JNI 23es Journées Nationales d'Infectiologie
Bordeaux et la région Aquitaine
Palais des Congrès
du mercredi 15 juin 2022
au vendredi 17 juin 2022

Quelle place pour les nouveaux antibiotiques ?

Florent Valour

florent.valour@chu-lyon.fr

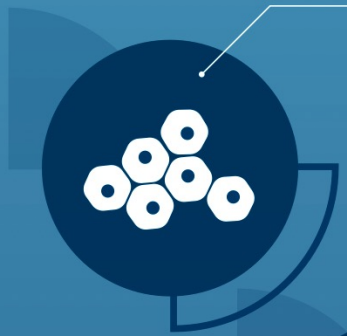
Déclaration de liens d'intérêt avec les industries de santé en rapport avec le thème de la présentation (loi du 04/03/2002) :

Intervenant : VALOUR Florent

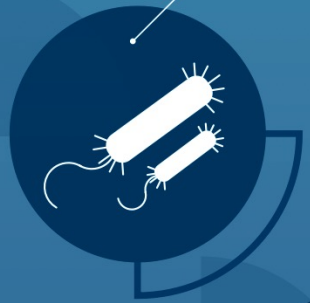
Titre : Quelle place pour les nouveaux antibiotiques ?

Consultant ou membre d'un conseil scientifique : Pfizer	☑ OUI	☐ NON
Conférencier ou auteur/rédacteur rémunéré d'articles ou documents : Pfizer, Ménarini, Correvio, Sanofi	☑ OUI	☐ NON
Prise en charge de frais de voyage, d'hébergement ou d'inscription à des congrès : Ménarini, Correvio, Pfizer, MSD, Sanofi	☑ OUI	☐ NON
Investigateur principal d'une recherche ou d'une étude clinique	☐ OUI	☑ NON

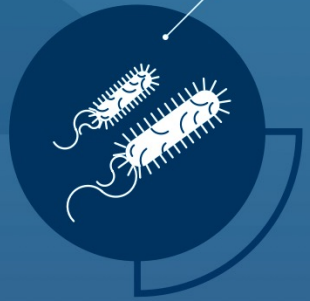
CRITICAL PRIORITY



Acinetobacter baumannii
carbapenem-resistant



Pseudomonas aeruginosa
carbapenem-resistant



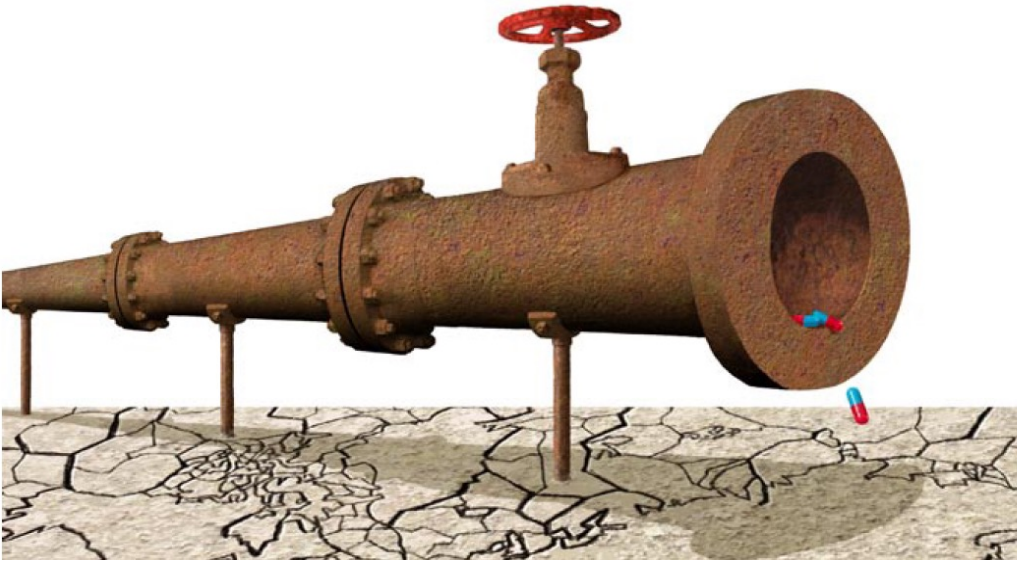
Enterobacteriaceae
carbapenem-resistant,
3rd gen. cephalosporin-resistant

© World Health Organization 2021 Antibacterial agents in clinical and preclinical development: an overview and analysis

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

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

Clinical Infectious Diseases 2009; 48:1–12



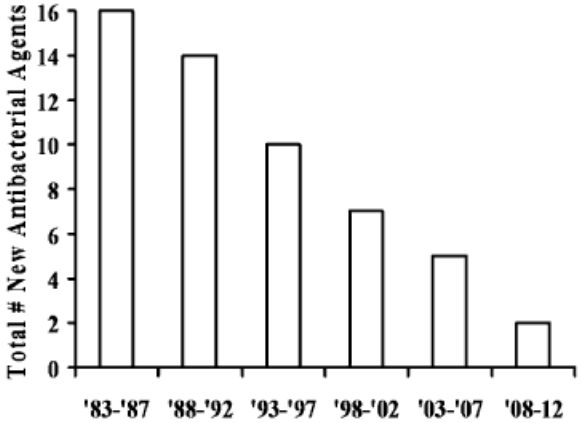


Figure 1. Number of New Molecular Entity (NME) Systemic Antibiotics Approved by the US FDA Per Five-year Period, Through 3/11.

