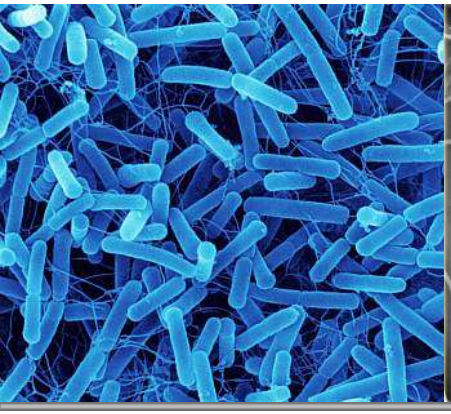
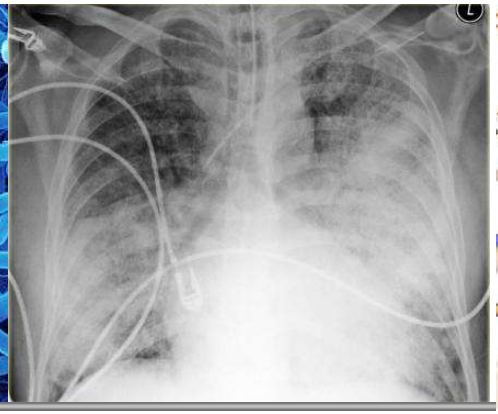
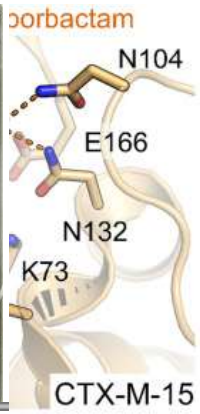
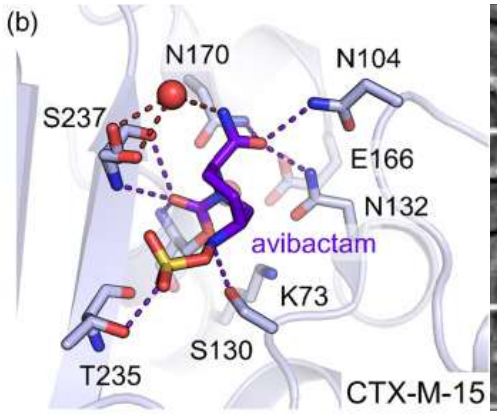
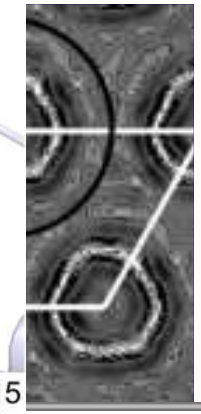
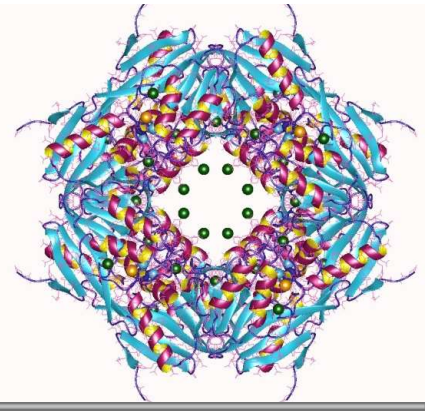
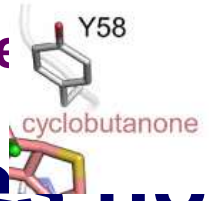
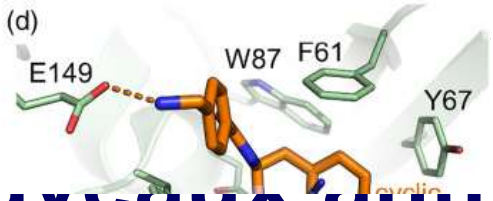






62ème Journée Claude Be embre 2019





Faut-il épargner les nouveaux antibiotiques?

François Barbier, MD PhD

Praticien hospitalier

Médecine Intensive & Réanimation - CHR Orléans

francois.barbier@chr-orleans.fr

CHR ORLÉANS

JEUDI 28 NOVEMBRE 2019
UFR Médecine Paris 7 Diderot, site Xavier-Bichat - Paris 18ème

62ème journée Claude-Bernard

Conflits d'intérêt potentiels

MSD

Pfizer

BioMérieux

Groupe de relecture / Recommandations HAS 2019 *« Antibiothérapie des infections à entérobactéries et Pseudomonas aeruginosa chez l'adulte : place des carbapénèmes et de leurs alternatives »*

Nouveaux antibiotiques anti-BGNMR

	Spectre d'activité clinique					
	ESBLE	**EPC KPC**	**EPC OXA-48**	**EPC MβL**	**MDR-*Pa***	**CR-*Ab***
Ceftolozane/tazobactam	++	-	-	-	+++	-
Ceftazidime/avibactam	+++	+++	+++	-	++	+/-
Méropénème/vaborbactam	+++	+++	-	-	+/-	-
Sulopenem	+++	-	-	-	-	-
Céfépime/AAI101	++	+/-	-	+/-	+/-	-
Imipénème/relebactam	+++	+++	+/-	-	++	+/-
Aztreonam/avibactam	+++	+++	+++	+++	+/-	-
Céfidérocol	+++	+++	+++	+++	+++	+++
Plazomicine	+++	+++	+++	+	-	-
Éravacycline	+++	++	++	++	-	+++

Nouveaux antibiotiques anti-BGNMR

	Spectre d'activité clinique					
	ESBLE	EPC KPC	EPC OXA-48	EPC MβL	MDR-*Pa*	CR-*Ab*
Ceftolozane/tazobactam	++	-	-	-	+++	-
Ceftazidime/avibactam	+++	+++	+++	-	++	+/-
Méropénème/vaborbactam	+++	+++	-	-	+/-	-
Sulopenem	+++	-	-	-	-	-
Céfépime/AAI101	++	+/-	-	+/-	+/-	-
Imipénème/relebactam	+++	+++	+/-	-	++	+/-
Aztreonam/avibactam	+++	+++	+++	+++	+/-	-
Céfidérocol	+++	+++	+++	+++	+++	+++
Plazomicine	+++	+++	+++	+	-	-
Éravacycline	+++	++	++	++	-	+++

Ceftolozane-tazobactam

Ceftolozane vs *Pseudomonas aeruginosa*
Souches sauvages : CMI CTZ < CAZ
Stabilité / céphalosporinase AmpC, efflux et imperméabilité (OprD)

Entérobactéries (sauvages) : CMI_{90} ≤ 0,125 mg/l

Tazobactam (inhibiteur de β-lactamases de classe A) : extension du spectre sur certaines EBLSE sans hyper-expression d'AmpC

Ceftazidime-avibactam

Ceftazidime : excellente activité sur souches sauvages de *P. aeruginosa* et entérobactéries

Avibactam : inhibiteur des β-lactamases de classes A (BLSE, carbapénémases de type KPC), C (AmpC hyperproduite) et certaines D (OXA)

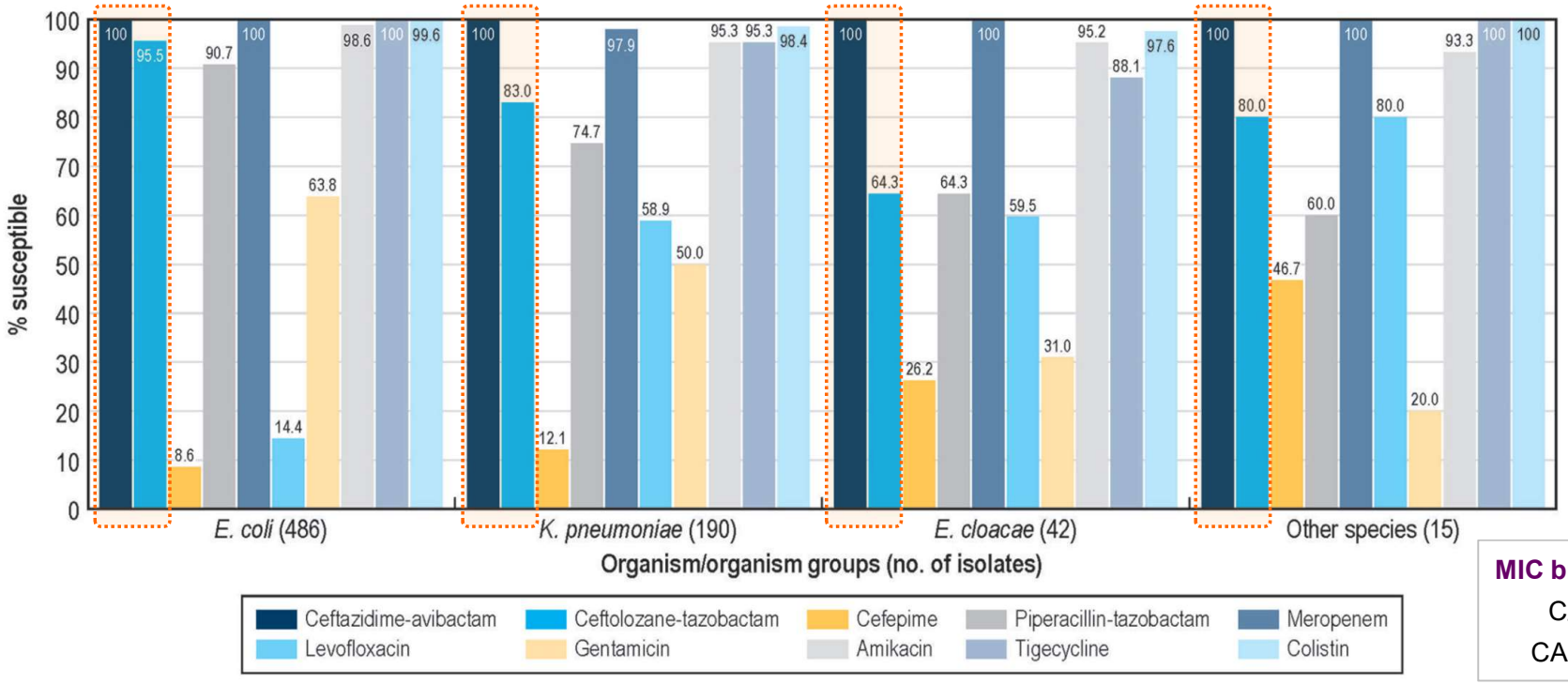
Pas d'inhibition des carbapénémases de classe B (métallo-β-lactamases type NDM, VIM, IMP)

Peu ou pas d'activité sur Gram + (sauf CTZ vs certains streptocoques), *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, anaérobies (sauf C/TZ vs *Bacteroides fragilis*, *Propionibacterium* spp, *Fusobacterium* spp & CAZ/AVI vs *Fusobacterium* spp, *Peptostreptococcus* spp, *Prevotella* spp)

Comparative Activities of Ceftazidime-Avibactam and Ceftolozane-Tazobactam against *Enterobacteriaceae* Isolates Producing Extended-Spectrum β-Lactamases from U.S. Hospitals

July 2019 Volume 63 Issue 7 e00160-19

Mariana Castanheira,[a] Timothy B. Doyle,[a] Rodrigo E. Mendes,[a] Helio S. Sader[a]



MIC breakpoints (CLSI)

C/TZ ≤2/4 mg/L

CAZ/AVI ≤8/4mg/L

Ceftazidime-avibactam et cetolozane-tazobactam sont indiqués dans le traitement des infections suivantes chez l'adulte :

✓ Infections intra-abdominales compliquées (en association avec le métronidazole)

✓ Infections urinaires compliquées, dont pyélonéphrites aiguës

✓ Pneumonies nosocomiales, dont PAVM

\+ Infections à BGN multi-résistants avec options thérapeutiques limitées (ceftazidime-avibactam)

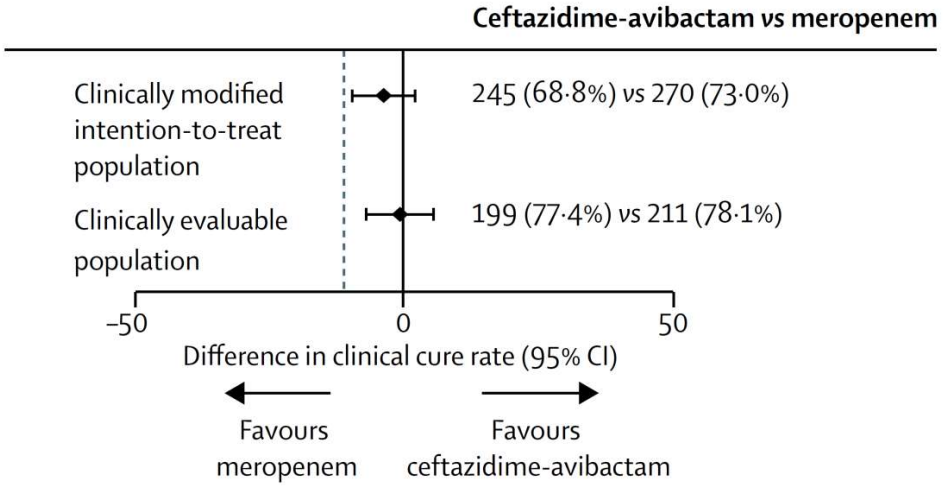
Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial

