# Place des nouvelles thérapeutiques anti-infectieuses

## Qu’y a t’il dans le pipeline ?

Florent Valour

Service des maladies infectieuses et tropicales – CRIOAc
Hospices Civils de Lyon

CIRI, INSERM U1111 – Faculté de médecine Lyon Sud Charles Mérieux
Université Claude Bernard Lyon 1

## CRITICAL PRIORITY

***Acinetobacter baumannii***
carbapenem-resistant

***Pseudomonas aeruginosa***
carbapenem-resistant

***Enterobacteriaceae***
carbapenem-resistant,
3rd gen. cephalosporin-resistant

## HIGH PRIORITY

***Enterococcus faecium***
vancomycin-resistant

***Staphylococcus aureus***
vancomycin-resistant
methicillin-resistant

***Helicobacter pylori***
clarithromycin-resistant

***Campylobacter species***
fluoroquinolone-resistant

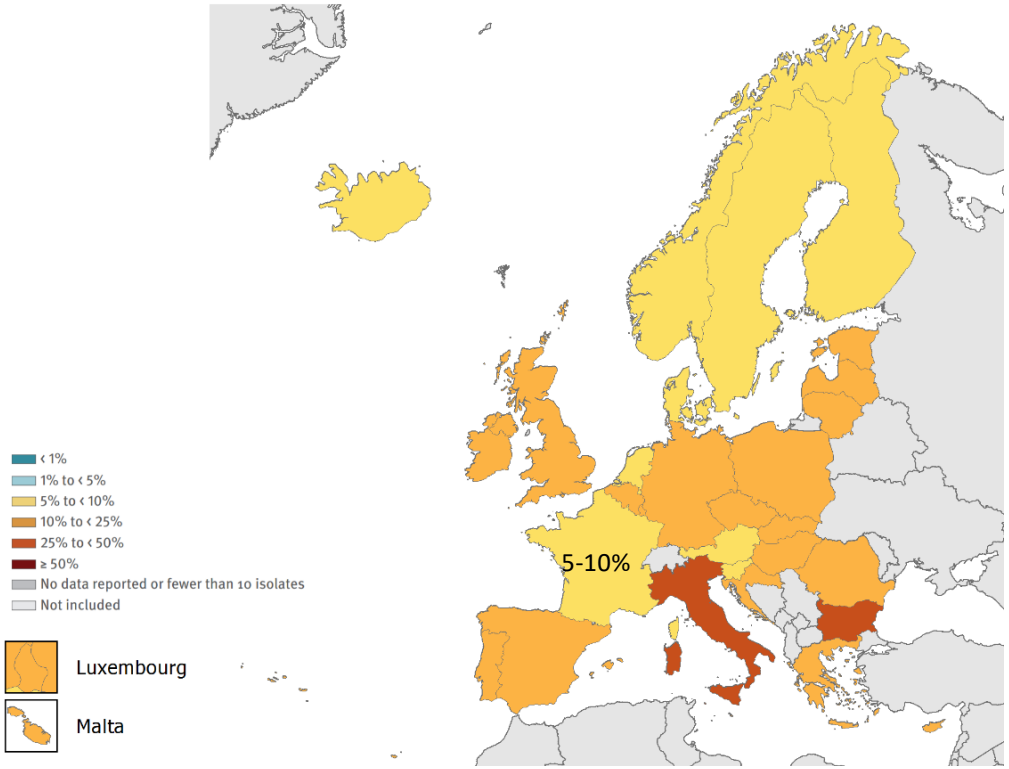
***Salmonella species***
fluoroquinolone-resistant

***Neisseria gonorrhoeae***
3rd gen. cephalosporin-resistant,
fluoroquinolone-resistant

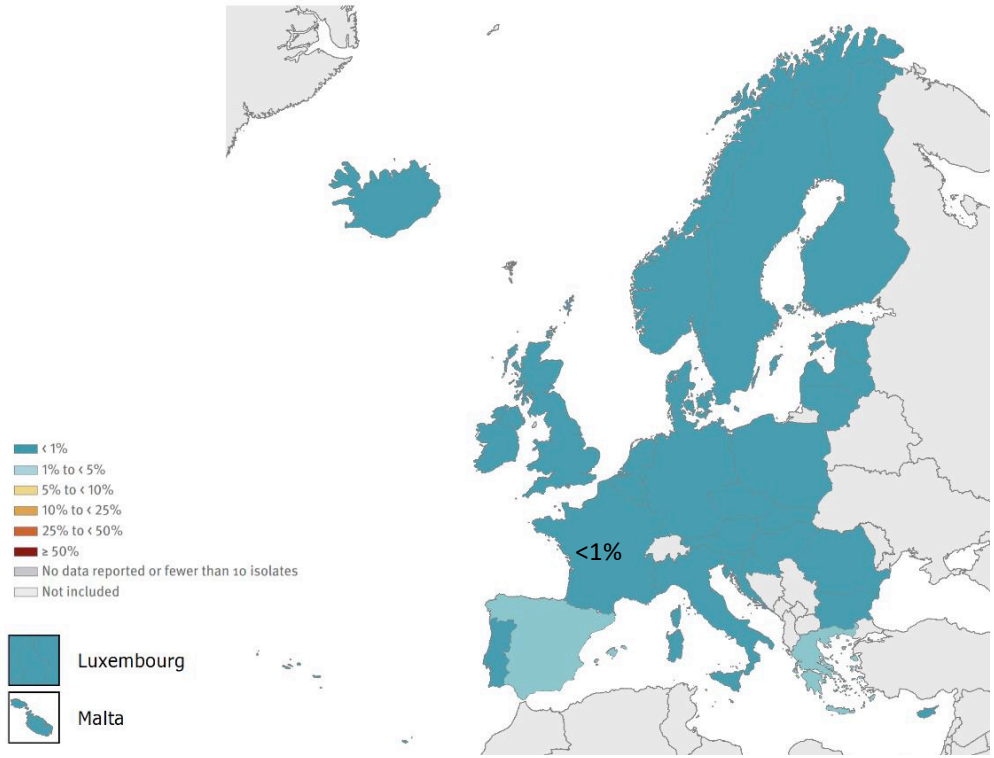
# Antimicrobial resistance in the EU/EEA (EARS-Net)

Annual epidemiological report for 2019

*E. coli* C3G-R



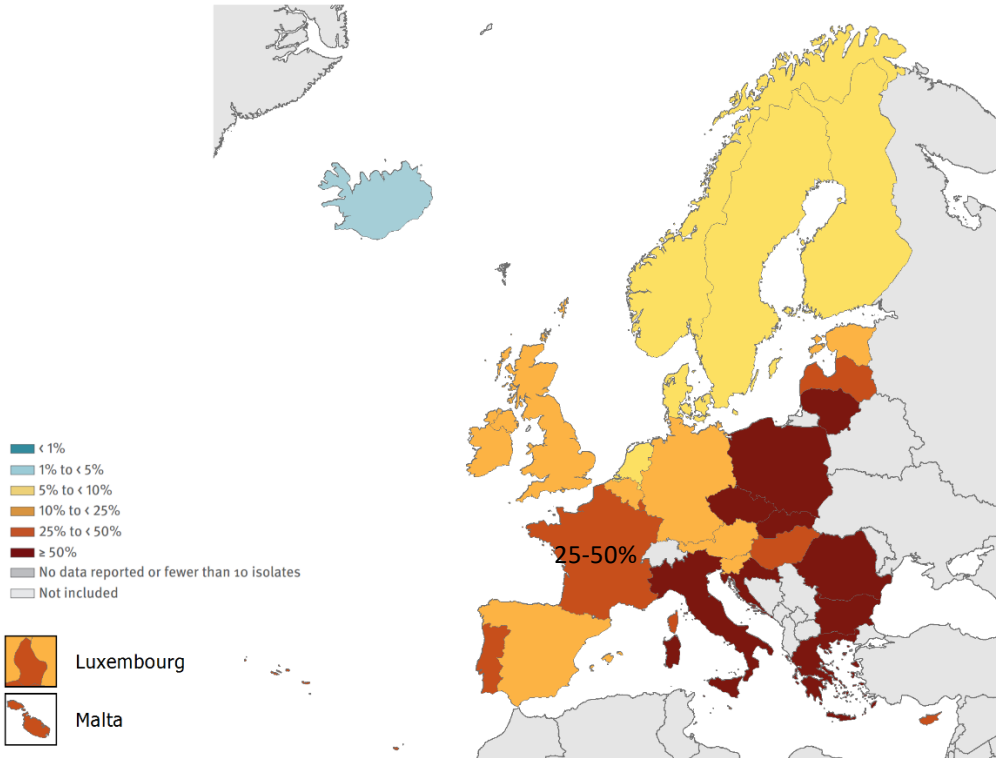

*E. coli* carba-R



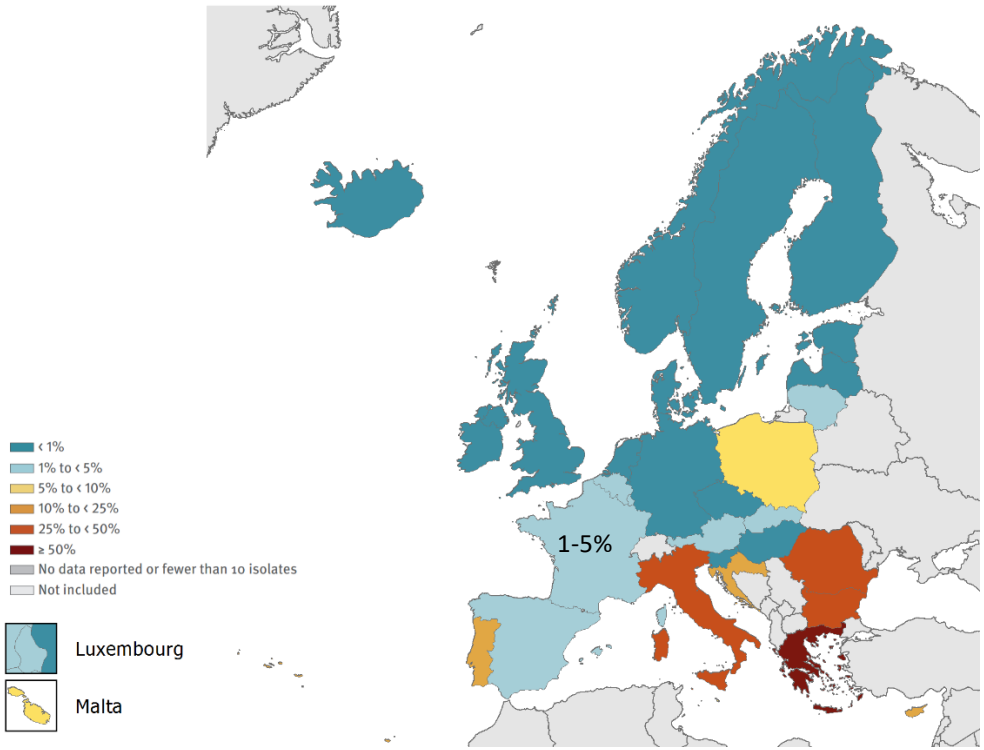
# Antimicrobial resistance in the EU/EEA (EARS-Net)

Annual epidemiological report for 2019

*K. pneumoniae* C3G-R



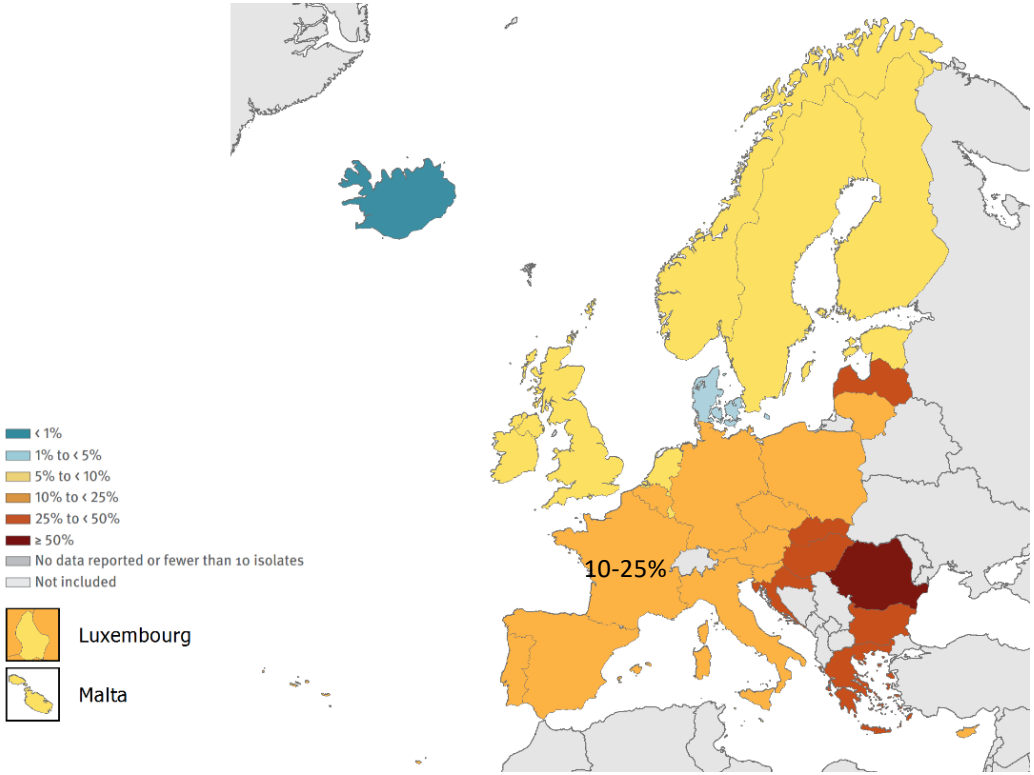

*K. pneumoniae* carba-R



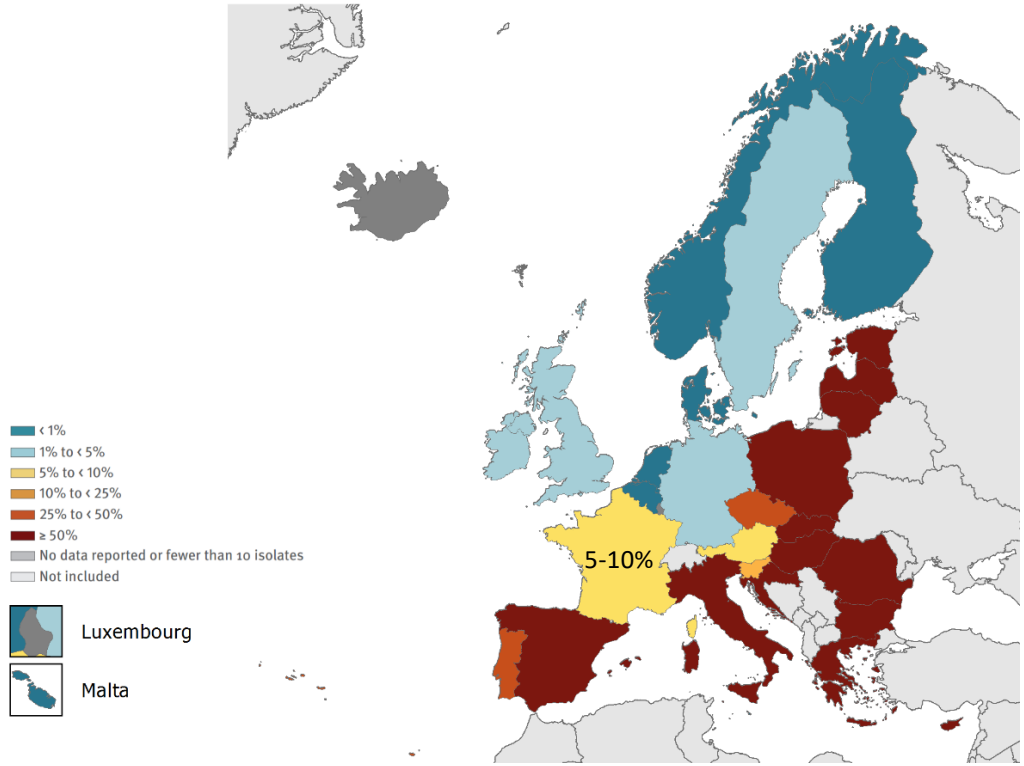
# Antimicrobial resistance in the EU/EEA (EARS-Net)

Annual epidemiological report for 2019

*P. aeruginosa* carba-R




*Acinetobacter spp.* carba-R



# Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America

Helen W. Boucher,[1] George H. Talbot,[2] John S. Bradley,[3,4] John E. Edwards, Jr,[5,6,7] David Gilbert,[8] Louis B. Rice,[9,10] Michael Scheld,[11] Brad Spellberg,[5,6,7] and John Bartlett[12]

Clinical Infectious Diseases 2009; 48:1–12

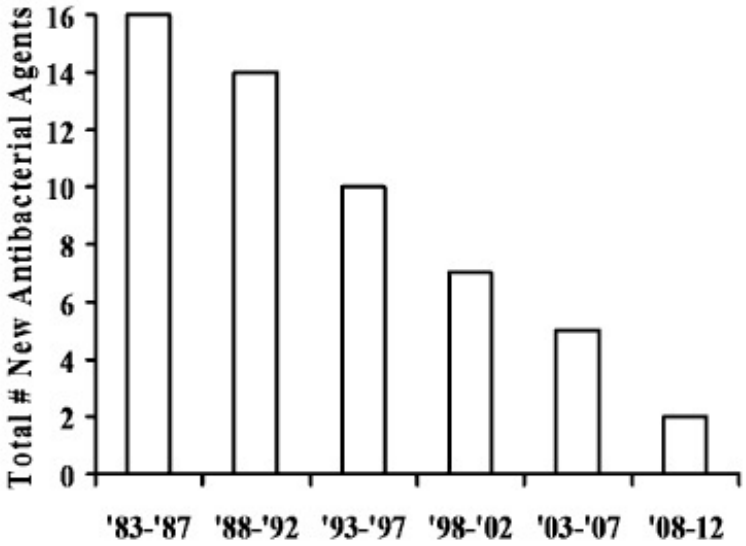
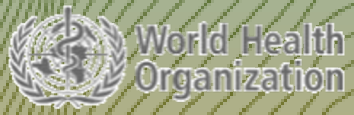


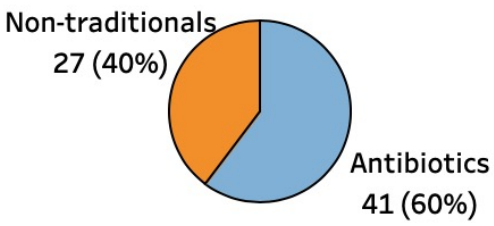

**Figure 1.** Number of New Molecular Entity (NME) Systemic Antibiotics Approved by the US FDA Per Five-year Period, Through 3/11.

# 2020 ANTIBACTERIAL AGENTS IN CLINICAL AND PRECLINICAL DEVELOPMENT

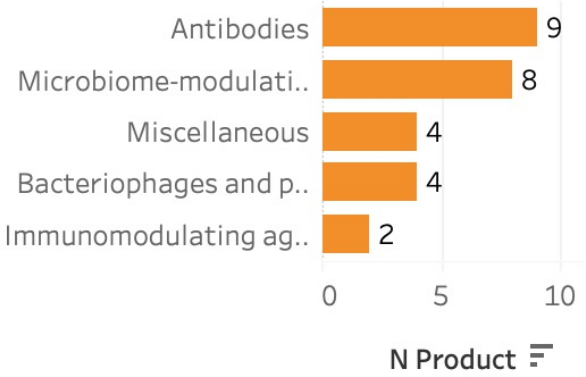
an overview and analysis



## A.1. Products by type




## A.2. No. of non traditional products by category




## A.3. Products by pathogen category and phase

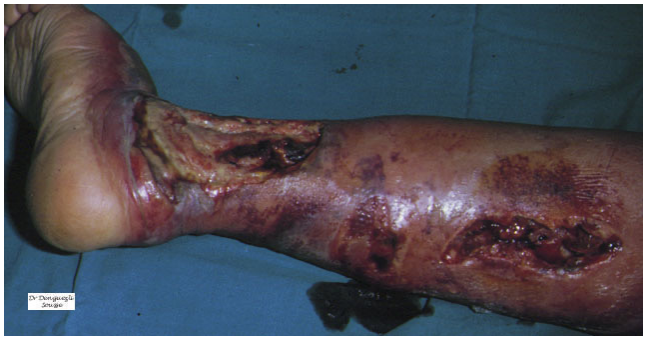
| Pathogen category | Phase I | Phase II | Phase | Unkno.. | Total |
|---|---|---|---|---|---|
| Priority pathogens | 18 | 15 | 9 | 1 | 43 |
| Mycobacterium tuberculosis | 3 | 9 | | | 12 |
| Clostridium difficile | 3 | 8 | 2 | | 13 |
| Total | 24 | 32 | 11 | 1 | 68 |

## B. Expected activity against priority pathogens

| | Critical priority pathogens | | | | | Other priority pathogens | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Active? | Acinetobac baumannii | Pseudomor aeruginosa | Enteroba.. | All critical priority pathogens | Subtotal | Gram-positive priority p.. | Neisseria gonnorhoe | Helicobact pylori | Staphyloco aureus | Enterococc faecium | Streptococ pneumonia | Campyloba spp. | Subtotal | Total |
| Yes | 7 | 7 | 14 | 3 | 21 | 17 | 3 | 2 | 17 | 3 | 2 | 2 | 21 | 38 |
| Possibly | 3 | 3 | 3 | 2 | 6 | 1 | 1 | 1 | 1 | 1 | | | 2 | 8 |
| No | 12 | 17 | 10 | 17 | 18 | 3 | 7 | 8 | 3 | 7 | 7 | 8 | 10 | 20 |

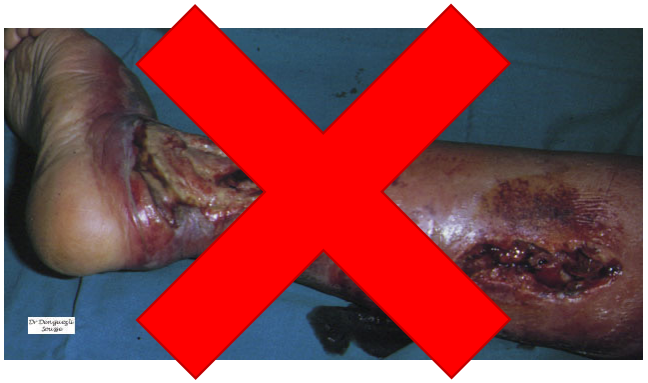
# Développement et AMM des nouveaux antibiotiques

## Infections compliquées de la peau et des tissus mous



# Développement et AMM des nouveaux antibiotiques

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



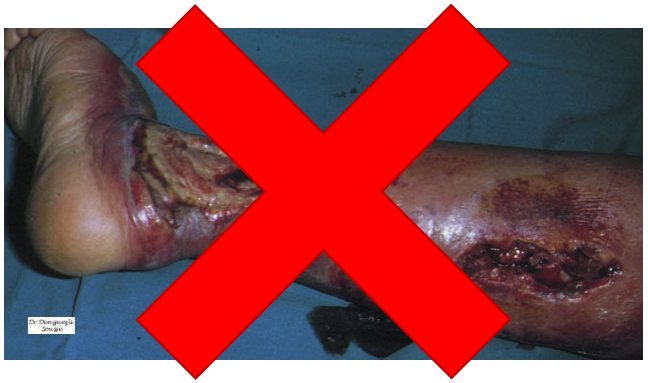
Bactériémie ?
Chirurgie ?
Documentation ?
Comparateur ?

FDA 1998

- « cellulites », abcès « majeurs » (??), lésions impétiginisées, furoncles
- Taille : non précisée
- Signes généraux non nécessaires
- Readout : guérison clinique en fin de traitement

# Développement et AMM des nouveaux antibiotiques

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



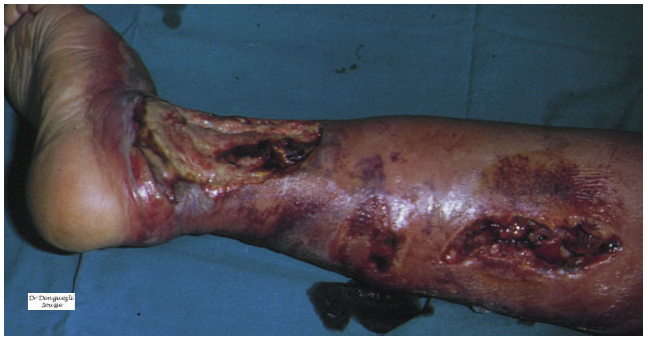
Bactériémie ?
Chirurgie ?
Documentation ?
Comparateur ?

