 essai dose unique J0 1500 mg
versus 1g J0 + 500 mg J8

OFF-LABEL

IOA

Dalbavancin for the management of osteomyelitis: a major step forward?

Thamer A. Almangour[1] and Abdullah A. Alhifany [2*]

12 études « real life »
> 200 patients

Dalbavancine (XYDALBA®)

Population Pharmacokinetics of Dalbavancin and Dosing Consideration for Optimal Treatment of Adult Patients with Staphylococcal Osteoarticular Infections

Pier Giorgio Cojutti,[a,b] Matteo Rinaldi,[c,d] Eleonora Zamparini,[c,d] Nicolò Rossi,[c,d] Sara Tedeschi,[c,d] Matteo Conti,[c] Federico Pea,[c,e] Pierluigi Viale[c,d]

Population Pharmacokinetic and Pharmacodynamic Analysis of Dalbavancin for Long-Term Treatment of Subacute and/or Chronic Infectious Diseases: The Major Role of Therapeutic Drug Monitoring

Pier Giorgio Cojutti [1], Sara Tedeschi [2,3], Milo Gatti [1,3], Eleonora Zamparini [2], Marianna Meschiari [4], Paola Della Siega [5], Maria Mazzitelli [6], Laura Soavi [7], Raffaella Binazzi [8], Elke Maria Erne [8], Marco Rizzi [7], Anna Maria Cattelan [6], Carlo Tascini [5], Cristina Mussini [4], Pierluigi Viale [2,3] and Federico Pea [1,3,*]

OFF-LABEL

1500 mg J1 + J8 → 6 sem de traitement

Si durée prolongée : dosages + simulation populationnelle pour adaptation dose / intervalles
Le plus souvent : 500 mg / mois

Cf. S. Goutelle (Lyon), M. Grégoire (Nantes)

Dalbavancine (XYDALBA®)

APPROVED

Infections « aiguës » PTM

DISCOVER 1 (n=573) et 2 (n=739)

+ 1 essai dose unique J0 1500 mg
versus 1g J0 + 500 mg J8

OFF-LABEL

IOA

Bactériémies et EI

Dalbavancin as Primary and Sequential Treatment for Gram-Positive Infective Endocarditis: 2-Year Experience at the General Hospital of Vienna
Selma Tobudic Christina Forstner Heinz Burgmann Heimo Lagler Michael RamharterChristoph Steininger Matthias (G) Vossen Stefan Winkler Florian Thalhammer
Clinical Infectious Diseases, ciy279, https://doi.org/10.1093/cid/ciy279

27 EI à cocci+
après contrôle bactériémie (24/27)
92,6% de succès clinique

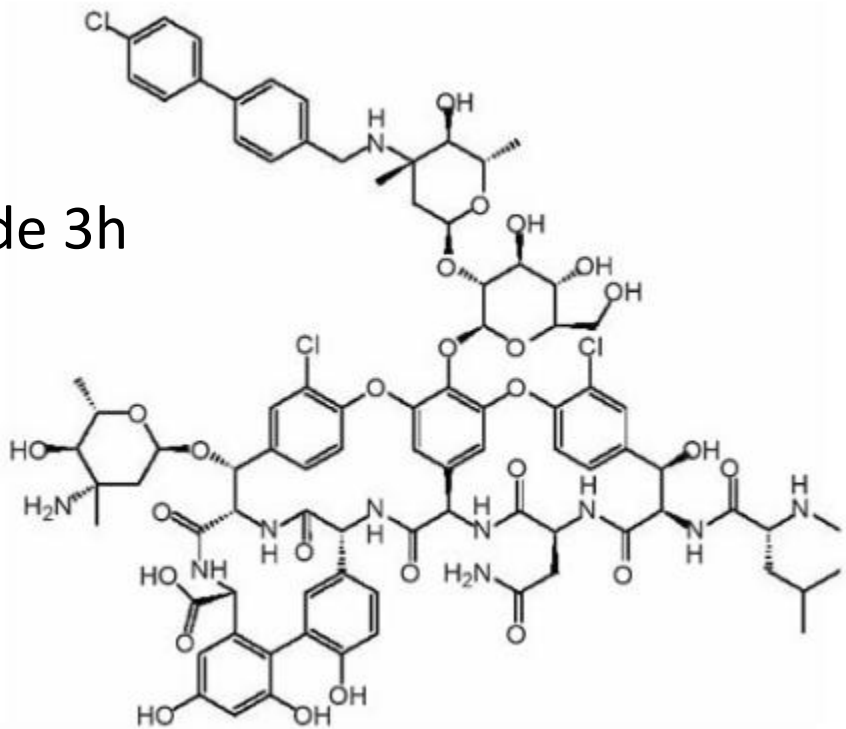
Emergence of dalbavancin non-susceptible, vancomycin-intermediate *Staphylococcus aureus* (VISA) after treatment of MRSA central line-associated bloodstream infection with a dalbavancin- and vancomycin-containing regimen
B.J. Werth
Clinical microbiology and infection
April 2018Volume 24, Issue 4, Pages 429.e1–429.e5

Unsuccessful treatment of methicillin-resistant *Staphylococcus aureus* endocarditis with dalbavancin

J. M. Steele PharmD, BCPS-AQ ID[1,2] | R. W. Seabury PharmD, BCPS, DABAT[1] | C. M. Hale PharmD, AAHIVP[3] | B. T. Mogle PharmD[1]

Oritavancine (ORBACTIV®)

- **Classe :** lipoglycopeptide
- **Cible :** synthèse peptidoglycane, bactéricidie rapide
- **Spectre :** cocci+
- **Biodisponibilité :** IV
- **Diffusion : ?**
- **½ vie : 245h (10 jours)**
- **Posologie :** 1200 mg en 1 perfusion de 3h
- **Adaptation :** pas si DFG > 50, sinon ?
- **Principale toxicité :** hépatique
- **Coût : 2500 euros**

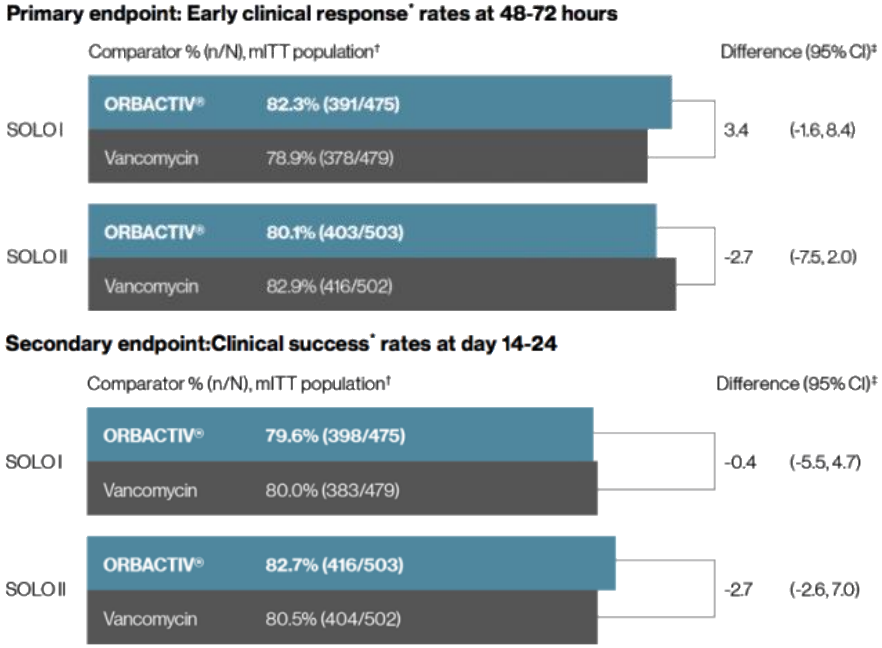


Oritavancine (ORBACTIV®)