Lancet Infect Dis 2018; 18: 285–95

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

RCT international, en aveugle, VAP (~35%) et vHAP (~65%)

Ceftazidime/avibactam (2000 mg / 500 mg x 3/24h) vs méropénème (1000 mg x 3/24h)



Clinical cure rates at ToC visit

Guérison clinique (TOC) chez les patients avec infection à BGN C3G-R :

80,6% (CAZ/AVI) versus 78,0% (méropénème)

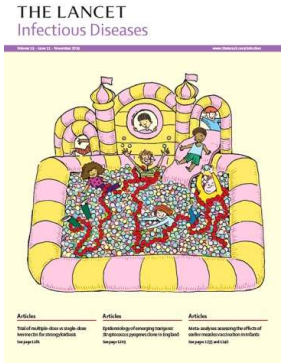
Différence 2,5% (IC 95% -16,4% à 20,7%)

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

Lancet Infect Dis 2019

Published **Online**
September 25, 2019



RCT international, non-infériorité, 726 patients ventilés avec **pneumonie nosocomiale (VAP ou vHAP)**

CTZ 2/1 gr x 3/24h versus méropénème 1 gr/8h

	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)

Mortalité à J28 :
24,0% (C/TZ) vs 25,3% (MER),
différence 1,1% (-5,1% ; 7,4%)

Guérison clinique, par pathogène (TOC, mITT)

REPROVE (HAP/VAP) - NCT01808092

CAZ/AVI versus méropénème

Torres et al. *Lancet Infect Dis* 2018; 18: 285-295

	Ceftazidime-avibactam (n=405)	Meropenem (n=403)
All-cause mortality	38 (9%)	30 (7%)
Deaths due to disease progression	13 (3%)	8 (2%)
Adverse events*		
Any	302 (75%)	299 (74%)
Any serious adverse events§	75 (19%)	54 (13%)
Any leading to discontinuation of study drug		
Any of severe intensity	66 (16%)	
Adverse events in ≥2% of patients*		
Diarrhoea	61 (15%)	62 (15%)
Hypokalaemia	43 (11%)	33 (8%)
Anaemia	25 (6%)	16 (4%)
Constipation	25 (6%)	31 (8%)
Vomiting	23 (6%)	22 (5%)
Alanine aminotransferase increased	16 (4%)	19 (5%)
Aspartate aminotransferase increased	16 (4%)	17 (4%)
Oedema peripheral	17 (4%)	15 (4%)

ASPECT (vHAP/VAP) - NCT02070757

C/TZ versus méropénème

Kollef et al. *Lancet Infect Dis* 2019 (on-line first)

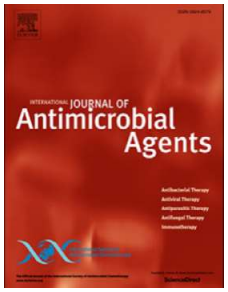
	Ceftolozane–tazobactam group (n=361)	Meropenem group (n=359)
At least one adverse event		
Overall	310 (86%)	299 (83%)
Severe	143 (40%)	136 (38%)
Serious	152 (42%)	129 (36%)
Leading to study drug discontinuation	37 (10%)	42 (12%)
Resulting in death	5 (1%)	4 (1%)
At least one treatment-related adverse event		
Overall	98 (27%)	27 (8%)
Severe	5 (1%)	3 (1%)
Serious	8 (2%)	2 (1%)
Leading to study drug discontinuation	4 (1%)	5 (1%)
Resulting in death	0	0
Most frequent* treatment-related adverse events		
Clostridium difficile colitis	4 (1%)	1 (<1%)
Diarrhoea	4 (1%)	6 (2%)
Liver function test abnormalities†	12 (3%)	5 (1%)
Increased aspartate aminotransferase	3 (1%)	3 (1%)
Increased γ-glutamyl-transferase	3 (1%)	0
Increased alanine aminotransferase	2 (1%)	4 (1%)
Unspecified‡	8 (2%)	2 (1%)

Ceftazidime/avibactam ou ceftolozane/tazobactam *versus* méropénème chez les patients avec pneumonie nosocomiale sévère

(VM à l'inclusion : 43% REPROVE, 100% ASPECT)

⇩

Effets indésirables : fréquences comparables



Clinical cure rate and cost-effectiveness of carbapenem-sparing beta-lactams vs. meropenem for Gram-negative infections: A systematic review, meta-analysis, and cost-effectiveness analysis

IJAA (e-pub 2019)

Chi Phuong Nguyen[a,b], Thuc Nguyen Dan Do[a], Roger Bruggemann[c], Jaap ten Oever[d], Eva Kolwijck[a], Eddy M.M. Adang[e], Heiman F.L. Wertheim[a,*]

Main outcome: incremental cost-effectiveness ratio (threshold: €20,000 per life-year gained [LYG])

Ceftolozane-tazobactam was cost-effective for ESBLE UTI (€13,398 per LYG)

Ceftazidime-avibactam (plus MTZ) was cost-effective for ESBLE IAI (€16,917 per LYG)

Total cost and LYG of meropenem and CSBs in 1000 patients due to ESBL-producing Gram-negative pathogens.

Strategy	Cost (€)	Increment cost (€)	LYG	Increment LYG	ICER
Patients with cIAIs					
Meropenem	3 372 748.02	-	4513.81	-	-
Ceftolozane-tazobactam	4 869 475.89	1 496 727.87	4 567.68	53.87	27 785.74
Ceftazidime-avibactam	5 196 037.46	1 823 289.44	4 621.59	107.78	16 916.77
Patients with cUTIs					
Meropenem	3 184 950.02	-	4 529.24	-	-
Temocillin	3 186 669.88	1 719.86	4 540.16	10.91	157.58
Ceftolozane-tazobactam	4 740 363.65	1 555 413.63	4 645.33	116.09	13 398.34
Ceftazidime-avibactam	4 954 404.11	1 769 454.09	4 320.75	-208.49	Dominated

HAS
HAUTE AUTORITÉ DE SANTÉ

SYNTHÈSE DE LA RECOMMANDATION DE BONNE PRATIQUE

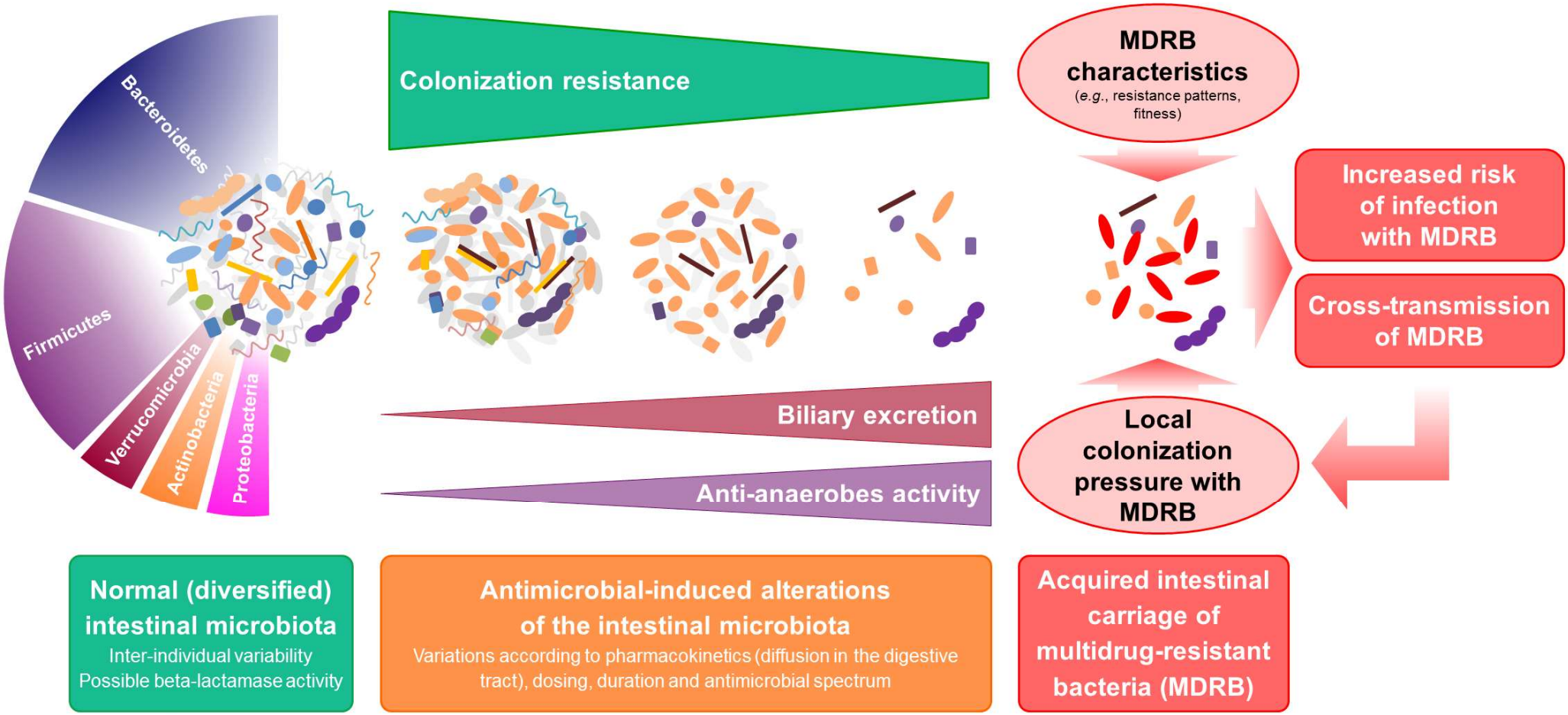
Mai 2019

Antibiothérapie des infections à entérobactéries et à *Pseudomonas aeruginosa* chez l'adulte : place des carbapénèmes et de leurs alternatives

Tableau 2. Proposition de classement des molécules antibiotiques pouvant être utilisées en désescalade thérapeutique des infections à entérobactérie résistante aux C3G, en fonction de leur impact potentiel sur le microbiote digestif

Impact écologique potentiellement croissant	Molécules
Rang 1	Aminosides (mais risque de toxicité)*
Rang 2	Témocilline, cotrimoxazole**
Rang 3	Céfoxitine, amoxicilline-clavulanate
Rang 4	Pipéracilline-tazobactam, céfépime, fluoroquinolones**
Rang 5	Carbapénèmes (incluant l'ertapénème), ceftazidime-avibactam, ceftolozane-tazobactam

Antibiothérapie et résistance à la colonisation intestinale



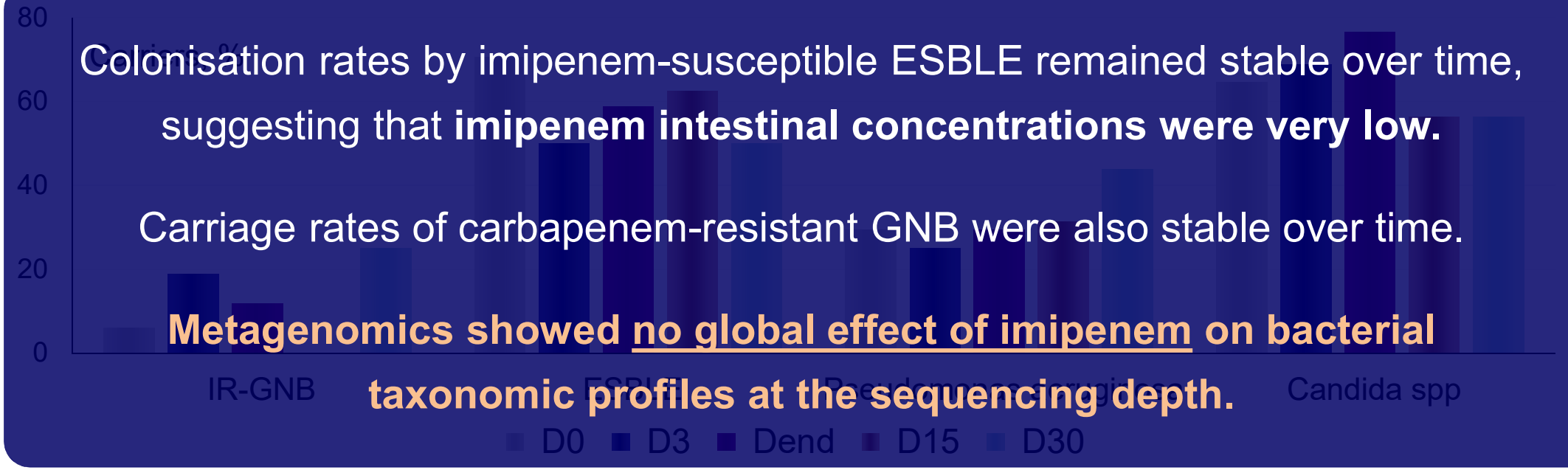
Woerther, Ruppé, Barbier. *Int J Antimicrob Agents* 2018; 52: 762-770

Unexpected persistence of extended-spectrum β-lactamase-producing Enterobacteriaceae in the faecal microbiota of hospitalised patients treated with imipenem

N. Grall [a,b,c,*,1], V. Lazarevic [d,1], N. Gaïa [d], C. Couffignal [a,b,e], C. Laouénan [a,b,e], E. Ilic-Habensus [f], I. Wieder [c], P. Plesiat [g], C. Angebault [h,i], M.E. Bougnoux [h,i], L. Armand-Lefevre [a,b,c], A. Andremont [a,b,c], X. Duval [a,b,f], J. Schrenzel [d,j]

International Journal of Antimicrobial Agents 50 (2017) 81–87

17 patients traités par imipénème, dont 12 porteurs d'EBLSE (CMI d'imipénème, 0,09-1 mg/l)



Colonisation rates by imipenem-susceptible ESBLE remained stable over time, suggesting that **imipenem intestinal concentrations were very low.**

Carriage rates of carbapenem-resistant GNB were also stable over time.

