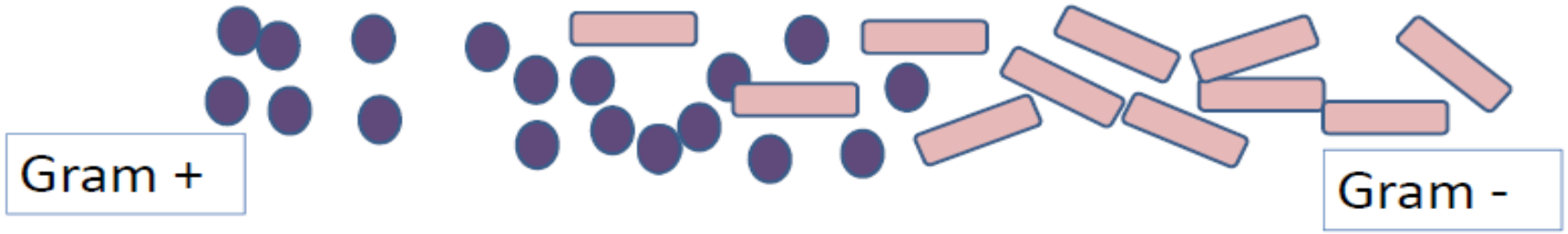
Nouveaux antibiotiques

France Roblot, CHU de Poitiers
INSERM U1070

Le panorama actuel… et à venir



Disponibles

- CEFTAROLINE
- CEFTOBIPROLE
- TEMOCILLINE
- TEDIZOLIDE
- CEFTOLOZANE/ TAZOBACTAM
- DALBAVANCINE
- CEFTAZIDIME/ AVIBACTAM

Plus tard

- ORITAVANCINE
- CEFTAROLINE/AVIBACTAM
- AVIBACTAM/AZTREONAM
- IMIPENEME/CILASTATINE/RELEBACTAM
- MEROPENEME/RPX7009
- ERAVACYCLINE
- PLAZAMYCINE

I- Les anti Gram positif

Tedizolide

- Oxazolidinone
- Inhibition de la synthèse des protéines
- Formes orale et IV
- Biodisponibilité 91% (indifféremment / repas)
- 70% fixation protéines
- Elimination : urines 10%, fèces 90%
- Peu d'interactions cytochromes

Pourquoi une nouvelle oxazolidinone ?

- **Linezolide**
  - Toxicité mitochondriale
    - Acidose lactique, neuropathies, toxicité hématologique (traitements longs)
  - Résistance par mutation *cfr*
- **Tedizolide**
  - Effet IMAO faible
  - Pas de neurotoxicité / rat (dose 8X dose thérapeutique)
  - Pas d'embryofoetotoxicité

Données cliniques

- Phase III, infections cutanées
- Tédizolide 6 j non inférieur à Linézolide 10j

Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections
The ESTABLISH-1 Randomized Trial

JAMA, February 13, 2013—Vol 309, No. 6

Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomised, double-blind, phase 3, non-inferiority trial

Gregory J Moran, Edward Fang, G Ralph Corey, Anita F Das, Carisa De Anda, Philippe Prokocimer

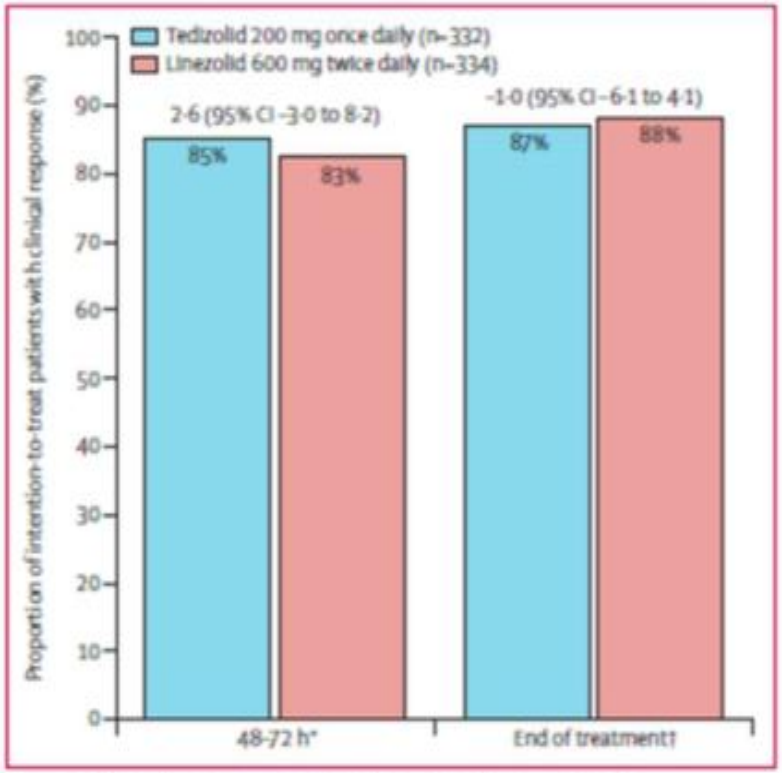


Figure 2: Clinical response rates based on objective assessments incorporating changes in lesion area, at 48-72 h (primary efficacy endpoint) and at end of treatment (secondary efficacy endpoint) in the intention-to-treat population

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]
Pulmonary and Critical Care Medicine, Washington Hospital Center, Washington, DC, USA[a]; Albany College of Pharmacy and Health Sciences, Albany, New York, USA[b]; Duke University Health System, Durham, North Carolina, USA[c]; Cubist Pharmaceuticals, San Diego, California, USA[d]; InClin, Inc., San Mateo, California, USA[e]

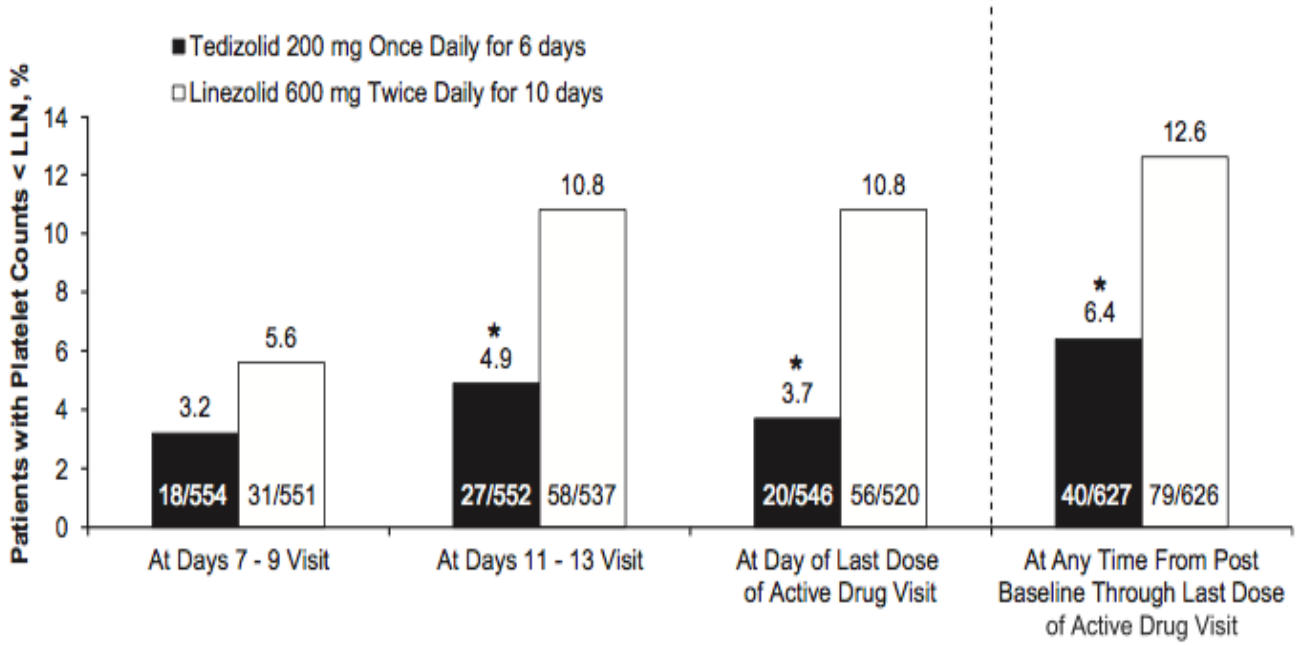


FIG 3 Patients with platelet counts below the lower limit of normal (LLN) (<150,000 cells/mm^3) over time. *, $P < 0.05$. EOT, end-of-therapy.

Durées très courtes +++

(Shorr AF et al Antimicrob Agents Chemother 2015)

Tedizolide
Toxicité hématologique

- Traitements longs

J Antimicrob Chemother 2017; **72**: 2135–2136
doi:10.1093/jac/dkx097
Advance Access publication 27 March 2017

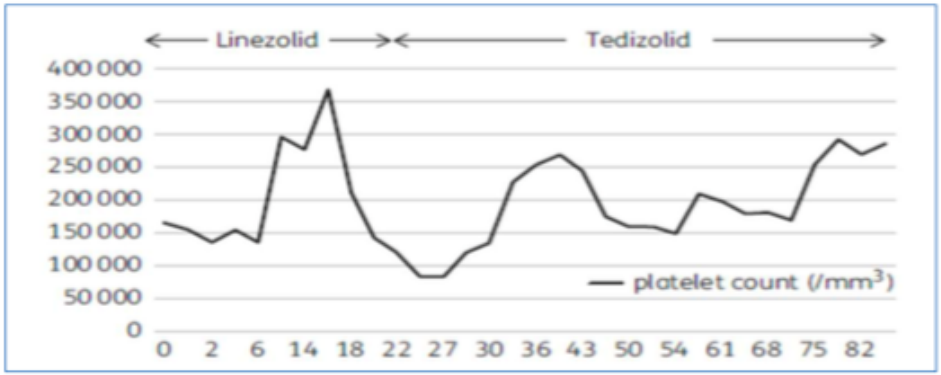
Correction of myelotoxicity after switch of linezolid to tedizolid for prolonged treatments

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]*

Correction de l'hématotoxicité induite par le Linézolide, chez 3 patients.

Après switch vers le Tédizolide.

Malgré des traitements prolongés.



Tedizolide
Toxicité hématologique

J Antimicrob Chemother
doi:10.1093/jac/dkw484 2017

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]

Relais par Tédizolide après hématotoxicité (thrombopénie) du Linézolide.

26 jours de wash-out avant introduction du Tédizolide.

38 jours de Tédizolide sans nouvelle thrombopénie.

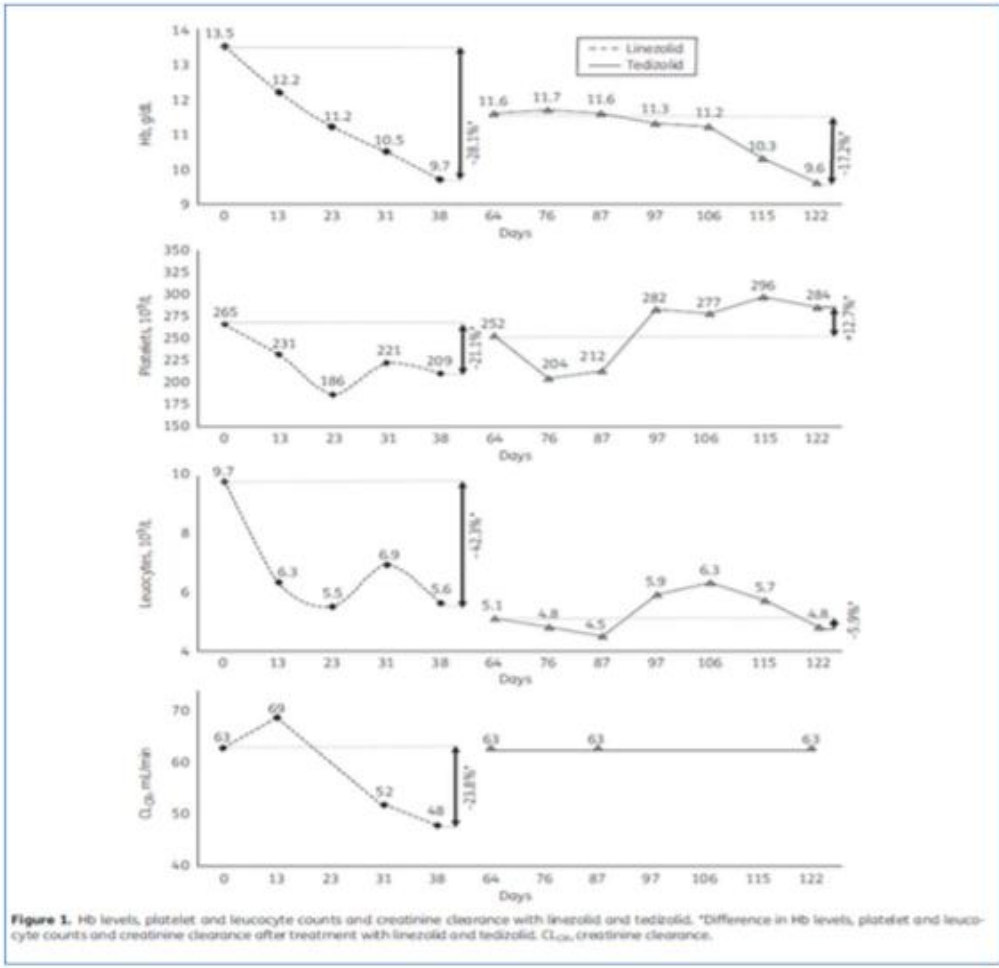


Figure 1. Hb levels, platelet and leucocyte counts and creatinine clearance with linezolid and tedizolid. *Difference in Hb levels, platelet and leucocyte counts and creatinine clearance after treatment with linezolid and tedizolid. Cl_{Cr}, creatinine clearance.