APPROVED

Infection aiguë PTM

2 ECR de non infériorité « SOLO » I et II versus vanco 7-10 jours



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Single-Dose Oritavancin in the Treatment of Acute Bacterial Skin Infections

G. Ralph Corey, M.D., Heidi Kabler, M.D., Purvi Mehra, M.D., Sandeep Gupta, M.D., J. Scott Overcash, M.D., Ashwin Porwal, M.D., Philip Giordano, M.D., Christopher Lucasti, M.D., Antonio Perez, M.D., Samantha Good, Ph.D., Hai Jiang, Ph.D., Greg Moeck, Ph.D., and William O'Riordan, M.D., for the SOLO I Investigators*

Single-Dose Oritavancin Versus 7–10 Days of Vancomycin in the Treatment of Gram-Positive Acute Bacterial Skin and Skin Structure Infections: The SOLO II Noninferiority Study

G. Ralph Corey,[1] Samantha Good,[2] Hai Jiang,[2] Greg Moeck,[2] Matthew Wikler,[2] Sinikka Green,[3] Paul Manos,[4] Richard Keech,[5] Rajesh Singh,[6] Barry Heller,[7] Natalia Bubnova,[8] and William O'Riordan[9]; for the SOLO II Investigators*

Oritavancine (ORBACTIV®)

APPROVED

Infection aiguë PTM

2 ECR de non infériorité « SOLO » I et II versus vanco 7-10 jours

OFF-LABEL

IOA

- Sensibilité de la quasi-totalité des souches
- Synergie avec la rifampicine fréquente
- Activité « anti-biofilm », notamment avec la rifampicine
- Concentration intra-osseuse > MIC90 > 7j (lapins)

In vitro activity of oritavancin against biofilms of staphylococci isolated from prosthetic joint infection

Qun Yan [a,b], Melissa J. Karau [a], Robin Patel [a,c,*]

in vitro Activity of Oritavancin in Combination with Rifampin or Gentamicin Against Prosthetic Joint Infection-Associated Methicillin-Resistant *Staphylococcus epidermidis* Biofilms

Qun Yan, Melissa J. Karau, Yash S. Raval, Robin Patel

Evaluation of Oritavancin in Combination with Rifampin, Gentamicin or Linezolid Against Prosthetic Joint Infection-Associated Methicillin-Resistant *Staphylococcus aureus* Biofilms by Time-Kill Assays

Qun Yan, Melissa J. Karau, Yash S. Raval, Robin Patel

AAC

Journals.ASM.org

Oritavancin Pharmacokinetics and Bone Penetration in Rabbits

Dario Lehoux, Valerie Ostiguy, Cordelia Cadieux, Mireille Malouin, Odette Belanger, Adel Rafai Far, Thomas R. Parr, Jr.

The Medicines Company, St. Laurent, Quebec, Canada

Oritavancine (ORBACTIV®)

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Infection aiguë PTM

2 ECR de non infériorité « SOLO » I et II
versus vanco 7-10 jours

OFF-LABEL

IOA

Autres ?

Multiple-Dose Oritavancin Evaluation in a Retrospective Cohort of Patients with Complicated Infections

Lucas T Schulz,[1,*] Emily Dworkin,[2] Jennifer Dela-Pena,[3] and Warren E. Rose[4,*]

Pharmacotherapy 2018

17 patients, infections diverses (IOA et endovasculaire notamment), 2-18 doses
Taux amélioration / succès : 100%

Délafloxacine (QUOFENIX®)

- **Classe :** fluoroquinolones
- **Cible :** topol + ADN girase
- **Spectre :** celui des FQ
  - *S. aureus* dont FQ-R
  - *Pseudomonas* : 30% des FQ-R
- **Biodisponibilité :** IV ou per os
- **Posologie :** 300 mg / 12h IV
  ou 450 mg / 12h per os
- **Adaptation :** DFG < 30 mL/min
- **Coût : 130 euros / j**

Délafloxacine (QUOFENIX®)

Pathogènes Gram positifs	Nb de souches	Antibiotique	CMI_{50} (mg/l)	CMI_{90} (mg/l)	Fourchette de CMI (mg/l)
S. aureus FQ-R	71	Lévofloxacine	16	32	4 – 64
		Moxifloxacine	4	8	0,25 – 16
		Délafloxacine	**0,25**	**1**	0,015 - 1
S. epidermidis FQ-R	10	Lévofloxacine	16	16	4 – 128
		Moxifloxacine	2	2	1 – >128
		Délafloxacine	**0,5**	**0,5**	0,12 - 1
Staphylocoques à coagulase-négative FQ-R	10	Lévofloxacine	8	64	4 – 128
		Délafloxacine	**0,25**	**0,5**	0,03 – 0,5
S. pneumoniae FQ-R	33	Lévofloxacine	16	32	2 – 32
		Moxifloxacine	2	4	0,25 - 8
		Délafloxacine	**0,12**	**0,5**	0,015 – 0,5
E. faecalis FQ-R	26	Lévofloxacine	32	128	16 – 128
		Moxifloxacine	8	32	2 – 64
		Délafloxacine	**0,25**	**8**	0,06 - 32
E. faecium FQ-R	28	Lévofloxacine	32	64	8 - >128
		Moxifloxacine	16	16	1 – 32
		Délafloxacine	**4**	**8**	0,25 - 16

Délafloxacine (QUOFENIX®)

Efficacy and safety of delafloxacin in the treatment of acute bacterial skin and skin structure infections: a systematic review and meta-analysis of randomized controlled trials

Shao-Huan Lan[1]
Chih-Cheng Lai[2]
Li-Chin Lu[3]
Shen-Peng Chang[4]
Hui-Ting Huang[4]

Study, year published	Study design	Study site	Study period	Study population	Number of patients		Dose regimen	
					Delafloxacin	Comparator	Delafloxacin	Comparator
O'Riordan et al, 2015[13]	Multicenter, randomized, double-blind trial	14 sites in USA	Between June and September 2008	Complicated skin and skin structure infection	49 (300 mg) 51 (450 mg)	50	Delafloxacin, 300 mg or 450 mg q12 h	Tigecycline 100 mg IV x 1, followed by 50 mg IV q12 h
Kingsley et al, 2016[11]	Multicenter, randomized, double-blind trial	23 center in USA	Between February and November, 2011	Acute bacterial skin and skin structureinfection (ABSSSI)	81 (300 mg)	77 (Linezolid) 98 (Vancomycin)	Delafloxacin 300 mg q12 h	Linezolid 600 mg or vancomycin 15 mg/kg
Pullman et al, 2017[14]	Multicenter, randomized, double-blind trial	34 center in seven countries	Between April 2013 and June, 2014	ABSSSI	331 (300 mg)	329	Delafloxacin 300 mg q12 h	Vancomycin 15 mg/kg plus aztreonam 2 g q12 h
O'Riordan et al, 2018[12]	Multicenter, randomized, double-blind trial	76 center in 16 countries	Between May 2014 and January, 2016	ABSSSI	423 (300 mg)	427	Delafloxacin 300 mg q12 h	Vancomycin 15 mg/kg plus aztreonam 2 g q12 h