Metagenomics showed no global effect of imipenem on bacterial taxonomic profiles at the sequencing depth.

Antibiotics with activity against intestinal anaerobes and the hazard of acquired colonization with ceftriaxone-resistant Gram-negative pathogens in ICU patients: a propensity score-based analysis

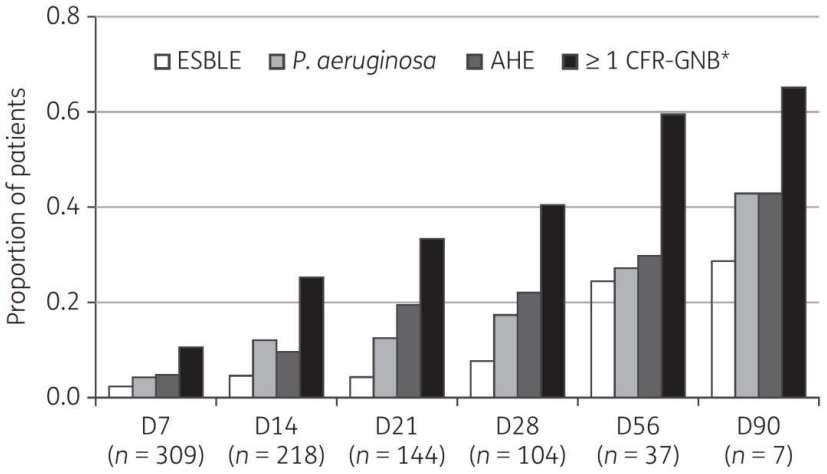
Maxime Boutrot[1], Khalid Azougagh[1], Jérôme Guinard[2], Thierry Boulain[3] and François Barbier[3]*

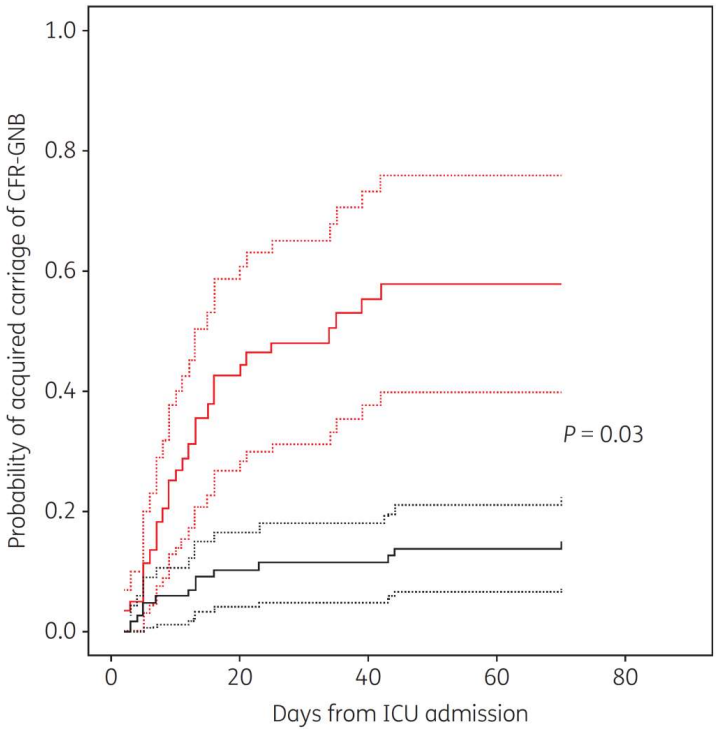
J Antimicrob Chemother
doi:10.1093/jac/dkz279

Exposition aux antibiotiques anti-anaérobies hors carbapénèmes (AAC, PTZ, métronidazole) : FdR indépendant d'acquisition d'un portage intestinal de BGN C3G-R (aHR 3,92, IC 95% 1,12-13,7)

Autres classes (dont IMI/MER et C3G) : pas d'impact indépendant

Portage intestinal de BGN C3G-R, %
(n = 309)

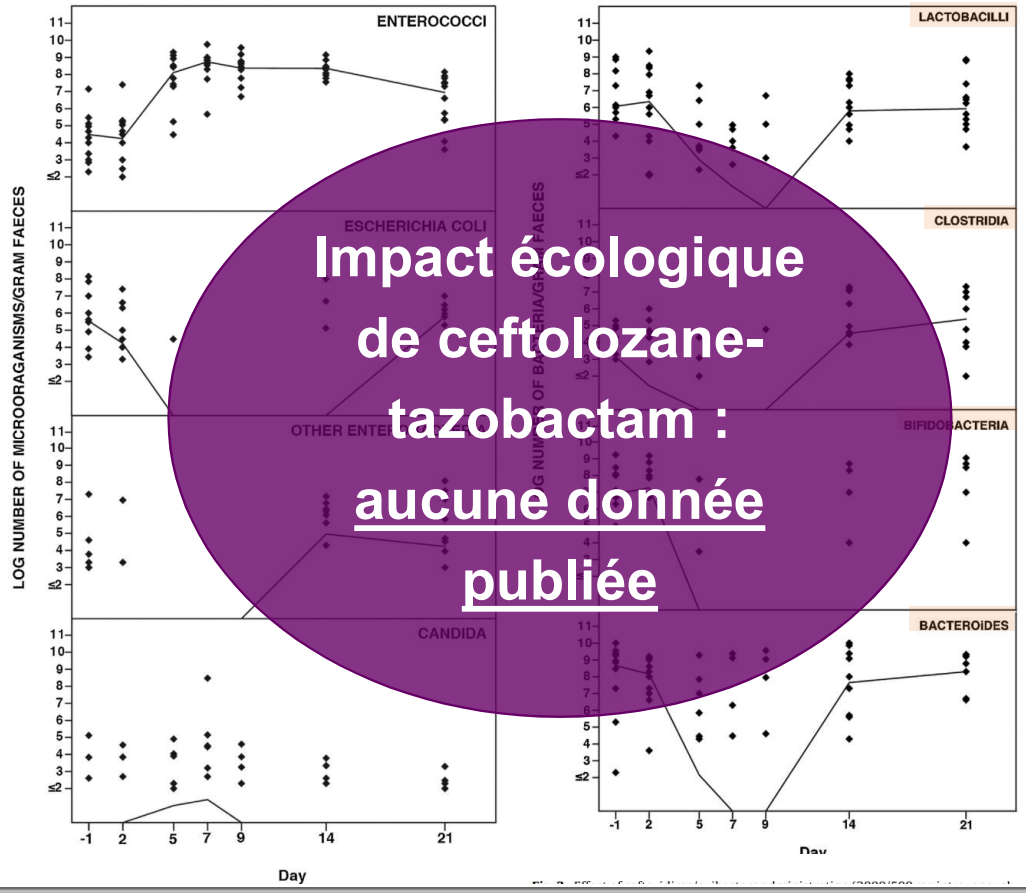




Ecological effect of ceftazidime/avibactam on the normal human intestinal microbiota

Mamun-Ur Rashid [a], Staffan Rosenborg [b,c], Georgios Panagiotidis [b,c], Karin Söderberg Löfdal [b,c], Andrej Weintraub [a], Carl Erik Nord [a,*]

International Journal of Antimicrobial Agents 46 (2015) 60–65



Impact écologique de ceftolozane-tazobactam : aucune donnée publiée

- 12 volontaires sains
- Ceftazidime 2 gr + avibactam 500 mg/8h x 7 jours
- Cultures (pas de BM)
- **Concentrations dans les selles :**
  - ✓ Ceftazidime 0-468 mg/kg
  - ✓ Avibactam 0-146 mg/kg
- ***Clostridium difficile* toxinogène :** acquisition sous traitement chez 5/12 volontaires

HAUTE AUTORITÉ DE SANTÉ

SYNTHÈSE DE LA RECOMMANDATION DE BONNE PRATIQUE

Mai 2019

Antibiothérapie des infections à entérobactéries

Antibiothérapie des infections à entérobactéries et à *Pseudomonas aeruginosa* chez l'adulte : place des carbapénèmes et de leurs alternatives

Associations ceftazidime-avibactam et ceftolozane/tazobactam

Il est recommandé de ne pas utiliser l'association ceftazidime/avibactam, une des rares molécules actuelles actives sur certaines entérobactéries productrices de carbapénémases, pour le traitement des infections à *P. aeruginosa* (AE).

En l'absence de donnée écologique comparative et compte tenu de la nécessité de préserver son efficacité, il est recommandé de ne pas utiliser le ceftolozane-tazobactam dans une stratégie d'épargne des carbapénèmes. Son utilisation peut être envisagée après avis spécialisé en antibiothérapie, sur des souches avec un profil de résistance particulier (souches sensibles uniquement aux carbapénèmes et au cefto-lozane-tazobactam) (AE).

Spanish nationwide survey on *Pseudomonas aeruginosa* antimicrobial resistance mechanisms and epidemiology

Ester del Barrio-Tofiño[1], Laura Zamorano[1], Sara Cortes-Lara[1], Carla López-Causapé[1], Irina Sánchez-Diener[1], Gabriel Cabot[1], Germán Bou[2], Luis Martínez-Martínez[3] and Antonio Oliver[1]*
on behalf of the GEMARA-SEIMC/REIPI *Pseudomonas* study Group†

J Antimicrob Chemother 2019;74:1825-1835

Résultats similaires sur autres collections (Europe, US, Asie)

Sensibilité *in vitro* au ceftolozane-tazobactam chez *P. aeruginosa*

(breakpoint EUCAST : CMI ≤ 4 mg/l)

Souches ceftazidime-R : 60%-80%

Souches méropénème-R : 60%-80%

Souches MDR/XDR : 40%-80%

Pfaller et al. *J Antimicrob Chemother* 2017; 72: 1386-1395

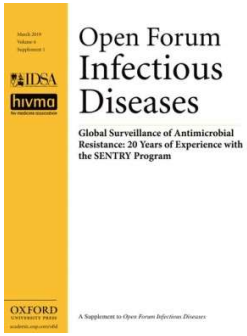
Castanheira et al. *Antimicrob Agents Chemother* 2018; 62: e02125-17

Pfaller et al. *Int J Antimicrob Agents* 2018; 51: 181-189

Ceftolozane-Tazobactam for the Treatment of Multidrug-Resistant *Pseudomonas aeruginosa* Infections: A Multicenter Study

Open Forum Infect Dis 2018;5:ofy280

Jason C. Gallagher,[1] Michael J. Satlin,[2] Abdulrahman Elabor,[3] Nidhi Saraiya,[4] Erin K. McCreary,[5] Esther Molnar,[3] Claudine El-Beyrouty,[6] Bruce M. Jones,[7] Deepali Dixit,[8] Emily L. Heil,[9] Kimberly C. Claeys,[9] Jon Hiles,[10] Nikunj M. Vyas,[11] Christopher M. Bland,[12] Jin Suh,[13] Kenneth Biason,[14] Dorothy McCoy,[14] Madeline A. King,[15] Lynette Richards,[16] Nicole Harrington,[17] Yi Guo,[18] Saira Chaudhry,[8] Xiaoning Lu,[19] and Daohai Yu[19]



20 centres (USA), 205 patients avec infection à *P. aeruginosa* multi-résistant

(ICU 51%, HAP/VAP 59%)

Mortalité hospitalière : 19% (HAP/VAP, 26%)

Guérison clinique : 74% (66%)

Succès microbiologique : 71% (57%)

Drug tested, %Susceptible (n/N Tested)

AMK	ATM	FEP/CAZ	GEN	MEM/IPM	TZP	TOB
78.6% (125 of 159)	7.2% (10 of 139)	14.4% (21 of 177)	57.7% (94 of 163)	3.4% (6 of 179)	5.8% (10 of 173)	74.3% (104 of 140)
Ceftolozane-tazobactam (n/N tested, % susceptible)					125 of 139 (89.9%)	

Table 4. Multivariable Analysis of Factors Associated With Clinical Outcomes

Effect	Point Estimate of Odds Ratio (OR)	95% Confidence Interval for OR
Mortality		
Ceftolozane-tazobactam started >4 days after culture	5.55	2.14–14.40
Age ≥60	0.20	0.07–0.57
Charlson Comorbidity Index (each 1 point)	1.24	1.01–1.52
Vasopressor use	5.68	2.15–14.98
APACHE II score (each 1 point)	1.14	1.08–1.22
Clinical success		
Ceftolozane-tazobactam started ≤4 days after culture	2.93	1.40–6.10
Vasopressor use	0.16	0.070–0.344
APACHE II score (each 1 point)	0.95	0.91–0.99

SURVEILLANCE DES INFECTIONS NOSOCOMIALES EN RÉANIMATION ADULTE

Réseau REA-Raisin, France. Résultats 2017

Santé publique France

Publication : avril 2019

BGN responsables d'IN en réanimation : 2 problématiques majeures

Entérobactéries
(n = 5246)