2021 ANTIBACTERIAL AGENTS IN CLINICAL AND PRECLINICAL DEVELOPMENT:

an overview and analysis

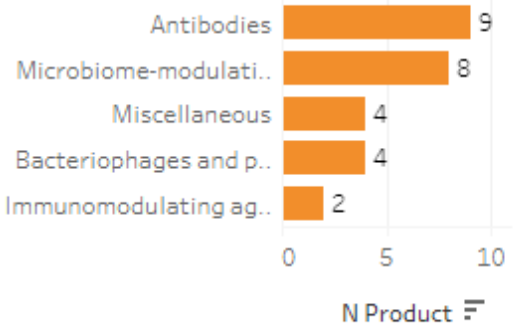
World Health

AMM depuis 01/07/17 – 01/11/21 (BGN)

Name (trade name USA/ EU)	Market authorization holder(s)	Approved by (date)	Antibacterial class	Route of administration	Indication/s	WHO EML & AWaRe classification	Expected activity against priority pathogens				Innovation			
								CRPA	CRE	OPP	NCR	CC	T	MoA
Vaborbactam + meropenem (Vabomere / Vaborem)	Melinta Therapeutics (USA) (Menarini, EU)	US FDA (8/2017) EMA (11/2018)	Boronate BLI + β-lactam (carbapenem)	iv	cUTI, (cUTI, cIAI, HAP/VAP in EU)	WHO EML: yes AWaRe: Reserve	○	○	●[1]	/	?[2]	✓	-	-
Plazomicin (Zemdri)	Achaogen (Cipla USA/ QiLu Antibiotics, China)	US FDA (8/2018)	Aminoglycoside	iv	cUTI	WHO EML: yes AWaRe: Reserve	○	○	●	/	-	-	-	-
Eravacycline (Xerava)	Tetraphase Pharmaceuticals (La Jolla Pharmaceutical Company, Everest Medicines)	US FDA (8/2018) EMA (9/2018)	Tetracycline	iv	cIAI	WHO EML: no AWaRe: Reserve	?	○	●	/	-	-	-	-
Relebactam + imipenem / cilastatin (Recarbrio)	Merck Sharp & Dohme	US FDA (7/2019 cUTI/cIAI, 7/2020 HAP/VAP) EMA (2/2020 G-ve)	O-BLI + β-lactam (carbapenem) / degradation inhibitor	iv	cUTI, cIAI, HAP/VAP	WHO EML: no AWaRe: Reserve	○	?	●[3]	/	-	-	-	-
Cefiderocol (Fetroja)	Shionogi	US FDA (11/2019 cUTI, 9/21 HAP/ VAP) EMA (4/2020)	Siderophore β-lactam (cephalosporin)	iv	cUTI, HAP/VAP, aerobic G-ve[5]	WHO EML: yes AWaRe: Reserve	●	●	●	/	?	-	-	-

A.1. Products by type

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



A.3. Products by pathogen category and phase

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

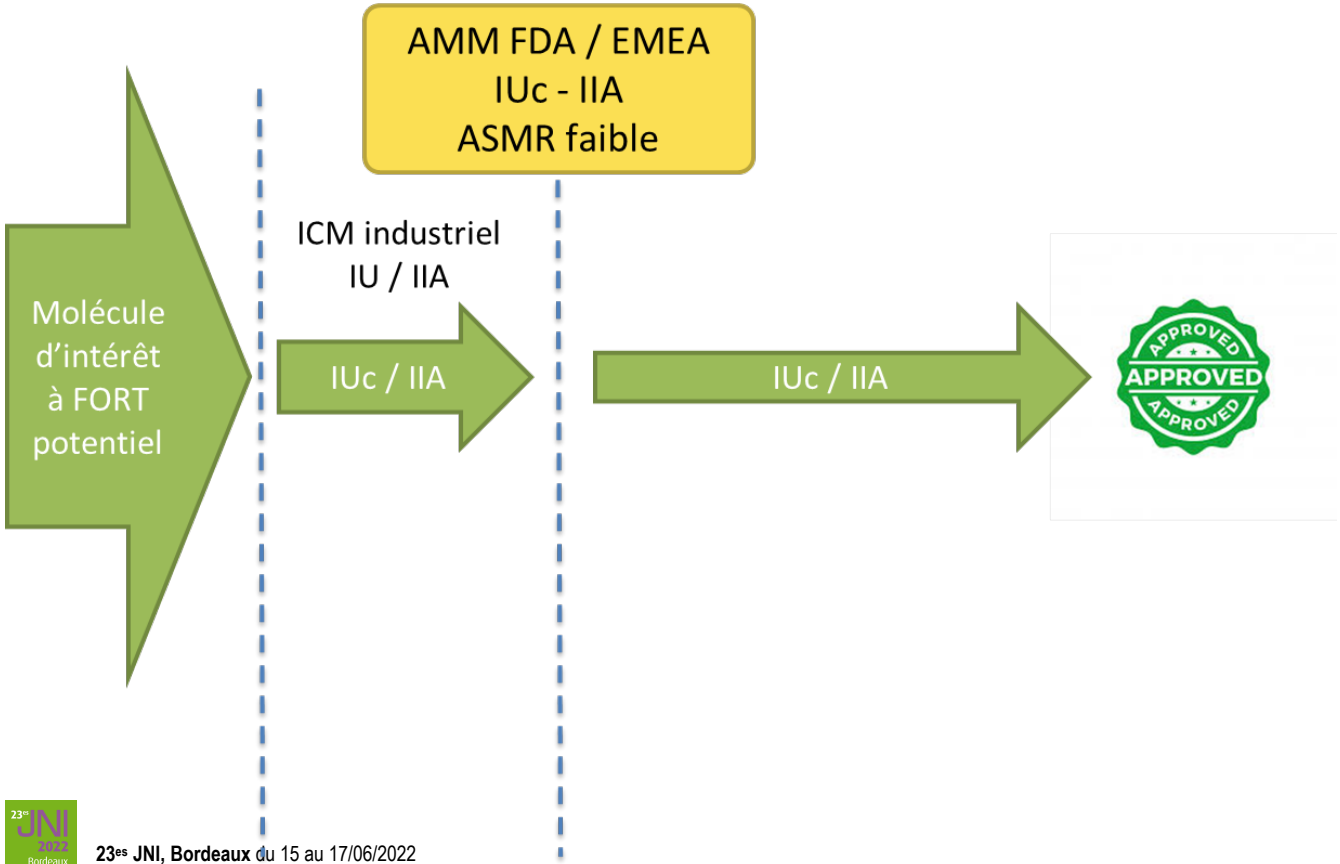
B. Expected activity against priority pathogens

37

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

Quelle place pour les nouvelles béta-lactamines à l'ère des BGN multi-résistants ?