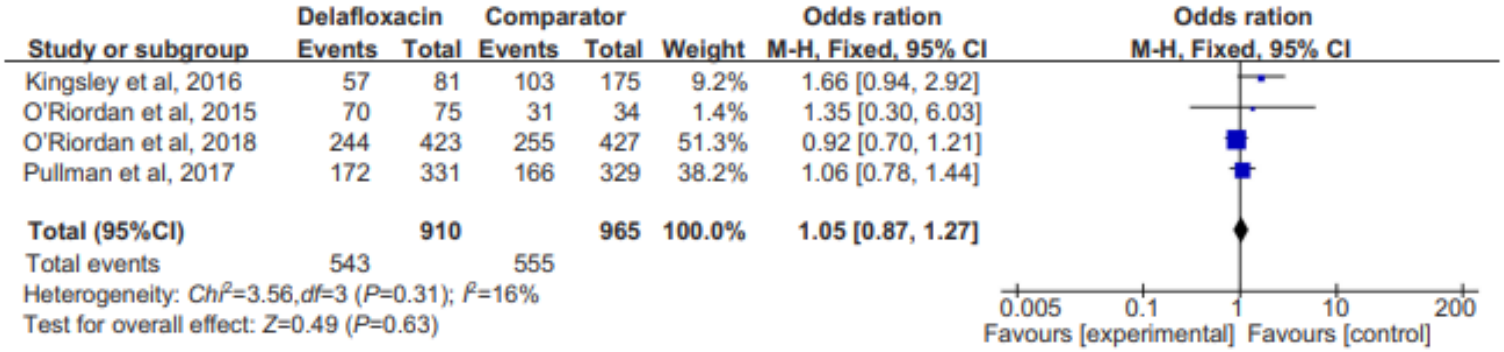


Figure 4 Overall clinical cure rates of delafloxacin and comparators in the treatment of acute bacterial skin and skin structure infections.

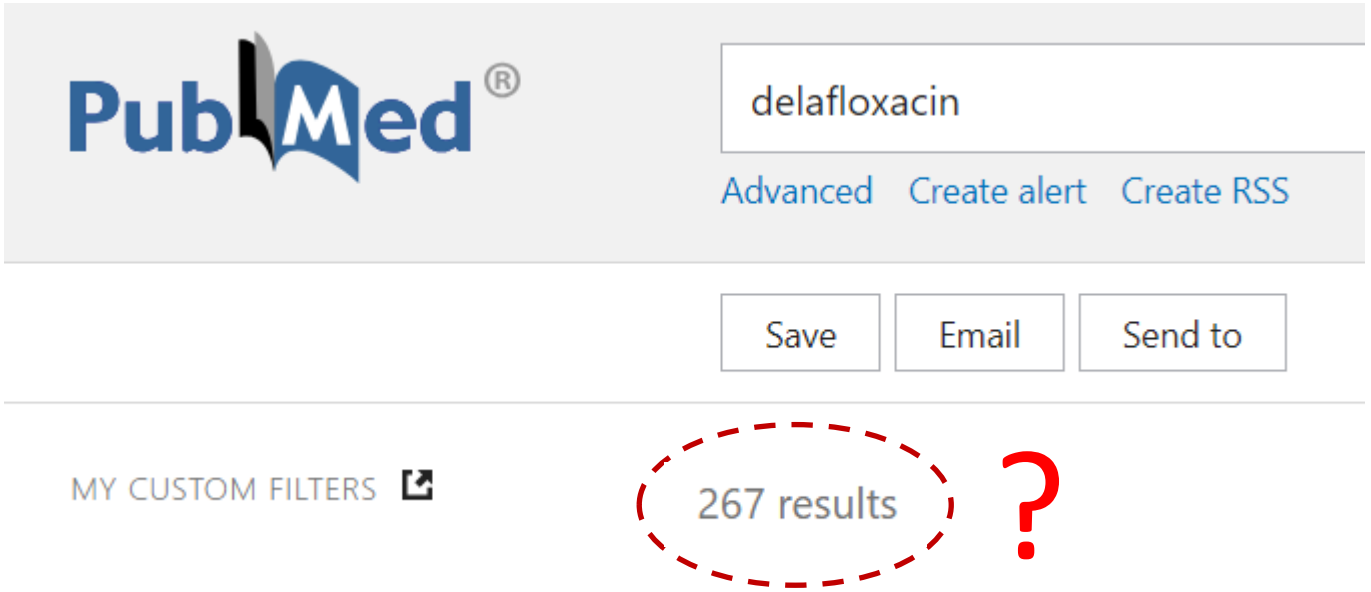
Délafloxacine (QUOFENIX®)

Efficacy and safety of delafloxacin in the treatment of acute bacterial skin and skin structure infections: a systematic review and meta-analysis of randomized controlled trials

A Phase 3 Study to Compare Delafloxacin With Moxifloxacin for the Treatment of Adults With Community-Acquired Bacterial Pneumonia (DEFINE-CABP)

Juan P. Horcajada,[1] Robert A. Salata,[2] Rodolfo Álvarez-Sala,[3] Floarea Mimi Nitu,[4] Laura Lawrence,[5] Megan Quintas,[5] Chun-Yen Cheng,[6] and Sue Cammarata[5,9]; for the DEFINE-CABP Study Group*