Pseudomonas aeruginosa
(n = 2089)

Prévalence des résistances

C3G : 28,3%
dont BLSE : 17,8%
dont AmpC déréprimée ≥ 10%

Pipéracilline-tazobactam : 28,0%
Ceftazidime : 21,3%
Carbapénèmes : 19,6%

Screening for Intestinal Carriage of Extended-spectrum Beta-lactamase–producing Enterobacteriaceae in Critically Ill Patients: Expected Benefits and Evidence-based Controversies

Jean-Ralph Zahar,[1,2] Stijn Blot,[3,4] Patrice Nordmann,[5,6,7] Romain Martischang,[8] Jean-François Timsit,[2,9] Stephan Harbarth,[8] and François Barbier[10]

Screening for Intestinal Carriage of Extended-spectrum Beta-lactamase–producing Enterobacteriaceae in Critically Ill Patients: Expected Benefits a Evidence-based Controversies

Jean-Ralph Zahar,[1,2] Stijn Blot,[3,4] Patrice Nordmann,[5,6,7] Romain Martischang,[8] Jean-François Timsit,[2,9] Stephan Harbarth,[8] and François Barbier[10]

Clinical Infectious Diseases® 2019;68(12):2125–30

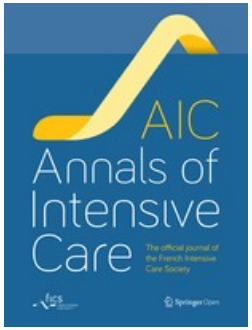
Clinical Infectious Diseases

- **Prévalence du portage d'EBLSE en réanimation, France : 5 à 25%** (importation > acquisition)
- **Infection acquise en réanimation à EBLSE chez 15 à 25% des patients colonisés**
- **Portage intestinal d'EBLSE (dépistage qualitatif) et risque d'IN à EBLSE :**
  - ✓ VPN excellente (>90%) si écouvillon rectal < 5-7 jours
  - ✓ VPP médiocre (15-45%)
- **Surconsommation probabiliste de carbapénèmes chez les patients porteurs :** facteur de risque d'**IN à BGN non-fermentants résistants aux carbapénèmes (dont *P. aeruginosa* +++)**

Planquette et al. *Am J Respir Crit Care Med* 2013; 188: 69-76
Luyt et al. Antimicrob Agents Chemother 2014; 58: 1372-80
Barbier et al. *J Antimicrob Chemother* 2016; 71:1088-97

Frequency, associated factors and outcome of multi-drug-resistant intensive care unit-acquired pneumonia among patients colonized with extended-spectrum β-lactamase-producing Enterobacteriaceae

Razazi *et al. Ann. Intensive Care (2017) 7:61*



Étude monocentrique, 2009-2015
6303 patients admis

843 porteurs d'EBLSE (13%)

111 porteurs d'ESBLE avec pneumonie acquise en réanimation (13%)

48 patients avec pneumonie à EBLSE (43%)

Co-infection avec BGN-NF
Carba-R : n = 6 (12%)

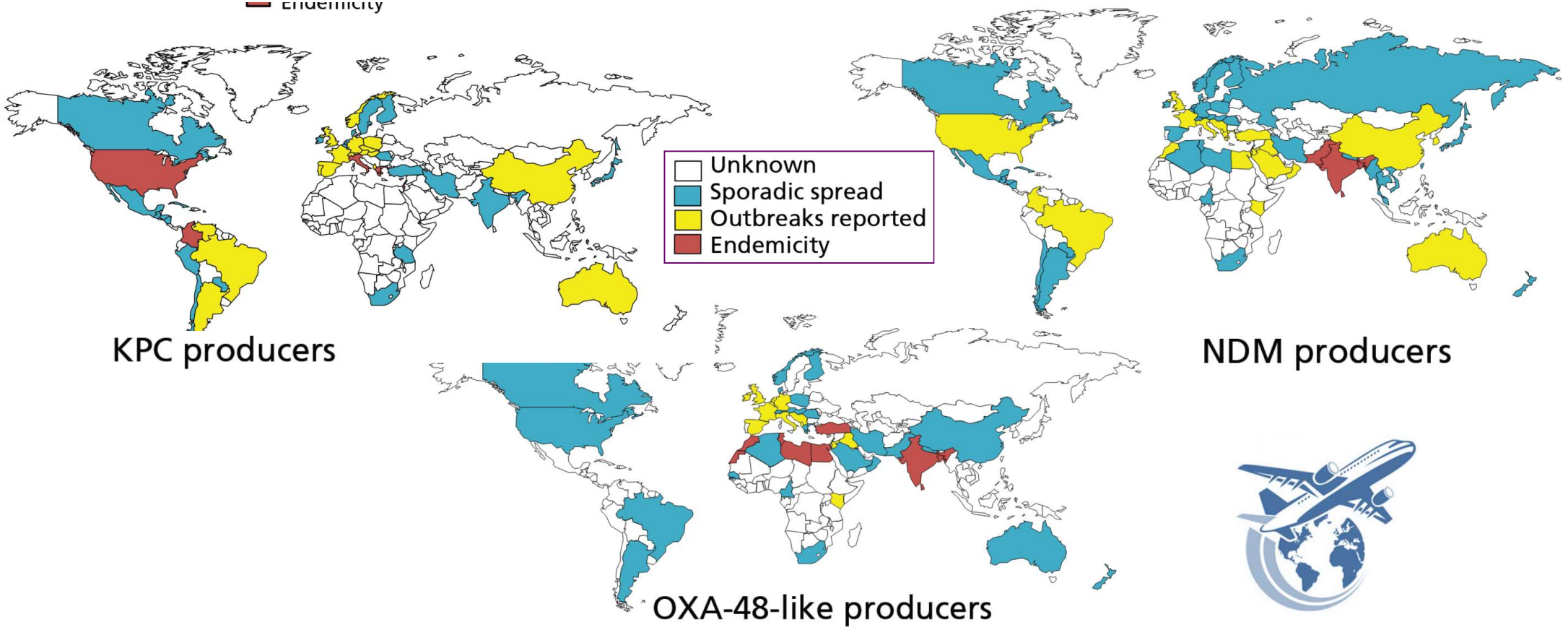
63 patients avec pneumonie non-EBLSE (57%)

BGN-NF : n = 37 (59%)
dont Carba-R : n = 17 (27%)

Carbapenemase-Producing Organisms: A Global Scourge

Robert A. Bonomo,[1] Eileen M. Burd,[2] John Conly,[3] Brandi M. Limbago,[4] Laurent Poirel,[5] Julie A. Segre,[6] and Lars F. Westblade[7]

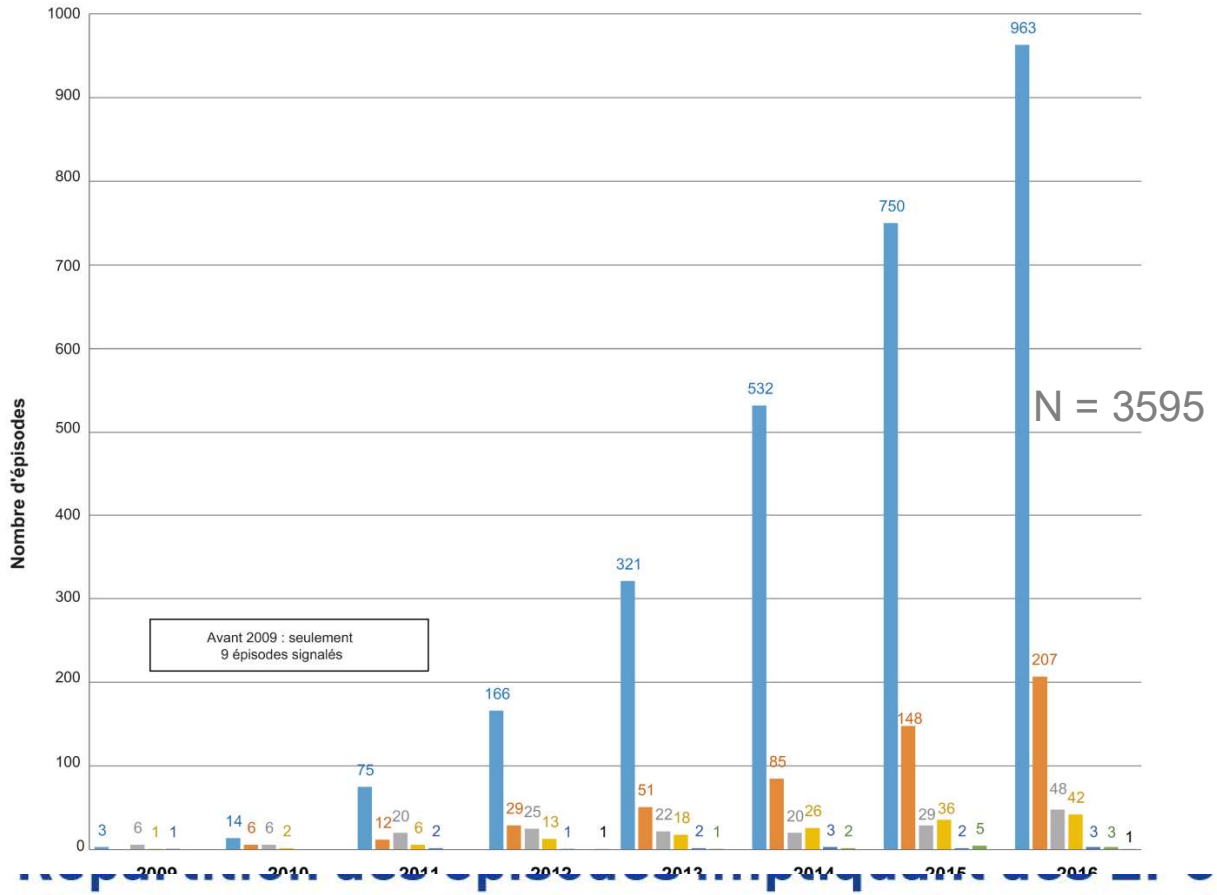
Clinical Infectious Diseases® 2018;66(8):1290–7



Surveillance des EPC en France : bilan 2004 - 2016

Santé publique France

Épisodes sans lien avec un séjour à l'étranger
(54 % des épisodes depuis 2004)
⇩
OXA-48 dans 82% des cas
(diffusion autochtone)



mécanismes de résistance impliqués et l'année

Treatment of Infections Caused by Extended-Spectrum-Beta-Lactamase-, AmpC-, and Carbapenemase-Producing *Enterobacteriaceae*

Jesús Rodríguez-Baño,[a] Belén Gutiérrez-Gutiérrez,[a] Isabel Machuca,[b] Alvaro Pascual[a]

April 2018 Volume 31 Issue 2

TABLE 3 Summary of recommended regimens for treatment of infections caused by carbapenem-resistant *Enterobacteriaceae*[a]

Risk level, therapy type, and isolate susceptibility	Drugs
High risk,[b] combination therapy	
Susceptible to a β-lactam (use according to susceptibility)	Backbone: ceftazidime-avibactam (preferred) or meropenem-vaborbactam; alternatively, meropenem (if MIC is ≤8 mg/liter) or ceftazidime or aztreonam Accompanying drug (no data available about the need for combination therapy if ceftazidime-avibactam or meropenem-vaborbactam is used as the backbone): colistin, tigecycline, aminoglycoside, or fosfomycin (if isolate is intermediate to the backbone drug, consider using 2 of these)
Resistant to all β-lactams (including isolates with meropenem MICs of >8 mg/liter), susceptible to at least 2 drugs, including colistin	Backbone: colistin Accompanying drug: tigecycline, aminoglycoside (high risk of nephrotoxicity), or fosfomycin
Resistant to all β-lactams and colistin, susceptible to at least 2 drugs	Backbone: tigecycline or aminoglycoside Accompanying drug: tigecycline or aminoglycoside, fosfomycin
Pandrug-resistant or susceptible to only one drug	Meropenem plus ertapenem or ceftazidime-avibactam plus aztreonam; add any active drug; consider active investigational drugs if available; consider *in vitro* testing of combinations for synergy
Low risk,[c] monotherapy	

Ceftazidime-Avibactam Is Superior to Other Treatment Regimens against Carbapenem-Resistant *Klebsiella pneumoniae* Bacteremia

August 2017 Volume 61 Issue 8 e00883-17

AAC Journals.ASM.org

Ryan K. Shields,[a,c] M. Hong Nguyen,[a,c] Liang Chen,[d] Ellen G. Press,[a] Brian A. Potoski,[a,c,e] Rachel V. Marini,[c] Yohei Doi,[a,c] Barry N. Kreiswirth,[d] Cornelius J. Clancy[a,b,f]

109 patients avec bactériémie à *K. pneumoniae* KPC

(ICU 50%, IIA 46%, bactériémie primitive 26%)