(Yuste JR et al J Antimicrobial Chemother 2017)

Long-term Use of Tedizolid as Suppressive Therapy for Recurrent Methicillin-Resistant *Staphylococcus aureus* Graft Infection

Masayuki Nigo,[1] Andrea M. Luce,[2] and Cesar A. Arias[1,3,4]

Table 1. Basic Hematological Counts After Initiation of Tedizolid

Months after initiation	0	2	4	6	8	9	11	13	15	17	18
WBC (k/μL)	7.2	8.5	7.7	8.6	11.5	7.8	7.7	8.0	8.8	8.6	12.7
Hgb (gm/dL)	7.8	8.4	12.3	12.0	12.4	12.9	12.5	7.6	10.3	11.7	10.9
Ht (%)	27.1	28.4	38.2	36.7	38.6	39.8	38.3	22.9	32.9	36.0	35.5
Platelet (k/μL)	261	330	210	201	254	234	186	157	307	314	360

Abbreviations: Hgb, hemoglobin; Ht, hematocrit; WBC, white blood cell counts.

(Nigo M et al. Clin Infect Dis 2018)

Open Forum Infectious Diseases

ID CASE

Correction of Linezolid-Induced Myelotoxicity After Switch to Tedizolid in a Patient Requiring Suppressive Antimicrobial Therapy for Multidrug-Resistant *Staphylococcus epidermidis* Prosthetic-Joint Infection

Tristan Ferry,[1,2,3,4] Cécile Batailler,[2,3,4,5] Anne Conrad,[1,2,3,4] Claire Triffault-Fillit,[1,3,4] Frédéric Laurent,[2,3,4,6] Florent Valour,[1,2,3,4] and Christian Chidiac[1,2,3,4]; on behalf of the Lyon BJI Study Group

[1]Service de Maladies Infectieuses, Hôpital de la Croix-Rousse, Hospices Civils de Lyon, France; [2]Université Claude Bernard Lyon 1, France; [3]Centre International de Recherche en Infectiologie, CIRI, Inserm U1111, CNRS UMR5308, ENS de Lyon, UCBL1, France; [4]Centre Interrégional de Référence des Infections Ostéo-articulaires Complexes (CRIOAc Lyon), Hospices Civils de Lyon, France; [5]Service de Chirurgie Orthopédique, Hôpital de la Croix-Rousse, Hospices Civils de Lyon, France; [6]Laboratoire de Bactériologie, Institut des Agents Infectieux, Hôpital de la Croix-Rousse, Hospices Civils de Lyon, France

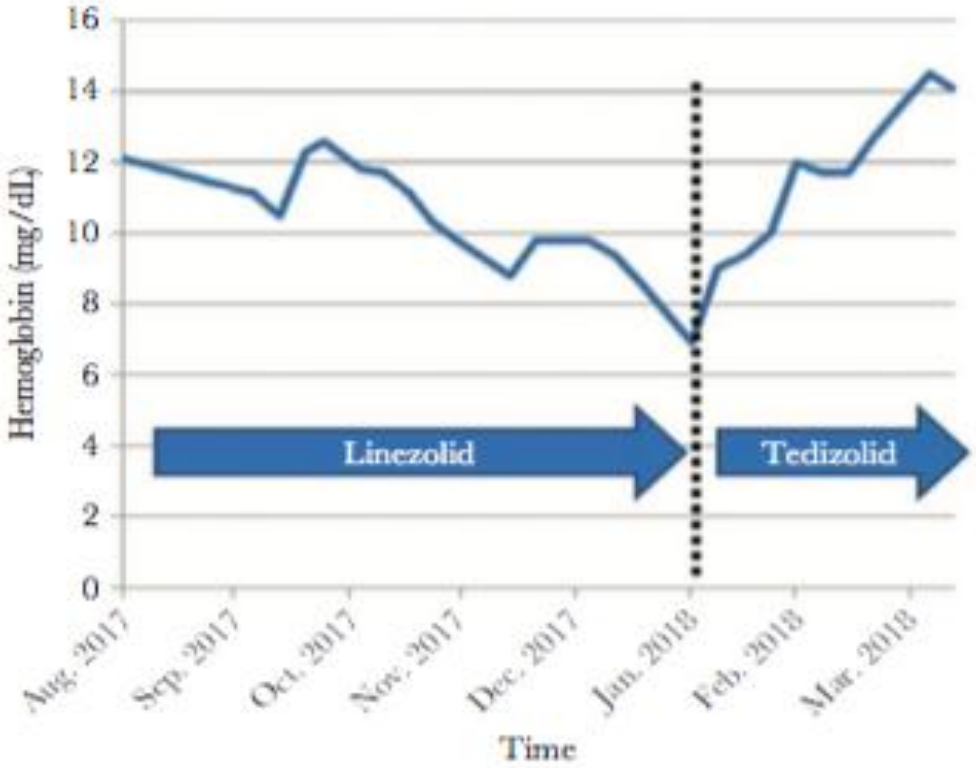


Figure 1. Hemoglobin during time, with continuous decrease under linezolid therapy, followed by a continuous increase after the switch to tedizolid.

(Ferry T et al Open Forum Infect Dis. 2018;10:ofy246)

Tedizolide en pratique

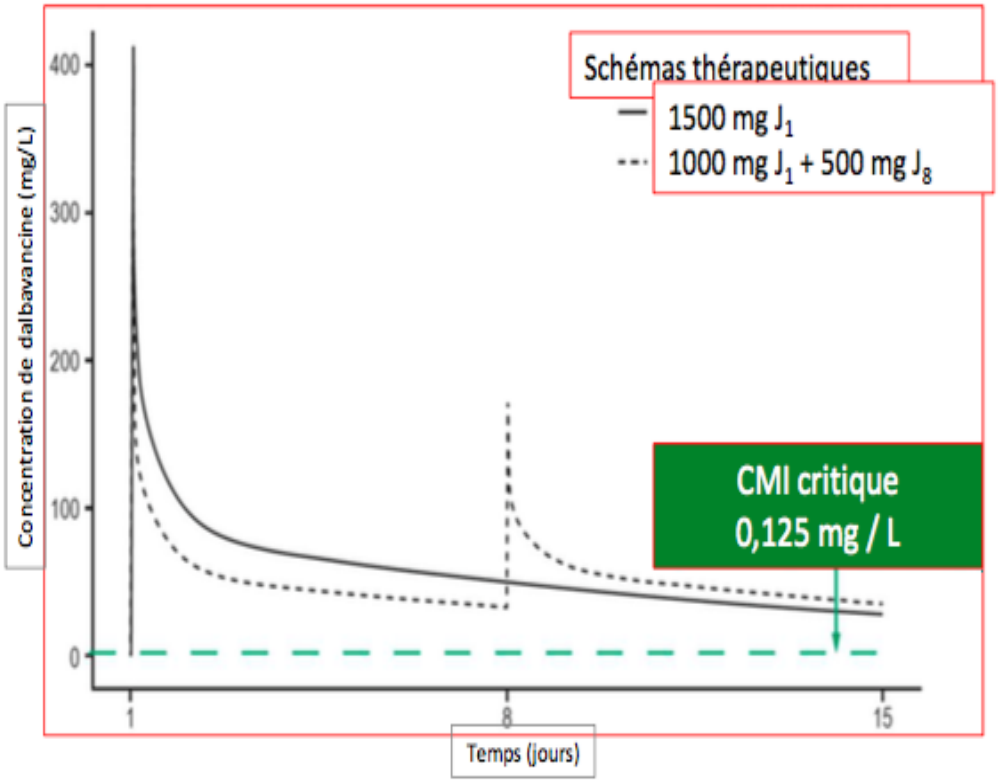
- Les avantages du linézolide.
- AMM 6 j dans les infections de la peau et des parties molles.
- 1prise par jour.
- Pas de neurotoxicité
- Pas de risque d’acidose lactique.
- Hematotoxicite moins importante
- Relais ?

Dalbavancine

- Lipoglycopeptide
- Inhibition de la transglycosylation par fixation substrat D-ala-D-ala de S. aureus et autres Cocci à Gram +
  - Résistance croisée vancomycine si gène VanA

Dalbavancine

- Pharmacocinétique
  - Concentration dose dépendante, PK linéaire
  - 1/2 vie 14 jours
- Posologie
  - 1500 mg à J1
  - 1000 mg J1 + 500 mg J7
- IV 30 mn



Dalbavancine

- Insuffisance rénale
  - Clairance > 30 ml/mn pas d'adaptation
  - Clairance ≤ 30 ml/mn et pas d'hémodialyse régulière
    - Dose unique 1000 mg
    - Ou 750 mg à J1 + 375 mg **J7**
- Insuffisance hépatocellulaire
  - Légère (Child_Pugh A) pas d'adaptation posologique
  - Modérée à sévère (Child-Pugh B et C) : pas de données disponibles

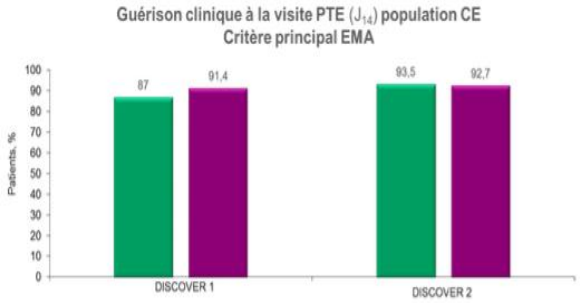
Indications

- AMM
  - Peau et tissus mous


The NEW ENGLAND JOURNAL of MEDICINE

JUNE 5, 2014

Once-Weekly Dalbavancin versus Daily Conventional Therapy for Skin Infection



- + d'intérêt …
  - OPAT
  - Pas de KTC
  - Tolérance OK

AAC Journals.ASM.org

2015

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

Michael W. Dunne,[a] Sailaja Puttagunta,[a] Craig R. Sprenger,[c]* Chris Rubino,[b] Scott Van Wart,[b] James Baldassarre[a]
Durata Therapeutics, Inc., Branford, Connecticut, USA[a]; Institute for Clinical Pharmacodynamics, Latham, New York, USA[b]; PRACS Institute, Ltd., Fargo, North Dakota, USA[c]

Phase 1
30 sujets
Chirurgie réglée

TABLE 4 Dalbavancin tissue concentrations (safety population)

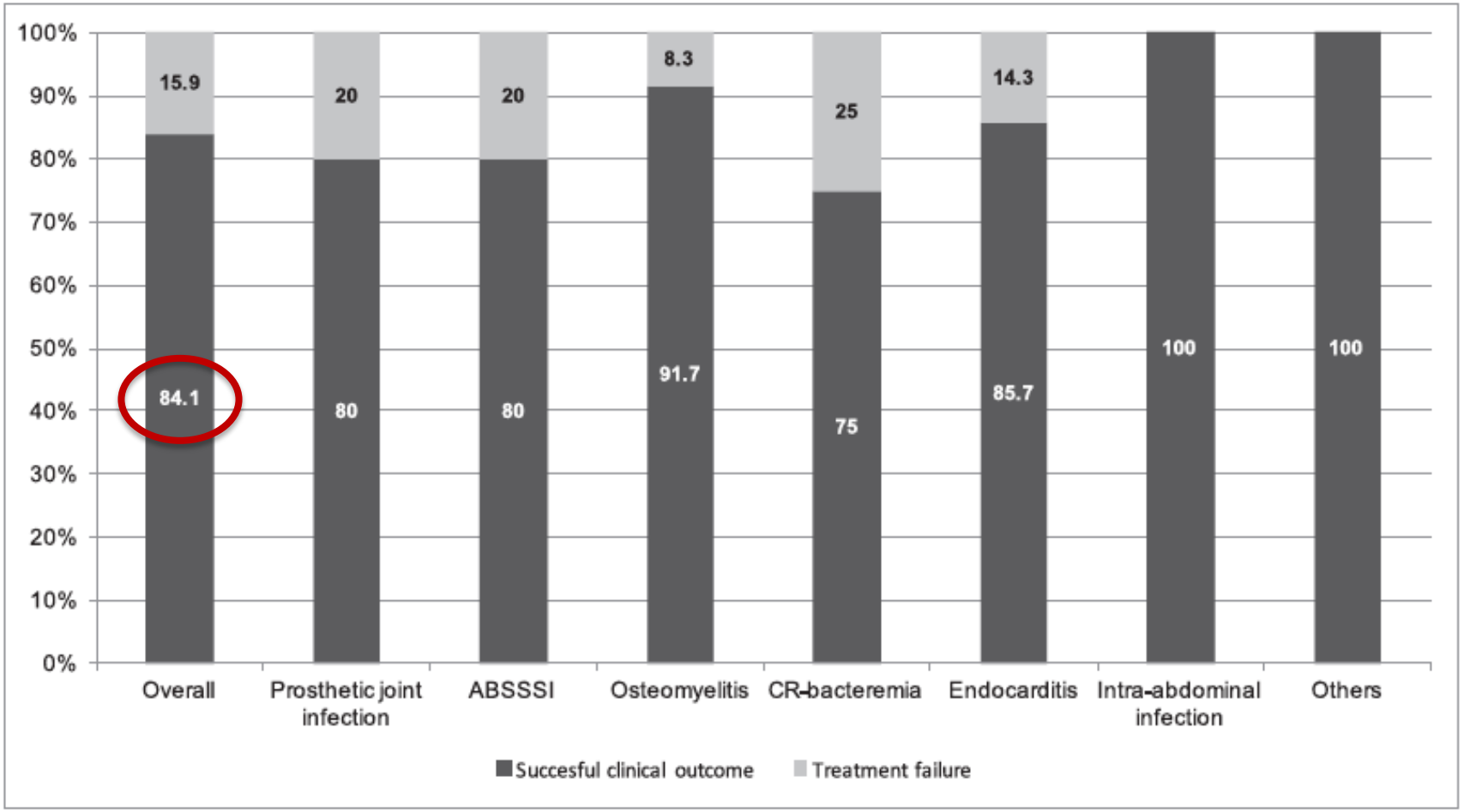
Tissue	Dalbavancin concn (mean [SD]; no. of samples) at hours (days) postdose that samples were collected:					
	12 (0.5)	24 (1)	72 (3)	168 (7)	240 (10)	336 (14)
Plasma (μg/ml)[a]	85.3 (18.9); 31	ND[b]	ND	ND	ND	15.3 (4.1); 31
Synovium (μg/g)[c]	25.0 (0); 3	17.9 (7.8); 3	19.5 (4.9); 3	19.2 (8.9); 4	25.0 (0); 2	15.9 (7.9); 3
Synovial fluid (μg/ml)[c]	22.9; 1	27.4 (10.8); 4	19.2 (4.9); 3	11.6 (3.3); 2	13.9 (1.0); 3	6.2 (1.7); 2
Bone (μg/g)	6.3 (3.1); 5	5.0 (3.5); 5	4.6 (3.8); 5	3.8 (2.7); 5	3.7 (2.2); 5	4.1 (1.6); 5
Skin (μg/g)[c]	19.4 (7.9); 2	12.5 (6.5); 3	13.8 (1.4); 2	15.7 (1.0); 2	21.6; 1	13.8 (2.1); 2