FDA 2013

- « cellulites », abcès « majeurs » (??), ~~lésions impétiginisées, furoncles,~~ « infections » de plaie
- Taille : 75 cm² (8,6 x 8,6 cm)
- Signes généraux non nécessaires
- Readout : % de réduction des lésions > 20% à 48-72h

# Développement et AMM des nouveaux antibiotiques

## Infections de la peau et des tissus mous



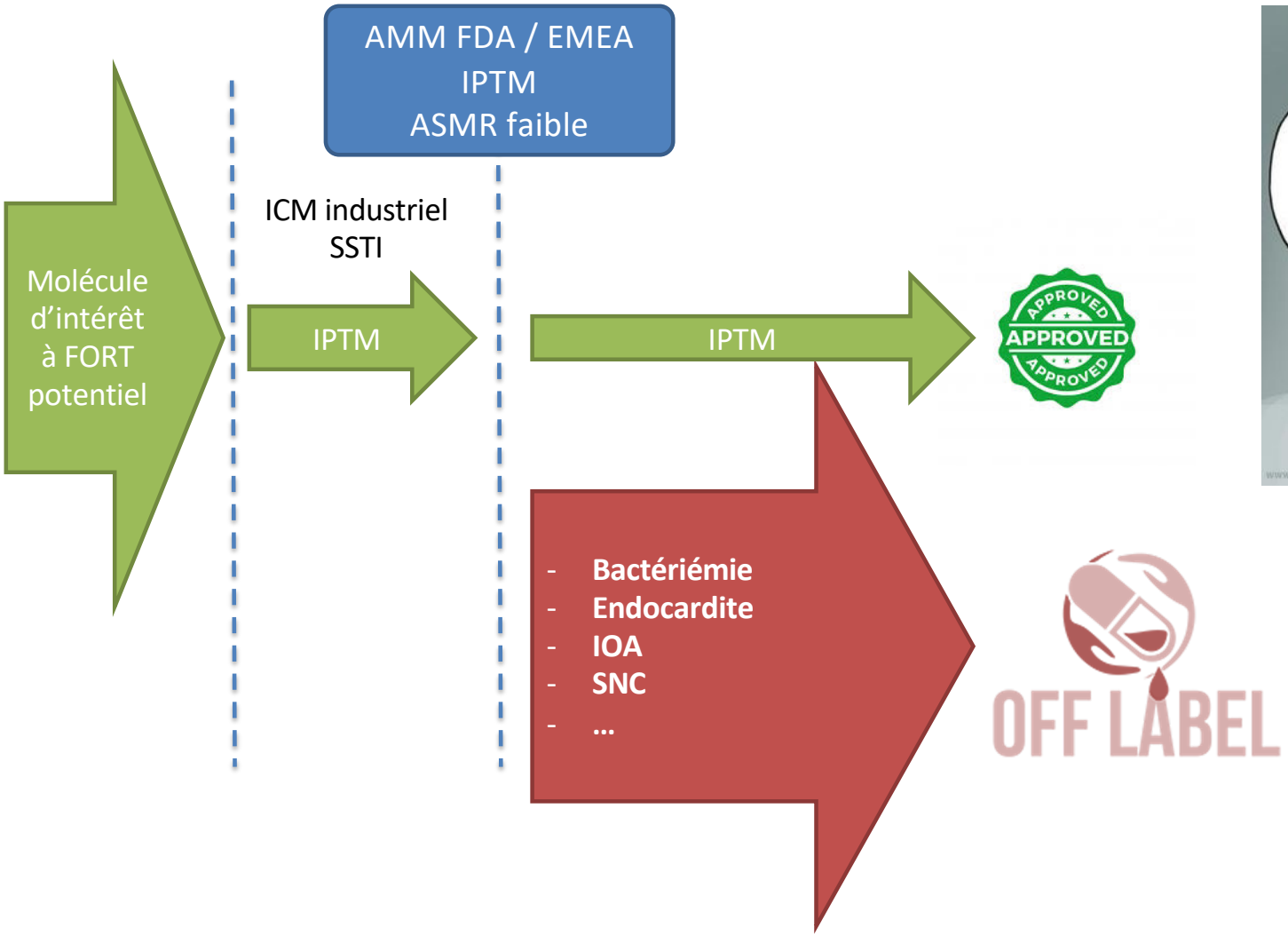
Bactériémie ?
Chirurgie ?
Documentation ?
Comparateur ?

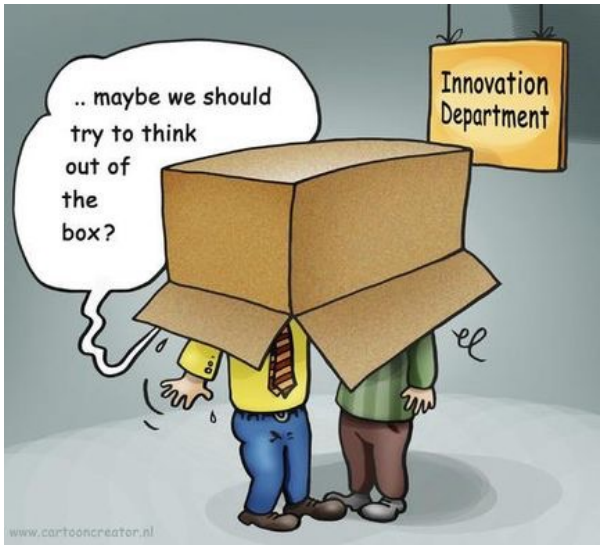
## Pneumopathies communautaires / nosocomiales

## Infections urinaires

## Infections intra-abdominales « compliquées »

# Développement et AMM des nouveaux antibiotiques



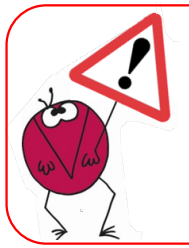




Dose ?
Durée ?
Efficacité ?
Tolérance ?

# Thérapies conventionnelles : nouveaux antibiotiques

# Tédizolide (SIVEXTRO®)

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



- Hématotoxicité ?
- Neurotoxicité moindre que le LNZ ?

AAC Journals.ASM.org

*In Vitro, In Vivo*, and Clinical Studies of Tedizolid To Assess the Potential for Peripheral or Central Monoamine Oxidase Interactions

S. Flanagan,[a] K. Bartizal,[a] S. L. Minassian,[b] E. Fang,[a] P. Prokocimer[a]

AAC Journals.ASM.org

Nonclinical and Pharmacokinetic Assessments To Evaluate the Potential of Tedizolid and Linezolid To Affect Mitochondrial Function

Shawn Flanagan,[a] Edward E. McKee,[b] Debaditya Das,[c*] Paul M. Tulkens,[c] Hiromi Hosako,[d] Jill Fiedler-Kelly,[e] Julie Passarell,[e] Ann Radovsky,[d] Philippe Prokocimer[a]

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

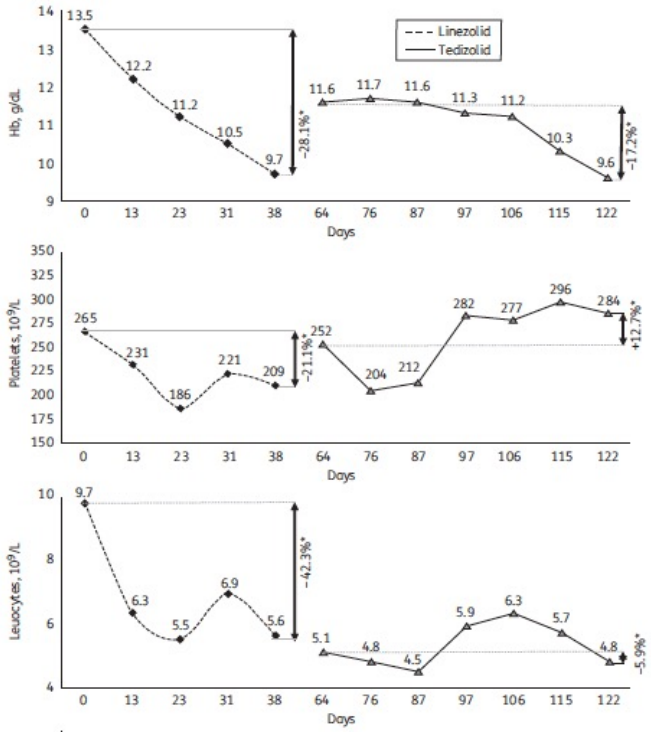
# Tédizolide (SIVEXTRO®)

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

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

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

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

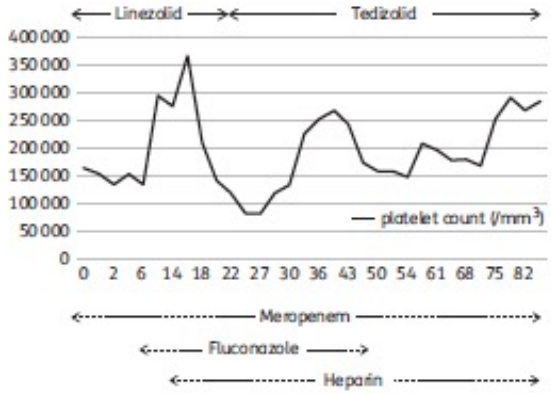



*J Antimicrob Chemother*
doi:10.1093/jac/dkx097

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

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

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



# Tédizolide (SIVEXTRO®)

APPROVED

Infections « aiguës » PTM

2 RCT, 1 333 patients

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

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

Fièvre : 23%
Bactériémie : 2%

Troubles digestifs +++

AAC
Journals.ASM.org

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]

# Tédizolide (SIVEXTRO®)

APPROVED

Infections « aiguës » PTM

2 RCT, 1 333 patients

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

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

Fièvre : 23%
Bactériémie : 2%

Troubles digestifs +++

AAC
Journals.ASM.org

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]

# 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 ?

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

AMERICAN SOCIETY FOR MICROBIOLOGY | 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] Rachelle Gonzales,[a] Yan Q. Xiong[a,b]

AAC
Journals.ASM.org

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

# Tédizolide (SIVEXTRO®)

APPROVED

Infections « aiguës » PTM

2 RCT, 1 333 patients

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

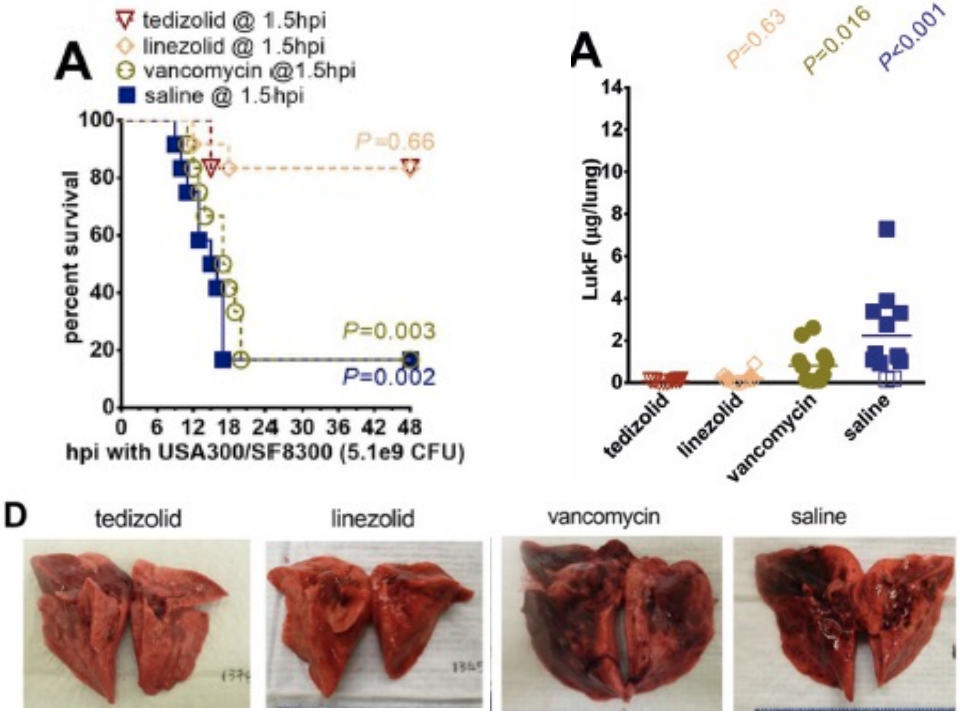
OFF-LABEL

Bactériémies et EI ?

Pneumonie nécrosante

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

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



# Tédizolide (SIVEXTRO®)

APPROVED

Infections « aiguës » PTM

2 RCT, 1 333 patients

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

OFF-LABEL

Bactériémies et EI ?

Pneumonie nécrosante

IOA

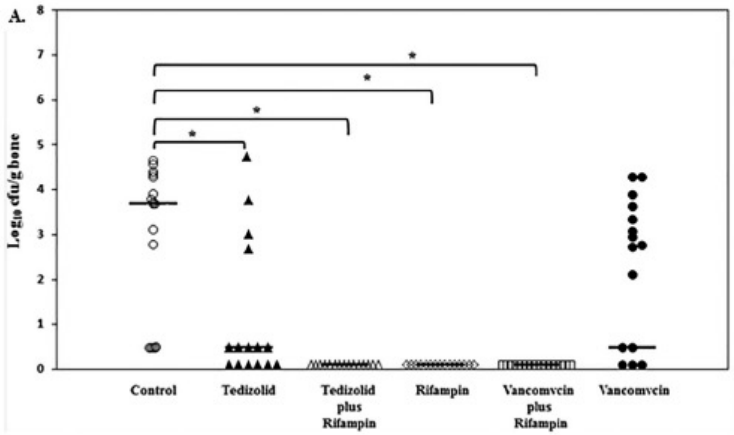
In vitro activity of tedizolid against staphylococci isolated from prosthetic joint infections☆

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

Intérêt de la moindre toxicité *vs* LNZ

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

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



# Tédizolide (SIVEXTRO®)

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

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**

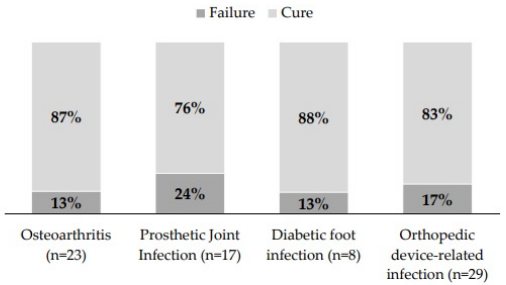
Eric Senneville [1,2,3,*], Aurélien Dinh [4,5], Tristan Ferry [6,7], Eric Beltrand [3,8], Nicolas Blondiaux [3,9] and Olivier Robineau [1,2,3]

33 PJI
Durée médiane : 8 sem (6–12)
2 arrêts / EI attribuables au TDZ (1 digestif, 1 douleurs articulaires)

**Long-Term Use of Tedizolid in Osteoarticular Infections: Benefits among Oxazolidinone Drugs**

Eva Benavent [1,2], Laura Morata [2,3,4], Francesc Escrihuela-Vidal [1], Esteban Alberto Reynaga [5], Laura Soldevila [1,2], Laia Albiach [3], Maria Luisa Pedro-Botet [5], Ariadna Padullés [6], Alex Soriano [2,3,4] and Oscar Murillo [1,2,4,*]

51 patients – Matériel : 59%
Durée médiane : 29 jours (15-44)
Stabilité Hb et P
Cure rate : 83%



# 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

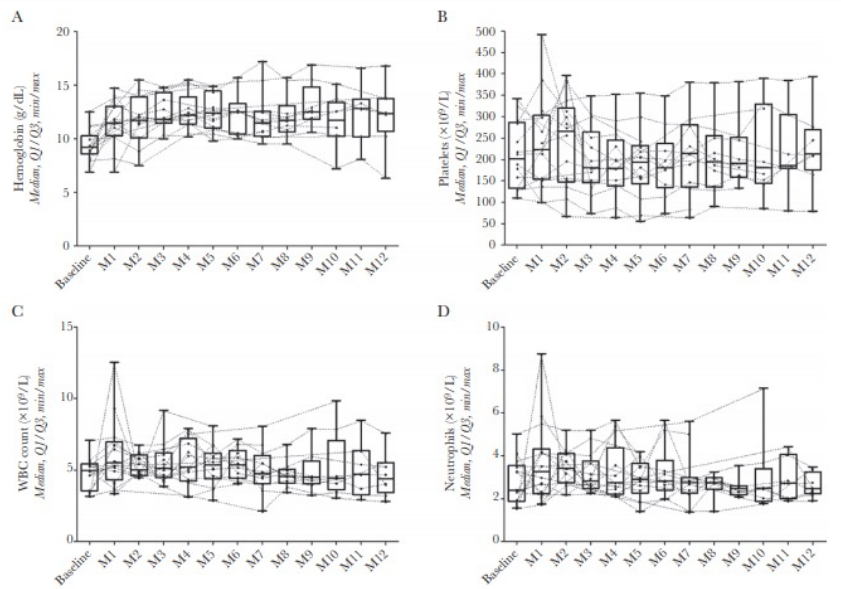
In vitro activity of tedizolid against staphylococci isolated from prosthetic joint infections☆

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

Safety of Tedizolid as Suppressive Antimicrobial Therapy for Patients With Complex Implant-Associated Bone and Joint Infection due to Multidrug-Resistant Gram-Positive Pathogens: Results From the TediSAT Cohort Study

Tristan Ferry,[1,2,3] Anne Conrad,[1,2,3] Eric Senneville,[4,5,6] Sandrine Roux,[1,2] Céline Dupieux-Chabert,[1,2,3] Aurélien Dinh,[7,8] Sébastien Lustig,[2,9] Sylvain Goutelle,[1,2,10] Thomas Briot,[1,2] Truong-Thanh Pham,[1,2,11] Florent Valour[1,2,3]

17 patients
Durée médiane 6 mois
Range 1-31 mois
Pas d'EIG
4 échecs (23,5%)



# 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

"Tedizolid also increased the bactericidal activity of BDQ+PMD, but they were less effective than the other oxazolidinones"

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, Paul 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]

***In Vitro* Activity of Tedizolid against *Mycobacterium tuberculosis***

Pilar Ruiz,[a] Manuel Causse,[b] Manuel Vaquero,[a] Manuel Casal[a]

American Society for Microbiology | 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]

# 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

"Tedizolid also increased the bactericidal activity of BDQ+PMD, but they were less effective than the other oxazolidinones"

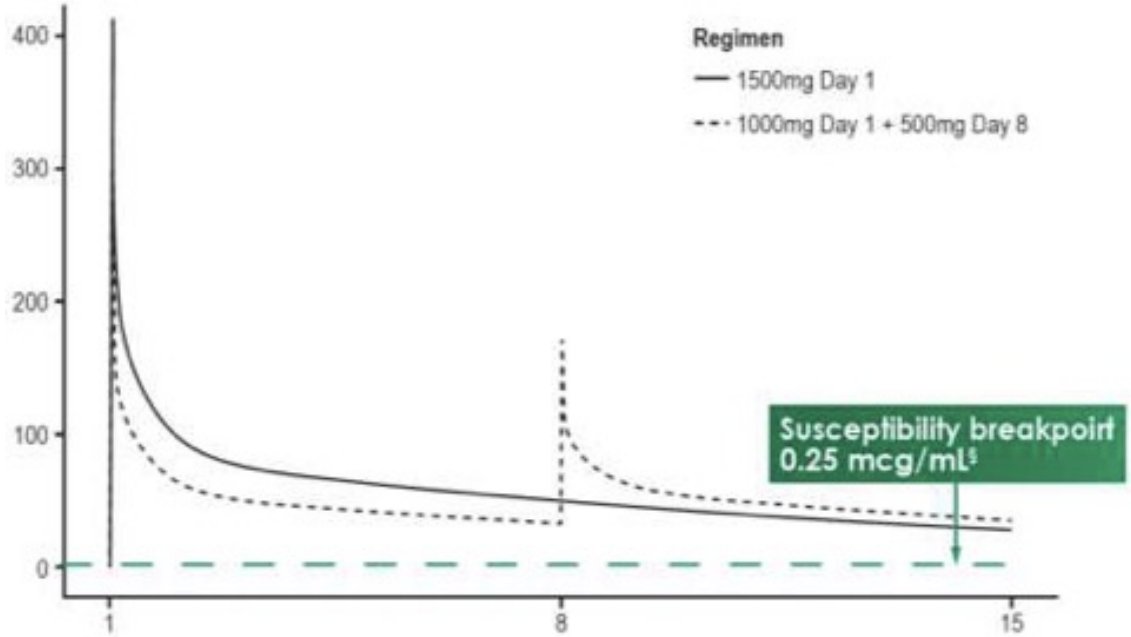
Tedizolid vs Linezolid for the Treatment of Nontuberculous Mycobacteria Infections in Solid Organ Transplant Recipients

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

SOT
9 LNZ vs 15 TDZ
Même tolérance, diminution significative des PNN, 20% arrêt
Outcome difficilement interprétable

# 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)
2 ECR double placebo
1g J0 + 500 mg J8
vs VANCO au moins 3 jours
puis relais possible LNZ 14 jours

The NEW ENGLAND JOURNAL of MEDICINE

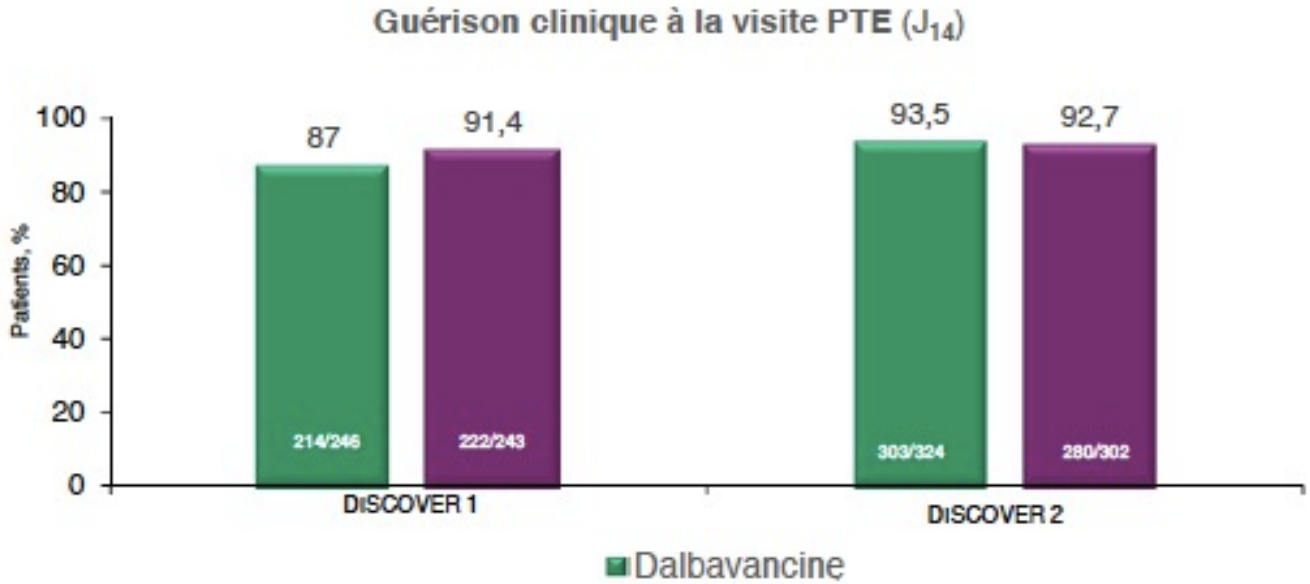
JUNE 5, 2014

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.