CAZ/AVI versus autres options

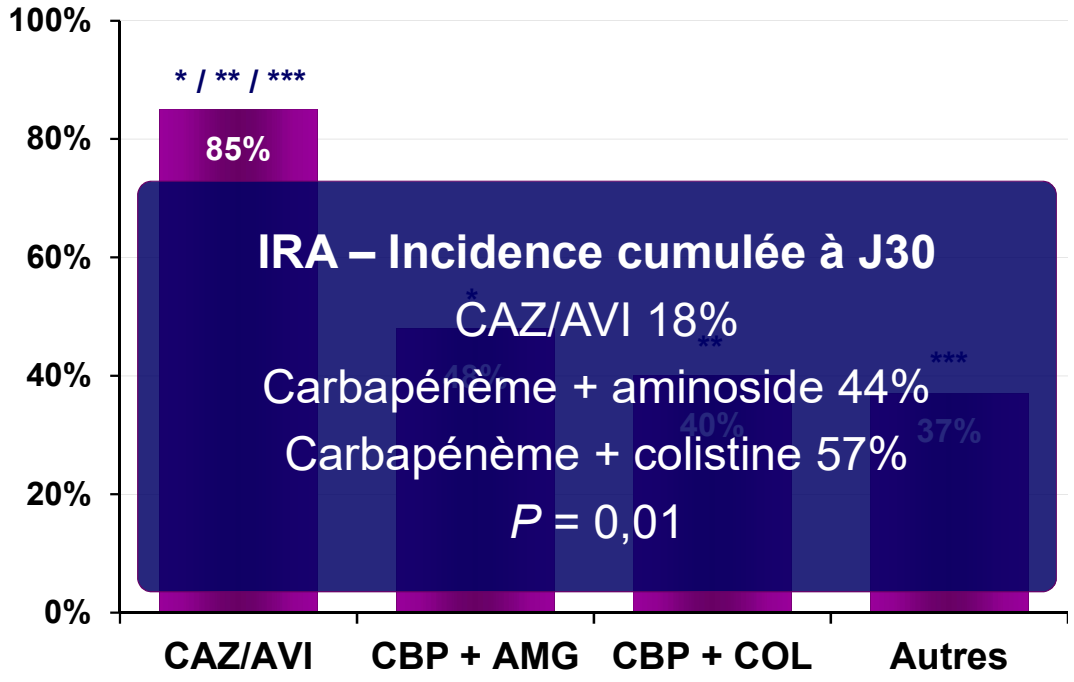
(comorbidités, sévérité, source : NS)

Succès clinique à J30, analyse multivariée

Bactériémie primitive : aHR 4,5 (1,5 - 13,2), *P* = 0,006

CAZ/AVI : aHR 8,6 (1,6 - 46,4), *P* = 0,01

Succès clinique à J30 (*//*** *P* <0,05)**



Effectiveness of ceftazidime/avibactam as salvage therapy for treatment of infections due to OXA-48 carbapenemase-producing Enterobacteriaceae

Adrian Sousa[1,2], María Teresa Pérez-Rodríguez[1,2]*, Adriana Soto[1], Lorena Rodríguez[1], Antonio Pérez-Landeiro[3], Lucia Martínez-Lamas[4], Andrés Nodar[1,2] and Manuel Crespo[1,2]

J Antimicrob Chemother 2018; **73**: 3170–3175

Table 2. Antimicrobial susceptibility of isolates ($n = 57$) from patients treated with ceftazidime/avibactam

Antibiotic	Susceptible isolates, *n* (%)
Colistin	43 (75)
Imipenem	2 (3)
Imipenem MIC <8 mg/L	27 (47)
Meropenem	1 (2)
Fosfomycin	10 (17)
Tigecycline	7 (12)
Amikacin	3 (5)
Ceftazidime/avibactam	57 (100)

- 57 patients avec infection à EPC OXA-48
- IAI 28%, HAP 26%, UTI 25%
- Sepsis/choc septique 51%
- Monothérapie 81%
- **Succès clinique 77%**
- **Mortalité (J14) 14%**

Ceftazidime-Avibactam and Aztreonam, an Interesting Strategy To Overcome β-Lactam Resistance Conferred by Metallo-β-Lactamases in *Enterobacteriaceae* and *Pseudomonas aeruginosa*

September 2017 Volume 61 Issue 9 e01008-17 Antimicrobial Agents and Chemotherapy

Benjamin Davido,[a] Lesly Fellous,[b] Christine Lawrence,[c,d] Virginie Maxime,[e]
Martin Rottman,[d,f] Aurélien Dinh[a]

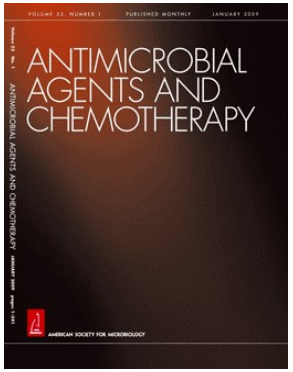
Ceftazidime/avibactam

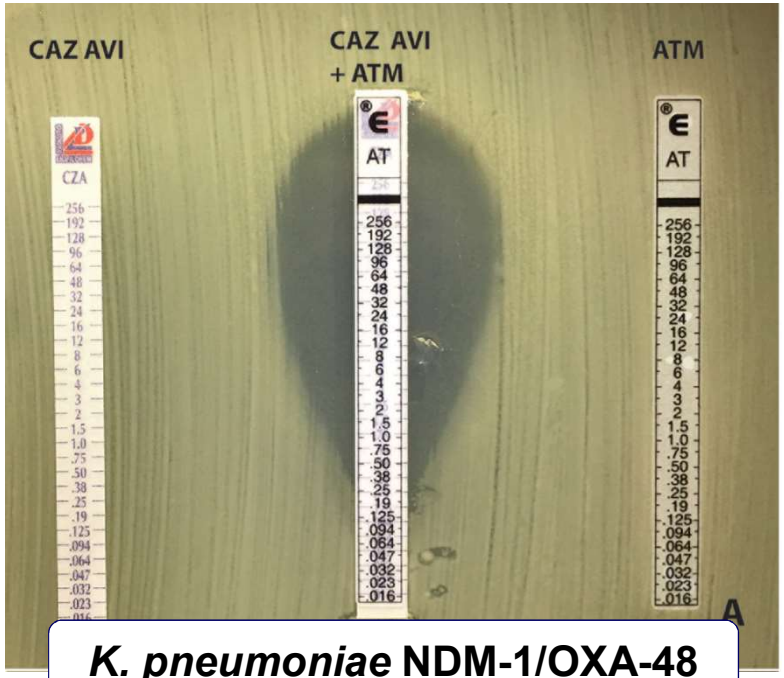
2000 mg / 500 mg x 3/24h

+

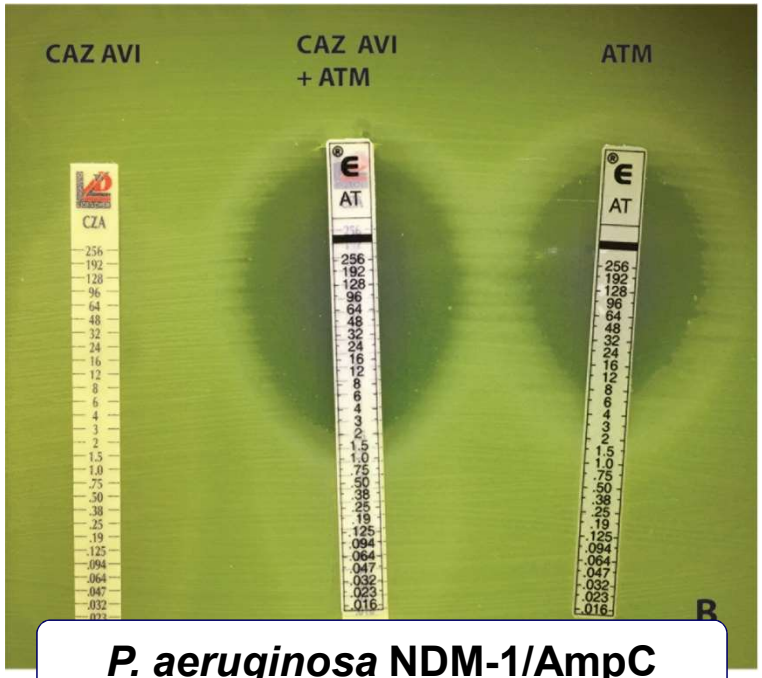
Aztréonam

2 gr x 2/24h





***K. pneumoniae* NDM-1/OXA-48**

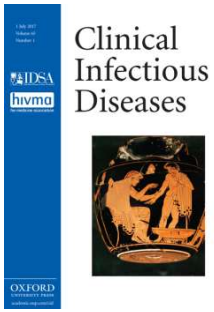


***P. aeruginosa* NDM-1/AmpC**

Ceftolozane-Tazobactam for the Treatment of Multidrug-Resistant *Pseudomonas aeruginosa* Infections: Clinical Effectiveness and Evolution of Resistance

Clinical Infectious Diseases® 2017;65(1):110–20

Ghady Haidar,[1] Nathan J. Philips,[2] Ryan K. Shields,[1,3,4] Daniel Snyder,[2] Shaoji Cheng,[4] Brian A. Potoski,[1,3,5] Yohei Doi,[1] Binghua Hao,[4] Ellen G. Press,[1] Vaughn S. Cooper,[2] Cornelius J. Clancy,[1,4,6a] and M. Hong Nguyen[1,3,4a]



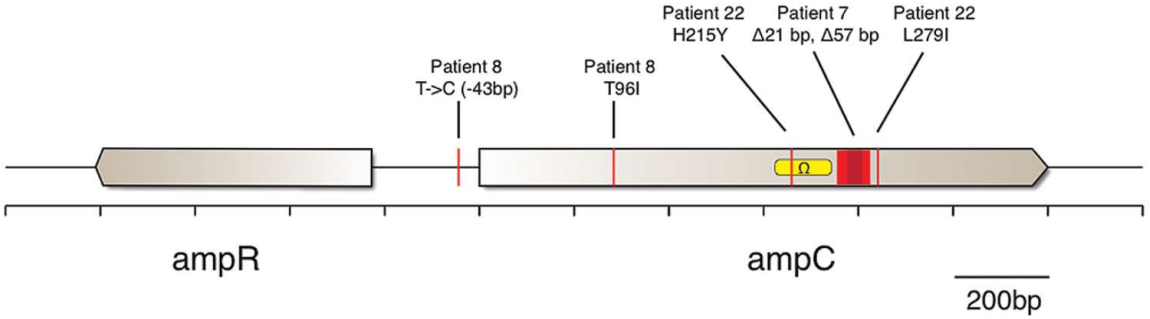
21 patients traités pour infection à *P. aeruginosa* MDR

(pneumonie 84%, durée médiane de traitement 14 [3-52] jours)

Émergence de mutants résistants sous traitement : **3/21 patients (14%)**

Principaux mécanismes de résistance acquise (WGS & qRT-PCR) :

mutation et hyper-expression de la céphalosporinase AmpC

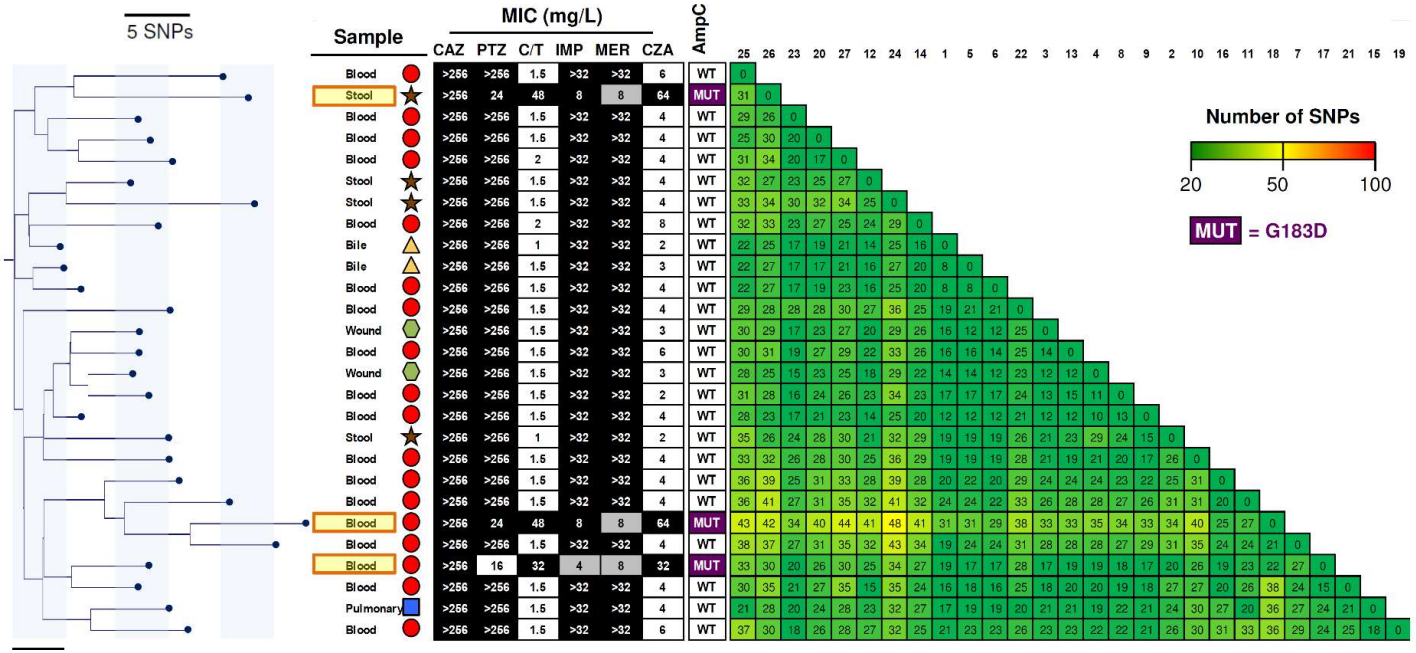


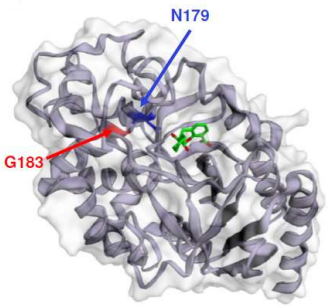
A 2.5-years within-patient evolution of a *Pseudomonas aeruginosa* with *in vivo* acquisition of ceftolozane-tazobactam and ceftazidime-avibactam resistance upon treatment

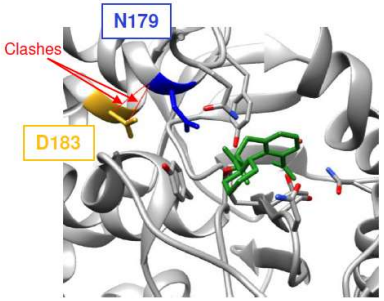
Thibaud Boulant, Agnès B. Jousset, Rémy A. Bonnin, Aurélie Barrail-Tran, Adrien Borgel, Saoussen Oueslati, Thierry Naas, and Laurent Dortet

Antimicrob Agents Chemother - Accepted manuscript posted online 21 October 2019

« Our results suggest resistance to ceftolozane-tazobactam in *P. aeruginosa* might occur *in vivo* upon treatment through amino-acid substitution in the intrinsic AmpC leading to ceftolozane-tazobactam and ceftazidime-avibactam resistance accompanied by re-sensitization to piperacillin-tazobactam and carbapenems.»