A garder en tête



A garder en tête

Molécule d'intérêt à FORT potentiel

ICM industriel
IU / IIA

IUc / IIA

AMM FDA / EMEA
IUc - IIA
ASMR faible

IUc / IIA

- **Bactériémie**
- **Prostatites**
- **ISO / IOA**
- **SNC**
- **Germes XDR**

OFF LABEL

Dose ?
Durée ?
Efficacité ?
Tolérance ?

Céphalosporines + Inhibiteurs

Clinical Infectious Diseases

INVITED ARTICLE

IDSA Infectious Diseases Society of America

hivma hiv medicine association

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

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

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

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

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

***Int J Antimicrob Agents* 2015**

	A KPC, GES	B NDM, VIM	C AmpC	D OXA-48	PA MDR	AB MDR	SM
Ceftolozane tazobactam	–	–	+	–	+/-	–	–

Actif Inactif

	A KPC, GES	B NDM, VIM	C AmpC	D OXA-48	PA MDR	AB MDR	SM
Ceftolozane tazobactam	–	–	+	–	+/-	–	–

RESISTANCE CEFTO/TAZO

- Toutes les carbapénémases
- Haut niveau de production d'AmpC
- Efflux/Modifications porines/imperméabilité

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

Actif Inactif

	A KPC, GES	B NDM, VIM	C AmpC	D OXA-48	PA MDR	AB MDR	SM
Ceftolozane tazobactam	–	–	+	–	+/-	–	–
Ceftazidime avibactam	+	–	+	+	+/-	–	–

RESISTANCE CEFTO/TAZO

- Toutes les carbapénémases
- Haut niveau de production d'AmpC
- Efflux/Modifications porines/imperméabilité

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

RESISTANCE CEFTA/AVI

- Métallo-BL (classe B)
- ABRI
- Efflux/Modifications porines/imperméabilité
- Mutation KPC (boucle oméga – KPC3)

- Jusqu'à 10% R / KPC
- Facteurs de risque : dialyse, posologie insuffisante

Actif Inactif

Ceftolozane + tazobactam (ZERBAXA®)

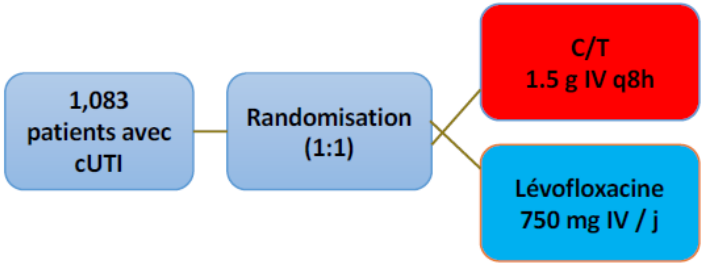
- IU compliquées (dont PNA)

ASPECT-cUTI :

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

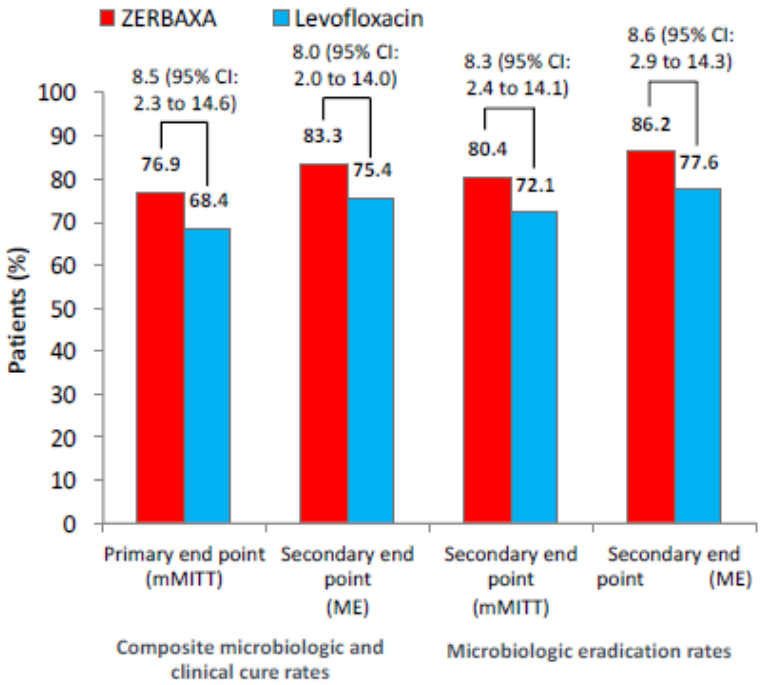
Critère principal :

Composite microbiologique et guérison clinique 5–9 jours après traitement



800 pyélonéphrites
C/T 7 jours > LVF 7 jours

Wagenlehner et al. Lancet 2015



Ceftolozane + tazobactam (ZERBAXA®)

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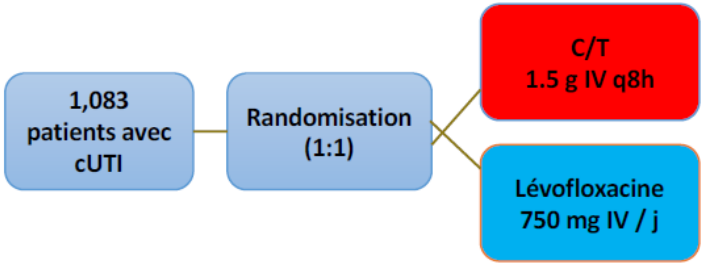

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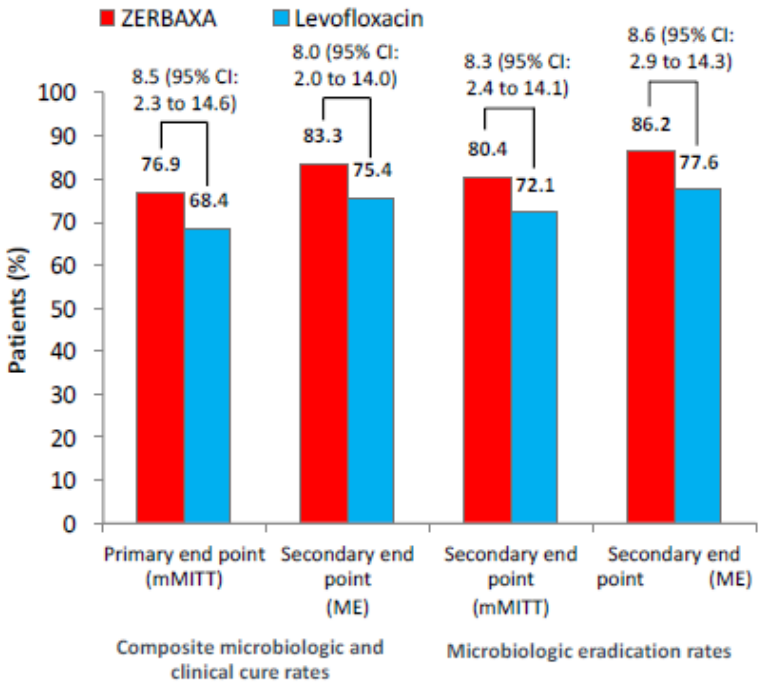


> 25% des entérobactéries LVF-R !!