Age moyen : 50 ans
Diabète : 12%
Ambulatoire : 25%
Bactériémie : 40 patients / grpe

Critères de jugement principal :
Arrêt extension et fièvre
(≠ guérison)




NON INFERIORITE

# 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

Age moyen : 48 ans
Diabète : 11%
Ambulatoire : 54%
Bactériémie : 40 patients / grpe

Critères de jugement principal :
Réduction d'au moins 20% à 48-72h
NON INFERIORITE

Evaluation à 26-30 jours : non infériorité non démontrée

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

# 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

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[3], Shiri Navon-Venezia[4], Eleanor Rachi[2], Michael W. Dunne[5], Sailaja Puttagunta[5] and Yehuda Carmeli[2]*

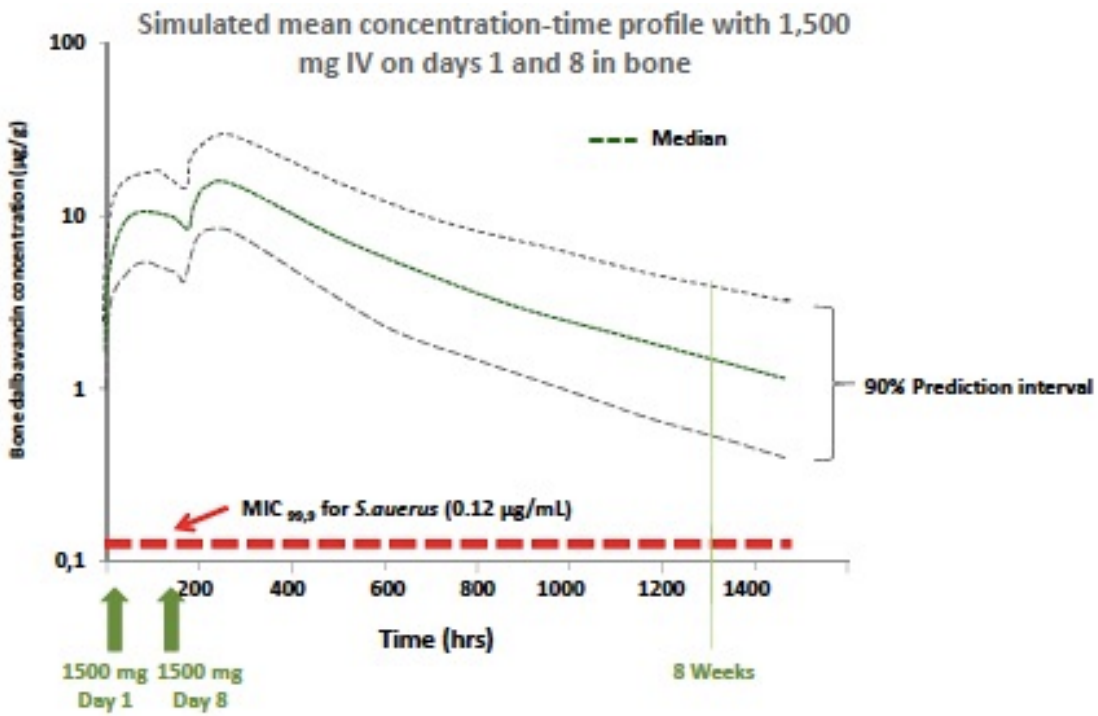
**Dalbavancin reduces biofilms of methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus epidermidis* (MRSE)**

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

AAC
JournalsASM.org

**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]



# Dalbavancine (XYDALBA®)

APPROVED

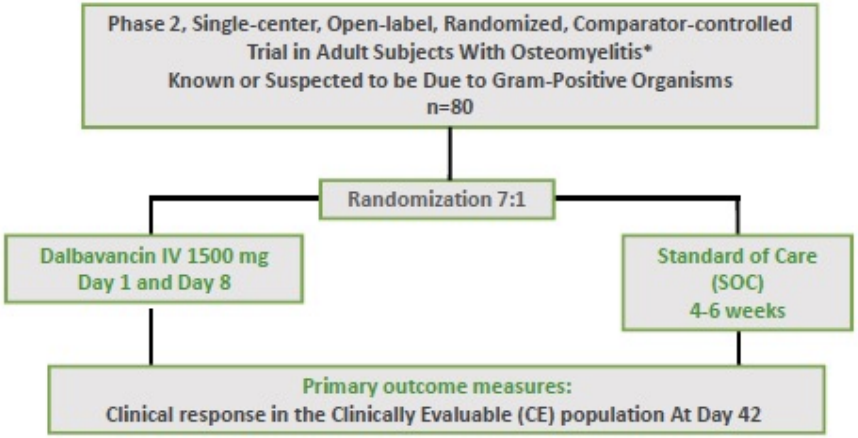
Infections « aiguës » PTM

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

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

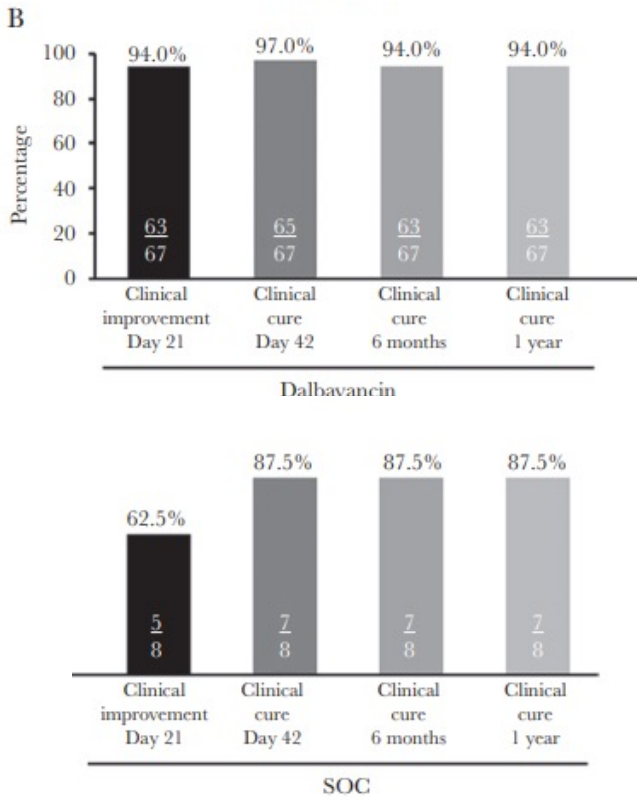
OFF-LABEL

IOA




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

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



# 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

**Table 2.** Clinical series published on the experience with DAL, including cases of bone and joint infection and prosthetic joint infection.

| Reference | *n* | Bone & Joint Infection (Other than PJI) | Episodes of PJI | PJI Outcome (Success, %) |
|---|---|---|---|---|
| Bouza et al., 2017 [51] | 69 | 13 | 20 | 80% |
| Morata et al., 2019 [50] | 64 | NP | 26 | NP |
| Tobudic et al., 2019 [45] | 72 | 20 | 8 | 75% |
| Wunsch et al., 2019 [49] | 101 | 30 | 32 | 94% |
| Martín et al., 2019 [48] | 16 | 0 | 16 | 88% |
| Dinh et al., 2019 [52] | 75 | 48 | NP | NP |

NP: not provided. PJI: prosthetic joint infection.

## Dalbavancin for the Treatment of Prosthetic Joint Infections: A Narrative Review

Luis Buzón-Martín [1,2,*], Ines Zollner-Schwetz [3], Selma Tobudic [4], Emilia Cercenado [5,6,7] and Jaime Lora-Tamayo [2,8,9]

| | DAIR (*n* = 2) | Prosthesis Removal (*n* = 27) | Implant Retention and Suppressive Treatment (*n* = 7) | All Patients (*n* = 36) |
|---|---|---|---|---|
| Sex (female) | 1 (50%) | 11 (40.7%) | 3 (42%) | 15 (43%) |
| Age [*,1] (years) | 69 (67–71) | 69 (18–87) | 62 (15–92) | 67 (15–92) |
| Number of surgeries before DAL | 1 | 2 (1–4) | 2.5 (1–3) | 1.8 (1–4) |
| Treatments | | | | |
| DAL alone | 2 (100%) | 11 (40.7%) | 5 (71%) | 18 (50%) |
| DAL + rifampin | 0 | 7 (26%) | 2 | 9 (25%) |
| DAL + other treatments | 0 | 9 (30%) | 0 | 9 (25%) |
| Etiology | | | | |
| *S. aureus* [2] | 0 | 5 (18.5%) | 1 (14%) | 6 (17%) |
| CoN staphylococci | 2 (100%) | 6 (22.2%) | 2 (29%) | 10 (28%) |
| *Enterococcus* spp [3] | 0 | 4 (14.8%) | 1 (14%) | 5 (14%) |
| Anaerobic GP | 0 | 1 (3.7%) | 0 | 1 (3%) |
| Other GP | 0 | | 2 (29%) | 2 (6%) |
| Mixed GP | 0 | 10 (37%) | | 10 (28%) |
| Unknown etiology | 0 | | 1 (14%) | 1 (3%) |
| Outcome (Success) | 1 (50%) | 25 (93%) | 4 (57%) [4] | 29 (81%) |
| Follow up (months) [*,1] | 4 (2–6) | 16 (3–40) | 6 (3–14) | 14 (2–40) |

# 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

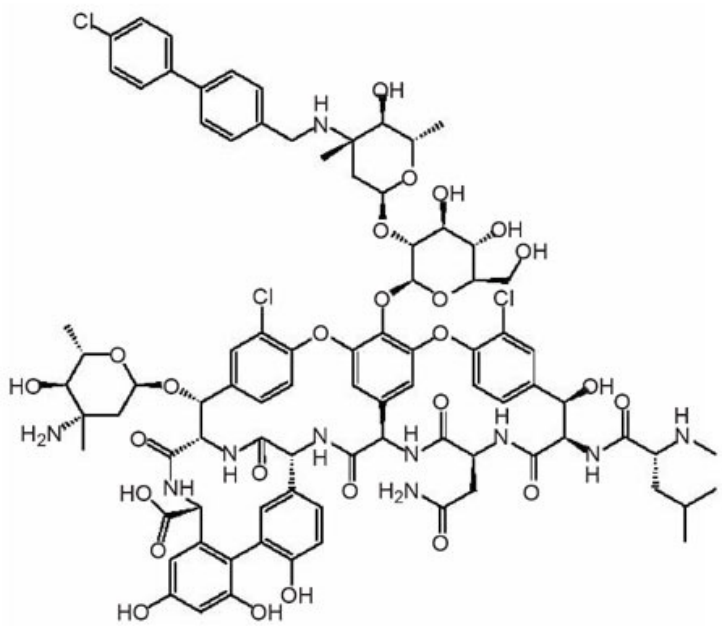
Emergence of dalbavancin non-susceptible, vancomycin-intermediate *Staphylococcus aureus* (VISA) after treatment of MRSA central line-associated bloodstream infection with a dalbavancin- and vancomycin-containing regimen
B.J. Werth
Clinical microbiology and Infection
April 2018Volume 24, Issue 4, Pages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

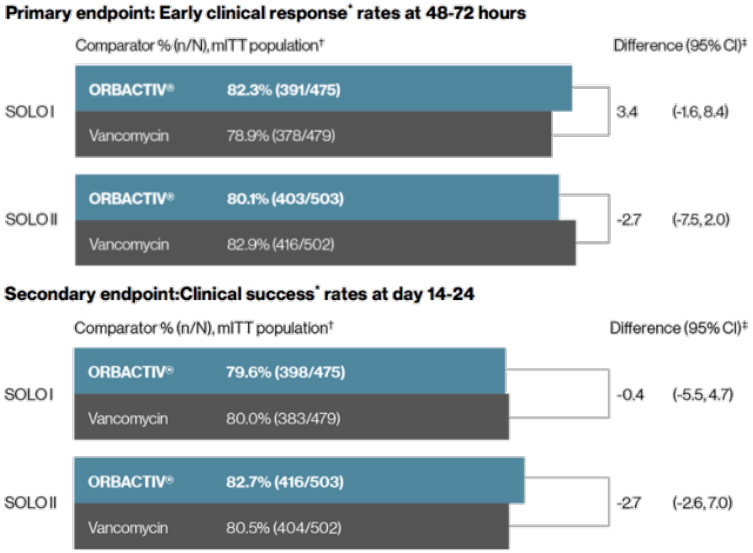


# Oritavancine (ORBACTIV®)

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

JournalsASM.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

- 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)

**Treatment of Acute Osteomyelitis with Once-Weekly Oritavancin: A Two-Year, Multicenter, Retrospective Study**

Nicholas W. Van Hise[1] · Vishnu Chundi[1] · Vishal Didwania[1] · Michael Anderson[1] · David McKinsey[2] · Ingrid Roig[3] · Akhilesh Sharma[4] · Russell M. Petrak[1]

134 patients

1200 mg puis 800 mg/sem
Nombre total d'injection : 4 (n=118) ou 5 (n=16)

88% de succès en fin de traitement
10% de récidive supplémentaires post-arrêt

# Oritavancine (ORBACTIV®)

APPROVED

Infection aiguë PTM

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

OFF-LABEL

IOA

Autres ?

The CHROME Study, a Real-world Experience of Single- and Multiple-Dose Oritavancin for Treatment of Gram-Positive Infections

Mark Redell,[1] Miguel Sierra-Hoffman,[2,3] Maha Assi,[4] Markian Bochan,[5] David Chansolme,[6] Anurag Gandhi,[7] Kathleen Sheridan,[8] Ivan Soosaipillai,[9] Thomas Walsh,[10] and Jill Massey[1]

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%

# Autres anti-Gram positifs en développement

| 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* |

# 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**

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

# Délafloxacine (QUOFENIX®)

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

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

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

| Study or subgroup | Delafloxacin Events | Delafloxacin Total | Comparator Events | Comparator Total | Weight | Odds ration M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Kingsley et al, 2016 | 57 | 81 | 103 | 175 | 9.2% | 1.66 [0.94, 2.92] |
| O'Riordan et al, 2015 | 70 | 75 | 31 | 34 | 1.4% | 1.35 [0.30, 6.03] |
| O'Riordan et al, 2018 | 244 | 423 | 255 | 427 | 51.3% | 0.92 [0.70, 1.21] |
| Pullman et al, 2017 | 172 | 331 | 166 | 329 | 38.2% | 1.06 [0.78, 1.44] |
| **Total (95%CI)** | | **910** | | **965** | **100.0%** | **1.05 [0.87, 1.27]** |
| Total events | 543 | | 555 | | | |

Heterogeneity: $Chi^2$=3.56, $df$=3 ($P$=0.31); $I^2$=16%
Test for overall effect: $Z$=0.49 ($P$=0.63)

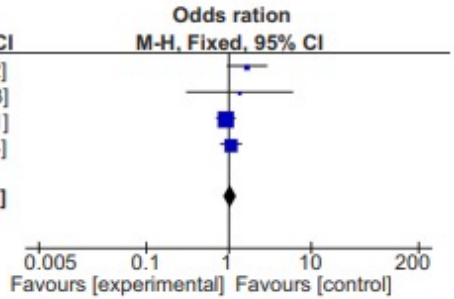



**Figure 4** Overall clinical cure rates of delafloxacin and comparators in the treatment of acute bacterial skin and skin structure infections.

# 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

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

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

| Study or subgroup | Delafloxacin Events | Delafloxacin Total | Comparator Events | Comparator Total | Weight | Odds ration M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Kingsley et al, 2016 | 57 | 81 | 103 | 175 | 9.2% | 1.66 [0.94, 2.92] |
| O'Riordan et al, 2015 | 70 | 75 | 31 | 34 | 1.4% | 1.35 [0.30, 6.03] |
| O'Riordan et al, 2018 | 244 | 423 | 255 | 427 | 51.3% | 0.92 [0.70, 1.21] |
| Pullman et al, 2017 | 172 | 331 | 166 | 329 | 38.2% | 1.06 [0.78, 1.44] |
| **Total (95%CI)** | | **910** | | **965** | **100.0%** | **1.05 [0.87, 1.27]** |
| Total events | 543 | | 555 | | | |

Heterogeneity: $Chi^2$=3.56, $df$=3 ($P$=0.31); $I^2$=16%
Test for overall effect: $Z$=0.49 ($P$=0.63)

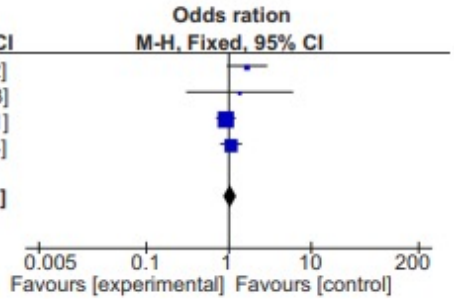



**Figure 4** Overall clinical cure rates of delafloxacin and comparators in the treatment of acute bacterial skin and skin structure infections.

# 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,@]; for the DEFINE-CABP Study Group[*]

Homme, 49 ans – 75 kg, DFG > 90 mL/min, pas d'allergie connue

19/09/20 : Pelvi-mandibulectomie pour carcinome, reconstruction par lambeau libre
J15 : sepsis aigu sur plaque d'ostéosynthèse mandibulaire à S. aureus méti-R
Traitement par DAPTOMYCINE – LEVOFLOXACINE

26/10/20 : réhospitalisation pour fièvre – Etat local satisfaisant
Hémocultures sur piccline positives à BGN en 6h – Mise sous CEFEPIME
27/10/20 : appel de la hotline devant le résultat suivant

**Quels renseignements demandez-vous au laboratoire pour décider de l'antibiothérapie à ce stade ?**

ATB

| | *Enterobacter cloacae* CMI (mg/l) |
|---|---|
| Ampicilline | R |
| Amoxicilline | R |
| Amoxicilline + Ac.Clavulanique | R |
| Ticarcilline | R |
| Ticarcilline + Ac. Clav | R |
| Temocilline | R |
| Pipéracilline | R |
| Pipéracilline + Tazobactam | R |
| Céfoxitine | R |
| Céfotaxime | R |
| Ceftazidime | R |
| Céfépime | R |
| Aztréonam | I |
| Ertapénème | R |
| Imipénème | I |
| Meropeneme | I |
| Gentamicine | S |
| Tobramycine | S |
| Amikacine | S |
| Ciprofloxacine | R |
| Moxifloxacine | R |
| Acide Nalidixique | R |
| Cotrimoxazole | R |
| Fosfomycine | R |

Homme, 49 ans – 75 kg, DFG > 90 mL/min, pas d'allergie connue

19/09/20 : Pelvi-mandibulectomie pour carcinome, reconstruction par lambeau libre
J15 : sepsis aigu sur plaque d'ostéosynthèse mandibulaire à S. aureus méti-R
Traitement par DAPTOMYCINE – LEVOFLOXACINE

26/10/20 : réhospitalisation pour fièvre – Etat local satisfaisant
Hémocultures sur piccline positives à BGN en 6h – Mise sous CEFEPIME
27/10/20 : appel de la hotline devant le résultat suivant

**Quels renseignements demandez-vous au laboratoire pour décider de l'antibiothérapie à ce stade ?**

| | |
|---|---|
| Recherche de carbapénémases | par technique ICT RESIST-4 O.K.N. K-SeT- (Coris BioConcept) |
| de type NDM | négative |
| de type KPC | négative |
| de type OXA 48 | négative |
| de type VIM | POSITIVE |
| Recherche de carbapénémases | par technique ICT IMP K-SeT - (Coris BioConcept) |
| de type IMP | négative |

**Quelle antibiothérapie prescrivez-vous ?**

ATB

| | *Enterobacter cloacae* CMI (mg/l) |
|---|---|
| Ampicilline | R |
| Amoxicilline | R |
| Amoxicilline + Ac.Clavulanique | R |
| Ticarcilline | R |
| Ticarcilline + Ac. Clav | R |
| Temocilline | R |
| Pipéracilline | R |
| Pipéracilline + Tazobactam | R |
| Céfoxitine | R |
| Céfotaxime | R |
| Ceftazidime | R |
| Céfépime | R |
| Aztréonam | I |
| Ertapénème | R |
| Imipénème | I |
| Meropeneme | I |
| Gentamicine | S |
| Tobramycine | S |
| Amikacine | S |
| Ciprofloxacine | R |
| Moxifloxacine | R |
| Acide Nalidixique | R |
| Cotrimoxazole | R |
| Fosfomycine | R |

| | |
|---|---|
| Aztreonam (Etest) | en cours |
| Ceftolozane-tazobactam (Etest) | en cours |
| Ceftazidime-Avibactam (Etest) | en cours |
| Colistine (UMIC) | en cours |

Céfidérocole : en cours

Synergie Azteonam + Ceftazidime-avibactam en cours

# Classification d'Ambler

| | CLASSE A | CLASSE B | CLASSE C | CLASSE D |
|---|---|---|---|---|
| | Sérine β-lactamases | Métallo-β-lactamases | Céphalosporinases | Oxacillinases |
| **Chromosomiques** | Pénicillinases | | AmpC non inductible<br>AmpC inductible<br>AmpC déréprimée | |
| **Plasmidiques** | | | AmpC plasmidique | |
| - BLSE | TEM, CTX-M, SHV | | | OXA |
| - Carbapénémases | KPC | VIM, IMP, NDM-1 | | OXA-48 |

# C3G + inhibiteurs de bétalactamases

*Clinical Infectious Diseases*

INVITED ARTICLE

IDSA Infectious Diseases Society of America

hivma hiv medicine association

REVIEW OF ANTI-INFECTIVE AGENTS: Louis D. Saravolatz, Section Editor

## Ceftazidime/Avibactam and Ceftolozane/Tazobactam: Second-generation β-Lactam/β-Lactamase Inhibitor Combinations

David van Duin[1] and Robert A. Bonomo[2,3,4,5]

## Ceftolozane/tazobactam and ceftazidime/avibactam: two novel β-lactam/β-lactamase inhibitor combination agents for the treatment of resistant Gram-negative bacterial infections

Jordan L. Liscio[a], Monica V. Mahoney[b], Elizabeth B. Hirsch[a,b,*]

*Int J Antimicrob Agents* 2015

# C3G + inhibiteurs de bétalactamases

| | *P. aeruginosa* | | Entérobactéries | | | | | *A. baumani* MDR |
|---|---|---|---|---|---|---|---|---|
| | AmpC | Efflux | ESBL | KPC | NDM | AmpC | Oxa48 | |
| Cefta-avi | + | +/- | +/- | +/- | - | ⊕ | + | - |
| Cefto-tazo | +/- | + | +/- | - | - | +/- | +/- | - |

| | **Ceftolozane tazobactam** | **Ceftazidime avibactam** |
|---|---|---|
| E. coli / KP BLSE | 80-95% | ≈ 100% |
| KPC | < 5% | > 95% |
| P. aeruginosa | 85-95% | 85-95% |
| PA méro-R | 60-80% | 85-90% |
| PA cefta-R | 60-80% | ≈ 80% |
| PA MDR/XDR | ≈ 50% | ≈ 70% |

# Ceftolozane – tazobactam (ZERBAXA®)

- **AMM**
  - IU compliquées (dont PNA)

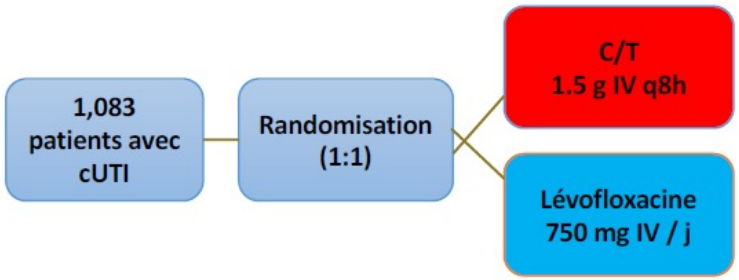
Wagenlehner et al. Lancet 2015

**ASPECT-cUTI :**

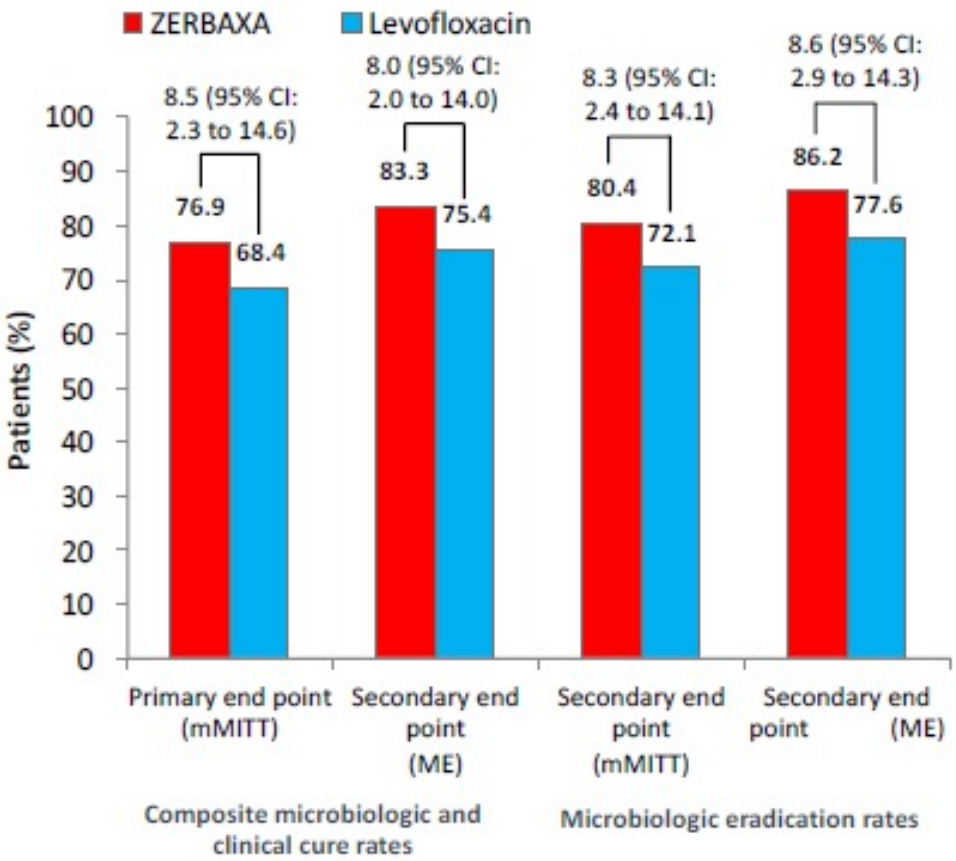
étude randomisée, multice,trique, double insu, double aveugle, de non-infériorité (marge de non infériorité 10%)