OFF-LABEL



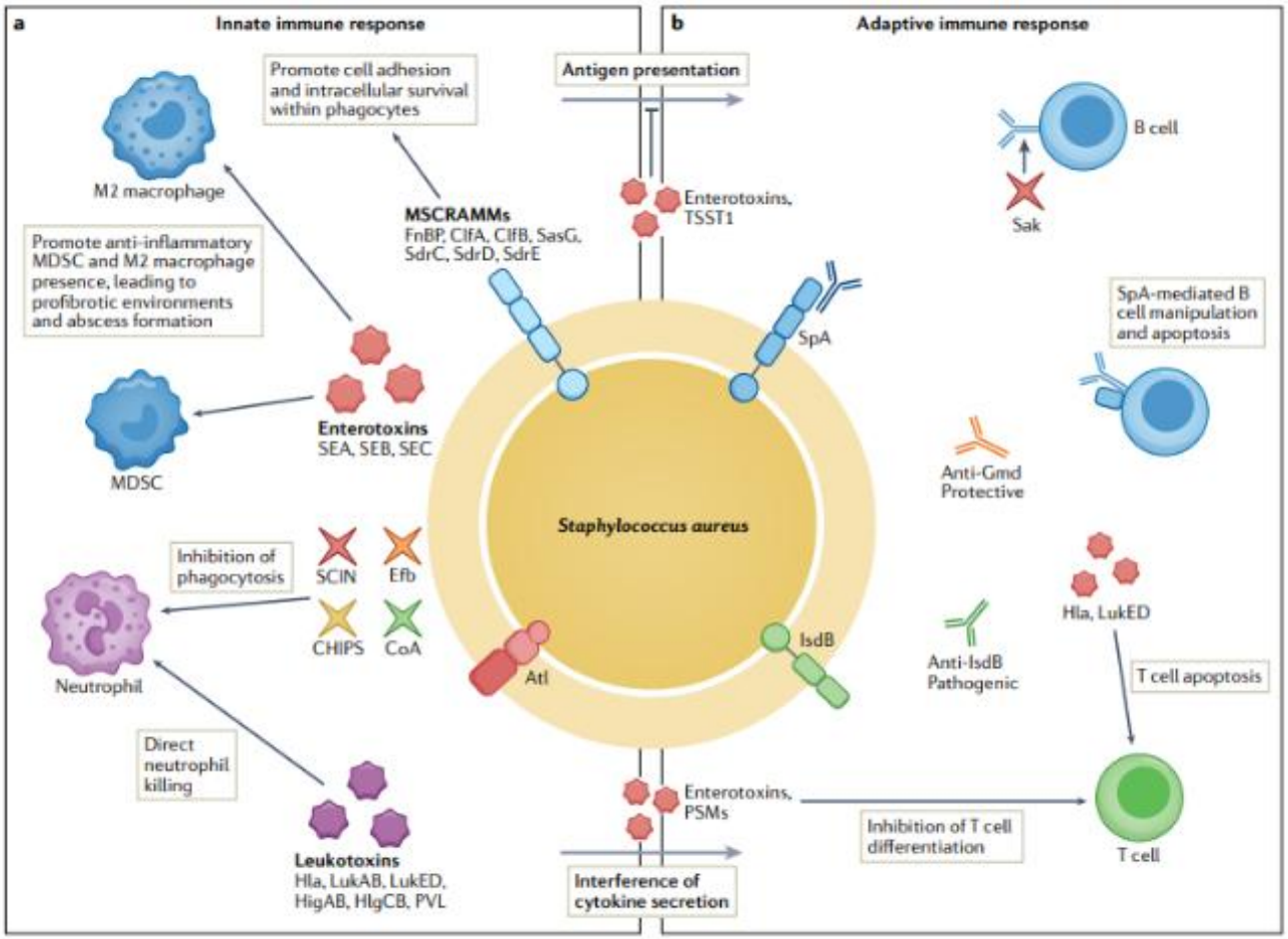
Dans le pipeline Gram+

Molécule	Classe	Dvlpmt	Spectre d'intérêt
Céfilavancine	Céphalo-glycopeptide	III	*S. aureus*
Contézolide	Oxazolidinone	III	*S. aureus, E. faecium,* mycobactéries
Iclaprim	Analogue TMP	III	*S. aureus*
Gépotidame	Inh de topoisomérase	III	*S. aureus,* BLSE, gono
Zolidoflacine	Spiropyrimidinetrione	III	*S. aureus,* gono
Solithromycine	Macrolide	III	Gono
Ridinilazole	Azolé	III	*C. difficile*

Molécule	Classe	Dvlpmt	Spectre d'intérêt
Léfamuline	Pleuromutiline	II	*S. aureus,* gono
Afabicine	Inh de Fab I	II	*S. aureus*
Brilacidine	Peptide antimicrobien	II	*S. aureus*

Stratégies non antibiotiques

Immunothérapie ciblée



① Echappement à la réponse innée

- Survie intracellulaire (MSCRAMMs)
- Inhibition de la phagocytose (MSCRAMMs, entérotoxines)
- Leucotoxines

② Action sur la synapse immunitaire

- Présentation d'Ag
- Production de cytokines

③ Echappement à la réponse adaptative

- Inhibition T (Hla, LukED, PSMs)
- Inhibition B (SpA, Sak)
- Effet superantigénique

④ Effet anticorps ambivalent

- Protecteur
- Facilitants : anti-IsdB

Muthukrishnan et al, J Orthop Res 2021
Kates et al, J Bone Joint Surg Am 2020

Immunothérapie ciblée

Ac monoclonaux anti-toxine ou anti-adhésines

Nombreuses molécules en développement pré-clinique voire phase II

- AR-301 (ARIDIS Pharmaceuticals) : AT
- 514G3 (XBiotech) : AT
- MEDI4893 (MedImmune) : AT
- MEDI6389 (MedImmune) : AT, ClfA, PVL, Hlg
- ASN100 (Arsanis) : AT + 4 leucocidines dont PVL

Principalement respiratoire (pneumonie nécrosante, VAP)

Targeting Alpha Toxin To Mitigate Its Lethal Toxicity in Ferret and Rabbit Models of *Staphylococcus aureus* Necrotizing Pneumonia

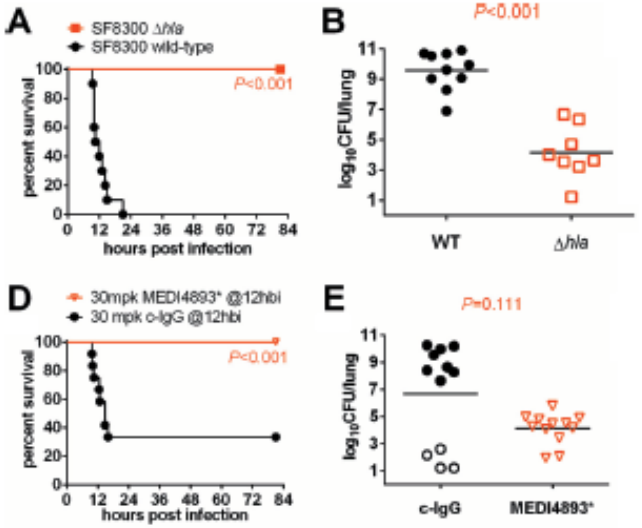
Binh An Diep,[a] Jamese J. Hilliard,[b] Vien T. M. Le,[a] Christine Tkaczyk,[b] Hoan N. Le,[a] Vuvi G. Tran,[a] Renee L. Rao,[a] Etyene Castro Dip,[a] Eliane P. Pereira-Franchi,[a] Paulyn Cha,[c] Scott Jacobson,[c] Rosemary Broome,[c] Lily I. Cheng,[d] William Weiss,[e] Laszlo Prokai,[e] Vien Nguyen,[e] C. Ken Stover,[b] Bret R. Sellman[b]

Improved Protection in a Rabbit Model of Community-Associated Methicillin-Resistant *Staphylococcus aureus* Necrotizing Pneumonia upon Neutralization of Leukocidins in Addition to Alpha-Hemolysin

Binh An Diep,[a] Vien T. M. Le,[a] Zehra C. Visram,[b] Harald Rouha,[b] Lukas Stulik,[b] Etyene Castro Dip,[a] Gábor Nagy,[b] Eszter Nagy[b]

Protective Efficacy of Monoclonal Antibodies Neutralizing Alpha-Hemolysin and Bicomponent Leukocidins in a Rabbit Model of *Staphylococcus aureus* Necrotizing Pneumonia

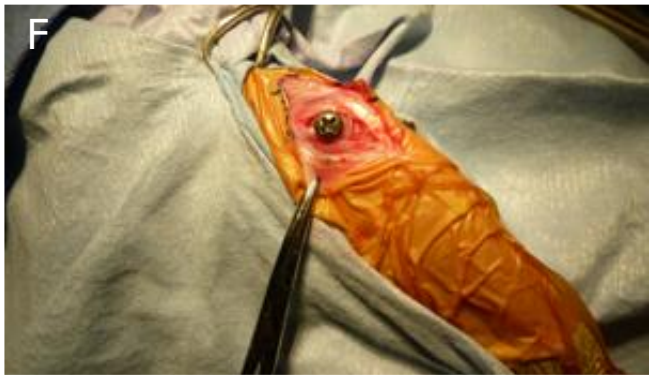
Trang T. T. Vu,[a] Nhu T. Q. Nguyen,[a] Vuvi G. Tran,[a] Emmanuelle Gras,[a,b] Yanjie Mao,[a,c] David H. Jung,[a] Christine Tkaczyk,[d] Bret R. Sellman,[d] Binh An Diep[a]