Ceftolozane + tazobactam (ZERBAXA®)

- IU compliquées (dont PNA)
- IIA compliquées

Wagenlehner et al. Lancet 2015

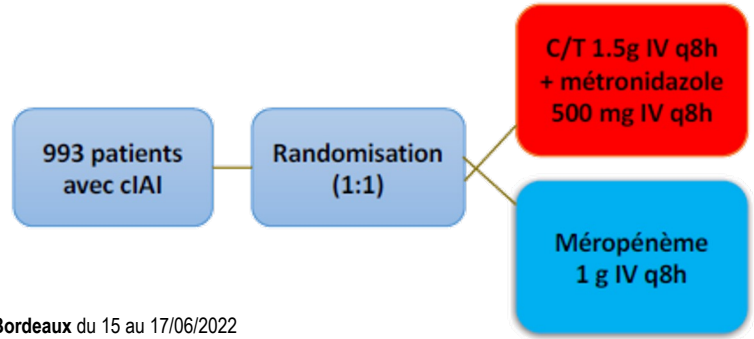
Solomkin et al. CID 2015

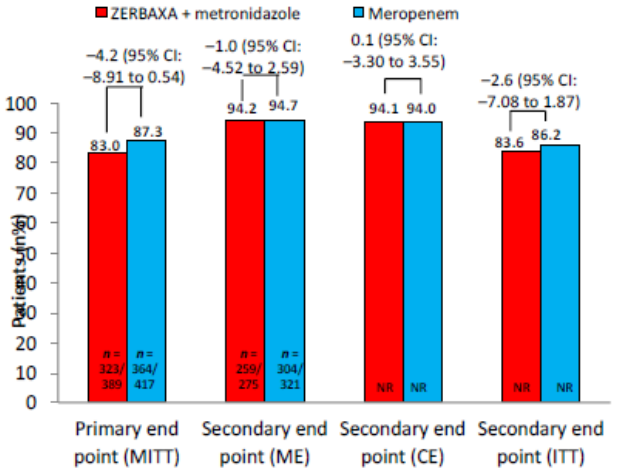
ASPECT-cIAI:

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

Critère principal:

Guérison clinique 24–32 jours après initiation du traitement





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

Ceftolozane + tazobactam (ZERBAXA®)

- IU compliquées (dont PNA)
- IIA compliquées
- PNP nosocomiales dont PAVM

Wagenlehner et al. Lancet 2015

Solomkin et al. CID 2015

- **En pratique :** « rescue therapy »
- **Posologie : 1g IV / 8h**
  Adaptation posologique si DFG < 50 mL/min
  Dose hors AMM (IOA, SNC, prostate …) ?
- **Toxicité :** cf. béta-lactamines

Ceftazidime + avibactam (ZAVICEFTA®)

- IU compliquées (dont PNA) – RECAPTURE 1 et 2 *Wagenlehner et al. CID 2016*
- IIA compliquées – RECLAIM 1, 2 et 3 *Mazuski et al. CID 2016*
- PNP nosocomiales / PAVM – REPROVE *Torres et al. LID 2018*
- **Autres infections à BGN sans autre option thérapeutique**

Données poolées de 5 RCT (phase III)

1051 entérobactéries MDR
95 *P. aeruginosa* MDR
Pas seulement des EPC

CEFTA/AVI vs comparateur (surtout carbapénèmes)

Réponses cliniques et biologiques similaires

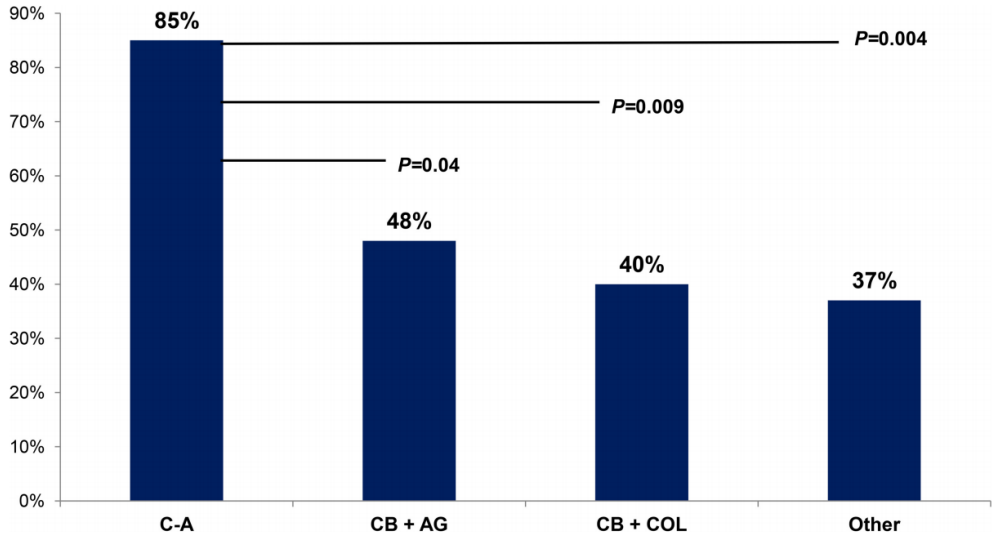
Stone et al, JAC 2018

Ceftazidime + avibactam (ZAVICEFTA®)

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

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]

