ß- lactamases et inhibiteurs de carbapénèmases

L. Dubreuil

Lille

Que retenir ? Les diapos marquées ***

Première ß-lactamase TEM

Evolution of TEM & SHV enzymes

Differences in amino acid substitution among sequenced enzymes

BLSE /TRI

Enzyme	37	102	162	235	236	237	261*	
TEM 1	Gln	Glu	Arg	Ala	Gly	Glu	Thr	
TEM 2	Lys	Glu	Arg	Ala	Gly	Glu	Thr	Sutcliffe (1971)
TEM 3	Lys	Lys	Arg	Ala	Ser	Gly	Thr	Ambler & Scott (1978)
TEM 4	Gln	Lys	Arg	Ala	Ser	Gly	Met	Sougakoff et al (1988)
TEM 5	Gln	Glu	Ser	Thr	Gly	Lys	Thr	Sougakoff et al (1989)
TEM 6	Gln	Lys	His	Ala	Gly	Gly	Thr	Sougakoff et al (1989)
TEM 7	Lys	Glu	Ser	Ala	Gly	Gly	Thr	Collatz et al (1971)
SHV 1	Gln	Asp	Arg	Ala	Gly	Glu	Leu	Labia (1986)
SHV 2	Gln	Glu	Arg	Ala	Ser	Gly	Thr	Barthelemy (1988)

* AA numered according to Sutcliffe

Pénicillinases classe A

ß lactamase producing E. coli : Activity of ß lactams

	MIC in mg/l			
	Wild type	TEM 1	TEM 1 + clavu 4 mg/l	TEM 2
Amoxicillin	4	512	4	>1024
Piperacillin	2	64	16	256
Cephalotin	4	4	ND	ND
Cefoxitin	4	4	4	ND
Cefotaxime	0.03	0.03	0.03	0.03
Imipenem	0.12	0.12	ND	0.12

Classification des ß-lactamases

Carbapénémases classe A

NMC-A	E cloacae	France (1990)
SME1	S. marcescens	Royaume UNI
SME2	S. marcescens	Etats Unis
IMI 1	E. cloacae	Etats Unis (1984)

Résistantes à IMP et ATZ mais Sensibles C3G

KPC 1	K. pneumoniae	Etats Unis (1996)
KPC21	K. pneumoniae	Etats Unis (1998)
GES 2	P. aeruginosa	Afrique du sud (2000)

Résistantes IMP, AZT, C3G

Susceptibility Profile of KPC-Producing *K. pneumoniae*

Antimicrobial	Interpretation	Antimicrobial	Interpretation
Amikacin	I	Chloramphenicol	R
Amox/clav	R	Ciprofloxacin	R
Ampicillin	R	Ertapenem	R
Aztreonam	R	Gentamicin	R
Cefazolin	R	Imipenem	R
Cefpodoxime	R	Meropenem	R
Cefotaxime	R	Pipercillin/Tazo	R
Cetotetan	R	Tobramycin	R
Cefoxitin	R	Trimeth/Sulfa	R
Ceftazidime	R	Polymyxin B	MIC >4μg/ml
Ceftriaxone	R	Colistin	MIC >4μg/ml
Cefepime	R	Tigecycline	S or R

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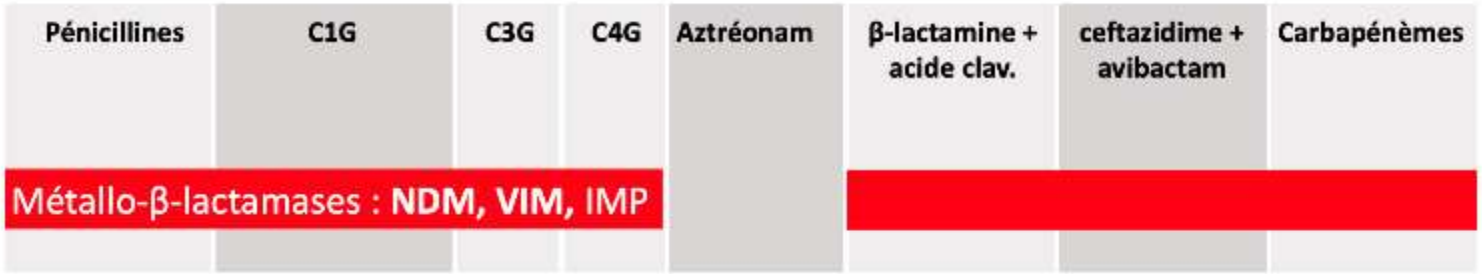
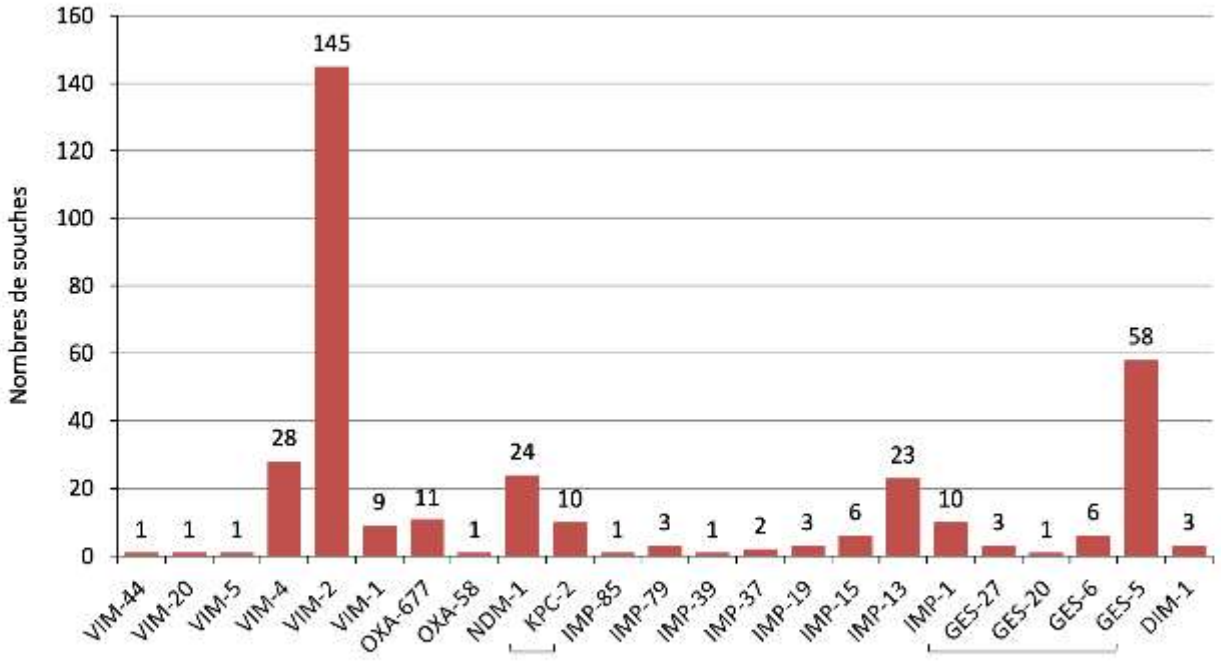
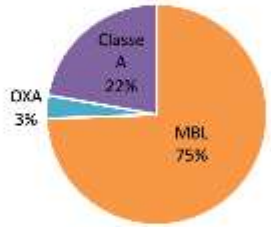
Metallo-β-lactamases in Enterobacterales (MBL)