Immunothérapie ciblée

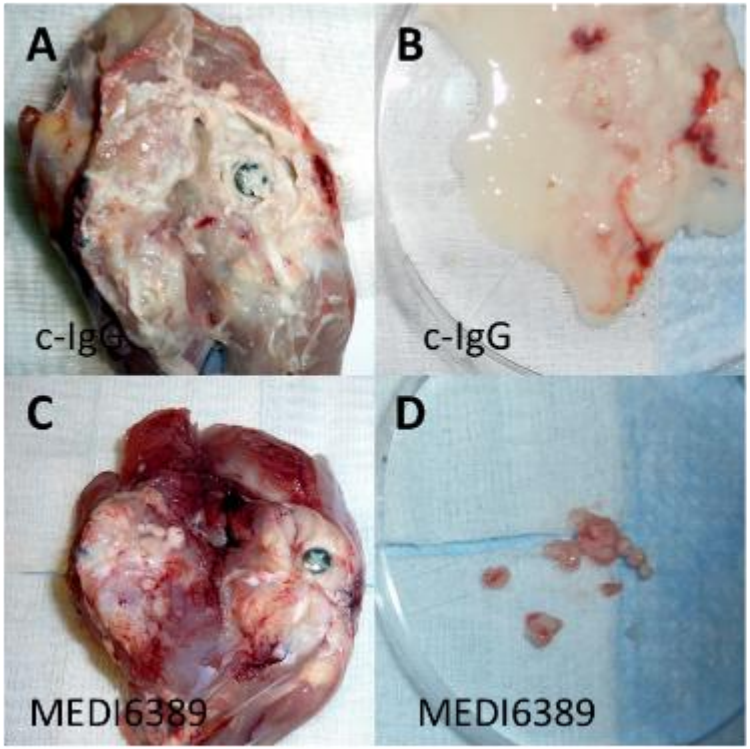
Multimechanistic Monoclonal Antibody Combination Targeting Key *Staphylococcus aureus* Virulence Determinants in a Rabbit Model of Prosthetic Joint Infection

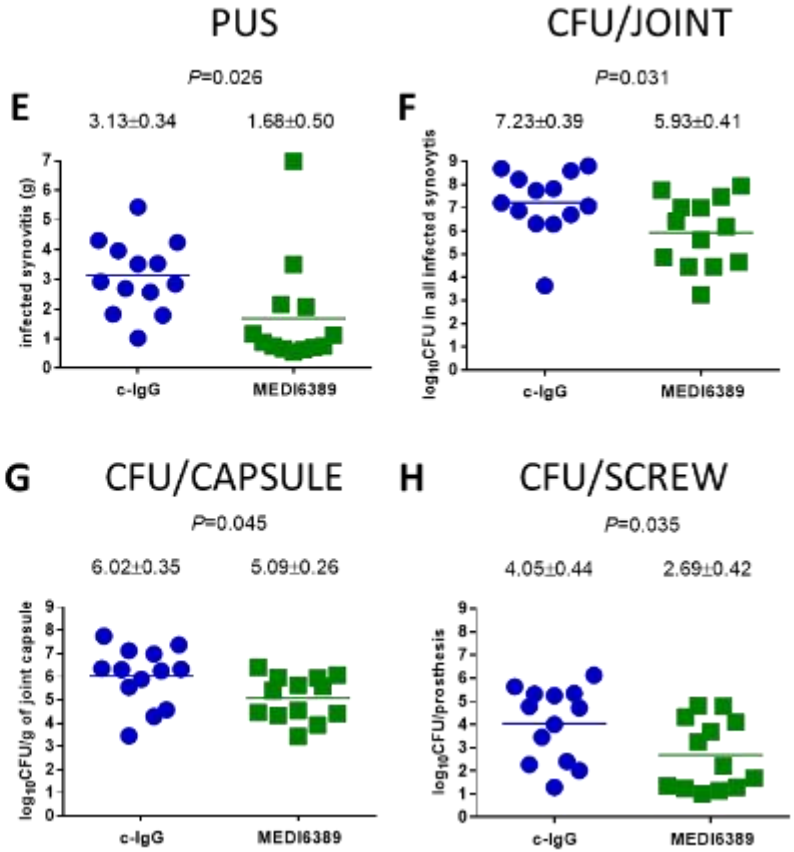
Yanjie Mao,[a,b*] Florent Valour,[a,c,d*] Nhu T. Q. Nguyen,[a] Thien M. N. Doan,[a] Holly Koelkebeck,[e] Christopher Richardson,[f] Lily I. Cheng,[e] Bret R. Sellman,[f] Christine Tkaczyk,[f] Binh An Diep[a]



MEDI6389 (AT, ClfA, PVL, Hlg) préventifs

Injection d'Ac spécifiques 12h avant la chirurgie





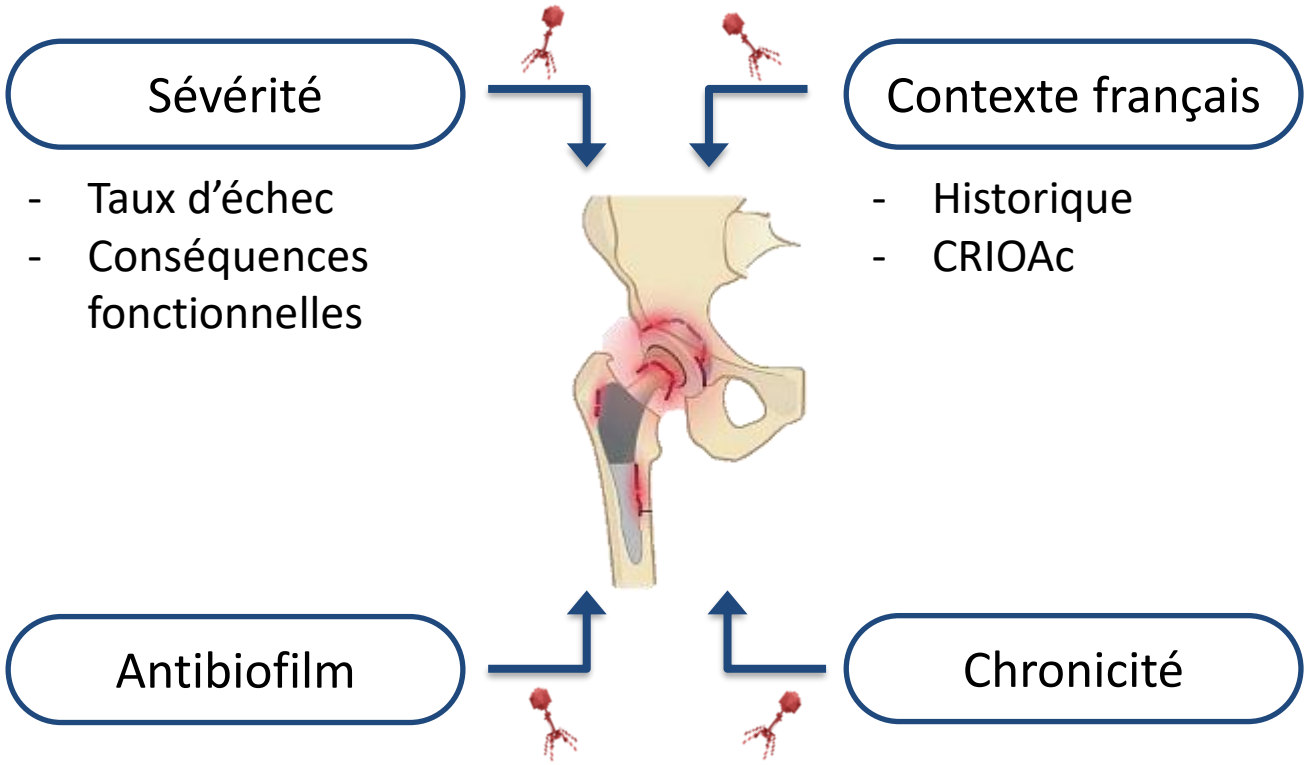
Immunothérapie ciblée

Nom	Espèce	Cible	Indication	Phase	Laboratoire
Tosatoxumab	***S. aureus***	**α-toxine**	**Adjuvant ttt VAP**	**3**	**Aridis**
Sevratoxumab	***S. aureus***	**α-toxine**	**Prévention VAP**	**2**	**Medimmune**
514G3	***S. aureus***	**Protéine A**	**Adjuvant ttt BSI**	**2**	**XBiotech**
ASN-100	***S. aureus***	**AT + 5 leucocidines**		**2**	**Arsansis**
RG7861	***S. aureus***	**Paroi + rifamycine**		**1**	**Roche**
MEDI3902	*PA*	T3SS PcrV + Psl	Adjuvant ttt VAP	2	Medimmune
AR101	*PA*	Alginate	Adjuvant ttt VAP	2	Aridis
ASN-4	*E. coli*	LPS			Arsansis
ASN-5	*KP*	O-Ag			Arsansis
AR401-mAb	*AB*		BSI		Aridis
VXD-003	*AB*				VaxDyn
PolyCAb	*CD*			1	Micropharm
Cd-ISTAb	*CD*				BioTherapeutics