Etude rétrospective, monocentrique
109 bactériémies à *K. pneumoniae* **KPC** surtout
13 traitées par **Ceftazidime-avibactam** vs
- carbapénème + aminoside
- carbapénème + colistine



85 % de succès

Ceftazidime + avibactam (ZAVICEFTA®)

Efficacy and Safety of Ceftazidime-Avibactam for the Treatment of Carbapenem-Resistant *Enterobacterales* Bloodstream Infection: a Systematic Review and Meta-Analysis

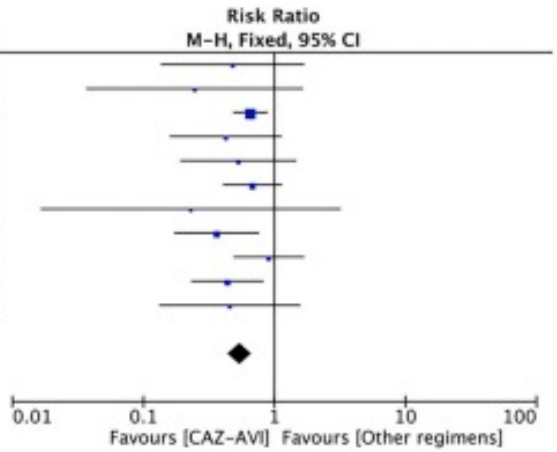
1,205 patients

Yan Chen,[a] Hui-Bin Huang,[b] Jin-Min Peng,[a] Li Weng,[a] Bin Du[a]

Study or Subgroup	CAZ-AVI Events	CAZ-AVI Total	Other regimens Events	Other regimens Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
16	2	8	12	23	3.2%	0.48 [0.14, 1.69]	2017
17	1	13	30	96	3.8%	0.25 [0.04, 1.66]	2017
18	38	104	58	104	30.4%	0.66 [0.48, 0.89]	2018
19	4	22	12	28	5.5%	0.42 [0.16, 1.14]	2019
21	3	13	34	78	5.1%	0.53 [0.19, 1.47]	2020
20	17	71	25	71	13.1%	0.68 [0.40, 1.14]	2020
24	0	4	57	131	2.2%	0.23 [0.02, 3.21]	2021
25	6	35	72	152	14.1%	0.36 [0.17, 0.76]	2021
26	12	32	12	29	6.6%	0.91 [0.49, 1.69]	2021
22	10	52	22	50	11.8%	0.44 [0.23, 0.83]	2021
23	2	9	39	80	4.1%	0.46 [0.13, 1.58]	2021
Total (95% CI)		**363**		**842**	**100.0%**	**0.55 [0.45, 0.68]**	
Total events	95		373				

Heterogeneity: $Chi^2 = 7.58$, df = 10 (P = 0.67); $I^2 = 0\%$

Test for overall effect: Z = 5.65 (P < 0.00001)

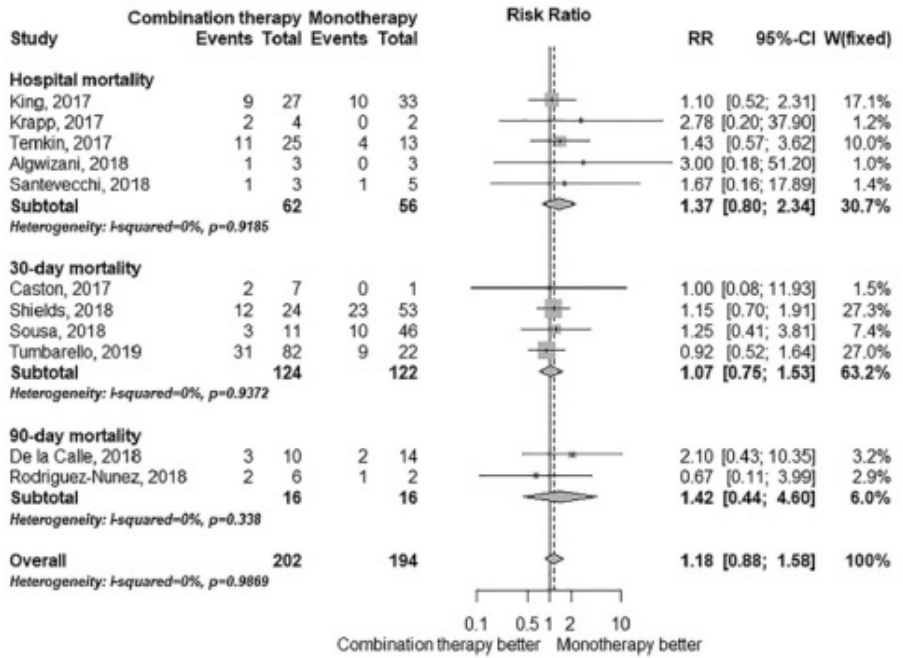


Ceftazidime + avibactam (ZAVICEFTA®)

Efficacy of ceftazidime/avibactam in monotherapy or combination therapy against carbapenem-resistant Gram-negative bacteria: A meta-analysis

Lorenzo Onorato[a,1], Giovanni Di Caprio[b,1], Simona Signoriello[c], Nicola Coppola[a,b,*]

