# Traitement des infections staphylococciques

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*Université Grenoble Alpes*
*1ère session – Janvier 2025*

# 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

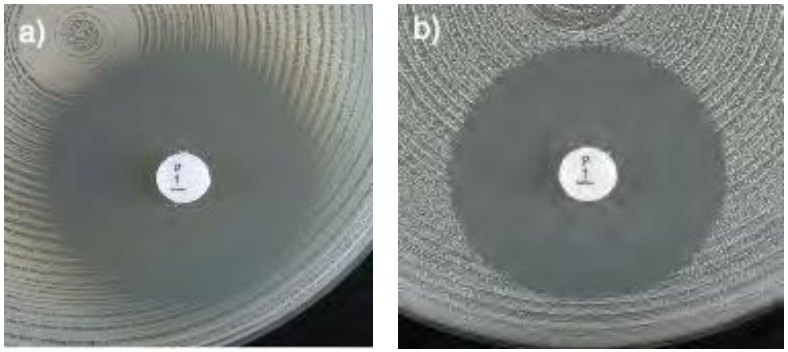
**Pénicilline G** → Sensibilité naturelle de *S. aureus* aux BL :

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
Quinupristine-dalfopristine
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

# Bactériémie à staphylocoque méti-S

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

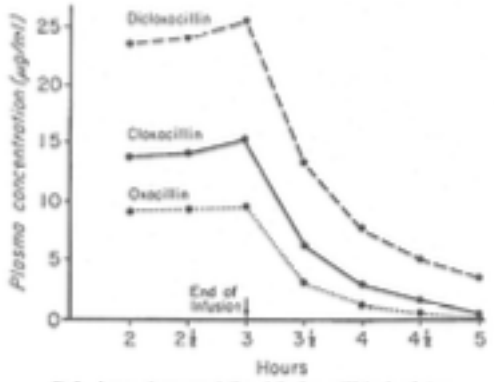
Oxacilline (BRISTOPEN®) ou Cloxacilline (ORBENINE®)

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 enIV 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<br>*n* = 541 patients,<br>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/$\mu$L 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 :**

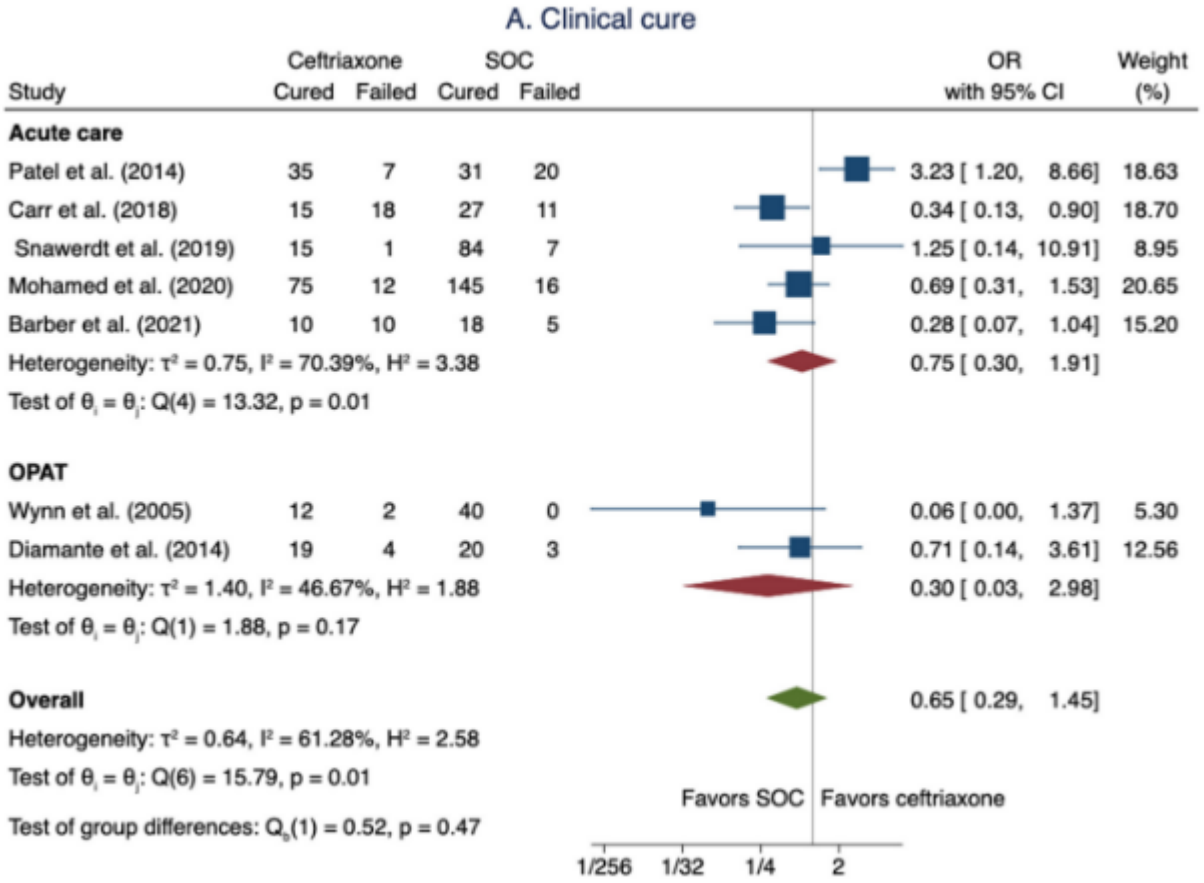
- C3G injectables
- Amox - Ac clav
- Pipé - Tazobactam

# 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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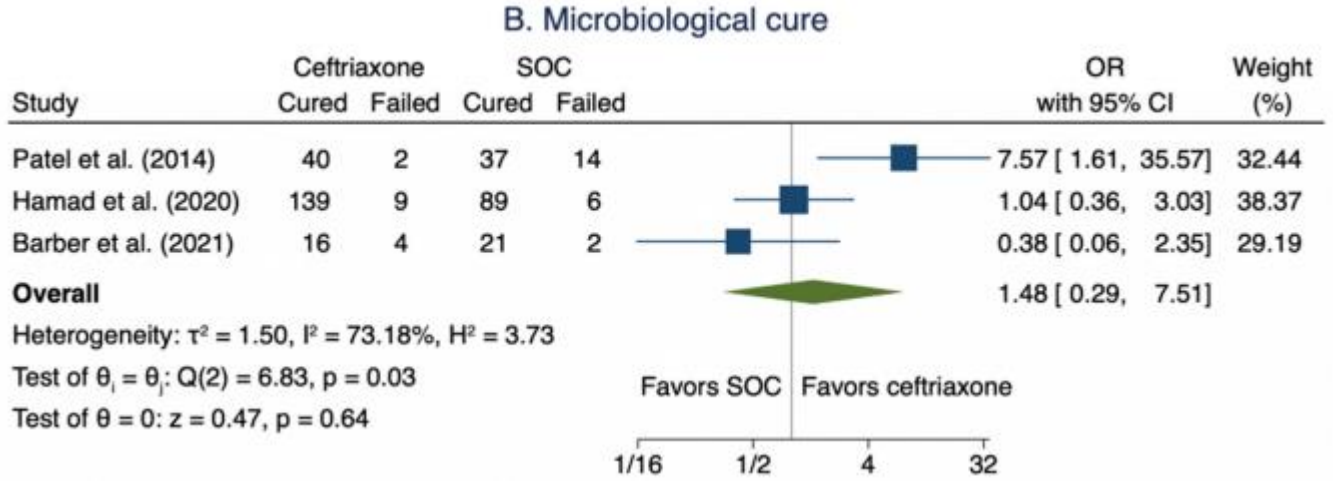
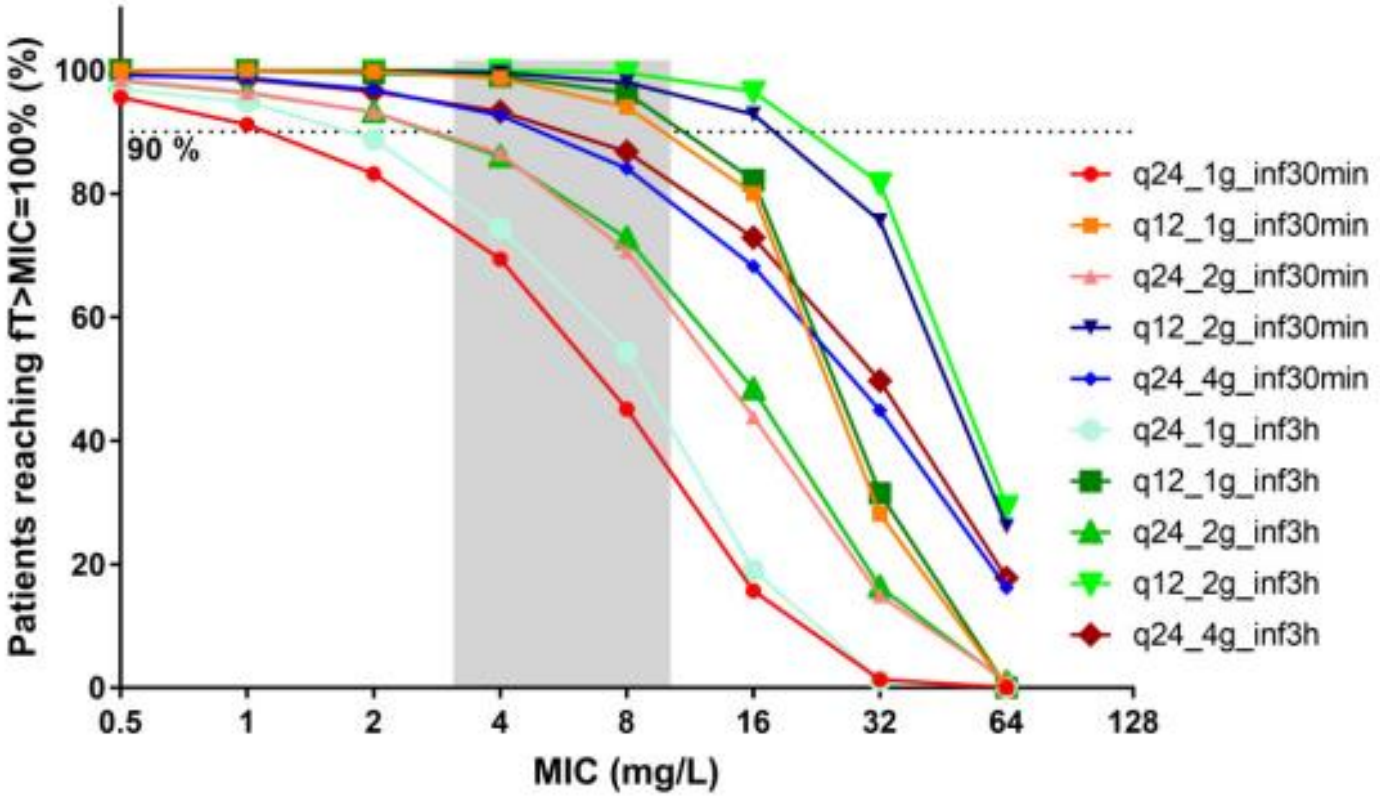


# Bactériémie à staphylocoque méti-S : C3G or not ?

## 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

J Antimicrob Chemother
doi:10.1093/jac/dky259

June, 2018

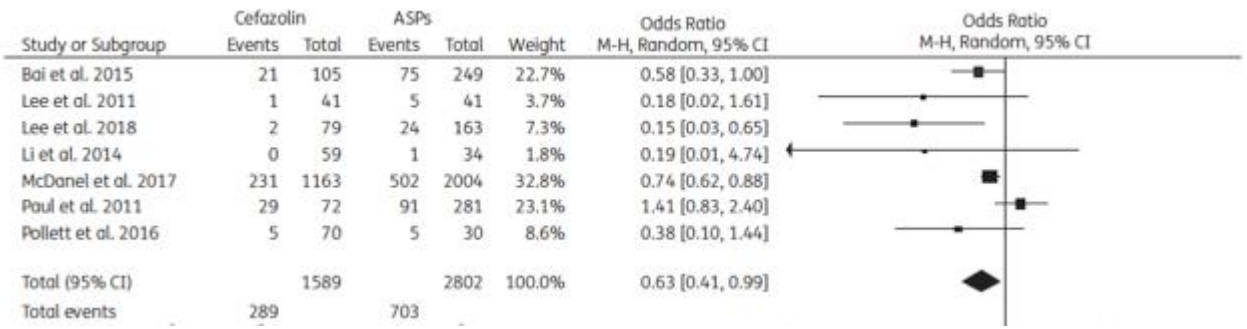
Journal of Antimicrobial Chemotherapy

**Optimal treatment of MSSA bacteraemias: a meta-analysis of cefazolin versus antistaphylococcal penicillins**

Monique R. Bidell, Nimish Patel and J. Nicholas O'Donnell *

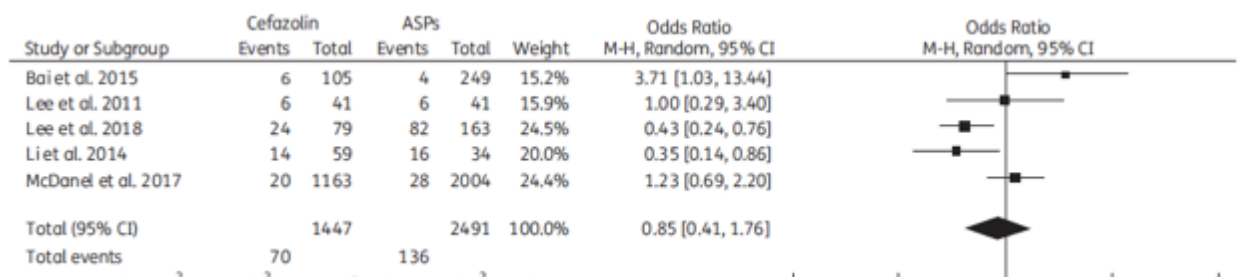
7 études rétrospectives
1589 pts céfazoline / 2802 pts ASP
EI : 8.5%
Localisation IIR : 25%

Mortalité J90



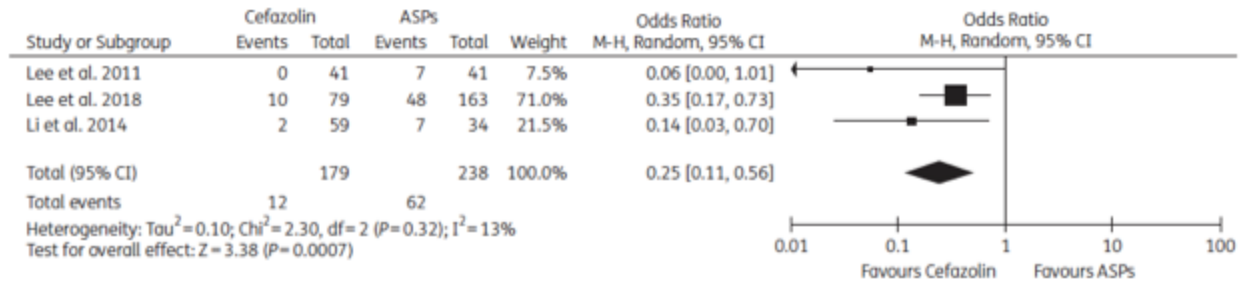
| Study or Subgroup | Cefazolin Events | Cefazolin Total | ASPs Events | ASPs Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Bai et al. 2015 | 21 | 105 | 75 | 249 | 22.7% | 0.58 [0.33, 1.00] |
| Lee et al. 2011 | 1 | 41 | 5 | 41 | 3.7% | 0.18 [0.02, 1.61] |
| Lee et al. 2018 | 2 | 79 | 24 | 163 | 7.3% | 0.15 [0.03, 0.65] |
| Li et al. 2014 | 0 | 59 | 1 | 34 | 1.8% | 0.19 [0.01, 4.74] |
| McDaniel et al. 2017 | 231 | 1163 | 502 | 2004 | 32.8% | 0.74 [0.62, 0.88] |
| Paul et al. 2011 | 29 | 72 | 91 | 281 | 23.1% | 1.41 [0.83, 2.40] |
| Pollett et al. 2016 | 5 | 70 | 5 | 30 | 8.6% | 0.38 [0.10, 1.44] |
| Total (95% CI) | | 1589 | | 2802 | 100.0% | 0.63 [0.41, 0.99] |
| Total events | 289 | | 703 | | | |

Echec clinique



| Study or Subgroup | Cefazolin Events | Cefazolin Total | ASPs Events | ASPs Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Bai et al. 2015 | 6 | 105 | 4 | 249 | 15.2% | 3.71 [1.03, 13.44] |
| Lee et al. 2011 | 6 | 41 | 6 | 41 | 15.9% | 1.00 [0.29, 3.40] |
| Lee et al. 2018 | 24 | 79 | 82 | 163 | 24.5% | 0.43 [0.24, 0.76] |
| Li et al. 2014 | 14 | 59 | 16 | 34 | 20.0% | 0.35 [0.14, 0.86] |
| McDaniel et al. 2017 | 20 | 1163 | 28 | 2004 | 24.4% | 1.23 [0.69, 2.20] |
| Total (95% CI) | | 1447 | | 2491 | 100.0% | 0.85 [0.41, 1.76] |
| Total events | 70 | | 136 | | | |

Tolérance



| Study or Subgroup | Cefazolin Events | Cefazolin Total | ASPs Events | ASPs Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Lee et al. 2011 | 0 | 41 | 7 | 41 | 7.5% | 0.06 [0.00, 1.01] |
| Lee et al. 2018 | 10 | 79 | 48 | 163 | 71.0% | 0.35 [0.17, 0.73] |
| Li et al. 2014 | 2 | 59 | 7 | 34 | 21.5% | 0.14 [0.03, 0.70] |
| Total (95% CI) | | 179 | | 238 | 100.0% | 0.25 [0.11, 0.56] |
| Total events | 12 | | 62 | | | |

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 2.30$, df = 2 ($P = 0.32$); $I^2 = 13\%$
Test for overall effect: $Z = 3.38$ ($P = 0.0007$)

0.01 0.1 1 10 100
Favours Cefazolin Favours ASPs

# Bactériémie à staphylocoque méti-S : céfazoline

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 |

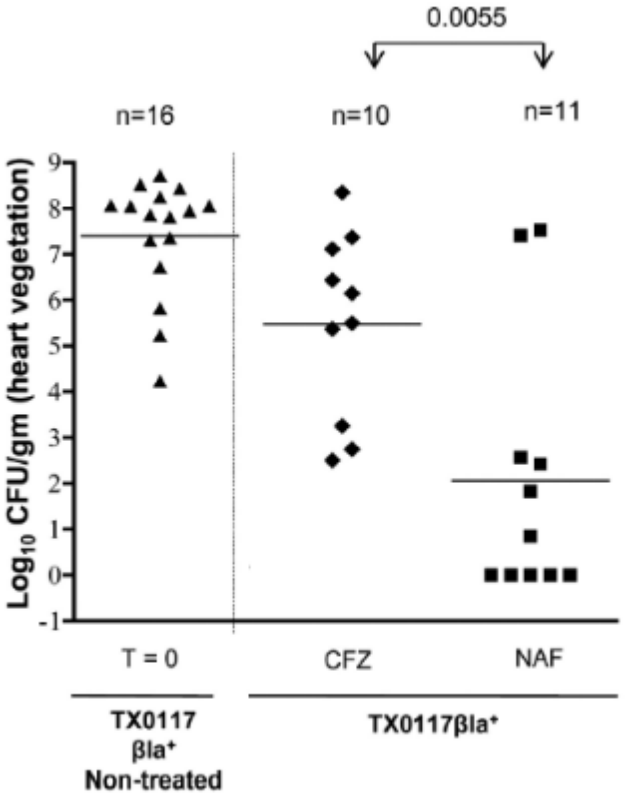
[a] CLSI breakpoint for nonsusceptibility.