NDM-1 (New Delhi metallo-beta-lactamase)

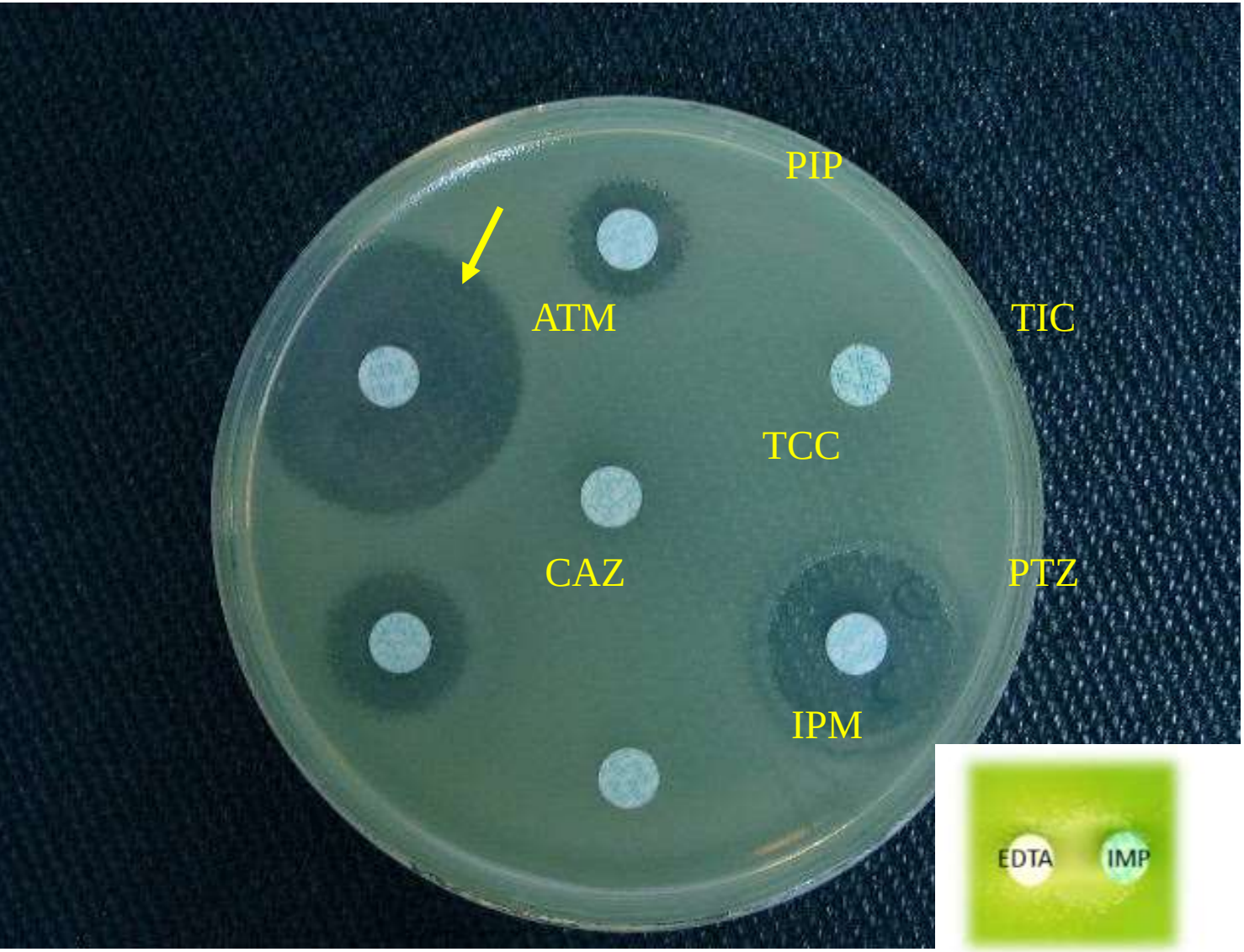
Carbapénèmases chez *P. aeruginosa* en France