Rapid Molecular Diagnostics to Inform Empiric Use of Ceftazidime/Avibactam and Ceftolozane/Tazobactam Against *Pseudomonas aeruginosa*: PRIMERS IV

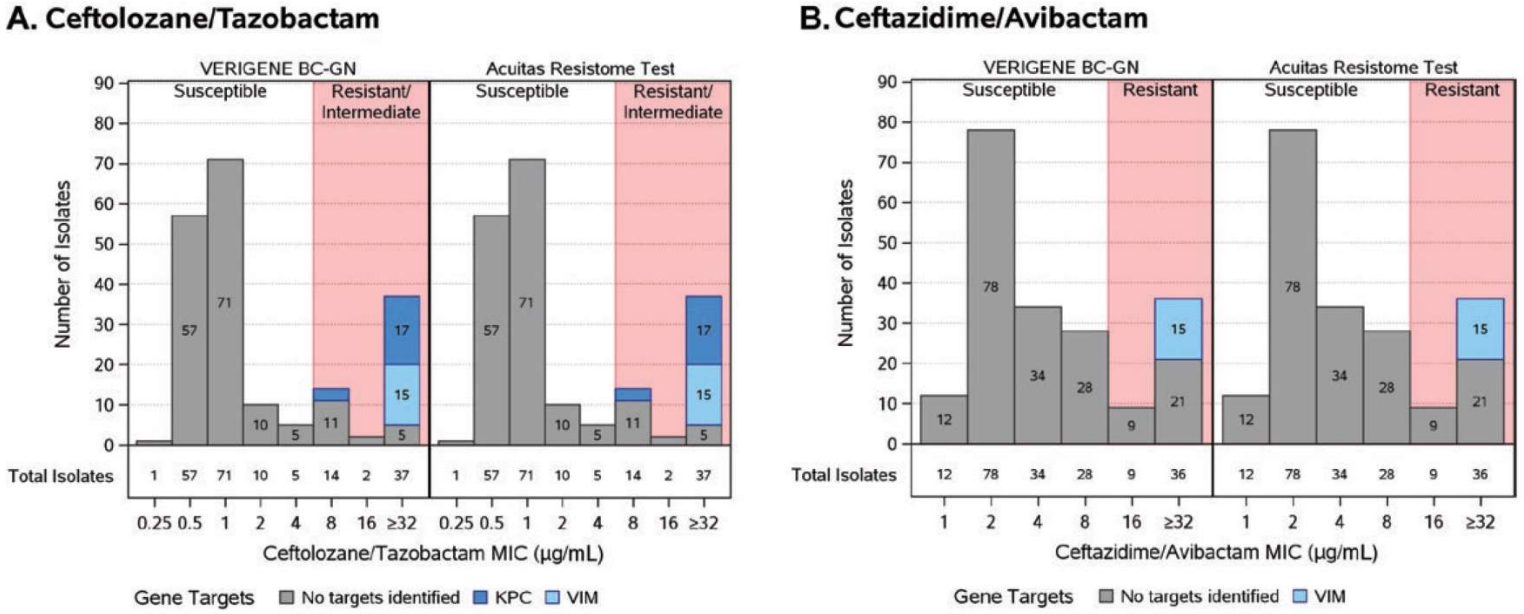
Scott R. Evans,[1] Thuy Tien T. Tran,[1] Andrea M. Hujer,[2,3] Carol B. Hill,[4] Kristine M. Hujer,[2,3] Jose R. Mediavilla,[5] Claudia Manca,[5] T. Nicholas Domitrovic,[2,3] Federico Perez,[2,3] Michael Farmer,[6] Kelsey M. Pitzer,[6] Brigid M. Wilson,[3] Barry N. Kreiswirth,[5] Robin Patel,[7] Michael R. Jacobs,[8] Liang Chen,[5] Vance G. Fowler Jr,[4,9] Henry F. Chambers,[10] and Robert A. Bonomo[2,3,11,12]; for the Antibacterial Resistance Leadership Group (ARLG)

Rapid Molecular Diagnostics to Inform Empiric U
Ceftazidime/Avibactam and Ceftolozane/Tazobactam
Against *Pseudomonas aeruginosa*: PRIMERS IV

Scott R. Evans,[1] Thuy Tien T. Tran,[1] Andrea M. Hujer,[2,3] Carol B. Hill,[4] Kristine M. Hujer,[2,3] Jose R. Mediavilla,[5] Claudia Manca,[5] T. Nicholas Domitrovic,[2,3] Federico Perez,[2,3] Michael Farmer,[6] Kelsey M. Pitzer,[6] Brigid M. Wilson,[3] Barry N. Kreiswirth,[5] Robin Patel,[7] Michael R. Jacobs,[8] Liang Chen,[5] Vance G. Fowler Jr,[4,9] Henry F. Chambers,[10] and Robert A. Bonomo[2,3,11,12]; for the Antibacterial Resistance Leadership Group (ARLG)

Clinical Infectious Diseases® 2019;68(11):1823–30

Results. We found that the studied RMD platforms were able to correctly identify BL-BLI susceptibility (susceptibility sensitivity, 100%; 95% confidence interval [CI], 97%, 100%) for both BLs-BLIs. However, their ability to detect resistance to these BLs-BLIs was lower (resistance sensitivity, 66%; 95% CI, 52%, 78% for TOL/TAZO and 33%; 95% CI, 20%, 49% for CZA).



J Antimicrob Chemother
doi:10.1093/jac/dkz149

ESBLs and resistance to ceftazidime/avibactam and ceftolozane/tazobactam combinations in *Escherichia coli* and *Pseudomonas aeruginosa*

José-Manuel Ortiz de la Rosa[1], Patrice Nordmann[1–4] and Laurent Poirel[1–3]*

Table 1. MICs for clinical isolates

Strain	MIC (mg/L)								
	IPM	MEM	CAZ	C/A[a]	C/A[b]	C/A[c]	COZ	C/T[d]	C/T[e]
P. aeruginosa (GES-1) R1189	1	2	16	2	2	2	64	**32**	**32**
P. aeruginosa (GES-2) R184	16	32	64	4	2	2	32	**16**	**8**
P. aeruginosa (GES-5) R186	32	128	64	**16**	8	8	16	**8**	**8**
P. aeruginosa (GES-6) R3451	16	64	32	2	2	2	32	**32**	**32**
P. aeruginosa (CTX-M-2) R1188	1	8	32	8	4	4	16	4	1
E. coli (CTX-M-15) R1818	0.12	<0.06	128	0.5	0.03	0.03	256	1	1
P. aeruginosa (PER-1) R1192	0.5	1	>512	**64**	**16**	**16**	512	**512**	**128**
P. aeruginosa (BEL-1) R1185	1	2	32	4	2	2	16	**8**	**8**
P. aeruginosa (BEL-2) R1187	0.5	2	128	8	4	2	64	**32**	**32**
P. aeruginosa (VEB-1) R1205	8	16	256	8	4	4	64	**64**	**32**
P. aeruginosa (TEM-4) R1217	1	0.5	8	2	1	1	4	0.5	0.5
P. aeruginosa (SHV-2a) R136	1	2	32	4	4	2	8	4	4

[a] AVI 4 mg/L
[b] AVI at 8 mg/L
[c] AVI at 16 mg/L
[d] TZB at 4 mg/L
[e] TZB at 8 mg/L

2019

(on-line first)

Unravelling ceftazidime/avibactam resistance of KPC-28, a KPC-2 variant lacking carbapenemase activity

Saoussen Oueslati[1], Bogdan I. Iorga [2], Linda Tlili[1], Cynthia Exilie[1], Agustin Zavala[2], Laurent Dortet[1,3,4], Agnès B. Jousset[1,3,4], Sandrine Bernabeu[1,3], Rémy A. Bonnin [1,4] and Thierry Naas [1,3,4]*

Phenotypic, biochemical and genetic analysis of KPC-41, a KPC-3 variant conferring resistance to ceftazidime-avibactam and exhibiting reduced carbapenemase activity

Linda Mueller, Amandine Masseron, Guy Prod'Hom, Tatiana Galperine, Gilbert Greub, Laurent Poirel, Patrice Nordmann

Bloodstream infection caused by KPC-producing *Klebsiella pneumoniae* resistant to ceftazidime/avibactam: epidemiology and genomic characterization

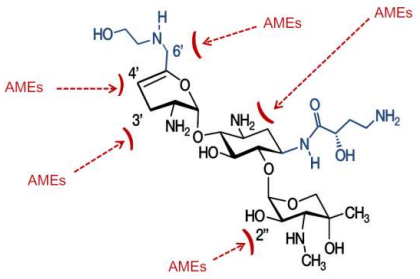
Paolo Gaibani, Maria Carla Re, Caterina Campoli, Pier-Luigi Viale, and Simone Ambretti

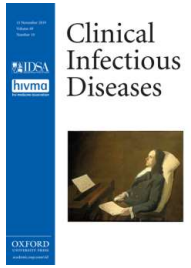
One CAZ/AVI-resistant KPC-*Kp* harbored a mixed population with **D179Y mutated KPC-2**, while the other two CAZ/AVI-resistant KPC-*Kp* possessed **non-functional ompK35-ompK37 and mutated ompK36 porins** associated with **higher copy number of *bla*$_{KPC}$ gene**.

Plazomicin: A New Aminoglycoside

Louis D. Saravolatz,[1,2] and Gary E. Stein,[3]

Clinical Infectious Diseases® 2019;XX(XX):1–6





Aminoglycoside de nouvelle génération actif sur les entérobactéries productrices d'*aminoglycoside-modifying enzymes* (AME), y compris EPC

Pas d'activité significative sur *P. aeruginosa*, *A. baumannii, S. maltophilia* et entérobactéries avec méthylases ribosomales acquises (16S RNA-MTase, ex: EPC/NDM-1)

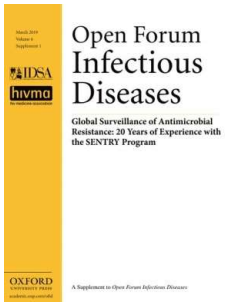
Table 2. Comparative In Vitro MIC90s of Plazomicin and Other Comparators Against Resistant Gram-negative Bacteria

	MIC90, µg/mL (% Susceptible)						
Organism (No. of Isolates Tested)	Plazomicin	Amikacin	Gentamicin	Tobramycin	Meropenem	Meropenem/ Vaborbactam	Ceftazidime-avibactam
ESBL-producing *Escherichia coli* (343)	1 (100)	8 (98.8)	>32 (67.1)	32 (55.7)	0.06 (99.7)	1 (100)	0.5 (NA)
ESBL-producing *Klebsiella pneumoniae* (73)	0.5 (98.6)	8 (100)	>32 (49.3)	32 (37.0)	0.5 (93.2)	0.5 (99.3)	1 (NA)
Carbapenem-resistant Enterobacteriaceae (110)	1 (98.1)	32 (23.6)	16 (81.8)	64 (3.6)	≥16 (2.7)	32 (79.6)	2 (97.5)
Colistin-resistant Enterobacteriaceae (95)	4 (93.7)	32 (21.0)	64 (12)	32 (8)	16 (12)	NA	2 (99.5)