***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

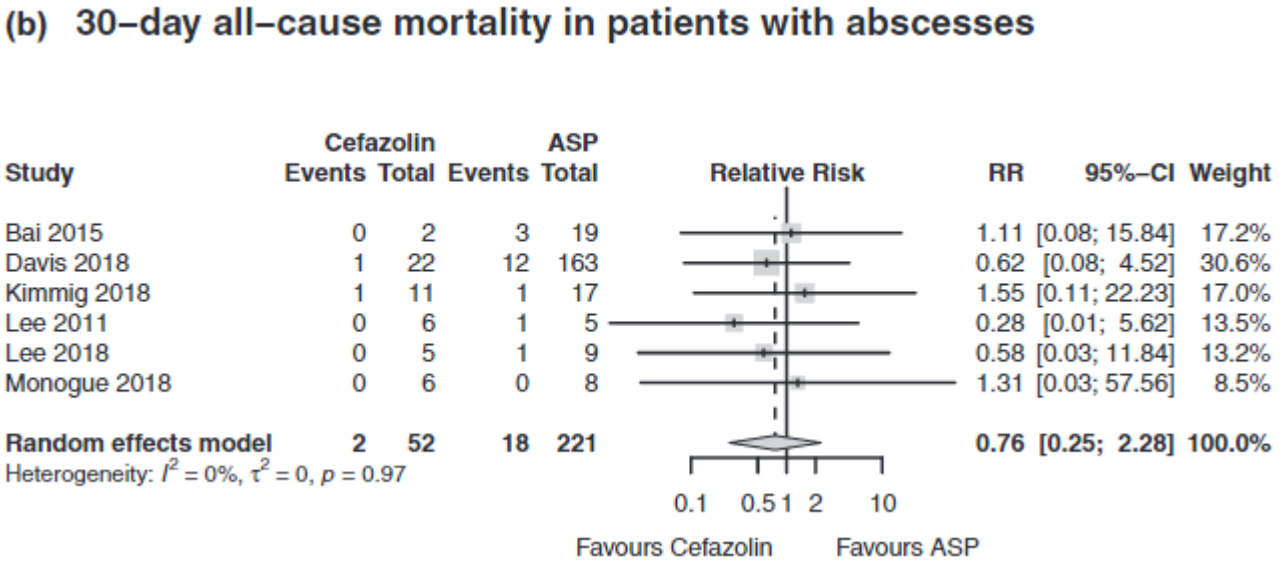
Clinical Infectious Diseases 2003; 37:1194–8

Esteban C. Nannini,[1,2] Kavindra V. Singh,[1,3] 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 : céfazoline

Cefazolin versus anti-staphylococcal penicillins for the treatment of patients with *Staphylococcus aureus* bacteraemia

S. Weis [1,2,3,*], M. Kesselmeier [2,4], J.S. Davis [5,6], A.M. Morris [7], S. Lee [8], A. Scherag [2,4,9], S. Hagel [1,2,†], M.W. Pletz [1,†]



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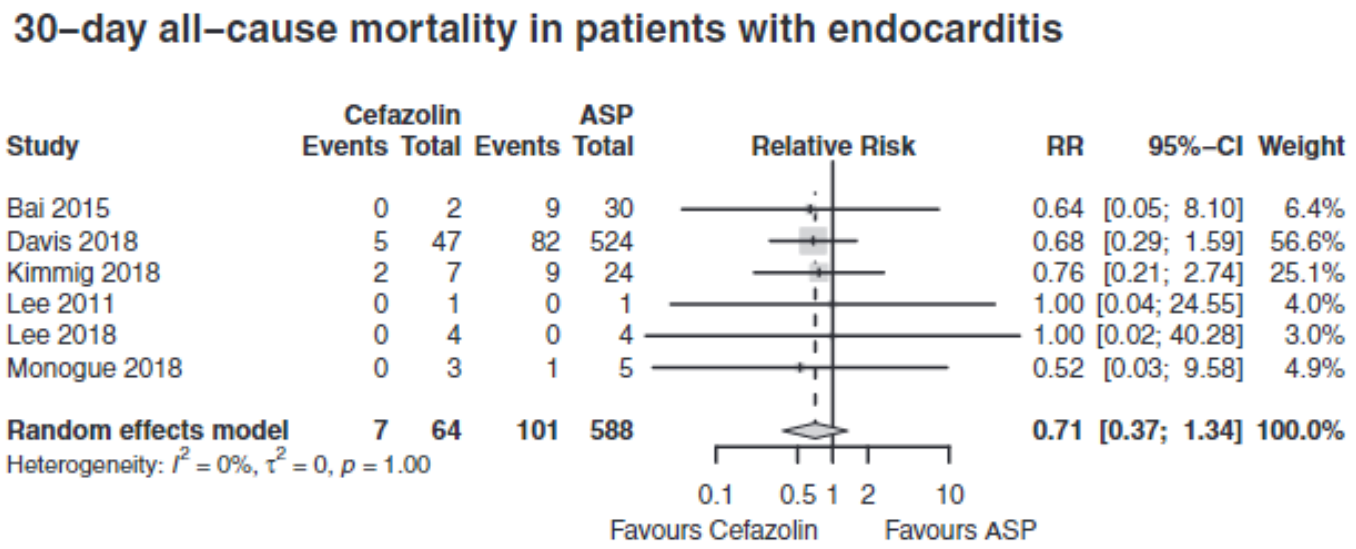
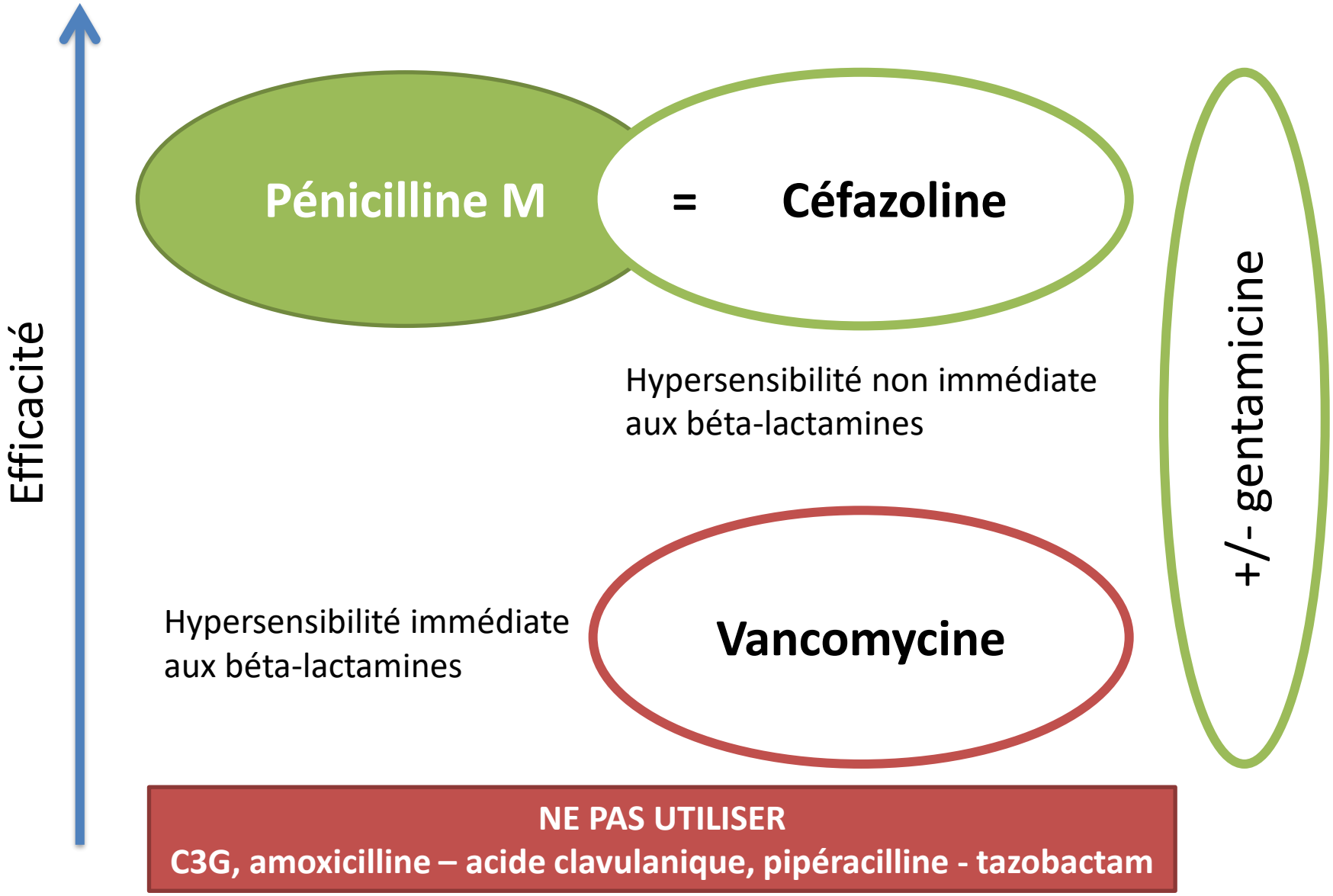


# Bactériémie à staphylocoque méti-S



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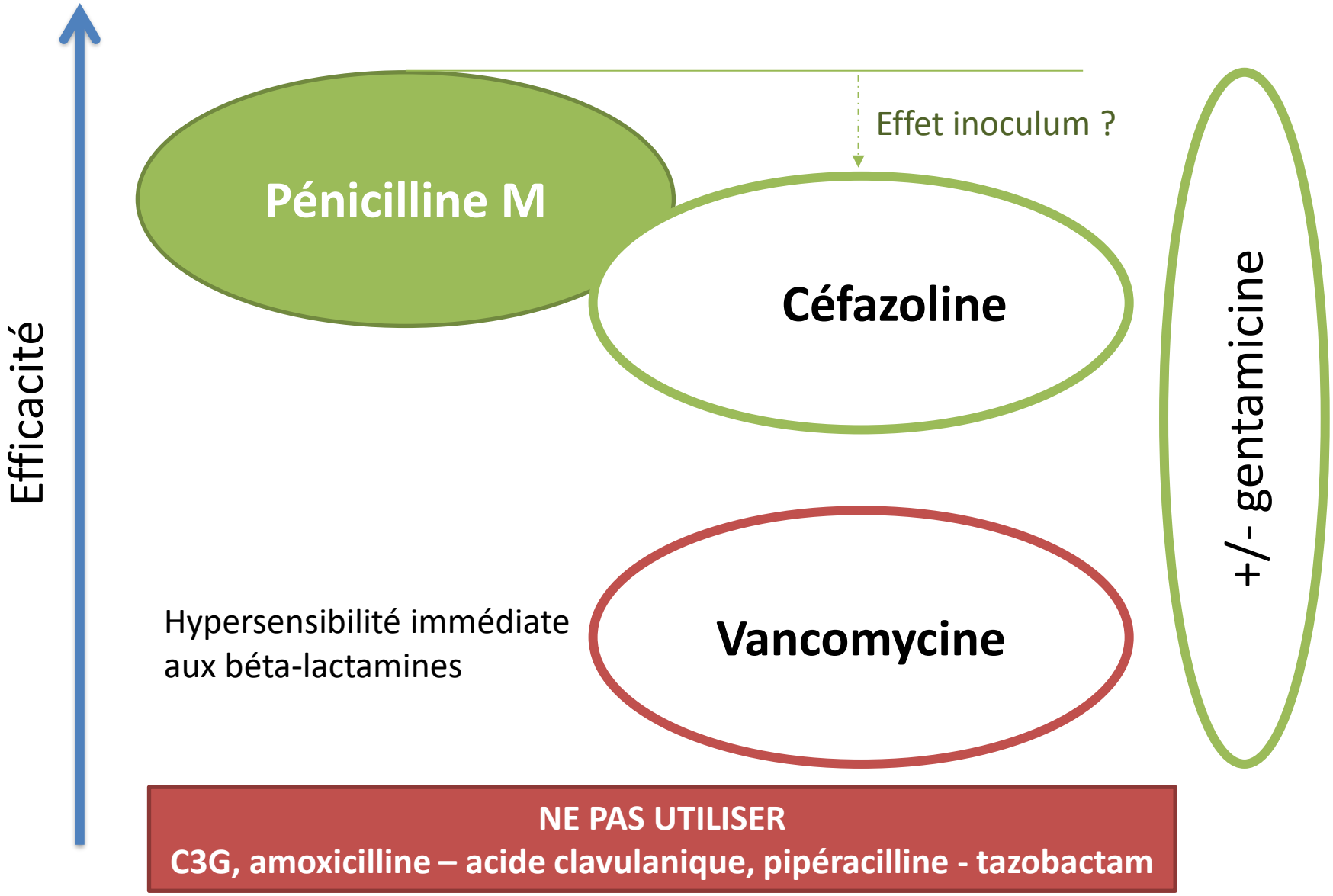

# Bactériémie à staphylocoque méti-S : bithérapies ?

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

# Bactériémie à staphylocoque méti-S : bithérapies ?

| SOC + | Type d'études | Population | Re | D |
|---|---|---|---|---|
| Rifampicine | RCT | MRSA, MSSA | | 1929035<br>29249276 |
| Aminoside | Observationnelles<br>RCT | | jours de moins<br>Toxicité +++ | Multiples |
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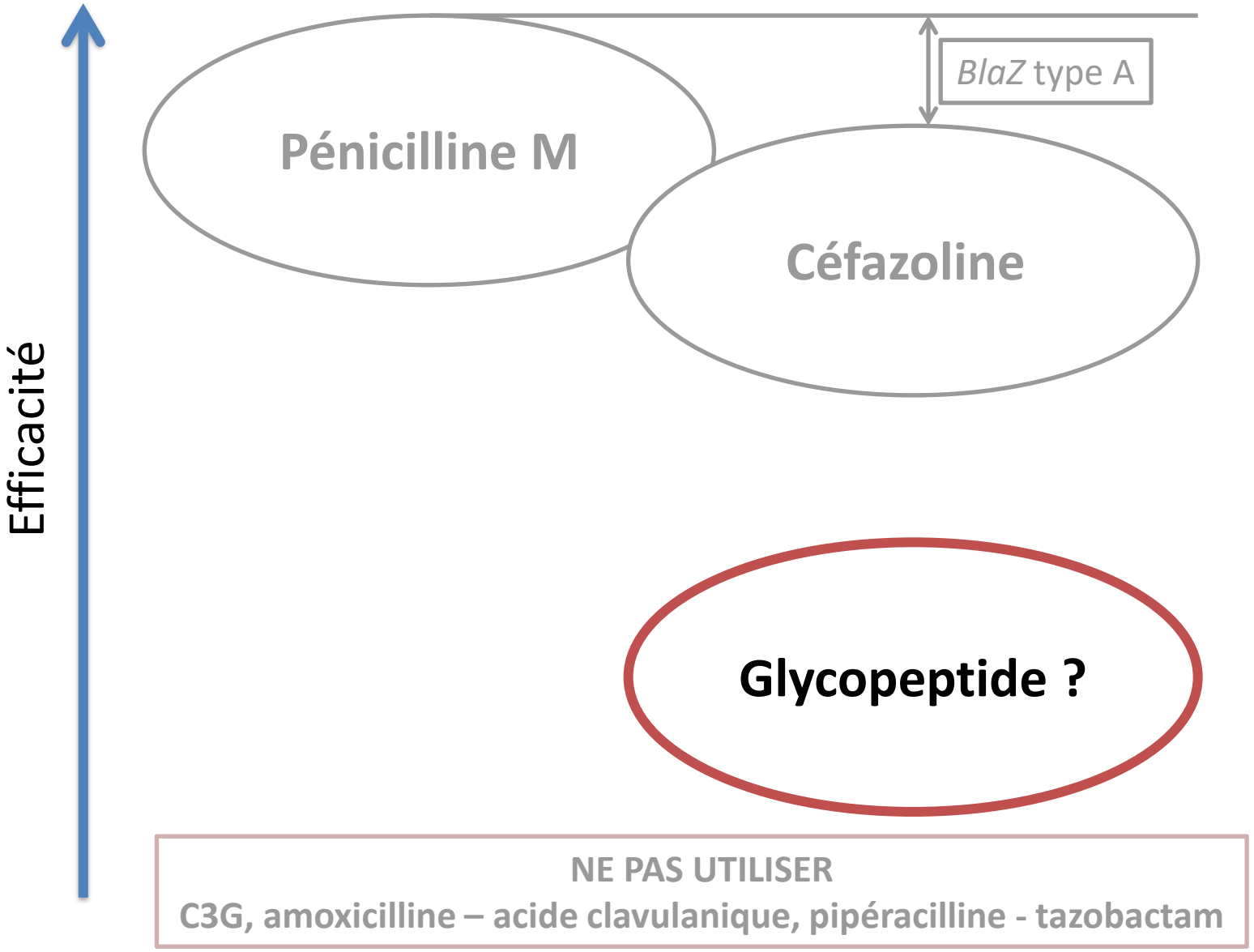
RESCUE THERAPY

# Bactériémie à staphylocoque méti-R



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

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

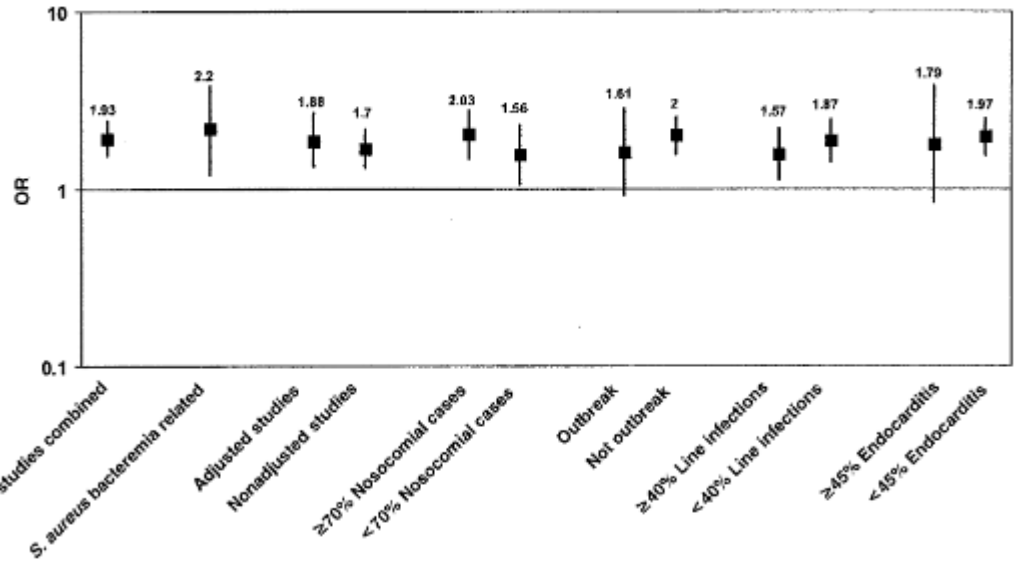
# Bactériémie à *S. aureus* méti-R : glycopeptides