- Pas de supériorité des bithérapies
- Sur-risque d'effets secondaires



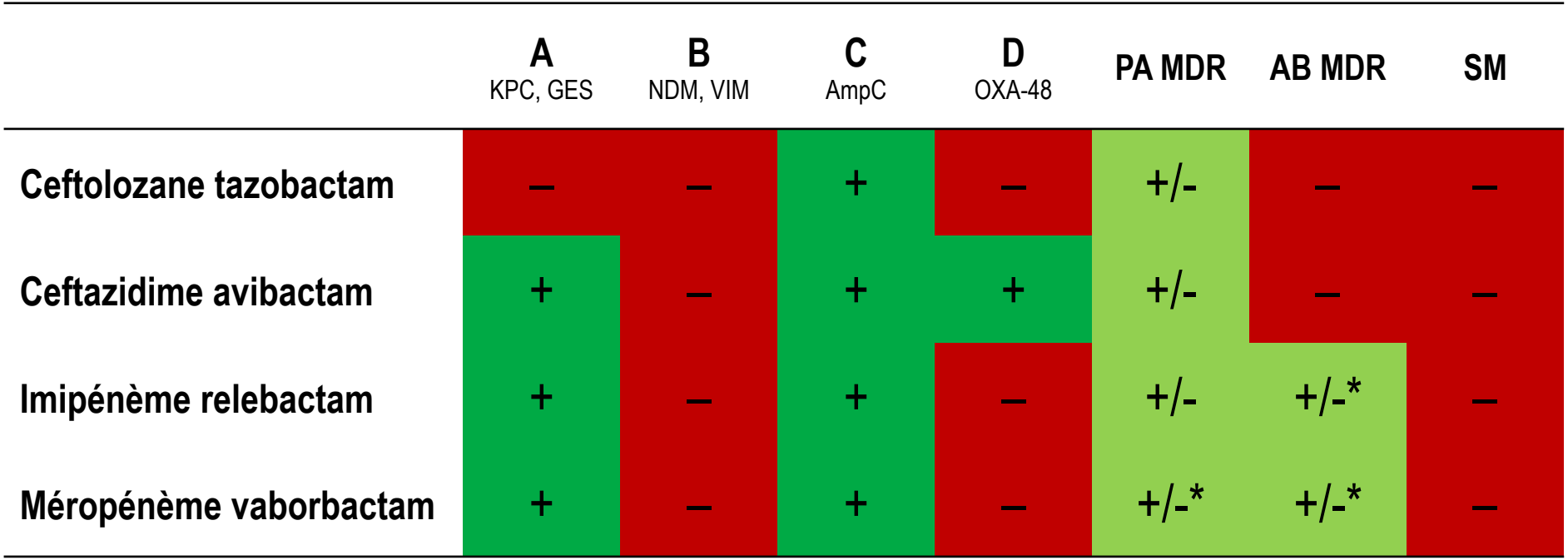
Carbapénèmes + Inhibiteurs

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

REVIEW ARTICLE

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

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



* Aucun gain vs carbapénème seul

Actif

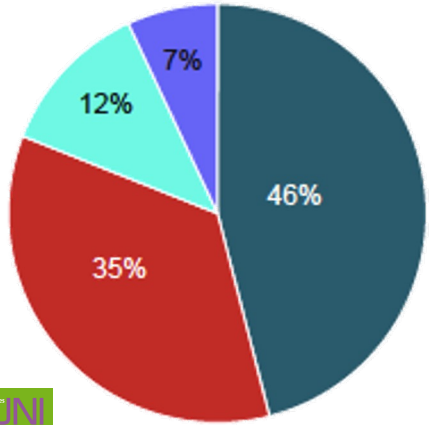
Inactif

Méropénème + vaborbactam (VABOREM®)

- IU compliquées (dont PNA) : essais TANGO I et TANGO II
- IIA compliquées

Wunderink RG et al. Infect Dis Ther 2018

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



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

20 bactériémies
60% de CRE

Efficacy Endpoints

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

Méropénème + vaborbactam (VABOREM®)

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

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

126 patients
20% ID

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

FR : initiation MV > 48h

Sources of infection	
Bone and joint	3 (2.4)
Infective endocarditis	1 (0.8)
Intraabdominal	24 (19.0)
Intravenous catheter	4 (3.2)
Other[i]	2 (1.6)
Primary bacteremia	12 (9.5)
Pneumonia	48 (38.1)
Mechanically ventilated for 48 h before pneumonia[i]	25 (19.8)
Skin and soft tissue	13 (10.3)
	17 (13.5)
	2 (1.6)

Pathogens targeted	
Carbapenem-resistant pathogen	99 (78.6)
Acinetobacter baumannii	2 (1.6)
Citrobacter freundii	4 (3.2)
Enterobacter cloacae	21 (16.7)
Escherichia coli	25 (19.8)
Klebsiella aerogenes	3 (2.4)
Klebsiella oxytoca	4 (3.2)
Klebsiella pneumoniae	53 (42.1)
Morganella morganii	1 (0.8)
Proteus mirabilis	4 (3.2)
Pseudomonas aeruginosa[k]	11 (8.7)
Serratia marcescens	4 (3.2)
Stenotrophomonas maltophilia	1 (0.8)

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

Imipénème + relebactam (RECARBRIO®)

- IU compliquées (dont PNA)
- IIA compliquées
- Infections à EPC

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

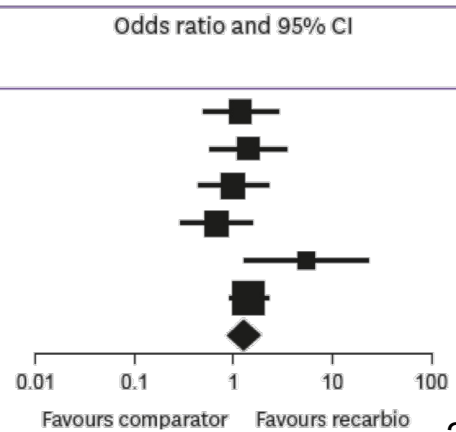
Imipénème + relebactam (RECARBRIO®)

- IU compliquées (dont PNA)
- IIA compliquées
- Infections à EPC

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

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

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



	A KPC, GES	B NDM, VIM	C AmpC	D OXA-48	PA MDR	AB MDR	SM
Ceftolozane tazobactam	–	–	+	–	+/-	–	–
Ceftazidime avibactam	+	–	+	+	+/-	–	–
Imipénème relebactam	+	–	+	–	+/-	+/-	–
Méropénème vaborbactam	+	–	+	–	+/-	+/-	–
Aztréonam avibactam	+	+	+	+	+/-[1]	+/-[2]	+

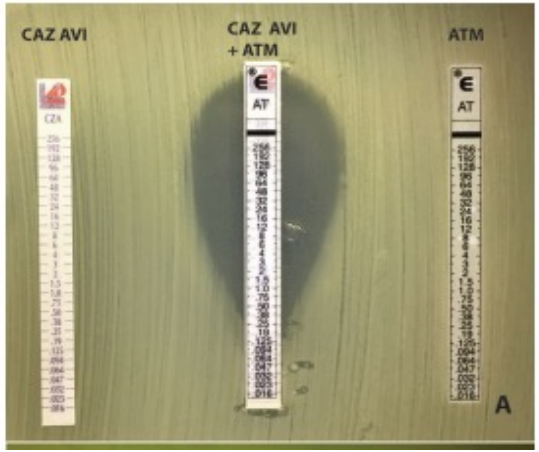
Actif sur 80% des enterobactérales MBL+, 85% des *S. maltophilia* et 6% des *P. aeruginosa* MBL+