**Critère principal :**

Composite microbiologique et guérison clinique 5–9 jours après traitement




800 pyélonéphrites
C/T 7 jours > LVF 7 jours



# Ceftolozane – tazobactam (ZERBAXA®)

- **AMM**
  - IU compliquées (dont PNA)

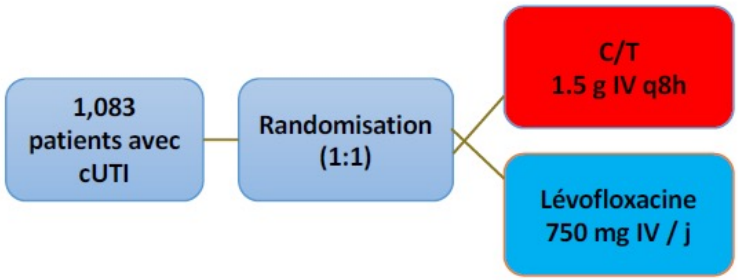
Wagenlehner et al. Lancet 2015

**ASPECT-cUTI :**

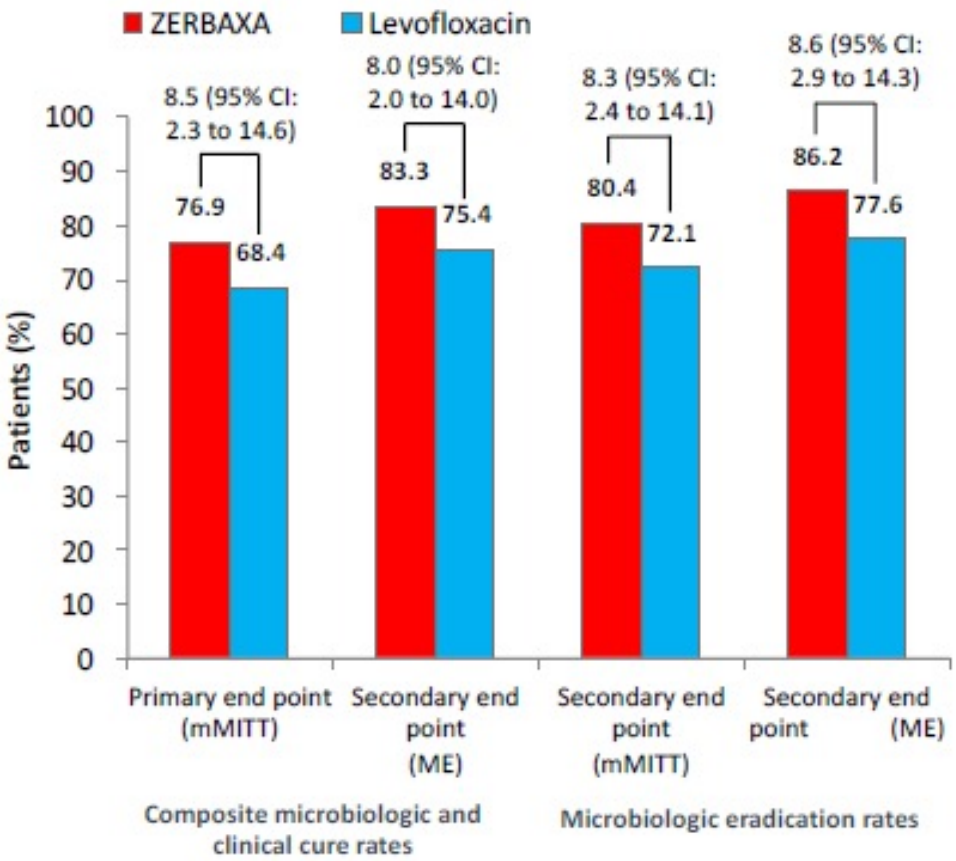
étude randomisée, multice,trique, double insu, double aveugle, de non-infériorité (marge de non infériorité 10%)

**Critère principal :**

Composite microbiologique et guérison clinique 5–9 jours après traitement




800 pyélonéphrites
C/T 7 jours > LVF 7 jours




**> 25% des entérobactéries LVF-R !!**

# Ceftolozane – tazobactam (ZERBAXA®)

- **AMM**
  - IU compliquées (dont PNA)
  - IIA compliquées

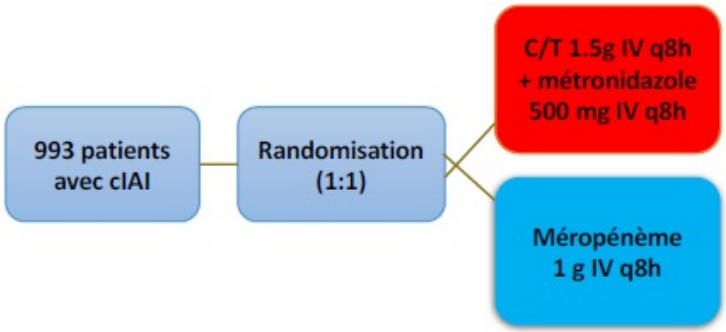
Solomkin et al. CID 2015

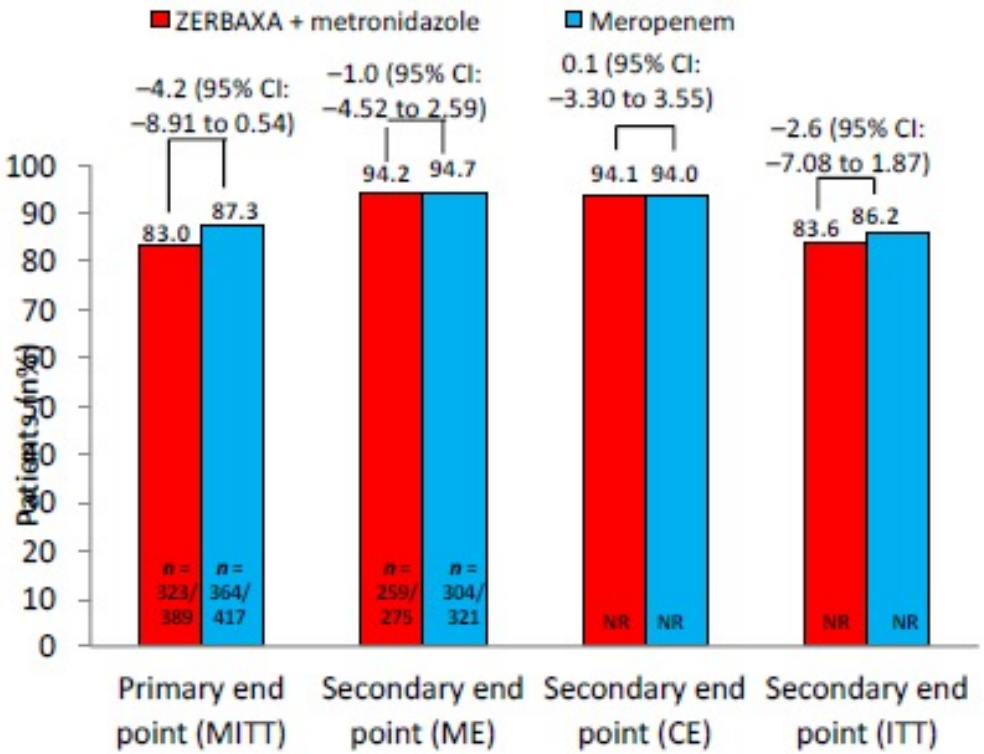
**ASPECT-cIAI:**

Étude randomisée, multicetrique, double insu, de non-infériorité (marge de non infériroté 10%)

**Critère principal:**

Guérison clinique 24–32 jours après initiation du traitement




Non infériorité

30% appendicites localisées
40% de péritonites « diffuses »
2% de bactériémies

# Ceftolozane – tazobactam (ZERBAXA®)

- **AMM**
  - IU compliquées (dont PNA)
  - IIA compliquées

- **En pratique :** « rescue therapy »

- **Posologie : 1g IV / 8h**
  Adaptation posologique si DFG < 50 mL/min
  Dose hors AMM (IOA, SNC, prostate …) ?

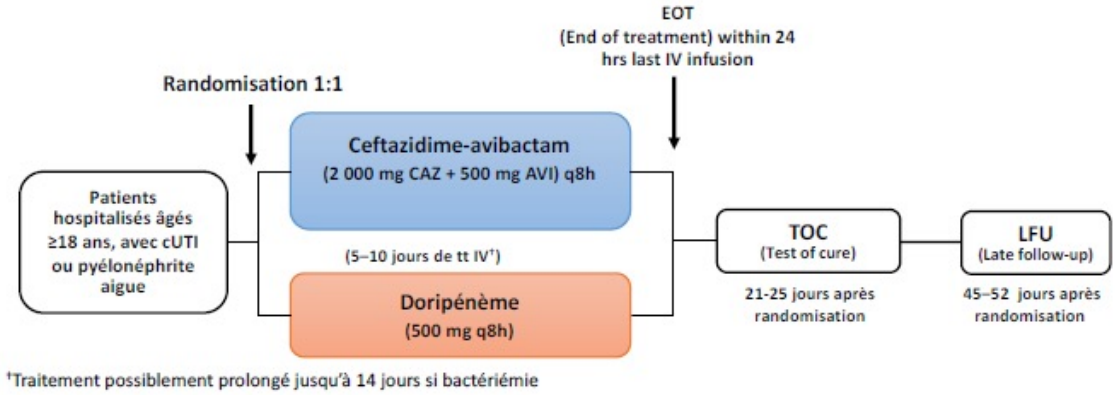
- **Toxicité :** cf. béta-lactamines

- **Emergence de résistance par mutation sur ampC**
- **Facteurs de risque : foyers mal drainés, faibles posologie**

# Ceftazidime – avibactam (ZAVICEFTA®)

- **AMM**
  - IU compliquées (dont PNA)

Wagenlehner et al. CID



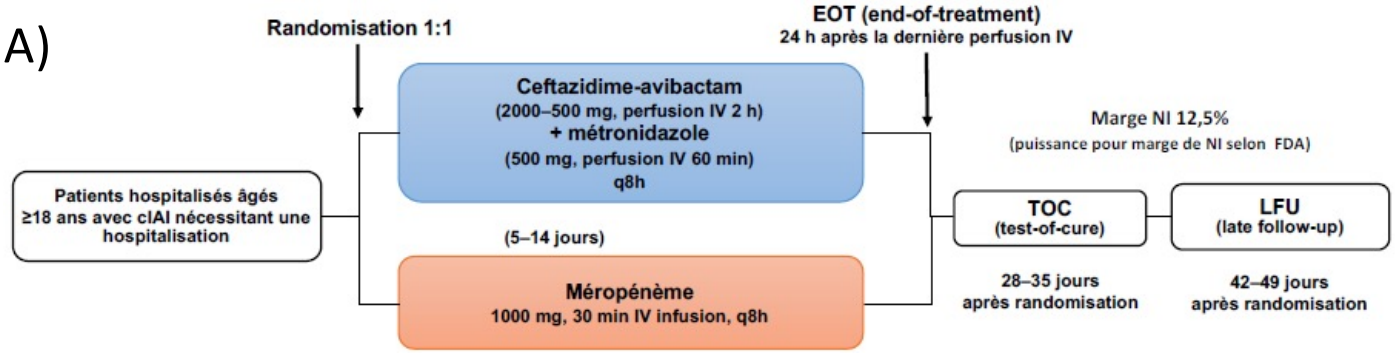

| | Patients, N (%) | | Difference, % (95% CI) |
|---|---|---|---|
| | CAZ-AVI (n=393) | Doripenem (n=417) | |
| **FDA co-primary endpoints** | | | |
| Patient-assessed symptomatic resolution at Day 5 | 276 (70.2) | 276 (66.2) | 4.0 (– 2.39, 10.42) |
| Combined patient-assessed symptomatic resolution and favourable per-patient microbiological response at TOC | 280 (71.2) | 269 (64.5) | 6.7 (0.30, 13.12) |
| Per-patient favourable microbiological response at TOC | 304 (77.4) | 296 (71.0) | 6.4 (0.33, 12.36) |
| Patient-reported symptomatic resolution at TOC | 332 (84.5) | 360 (86.3) | – 1.9 (– 6.78, 3.02) |
| **EMA primary endpoint** | | | |
| Per-patient favourable microbiological response at TOC | 304 (77.4) | 296 (71.0) | 6.4 (0.33, 12.36) |

Non-infériorité démontrée selon le critère principal composite FDA, et superiorité démontrée selon le critère principal EMA

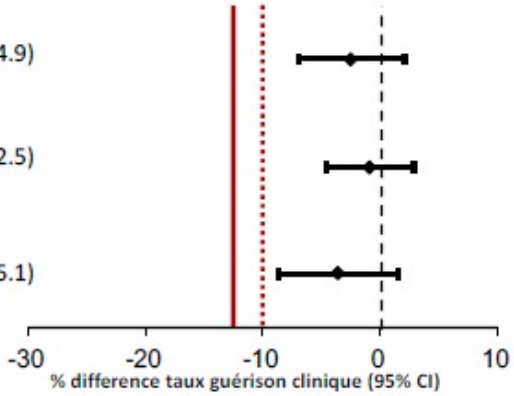
# Ceftazidime – avibactam (ZAVICEFTA®)

- **AMM**
  - IU compliquées (dont PNA)
  - IIA compliquées

Mazuski et al, CID 2016




| Population | n | Guérison cliniquen/N (%) CAZ-AVI + MTZ | MER | Difference, % (IC 95% ) |
|---|---|---|---|---|
| MITT (EMA co-primary analysis population) | 1043 | 429/520 (82.5) | 444/523 (84.9) | −2.4 (−6.90, 2.10) |
| CE at TOC (EMA co-primary analysis population) | 826 | 376/410 (91.7) | 385/416 (92.5) | −0.8 (−4.61, 2.89) |
| mMITT (FDA primary analysis population) | 823 | 337/413 (81.6) | 349/410 (85.1) | −3.5 (−8.64, 1.58) |




→ **NON INFERIORITE, y compris sur les souches CEFTA-R**

# Ceftazidime – avibactam (ZAVICEFTA®)

- **AMM**
  - IU compliquées (dont PNA)
  - IIA compliquées
  - Pneumonies nosocomiales dont PAVM
  - **<u>Autres infections à BGN sans autre option thérapeutique</u>**

- **Posologie :** 2g/8h

- **Toxicité :** cf. béta-lactamines

- **Jusqu'à 10% de résistance / KPC**
- **Facteurs de risque : dialyse, posologies insuffisantes**

# Carbapénèmes + inhibiteurs de bétalactamases

Drugs (2018) 78:65–98
https://doi.org/10.1007/s40265-017-0851-9

REVIEW ARTICLE

## Imipenem–Relebactam and Meropenem–Vaborbactam: Two Novel Carbapenem-β-Lactamase Inhibitor Combinations

George G. Zhanel[1,4] · Courtney K. Lawrence[2] · Heather Adam[1,6] · Frank Schweizer[1,3] · Sheryl Zelenitsky[2] · Michael Zhanel[1] · Philippe R. S. Lagacé-Wiens[1,6] · Andrew Walkty[1,4,6] · Andrew Denisuik[1] · Alyssa Golden[1] · Alfred S. Gin[1,2,5] · Daryl J. Hoban[1,6] · Joseph P. Lynch III[7] · James A. Karlowsky[1,6]

# Carbapénèmes + inhibiteurs de bétalactamases

| | *P. aeruginosa* | | Entérobactéries | | | | | *A. baumani* MDR |
|---|---|---|---|---|---|---|---|---|
| | AmpC | Efflux | ESBL | KPC | NDM | AmpC | Oxa48 | |
| Cefta-avi | + | +/- | +/- | +/- | - | ⊕ | + | - |
| Cefto-tazo | +/- | + | +/- | - | - | +/- | +/- | +/- |
| Imi-rele | + | + | + | + | - | + | +/- | +/- |
| Méro-vabor | + | - | + | + | - | + | +/- | +/- |

# Carbapénèmes + inhibiteurs de bétalactamases

| | Méropénème – Vaborbactam (VABOMERE®) | Imipénème – Relebactam (RECARBRIO®) |
|---|---|---|
| **AMM** | cUTI | en cours |
| **Posologie** | 4g (2+2) IV /8h | |
| **Adaptation** | DFG < 50 mL/min | |
| **Prix** | 850 euros / jour | |

- **N'augmente pas la sensibilité sur PA méro-R**
- **80% d'activité sur les souches de KPC cefta-avi-R**

- **Possible récupération des PA imi-R (possible …)**

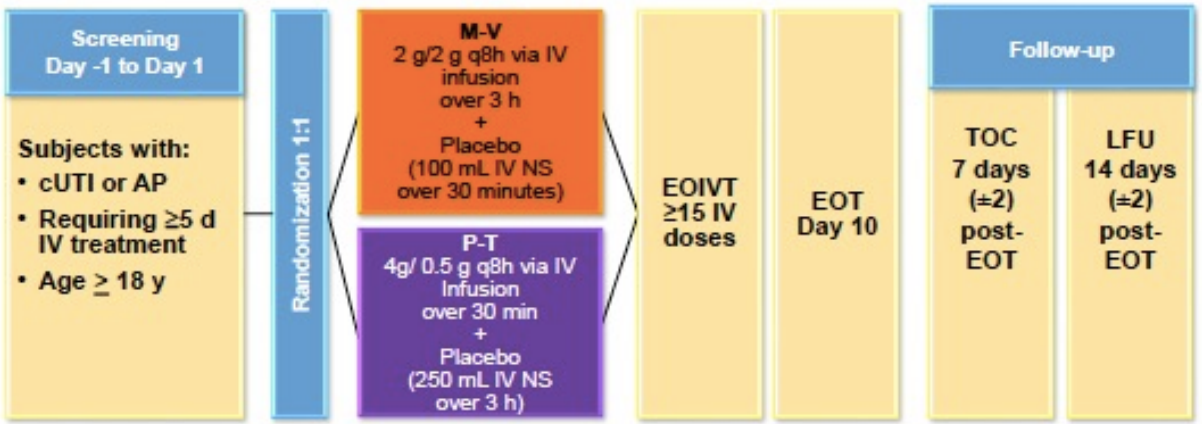
# Méropénème – vaborbactam (VABOREM®)

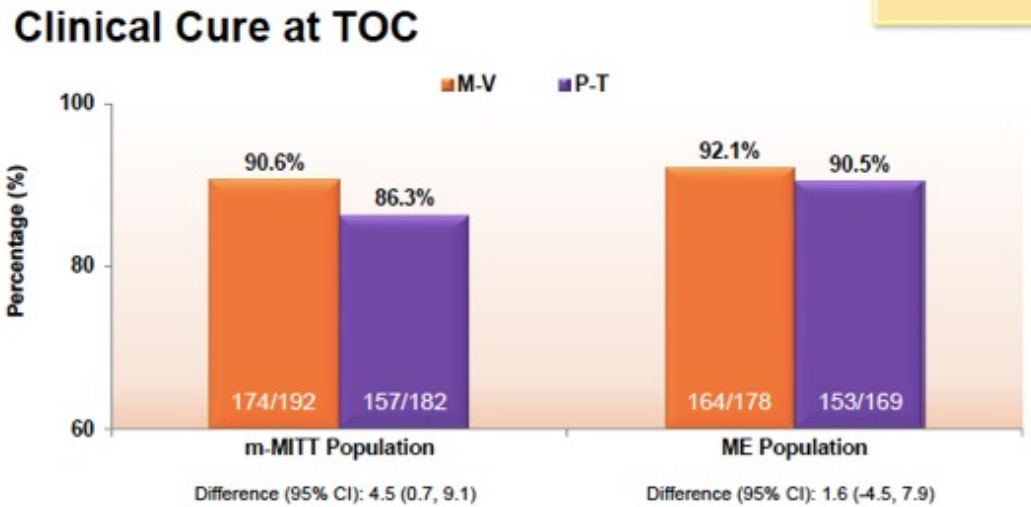
APPROVED

IU « compliquées », dont PNA

TANGO I

IU compliquées dont pyélonéphrites
vs pipéracilline-tazobactam




Non-infériorité démontrée
Supérorité statistique

Profil de sensibilité des germes ?

# Méropénème – vaborbactam (VABOREM®)

APPROVED

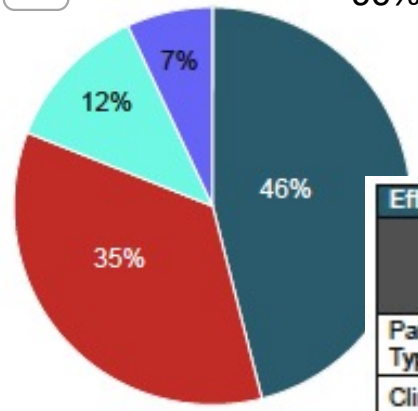
IU « compliquées », dont PNA

TANGO II

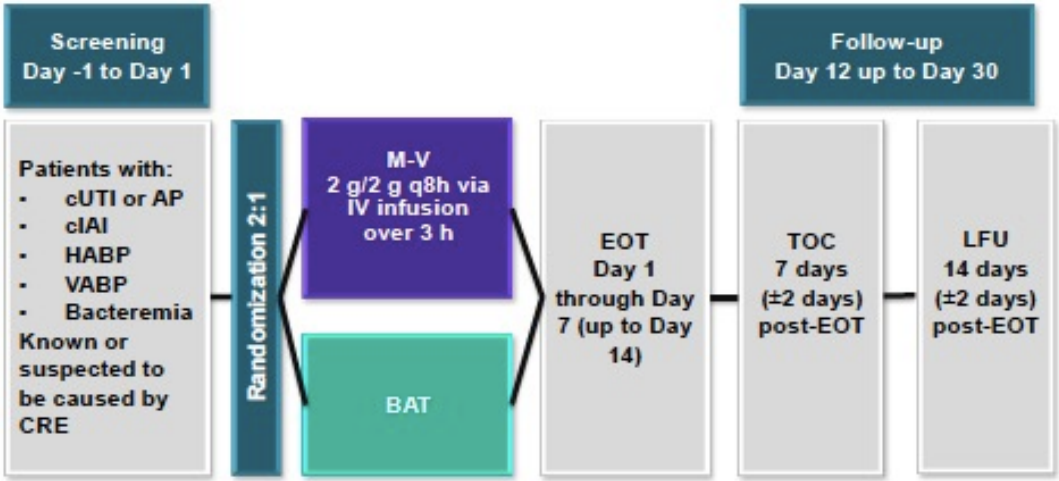
Wunderink RG *et al*. Infect Dis Ther 2018

72 infections sévères
à ENB résistantes
aux carbapénèmes
vs best available therapy (BAT)

20 bactériémies
60% de CRE




- Bacteremia (20)
- cUTI/AP (15)
- HABP/VABP (5)
- cIAI (3)



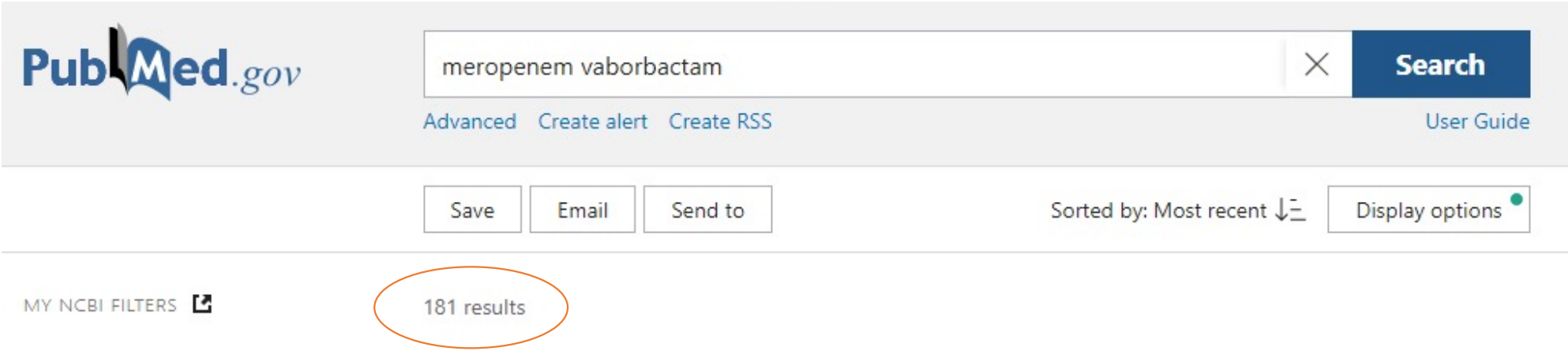

| Efficacy Endpoints | M-V N=28 n (%) | BAT N=15 n (%) | Absolute Difference[a] (95% CI) | *P* value | Relative Difference[b] |
|---|---|---|---|---|---|
| Patients with All Infection Types | | | | | |
| Clinical Cure at EOT | 18 (64.3) | 5 (33.3) | 31.0 (1.2 to 60.7) | .04 | 93.1 |
| Clinical Cure at TOC | 16 (57.1) | 4 (26.7) | 30.5 (1.5 to 59.4) | .04 | 114.2 |
| Microbiologic Cure[c] at EOT | 18 (64.3) | 6 (40.0) | 24.3 | NA | 60.8 |
| Microbiologic Cure[c] at TOC | 14 (50.0) | 5 (33.3) | 16.7 | NA | 50.1 |
| Day-28 Mortality | 5 (17.9) | 5 (33.3) | −15.5 (-43.2 to 12.3) | .27 | −46.5 |