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

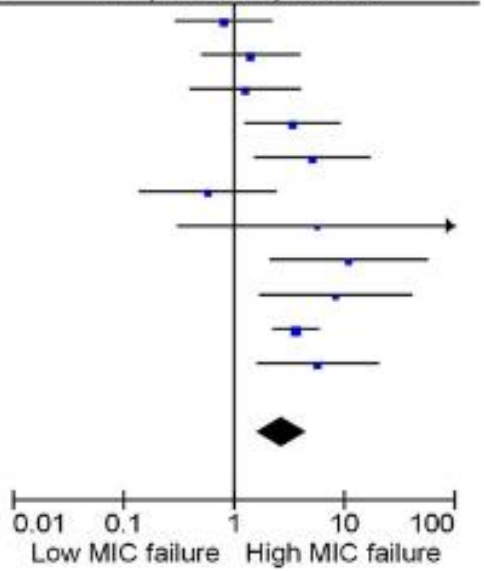
S. J. van Hal,[1,2] T. P. Lodise,[3] and D. L. Paterson[4]

*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)

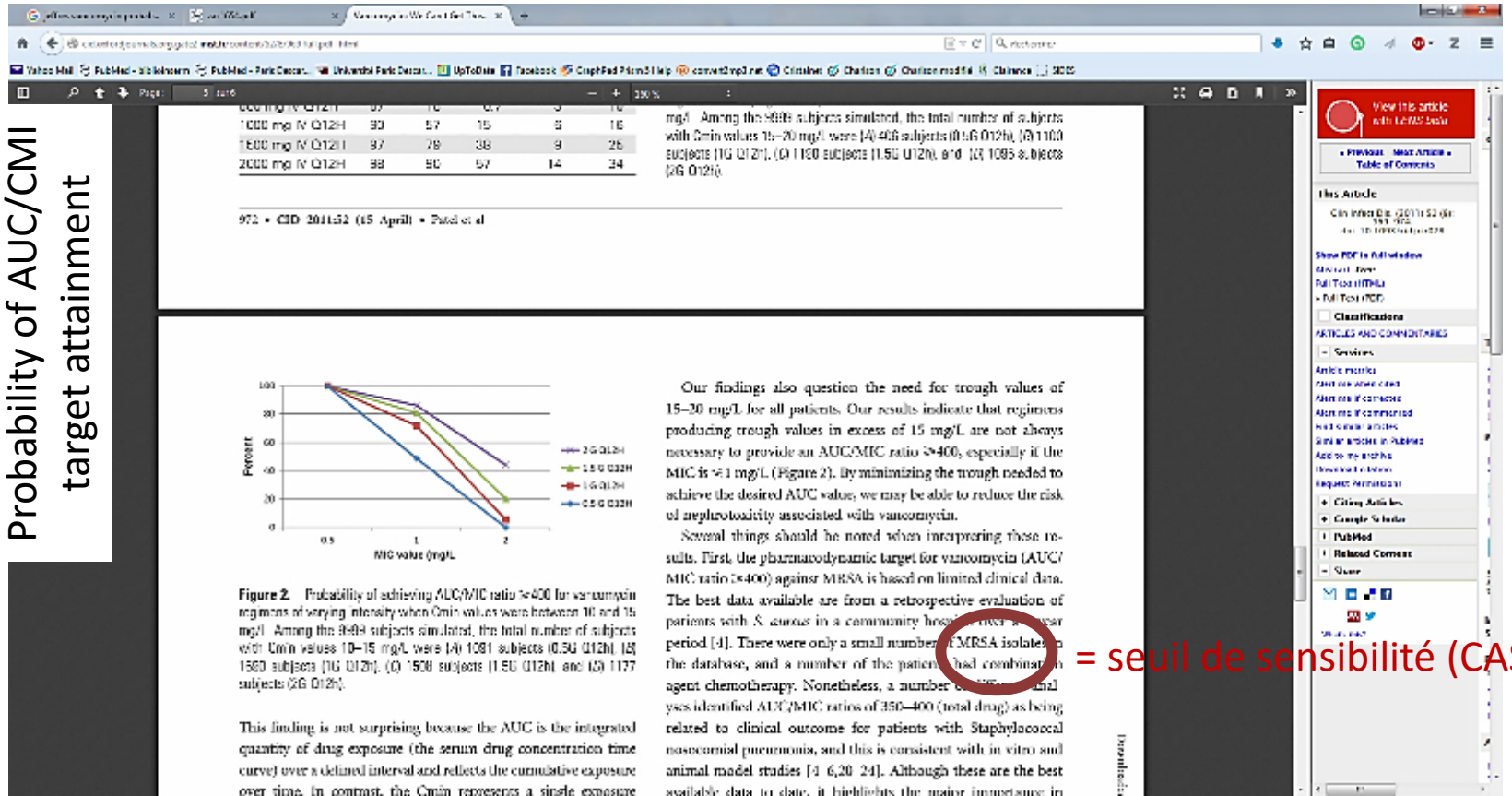


# Bactériémie à *S. aureus* méti-R

## 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



# 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 |

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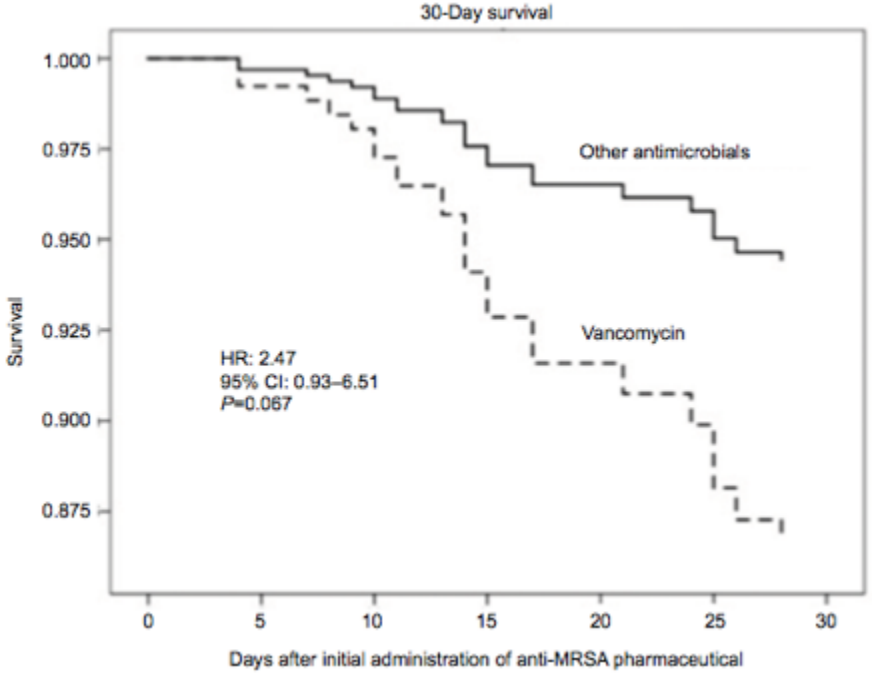
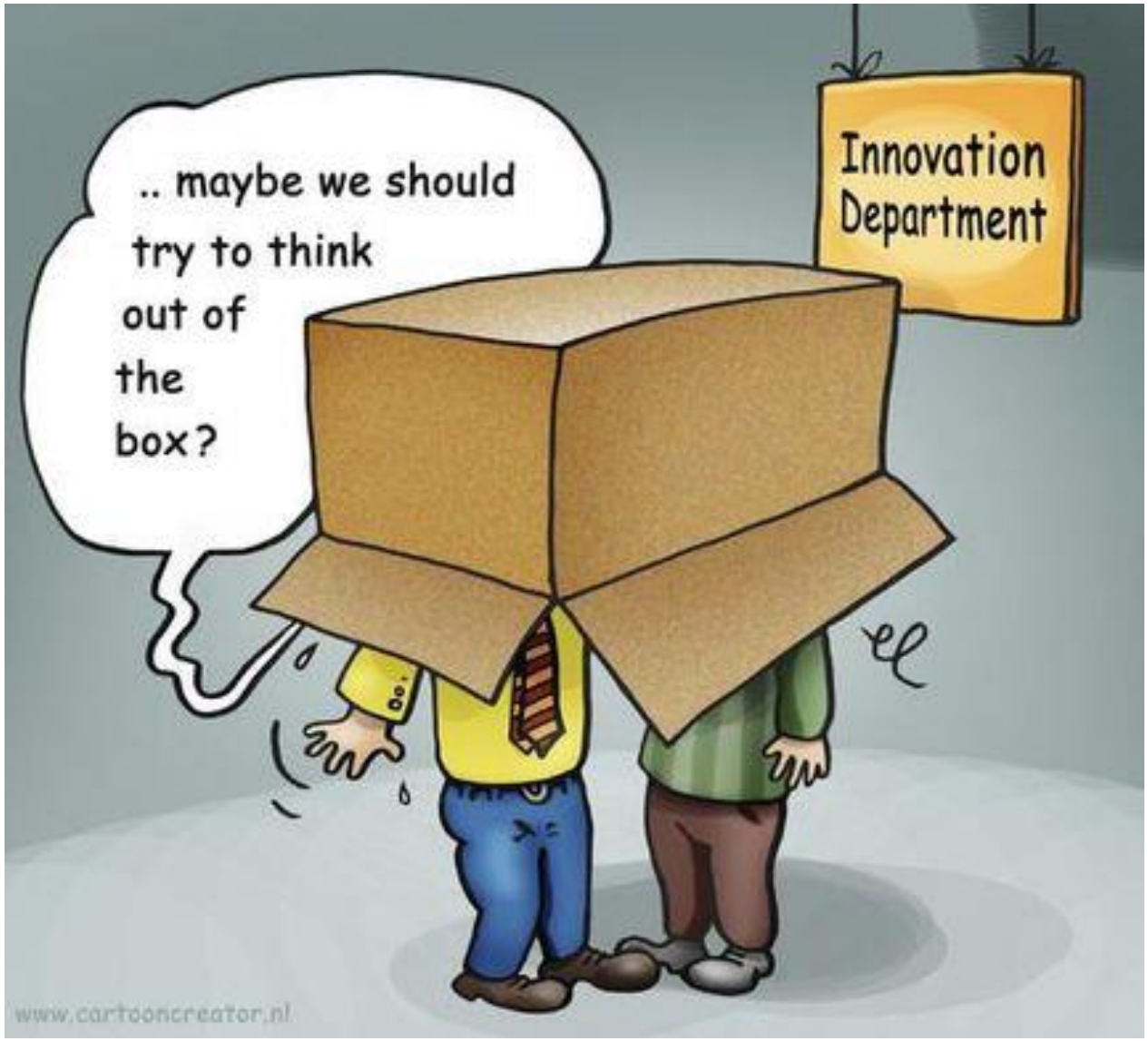



| Variable | Cox model | | | | | |
|---|---|---|---|---|---|---|
| | Unadjusted | | | Adjusted | | |
| | HR | 95% CI | *P*-value | HR | 95% CI | *P*-value |
| Vancomycin versus non-vancomycin | | | | | | |
| 30-day mortality | 2.28 | 0.88–5.93 | 0.09 | 2.47 | 0.93–6.51 | 0.06 |
| Newly acquired renal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

# « Nouveaux » anti-staphylococciques

# A garder en tête …



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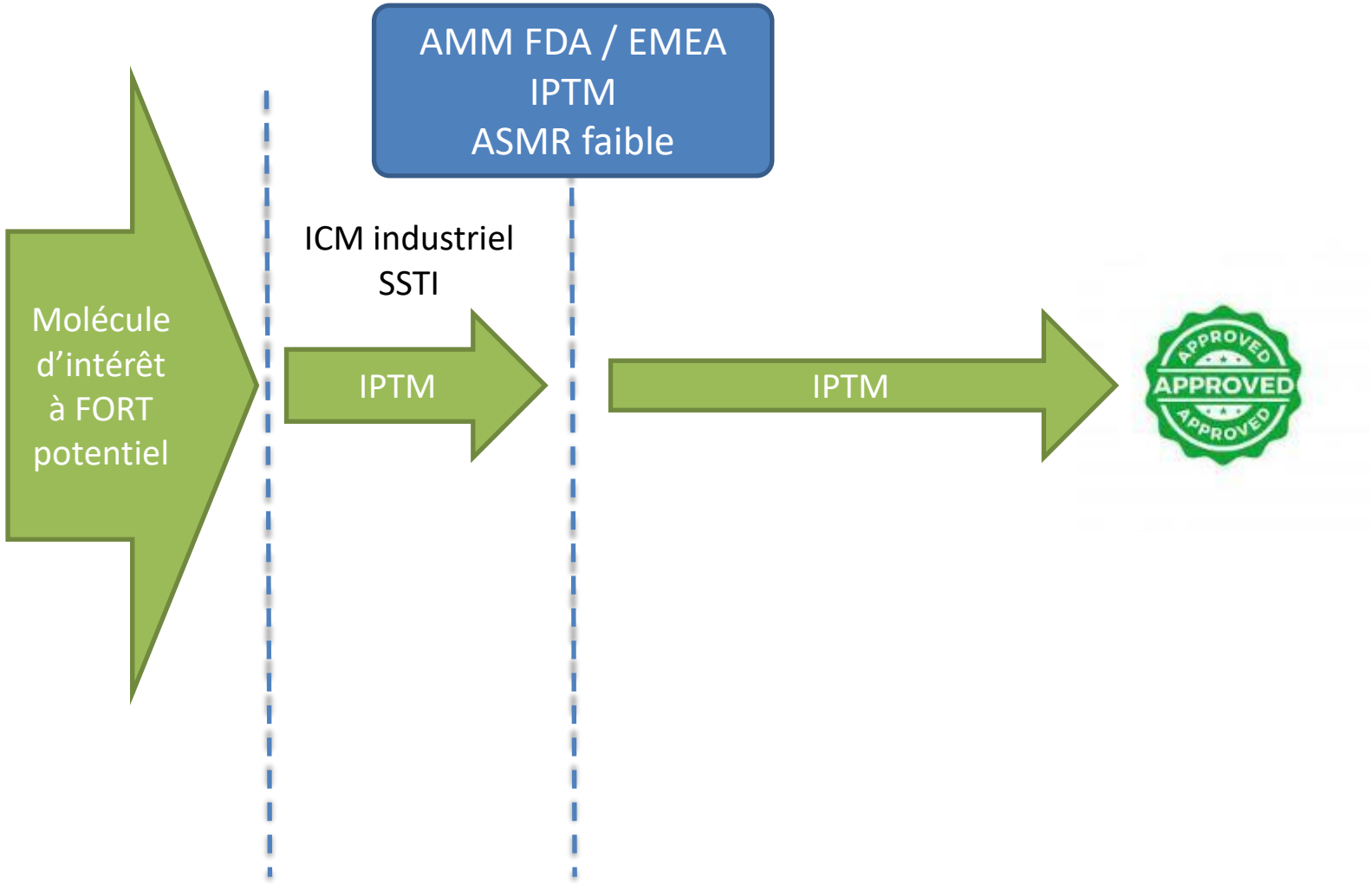

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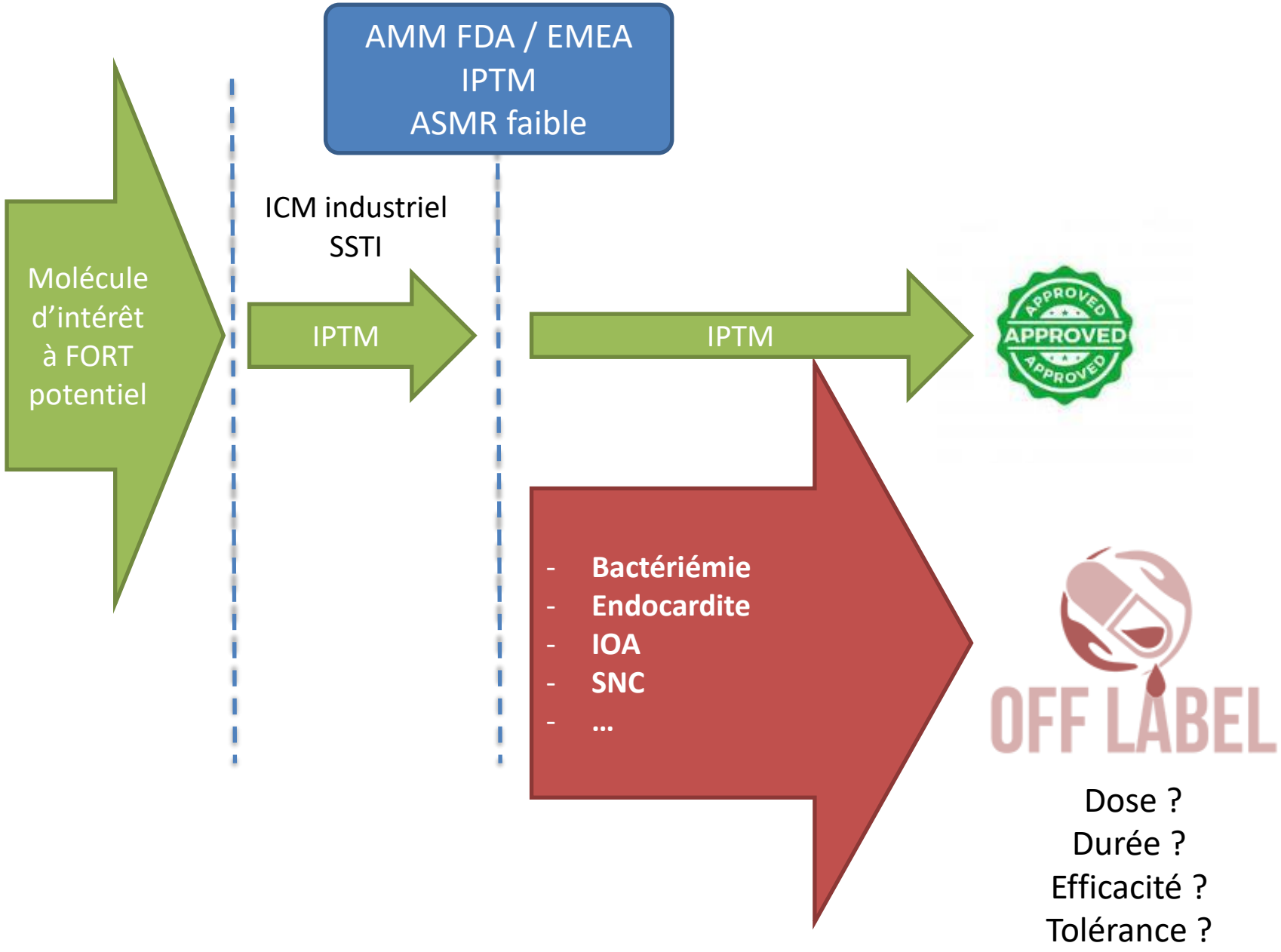
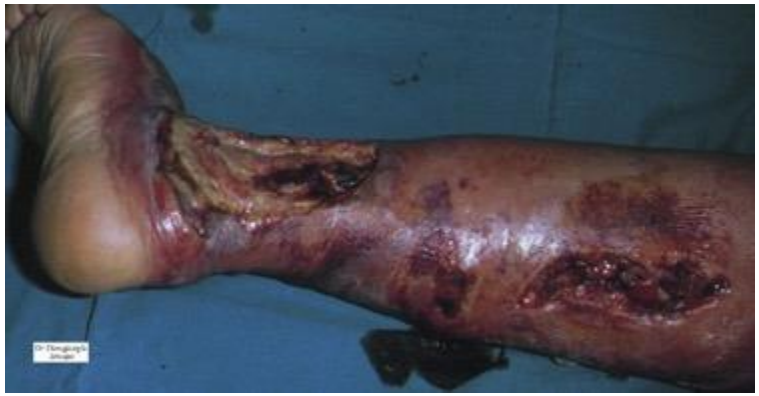
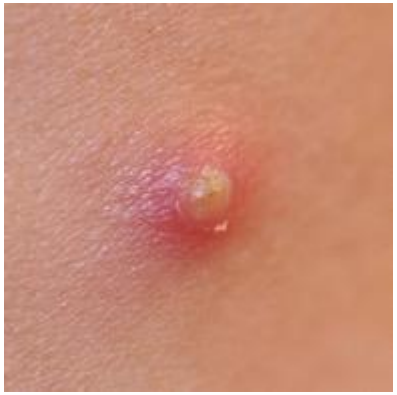