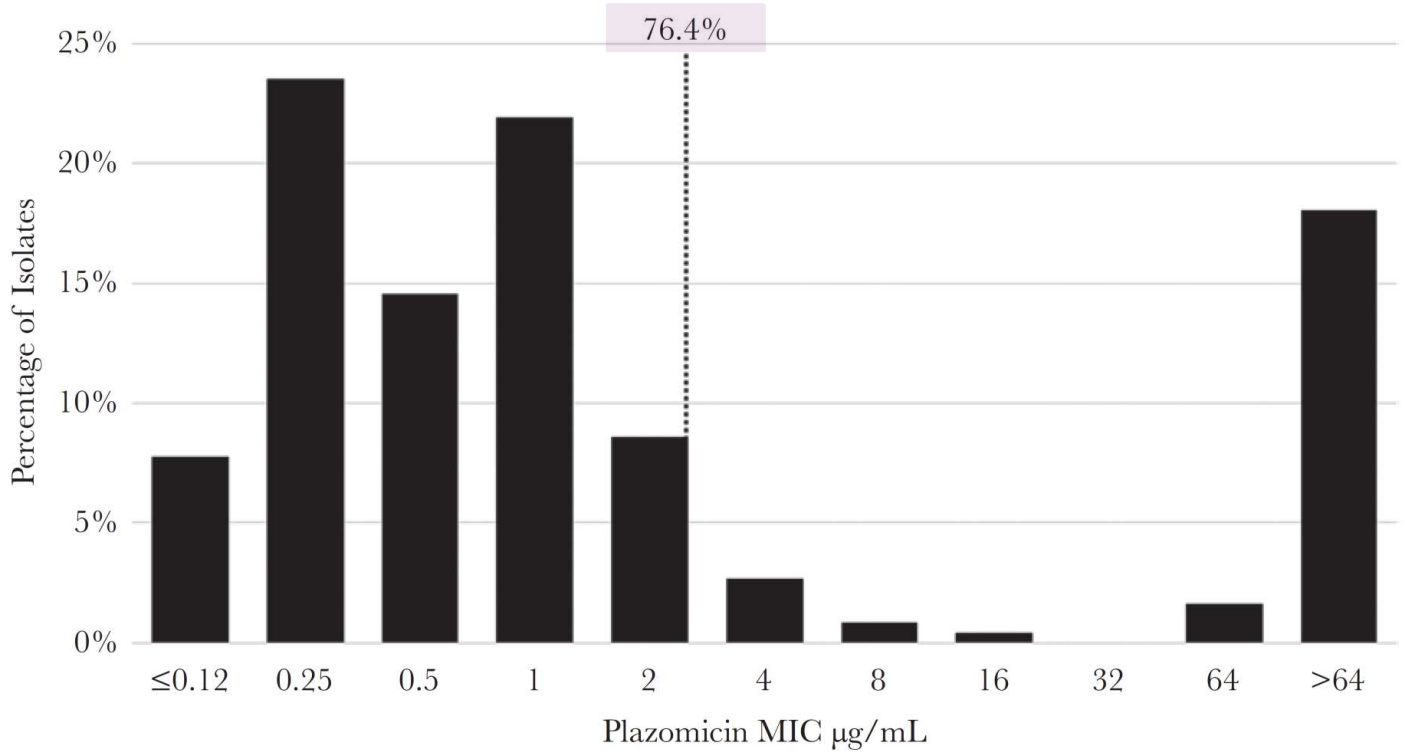
Plazomicin Is Active Against Metallo-β-Lactamase-Producing Enterobacteriaceae

Alisa W. Serio, Tiffany Keepers, and Kevin M. Krause

***Open Forum Infect Dis* 2019 (e-pub)**



Among the 488 isolates, 282 isolates had an NDM gene, and of these isolates, ***64 had plazomicin MICs ≥64 µg/mL, indicative of 16S-RMTase production****. These 64 isolates represent 22.7% of the NDM-positive isolates and* ***13.1% of the total isolates****.*



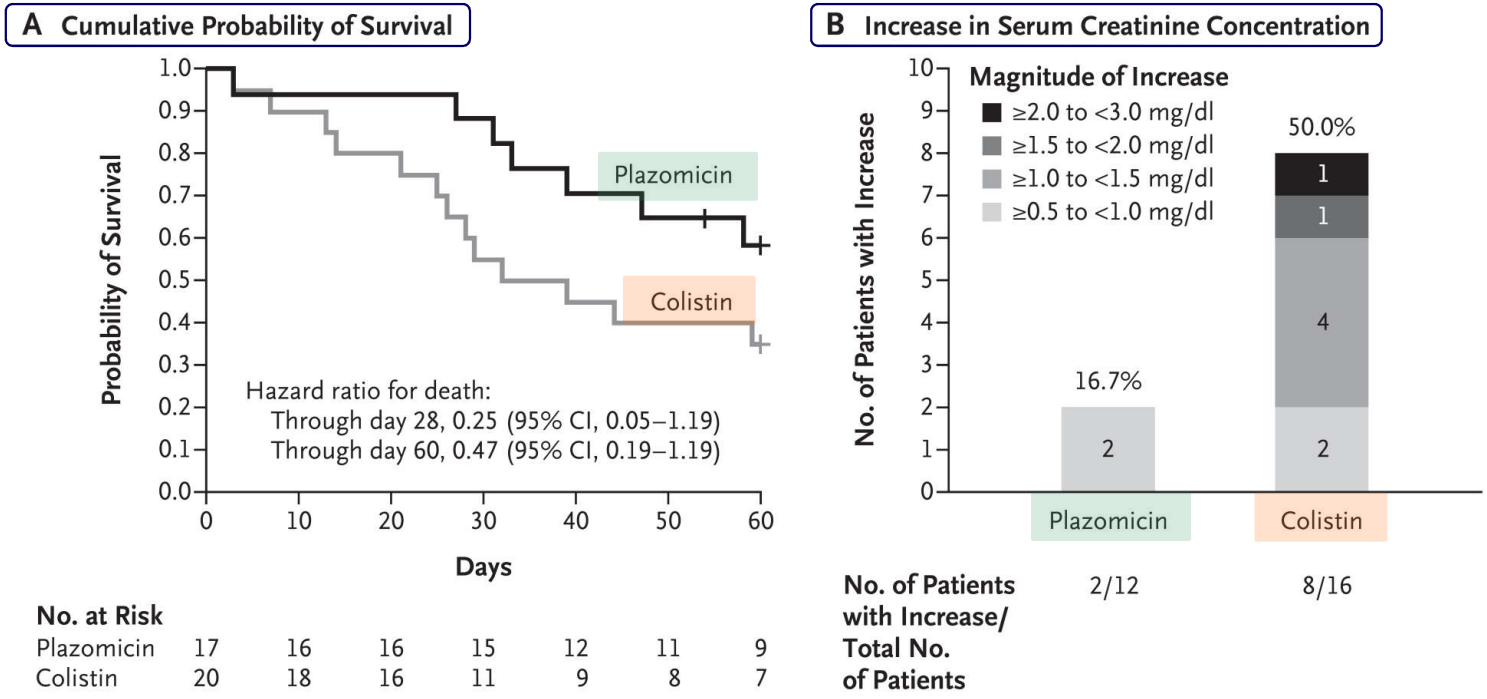
NEJM

Plazomicin for Infections Caused by Carbapenem-Resistant Enterobacteriaceae

N ENGL J MED 380;8 NEJM.ORG FEBRUARY 21, 2019

RCT / BSI et HAP-VAP à EPC

Plazomicine (15 mg/kg/24h) versus colistine, en association avec méropénème ou tigécycline



Recently approved antibacterials for methicillin-resistant *Staphylococcus aureus* (MRSA) and other Gram-positive pathogens: the shock of the new

International Journal of Antimicrobial Agents 50 (2017) 303–307

Michael Z. David [a,*], Matthew Dryden [b], Thomas Gottlieb [c], Pierre Tattevin [d], Ian M. Gould [e]

	Tedizolid	Oritavancin	Dalbavancin	Ceftaroline	Ceftobiprole
Drug class	Oxazolidinone	Lipoglycopeptide		Cephalosporin	
Spectrum	Most Gram-positive bacteria, including anaerobes, streptococci, staphylococci and enterococci	Most Gram-positive bacteria, including VRE, small-colony variants of *Staphylococcus aureus*, *mecC*-positive MRSA, VRSA (oritavancin) and some VISA/hVISA		Most Gram-positive bacteria, including methicillin-resistant staphylococci, and Enterobacteriaceae (although not those with ESBL or AmpC β-lactamase)	
Pharmacokinetics	Bioavailability, 91% Half-life, 12 h Extensive tissue distribution Protein binding, 80%	Half-life, >250 h Extensive tissue distribution Protein binding, 90%	Half-life, 350 h Extensive tissue distribution Protein binding, 95%	Half-life, 2 h Good tissue distribution Protein binding, 20% Time/MIC	Half-life, 3.5 h Good tissue distribution Protein binding, 16% Time/MIC
Dosage	200 mg daily, i.v. or p.o.	1200 mg i.v., only one dose	1000 mg i.v. Day 1, 500 mg i.v. Day 8	600 mg i.v. twice daily	500 mg i.v. three times daily
Approved for	ABSSSI	ABSSSI		ABSSSI and CAP	
Weaknesses	Bacteriostatic Cost	Only i.v. Cost		Only i.v. Cost	Only i.v. Cost
Strengths	Oral drug Tissue diffusion No dose adjustment for renal failure Safety profile better than linezolid Active against *cfr*-positive *S. aureus*	Bactericidal Long half-life Convenient dosing Safety profile Reduce duration of inpatient stay		Bactericidal Safety profile Some Gram-negative coverage	Bactericidal Safety profile Some Gram-negative coverage
Comments	May be useful for CNS and osteoarticular infections	May be useful for osteoarticular, bloodstream and foreign body-related infections		May be useful for bloodstream infections, including endocarditis. Ceftaroline under development as a combination with avibactam	

Tédizolide (TDZ) versus linézolide (LNZ)

***S. aureus* cfr+ (méthylase ribosomale) :**

CMI LNZ = CMI TDZ x 32-128

***E. faecium* avec CMI TDZ ≥ 1 mg/L : 100% LNZ-R**

(cfr-, probables mutations ARNr 23S ou protéines ribosomales)

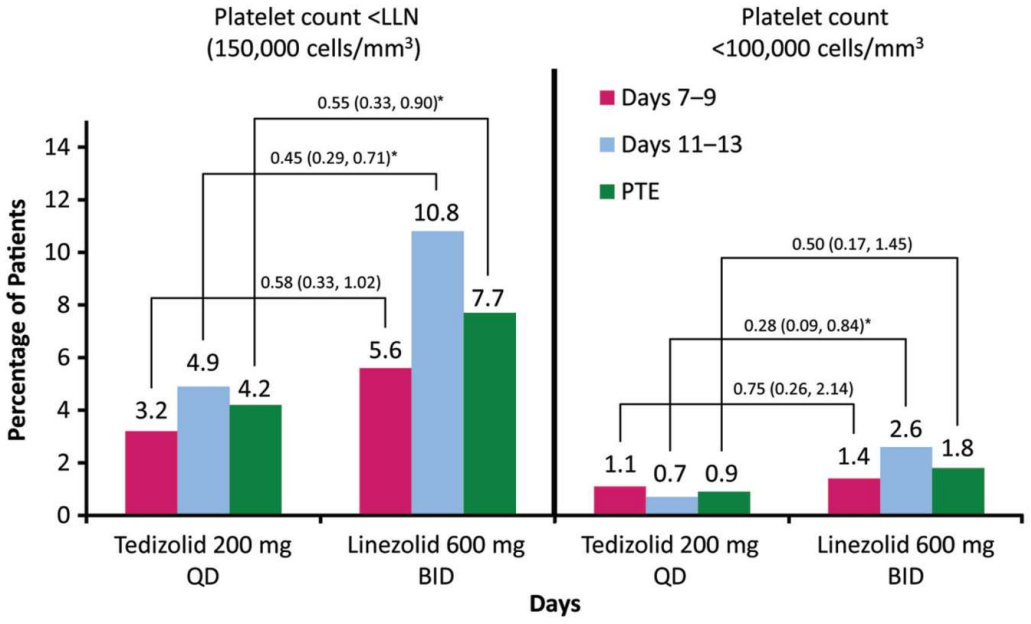
	TZD—number (cumulative percentage) inhibited at MI					
Strain	)63	0.125	0.25	0.5	1	2
MRSA						
hVISA (*n*=120)	5.8)	18 (20.8)	55 (66.7)	38 (98.3)	2[a] (100)	— (1
VISA (*n*=100)	7)	52 (59)	25 (84)	16 (100)	— (100)	— (1
DNS (*n*=75)	))	23 (30.7)	38 (81.3)	14 (100)	— (100)	— (1
LR[b] (*n*=7)	14.3)	1 (28.6)	2 (57.1)	— (57.1)	3 (100)	— (1
VRE						
E. faecium (*n*=120)	))	6 (5)	51 (47.5)	32 (74.2)	25 (95)	3 (9
E. faecalis (*n*=100)	1)	29 (30)	69 (99)	1 (100)	— (100)	— (1
LR *E. faecium* (*n*=10)	))	— (0)	— (0)	— (0)	4 (40)	3 (7
DNS *E. faecium* (*n*=25)	))	— (0)	11 (44)	3 (56)	8 (88)	2 (9