# Méropénème – vaborbactam (VABOREM®)

APPROVED

IU « compliquées », dont PNA

OFF-LABEL



# Méropénème – vaborbactam (VABOREM®)

Real-world, Multicenter Experience With Meropenem-Vaborbactam for Gram-Negative Bacterial Infections Including Carbapenem-Resistant *Enterobacterales* and *Pseudomonas aeruginosa*

Sara Alosaimy,[1] Abdalhamid M. Lagnf,[1] Taylor Morrisette,[1] Marco R. Scipione,[2] Jing J. Zhao,[2] Sarah C. J. Jorgensen,[1,3] Ryan Mynatt,[1,4] Travis J. Carlson,[5,6] Jinhee Jo,[5] Kevin W. Garey,[5] David Allen,[7] Kailynn DeRonde,[8] Ana D. Vega,[8] Lilian M. Abbo,[8] Veena Venugopalan,[9] Vasilios Athans,[10] Stephen Saw,[10] Kimberly C. Claeys,[11] Mathew Miller,[12] Kyle C. Molina,[12] Michael Veve,[1,13,14] Wesley D. Kufel,[15,16] Lee Amaya,[17,18] Christine Yost,[17] Jessica Ortwine,[19] Susan L. Davis,[1,20] and Michael J. Rybak[1,2,21]

Mortalité J30 : 18,3%
Récurrence J30 : 11,9%

FR : initiation MV > 48h

4 effets secondaires :
- 2 IR
- 1 hépatique
- 1 rash

| Criteria[a] | Population (n = 126 |
|---|---|
| Demographics | |
| Age, y | 56.0 (37.0–68.0) |
| Age ≥65 y | 39 (31.0) |
| Sources of infection | |
| Bone and joint | 3 (2.4) |
| Infective endocarditis | 1 (0.8) |
| Intraabdominal | 24 (19.0) |
| Intravenous catheter | 4 (3.2) |
| Other[j] | 2 (1.6) |
| Primary bacteremia | 12 (9.5) |
| Pneumonia | 48 (38.1) |
| Mechanically ventilated for 48 h before pneumonia[i] | 25 (19.8) |
| Skin and soft tissue | 13 (10.3) |
| Urinary | 17 (13.5) |
| Unknown | 2 (1.6) |
| Pathogens targeted | |
| *Carbapenem-resistant pathogen* | 99 (78.6) |
| *Acinetobacter baumannii* | 2 (1.6) |
| *Citrobacter freundii* | 4 (3.2) |
| *Enterobacter cloacae* | 21 (16.7) |
| *Escherichia coli* | 25 (19.8) |
| *Klebsiella aerogenes* | 3 (2.4) |
| *Klebsiella oxytoca* | 4 (3.2) |
| *Klebsiella pneumoniae* | 53 (42.1) |
| *Morganella morganii* | 1 (0.8) |
| *Proteus mirabilis* | 4 (3.2) |
| *Pseudomonas aeruginosa*[k] | 11 (8.7) |
| *Serratia marcescens* | 4 (3.2) |
| *Stenotrophomonas maltophilia* | 1 (0.8) |

# Imipénème – relebactam (RECARBRIO®)

- IU « compliquées », dont PNA
- IIA « compliquées »
- Infections à EPC

| | | |
|---|---|---|
| Lucasti et al, AAC 2016 | Phase 2 | IIA « compliquées » |
| Sims et al, JAC 2017 | Phase 2 | IU « compliquées » |
| Titov et al, CID 2020 | Phase 3 | HAP, VAP vs. pipé/tazo (RESTORE-IMI-2) |
| Motsch et al, CID 2020 | Phase 3 | HAP/VAP (40%), IU (50%) et IIA (10%)<br>BGN IMI-R (80% P. aeruginosa)<br>vs. IMI + COLI (RESTORE-IMI-1) |

# Imipénème – relebactam (RECARBRIO®)

:271-283
051
48

Infection & Chemotherapy

## Clinical and Microbiologic Efficacy and Safety of Imipenem/Cilastatin/ Relebactam in Complicated Infections: A Meta-analysis

Syeda Sahra [1], Abdullah Jahangir [1], Rachelle Hamadi [1], Ahmad Jahangir [2], and Allison Glaser [1]

| Study | Statistics for each study | | | | |
|---|---|---|---|---|---|
| | Odds ratio | Lower limit | Upper limit | Z-value | *P*-value |
| Lucasti (2016)[28] REL 250 | 0.783 | 0.320 | 1.915 | −0.537 | 0.591 |
| Lucasti (2016)[28] REL 125 | 0.942 | 0.380 | 2.338 | −0.128 | 0.898 |
| Sims (2017)[29] REL 250 | 0.745 | 0.320 | 1.735 | −0.682 | 0.495 |
| Sims (2017)[29] REL 125 | 0.923 | 0.394 | 2.165 | −0.184 | 0.854 |
| Motsch (2020)[40] | 9.350 | 2.049 | 42.658 | 2.887 | 0.004 |
| Titov (2020)[38] | 1.238 | 0.876 | 1.749 | 1.210 | 0.226 |
| | 1.126 | 0.717 | 1.769 | 0.517 | 0.605 |

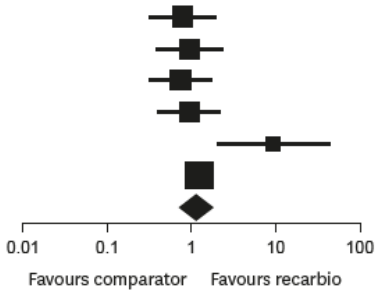



**Figure 2.** Overall clinical response at early follow up.
CI, confidence interval.

Tolérance identique

| Study | Statistics for each study | | | | |
|---|---|---|---|---|---|
| | Odds ratio | Lower limit | Upper limit | Z-value | *P*-value |
| Lucasti (2016)[28] REL 250 | 1.167 | 0.493 | 2.762 | 0.351 | 0.726 |
| Lucasti (2016)[28] REL 125 | 1.415 | 0.587 | 3.409 | 0.774 | 0.439 |
| Sims (2017)[29] REL 250 | 1.000 | 0.449 | 2.229 | 0.000 | 1.000 |
| Sims (2017)[29] REL 125 | 0.665 | 0.295 | 1.499 | −0.984 | 0.325 |
| Motsch (2020)[40] | 5.500 | 1.331 | 22.734 | 2.354 | 0.019 |
| Titov (2020)[38] | 1.435 | 0.923 | 2.230 | 1.604 | 0.109 |
| | 1.264 | 0.858 | 1.861 | 1.186 | 0.236 |

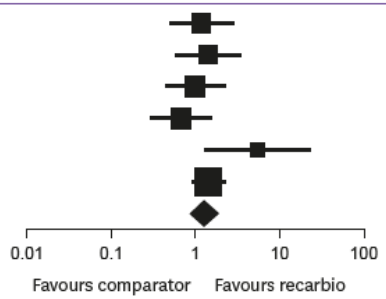
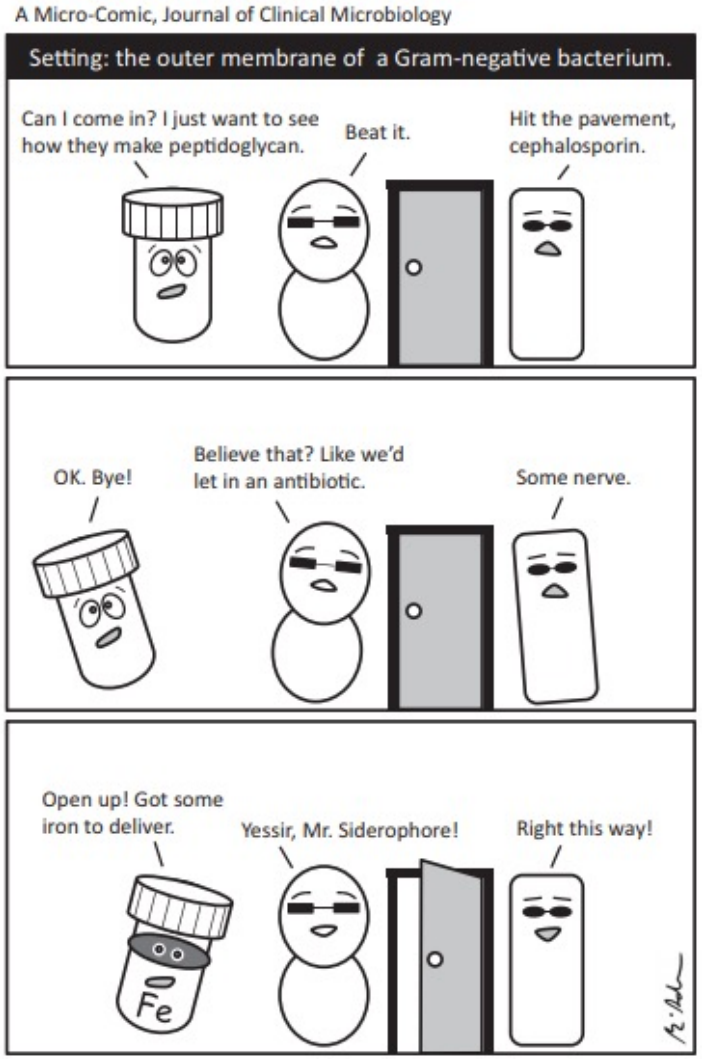



**Figure 3.** Overall clinical response at late follow up.
CI, confidence interval.

# Céfidérocole (FETCROJA®)



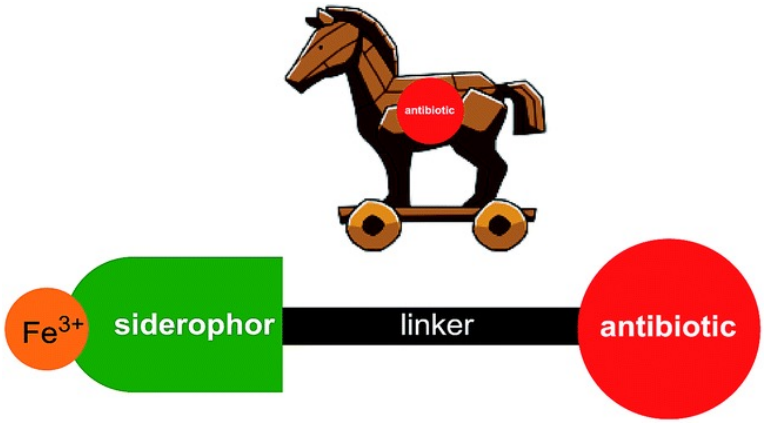

Infect Dis Ther (2020) 9:17–40
https://doi.org/10.1007/s40121-020-00286-6

REVIEW

**Cefiderocol: A Novel Agent for the Management of Multidrug-Resistant Gram-Negative Organisms**

Janet Y. Wu · Pavithra Srinivas · Jason M. Pogue

Céphalosporine + sidérophore
Liaison au fer → transport actif indépendant des porines
Haute stabilité / bétalactamases (+ transport passif)



# Céfidérocole (FETCROJA®)

| | *P. aeruginosa* | | Entérobactéries | | | | | *A. baumani* MDR |
|---|---|---|---|---|---|---|---|---|
| | AmpC | Efflux | ESBL | KPC | NDM | AmpC | Oxa48 | |
| Cefta-avi | + | +/- | +/- | +/- | - | ⊕ | + | - |
| Cefto-tazo | +/- | + | +/- | - | - | +/- | +/- | - |
| Imi-rele | + | + | + | + | - | + | +/- | +/- |
| Méro-vabor | + | - | + | + | - | + | + | +/- |
| Céfidérocol | + | + | + | + | +/- | + | + | + |

# Céfidérocole (FETCROJA®)

## Cefiderocol: A Review in Serious Gram-Negative Bacterial Infections

Yahiya Y. Syed[1]

Drugs, 2021

**Table 3 Design of randomized, multinational cefiderocol trials in hospitalized adults with aerobic Gram-negative bacterial infections**

| | APEKS-cUTI [74] | APEKS-NP [75] | CREDIBLE-CR [76] |
|---|---|---|---|
| Design | Double-blind, noninferiority, phase 2, US FDA-approved design | Double-blind, noninferiority, phase 3, US FDA-approved design | Open-label, pathogen-focused, descriptive, phase 3, EMA-approved design |
| Treatments[a] | Cefiderocol 2 g q8h 1-h infusion or imipenem/cilastatin 1 g q8h infusion | Cefiderocol 2 g q8h 3-h infusion or meropenem 2 g q8h 3-h infusion[b] | Cefiderocol[c] 2 g q8h 3-h infusion or best available therapy[d] |

*BSI* bloodstream infection, *cUTI* complicated urinary tract infection, *HAP* hospital-acquired pneumonia, *HCAP* healthcare-associated pneumonia, *pts* patients, *q8h* every 8 h, *VAP* ventilator-associated pneumonia

| APEKS-cUTI | APEKS-NP | CREDIBLE-CR |
|---|---|---|
| Phase 2<br>IU « compliquées » | Phase 2<br>PNP nosocomiales | Phase 3<br>30% PNP nosocomiales<br>25% IU « compliquées »<br>20% bactériémies |

# Céfidérocole (FETCROJA®)

| Treatment (no. of pts[a]) | ACM at day 14 (% pts) [95% CI] | Clinical cure at TOC[b] (% pts) [95% CI] | Microbiological eradication at TOC[b] (% pts) [95% CI] |
|---|---|---|---|
| In pts with complicated urinary tract infection | | | |
| APEKS-cUTI [74] | | | |
| Cefiderocol (252)[c] | ND | 90 | 73 |
| Imipenem/cilastatin (119) | ND | 87 | 56 |
| Treatment difference | ND | 2.39 [−4.66 to 9.44] | 17.25 [6.92–27.58] |
| CREDIBLE-CR [76] | | | |
| Cefiderocol (17) | 12 [1.5–36.4] | 71 [44.0–89·7] | 53[d] [27.8–77.0] |
| Best available therapy (5) | 40 [5.3–85.3] | 60 [14.7–94.7] | 20[d] [0.5–71.6] |
| In pts with nosocomial pneumonia | | | |
| APEKS-NP [75] | | | |
| Cefiderocol (145] | 12.4 | 65 | 41 |
| Meropenem (147) | 11.6 | 67 | 42 |
| Treatment difference | 0.8* [–6.6 to 8.2][d] | –1.8 [–12.7 to 9.0] | –0.8 [–12.1 to 10.5] |
| CREDIBLE-CR [76] | | | |
| Cefiderocol (40) | 25 [12.7–41.2] | 50[d] [33.8–66.2] | 23 [10.8–38.5] |
| Best available therapy (19) | 11 [1.3–43.7] | 53[d] [28.9–75.6] | 21 [6.1–45.6] |
| In pts with bloodstream infection or sepsis (CREDIBLE-CR) [76] | | | |
| Cefiderocol (23) | 22 [7.5–43.7] | 43[d] [23.2–65.5] | 30 [13.2–52.9] |
| Best available therapy (14) | 7 [0.2–33.9] | 43[d] [17.7–71.1] | 29 [8.4–58.1] |
| In overall population with CR infections (CREDIBLE-CR) [76] | | | |
| Cefiderocol (80) | 21 [12.9–31.8] | 53 [41.0–63.8] | 31 [21.3–42.6] |
| Best available therapy (38) | 13 [4.4–28.1] | 50 [33.4–66.6] | 24 [11.4–40.2] |

*ACM* all-cause mortality, *ITT* intent-to-treat, *ND* not determined, *pts* patients, *TOC* test of cure

# Autres bétalactamines

| | *P. aeruginosa* | | Entérobactéries | | | | | *A. baumani* MDR |
|---|---|---|---|---|---|---|---|---|
| | AmpC | Efflux | ESBL | KPC | NDM | AmpC | Oxa48 | |
| Cefta-avi | + | +/- | +/- | +/- | - | ⊕ | + | - |
| Cefto-tazo | +/- | + | +/- | - | - | +/- | +/- | - |
| Imi-rele | + | + | + | + | - | + | +/- | +/- |
| Méro-vabor | + | - | + | + | - | + | + | +/- |
| Céfidérocol | + | + | + | + | +/- | + | + | + |
| Aztréo-avi | - | - | + | + | ⊕/- | + | + | - |
| Céfépime taniborbactam | + | + | + | + | + | + | + | + |
| Méro-nacubactam | + | + | + | + | + | + | +/- | + |

# Autres bétalactamines

| | *P. aeruginosa* | | Entérobactéries | | | | | *A. baumani* MDR |
|---|---|---|---|---|---|---|---|---|
| | AmpC | Efflux | ESBL | KPC | NDM | AmpC | Oxa48 | |
| Cefta-avi | + | +/- | +/- | +/- | - | ⊕ | + | - |
| Cefto-tazo | +/- | + | +/- | - | - | +/- | +/- | - |
| Imi-rele | + | + | + | + | - | + | +/- | +/- |
| Méro-vabor | + | - | + | + | - | + | + | +/- |
| Céfidérocol | + | + | + | + | +/- | + | + | + |
| Aztréo-avi | - | - | + | + | ⊕/- | + | + | - |
| Céfépime taniborbactam | + | + | + | + | + | + | + | + |
| Méro-nacubactam | + | + | + | + | + | + | +/- | + |

Tébipénème, sulopénème

Nouveaux carbapénèmes, PER OS

# Autres anti-BGN

| | *P. aeruginosa* | | Entérobactéries | | | | | *A. baumani* MDR |
|---|---|---|---|---|---|---|---|---|
| | AmpC | Efflux | ESBL | KPC | NDM | AmpC | Oxa48 | |
| Cefta-avi | + | +/- | +/- | ⊕/- | - | ⊕ | + | - |
| Cefto-tazo | +/- | + | +/- | - | - | +/- | +/- | - |
| Imi-rele | + | + | + | + | - | + | +/- | +/- |
| Méro-vabor | + | - | + | + | - | + | + | +/- |
| Céfidérocol | + | + | + | + | ⊕/- | + | + | + |
| Aztréo-avi | - | - | + | + | ⊕/- | + | + | - |
| Céfépime taniborbactam | + | + | + | + | + | + | + | + |
| Méro-nacubactam | + | + | + | + | + | + | +/- | + |
| Plazomicine | - | +/- | + | + | - | + | + | +/- |
| Eravacycline | - | - | + | + | + | + | + | + |

Homme, 49 ans – 75 kg, DFG > 90 mL/min, pas d'allergie connue

19/09/20 : Pelvi-mandibulectomie pour carcinome, reconstruction par lambeau libre
J15 : sepsis aigu sur plaque d'ostéosynthèse mandibulaire à S. aureus méti-R
Traitement par DAPTOMYCINE – LEVOFLOXACINE

26/10/20 : réhospitalisation pour fièvre – Etat local satisfaisant
Hémocultures sur piccline positives à BGN en 6h – Mise sous CEFEPIME
27/10/20 : appel de la hotline devant le résultat suivant

**Quels renseignements demandez-vous au laboratoire pour décider de l'antibiothérapie à ce stade ?**

| | |
|---|---|
| Recherche de carbapénémases | par technique ICT RESIST-4 O.K.N. K-SeT- (Coris BioConcept) |
| de type NDM | négative |
| de type KPC | négative |
| de type OXA 48 | négative |
| de type VIM | POSITIVE |
| Recherche de carbapénémases | par technique ICT IMP K-SeT - (Coris BioConcept) |
| de type IMP | négative |

**Quelle antibiothérapie prescrivez-vous ?**

ATB

| | *Enterobacter cloacae* CMI (mg/l) |
|---|---|
| Ampicilline | R |
| Amoxicilline | R |
| Amoxicilline + Ac.Clavulanique | R |
| Ticarcilline | R |
| Ticarcilline + Ac. Clav | R |
| Temocilline | R |
| Pipéracilline | R |
| Pipéracilline + Tazobactam | R |
| Céfoxitine | R |
| Céfotaxime | R |
| Ceftazidime | R |
| Céfépime | R |
| Aztréonam | I |
| Ertapénème | R |
| Imipénème | I |
| Meropeneme | I |
| Gentamicine | S |
| Tobramycine | S |
| Amikacine | S |
| Ciprofloxacine | R |
| Moxifloxacine | R |
| Acide Nalidixique | R |
| Cotrimoxazole | R |
| Fosfomycine | R |

| | |
|---|---|
| Aztreonam (Etest) | en cours |
| Ceftolozane-tazobactam (Etest) | en cours |
| Ceftazidime-Avibactam (Etest) | en cours |
| Colistine (UMIC) | en cours |

Céfidérocole : en cours

Synergie Azteonam + Ceftazidime-avibactam en cours

Homme, 49 ans – 75 kg, DFG > 90 mL/min, pas d'allergie connue

19/09/20 : Pelvi-mandibulectomie pour carcinome, reconstruction par lambeau libre
J15 : sepsis aigu sur plaque d'ostéosynthèse mandibulaire à S. aureus méti-R
Traitement par DAPTOMYCINE – LEVOFLOXACINE

26/10/20 : réhospitalisation pour fièvre – Etat local satisfaisant
Hémocultures sur piccline positives à BGN en 6h – Mise sous CEFEPIME
27/10/20 : appel de la hotline devant le résultat suivant

**Quels renseignements demandez-vous au laboratoire pour décider de l'antibiothérapie à ce stade ?**

| | |
|---|---|
| Recherche de carbapénémases | par technique ICT RESIST-4 O.K.N. K-SeT- (Coris BioConcept) |
| de type NDM | négative |
| de type KPC | négative |
| de type OXA 48 | négative |
| de type VIM | POSITIVE |
| Recherche de carbapénémases | par technique ICT IMP K-SeT - (Coris BioConcept) |
| de type IMP | négative |

**Quelle antibiothérapie prescrivez-vous ?**

CEFTAZIDIME-AVIBACTAM + AZTREONAM + AMIKACINE

ATB

| | *Enterobacter cloacae* CMI (mg/l) |
|---|---|
| Ampicilline | R |
| Amoxicilline | R |
| Amoxicilline + Ac.Clavulanique | R |
| Ticarcilline | R |
| Ticarcilline + Ac. Clav | R |
| Temocilline | R |
| Pipéracilline | R |
| Pipéracilline + Tazobactam | R |
| Céfoxitine | R |
| Céfotaxime | R |
| Ceftazidime | R |
| Céfépime | R |
| Aztréonam | I |
| Ertapénème | R |
| Imipénème | I |
| Meropeneme | I |
| Gentamicine | S |
| Tobramycine | S |
| Amikacine | S |
| Ciprofloxacine | R |
| Moxifloxacine | R |
| Acide Nalidixique | R |
| Cotrimoxazole | R |
| Fosfomycine | R |

| | |
|---|---|
| Aztreonam (Etest) | en cours |
| Ceftolozane-tazobactam (Etest) | en cours |
| Ceftazidime-Avibactam (Etest) | en cours |
| Colistine (UMIC) | en cours |

Céfidérocole : en cours

Synergie Azteonam + Ceftazidime-avibactam en cours

Homme, 49 ans – 75 kg, DFG > 90 mL/min, pas d'allergie connue

19/09/20 : Pelvi-mandibulectomie pour carcinome, reconstruction par lambeau libre
J15 : sepsis aigu sur plaque d'ostéosynthèse mandibulaire à S. aureus méti-R
Traitement par DAPTOMYCINE – LEVOFLOXACINE

26/10/20 : réhospitalisation pour fièvre – Etat local satisfaisant
Hémocultures sur piccline positives à BGN en 6h – Mise sous CEFEPIME
27/10/20 : appel de la hotline devant le résultat suivant