# A garder en tête … (2)

## Infections « compliquées » de la peau et des tissus mous





Age
Comorbidités
Bactériémie
Chirurgie
Documentation
Comparateur

# A garder en tête … (3)









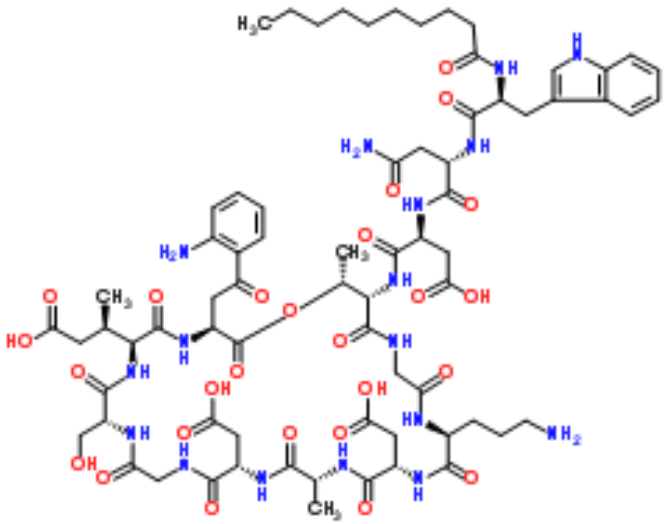


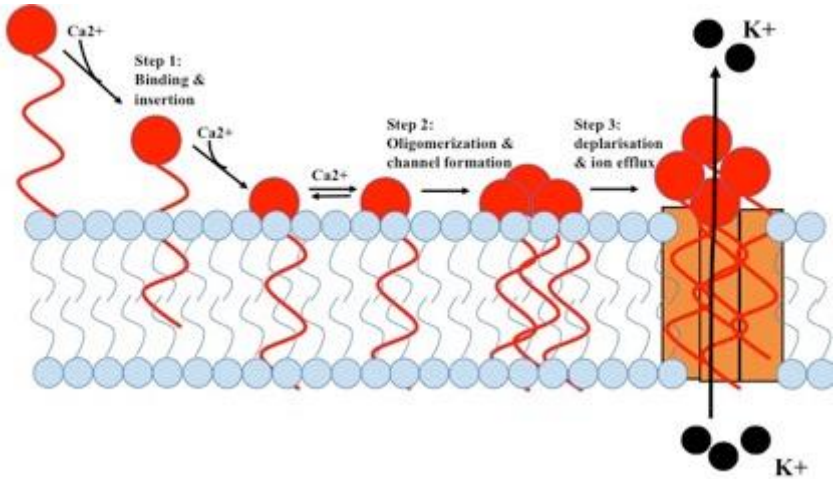




# Daptomycine (CUBICIN®)

- **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)





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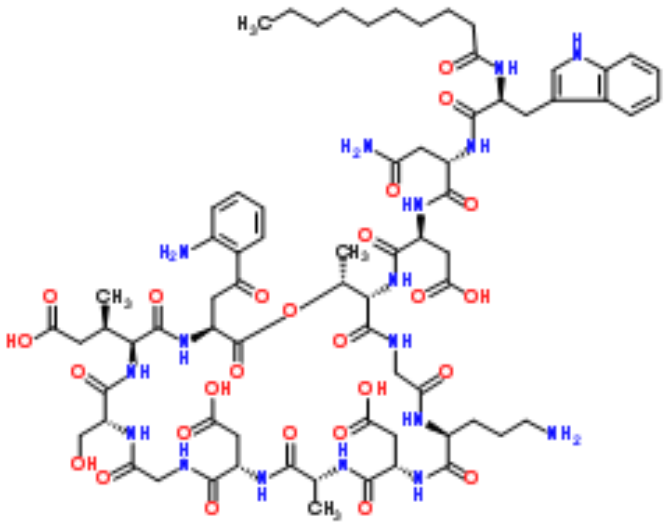
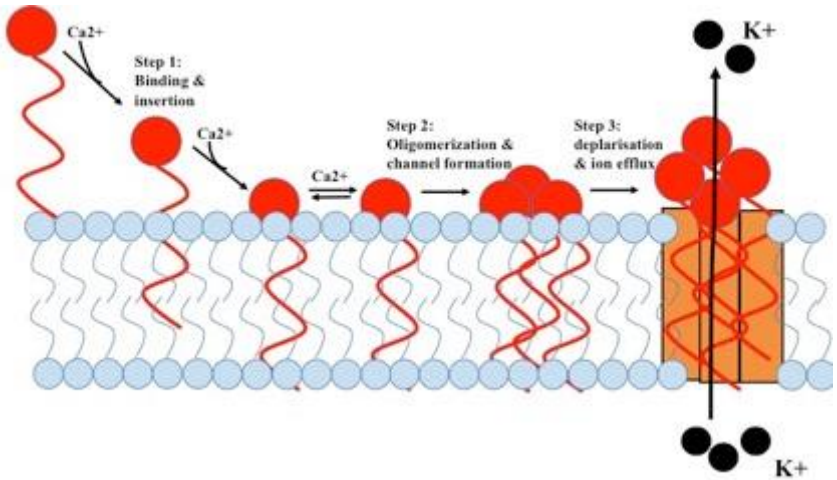
- **Adaptation :** 1/48h si DFG < 30
- **Coût :** [illegible] € / j (hospitalier)

**Générique !!**





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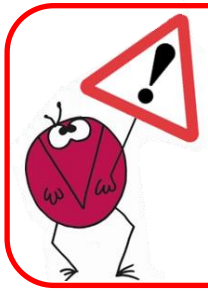


- **Rhabdomyolyse +++**
ARRET DES STATINES, CPK
- **PNP éosinophiles**
- neuropathie périphérique
- IRA (rare)

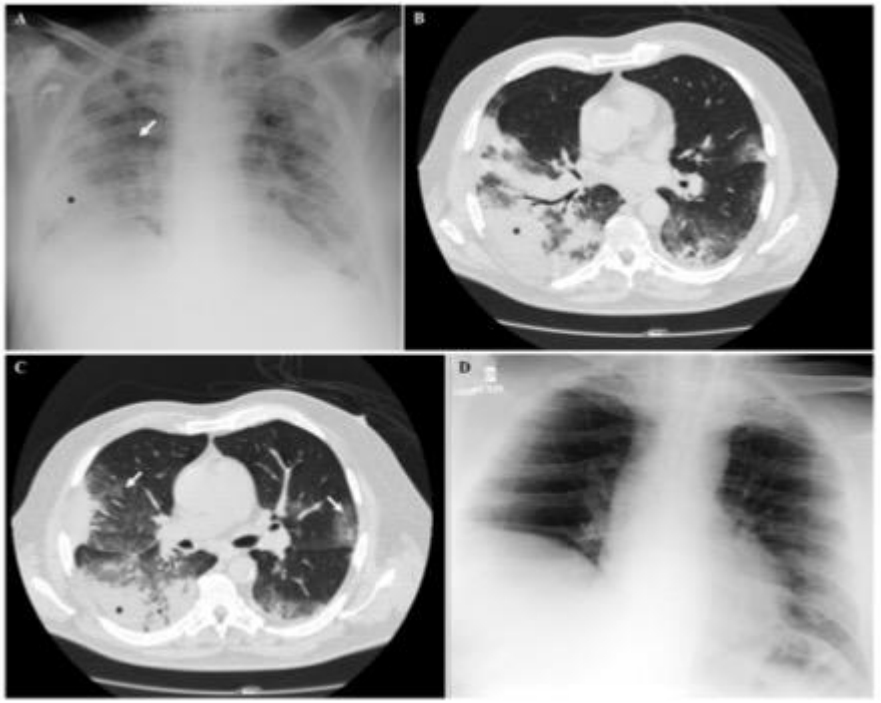
Seventeen Cases of Daptomycin-Induced Eosinophilic Pneumonia in a Cohort of Patients Treated for Bone and Joint Infections: Proposal for a New Algorithm

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

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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**

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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

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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

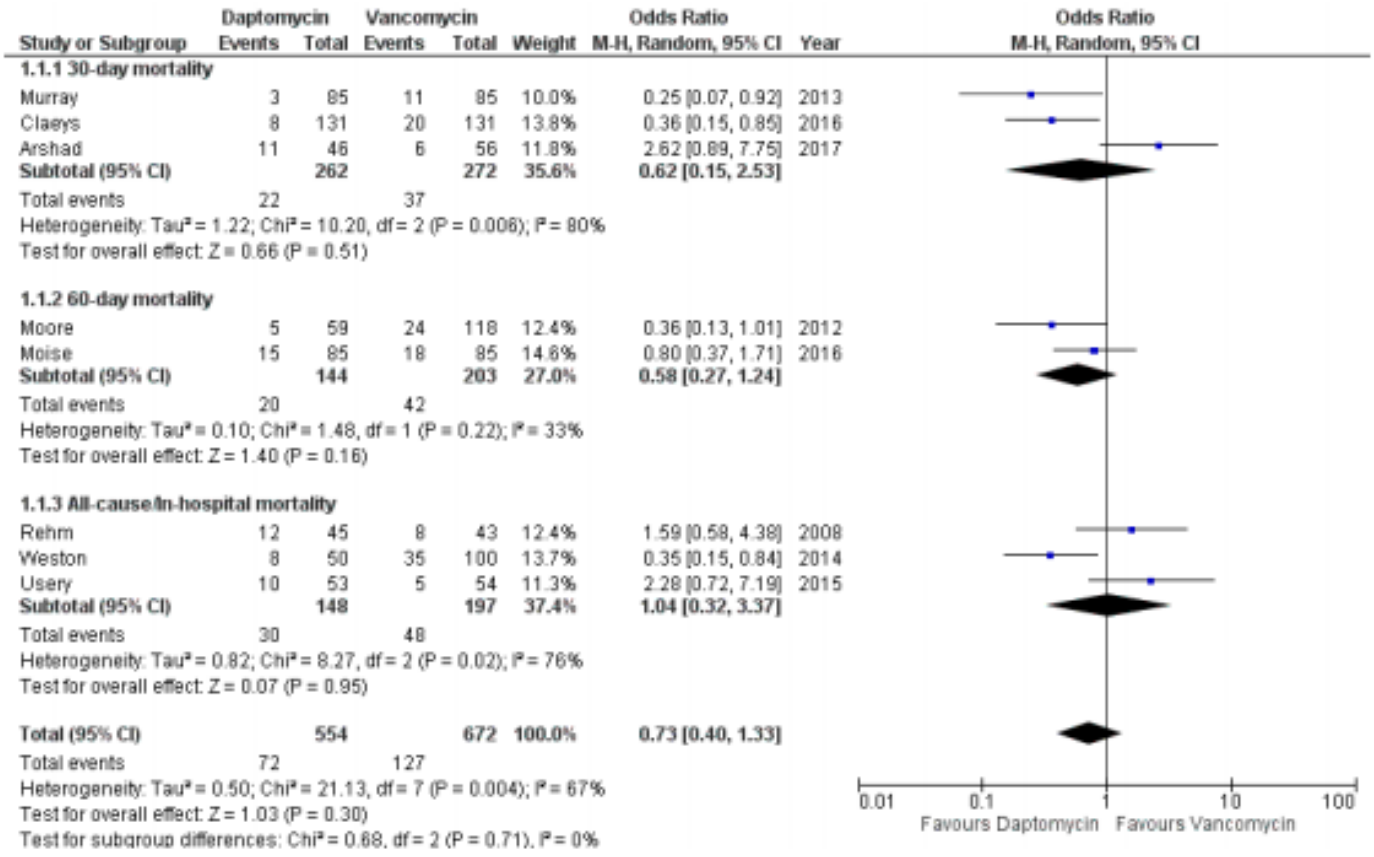
# Daptomycine vs. Vancomycine

*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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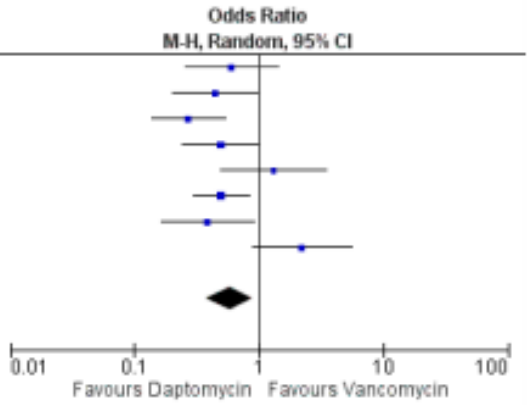
ECHEC CLINIQUE

| 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 | | | | |

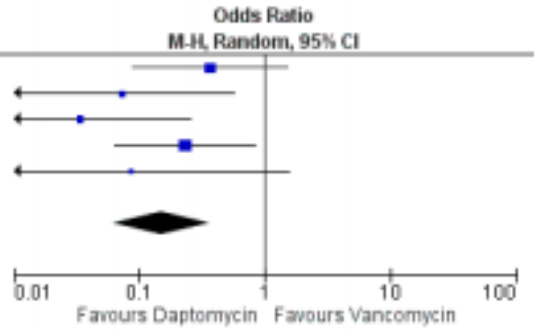
Heterogeneity: Tau² = 0.22; Chi² = 17.35, df = 7 (P = 0.02); I² = 60%
Test for overall effect: Z = 2.52 (P = 0.01)




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

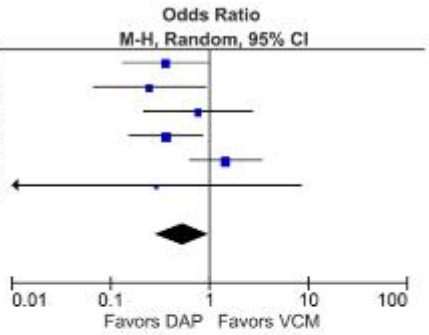
Masaru Samura [1,†], Yuki Kitahiro [1,†], Sho Tashiro [1], Hiromu Moriyama [1], Yuna Hamamura [1], Isamu Takahata [1], Rina Kawabe [1], Yuki Enoki [1,*], Kazuaki Taguchi [1], Yoshio Takesue [2,3] and Kazuaki Matsumoto [1]

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)

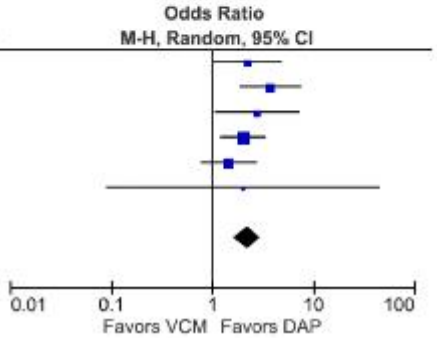



ECHECS CLINIQUES

(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

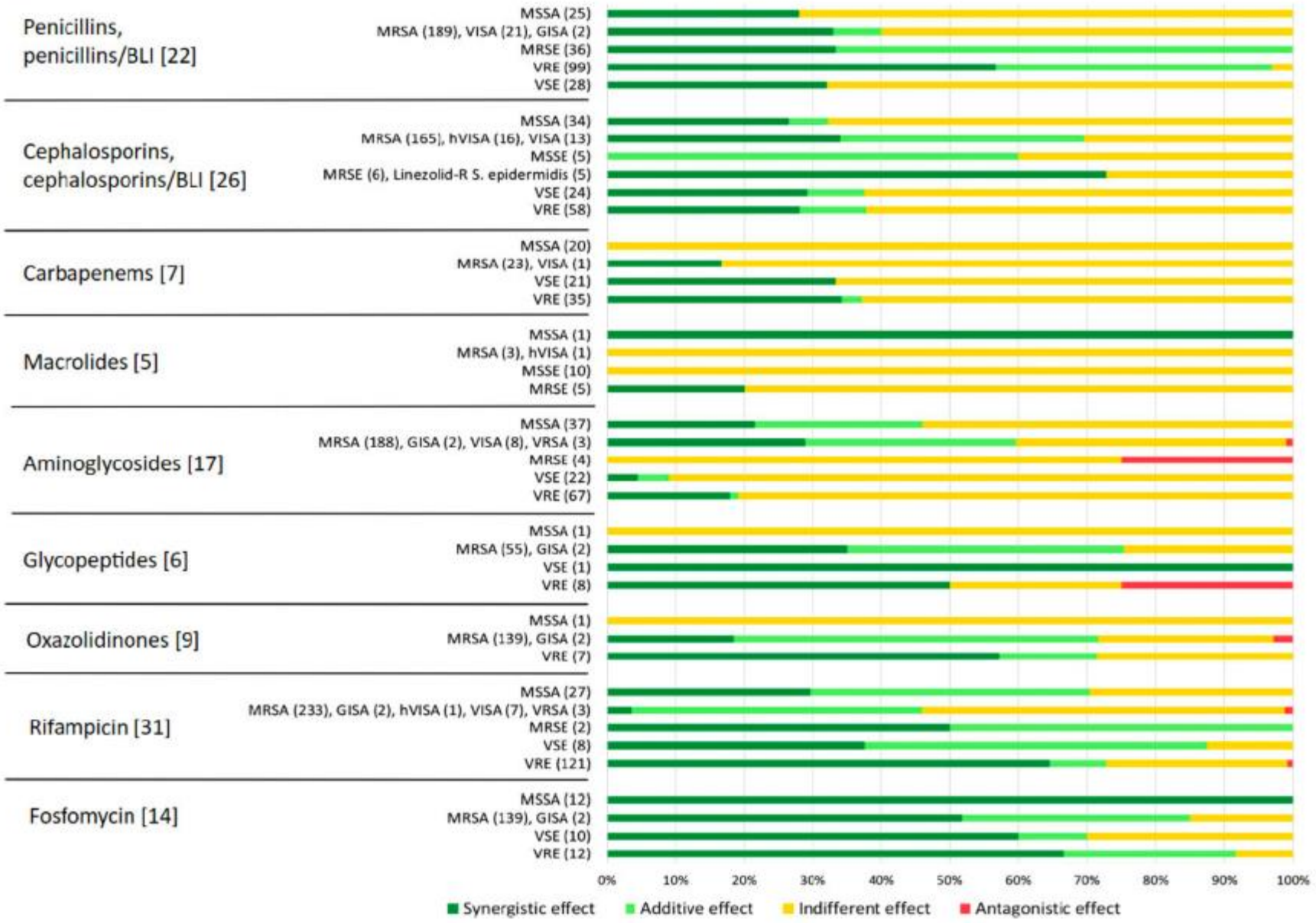
- Traitement prolongé
- Pré-exposition à la vancomycine

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)