Données CNR 2019 - 2020

β-lactamines et *P. aeruginosa*
Carbapénémase VIM-2

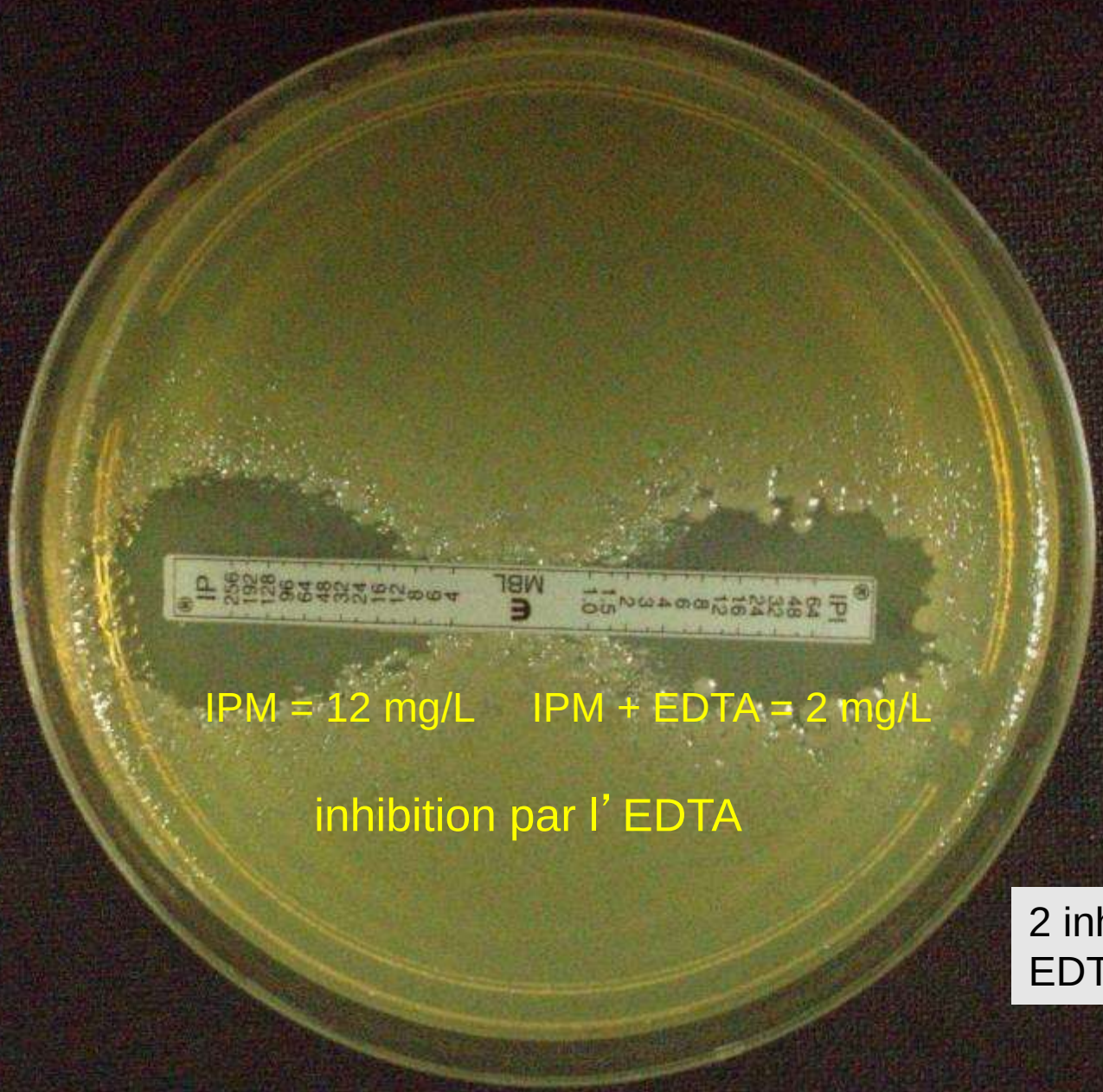


Class B

2 motifs

1 sensibilité aztréonam

2 inhibition par EDTA

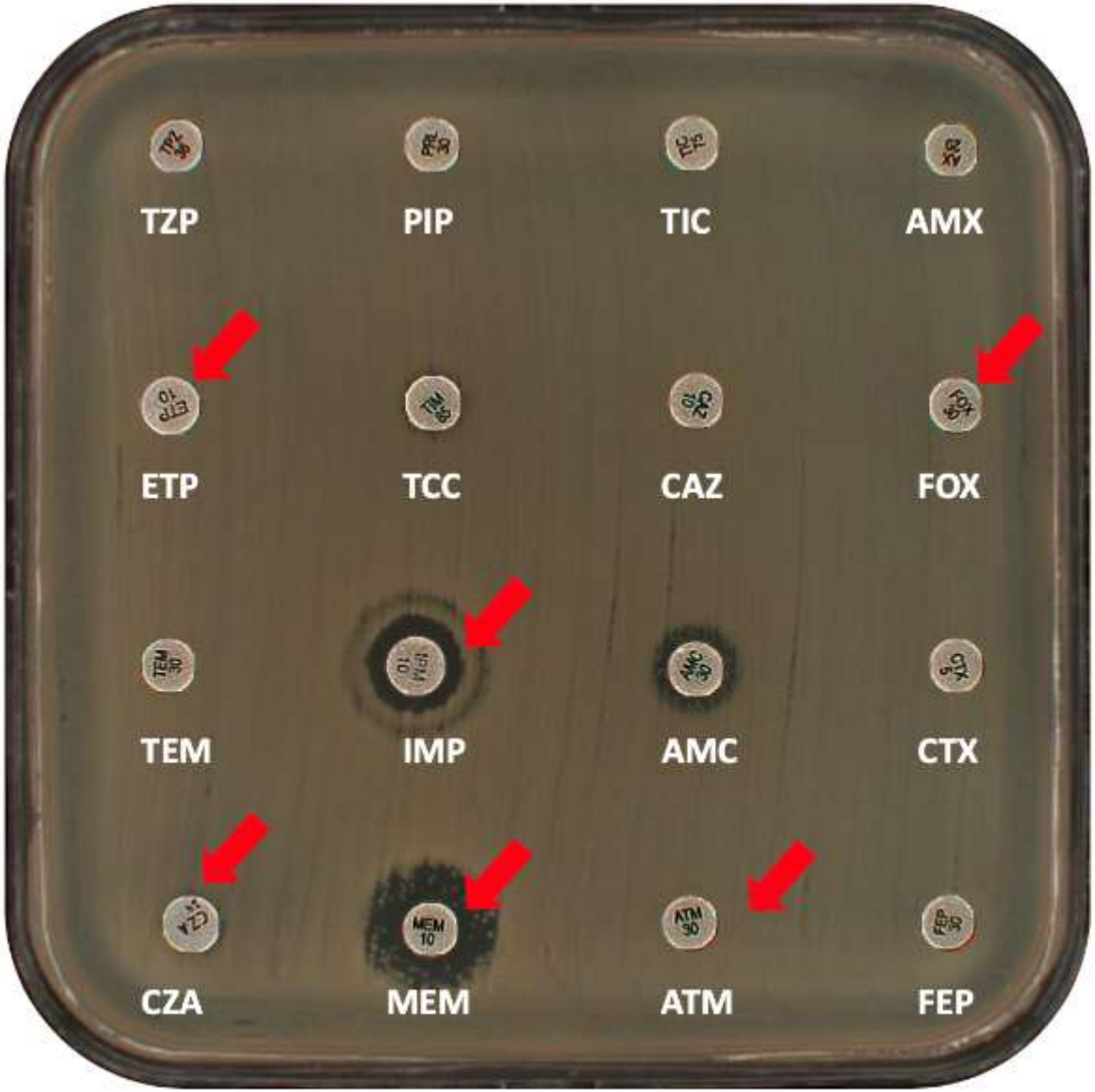


IPM = 12 mg/L IPM + EDTA = 2 mg/L

inhibition par l'EDTA

2 inhibé par EDTA

NDM-1 + CTX-M-15 producing E. coli



Aztréonam résistance due à la BLSE associée à NDM

Céphalosporinase classe C