**Quels renseignements demandez-vous au laboratoire pour décider de l'antibiothérapie à ce stade ?**

| | |
|---|---|
| Recherche de carbapénémases | par technique ICT RESIST-4 O.K.N. K-SeT- (Coris BioConcept) |
| de type NDM | négative |
| de type KPC | négative |
| de type OXA 48 | négative |
| de type VIM | POSITIVE |
| Recherche de carbapénémases | par technique ICT IMP K-SeT - (Coris BioConcept) |
| de type IMP | négative |

**Quelle antibiothérapie prescrivez-vous ?**

CEFTAZIDIME-AVIBACTAM + AZTREONAM ~~+ AMIKACINE~~

Retrait du piccline
Négativation des hémocultures à J3
EDVMS : thrombose
Durée : 4 sem

ATB

| | *Enterobacter cloacae* CMI (mg/l) |
|---|---|
| Ampicilline | R |
| Amoxicilline | R |
| Amoxicilline + Ac.Clavulanique | R |
| Ticarcilline | R |
| Ticarcilline + Ac. Clav | R |
| Temocilline | R |
| Pipéracilline | R |
| Pipéracilline + Tazobactam | R |
| Céfoxitine | R |
| Céfotaxime | R |
| Ceftazidime | R |
| Céfépime | R |
| Aztréonam | I |
| Ertapénème | R |
| Imipénème | I |
| Meropeneme | I |
| Gentamicine | S |
| Tobramycine | S |
| Amikacine | S |
| Ciprofloxacine | R |
| Moxifloxacine | R |
| Acide Nalidixique | R |
| Cotrimoxazole | R |
| Fosfomycine | R |

| | |
|---|---|
| Aztreonam (Etest) | R<br>CMI : 12 |
| Ceftolozane-tazobactam (Etest) | R<br>CMI : > 256 |
| Ceftazidime-Avibactam (Etest) | R<br>CMI : > 256 |
| Colistine (UMIC) | R<br>CMI : 12 |

Céfidérocole : R

Synergie Azteonam + Ceftazidime-avibactam : CMI = 1 mg/L (sensible)

# Recommandations IDSA

| BGN | Traitement | Alternative |
|---|---|---|
| KPC<br>(Ou carbapénémase positive non identifiée) | Ceftazidime-avibactam, méropénème-vaborbactam, imipéneme-cilastatin-relebactam | Cefiderocol<br>Tigécycline, eravacycline (IIA non compliquée seulement) |
| Metallo-β-lactamase (NDM, VIM, ou IMP) carbapenemase | Ceftazidime-avibactam + aztreonam, cefiderocol | Tigécycline, eravacycline (IIA non compliquée seulement) |
| OXA-48-like carbapenemase | Ceftazidime-avibactam | Cefiderocol<br><br>Tigécycline, eravacycline (IIA non compliquée seulement) |

Tamma PD *et al*. Clin Infect Dis 2020

# Thérapies non conventionnelles : nouvelles stratégies

# Anticorps monoclonaux

Review

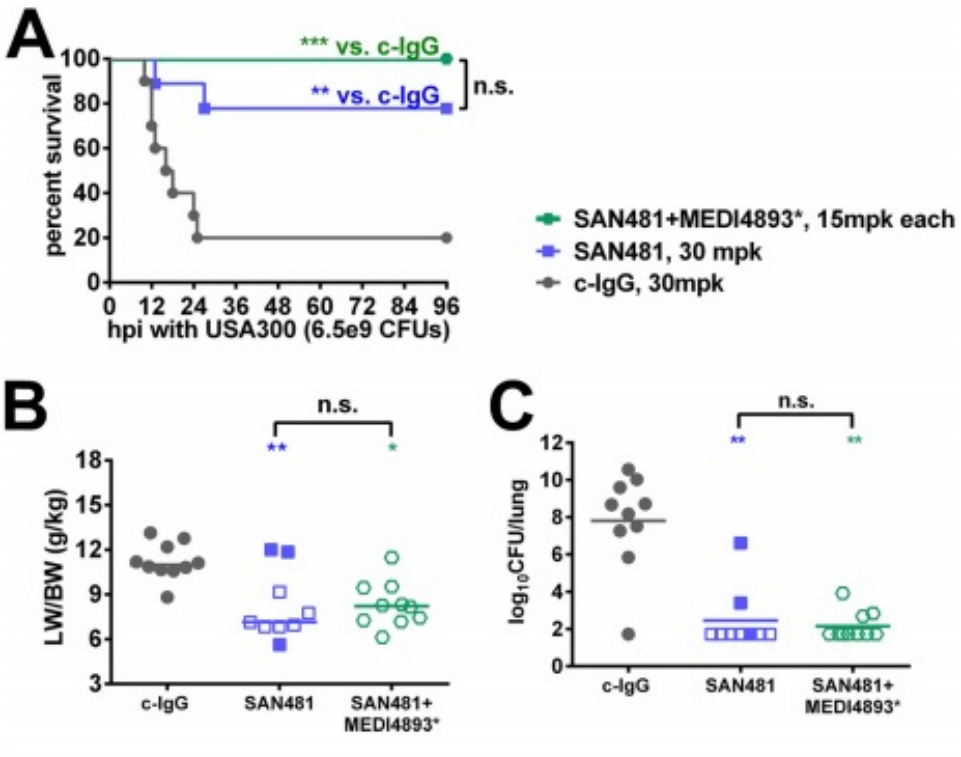
## Tackling COVID-19 with neutralizing monoclonal antibodies

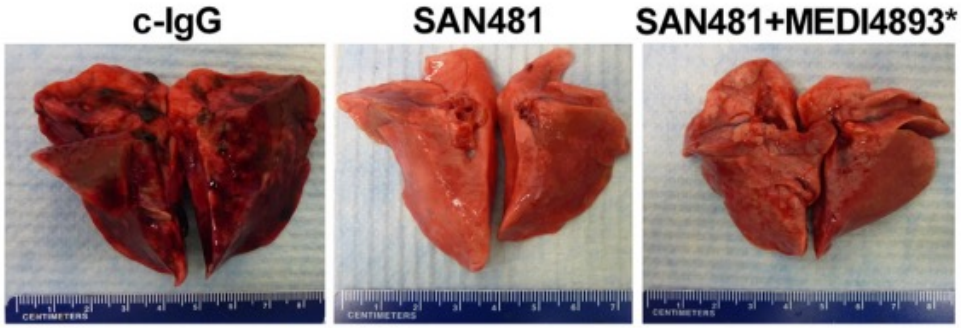
Davide Corti,[1,*] Lisa A. Purcell,[2] Gyorgy Snell,[3] and David Veesler[4]

# Anticorps monoclonaux

## 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]



# Anticorps monoclonaux

> Antimicrob Agents Chemother. 2021 Jun 17;65(7):e0183220. doi: 10.1128/AAC.01832-20. Epub 2021 Jun 17.

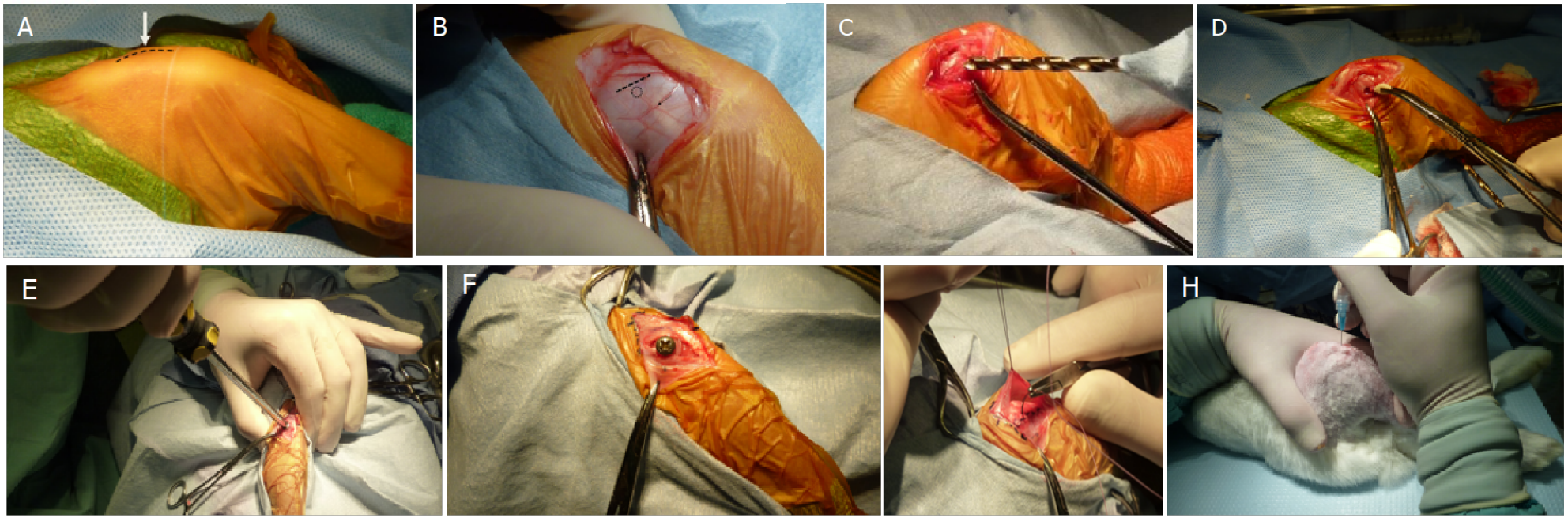
## Multimechanistic Monoclonal Antibody Combination Targeting Key Staphylococcus aureus Virulence Determinants in a Rabbit Model of Prosthetic Joint Infection

Yanjie Mao [#1 2], Florent Valour [#1 3 4], Nhu T Q Nguyen [1], Thien M N Doan [1], Holly Koelkebeck [5], Christopher Richardson [6], Lily I Cheng [5], Bret R Sellman [6], Christine Tkaczyk [6], Binh An Diep [1]

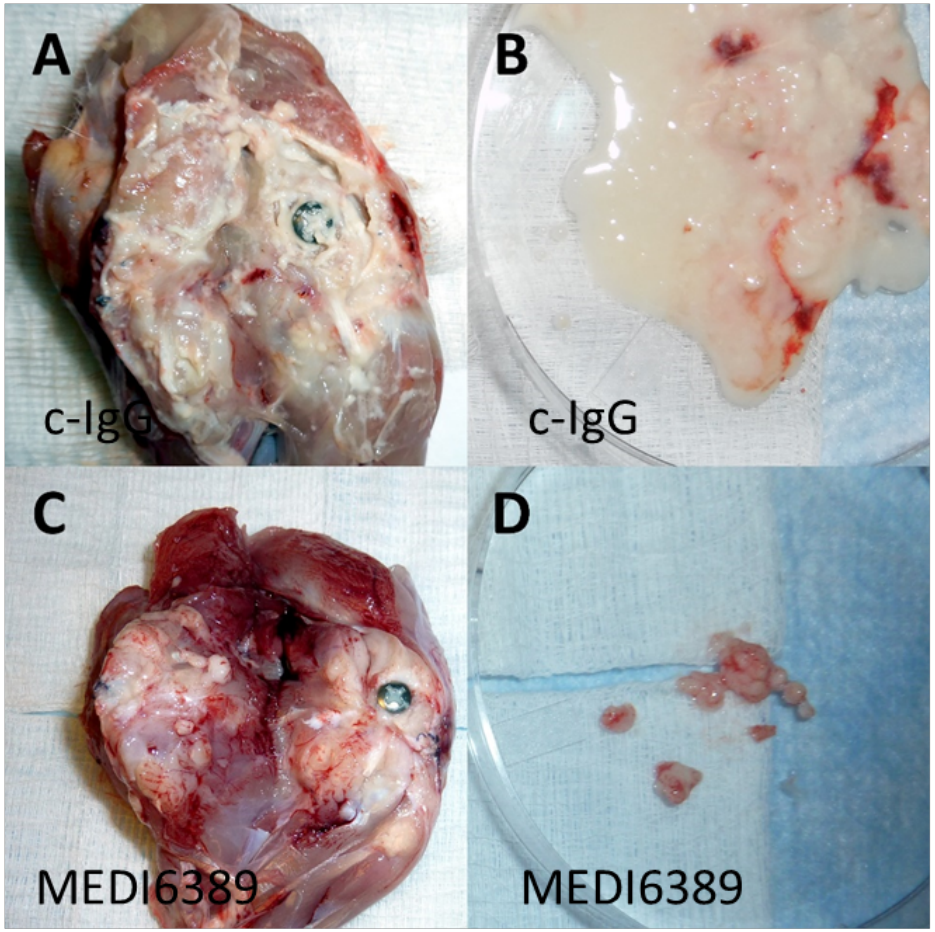
**Modèle lapin d'infection de prothèse articulaire à *S. aureus* USA300**

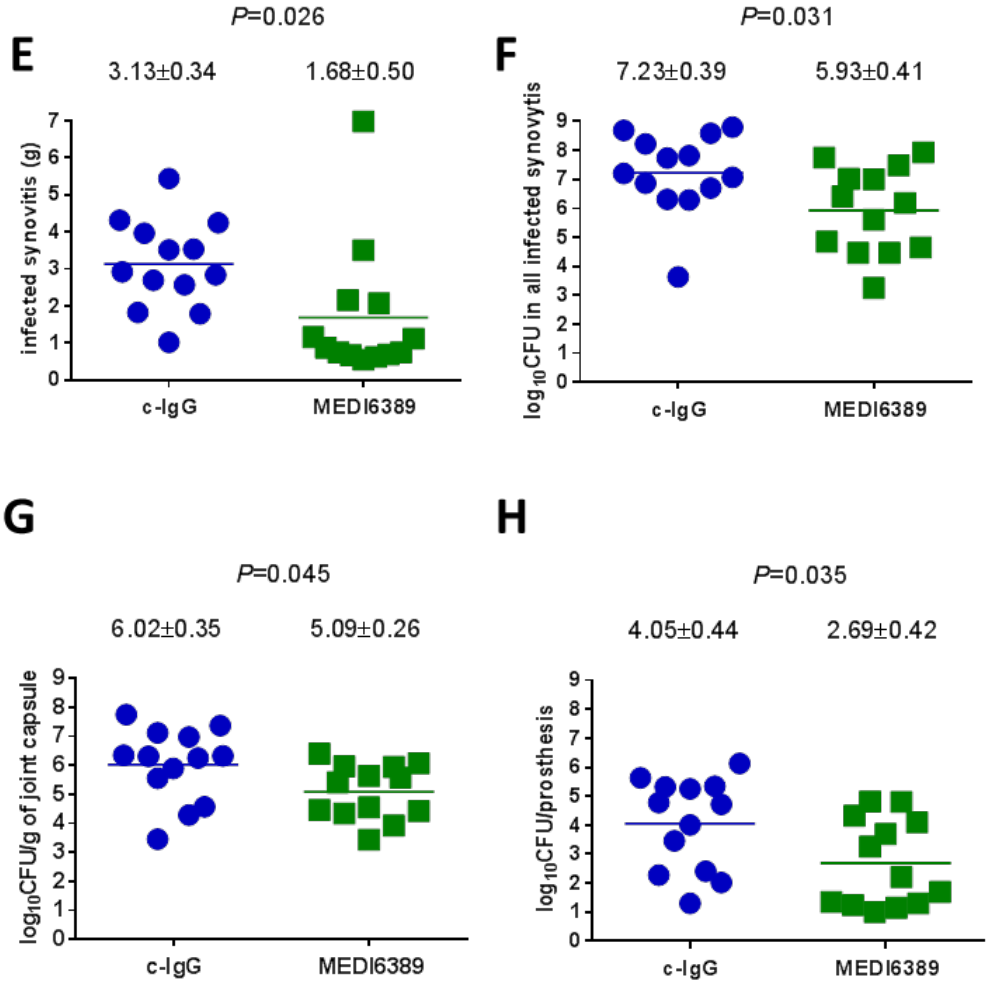
Randomisation pour injection 12h pré-opératoire

- Ig polyvalentes
- MEDI6389 : **mAb anti-*S. aureus* ciblant AT, PVL, lukED, gamma-hémolysine et ClfA**



# Anticorps monoclonaux



# Anticorps monoclonaux

| Nom | Espèce | Cible | Indication | Phase | Laboratoire |
|---|---|---|---|---|---|
| Tosatoxumab (AR301) | *S. aureus* | α-toxine | Adjuvant ttt VAP | Phase 3 | Aridis |
| Sevratoxumab (MEDI4893) | *S. aureus* | α-toxine | Prévention VAP | Phase 2 | Medimmune |
| 514G3 | *S. aureus* | Protéine A | Adjuvant ttt BSI | Phase 2 | XBiotech |
| ASN-100 | *S. aureus* | AT + 5 leucocidines | | Phase 2 | Arsansis |
| RG7861 | *S. aureus* | Paroi + rifamycine | | Phase 1 | Roche |
| MEDI3902 | *P. aeruginosa* | T3SS PcrV + Psl | Adjuvant ttt VAP | Phase 2 | Medimmune |
| AR101 | *P. aeruginosa* | Alginate | Adjuvant ttt VAP | Phase 2 | Aridis |
| ASN-4 | *E. coli* | LPS | | Préclinique | Arsansis |
| ASN-5 | *K. pneumoniae* | O-Ag | | Préclinique | Arsansis |
| AR401-mAb | *A. baumannii* | | BSI | Préclinique | Aridis |
| VXD-003 | *A. baumannii* | | | Préclinique | VaxDyn |
| PolyCAb | *C. difficile* | | | Phase 1 | Micropharm |
| Cd-ISTAb | *C. difficile* | | | Préclinique | BioTherapeutics |

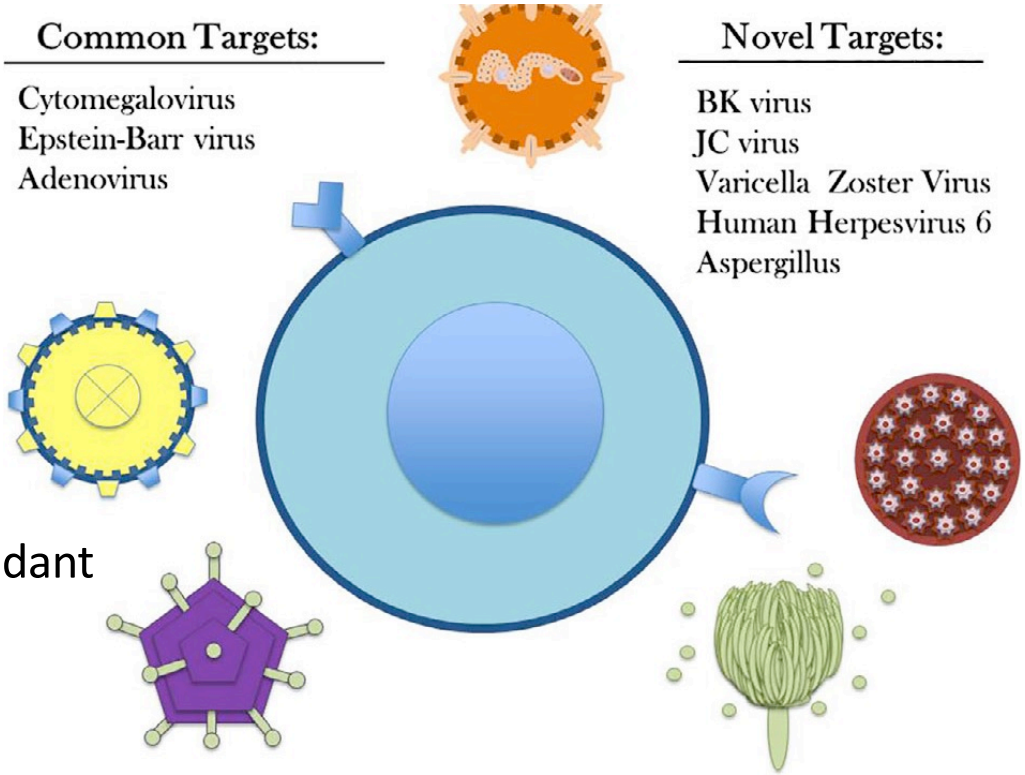
*Zurawski et al, Antibiotics 2020 – Theuretzbacher et al, Cell Host Microbe 2019*

# Transferts adoptifs cellulaires

Principe général : transfusion de T effecteurs spécifiques

- **Priming lymphocytaire**
  cellules du patient / donneur
  incubation avec Ag cible in vitro
  réinfusion

- **Modifications génétiques**
  Re-engenering cellulaire visant à
  l'expression de TCRs spécifiques des Ag cibles
  - 1e génération : problème du CMH correspondant
  - CAR-T-cells




*Naran et al, Front Microbial 2018 – Fatic et al, Transfusion 2020*

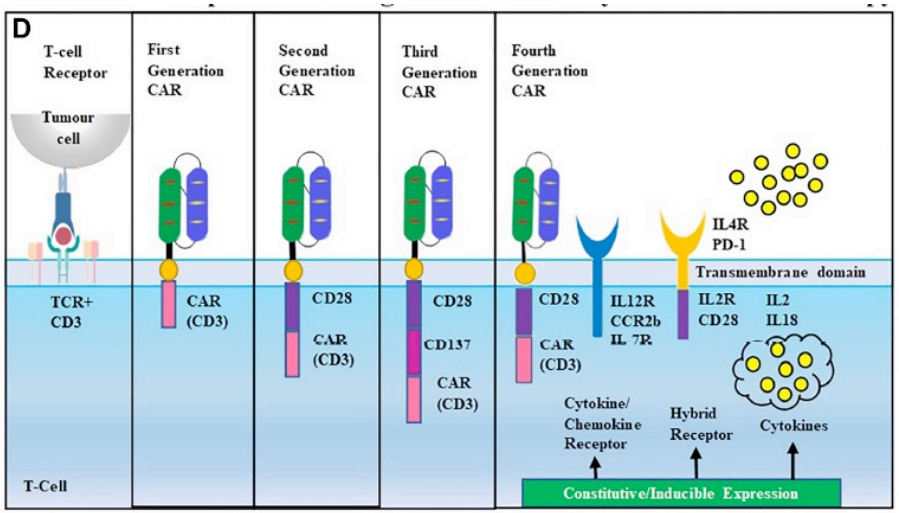
# Transferts adoptifs cellulaires

## CAR-T-cells

Chimeric Ag receptor T cells

Récepteur recombinant

- scFV : redirection de la spécificité des T effecteurs
- Récepteur transmembranaire : activation cellulaire sans lien avec le CMH




## Application of CAR-T Cell Therapy beyond Oncology: Autoimmune Diseases and Viral Infections

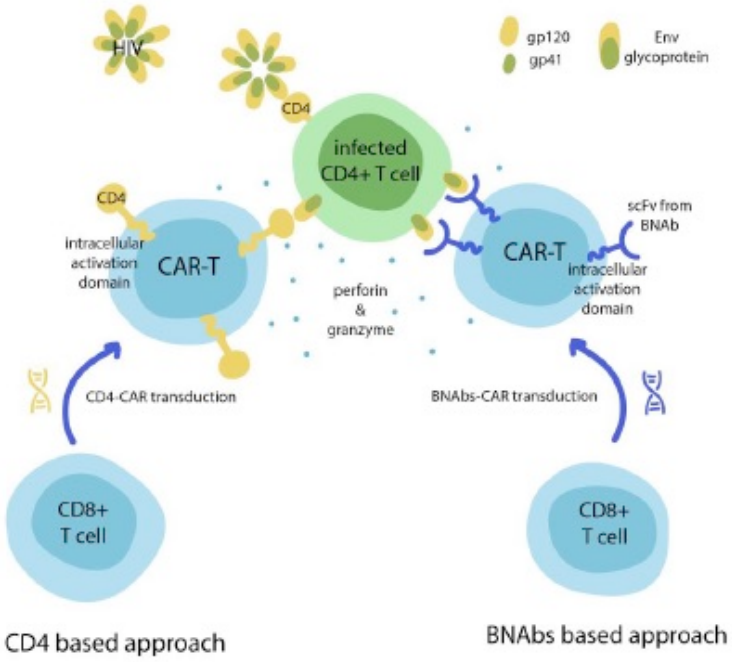
Ekaterina Zmievskaya [1], Aygul Valiullina [1], Irina Ganeeva [1], Alexey Petukhov [2], Albert Rizvanov [1] and Emil Bulatov [1,3,*]

| Disease | Target for CAR-T Cell |
|---|---|
| **Autoimmunity and allergy** | |
| Pemphigus vulgaris | Keratinocyte adhesion protein Dsg3 [6] |
| Hemophilia A | Anti-FVIII antibody [7] |
| Type 1 diabetes | Insulin-B chain [8–10]<br>Islet-specific glucose-6-phosphatase catalytic subunit-related protein [8] |
| Multiple sclerosis | Myelin oligodendrocyte glycoprotein [11] |
| Ulcerative colitis | Carcinoembryonic antigen [12] |
| Allergy | Transmembrane form of IgE [14] |
| Allergic asthma | Carcinoembryonic antigen [15] |
| **Infectious diseases** | |
| HBV | S domain of HBsAg [17–19] |
| HCV | Glycoprotein E2 [20] |
| HCMV | Glycoprotein B [21] |
| Aspergillus | Carbohydrate of cell surface [22] |
| Influenza A | M2e protein [23] |
| HIV | gp120 [24,26–30,32]<br>gp41 [29,30]<br>Oligomannose patch on Envs [33] |
| SARS-CoV-2 | S protein [35] |
| **Other** | |
| Cardiac fibrosis | Fibroblast activation protein [39] |