Barber et al. *J Antimicrob Chemother* 2016; 71: 152-155

Essais randomisés ESTABLISH-1 & 2 (IPTMc)

TDZ 6 jours versus LNZ 10 jours

Incidence des thrombopénies



Lodise et al. *Antimicrob Agents Chemother* 2014; 58: 7198-204

Recently approved antibacterials for methicillin-resistant *Staphylococcus aureus* (MRSA) and other Gram-positive pathogens: the shock of the new

International Journal of Antimicrobial Agents 50 (2017) 303–307

Michael Z. David [a,*], Matthew Dryden [b], Thomas Gottlieb [c], Pierre Tattevin [d], Ian M. Gould [e]

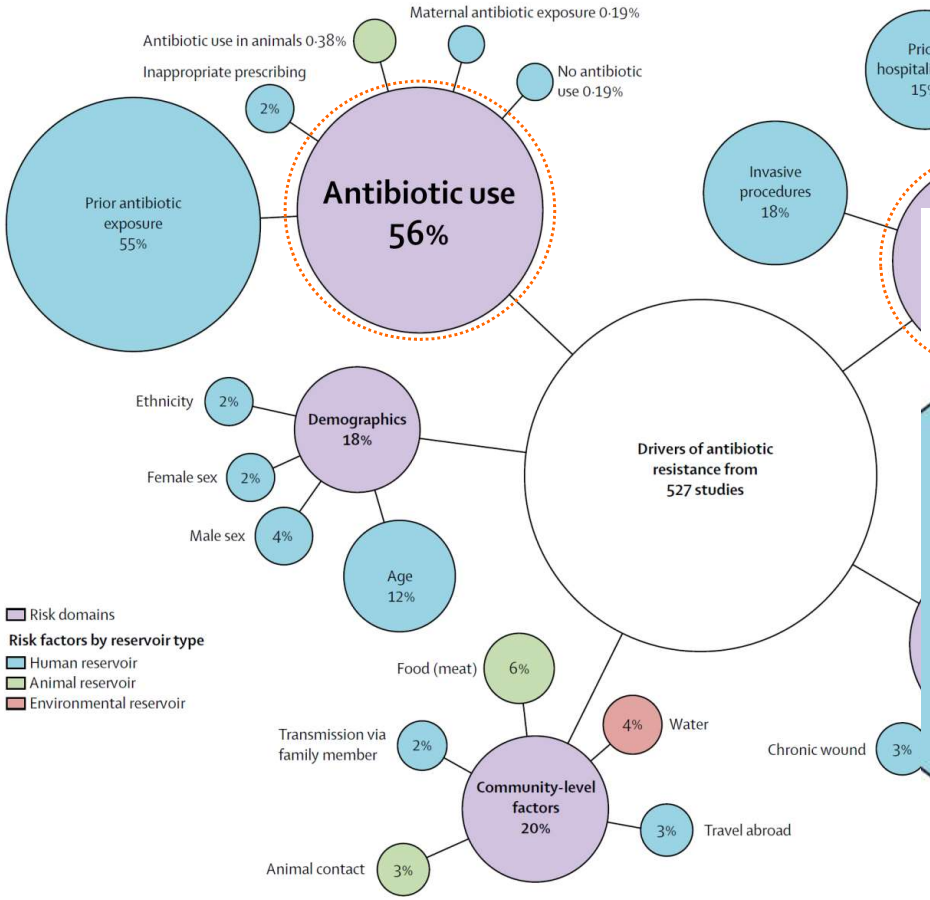
INTERNATIONAL JOURNAL OF Antimicrobial Agents

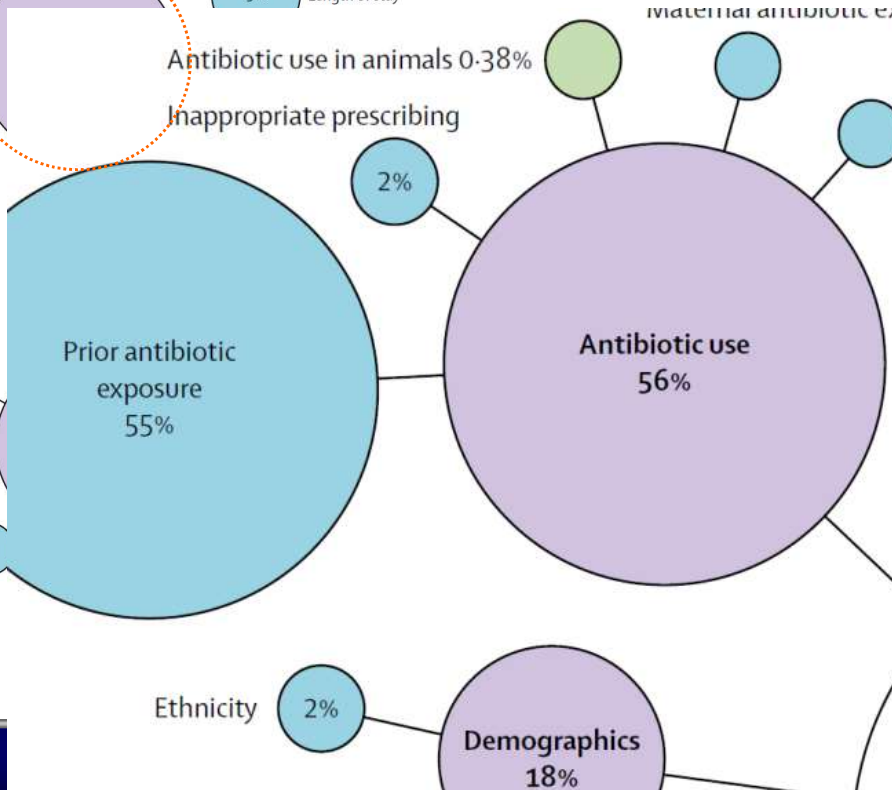
	Tedizolid	Oritavancin	Dalbavancin	Ceftaroline	Ceftobiprole
Drug class	Oxazolidinone	Lipoglycopeptide		Cephalosporin	
Spectrum	Most Gram-positive bacteria, including anaerobes, streptococci, staphylococci and enterococci	Most Gram-positive bacteria, including VRE, small-colony variants of *Staphylococcus aureus*, *mecC*-positive MRSA, VRSA (oritavancin) and some VISA/hVISA		Most Gram-positive bacteria, including methicillin-resistant staphylococci, and Enterobacteriaceae (although not those with ESBL or AmpC β-lactamase)	
Pharmacokinetics	Bioavailability, 91% Half-life, 12 h Extensive tissue distribution Protein binding, 80%	Half-life, >250 h Extensive tissue distribution Protein binding, 90%	Half-life, 350 h Extensive tissue distribution Protein binding, 95%	Half-life, 2 h Good tissue distribution Protein binding, 20% Time/MIC	Half-life, 3.5 h Good tissue distribution Protein binding, 16% Time/MIC
Dosage	200 mg daily, i.v. or p.o.	1200 mg i.v., only one dose	1000 mg i.v. Day 1, 500 mg i.v. Day 8	600 mg i.v. twice daily	500 mg i.v. three times daily
Approved for	ABSSSI	ABSSSI		ABSSSI and CAP	
Weaknesses	Bacteriostatic Cost	Only i.v. Cost		Only i.v. Cost	Only i.v. Cost
Strengths	Oral drug Tissue diffusion No dose adjustment for renal failure Safety profile better than linezolid Active against *cfr*-positive *S. aureus*	Bactericidal Long half-life Convenient dosing Safety profile Reduce duration of inpatient stay		Bactericidal Safety profile Some Gram-negative coverage	Bactericidal Safety profile Some Gram-negative coverage
Comments	May be useful for CNS and osteoarticular infections	May be useful for osteoarticular, bloodstream and foreign body-related infections		May be useful for bloodstream infections, including endocarditis. Ceftaroline under development as a combination with avibactam	

Quantifying drivers of antibiotic resistance in humans: a systematic review

Anuja Chatterjee, Maryam Modarai, Nichola R Naylor, Sara E Boyd, Rifat Atun, James Barlow, Alison H Holmes, Alan Johnson, Julie V Robotham

Lancet Infect Dis 2018; 18: e368–78





SURVEILLANCE DE LA CONSOMMATION DES ANTIBIOTIQUES

Réseau ATB-Raisin. Résultats 2015

Santé publique France

Publication : avril 2017

Consommation d'antibiotiques en DDJ pour 1000 jours d'hospitalisation, médiane (IQR)

	Toutes classes confondues	Pipéracilline-tazobactam	C3G/C4G anti-pyocyanique	Carbapénèmes	Fluoroquinolones
Tous services MCO confondus	515 (364-627)	5 (1-13)	2 (0,5-5)	3 (1-6)	53 (35-72)
Services de médecine	549 (391-645)	5 (1-12)	2 (0,5-6)	3 (1-6)	61 (40-83)
Services d'onco-hématologie	**1002 (759-1241)**	**138 (44-205)**	**39 (22-84)**	**76 (28-117)**	**98 (58-133)**
Services de réanimation	**1475 (1285-1795)**	**114 (79-147)**	**46 (24-81)**	**66 (36-106)**	**133 (89-204)**

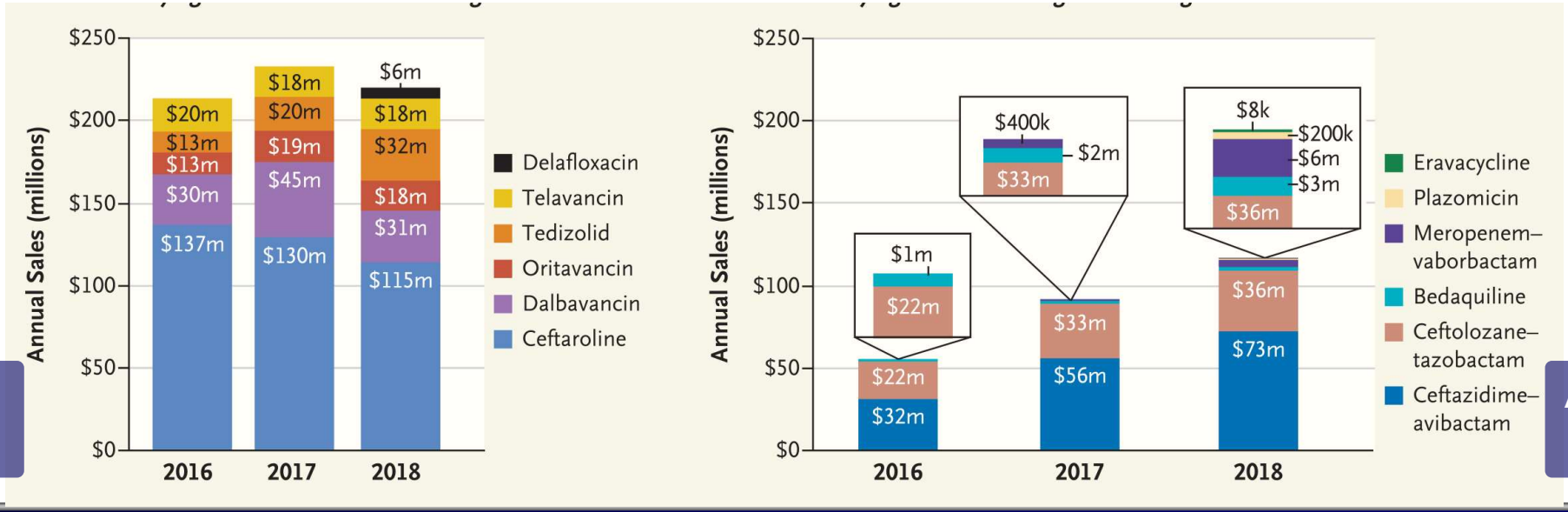
Sustainable Discovery and Development of Antibiotics — Is a Nonprofit Approach the Future?

Travis B. Nielsen, Ph.D., Eric P. Brass, M.D., Ph.D., David N. Gilbert, M.D., John G. Bartlett, M.D., and Brad Spellberg, M.D.

N ENGL J MED 381;6 NEJM.ORG AUGUST 8, 2019

NEJM

« All antibiotics approved in the past decade have had disappointing sales, triggering renewed threats of companies exiting the antibiotics business. Nonprofits can eschew opportunities to enter larger markets in favor of addressing unmet needs because they don't face pressure to generate continuous revenue growth.»



Anti-Gram positive

Anti-GNB & TBC

Faut-il épargner les nouveaux antibiotiques ?

OUI…

…comme tous les autres!

Épargne des nouveaux antibiotiques

Take-home messages

1. **Plus-value certaine** (spectre, toxicité, modalités d'administration) et **indications très ciblées**
2. **C/TZ :** alternative fiable (versus polymyxines et/ou aminosides) dans les infections à *Pseudomonas aeruginosa* MDR/XDR
3. **CAZ/AVI :** 1ère ligne dans les infections à EPC / KPC & OXA-48
4. **Carbapénèmes : 1ère ligne dans les infections sévères à EBLSE** (C/TZ et CAZ/AVI : options pour les co-infections à EBLSE et *P. aeruginosa* carba-R)
5. **Prescriptions probabilistes :** apport des outils de diagnostic microbiologique rapide ?
6. **Besoin urgent de données écologiques comparatives**
7. **Diffusion de la résistance aux nouvelles molécules ou associations : inéluctable ?**