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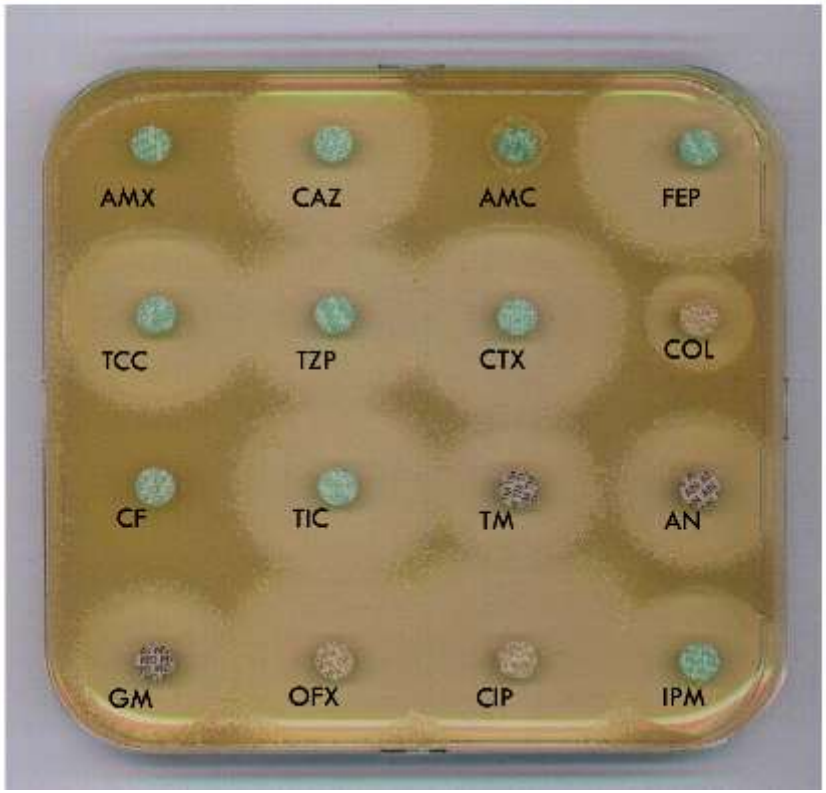
Chromosomique Entérobacterales groupe 3, Pyo, *Acinetobacter*

Plasmidique *E. coli; Klebsie*lla. CMY, DHA, ACT

Enterobacter cloacae



Groupe 3

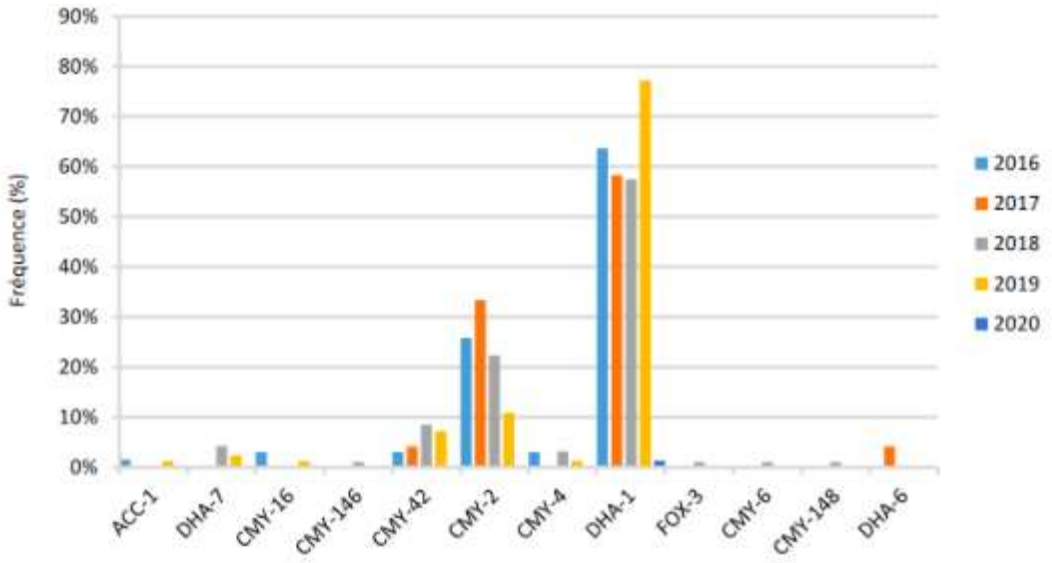
E. cloacae, K. aerogenes (ex Enterobacter) , S. marcescens, C. freundii, M. morganii, H. alvei, P. stuartii, P. agglomerans ...