[a] Mean (SD) plasma concentrations in 31 subjects at 772 and 1,080 h were 6.2 (2.4) and 3.4 (1.7), respectively.
[b] ND, not detected.
[c] Concentrations above the upper limit of quantification are reported as 25 μg/unit.

- Attention :
  - Transaminases
  - Quid si allergie ??

Dalbavancin in the treatment of different gram-positive infections: a real-life experience

Emilio Bouza [a,b,c,d], Maricela Valerio [a,*], Alex Soriano [e], Laura Morata [e], Enrique García Carus [e], Carmen Rodríguez-González [b,f], Ma Carmen Hidalgo-Tenorio [g], Antonio Plata [h], Patricia Muñoz [a,b,c,d,*], Antonio Vena [a,b,d] on behalf of the DALBUSE Study



(Bouza E et al. Intern J Antimicrob Agents 2018)

Oritavancine

- Lipoglycopeptide
- CMI basses
  - 8 X + faibles que daptomycine
  - 16 – 32 X + faibles que linezolide et vancomycine

Infect Dis Ther (2017) 6:277–289
DOI 10.1007/s40121-017-0156-z

CASE SERIES

Real-World Experience with Oritavancin Therapy in Invasive Gram-Positive Infections

Cassie L. Stewart · Michelle S. Turner · Jeremy J. Frens · Cynthia B. Snider · Jordan R. Smith

- 10 patients
- 7 bactériémies (5 SAMS, 1 streptocoque B, 1 entérocoque)
- Traitement antérieur + 1 dose
- Efficacité 7/10

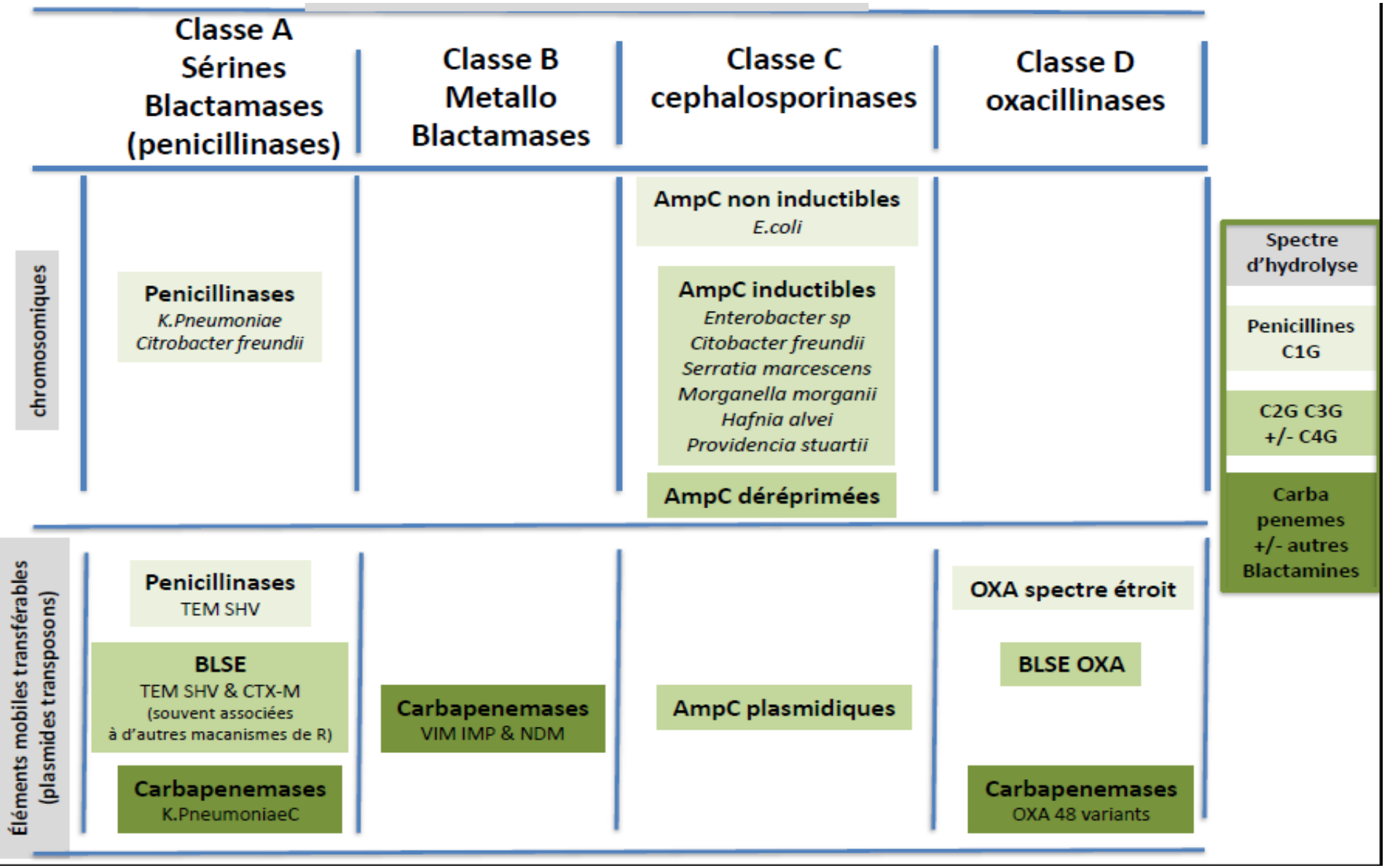
(Cassie LS et al Infect Dis Ther 2017)

Les anti Gram + en pratique

	Dalbavancine (Xydalba®)	Oritavancine (Orbactiv®)	Tedizolide (Sivextro®)
Famille	Lipopeptide	Lipopeptide	Oxazolidinone
Statut	AMM 2015	AMM 2015	AMM 2015
Intérêt principal	½ vie 321 h 1 Injection/sem	½ vie 245 h 1 Injection/sem	IV et PO Meilleure tolérance que linézolide
Défauts	Coût ½ vie 321 h Résistance croisée avec vanco Non dialysable Tolérance ?	Coût ½ vie 245 h Pas activité sur VRE Dialysable ? Interférence avec INR	Coût
Indication AMM	SSTI	SSTI	SSTI

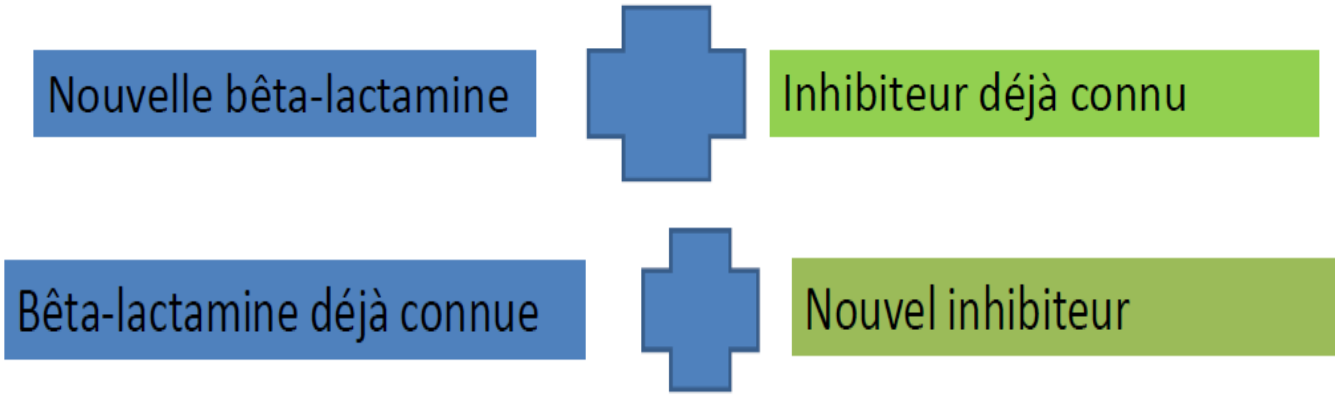
II- Les anti Gram négatif

Classification d'Ambler



Les anti Gram négatif

- Anciennes béta-lactamines « actualisées »
- Nouvelles associations béta-lactamine + inhibiteur de béta-lactamase



Témocilline

- Pénicilline, dérivée de ticarcilline
- Caractéristiques
  - - spectre étroit : Gram négatif (entérobactéries, bactéries non fermentaires, autres : *Haemophilus*, *Neisseria*, *Pasteurella*)
  - Stabilité vis-à-vis des béta-lactamases (groupe 6-a-methoxy)
    - BLSE, AmpC, KPC
    - Pas les métallo-β–lactamases

Témocilline

- Inactive vis-à-vis de
  - *P. aeruginosa*
  - *Acinetobacter baumanii*
  - *Stenotrophomonas maltophilia*
  - Bactéries à Gram +
  - Bacteries anaérobies
- AMM par « reconnaissance mutuelle »
  - Infections des voies urinaires compliquées
  - Infections des voies respiratoires basses
  - Bactériémies
  - Infections des plaies

Données cliniques

- Données cliniques anciennes
  - Infections urinaires (453, succès clinique 94,3%)
  - Infections respiratoires basses (164, succès clinique 86,9%)
  - Bactériémies (115, succès clinique 88,5%)
  - Infections de la peau et des tissus mous (37, succès clinique 87,9%)
- Données récentes
  - Case report
  - Données rétrospectives
  - Infections urinaires enfant
  - Données Pk/Pd

Caractéristiques Pk/Pd

- Fixation aux protéines 80%
- ½ vie d'élimination 5H
- Modèle animal (pyélonéphrite)
  - T>CMI 40% : bactériostase et efficacité
  - T > CMI 80% souches CTX-M15 ou non BLSE
- Patients de réanimation (pneumonie)

J Antimicrob Chemother 2015; **70**: 1466–1472
doi:10.1093/jac/dku542 Advance Access publication 5 January 2015

Journal of Antimicrobial Chemotherapy

Activity of temocillin in a murine model of urinary tract infection due to *Escherichia coli* producing or not producing the ESBL CTX-M-15

J. F. Soubirou[1,2], B. Rossi[1,2], C. Couffignal[1,2], E. Ruppé[1–3], F. Chau[2], L. Massias[1,4], R. Lepeule[5], F. Mentre[1,2] and B. Fantin[1,2,5]*

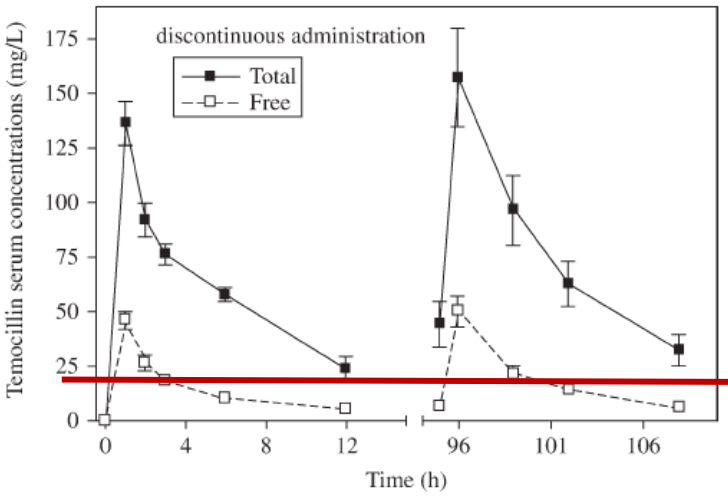
Journal of Antimicrobial Chemotherapy (2008) **61**, 382–388
doi:10.1093/jac/dkm467
Advance Access publication 10 December 2007