## Daptomycine + fosfomycine

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

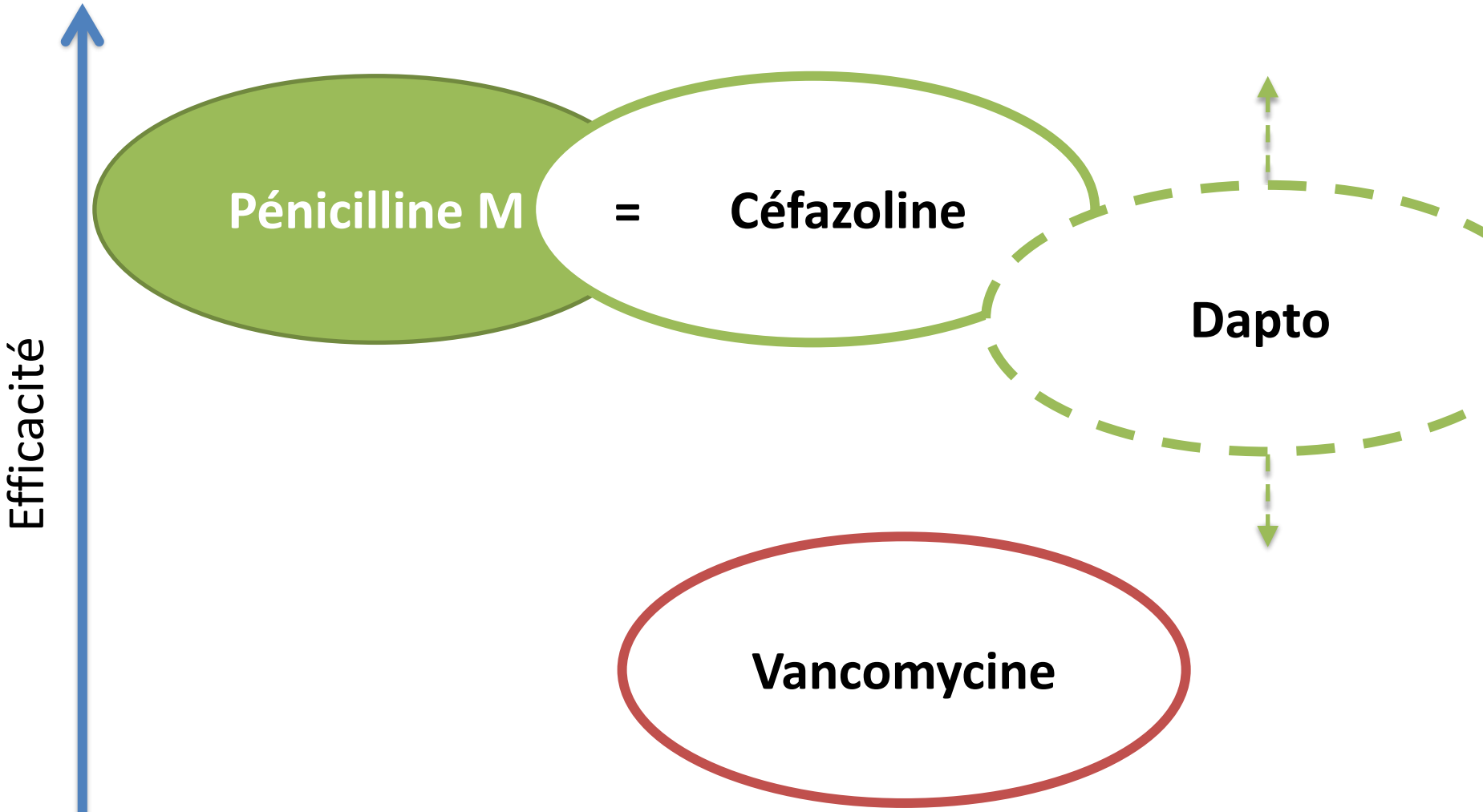
## Daptomycine + rifampicine

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

## Daptomycine + cotrimoxazole

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

# Bactériémie à staphylocoque

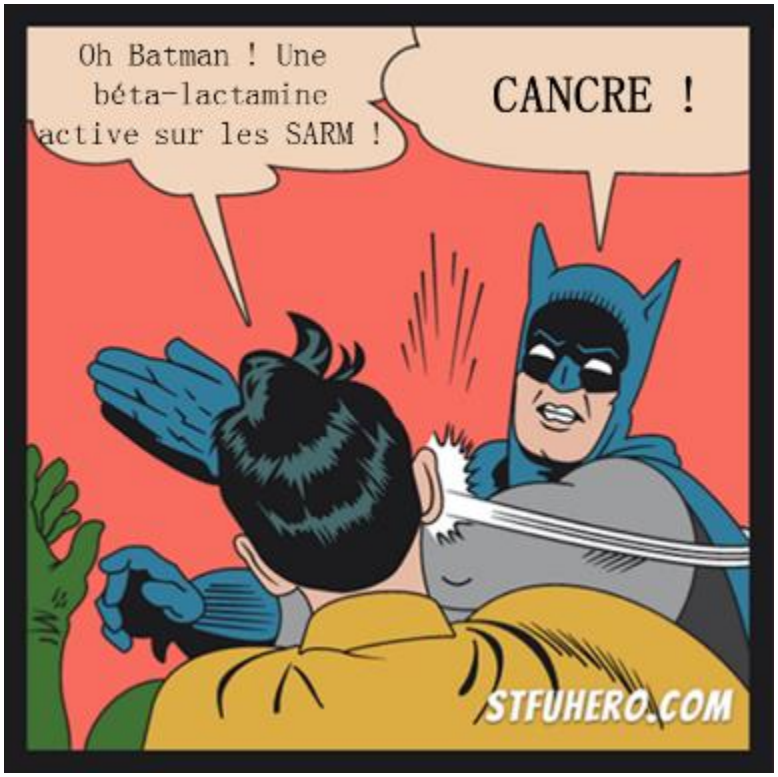



NE PAS UTILISER

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)



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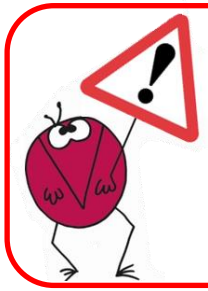
- **Coût :** 180-200 € / j (hospitalier)

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]

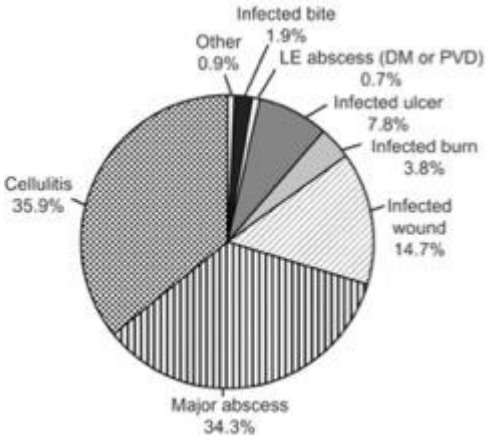
AAC Accepted Manuscript Posted Online 26 October 2015
Antimicrob. Agents Chemother. doi:10.1128/AAC.01471-15


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]

[1]Duke Clinical Research Institute, Durham, North Carolina; [2]Cerexa, Inc., Oakland, and [3]AxiStat, Inc, San Francisco, California; [4]Leeds Teaching Hospitals and University of Leeds, Leeds, United Kingdom

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

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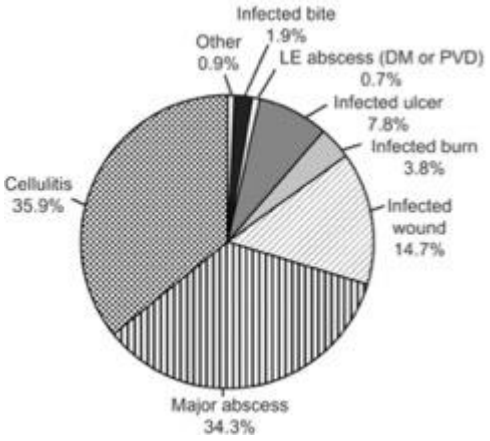
Infections « compliquées » PTM

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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 :

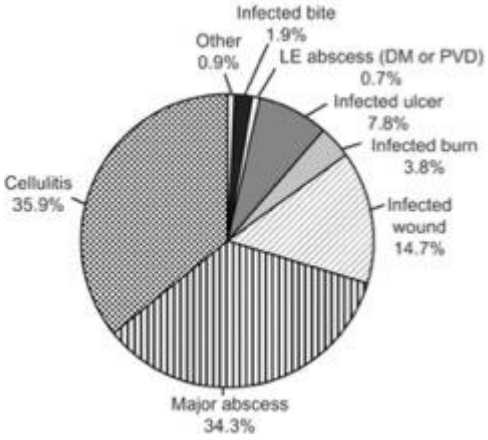
- Infections graves ?
- Immunodéprimés ?
- SARM, PSDP ?

| | |
|---|---|
| **stratégie thérapeutique** | Dans le traitement des PAC<br>La ceftaroline n'a pas démontré d'intérêt dans les pneumopathies communautaires en raison :<br>- de l'absence de données d'efficacité en cas de pneumopathies à staphylocoque et à *S. pneumoniae* non sensibles à la pénicilline,<br>- d'un risque de sélection de résistance du à son spectre trop large.<br>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 :**<br>- **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 »**<br>- **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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## Pneumopathies

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

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

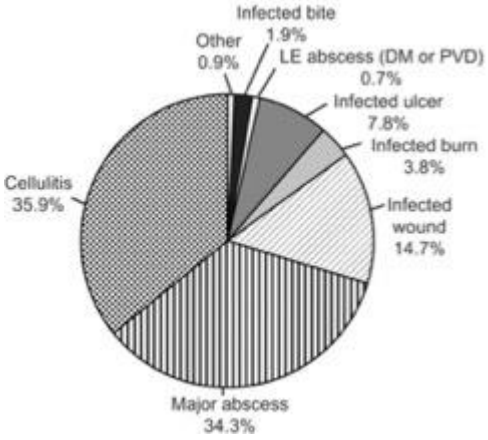
*Original Research*

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

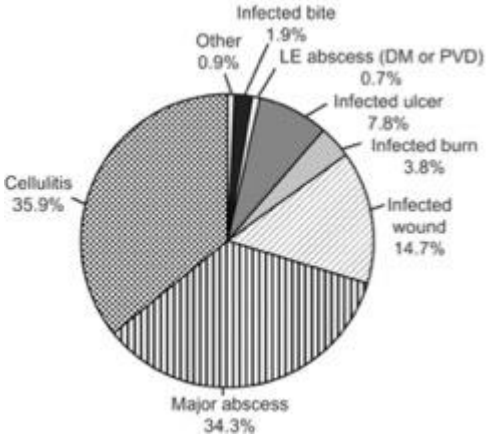
+ DAPTOMYCINE ?

| 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

**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]

OFF-LABEL

Bactériémies

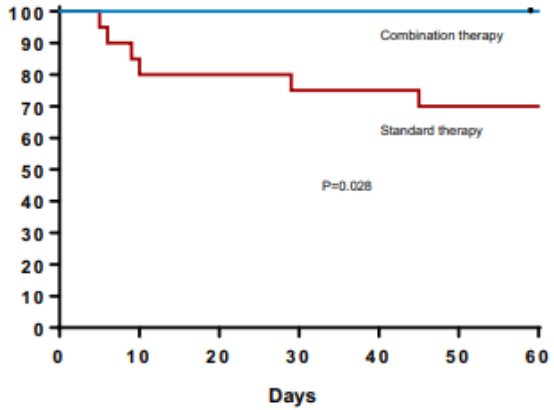
+ DAPTOMYCINE ?

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

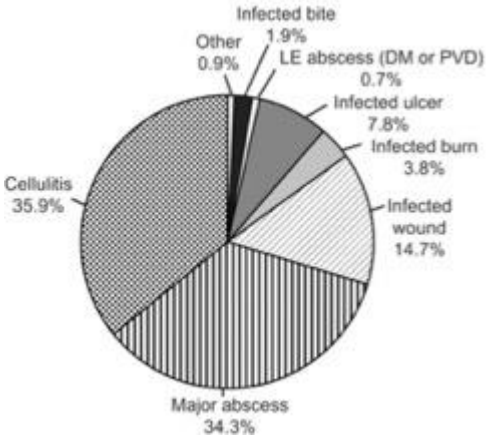
23 Patients
Standard Monotherapy
Vancomycin n=21; Daptomycin n= 2



# Ceftaroline (ZINFORO®)

APPROVED

Infections « compliquées » PTM

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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,[3] Tanya Baculik,[3] Gary W. Witherell,[3] Ian Critchley,[3] Anita F. Das,[3] and Dirk Thye[3]

[1]Duke Clinical Research Institute, Durham, North Carolina; [2]Cerexa, Inc., Oakland, and [3]AxiStat, Inc, San Francisco, California; [4]Leeds Teaching Hospitals and University of Leeds, Leeds, United Kingdom

**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]

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®)

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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 :<br>- <u>modéré</u> dans l'indication « traitement chez l'adulte, des pneumonies nosocomiales à l'exclusion des pneumonies acquises sous ventilation mécanique »<br>- <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.<br>• 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.<br>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.<br>• 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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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*

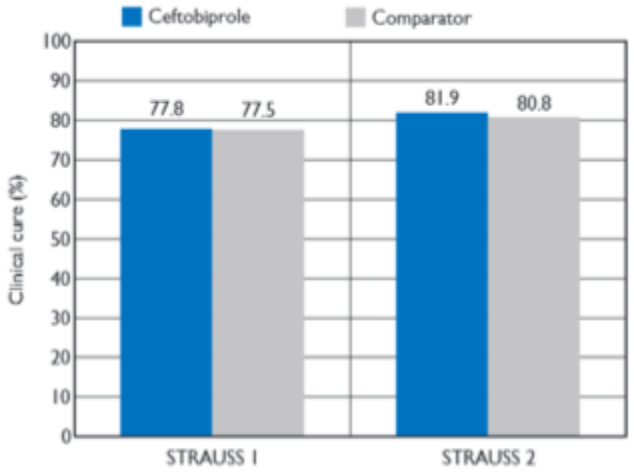


Figure 1 Clinical cure rates for the intent-to-treat population.
(Data from Noel GJ, Straus RS, Amsler K, et al. *Antimicrob Agents Chemother* 2008; 52:37–44;[24] and Noel GJ, Bush K, Bagchi P, et al. *Clin Infect Dis* 2008;46:647–655.[26])

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

Cellulitis < 20%

# Ceftobiprole (MABELIO®)

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OFF-LABEL

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Stanley C. Deresinski*

Bactériémies ? EI ? IOA ? SNC ?

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 2005, p. 884–888
0066-4804/05/$08.00+0 doi:10.1128/AAC.49.3.884–888.2005

Vol. 49, No. 3

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

**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) |

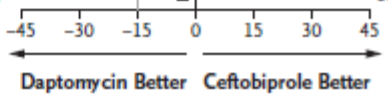
# Ceftobiprole (MABELIO®)

## 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

| 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) |



# Tédizolide (SIVEXTRO®)

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

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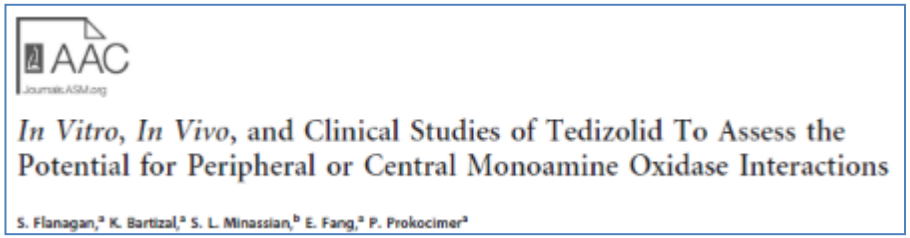
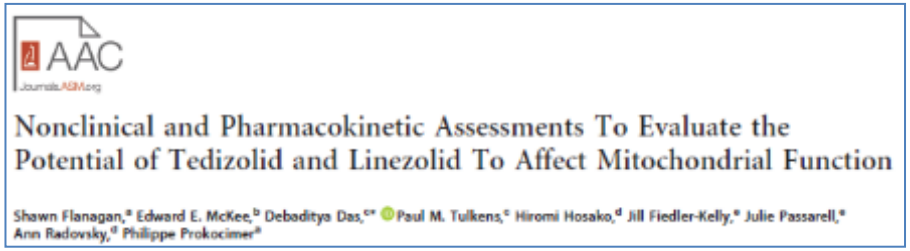
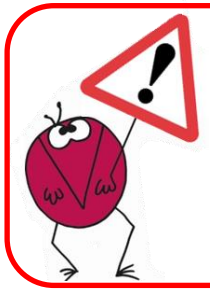



Plus forte inhibition des protéines mitochondriales mais liaison moins prolongée (effet cumulatif)
9 mois de ttt (rat) : moins d'EI neuro et hémato



- Hématotoxicité ?
- Neurotoxicité moindre que le LNZ ?

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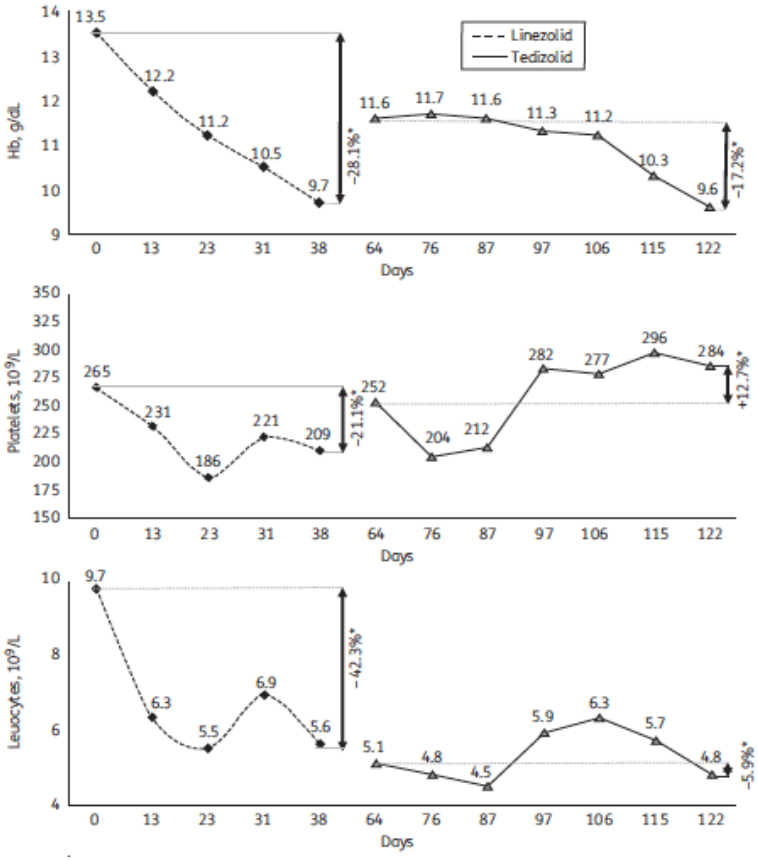
*J Antimicrob Chemother*
doi:10.1093/jac/dkw484

**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]**

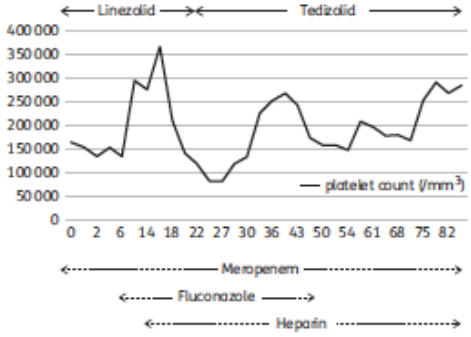



*J Antimicrob Chemother*
doi:10.1093/jac/dkx097

**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®)

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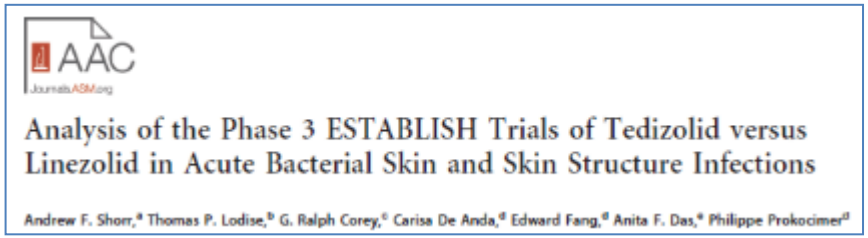
Infections « aiguës » PTM




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®)

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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]

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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 ?!