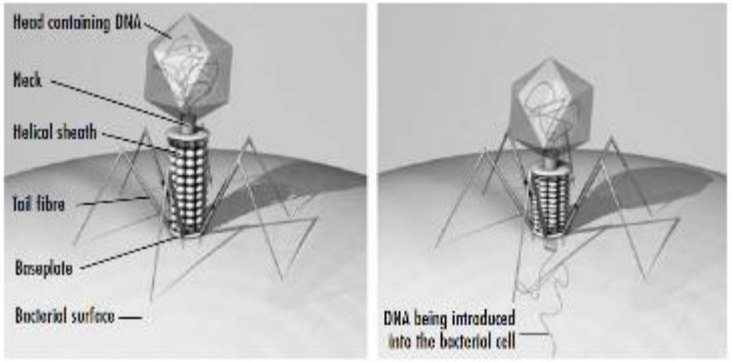
Phagothérapie

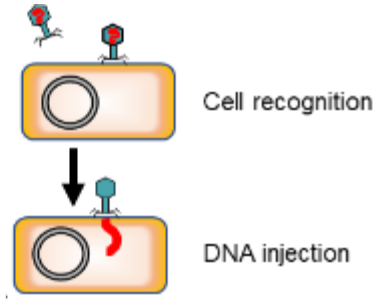
Past and Future of Phage Therapy and Phage-Derived Proteins in Patients with Bone and Joint Infection

Tristan Ferry [1,2,3,4,*], Camille Kolenda [1,2,3,4], Thomas Briot [1], Aubin Souche [1,2,3,4], Sébastien Lustig [1,2,3], Jérôme Josse [1,2,3,4], Cécile Batailler [1,2,3], Fabrice Pirot [1,2,5], Mathieu Medina [1], Gilles Leboucher [1], Frédéric Laurent [1,2,3,4], on behalf of the Lyon BJI Study Group [†] and on behalf of the PHAGE*in*LYON Study Group [‡]



Phagothérapie





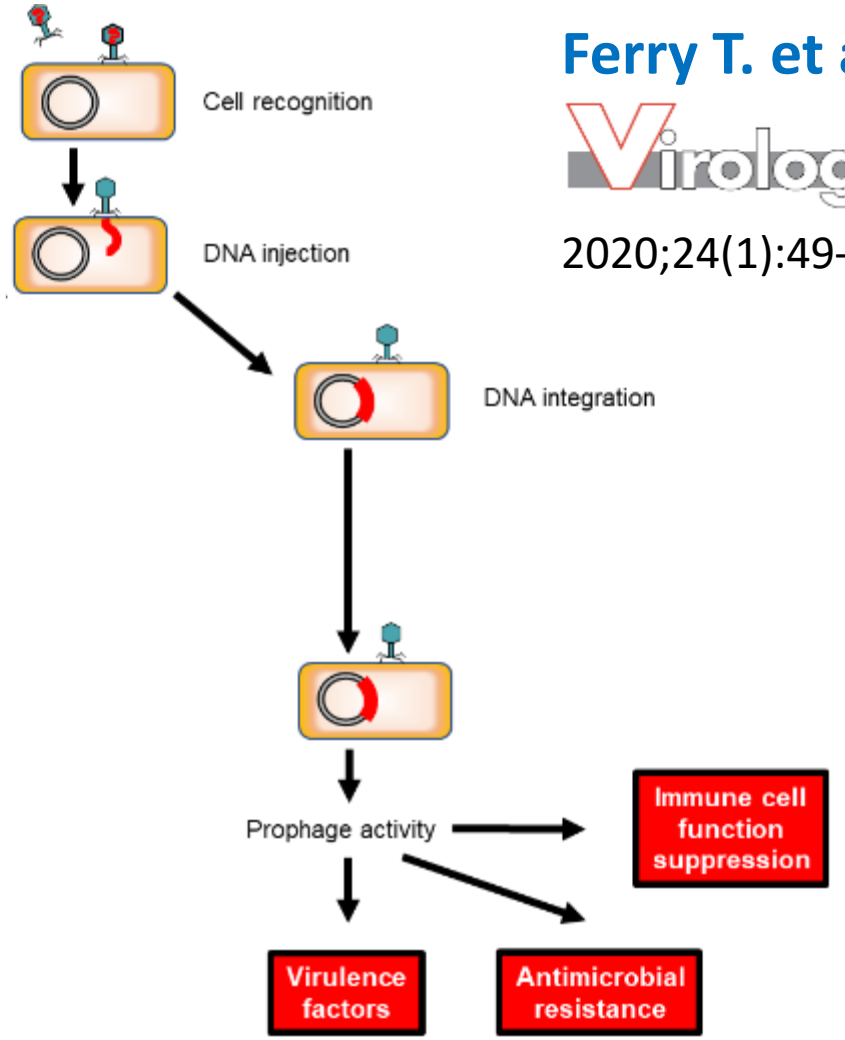
Ferry T. et al.

Virologie

2020;24(1):49-56

Virus environnementaux
ciblant des bactéries spécifiques

Phagothérapie



Ferry T. et al.