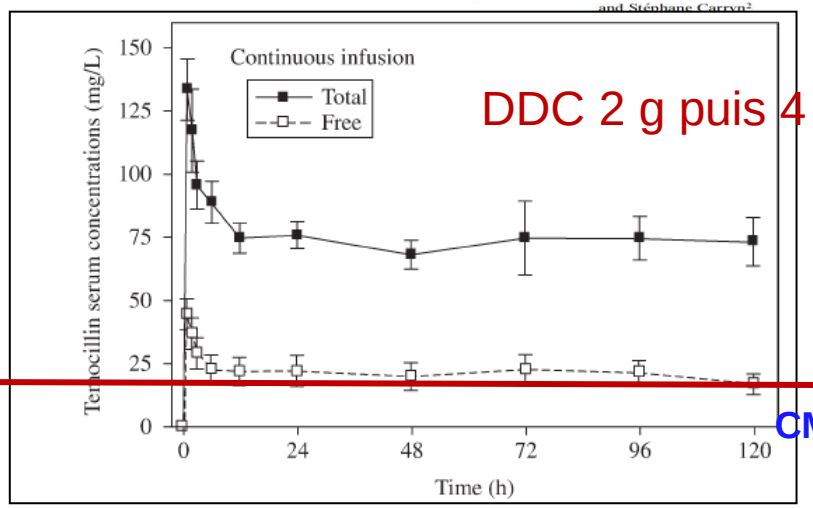
JAC

Continuous versus intermittent infusion of temocillin, a directed spectrum penicillin for intensive care patients with nosocomial pneumonia: stability, compatibility, population pharmacokinetic studies and breakpoint selection

Raf De Jongh[1], Ria Hens[1], Violetta Basma[2], Johan W. Mouton[3], Paul M. Tulkens[2]* and Stéphane Carryn[2]

2g x 2 / j





DDC 2 g puis 4 g IVSE

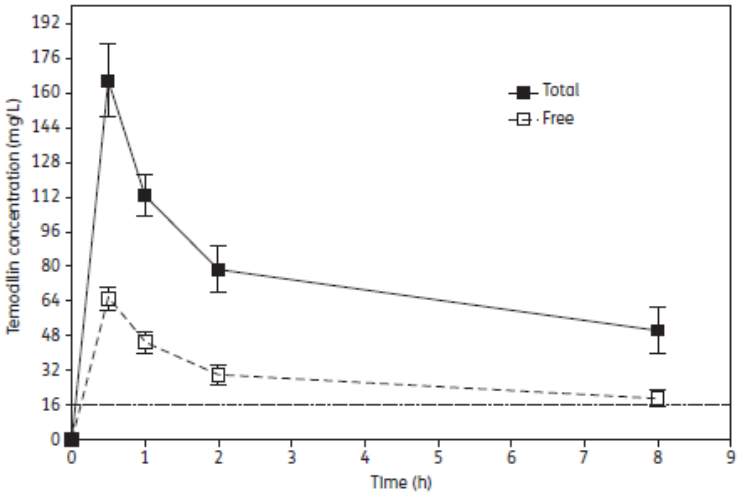
CMI = 16 mg/l

J Antimicrob Chemother 2015; **70**: 891–898
doi:10.1093/jac/dku465 Advance Access publication 27 November 2014

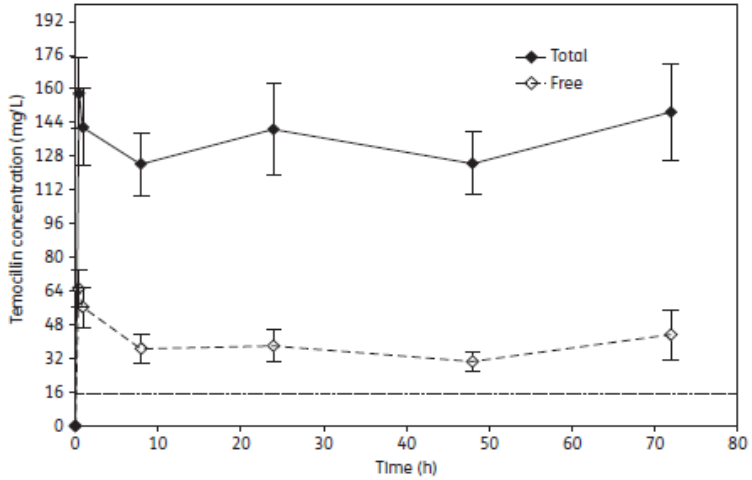
Journal of Antimicrobial Chemotherapy

Temocillin (6 g daily) in critically ill patients: continuous infusion versus three times daily administration

Pierre-François Laterre[1], Xavier Wittebole[1], Sebastien Van de Velde[2]†, Anouk E. Muller[3], Johan W. Mouton[4], Stéphane Carryn[2]‡, Paul M. Tulkens[2]* and Thierry Dugernier[1,5]



13 patients, infections intra abdominales ou pneumonies
2 g x 3 / j



11 patients, infections intra abdominales ou pneumonies
DDC 2 g puis 2 g x 3 / j

Témocilline en pratique

- Alternative aux carbapénèmes, infections documentées à BLSE
- Impact écologique faible
- Posologie
  - 4 g à 6 g (infections sévères ou réa)
  - IVSE (CMI > 16 mg/l ou situations particulières)

Ceftolozane - Tazobactam

- Ceftolozane = activité *P. aeruginosa*
- + Tazobactam :
- - spectre plus large incluant les EBLSE
- Cocci à Gram + (*S. anginosus, S. constellatus, S. salivarius*)
- Anaérobies activité limitée
  - *Fusobacterium* et *Cutibacterium acnes*
  - *B. fragilis et Clostridium :* inactif
- **Inactif sur KPC et carbapénémases (classe B :VIP, NDM-1)**

Spectre d'activité

	Classe A	Classe B	Classe C	Classe D
	Sérine β-lactamases	Metallo-β-lactamases	Céphalosporinases	Oxacillinases
Chromosomiques				
	Pénicillinases (*C. koseri*, *Klebsiella*)		AmpC non inductible (*E. coli*)	
			AmpC inductible	
			AmpC déréprimée	
Plasmidiques	TEM, SHV		AmpC plasmidique	OXA spectre étroit
	BLSE TEM, SHV, CTX-M			BLSE de type OXA
	Carbapénémases KPC	Carbapénémases VIP, IMP, NDM-1		Carbapénémases Ex. OXA-48

Ceftolozane - Tazobactam

- Formulation et posologie
  - Flacons de 1g ceftolozane/0,5 g tazobactam
  - Posologie 1500 mg x 3 / j (x 2 si CMI élevées, situations complexes)
  - Élimination rénale, adaptation clairance (< 50 ml/mn)
- *P. aeruginosa*
  - Peu d'impact mécanismes d'efflux et délétion OprD
  - Faible potentiel de sélection de résistances (X mutations)

INTERÊT +++

Intérêt pour *P. aeruginosa*

- 102 souches meropenem-R
- CA et CT toujours > cefepime, pipéracilline – tazobactam et ceftazidime
- CMI50 CT 1 mg/l vs CMI50 CA 4 mg/l

Figure Legends

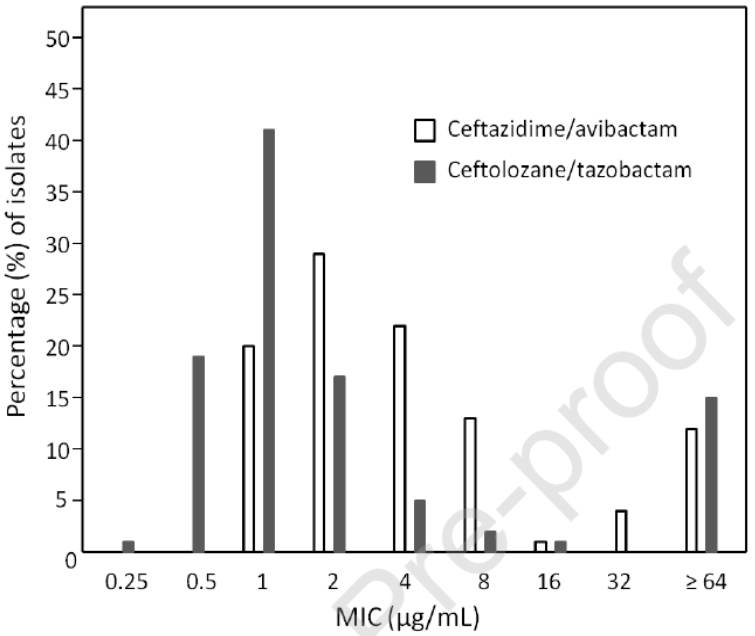


Figure 1. Ceftazidime/avibactam and ceftolozane/tazobactam MIC distributions for 102 meropenem- non-susceptible *P. aeruginosa* isolates

(Mirza HC et al J Glob Antimicrob Resist 2019)

Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI)

Florian M Wagenlehner, Obiamiwe Umeh, Judith Steenbergen, Guojun Yuan, Rabih O Darouiche

- 800 IU communautaires dont 82% PNA
- CT 1,5 g x 3 / j vs Levofloxacine 750 mg / j, durée 7 j
- 26% entérobactéries LEV-R; 2,7% enterobactéries CT-R; 14% BLSE

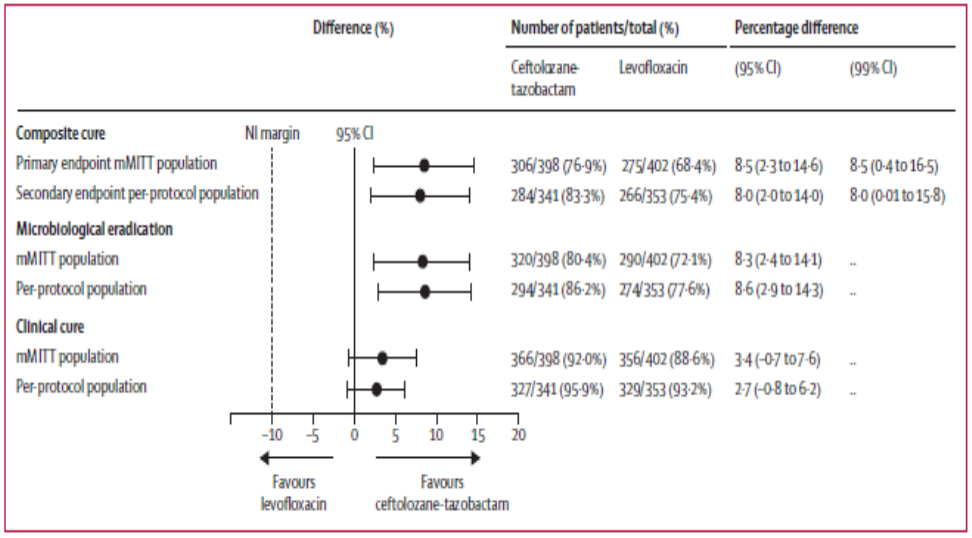


Figure 2: Primary and secondary endpoints at the test-of-cure visit
mMITT=microbiological modified intention-to-treat population. NI=non-inferiority.