Céphalosporinase chromosomique de bas niveau mais inductible (gène *ampC*) :

R AMX et C1G

Non inhibée par IBL → résistance à AMC

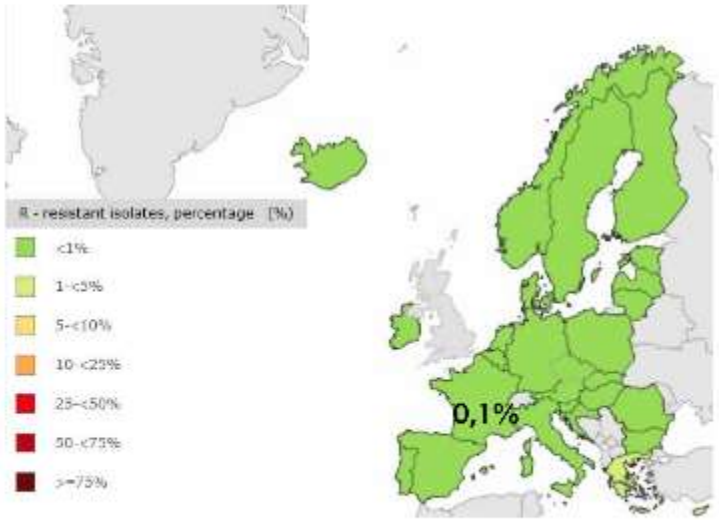
Données CNR : Diversité des céphalosporinases plasmidiques identifiées chez les entérobactéries (2016-2020)



Centre National de Référence de la Résistance aux Antibiotiques, Rapport d'activité 2019-2020