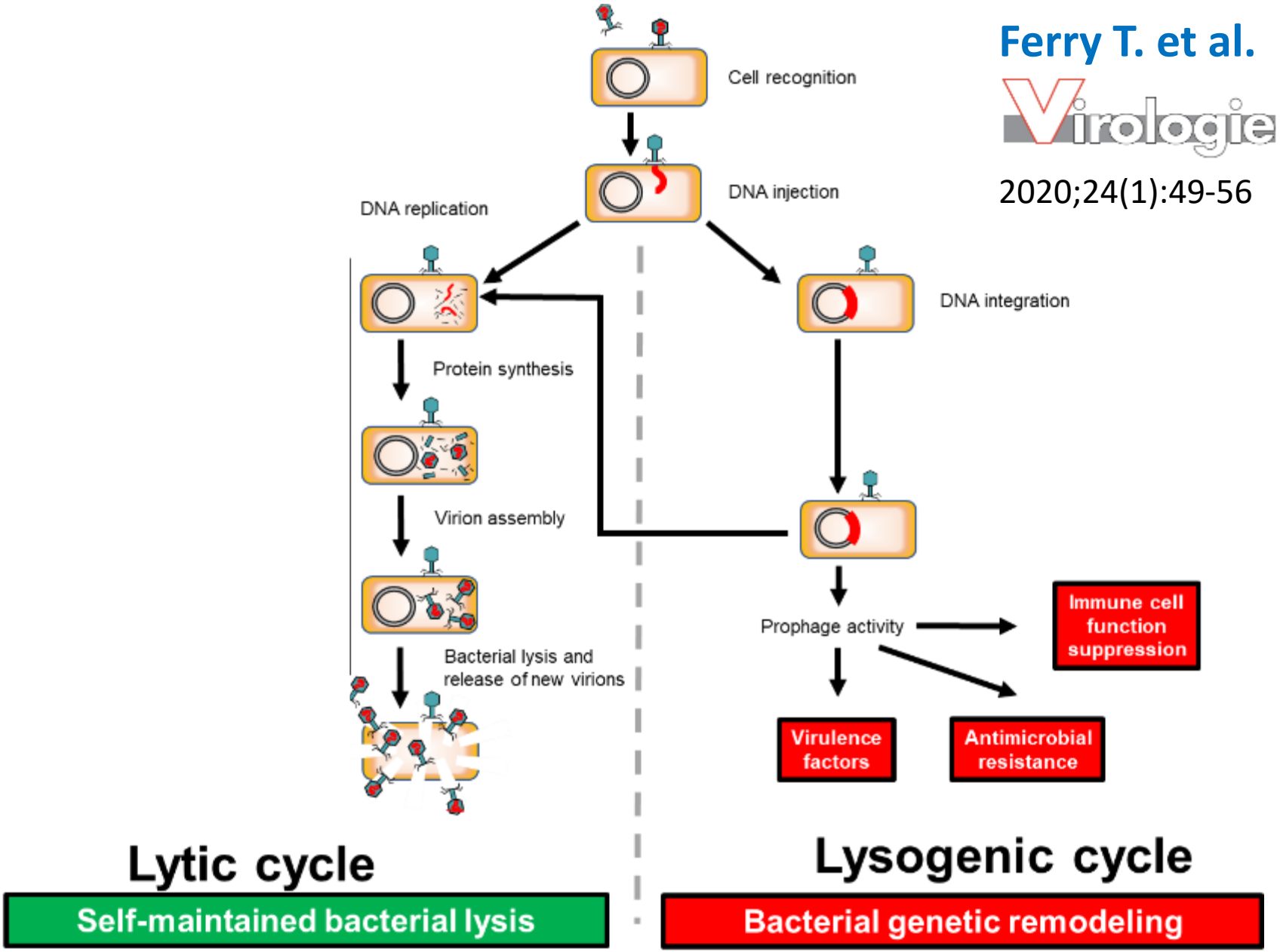
Virologie

2020;24(1):49-56

Lysogenic cycle

Bacterial genetic remodeling

Phagothérapie



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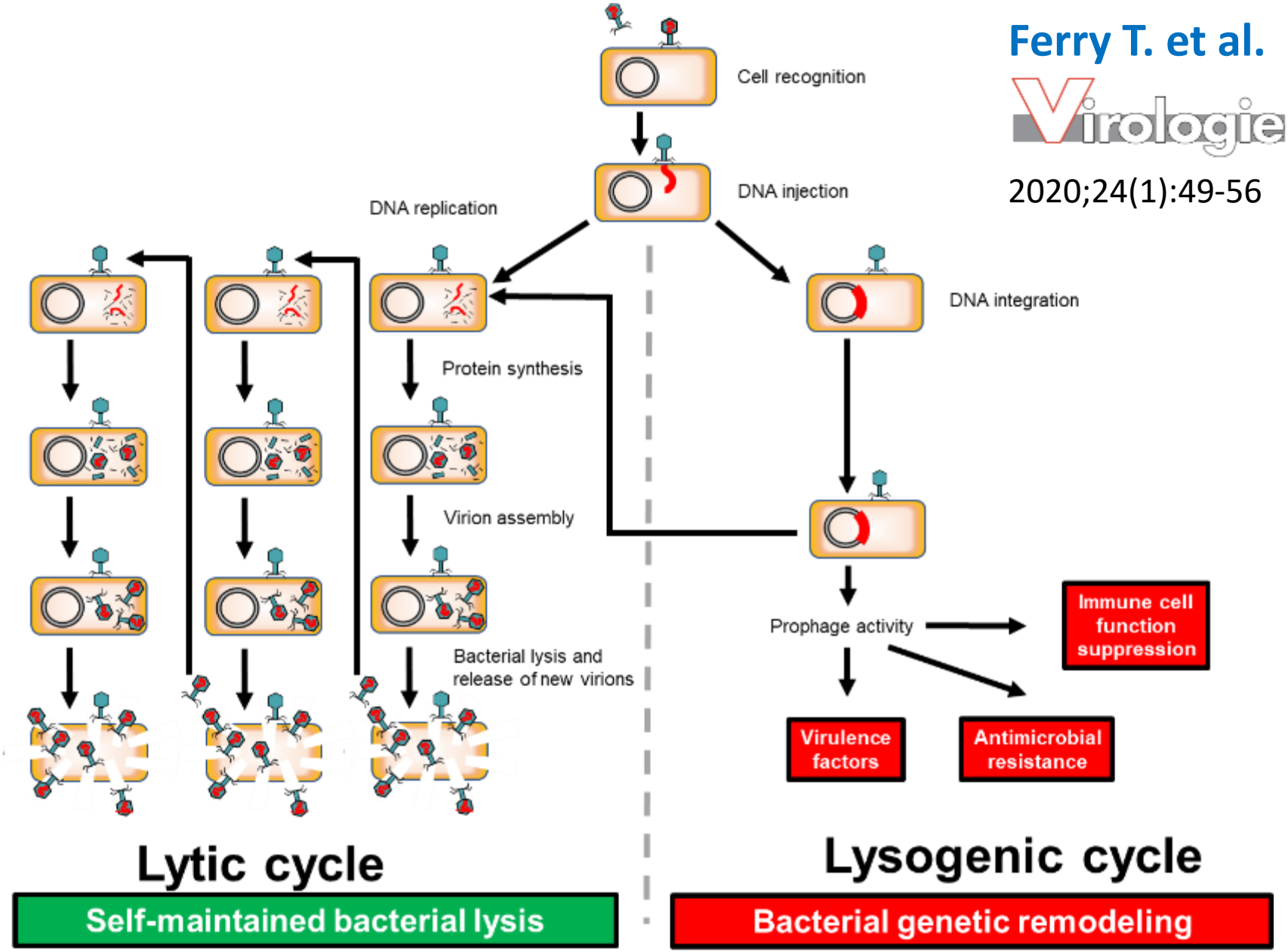

Ferry T. et al.