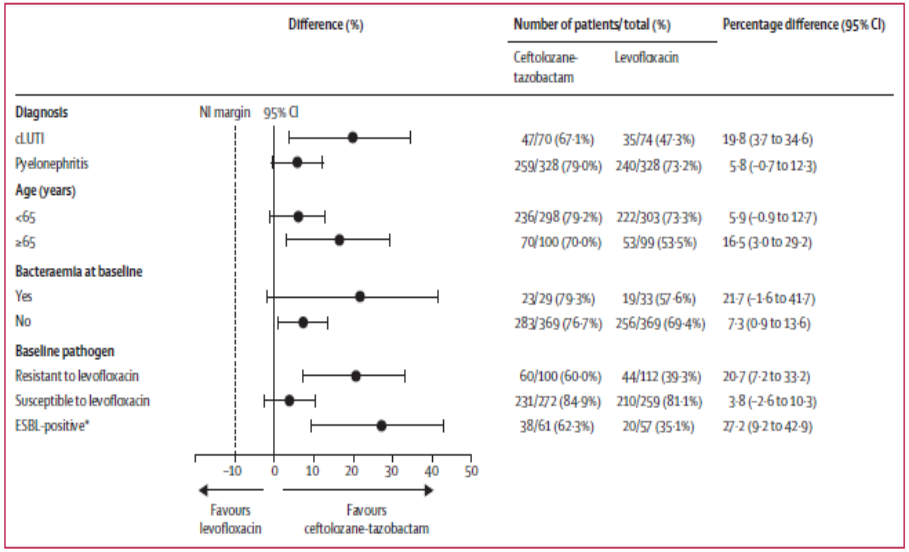


Figure 3: Composite cure at test-of-cure visit, by subgroup, in the microbiological modified intention-to-treat population
NI=non-inferiority. cUTI=complicated lower-urinary-tract infection. ESBL=extended-spectrum β-lactamase. *Includes isolates of *Escherichia coli*, *Klebsiella*

(Wagenlehner FM et al, Lancet 2015)

MAJOR ARTICLE

Ceftolozane/Tazobactam Plus Metronidazole for Complicated Intra-abdominal Infections in an Era of Multidrug Resistance: Results From a Randomized, Double-Blind, Phase 3 Trial (ASPECT-cIAI)

Joseph Solomkin,[1] Ellie Hershberger,[2] Benjamin Miller,[2] Myra Popejoy,[2] Ian Friedland,[2,a] Judith Steenbergen,[2] Minjung Yoon,[2] Sylva Collins,[2] Guojun Yuan,[2] Philip S. Barie,[3] and Christian Eckmann[4]

- 806 Infections intra abdominales compliquées
- Meropenem 1 g x 3 / j vs CT 1,5 g + metronidazole 500 mg x 3 / j / 7 à 10 j

	Ceftolozane/ tazobactam plus metronidazole No. (%)	Meropenem No. (%)	Percentage difference (95% CI)
MITT population	n = 389	n = 417	
Cure	323 (83.0)	364 (87.3)	–4.2 (–8.91 to .54)
Failure	32 (8.2)	34 (8.2)	
Indeterminate	34 (8.7)	19 (4.6)	
ME population	n = 275	n = 321	
Cure	259 (94.2)	304 (94.7)	–1.0 (–4.52 to 2.59)
Failure	16 (5.8)	17 (5.3)	

APACHE II score			
<10	213/222 (95.9)	262/274 (95.6)	0.3 (–3.61 to 3.98)
≥10	45/52 (86.5)	42/47 (89.4)	–2.8 (–16.08 to 10.92)

(Solomkin J et al Clin Infect Dis 2015)

Ceftolozane–tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial

Marin H Kollef, Martin Nováček, Ülo Kivistik, Álvaro Réa-Neto, Nobuaki Shime, Ignacio Martin-Loeches, Jean-François Timsit, Richard G Wunderink, Christopher J Bruno, Jennifer A Huntington, Gina Lin, Brian Yu, Joan R Butterton, Elizabeth G Rhee

- 726 pneumonies
- CT **3 g x 3** / j vs meropenem 1 g x 3; 7 à 14 j

	Ceftolozane-tazobactam group	Meropenem group	% difference (95% CI)*
28-day all-cause mortality (ITT population)†			
Overall	87/362 (24·0%)	92/364 (25·3%)	1·1 (−5·1 to 7·4)‡
Ventilator-associated pneumonia	63/263 (24·0%)	52/256 (20·3%)	−3·6 (−10·7 to 3·5)§
Ventilated hospital-acquired pneumonia	24/99 (24·2%)	40/108 (37·0%)	12·8 (0·2 to 24·8)§
28-day all-cause mortality (microbiological ITT population)†	53/264 (20·1%)	63/247 (25·5%)	4·4 (−2·8 to 11·8)‡
Clinical cure at test of cure (ITT population)†			
Overall	197/362 (54·4%)	194/364 (53·3%)	1·1 (−6·2 to 8·3)‡
Ventilator-associated pneumonia	147/263 (55·9%)	146/256 (57·0%)	−1·1 (−9·6 to 7·4)§
Ventilated hospital-acquired pneumonia	50/99 (50·5%)	48/108 (44·4%)	6·1 (−7·4 to 19·3)§
Clinical cure at test of cure (clinically evaluable population)¶			
Overall	139/218 (63·8%)	143/221 (64·7%)	−1·3 (−10·2 to 7·7)‡
Ventilator-associated pneumonia	105/159 (66·0%)	111/172 (64·5%)	1·5 (−8·7 to 11·6)§
Ventilated hospital-acquired pneumonia	34/59 (57·6%)	32/49 (65·3%)	−7·7 (−25·0 to 10·6)§
Microbiological eradication at test of cure (microbiological ITT population)†	193/264 (73·1%)	168/247 (68·0%)	4·5 (−3·4 to 12·5)‡

	Ceftolozane-tazobactam group	Meropenem group	% difference (95% CI)*
Gram-negative pathogens	157/259 (60·6%)	137/240 (57·1%)	3·5 (−5·1 to 12·1)
Enterobacteriaceae	120/195 (61·5%)	105/185 (56·8%)	4·8 (−5·1 to 14·5)
ESBL-producing Enterobacteriaceae	48/84 (57·1%)	45/73 (61·6%)	−4·5 (−19·3 to 10·7)
Pseudomonas aeruginosa	36/63 (57·1%)	39/65 (60·0%)	−2·9 (−19·4 to 13·8)
Multidrug-resistant *P aeruginosa*	13/24 (54·2%)	6/11 (54·5%)	−0·4 (−31·2 to 31·7)
Extensively drug-resistant *P aeruginosa*	4/10 (40·0%)	2/5 (40·0%)	0·0 (−43·6 to 40·3)

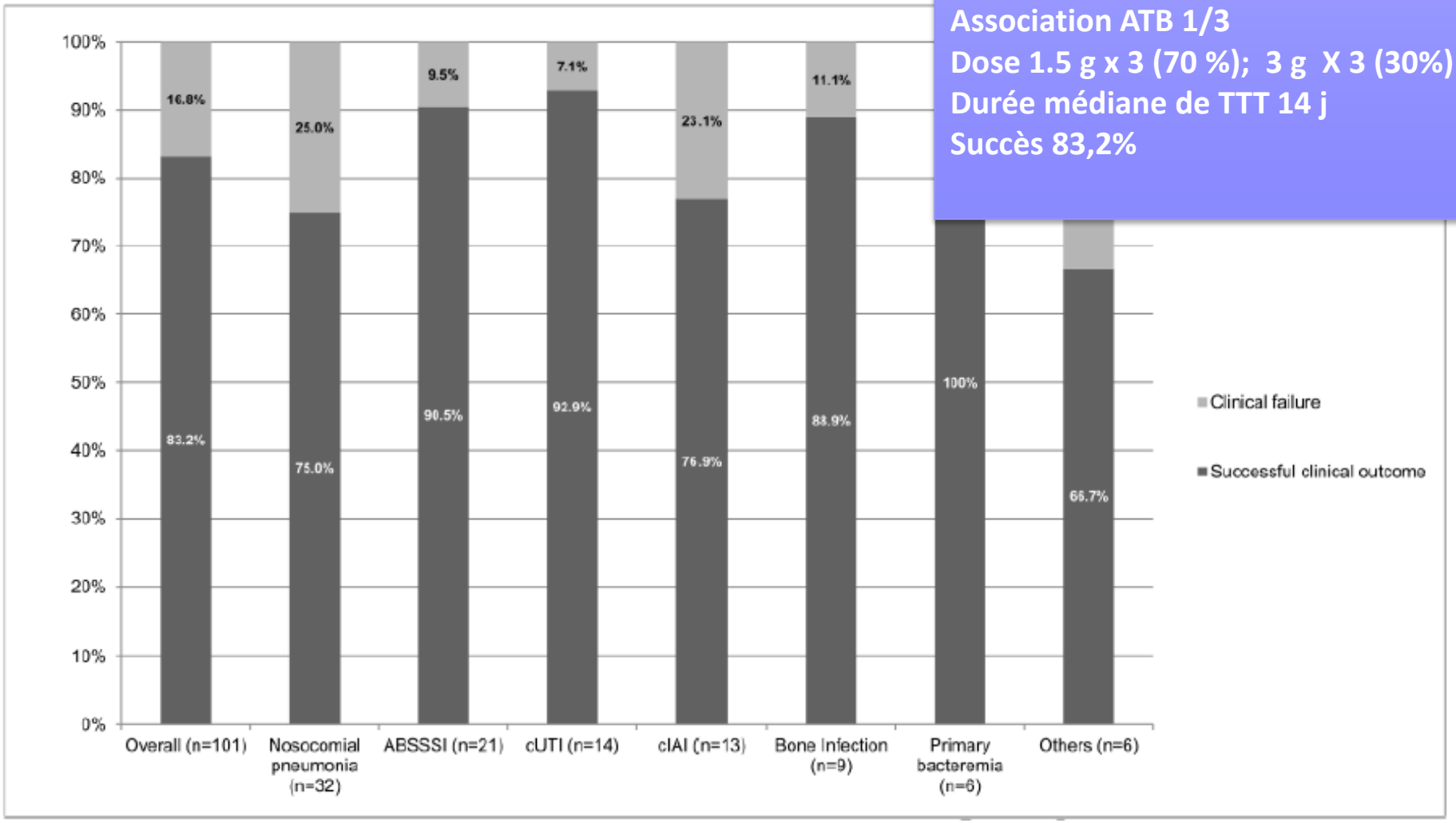
Data are n/N (%). *Unstratified Newcombe CIs; inferences drawn from these intervals might therefore not be reproducible.

Table 3: Per-pathogen clinical cure at test-of-cure visit in the microbiological intention-to-treat population

(Kollef M et al Lancet Infect Dis 2019)

Ceftolozane/tazobactam for the treatment of serious *P. aeruginosa* infections: a multicenter nationwide clinical experience

101 patients
P. aeruginosa
***50.5%* XDR**
78.2% R ≥ 1 carbapénème
Association ATB 1/3
Dose 1.5 g x 3 (70 %); 3 g X 3 (30%)
Durée médiane de TTT 14 j
Succès 83,2%



(Bassetti M et al. Intern J Antimicrob Agents 2019;53:408-15)

Ceftazidime - avibactam

- Avibactam
  - Inhibiteur non béta-lactamine
  - Activité :
    - BLSE de classe A et C
    - Enzymes de classe A (dont KPC)
    - Enzymes de classe C : AmpC
    - Certaines enzymes de classe D : certaines OXA-48
    - *M. tuberculosis*

Spectre d'activité

	Classe A	Classe B	Classe C	Classe D
	Sérine β-lactamases	Metallo-β-lactamases	Céphalosporinases	Oxacillinases
Chromosomiques				
	Pénicillinases (*C. koseri*, *Klebsiella*)		AmpC non inductible (*E. coli*)	
			AmpC inductible	
			AmpC déréprimée	
Plasmidiques	TEM, SHV		AmpC plasmidique	OXA spectre étroit
	BLSE TEM, SHV, CTX-M			BLSE de type OXA
	Carbapénémases KPC	Carbapénémases VIP, IMP, NDM-1		Carbapénémases Ex. OXA-48

Peu d'activité / bactéries à Gram + et *Acinetobacter*

Activité variable / *B. fragilis*

Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial

Antoni Torres, Nanshan Zhong, Jan Pachl, Jean-François Timsit, Marin Kollef, Zhangjing Chen, Jie Song, Dianna Taylor, Peter J Laud, Gregory G Stone, Joseph W Chow

Etude de non infériorité, 527 pneumonies

Pas de différence

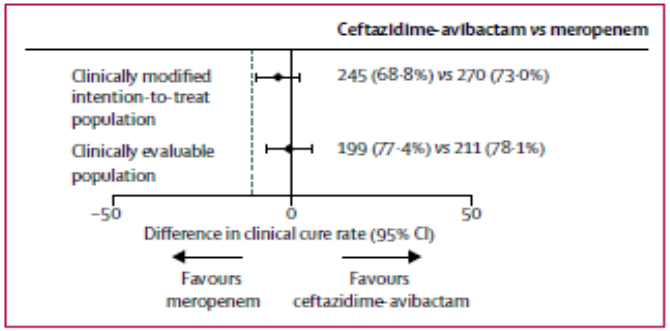


Figure 2: **Clinical cure rates at test-of-cure visit**
Data are number of patients with clinical cure (%). Dashed line indicates non-inferiority margin of −12·5%.