E. coli et *K. pneumoniae* R aux carbapénèmes

E. coli



K. pneumoniae

0,8% en France,
26,7 % en Italie,
73,7% en Grèce en 2021

ECDC, Annual surveillance report, 2021

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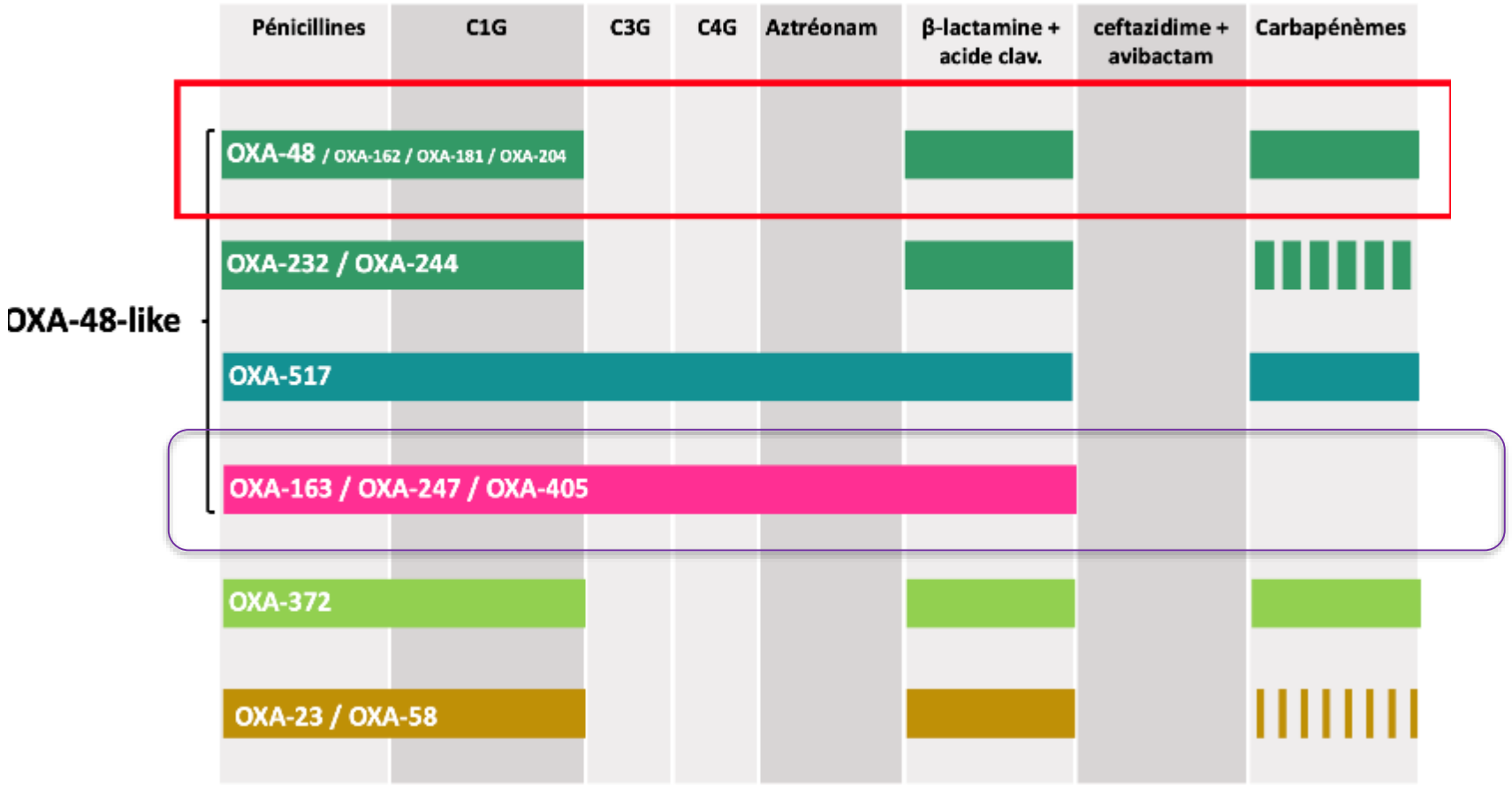
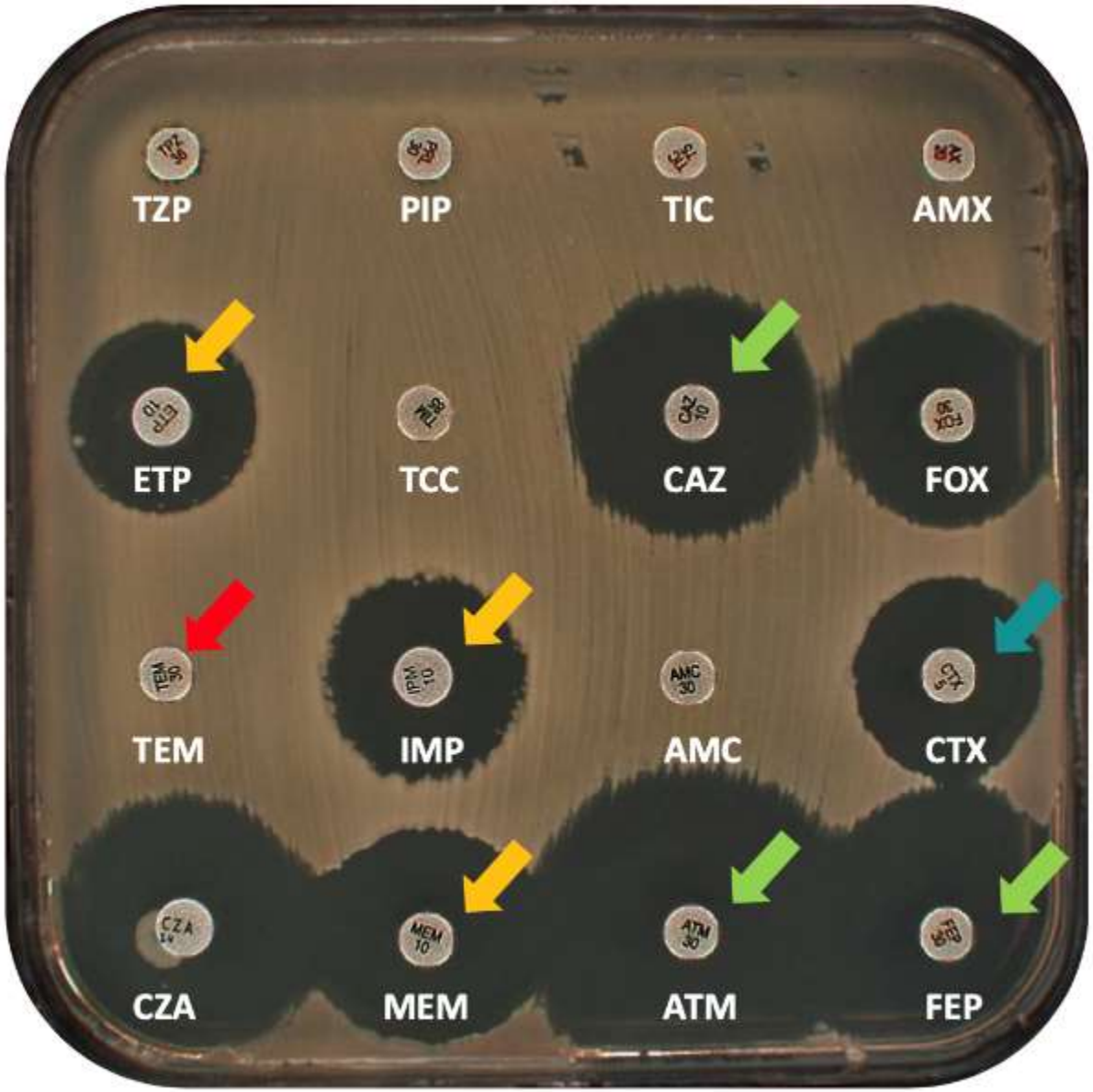
Class D carbapenemases in Enterobacterales