[1] R : imperméabiliité, AmpC hyperproduite
[2] R : ABRI

Aztréonam + avibactam (+ ceftazidime)

The Revival of Aztreonam in Combination with Avibactam against Metallo-β-Lactamase-Producing Gram-Negatives: A Systematic Review of In Vitro Studies and Clinical Cases

Antibiotics **2021**, *10*, 1012



Antimicrobial Resistance and Infection Control 2018

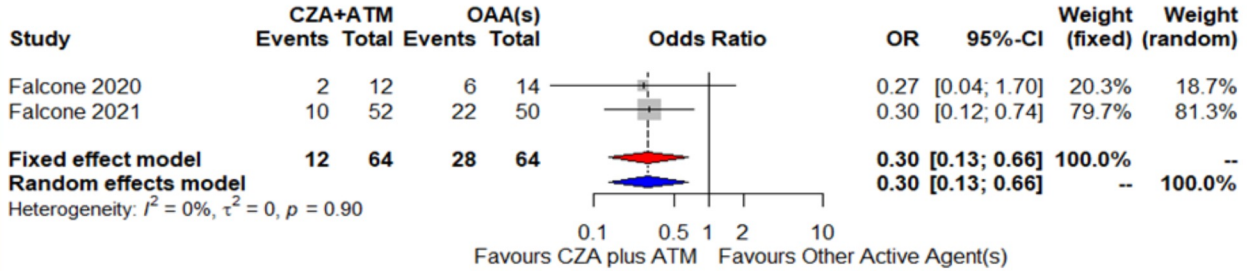
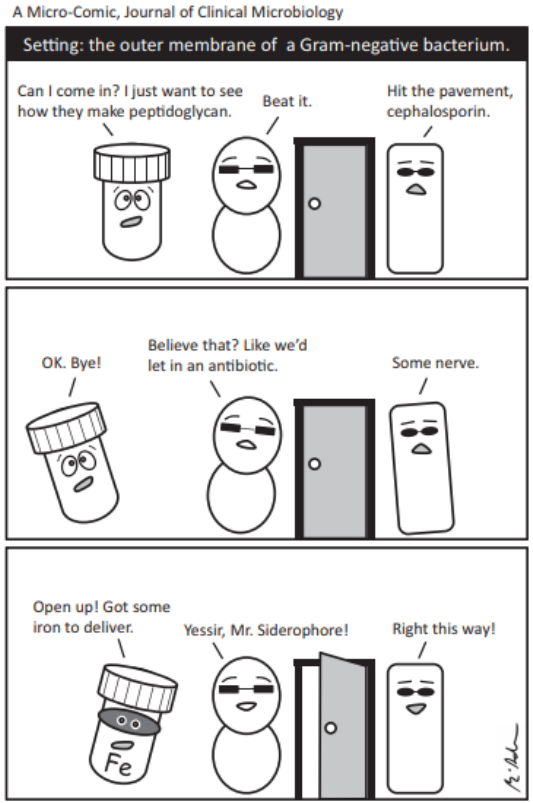


Figure 3. Forest plot of the 30-day mortality odds ratio between CZA plus ATM and other regimens against infections by MBL-producing strains. ATM, aztreonam; CZA, ceftazidime/avibactam; OAA, other active agent.

- 94 patients – résolution clinique à 30 jours: 80%
- OR=0,3 en faveur de l'association
- Peu de données sur *P. aeruginosa* et *S. maltophilia*

Céfidérocol (FETCROJA®)



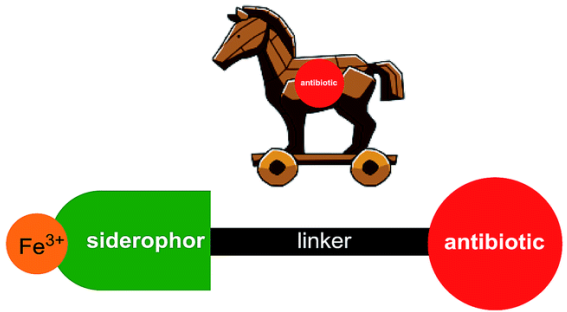
Infect Dis Ther (2020) 9:17–40
https://doi.org/10.1007/s40121-020-00286-6