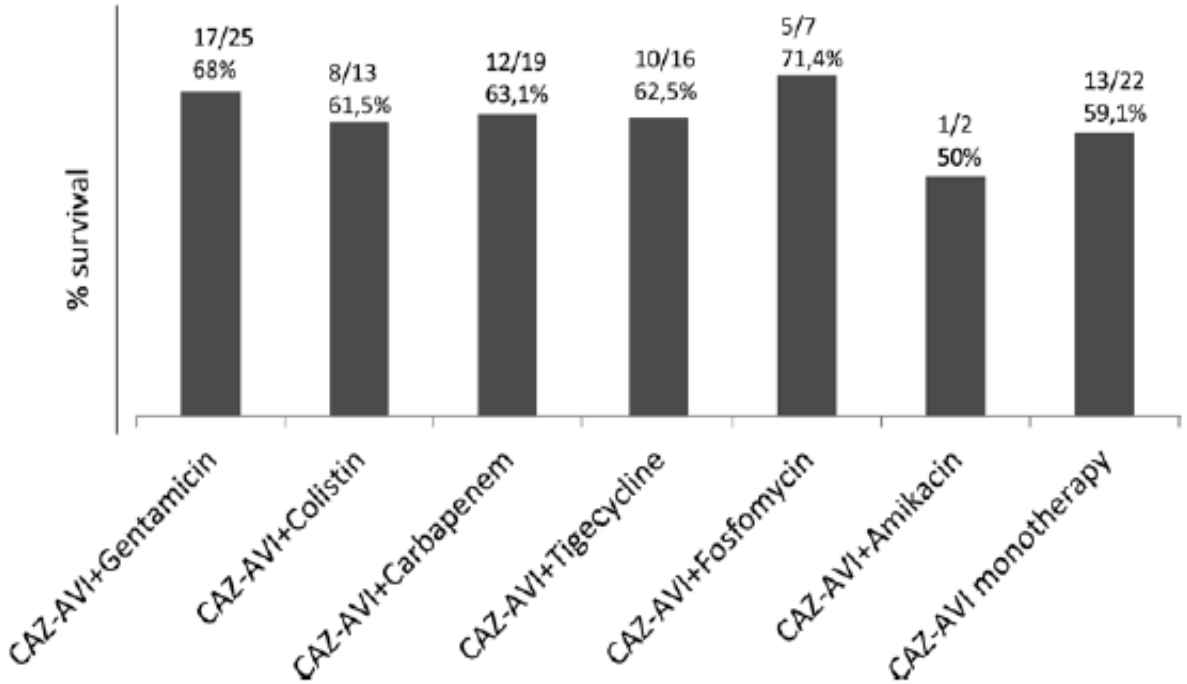
	Patients with clinical cure (clinically evaluable population)			Patients with favourable microbiological response* (extended microbiologically evaluable population)		
	Ceftazidime-avibactam (n=257)	Meropenem (n=270)	% difference (95% CI)	Ceftazidime-avibactam (n=125)	Meropenem (n=131)	% difference (95% CI)
Enterobacteriaceae						
Klebsiella pneumoniae	31/37 (83·8%)	39/49 (79·6%)	4·2 (−13·49 to 20·50)	29/37 (78·4%)	39/49 (79·6%)	−1·2 (−19·60 to 15·96)
Enterobacter cloacae	20/21 (95·2%)	7/11 (63·6%)	31·6 (4·79 to 61·30)	18/21 (85·7%)	7/11 (63·6%)	22·1 (−8·07 to 53·69)
Escherichia coli	8/11 (72·7%)	14/18 (77·8%)	−5·1 (−39·26 to 25·79)	10/11 (90·9%)	16/18 (88·9%)	2·0 (−29·11 to 26·44)
Proteus mirabilis	11/11 (100·0%)	7/8 (87·5%)	12·5 (−16·54 to 48·07)	9/11 (81·8%)	6/8 (75·0%)	6·8 (−30·73 to 46·51)
Serratia marcescens	10/12 (83·3%)	8/8 (100·0%)	−16·7 (−45·58 to 19·48)	9/12 (75·0%)	5/8 (62·5%)	12·5 (−27·47 to 51·82)
Enterobacter aerogenes	4/6 (66·7%)	2/5 (40·0%)	26·7 (−31·92 to 70·73)	5/6 (83·3%)	3/5 (60·0%)	23·3 (−31·30 to 68·33)
Gram-negative pathogens other than Enterobacteriaceae						
Pseudomonas aeruginosa	27/42 (64·3%)	27/35 (77·1%)	−12·8 (−32·25 to 8·01)	18/42 (42·9%)	14/35 (40·0%)	2·9 (−19·13 to 24·32)
Haemophilus influenzae	10/11 (90·9%)	11/13 (84·6%)	6·3 (−26·19 to 36·09)	11/11 (100·0%)	12/13 (92·3%)	7·7 (−20·08 to 34·00)
Gram-positive aerobes						
Staphylococcus aureus	11/14 (78·6%)	16/22 (72·7%)	5·8 (−25·24 to 32·67)	5/14 (35·7%)	17/22 (77·3%)	−41·6 (−67·04 to −8·36)

(Torres A et al. Lancet Infect Dis 2018)

Efficacy of Ceftazidime-Avibactam Salvage Therapy in Patients With Infections Caused by *Klebsiella pneumoniae* Carbapenemase–producing *K. pneumoniae*

Mario Tumbarello,[1,a] Enrico Maria Trecarichi,[1,a] Alberto Corona,[2] Francesco Giuseppe De Rosa,[3] Matteo Bassetti,[4] Cristina Mussini,[5] Francesco Menichetti,[6] Claudio Viscoli,[7] Caterina Campoli,[8] Mario Venditti,[9] Andrea De Gasperi,[10] Alessandra Mularoni,[11] Carlo Tascini,[12] Giustino Parruti,[13] Carlo Pallotto,[14] Simona Sica,[15] Ercole Concia,[16] Rosario Cultrera,[17] Gennaro De Pascale,[18] Alessandro Capone,[19] Spinello Antinori,[20] Silvia Corcione,[3] Elda Righi,[4] Angela Raffaella Losito,[1] Margherita Digaetano,[5] Francesco Amadori,[6] Daniele Roberto Giacobbe,[7] Giancarlo Ceccarelli,[9] Ernestina Mazza,[10] Francesca Raffaelli,[1] Teresa Spanu,[21] Roberto Cauda,[1] and Pierluigi Viale[8]

- 138 patients
- 104 bactériémies, KPC
- Mortalité à J30 vs groupe « contrôle » traité sans Caz-Avi (36.5% vs 55.8%, *P* = .005)
- Analyse multivariée Caz-Avi = seul facteur de survie



(Tumbarello M et al Clin Infect dis 2019)

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Review

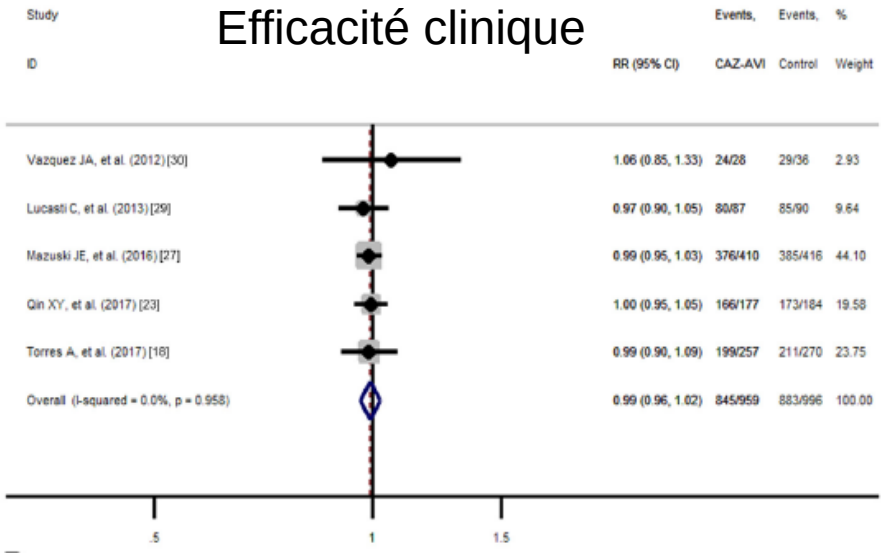
Evaluation of the efficacy and safety of ceftazidime/avibactam in the treatment of Gram-negative bacterial infections: a systematic review and meta-analysis

Han Zhong[a,1], Xian-Yuan Zhao[b,1], Zai-Li Zhang[a], Zhi-Chun Gu[a], Chi Zhang[a], Yuan Gao[b,*], Min Cui[a,*]

- IU, IIA, bactériémies et pneumonies

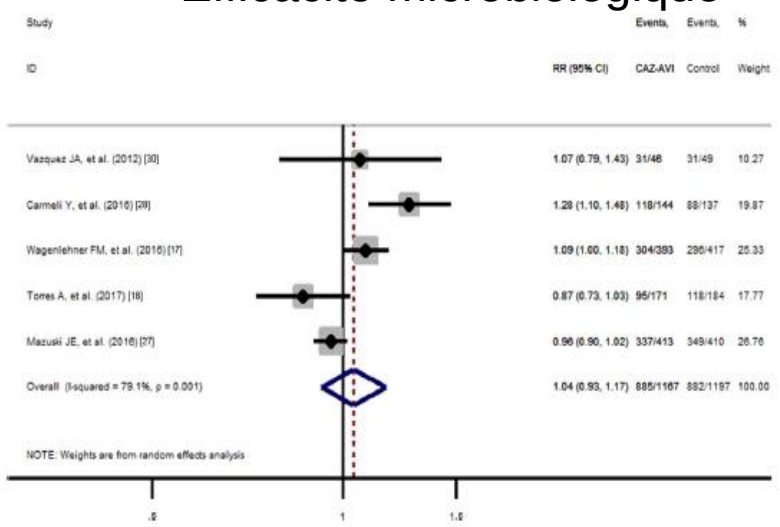
A

Efficacité clinique



B

Efficacité microbiologique



Efficacité comparable à celle des carbapénèmes

EBLSE et ERC

(Zhong H et al, Int J Antimicrob Agents 2018)

Les anti-Gram- récents en pratique

	Témocilline (négaban®)	Ceftazidime-Avibactam (zavicefta®)	Ceftolozane-tazobactam (zerbaxa®)
Statut	**AMM 2014** IU compliquées, respi basses, bactériémies, Infections plaies	**AMM 2016** Infections bactériennes multi-résistantes de l'adulte	**AMM 2015** Intra-abdominales, pyélonéphrites, IU complexes
Forces	**Epargneur de carbapénèmes**	**Activité sur :** •BLSE, AmpC •**Carbapénèmases** (KPC, OXA 48)	**Activité sur :** •***P. Aeruginosa* résistant** (ceftazidime, imipénème) •Anaérobies, BLSE
Faiblesses	**Pk/Pd fragile** (nécessité fortes doses, perfusions prolongées)	**Pas d'activité sur :** •Anaérobies •Metallocarbapénèmases	**Pas d'activité sur :** •Carbapénèmases •AmpC hyperproduite **Doubler les doses ?**

Nouvelles β-lactamines ‘dans les tuyaux’

	EBLSE	AmpC	Carbapénémases			*Pseudomonas spp*	*Acineto-bacter*	Phase
			KPC	Oxa-48 like	MBL			
Ceftaroline/avibactam	++	++	+	-	-	-	-	
Aztréonam/avibactam	++	++	++	+	++	+	-	3
Imipenem/relebactam	++	++	++	-	-	+	-	3
Meropenem/vaborbactam	++	++	++	-	-	+/-	-	3
Cefépime/zidebactam	++	++	++	++	++	++	-	2
Céfidérocol (Céphalosporine sidérophore)	++	++	++	++	++	++	+	3

Aztreonam - avibactam

- Données microbiologiques
- Modèle animal : péritonite (Chauzy A, Antimicrob Agents Chemother 2018)
- Quelques case-reports
  - Carbapénémases de type NDM
  - *Stenotrophomonas maltophilia*

(Marshall S et al, Antimicrobial Agents Chemother 2017)

(Davido B et al Antimicrobial Agents Chemother 2017)

(Benchetrit L et al Int J Antimicrob Agents. 2019)

Spectre d'activité

	Classe A	Classe B	Classe C	Classe D
	Sérine β-lactamases	Metallo-β-lactamases	Céphalosporinases	Oxacillinases
Chromosomiques				
	Pénicillinases (*C. koseri, Klebsiella*)		AmpC non inductible (*E. coli*)	
			AmpC inductible	
			AmpC déréprimée	
Plasmidiques	TEM, SHV		AmpC plasmidique	OXA spectre étroit
	BLSE TEM, SHV, CTX-M			BLSE de type OXA
	Carbapénémases KPC	Carbapénémases VIP, IMP, NDM-1		Carbapénémases Ex. OXA-48

Successful treatment of a bacteremia due to NDM-1-producing *Morganella morganii* with Aztreonam and Ceftazidime-avibactam combination in a pediatric patient with hematologic malignancy

Antimicrobial Agents and Chemotherapy AAC

Claire Amaris Hobson[1], Stéphane Bonacorsi[1,2], Mony Fahd[3], André Baruchel[3], Aurélie Cointe[1,2], Nora Poey[4], Hervé Jacquier[1,5], Catherine Doit[1,2], Audrey Monjault[2], Olivier Tenaillon[1], André Birgy[1,2*].