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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]

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APPROVED

Infections « aiguës » PTM

2 RCT, 1 333 patients

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Journals.ASM.org

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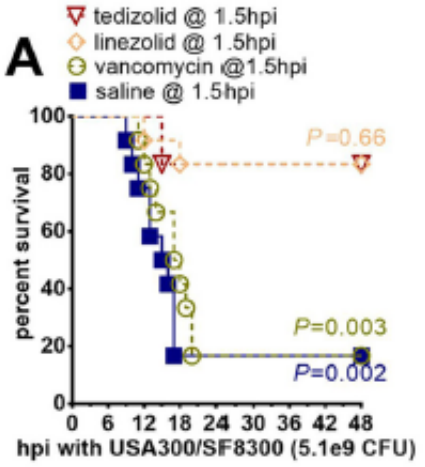
OFF-LABEL

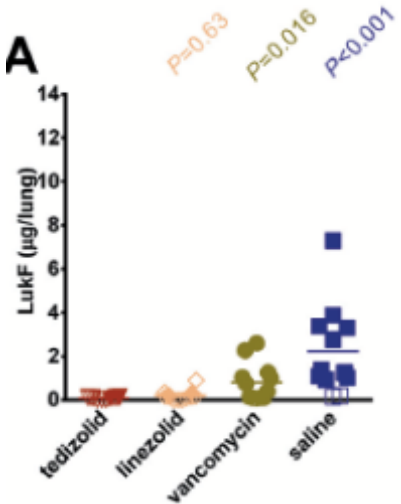
Bactériémies et EI ?

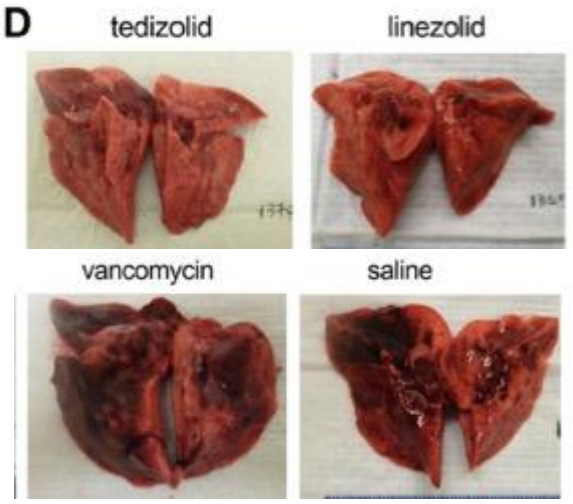
Pneumonie nécrosante

**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]



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OFF-LABEL

Bactériémies et EI ?

Pneumonie nécrosante

IOA

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

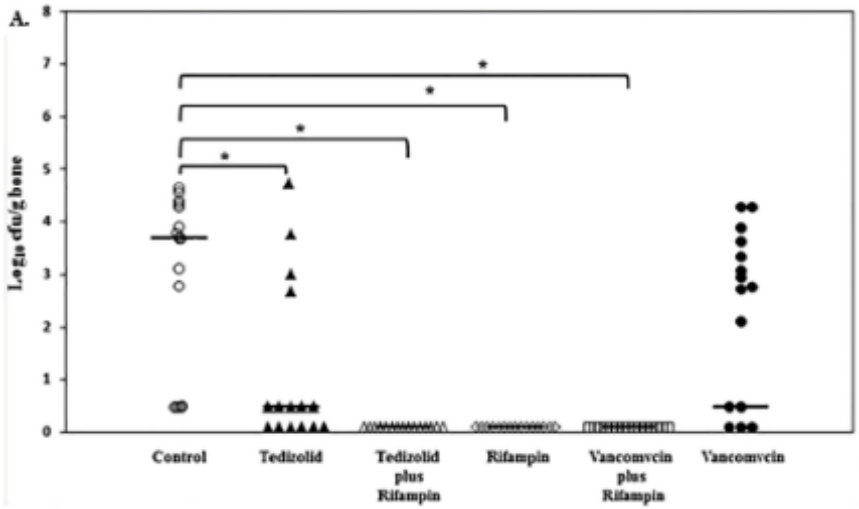
Kyung-Hwa Park,[a,d] Kerryl E. Greenwood-Quaintance,[a] Audrey N. Schuetz,[a] Jayawant N. Mandrekar,[c] Robin Patel[a,b]

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]



# Tédizolide (SIVEXTRO®)

APPROVED

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

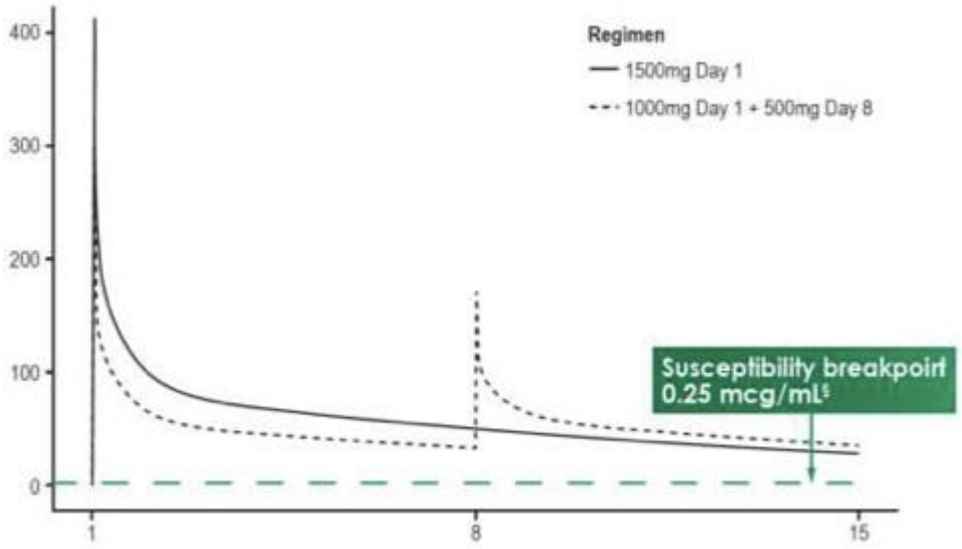
Rokeya Tasneen,[a] Fabrice Betoudji,[a] Sandeep Tyagi,[a] Si-Yang Li,[a] Kathy Williams,[a] Paul J. Converse,[a] Véronique Dartois,[b] Tian Carl M. Mendel,[a] Khisimuzi E. Mdluli,[a] Eric L. Nuermberger[a,c]

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**



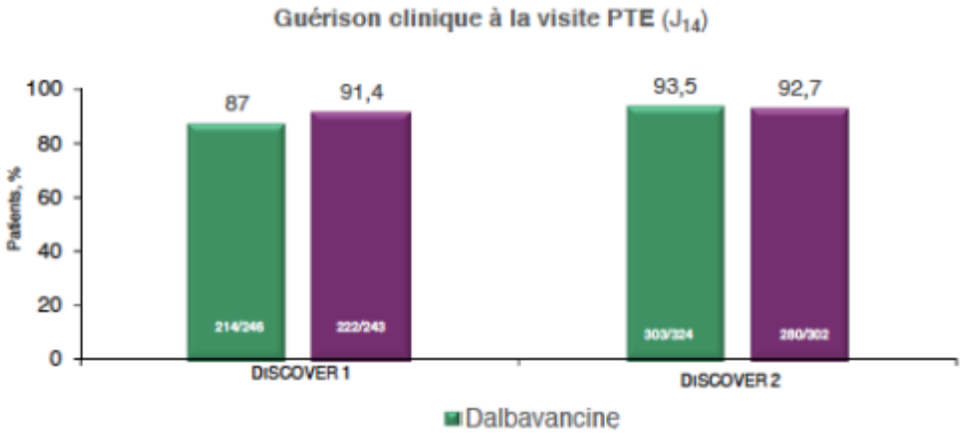

# Dalbavancine (XYDALBA®)

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

OFF-LABEL

IOA

Quelle dose ?

Case report 1g J0 puis 500 mg/sem

… en fait probablement moins :

AAC

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

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

Eur J Clin Microbiol Infect Dis (2017) 36:677–68
DOI 10.1007/s10096-016-2845-z

ORIGINAL ARTICLE

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

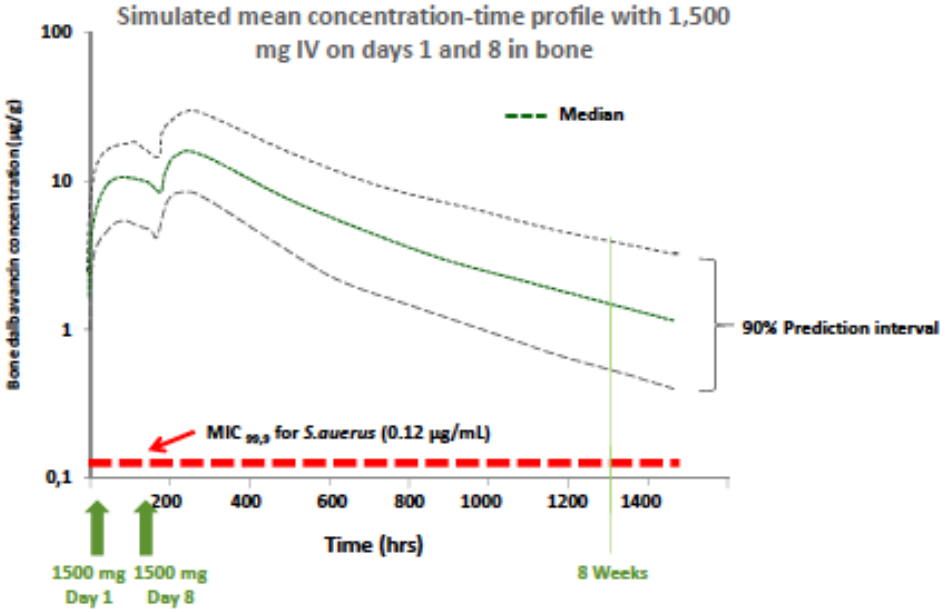
D. Knoll[1] · S. Tobalic[1] · S. C. Cheng[2] · B. R. Bellamy[3] · F. Thalhammer[1]

*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]*



# Dalbavancine (XYDALBA®)

APPROVED

Infections « aiguës » PTM

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

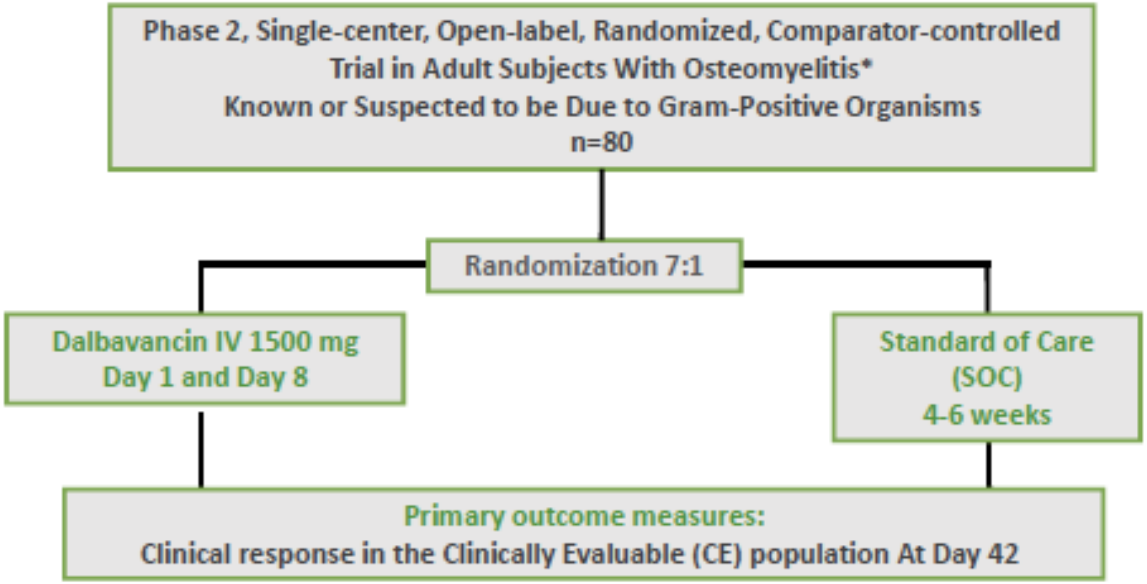
+ 1 essai dose unique J0 1500 mg
versus 1g J0 + 500 mg J8

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,*] Pedro L. Gonzalez,[1] Amy Suen,[1] Veronica Mas Casullo,[1] David Meleick,[1,*] Rosa Miceli,[1] Milan Kovacevic,[1] Gertjan De Bock,[1,*] and Michael W. Dunne[1,*]



# Dalbavancine (XYDALBA®)

APPROVED

Infections « aiguës » PTM

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

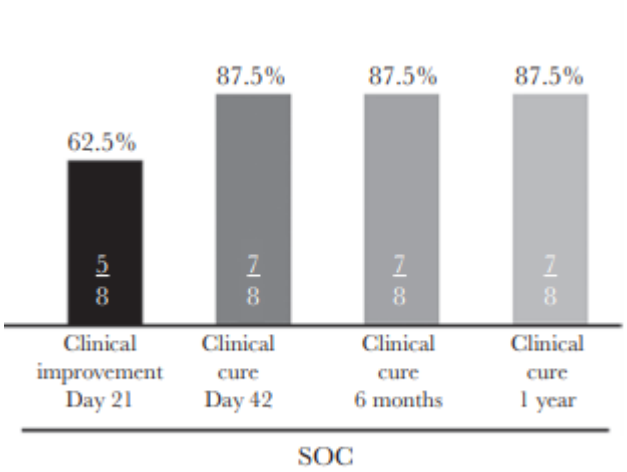
+ 1 essai dose unique J0 1500 mg
versus 1g J0 + 500 mg J8

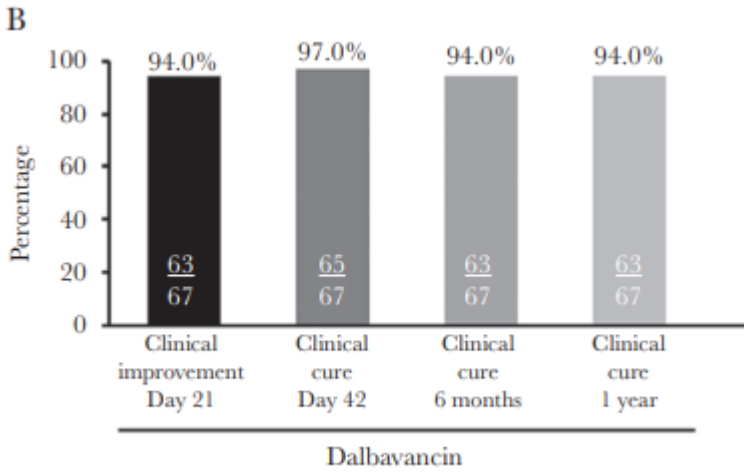
OFF-LABEL

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 Meleick,[1,4] Rosa Miceli,[1] Milan Kovacevic,[1] Gertjan De Bock,[1,4] and Michael W. Dunne[1,5]



# 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

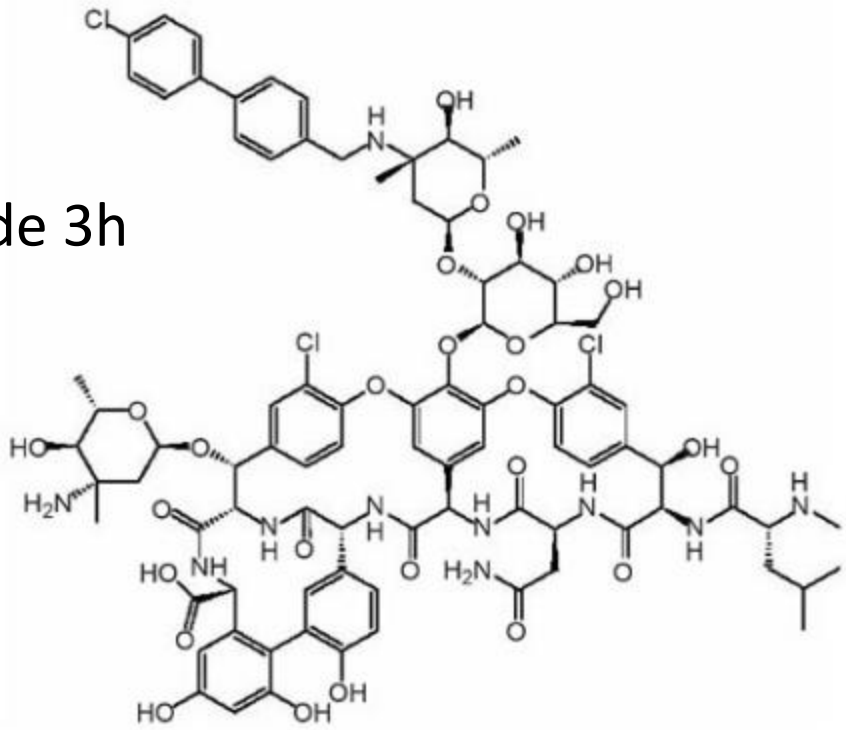
Emergence of dalbavancin non-susceptible, vancomycin-intermediate *Staphylococcus aureus* (VISA) after treatment of MRSA central line-associated bloodstream infection with a dalbavancin- and vancomycin-containing regimen
B.J. Werth
Clinical microbiology and infection
April 2018Volume 24, Issue 4, Pages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

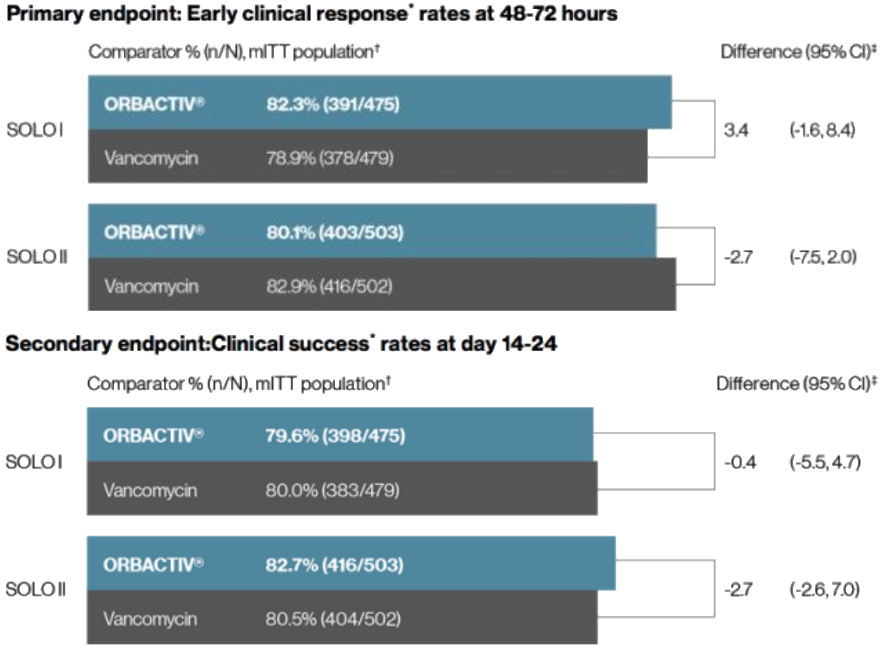


# Oritavancine (ORBACTIV®)

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®)

APPROVED

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)<br>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)<br>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 |

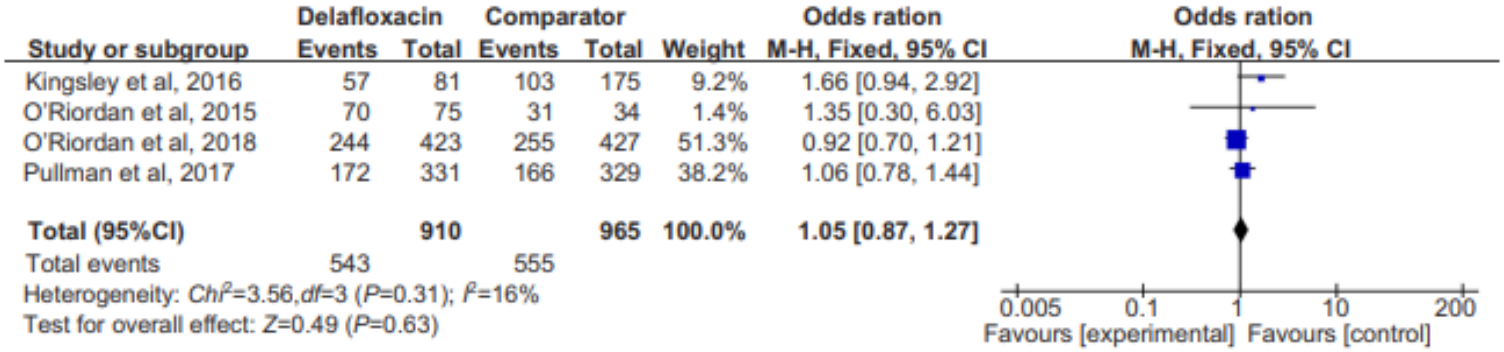



**Figure 4** Overall clinical cure rates of delafloxacin and comparators in the treatment of acute bacterial skin and skin structure infections.