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2020;24(1):49-56

Lysines de phage

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

EXPERIMENTAL THERAPEUTICS
September 2021 Volume 65 Issue 9 e02723-20
https://doi.org/10.1128/AAC.02723-20

Exebacase Is Active *In Vitro* in Pulmonary Surfactant and Is Efficacious Alone and Synergistic with Daptomycin in a Mouse Model of Lethal *Staphylococcus aureus* Lung Infection

Steven M. Swift, Karen Sauve, Cara Cassin

Synergistic Activity of Exebacase (CF-301) in Addition to Daptomycin against *Staphylococcus aureus* in a Neutropenic Murine Thigh Infection Model

Tomefa E. Asempa,[a] Kamilia Abdelraouf,[a] Teresa Carabeo,[b] Raymond Schuch,[b] David P. Nicolau[a,c]

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

Exebacase in Addition to Daptomycin Is More Active than Daptomycin or Exebacase Alone in Methicillin-Resistant *Staphylococcus aureus* Osteomyelitis in Rats

Melissa J. Karau,[a] Suzannah M. Schmidt-Malan,[a] Qun Yan,[b] Kerryl E. Greenwood-Quaintance,[a] Jayawant Mandrekar,[c] Dario Lehoux,[d] Raymond Schuch,[d] Cara Cassino,[d] Robin Patel[a,e]

Effect of the Lysin Exebacase on Cardiac Vegetation Progression in a Rabbit Model of Methicillin-Resistant *Staphylococcus aureus* Endocarditis as Determined by Echocardiography

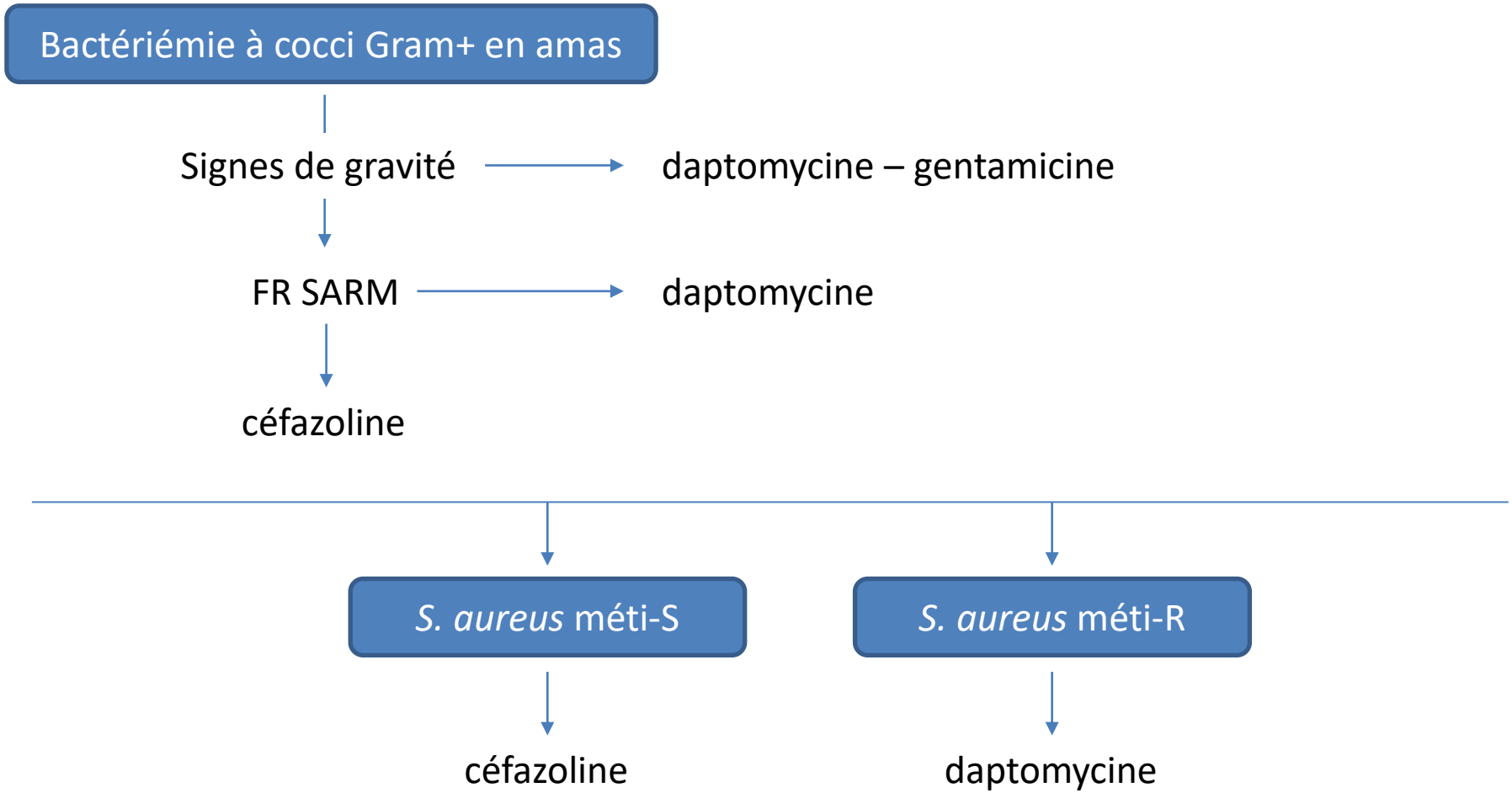
Sonia U. Shah,[a,b,c] Yan Q. Xiong,[b,c] Wessam Abdelhady,[b] James Iwaz,[a] Youngju Pak,[b,c] Raymond Schuch,[d] Cara Cassino,[d] Dario Lehoux,[d] Arnold S. Bayer[b,c]

Phagothérapie

- Mission confiée en février 2023 au CRIOAc Lyon (Pr. T. Ferry) par la DGOS
- RCP en ligne via TEAMS®
- Remplir un fichier powerpoint (à partir d'un template) et convenir d'un RDV de passage

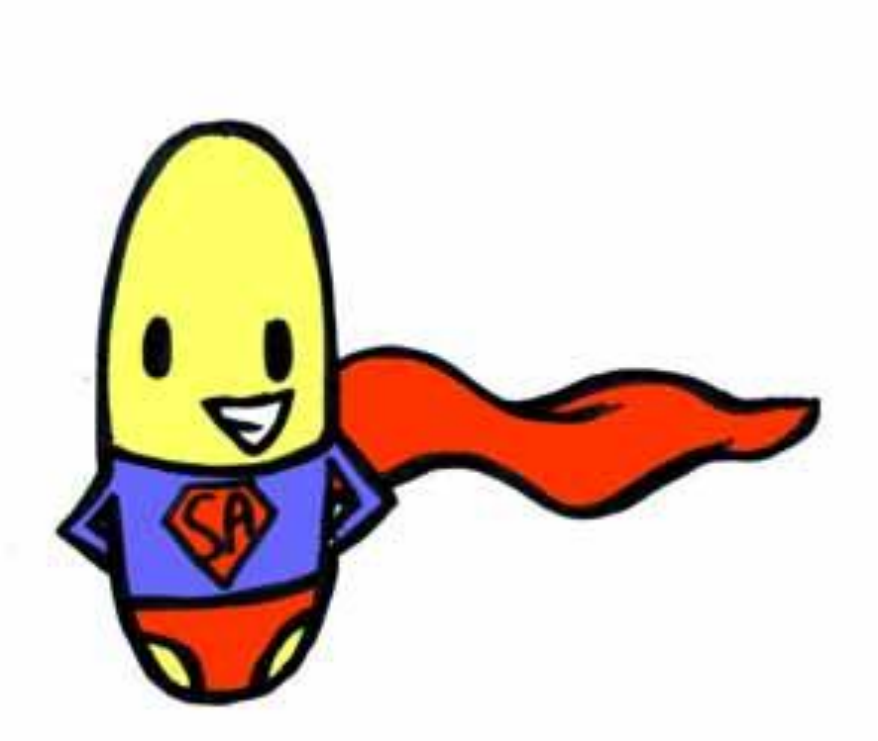
- Supervision ANSM via **RCP Phagothérapie @HCL** pour les indications jugées pertinentes rentrant dans le cadre de traitements compassionnels ou d'essais thérapeutiques

HCR.REFERENCE-IOA@chu-lyon.fr



Durée de traitement : <u>14 jours IV</u> (sauf complication)

Hémocultures de contrôle systématique / 24-48h jusqu'à négativation
Retrait systématique des cathéters
ETT systématique
ETO si patient à risque : FR EI, bactériémie > 48h ou récidive < 90 jours, matériel intra-cardiaque, toxicomanie IV, localisations secondaires …


SA