(Amaris C et al. Antimicrob Agents Chemother 2018)

Imipenem – cilastatine / Relebactam

- Activité vis-à-vis des bêta-lactamases de classe A et C
- Pas d'activité sur classe D
  - Oxa-48
  - Oxa 23 (*A. baumanii*)
- Phases III en cours :
  - Pneumonies nosocomiales
  - Bactéries MDR vs Imipenem – colistine
- Phase II : IU
  - Imipenem + 125 ou 250 mg relebactam vs imipenem

Meropenem - Varbobactam

- Activité sur classe A, KPC
- Mais pas d'activité classe B ou D
  - OXA d'A. baumanii
  - Carbapénémases de P. aeruginosa

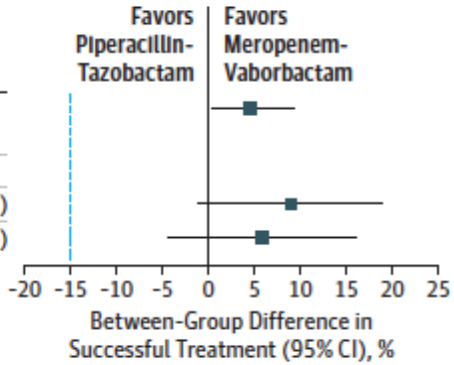
- Données cliniques :
  - 2 études de phase III : IU et ERC vs meilleure alternative
  - Cas cliniques (Shields RK et al, Clin Infect dis 2019)

Effect of Meropenem-Vaborbactam vs Piperacillin-Tazobactam on Clinical Cure or Improvement and Microbial Eradication in Complicated Urinary Tract Infection
The TANGO I Randomized Clinical Trial

Keith S. Kaye, MD, MPH; Tanaya Bhowmick, MD; Symeon Metallidis, MD; Susan C. Bleasdale, MD; Olexiy S. Sagan, MD; Viktor Stus, MD, PhD; Jose Vazquez, MD; Valerii Zaitsev, PhD; Mohamed Bidair, MD; Erik Chorvat, MD; Petru Octavian Dragoescu, MD; Elena Fedosiuk, MD; Juan P. Horcajada, MD, PhD; Claudia Murta, MD; Yaroslav Sarychev, MD; Ventsislav Stoev, MD; Elizabeth Morgan, BS; Karen Fusaro, BS; David Griffith, BS; Olga Lomovskaya, PhD; Elizabeth L. Alexander, MD; Jeffery Loutit, MBChB; Michael N. Dudley, PharmD; Evangelos J. Giamarellos-Bourboulis, MD, PhD

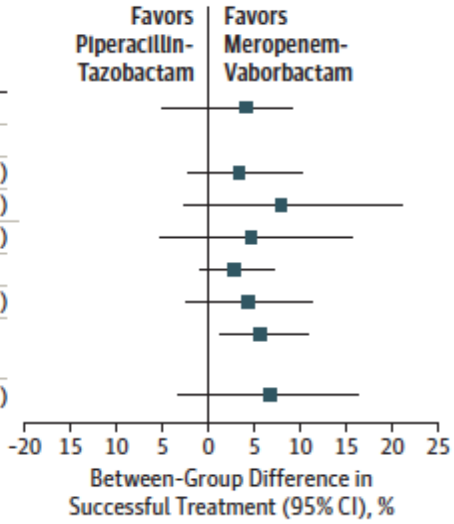
A Primary end points

	No. of Patients Successfully Treated/Total No. (%)		Between-Group Difference (95% CI), %
	Meropenem-Vaborbactam	Piperacillin-Tazobactam	
FDA primary: overall success at end of intravenous treatment (microbiologic MITT analysis)[a,b]	189/192 (98.4)	171/182 (94.0)	4.5 (0.7 to 9.1)
EMA primary: microbial eradication at test of cure			
Microbiologic MITT analysis[b]	128/192 (66.7)	105/182 (57.7)	9.0 (-0.9 to 18.7)
Microbiologic evaluable analysis	118/178 (66.3)	102/169 (60.4)	5.9 (-4.2 to 16.0)



B Secondary end points

	No. of Patients Successfully Treated/Total No. (%)		Between-Group Difference (95% CI), %
	Meropenem-Vaborbactam	Piperacillin-Tazobactam	
Overall success at test of cure[a]	143/192 (74.5)	128/182 (70.3)	4.1 (-4.9 to 9.1)
Overall success at end of intravenous treatment[a]			
Acute pyelonephritis	117/120 (97.5)	95/101 (94.1)	3.4 (-2.0 to 10.2)
Complicated UTI, removable infection source[c]	35/35 (100)	35/38 (92.1)	7.9 (-2.5 to 20.9)
Complicated UTI, nonremovable infection source	37/37 (100)	41/43 (95.3)	4.7 (-5.1 to 15.6)
Clinical cure at end of intravenous treatment[d]	189/192 (98.4)	174/182 (95.6)	2.8 (-0.7 to 7.1)
Clinical cure at test of cure	174/192 (90.6)	157/182 (86.3)	4.4 (-2.2 to 11.1)
Microbial eradication at end of intravenous treatment (FDA criteria)	188/192 (97.9)	168/182 (92.3)	5.6 (1.4 to 10.7)
Microbial eradication at test of cure (FDA criteria)	132/192 (68.8)	113/182 (62.1)	6.7 (-3.0 to 16.2)



Meropenem / varbobactam non < Pipéracilline / tazobactam

(Kayke KS et al. JAMA 2018)

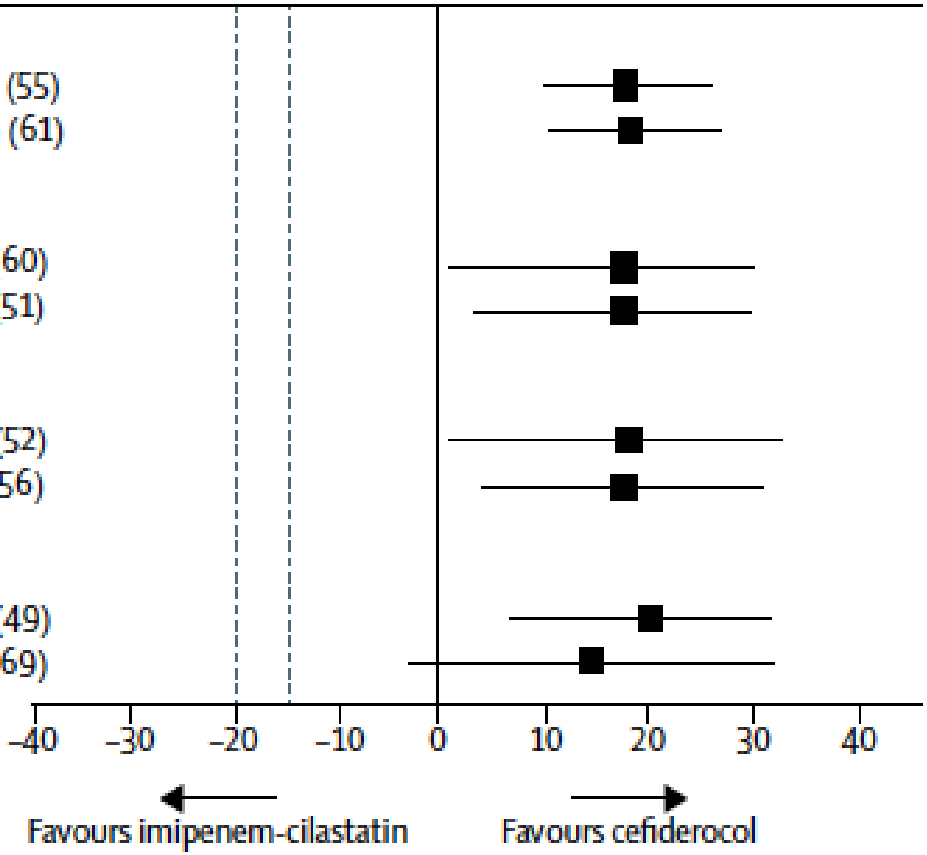
Cefiderocol

- Céphalosporine sidérophore
- C4G (structure proche cefepime) + groupe catechol
- Fixation aux ions ferriques : transport actif en intra bactérien
- Spectre large +++ : classes A, B, C, D
  - *A. baumanii, P. aeruginosa, S. maltophilia*

Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial

Simon Portsmouth, David van Veenhuyzen, Roger Echols, Mitsuaki Machida, Juan Camilo Arjona Ferreira, Mari Ariyasu, Peter Tenke, Tsutae Den Nagata

	n/N (%)	
	Cefiderocol	Imipenem-cilastatin
Analysis population		
mITT population	183/252 (73)	65/119 (55)
Microbiologically evaluable population	182/228 (80)	65/106 (61)
Age, years		
<65	87/113 (77)	32/54 (60)
≥65	96/139 (69)	33/65 (51)
Sex		
Men	84/119 (71)	25/48 (52)
Women	99/133 (74)	40/71 (56)
Clinical diagnosis		
cUTI with or without pyelonephritis	129/187 (69)	41/84 (49)
Acute uncomplicated pyelonephritis	54/65 (83)	24/35 (69)



Non < imipenem-cilastatine

Analyse post hoc : efficacité ++

(Portsmouth S et al. Lancet Infect Dis 2018)

III-Divers

PLAZOMICINE

ERAVACYCLINE

ZOLIFLODACIN

DELAMANIDE / BÉDAQUILINE

PLAZOMICINE

- Aminoside
- Activité :
  - BLSE
  - KPC
  - OXA d' *A. baumanii*
- Pas d'activité NDM

A Multicenter, Randomized, Double-Blind, Phase 2 Study of the Efficacy and Safety of Plazomicin Compared with Levofloxacin in the Treatment of Complicated Urinary Tract Infection and Acute Pyelonephritis

Lynn E. Connolly,[a] Valerie Riddle,[b] Deborah ... Miller[c]

Antimicrobial Agents and Chemotherapy AAC

- Plazomicine 10 mg/kg vs plazomicine 15 mg/kg vs lévofloxaine 750 mg pendant 5 j
- 28 Infections urinaires compliquées, 35 PN
- Efficacité comparable

TABLE 2 Microbiological outcome at TOC (primary efficacy endpoint)[a]

Population	Treatment	No. of patients	No. (%) of patients with eradication
MITT	Plazomicin at 10 mg/kg	12	6 (50.0)
	Plazomicin at 15 mg/kg	51	31 (60.8)
	Levofloxacin at 750 mg	29	17 (58.6)
ME	Plazomicin at 10 mg/kg	7	6 (85.7)
	Plazomicin at 15 mg/kg	35	31 (88.6)
	Levofloxacin at 750 mg	21	17 (81.0)

(Connolly LE et al. Antimicrob Agents Chemother 2018)

A Multicenter, Randomized, Double-Blind, Phase 2 Study of the Efficacy and Safety of Plazomicin Compared with Levofloxacin in the Treatment of Complicated Urinary Tract Infection and Acute Pyelonephritis

Lynn E. Connolly,[a] Valerie Riddle,[b] Deborah Cebrik,[a] Eliana S. Armstrong,[a] Loren G. Miller[c]

TABLE 6 Safety analysis (safety population)

Event[a]	Values for patients receiving: Plazomicin at 10 mg/kg (*n* = 22)	Plazomicin at 15 mg/kg (*n* = 74)	Levofloxacin at 750 mg (*n* = 44)
No. (%) of patients with any AE	7 (31.8)	26 (35.1)	21 (47.7)
No. (%) of patients with the following AEs reported in ≥5% of patients in any treatment group:			
Headache	2 (9.1)	6 (8.1)	3 (6.8)
Diarrhea	0 (0.0)	4 (5.4)	2 (4.5)
Vomiting	0 (0.0)	4 (5.4)	1 (2.3)
Nausea	0 (0.0)	4 (5.4)	0 (0.0)
Dizziness	0 (0.0)	4 (5.4)	0 (0.0)
No. (%) of patients with:			
AE related to renal function[b]	0 (0.0)	2 (2.7)	0 (0.0)
AE related to vestibular or cochlear function[c]	0 (0.0)	2 (2.7)	1 (2.3)
AE related to study drug	2 (9.1)	15 (20.3)	12 (27.3)
AE leading to study drug discontinuation	0 (0.0)	4 (5.4)	1 (2.3)
Any serious AE	0 (0.0)	1 (1.4)	2 (4.5)
No. of patients with a ≥0.5-mg/dl increase in serum creatinine concn/total no. of patients tested (%):			
At any time during the study	1/22 (4.5)	4/72 (5.6)	1/41 (2.4)
While on i.v. study drug	0/22 (0.0)	3/72 (4.2)	0/41 (0.0)

(Connolly LE et al. Antimicrob Agents Chemother 2018)

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Plazomicin for Infections Caused by Carbapenem-Resistant Enterobacteriaceae

- 37 patients (bactériémies, PAVM)
- Plazomicine (15 mg/kg) vs colistine + meropenem ou tigécycline