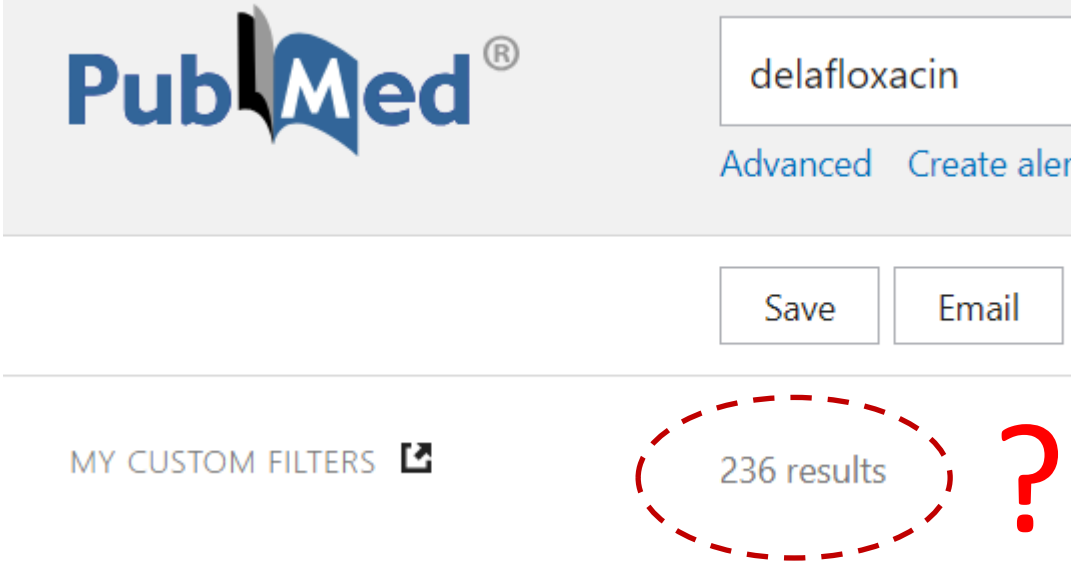
# Délafloxacine (QUOFENIX®)

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



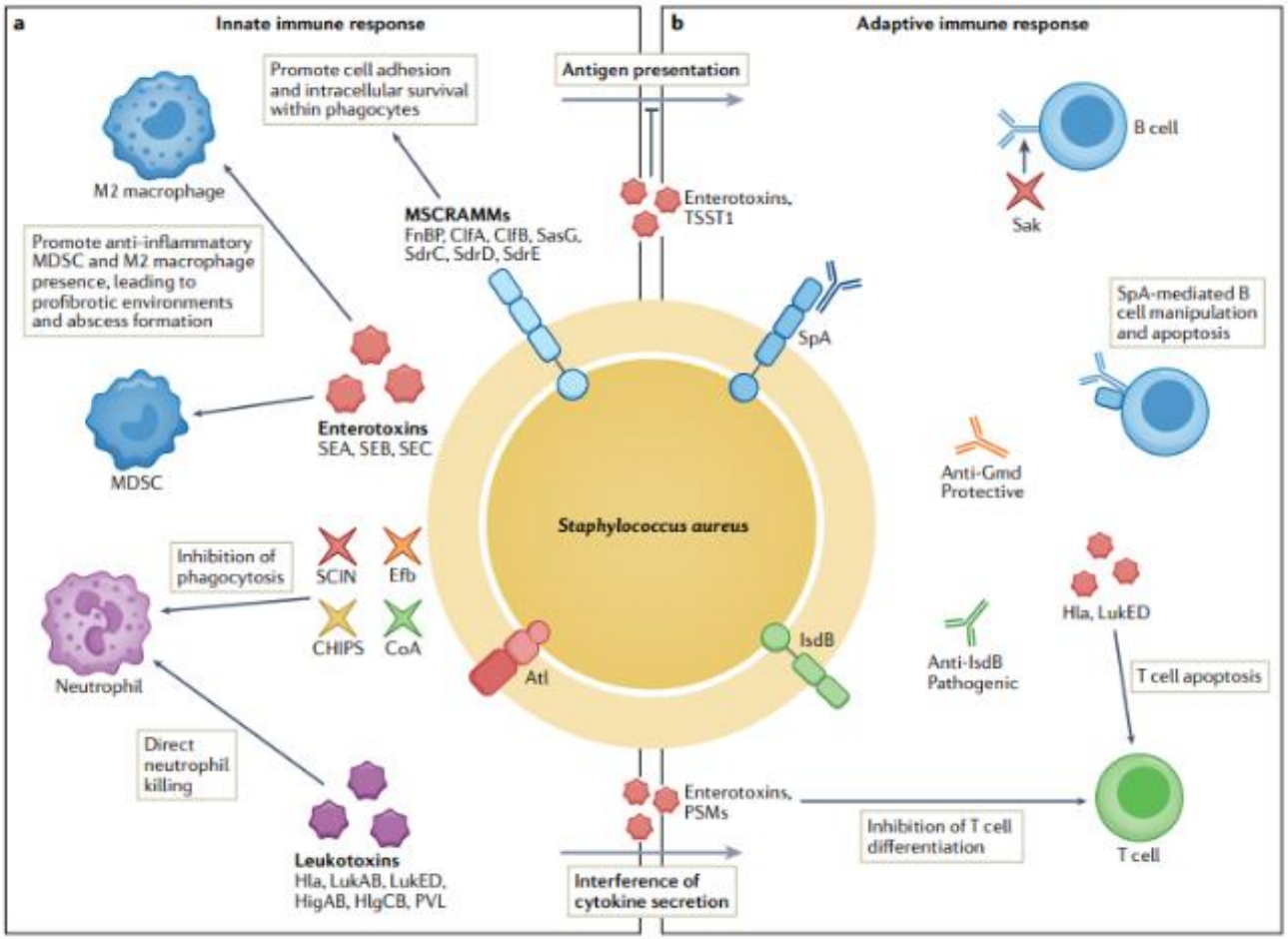
# Dans le pipeline Gram+

| 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**

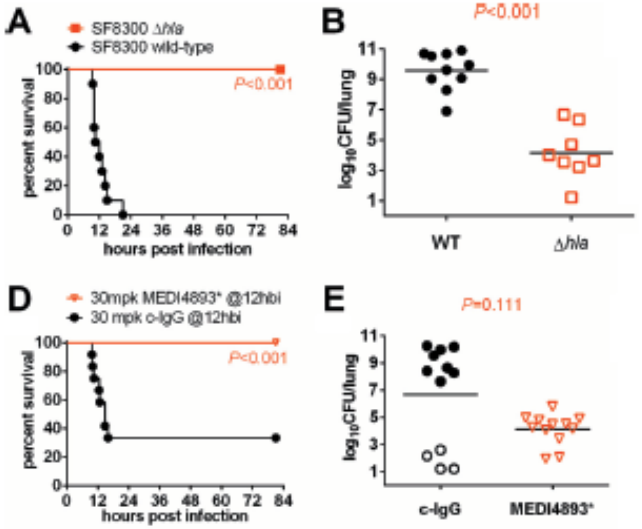
Binh An Diep,[a] Jamese J. Hilliard,[b] Vien T. M. Le,[a] Christine Tkaczyk,[b] Hoan N. Le,[a] Vuvi G. Tran,[a] Renee L. Rao,[a] Etyene Castro Dip,[a] Eliane P. Pereira-Franchi,[a] Paulyn Cha,[c] Scott Jacobson,[c] Rosemary Broome,[c] Lily I. Cheng,[d] William Weiss,[e] Laszlo Prokai,[e] Vien Nguyen,[e]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

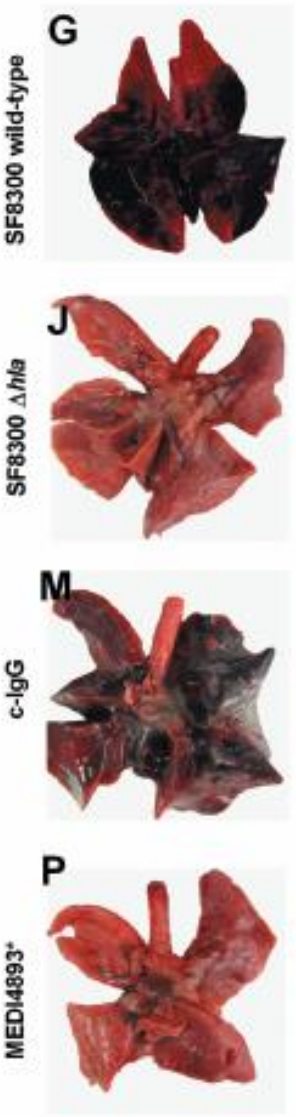
**Improved Protection in a Rabbit Model of Community-Associated Methicillin-Resistant *Staphylococcus aureus* Necrotizing Pneumonia upon Neutralization of Leukocidins in Addition to Alpha-Hemolysin**

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]

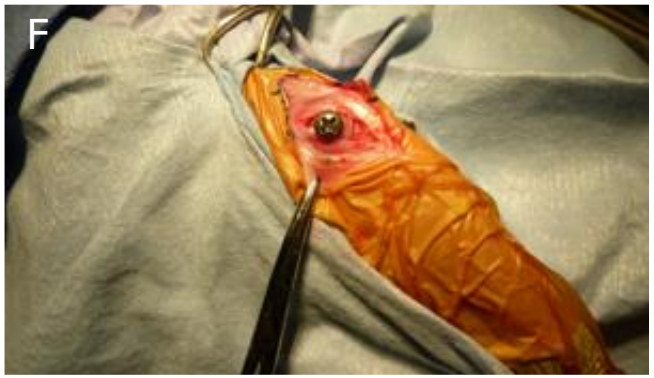


# Immunothérapie ciblée

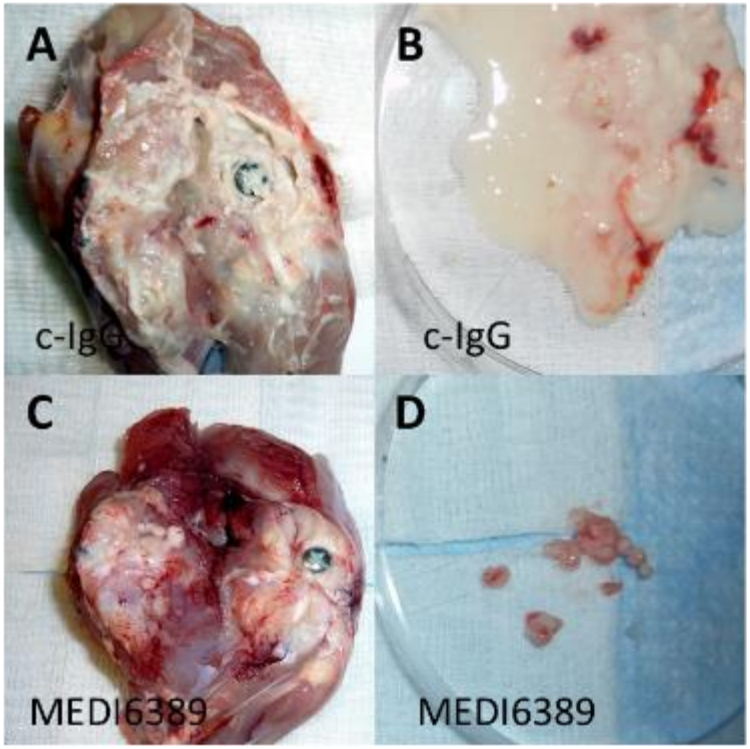
## Multimechanistic Monoclonal Antibody Combination Targeting Key *Staphylococcus aureus* Virulence Determinants in a Rabbit Model of Prosthetic Joint Infection

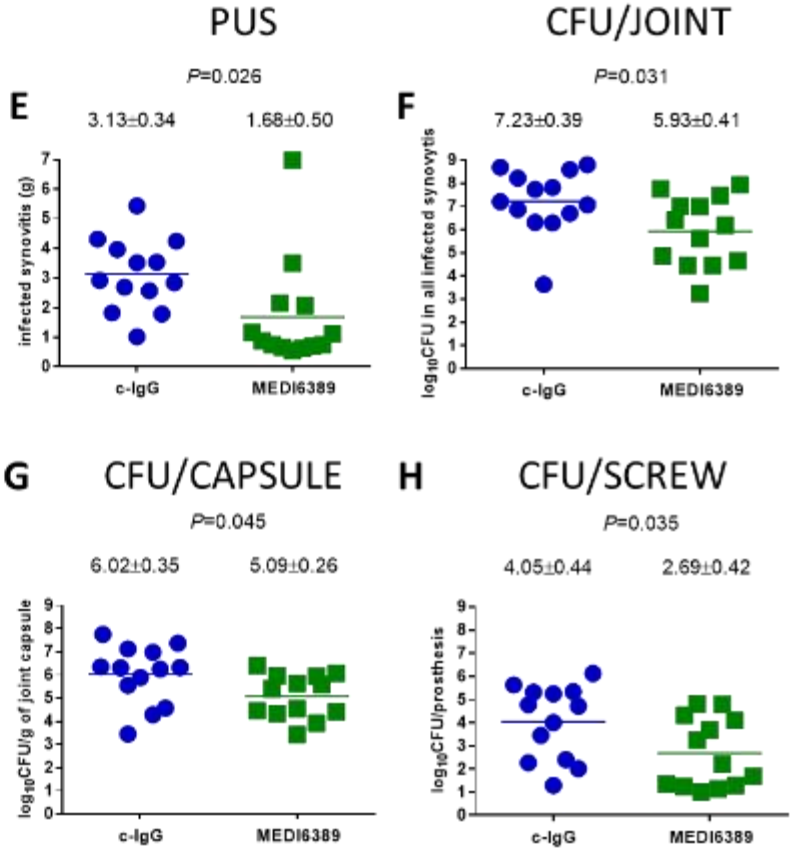
Yanjie Mao,[a,b*] Florent Valour,[a,c,d*] Nhu T. Q. Nguyen,[a] Thien M. N. Doan,[a] Holly Koelkebeck,[e] Christopher Richardson,[f] Lily I. Cheng,[e] Bret R. Sellman,[f] Christine Tkaczyk,[f] Binh An Diep[a]




**MEDI6389 (AT, ClfA, PVL, Hlg) préventifs**

Injection d'Ac spécifiques 12h avant la chirurgie



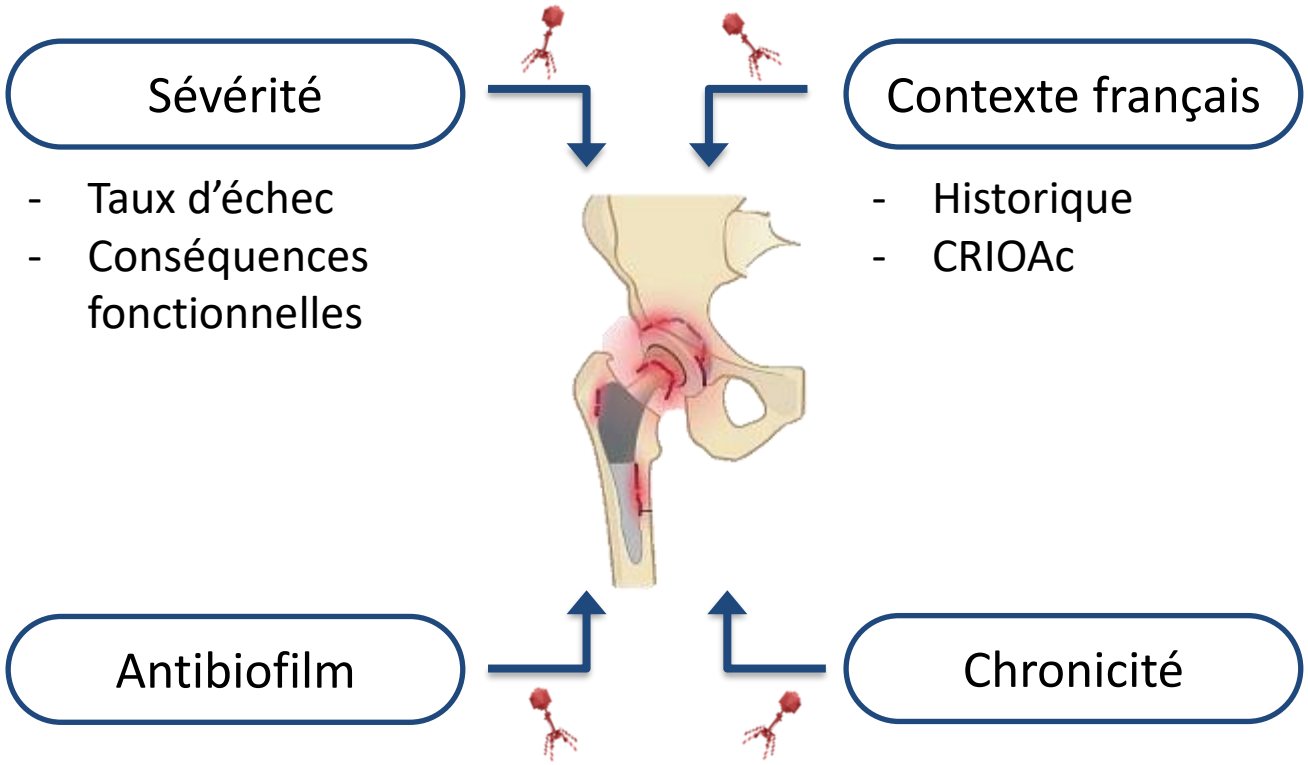
# Immunothérapie ciblée

| 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 |

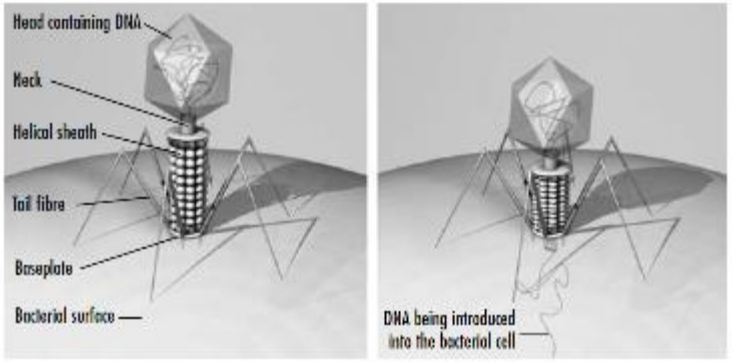
# Phagothérapie

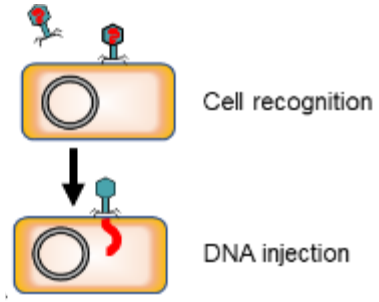
## Past and Future of Phage Therapy and Phage-Derived Proteins in Patients with Bone and Joint Infection