Complexe car:

Sensibles C3G, C4G et carbapénèmes R
Résistantes C3G, C4G et carbapénèmes S
Résistantes C3G, C4G et carbapénèmes R

OXA-48 producing *E. coli*

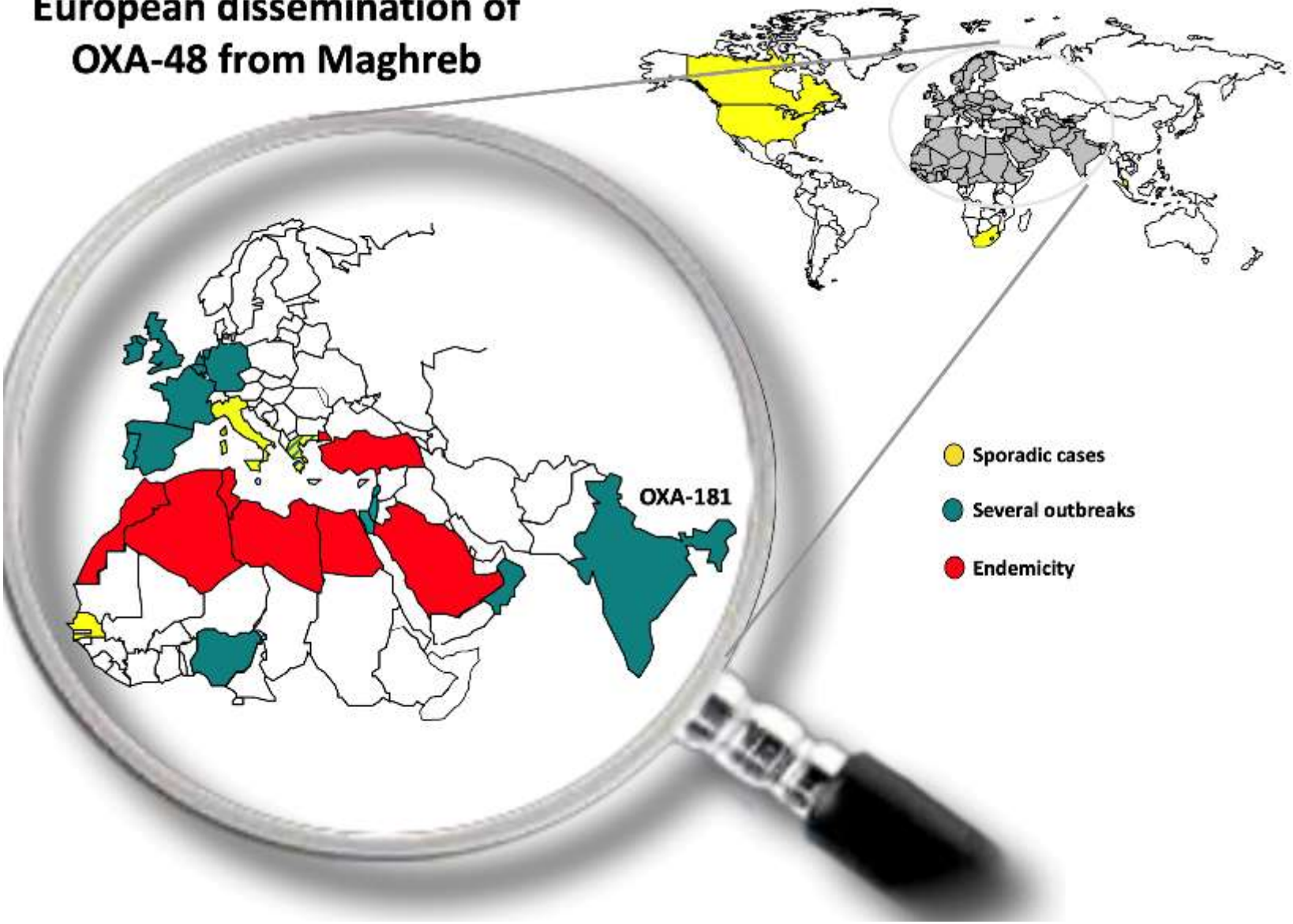


Classe D

C3G active si pas de BLSE associée

Résistance à la Témocilline

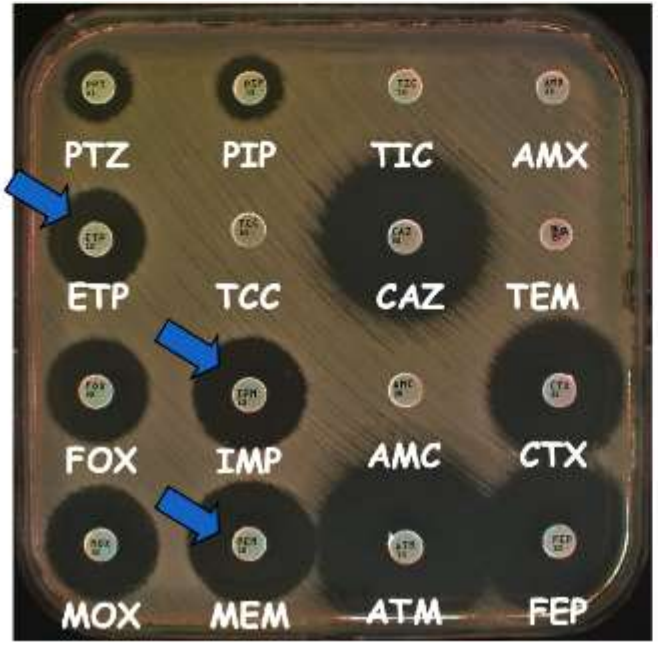
European dissemination of OXA-48 from Maghreb



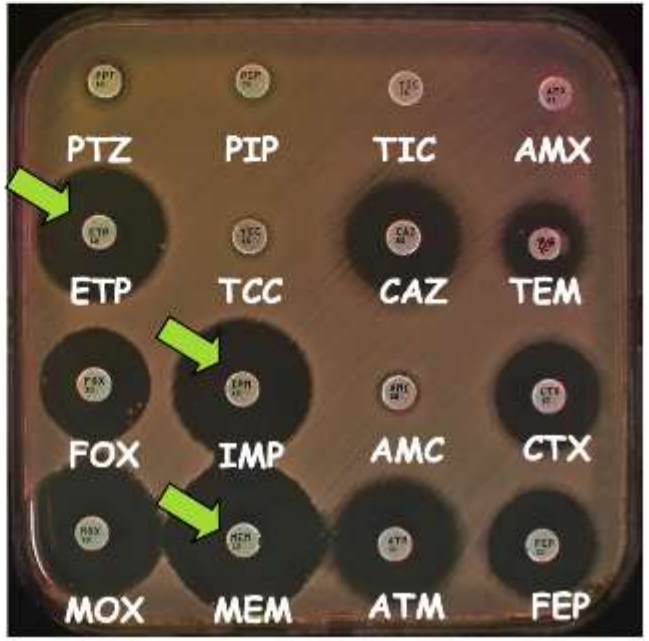
OXA-48 variants without carbapénèmase activity : OXA-163, OXA-247, OXA-405

- **No carbapenemase activity** : deletion in the active site

OXA-48



OXA-163



Dissémination à bas bruit de la carbapénèmase OXA-244 car difficultés de détection

Non R à la témocilline =
Problème de détection

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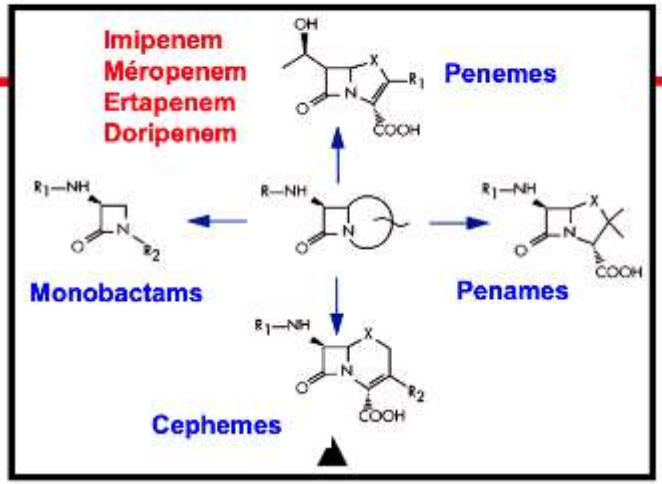
Resistance to β-lactams: β-lactamases