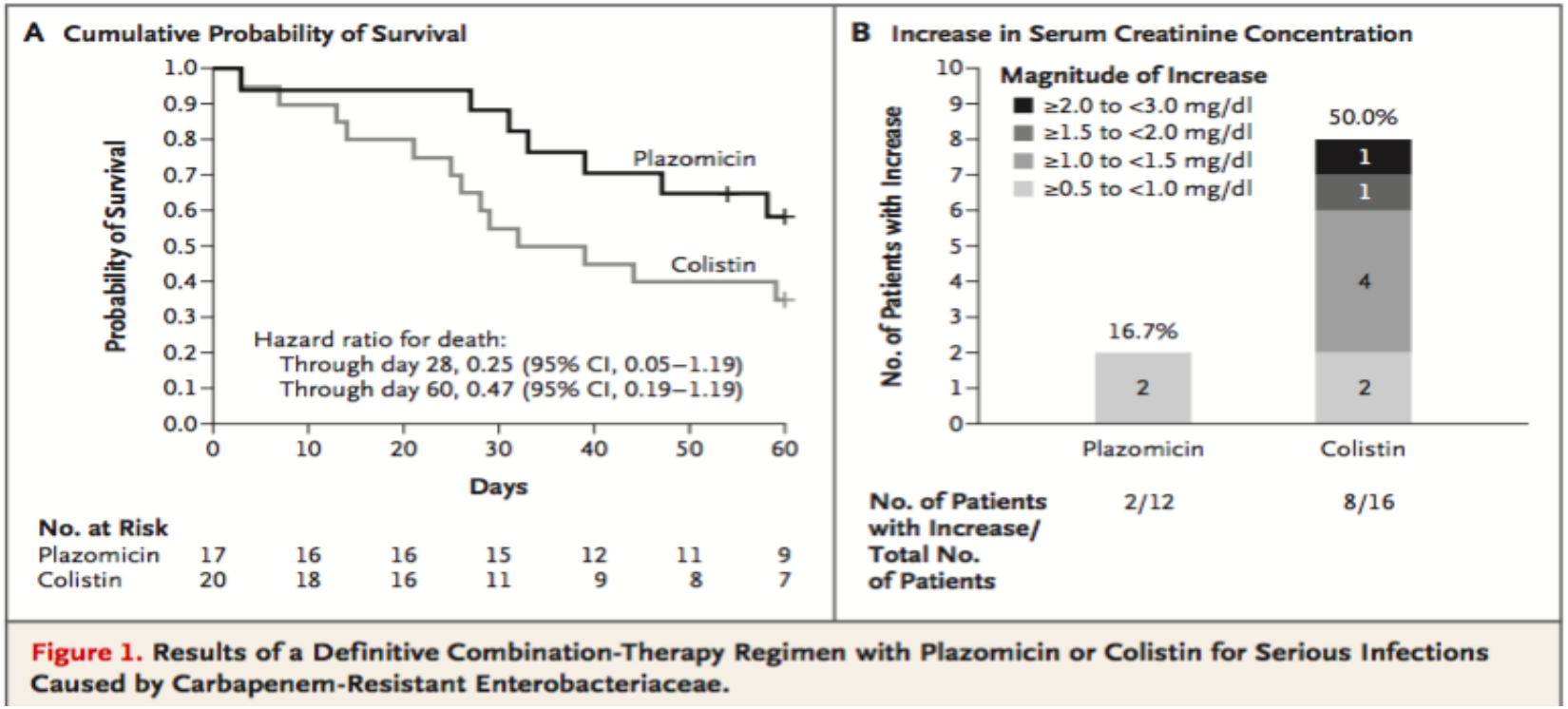


Figure 1. Results of a Definitive Combination-Therapy Regimen with Plazomicin or Colistin for Serious Infections Caused by Carbapenem-Resistant Enterobacteriaceae.

(Mc Kinnell JA et al N Engl J Med 2019)

ERAVACYCLINE

- Fluorocycline
- IV x 2 / 24H
- Fixation protéines 80%, ½ vie 20h
- Spectre d'activité
  - Enterocoque, EBLSE, *Acinetobacter baumannii* et anaérobies
- Infections intra abdominales :
  - Non < ertapeneme et meropeneme
- Infections urinaires compliquées :
  - **< Levofloxacine**

(Lee YR et al Eur J Clin Microbiol Infect Dis 2019)

Clinical Infectious Diseases
MAJOR ARTICLE

IGNITE4: Results of a Phase 3, Randomized, Multicenter, Prospective Trial of Eravacycline vs Meropenem in the Treatment of Complicated Intraabdominal Infections

Joseph S. Solomkin,[1] Janis Gardovskis,[2] Kenneth Lawrence,[3] Philippe Montravers,[4,5,6] Angie Sway,[7] David Evans,[8] and Larry Tsai[3]

(Eravacycline 1 mg /kg x 2 vs meropenem 1 g x 3)

Table 3. Clinical Response at Test-of-cure Visit

Population	Eravacycline	Meropenem	Difference (95% Confidence Interval)
Modified intent-to-treat	N = 250	N = 249	...
Clinical cure	231 (92.4)	228 (91.6)	0.8 (–4.1, 5.8)
Clinical failure	7 (2.8)	9 (3.6)	...
Indeterminate/Missing	12 (4.8)	12 (4.8)	...

Table 4. Clinical Response at Follow-up Visit

Population	Eravacycline (Clinical Cure/Total)	Meropenem (Clinical Cure/Total)	Difference (95% Confidence Interval)
Intent-to-treat	224/250 (89.6)	226/250 (90.4)	–0.8 (–6.2, 4.6)
Modified intent-to-treat	224/250 (89.6)	226/249 (90.8)	–1.2 (–6.5, 4.2)
Microbiological intent-to-treat	170/195 (87.2)	185/205 (90.2)	–3.1 (–9.5, 3.2)
Clinically evaluable	220/229 (96.1)	221/231 (95.7)	0.4 (–3.5, 4.3)
Microbiologically evaluable	168/177 (94.9)	184/192 (95.8)	–0.9 (–5.7, 3.6)

(Solomkin JS et al. Clin Infect Dis 2019)

New agents for the treatment of infections with Gram-negative bacteria: restoring the miracle or false dawn?

H. Wright [1], R.A. Bonomo [2], D.L. Paterson [1,*]

Table 1
Recent trials in complicated urinary tract infections and outcomes

Study	Design	Drug	Comparator
EPIC cUTI	Phase III Non-Inferiority	Plazomicin 15 mg/kg q24h	Meropenem 1 g q8h
APEKs cUTI	Phase III Non-Inferiority	Cefiderocol 2g q8h	Imipenem-cilastatin 1 g/1 g q8h
TANGO — 1	Phase III Non-Inferiority	Meropenem-vaborbactam 2 g/2 g q8h	Piperacillin-tazobactam 4.5 g q8h
RECAPTURE	Phase III Non-Inferiority	Ceftazidime-avibactam 2.5 g q8h	Doripenem 500 mg q8h
ASPECT-cUTI	Phase III Non-Inferiority	Ceftolozane-tazobactam 1.5 g q8h	Levofloxacin 750 mg q24h

(Wright H et al. Clin Microbiol Infect 2017)

New agents for the treatment of infections with Gram-negative bacteria: restoring the miracle or false dawn?

H. Wright [1], R.A. Bonomo [2], D.L. Paterson [1,*]

Table 2
Recent trials in complicated intra-abdominal infections and outcomes

Study	Design	Drug	Comparator
RECLAIM	Phase III Non-Inferiority	Ceftazidime-avibactam 2.5 g q8h and metronidazole 500 mg q8h	Meropenem 1 g q8h
ASPECT-cIAI	Phase III Non-Inferiority	Ceftolozane-tazobactam 1.5 g q8h and metronidazole 500 mg q8h	Meropenem 1 g q8h
IGNITE 1	Phase III Non-Inferiority	Eravacycline 1 mg/kg q12h	Ertapenem 1 g q24h
MK-7655-004	Phase II Assigned 1:1:1	Imipenem-cilastatin-relebactam 500 mg + 250 mg or 125 mg relebactam q6h	Imipenem-cilastatin

(Wright H et al. Clin Microbiol Infect 2017)

Zodiflodacine

- Nouvelle classe : spiropyrimidine- trione
- Action sur ADN gyrase
- *N. gonorrhoeae*
- *S. aureus*
- *C. trachomatis, C. pneumoniae, M.genitalium, Ureaplasma*
- Essais cliniques *N. gonorrhoeae*

Single-Dose Zoliflodacin (ETX0914) for Treatment of Urogenital Gonorrhea

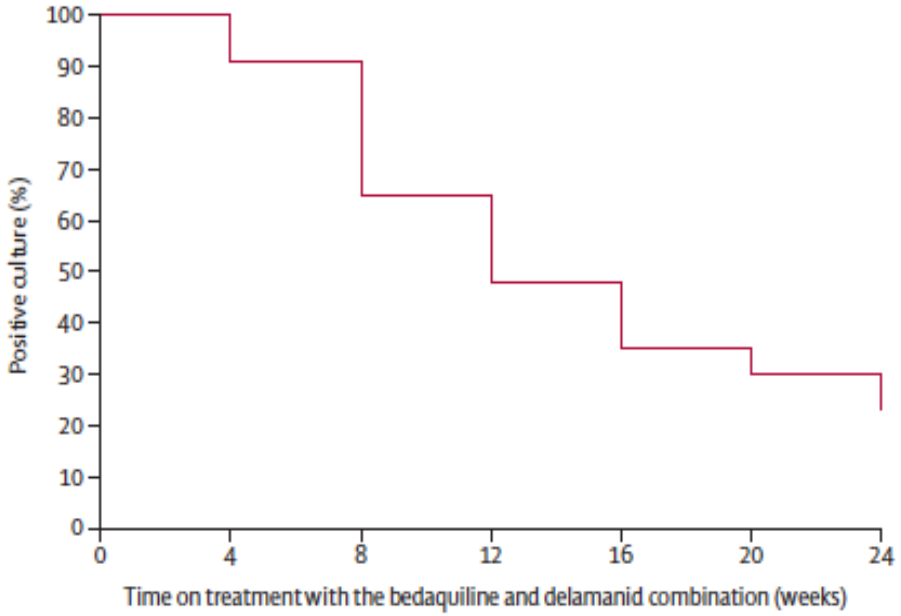
Stephanie N. Taylor, M.D., Jeanne Marrazzo, M.D., M.P.H., Byron E. Batteiger, M.D., Edward W. Hook, III, M.D., Arlene C. Seña, M.D., M.P.H., Jill Long, M.D., M.P.H., Michael R. Wierzbicki, Ph.D., Hannah Kwak, M.H.S., Shacondra M. Johnson, B.S.P.H., Kenneth Lawrence, Pharm.D., and John Mueller, Ph.D.

Population, Site, and Treatment	Confirmed Infections	Cures	Microbiologic Cure
	number		*% (95% CI)*
Micro-ITT			
Urethra or cervix			
Zoliflodacin, 2 g	57	55	96 (88–100)
Zoliflodacin, 3 g	56	54	96 (88–100)
Ceftriaxone, 500 mg	28	28	100 (88–100)
Rectum			
Zoliflodacin, 2 g	5	5	100 (48–100)
Zoliflodacin, 3 g	7	7	100 (59–100)
Ceftriaxone 500 mg	3	3	100 (29–100)
Pharynx			
Zoliflodacin, 2 g	8	4	50 (16–84)
Zoliflodacin, 3 g	11	9	82 (48–98)
Ceftriaxone, 500 mg	4	4	100 (40–100)

(Taylor N et al. New Engl J Med 2018)

Early safety and efficacy of the combination of bedaquiline and delamanid for the treatment of patients with drug-resistant tuberculosis in Armenia, India, and South Africa: a retrospective cohort study

Gabriella Ferlazzo, Erika Mohr, Chinmay Laxmeshwar, Catherine Hewison, Jennifer Hughes, Sylvie Jonckheere, Naira Khachatryan, Virginia De Avezedo, Lusine Egazaryan, Amir Shroufi, Stobdan Kalon, Helen Cox, Jennifer Furin, Petros Isaakidis



Number of patients at risk	23	21	15	11	8	7	6
Proportion remaining culture positive	100	91 (70–98)	62 (44–81)	48 (27–66)	35 (17–54)	30 (14–49)	23 (7–43)

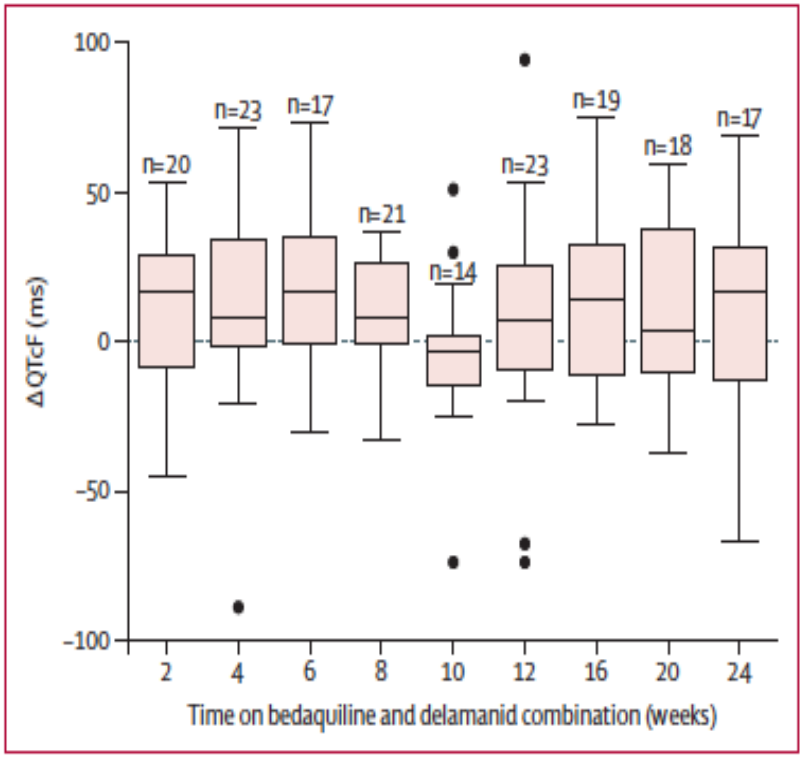


Figure 3: Change in QTcF from baseline

28 patients, durée médiane 12 mois (interquartile range [IQR] 5·9–20·0); 17 (61%) ttt > 6 mois. 13 (46%) succès, 5 (18%) décès, 5 (18%) PDV, 4 (14%) échecs.

(Ferlazzo G et al. Lancet Infect Dis 2018)

Conclusions

- **Anti-Gram +:**
  - **Pas de situation d'impasse thérapeutique en 2019 en France**
  - **Récents progrès = PK**

- **Un avenir pas si sombre pour les anti-BGN**
  - **Multiples combinaisons BL-IBL nouvelles**
  - **Un pipeline assez riche**
  - **Cephalosporines siderophores …**