# Transferts adoptifs cellulaires

## CAR-T-cells

Chimeric Ag receptor T cells




Exemple VIH

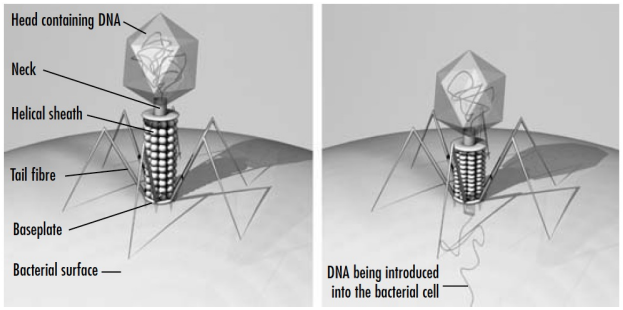
- Approche 1 : basée sur l'interaction gp120/CD4
- Approche 2 : Ac neutralisants gp120 et gp41

## Application of CAR-T Cell Therapy beyond Oncology: Autoimmune Diseases and Viral Infections

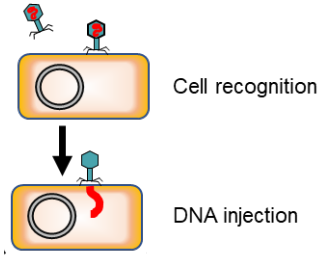
Ekaterina Zmievskaya [1], Aygul Valiullina [1], Irina Ganeeva [1], Alexey Petukhov [2], Albert Rizvanov [1] and Emil Bulatov [1,3,*]

| Disease | Target for CAR-T Cell |
|---|---|
| **Autoimmunity and allergy** | |
| Pemphigus vulgaris | Keratinocyte adhesion protein Dsg3 [6] |
| Hemophilia A | Anti-FVIII antibody [7] |
| Type 1 diabetes | Insulin-B chain [8–10]<br>Islet-specific glucose-6-phosphatase catalytic subunit-related protein [8] |
| Multiple sclerosis | Myelin oligodendrocyte glycoprotein [11] |
| Ulcerative colitis | Carcinoembryonic antigen [12] |
| Allergy | Transmembrane form of IgE [14] |
| Allergic asthma | Carcinoembryonic antigen [15] |
| **Infectious diseases** | |
| HBV | S domain of HBsAg [17–19] |
| HCV | Glycoprotein E2 [20] |
| HCMV | Glycoprotein B [21] |
| Aspergillus | Carbohydrate of cell surface [22] |
| Influenza A | M2e protein [23] |
| HIV | gp120 [24,26–30,32]<br>gp41 [29,30]<br>Oligomannose patch on Envs [33] |
| SARS-CoV-2 | S protein [35] |
| **Other** | |
| Cardiac fibrosis | Fibroblast activation protein [39] |

# Phagothérapie et lysines de phage




Virus environnementaux
ciblant des bactéries spécifiques

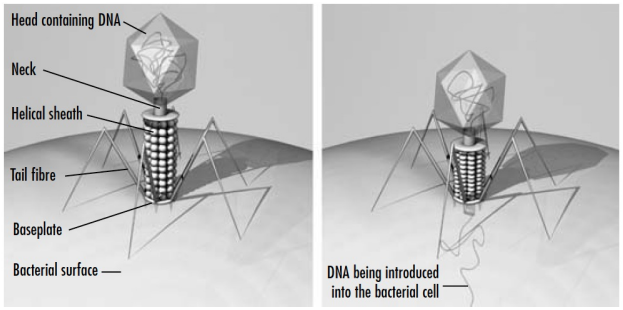



Ferry T. et al.

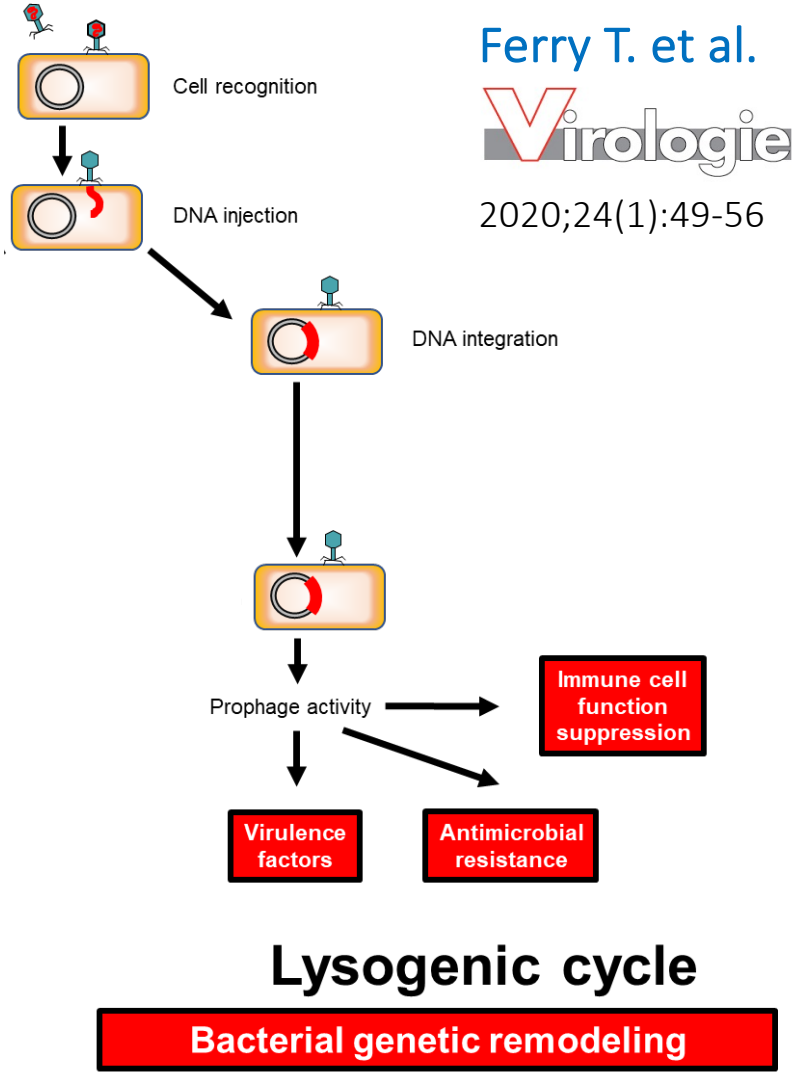
Virologie

2020;24(1):49-56

# Phagothérapie et lysines de phage




Virus environnementaux
ciblant des bactéries spécifiques

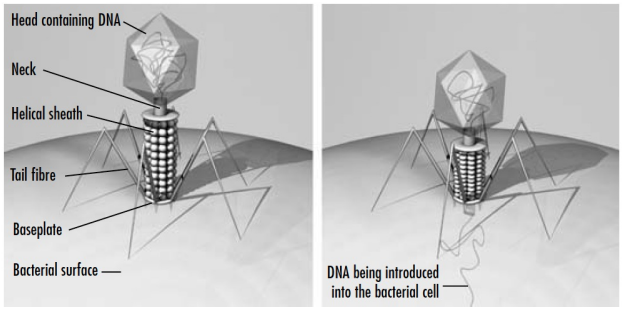



Ferry T. et al.

Virologie

2020;24(1):49-56

# Phagothérapie et lysines de phage

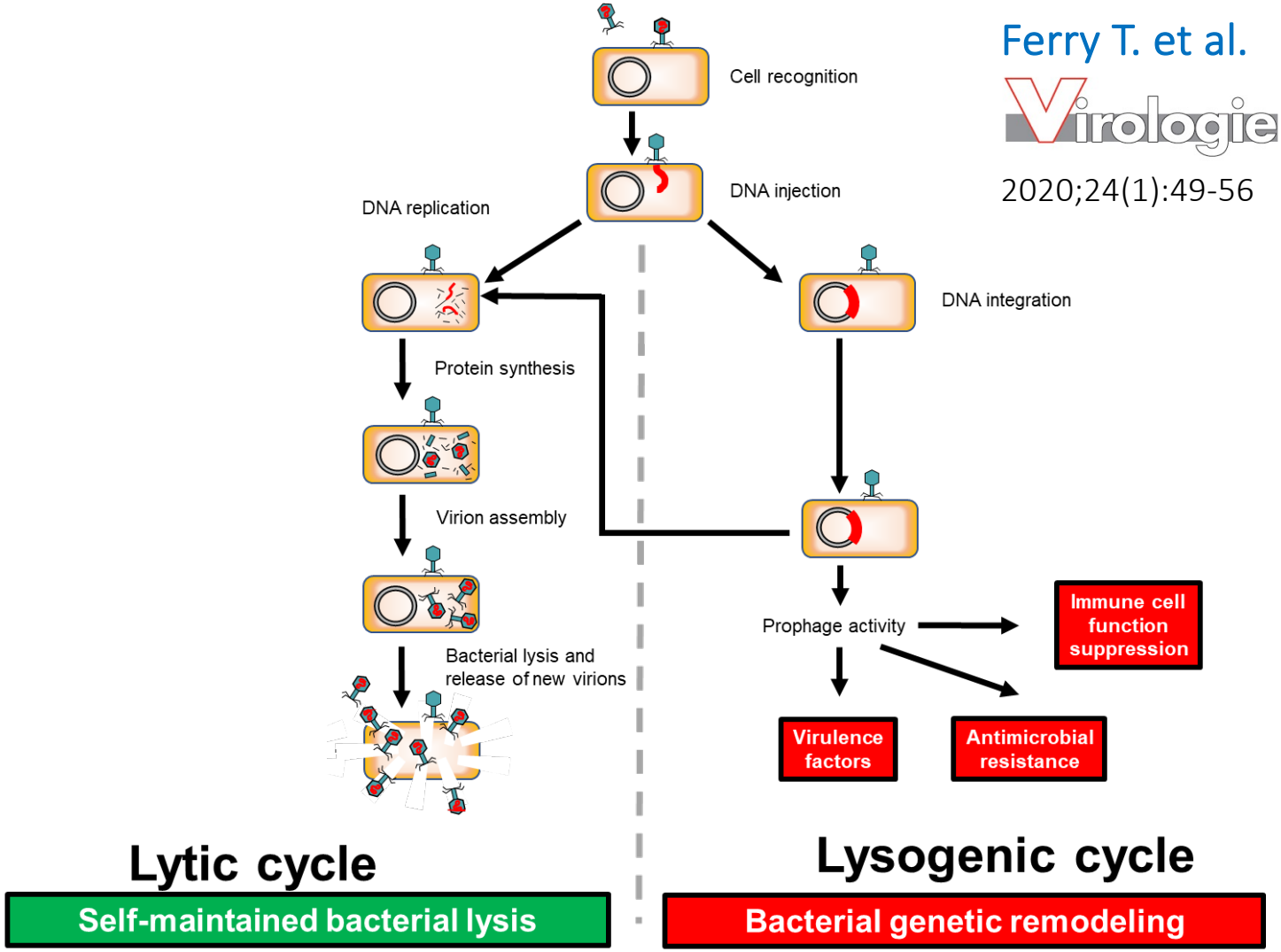



Virus environnementaux
ciblant des bactéries spécifiques

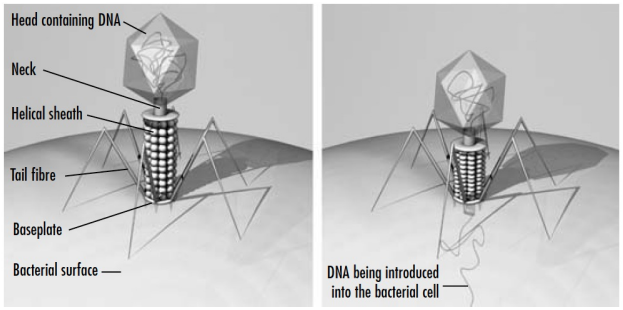
Ferry T. et al.

Virologie

2020;24(1):49-56



# Phagothérapie et lysines de phage

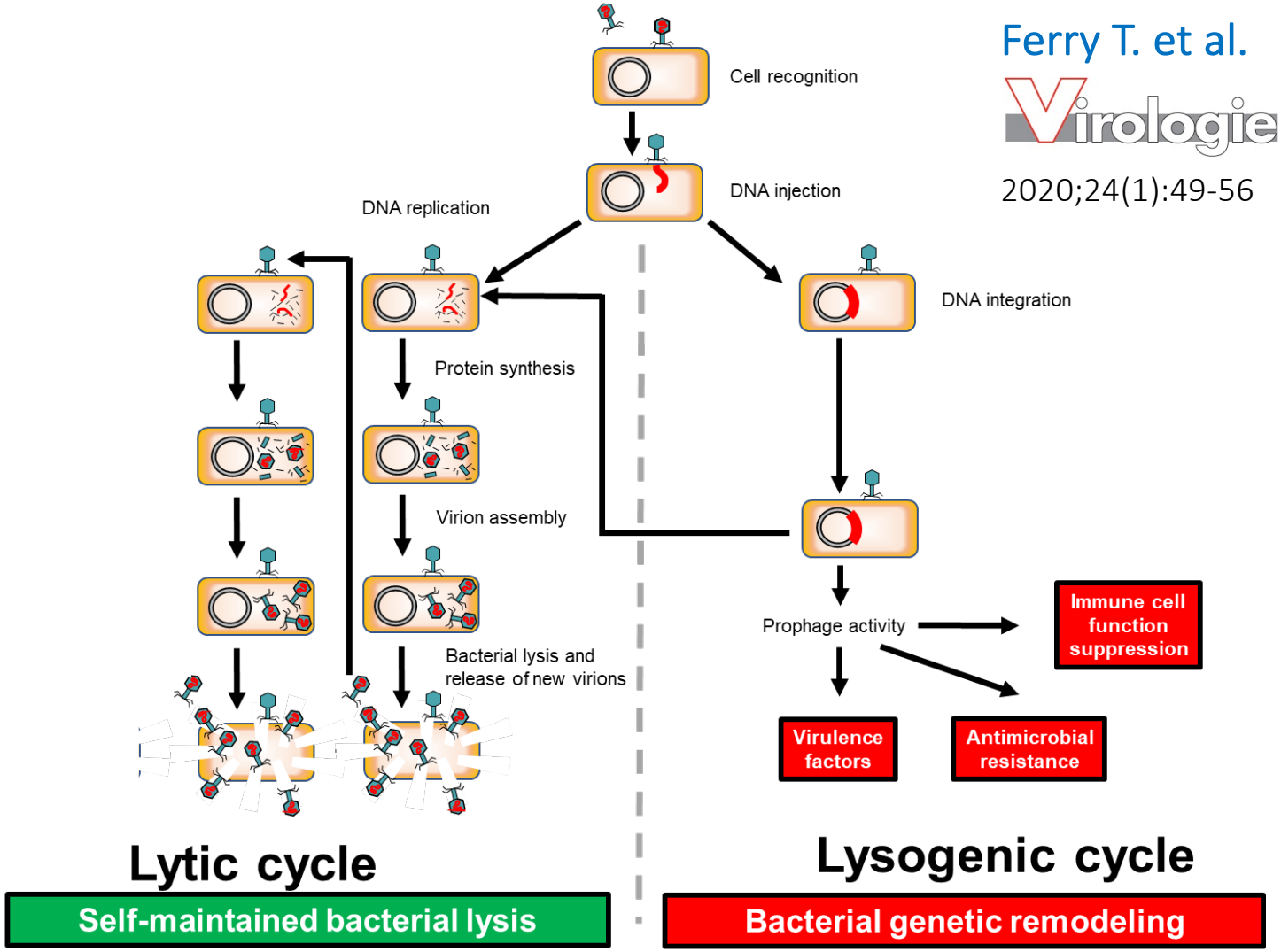



Virus environnementaux
ciblant des bactéries spécifiques

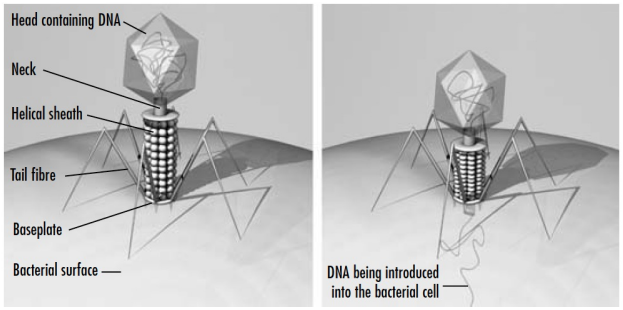
Ferry T. et al.

Virologie

2020;24(1):49-56



# Phagothérapie et lysines de phage

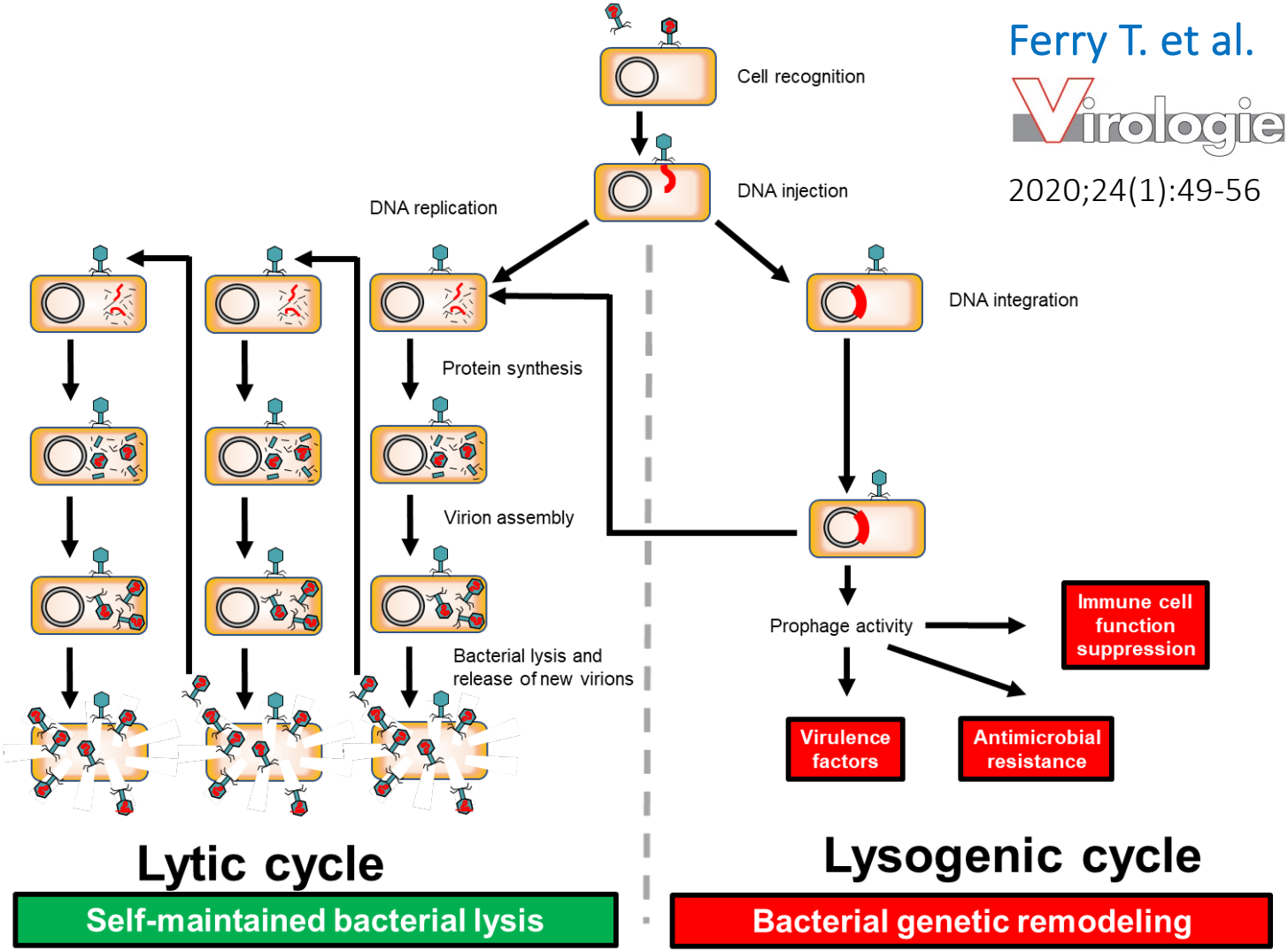



Virus environnementaux
ciblant des bactéries spécifiques

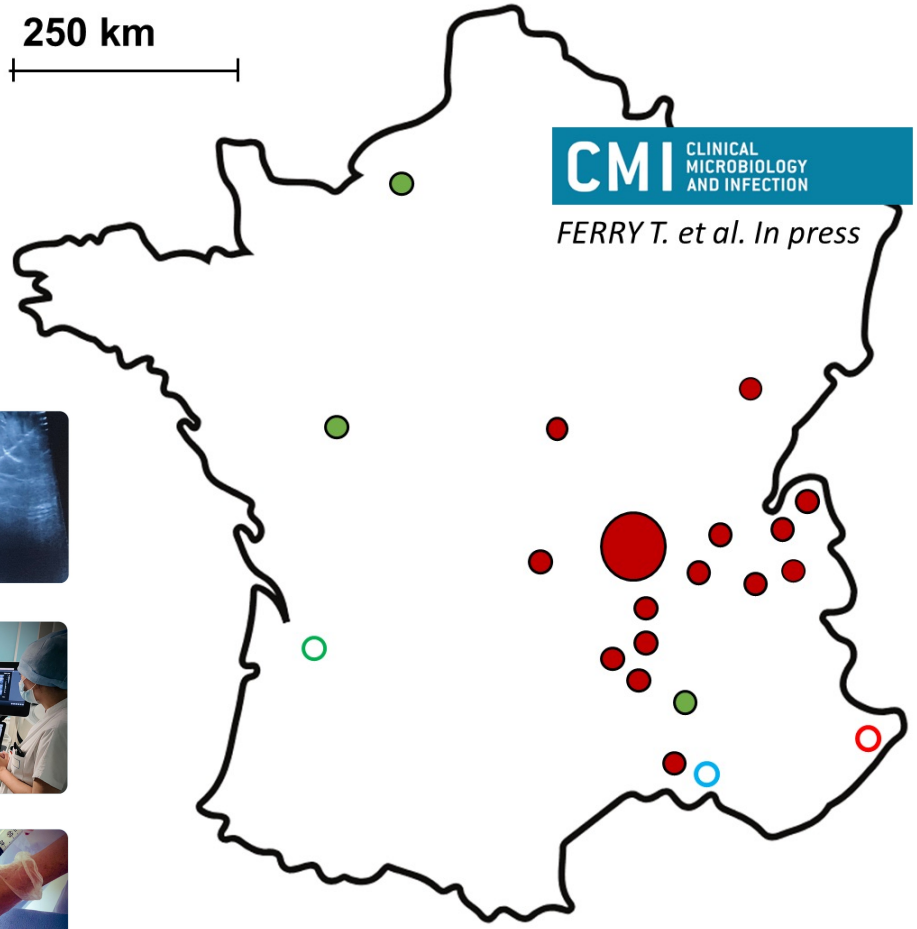
Ferry T. et al.