REVIEW

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

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

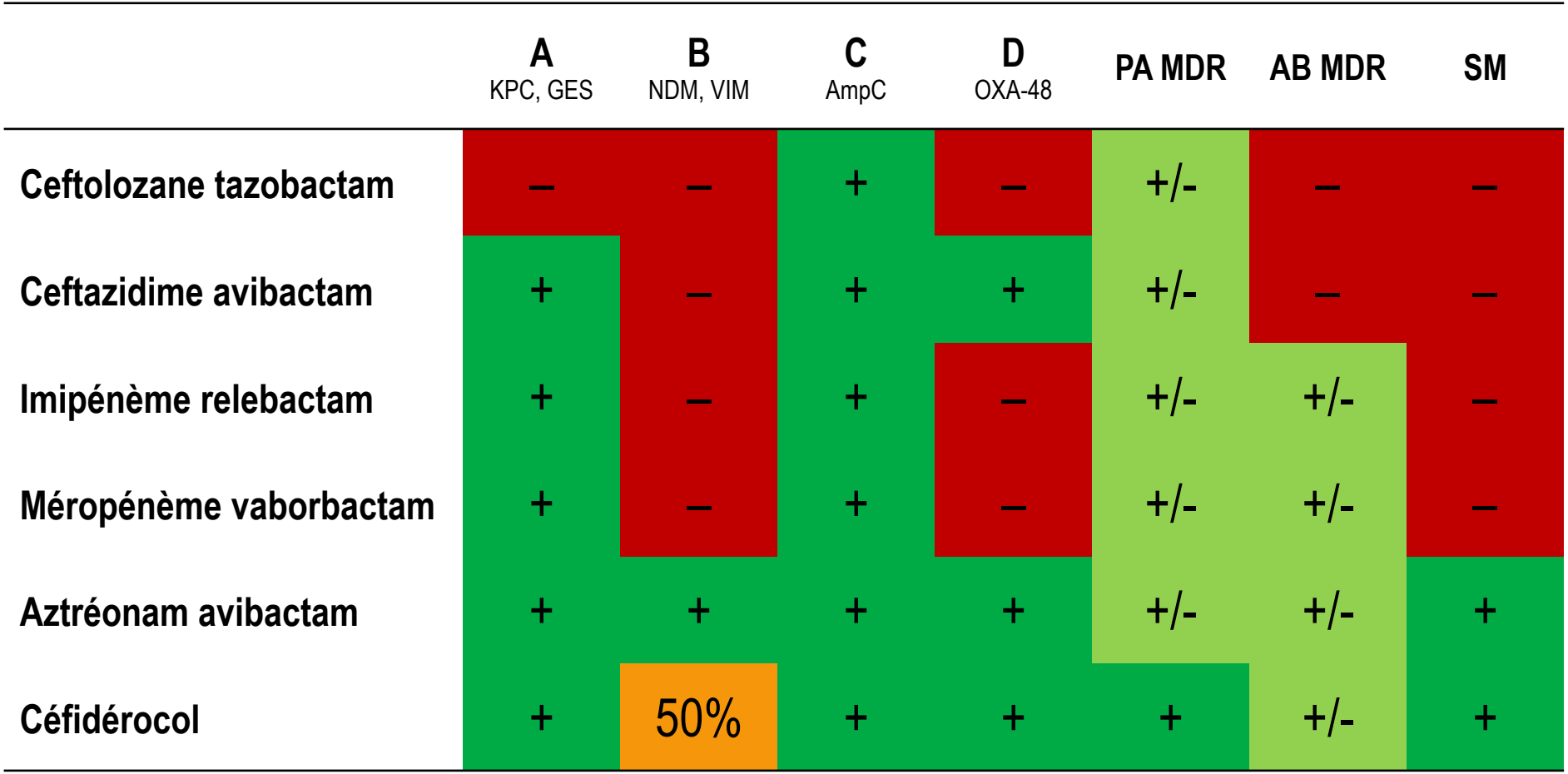
Céphalosporine + sidérophore
Liaison au fer → transport actif indépendant des porines
Haute stabilité / bétalactamases (+ transport passif)



	A KPC, GES	B NDM, VIM	C AmpC	D OXA-48	PA MDR	AB MDR	SM
Ceftolozane tazobactam	–	–	+	–	+/-	–	–
Ceftazidime avibactam	+	–	+	+	+/-	–	–
Imipénème relebactam	+	–	+	–	+/-	+/-	–
Méropénème vaborbactam	+	–	+	–	+/-	+/-	–
Aztréonam avibactam	+	+	+	+	+/-	+/-	+
Céfidérocol	+	+	+	+	+	+/-	+

Actif

Inactif



Actif

Inactif

Céfidérocol (FETCROJA®)

Cefiderocol: A Review in Serious Gram-Negative Bacterial Infections

Yahiya Y. Syed[1]

Drugs, 2021

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

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

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

Phase 2
IU « compliquées »

Phase 2
PNP nosocomiales

Phase 3
30% PNP nosocomiales
25% IU « compliquées »
20% bactériémies

Céfidérocol (FETCROJA®)

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

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

Le futur (plus ou moins) proche

	A KPC, GES	B NDM, VIM	C AmpC	D OXA-48	PA MDR	AB MDR	SM
Ceftaroline avibactam	+	–	+	+	–	–	–
Céfépime enmetazobactam	–	–	+	–	+/-	–	–
Céfépime taniborbactam	+	+	+	+	+	–	+
Céfépime zidébactam	+	–	+	+	+	–	+
Méropénème nacubactam	+	–	+	–	+	–	–

Conclusions

De l'espoir dans le pipeline !

- **PAS** en épargne carbapénèmes
- **PAS** en probabiliste (sauf …)

- Absence d'alternative
- Prescription documentée 2.0
- Antibiogramme génotypique selon la résistance théorique

	A KPC, GES	B NDM, VIM	C AmpC	D OXA-48	PA MDR	AB MDR	SM
Ceftolozane tazobactam	–	–	+	–	+/-	–	–
Ceftazidime avibactam	+	–	+	+	+/-	–	–
Imipénème relebactam	+	–	+	–	+/-	+/-	–
Méropénème vaborbactam	+	–	+	–	+/-	+/-	–
Aztréonam avibactam	+	+	+	+	+/-	+/-	+
Céfidérocol	+	+	+	+	+	+/-	+

PRIORISATION	A KPC, GES	B NDM, VIM	C AmpC	D OXA-48	PA MDR	AB MDR	SM
Ceftolozane tazobactam	NON	NON	1e	NON	1e	NON	NON
Ceftazidime avibactam	1e	NON	2e	1e	2e	NON	NON
Imipénème relebactam	2e	NON	X	NON	3e	X	NON
Méropénème vaborbactam	2e	NON	X	NON	NON	X	NON
Aztréonam avibactam		1e	X	X	4e	1e	1e
Céfidérocol	3e	2e	X	2e	5e	+/-	2e

ESCMID Clinical Microbiology and Infection 28 (2022) 521–547

European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine)

IDSA Infectious Diseases Society of America

Last updated March 7, 2022, and posted online

https://www.idsociety.org/practice-guideline/amr-guidance/

Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*)

pharmaceuticals

MDPI

Review

Microbiological, Clinical, and PK/PD Features of the New Anti-Gram-Negative Antibiotics: β-Lactam/β-Lactamase Inhibitors in Combination and Cefiderocol—An All-Inclusive Guide for Clinicians

Luigi Principe [1], Tommaso Lupia [2], Lilia Andriani [3], Floriana Campanile [4], Davide Carcione [5], Silvia Corcione [6], Francesco Giuseppe De Rosa [2,6], Roberto Luzzati [7], Giacomo Stroffolini [6], Marina Steyde [7], Giuliana Decorti [7,8,*] and Stefano Di Bella [7]