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



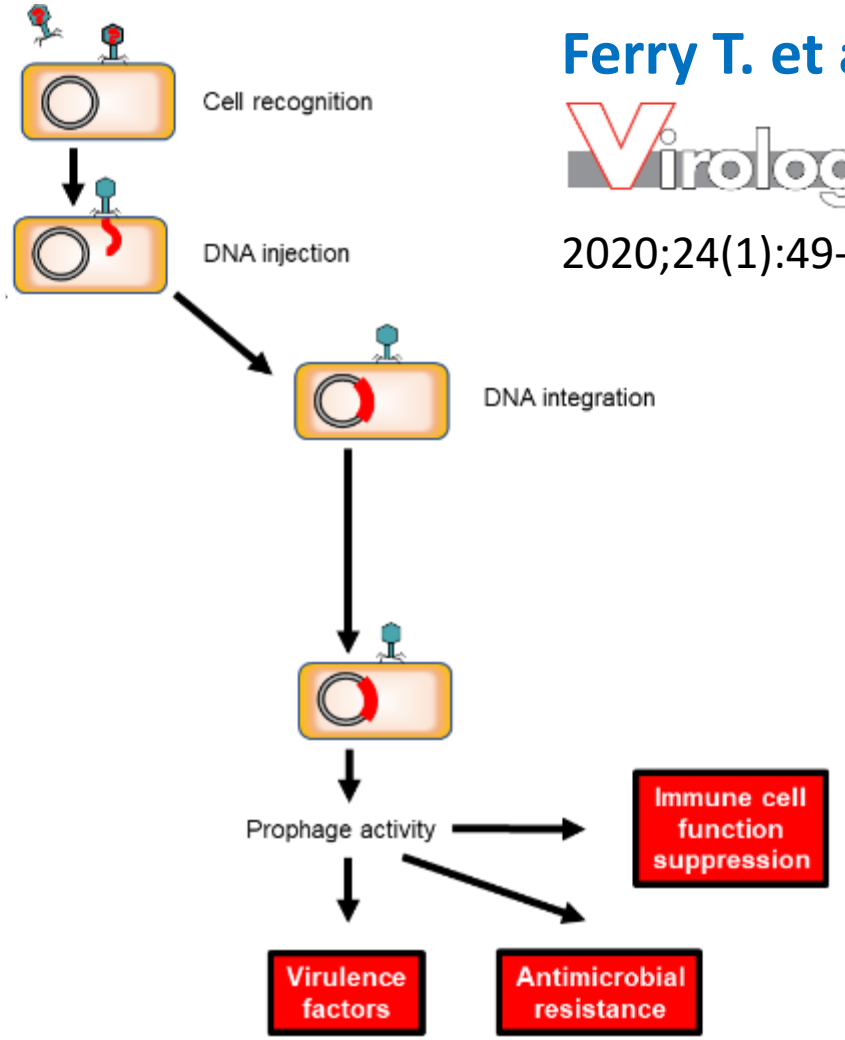

Ferry T. et al.

Virologie

2020;24(1):49-56

Virus environnementaux
ciblant des bactéries spécifiques

# Phagothérapie




Ferry T. et al.

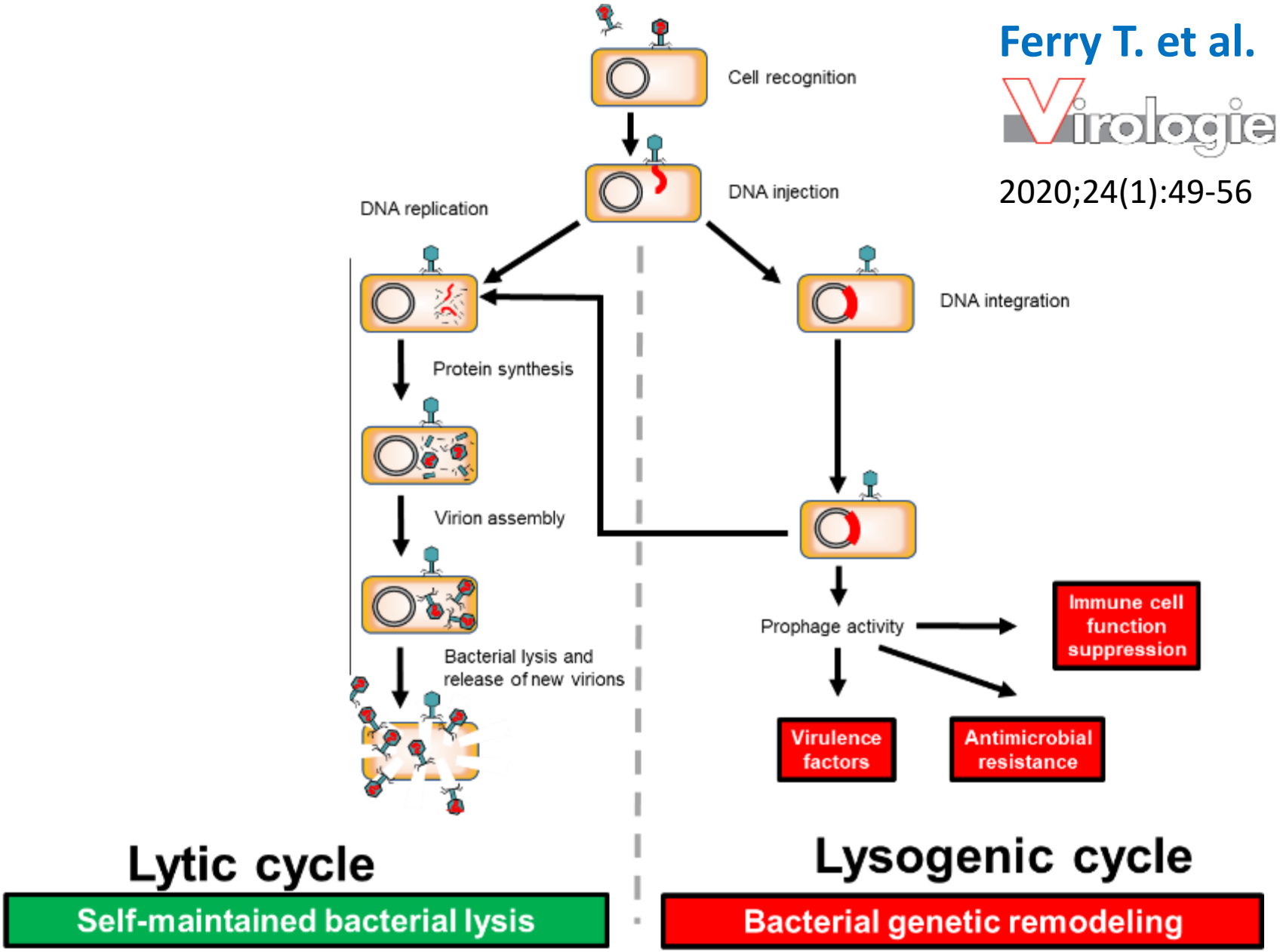
Virologie

2020;24(1):49-56

**Lysogenic cycle**

**Bacterial genetic remodeling**

# Phagothérapie

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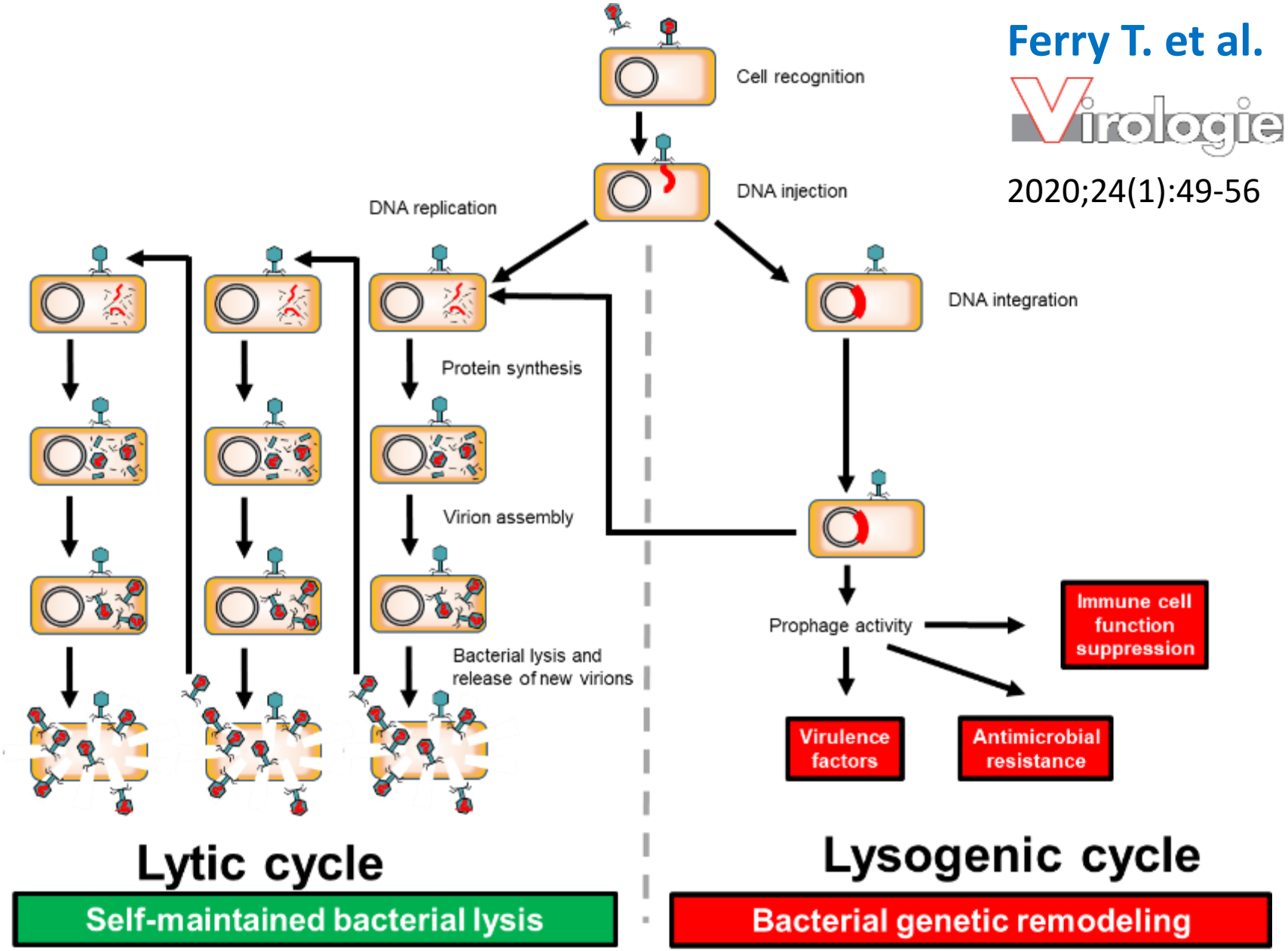
# Phagothérapie

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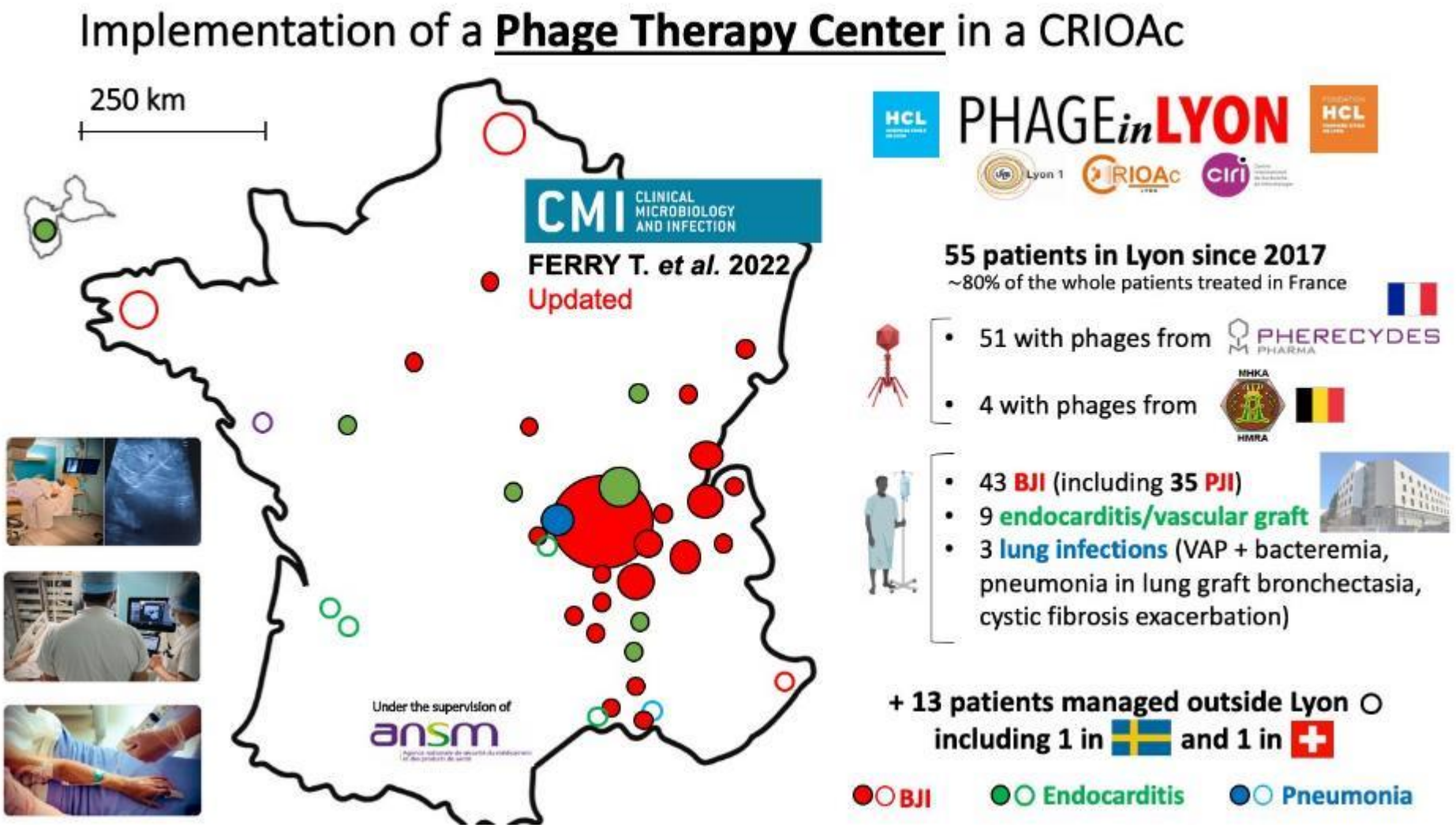
# Phagothérapie




Courtesy *Ferry T*

# 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]

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## 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

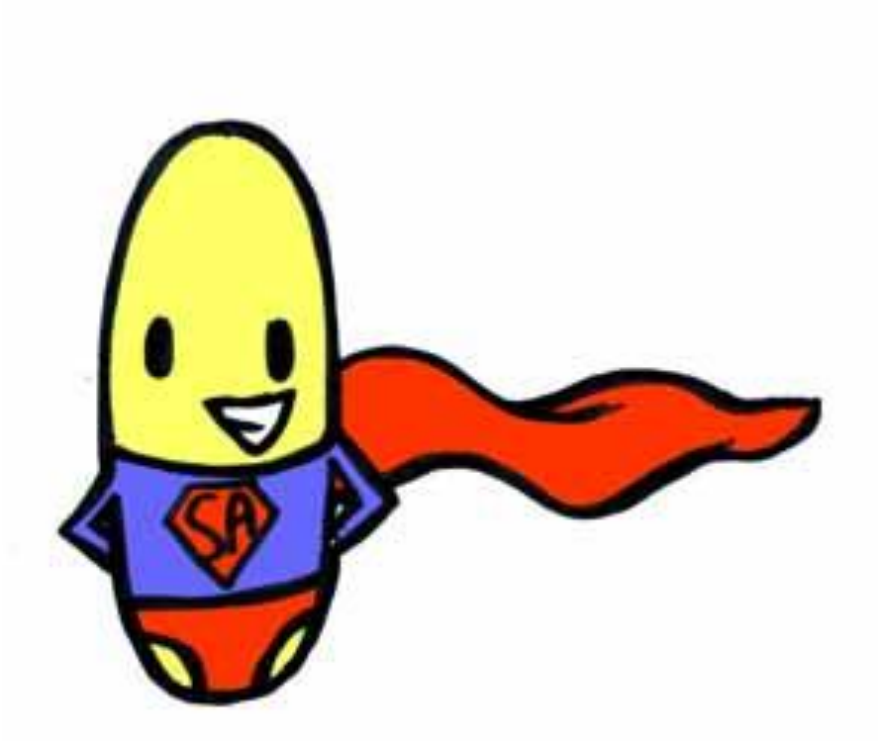
Sonia U. Shah,[a,b,c] Yan Q. Xiong,[b,c] Wessam Abdelhady,[b] James Iwaz,[a] Youngju Pak,[b,c] Raymond Schuch,[d] Cara Cassino,[d] Dario Lehoux,[d] Arnold S. Bayer[b,c]

# 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**


SA