Virologie

2020;24(1):49-56



# Phagothérapie et lysines de phage



**29 patients traités aux HCL depuis 2017** ●●

- 26 avec des phages de PHERECYDES PHARMA
- 3 avec des phages MHKA HMRA

- 26 **IOA** (dont **22 infections de prothèse**)
- 3 **endocardites**

**+ 3 patients accompagnés et traités hors HCL** ○○○

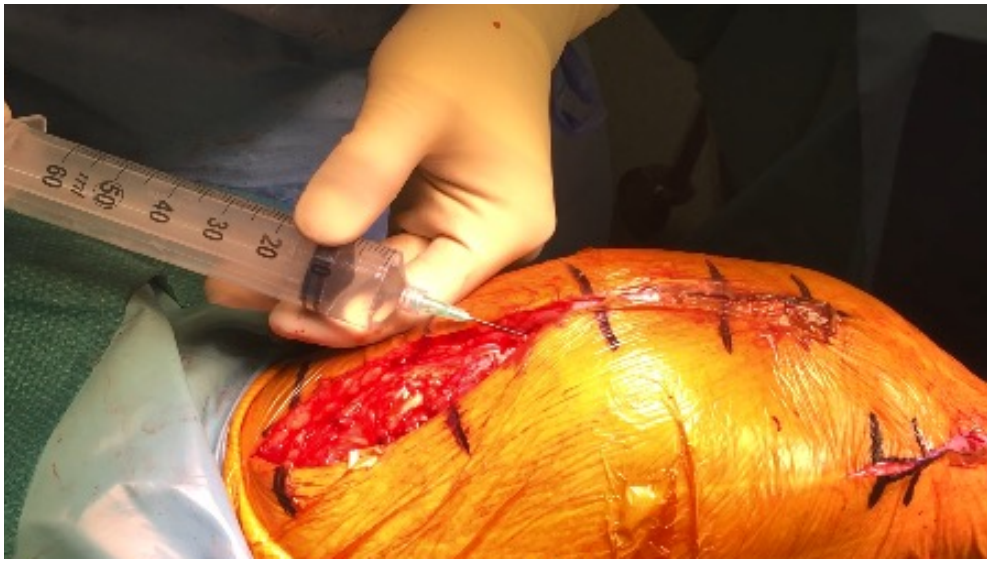
●○ **IOA** ●○ **Endocardite** ●○ **Pneumonies**

# Phagothérapie et lysines de phage

## Phage Therapy as Adjuvant to Conservative Surgery and Antibiotics to Salvage Patients With Relapsing *S. aureus* Prosthetic Knee Infection

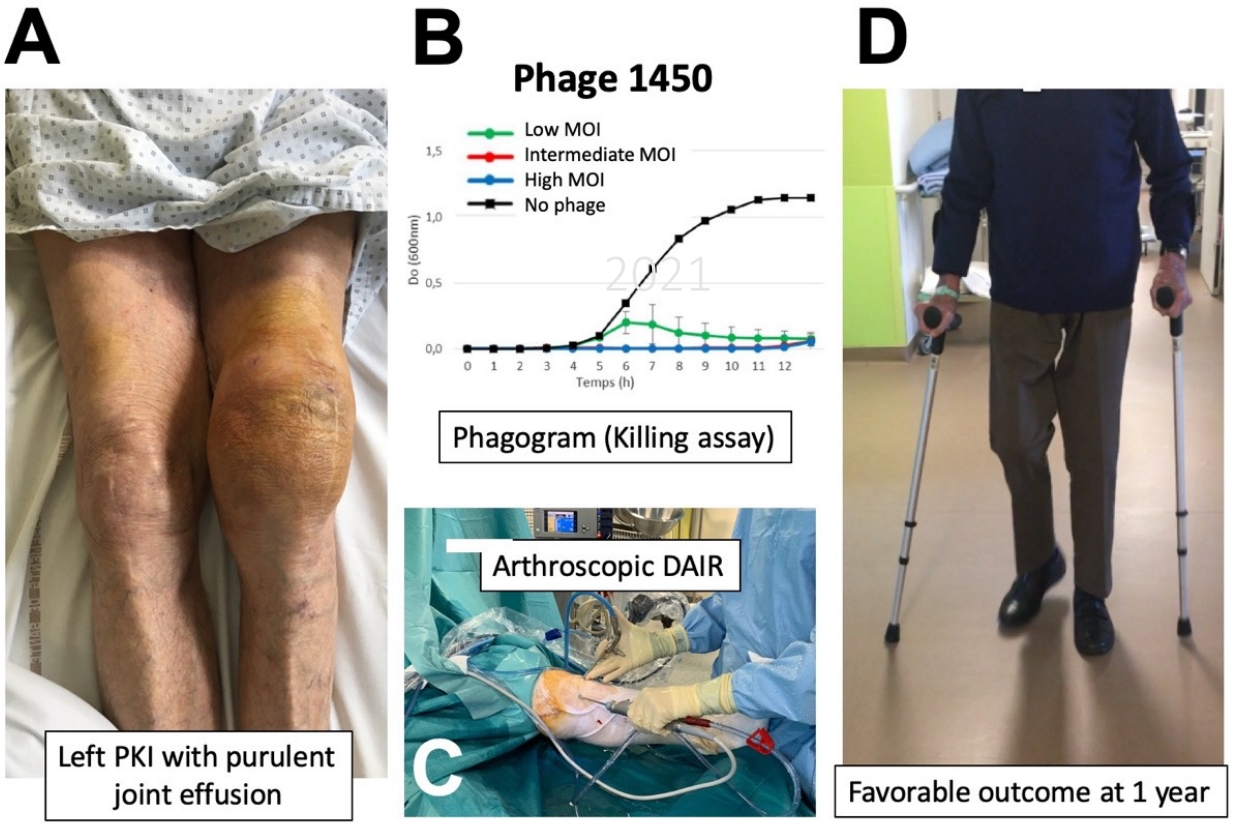
*Tristan Ferry[1,2,3,4*], Camille Kolenda[2,3,4,5], Cécile Batailler[2,3,6], Claude-Alexandre Gustave[2,3,4,5], Sébastien Lustig[2,3,6], Matthieu Malatray[3,6], Cindy Fevre[7], Jérôme Josse[2,3,4,5], Charlotte Petitjean[7], Christian Chidiac[1,2,3,4], Gilles Leboucher[8] and Frédéric Laurent[2,3,4,5] on behalf of the Lyon BJI Study group*

« phago-DAIR »



## Phagothérapie et lysines de phage

Arthroscopic "Debridement Antibiotics and Implant Retention" with phages to salvage *Pseudomonas aeruginosa* prosthetic knee infection

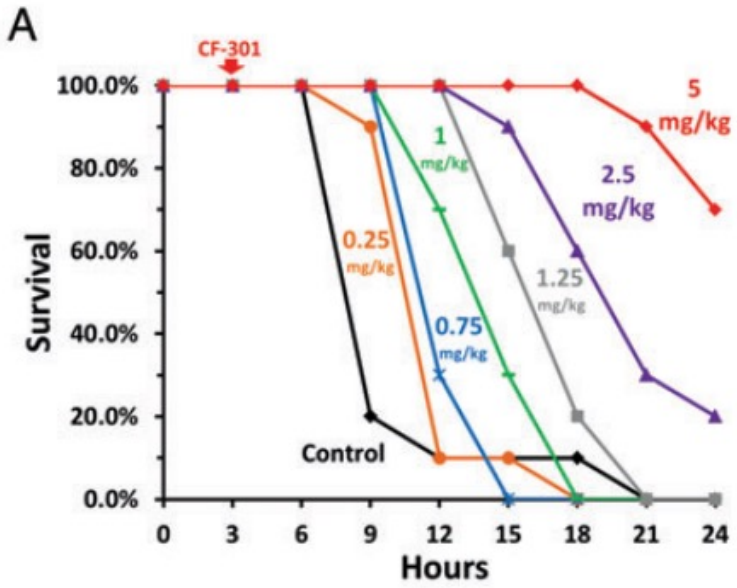


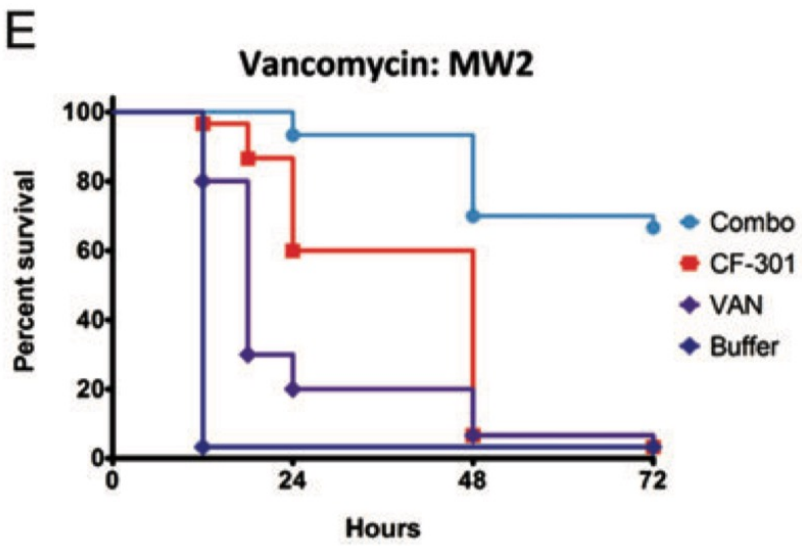
# Phagothérapie et lysines de phage

## Combination Therapy With Lysin CF-301 and Antibiotic Is Superior to Antibiotic Alone for Treating Methicillin-Resistant *Staphylococcus aureus*–Induced Murine Bacteremia

**Raymond Schuch,[1] Han M. Lee,[1] Brent C. Schneider,[1] Karen L. Sauve,[1] Christina Law,[1] Babar K. Khan,[1] Jimmy A. Rotolo,[1] Yuki Horiuchi,[1] Daniel E. Couto,[1] Assaf Raz,[2] Vincent A. Fischetti,[2] David B. Huang,[1] Robert C. Nowinski,[1] and Michael Wittekind[1]**

[1]ContraFect Corporation, Yonkers, NY, and [2]Department of Bacterial Pathogenesis and Immunology, The Rockefeller University, New York, New York



# Phagothérapie et lysines de phage

## Combination Therapy With Lysin CF-301 and Antibiotic Is Superior to Antibiotic Alone for Treating Methicillin-Resistant *Staphylococcus aureus*–Induced Murine Bacteremia

**Raymond Schuch,[1] Han M. Lee,[1] Brent C. Schneider,[1] Karen L. Sauve,[1] Christina Law,[1] Babar K. Khan,[1] Jimmy A. Rotolo,[1] Yuki Horiuchi,[1] Daniel E. Couto,[1] Assaf Raz,[2] Vincent A. Fischetti,[2] David B. Huang,[1] Robert C. Nowinski,[1] and Michael Wittekind[1]**

[1]ContraFect Corporation, Yonkers, NY, and [2]Department of Bacterial Pathogenesis and Immunology, The Rockefeller University, New York, New York

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 Cassino, and Raymond Schuch**

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

## 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]**

## 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]**

## 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]**

# Phagothérapie et lysines de phage

CLINICAL MEDICINE

The Journal of Clinical Investigation

## Exebacase for patients with *Staphylococcus aureus* bloodstream infection and endocarditis

121 bactériémies à S. aureus
1 dose d'EXEBACASE ou placebo

Vance G. Fowler Jr.,[1,2] Anita F. Das,[3] Joy Lipka-Diamond,[4] Raymond Schuch,[5] Roger Pomerantz,[5] Luis Jáuregui-Peredo,[6] Adam Bressler,[7] David Evans,[8] Gregory J. Moran,[9] Mark E. Rupp,[10] Robert Wise,[11] G. Ralph Corey,[1] Marcus Zervos,[12] Pamela S. Douglas,[1,2] and Cara Cassino[5]

| | Total Population | | MRSA[A] | | MSSA[A] | |
|---|---|---|---|---|---|---|
| | Exebacase + Antibiotics (*N* = 71) *n* (%) | Antibiotics Alone (*N* = 45) *n* (%) | Exebacase + Antibiotics (*N* = 27) *n* (%) | Antibiotics Alone (*N* = 16) *n* (%) | Exebacase + Antibiotics (*N* = 44) *n* (%) | Antibiotics Alone (*N* = 30) *n* (%) |
| **Disease Characteristics** | | | | | | |
| Final Diagnosis by Adjudication Committee | | | | | | |
| Endocarditis | 16 (22.5) | 6 (13.3) | 5 (18.5) | 1 (6.3) | 11 (25.0) | 5 (16.7) |
| Right-sided endocarditis | 5 (7.0) | 3 (6.7) | 2 (7.4) | 1 (6.3) | 3 (6.8) | 2 (6.7) |
| Left-sided endocarditis | 11 (15.5) | 3 (6.7) | 3 (11.1) | 0 | 8 (18.2) | 3 (10.0) |
| BSI | 55 (77.5) | 39 (86.7) | 22 (81.5) | 15 (93.8) | 33 (75.0) | 25 (83.3) |
| Complicated BSI | 42 (59.2) | 36 (80.0) | 17 (63.0) | 13 (81.3) | 25 (56.8) | 24 (80.0) |
| Uncomplicated BSI | 13 (18.3) | 3 (6.7) | 5 (18.5) | 2 (12.5) | 8 (18.2) | 1 (3.3) |

# Phagothérapie et lysines de phage

CLINICAL MEDICINE

The Journal of Clinical Investigation

## Exebacase for patients with *Staphylococcus aureus* bloodstream infection and endocarditis

Vance G. Fowler Jr.,[1,2] Anita F. Das,[3] Joy Lipka-Diamond,[4] Raymond Schuch,[5] Roger Pomerantz,[5] Luis Jáuregui-Peredo,[6] Adam Bressler,[7] David Evans,[8] Gregory J. Moran,[9] Mark E. Rupp,[10] Robert Wise,[11] G. Ralph Corey,[1] Marcus Zervos,[12] Pamela S. Douglas,[1,2] and Cara Cassino[5]

121 bactériémies à S. aureus
1 dose d'EXEBACASE ou placebo

**Table 2. Standard-of-care antibiotics received (mITT population)**

| | Total Population | | MRSA[A] | | MSSA[A] | |
|---|---|---|---|---|---|---|
| | Exebacase + Antibiotics (*N* = 71) *n* (%) | Antibiotics Alone (*N* = 45) *n* (%) | Exebacase + Antibiotics (*N* = 27) *n* (%) | Antibiotics Alone (*N* = 16) *n* (%) | Exebacase + Antibiotics (*N* = 44) *n* (%) | Antibiotics Alone (*N* = 30) *n* (%) |
| Standard-of-Care Antibiotic Exposure Through Day 14[B] | | | | | | |
| Daptomycin | 5 (11.1) | 5 (7.0) | 5 (18.5) | 3 (18.8) | 0 | 3 (10.0) |
| Vancomycin | 24 (33.8) | 17 (37.8) | 21 (77.8) | 13 (81.3) | 3 (6.8) | 4 (13.3) |
| β-lactam antibiotics | 42 (59.2) | 23 (51.1) | 1 (3.7) | 0 | 41 (93.2) | 23 (76.7) |

# Phagothérapie et lysines de phage

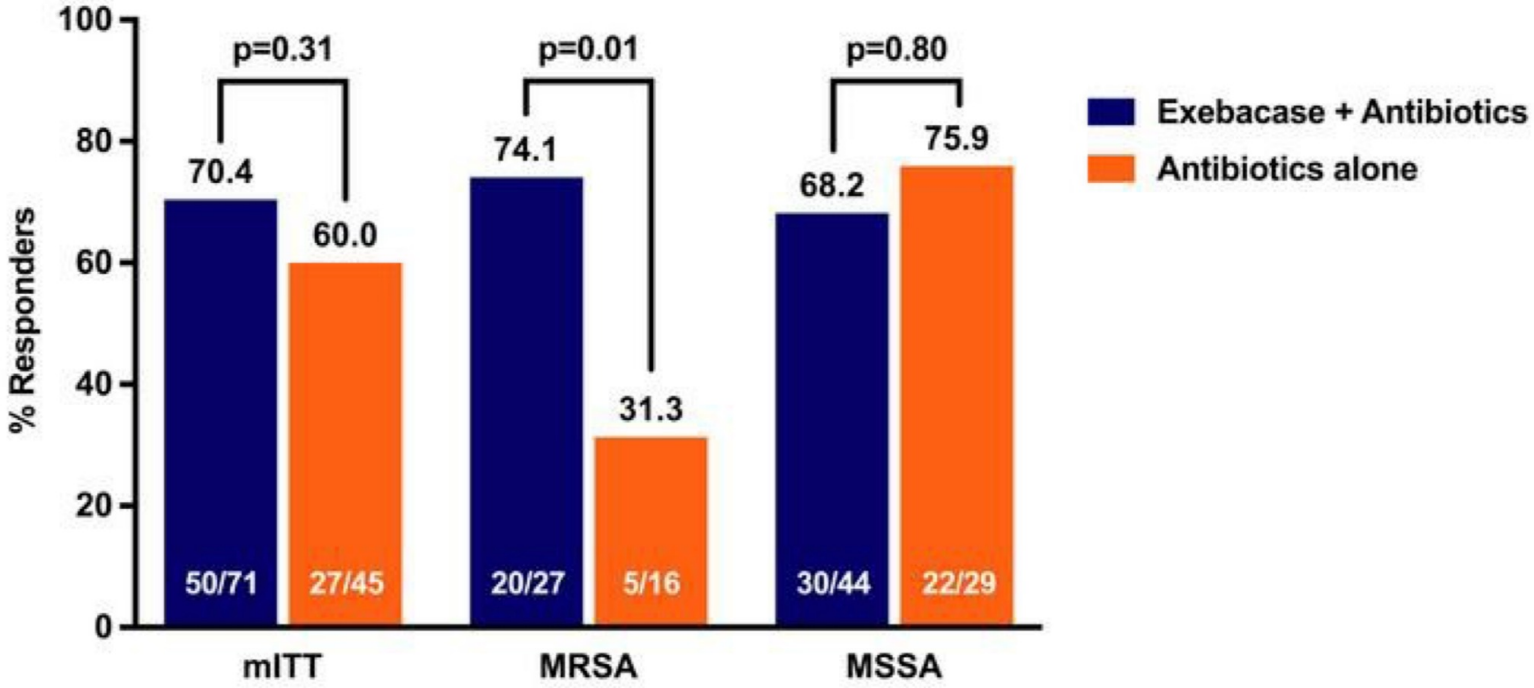
CLINICAL MEDICINE

The Journal of Clinical Investigation

## Exebacase for patients with *Staphylococcus aureus* bloodstream infection and endocarditis

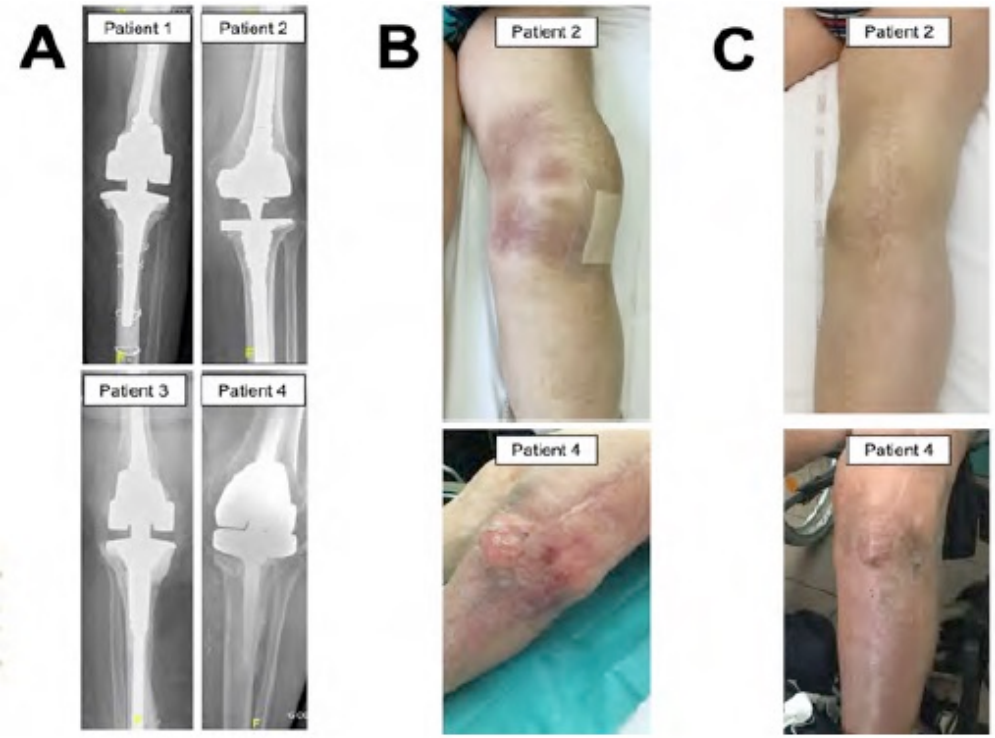
Vance G. Fowler Jr.,[1,2] Anita F. Das,[3] Joy Lipka-Diamond,[4] Raymond Schuch,[5] Roger Pomerantz,[5] Luis Jáuregui-Peredo,[6] Adam Bressler,[7] David Evans,[8] Gregory J. Moran,[9] Mark E. Rupp,[10] Robert Wise,[11] G. Ralph Corey,[1] Marcus Zervos,[12] Pamela S. Douglas,[1,2] and Cara Cassino[5]

121 bactériémies à S. aureus
1 dose d'EXEBACASE ou placebo



# Phagothérapie et lysines de phage

**Arthroscopic debridement, antibiotic and implant retention (DAIR) with local administration of Exebacase (Lysin CF-301) (LysinDAIR) followed by suppressive tedizolid as salvage therapy in elderly patients for relapsing multidrug-resistant *Staphylococcus epidermidis* prosthetic knee infection**



**Conclusions:** Exebacase has the potential to be used as salvage therapy during arthroscopic DAIR in patients with relapsing MDR *S. epidermidis* PKI, to improve the efficacy of suppressive antibiotics, and to avoid considerable loss of function.

# Modification du microbiome

| Approach | Indication | Comments |
|---|---|---|
| Transfer of human intestinal microbiota | Prevention of recurrent CDI | FMT: Transfer of stool suspension from a donor via colonoscopy, enema, nasogastric routes or pills (Finch, Open Biome) |
| | | Fecal microbiota suspension: standardized number of live bacteria from stool suspension from donors via enema or capsules, GMP produced (Rebiotix (Ferring)) |
| | | Rationally selected microbiota: Well-characterized selection of bacterial strains via capsules (Seres, Finch Therapeutics, Vedanta) |
| | | Spore suspension: Spores, fractionated from stool specimens from donors via capsules (Seres) |
| Synthetic microbiota | Intestinal, dermatological (e.g., atopic dermatitis), lung conditions (e.g., CF) | Selected live bacteria producing specific metabolites or cocktail of secondary metabolites |
| | | Selected live bacteria from skin microbiota (MatriSys Bio) |
| | | Selected live bacteria for balancing the lung microbiota |
| Manipulating the metabolism of microbiota | – | Manipulating the metabolic balance through specific bacterial nutrients, e.g., Glycans (Kaleido) |
| Competition | Prevention of recurrent CDI, catheter-associated UTI | Non-toxinogenic *C. difficile* that is assumed to outcompete the toxic strain (Microbiotica) |
| | | Apathogenic *E. coli* introduced into the bladder via catheter coating (Atterx) |
| Engineering probiotics to deliver antibacterial proteins | Various indications (Bäumler and Sperandio, 2016) | Engineered *Lactobacillus* to express bacteriocin against *P. aeruginosa* (inhaled, CF) and *C. difficile* (SciBac) |
| | | Engineered *Lactobacillus* to express SagA protein that promotes tolerance to enteric infections including *C. difficile* infection (Rise Therapeutics) |
| | | R-type bacteriocins against *C. difficile* |
| Prevention of disbalance of microbiome due to antibiotic therapy | Prevention of recurrent CDI | Hydrolyzing specific beta-lactam antibiotics in the gut (beta-lactamase, Synthetic Biologics, DaVolterra) |
| Decolonization of MDR Gram-negative pathogens in high-risk patients | Various indications | Decolonization of asymptomatic carriers with live bacteria (e.g., carriers of *C. difficile*, MDR Gram-negative pathogens in high-risk patients, *Salmonella* Typhi) |

Cell Host & Microbe
Review 2019
CellPress

# Non-traditional Antibacterial Therapeutic Options and Challenges

Ursula Theuretzbacher[1] and Laura J.V. Piddock[2,*]
[1]Centre for Anti-Infective Agents, Vienna, Austria
[2]Institute of Microbiology and Infection, University of Birmingham, Birmingham, West Midlands
*Correspondence: l.j.v.piddock@bham.ac.uk
https://doi.org/10.1016/j.chom.2019.06.004

# 2020 ANTIBACTERIAL AGENTS IN CLINICAL AND PRECLINICAL DEVELOPMENT

an overview and analysis

World Health Organization

nature COMMUNICATIONS

NATURE COMMUNICATIONS | (2019)10:3416

PERSPECTIVE

https://doi.org/10.1038/s41467-019-11303-9 OPEN

# Designing development programs for non-traditional antibacterial agents

John H. Rex[1,2], Holly Fernandez Lynch[3], I. Glenn Cohen[4,5], Jonathan J. Darrow[6] & Kevin Outterson[7]