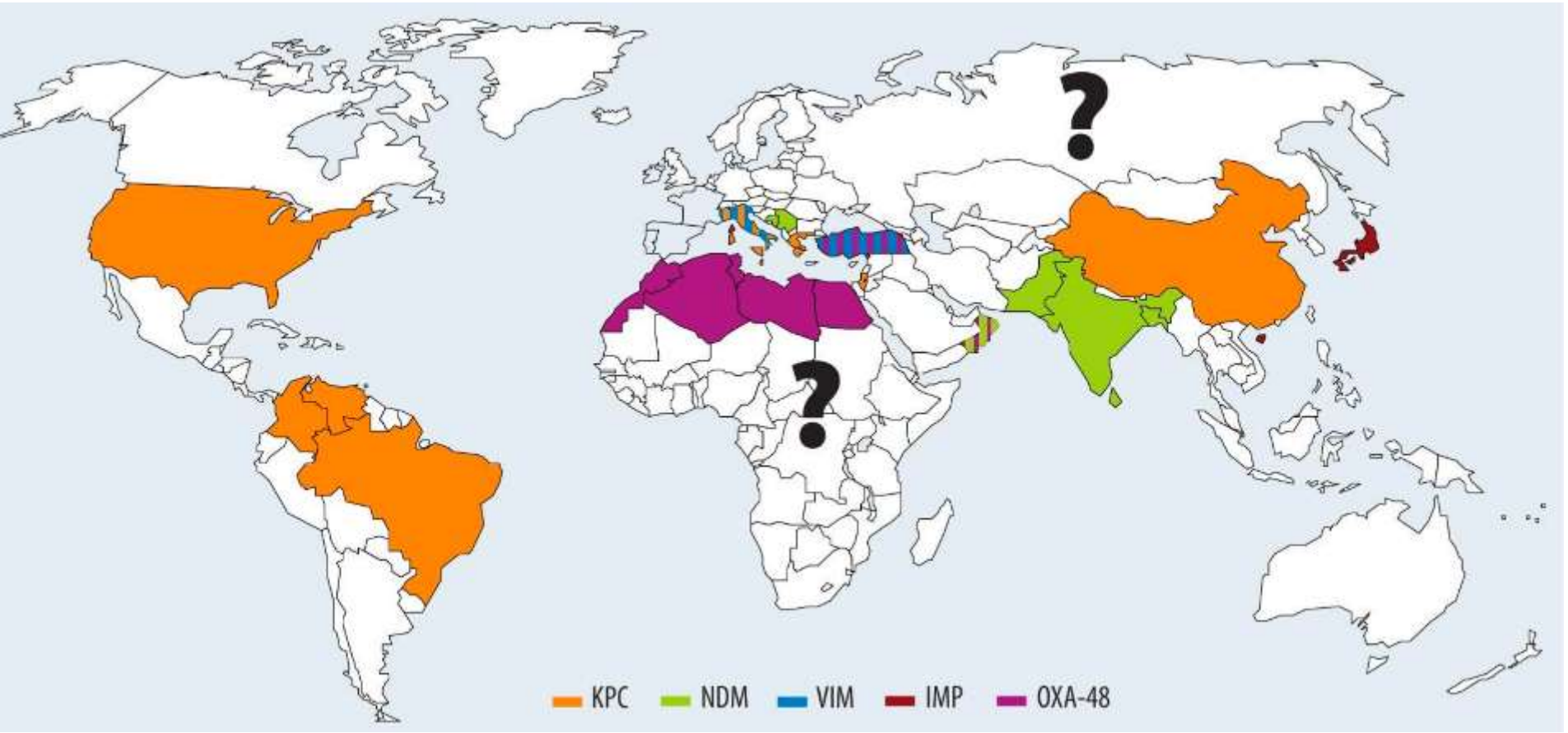


β-lactamases

	Active site		G		KTG	Groupe	Inhibitors	
A	SXXK 70-73	SXN 130-132	156	Ωloop 164-179	234-236	Penicillinase	clavulanic acid	KPC
C	SXXK 64-67	YXN		Ωloop 208-213	315-317	Cephalosporinase	Cloxacillin	
D	SXXK 70-73	YGN 144-146		WxExxL 164-169	216-218	Oxacillinase	Avibactam	OXA-48
B Zn++	61-65	Zn1 ligand His116, 118,196		Zn2 ligand Asp120, Cys221,His263		Metallo-enzyme	EDTA	NDM/VIM/IMP

Aztreonam

Entérobactérales productrices de carbapénèmases EPC



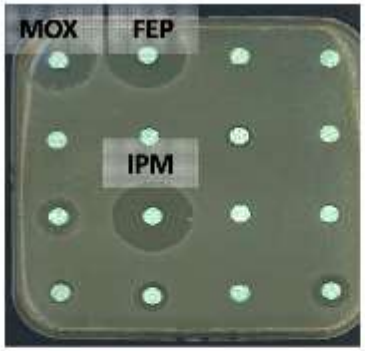
CRE : Carbapenem resistance in enterobacteriaceae

1) Decreased outer membrane permeability + β-lactamase with no (or very poor) hydrolytic activity against carbapenems

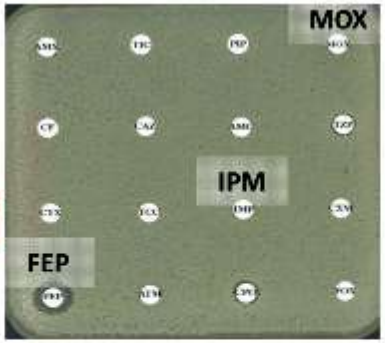
Resistance to Expanded spectrum cephalosporins BUT Carbapenem susceptible,

→ Lee EH, Nicolas MH, Kitzis MD, Pialoux G, Collatz E, Gutmann L. AAC 1991, 35:1093-8

Resistance to carbapenems by decreased permeability



after 21 days of imipenem mono therapy

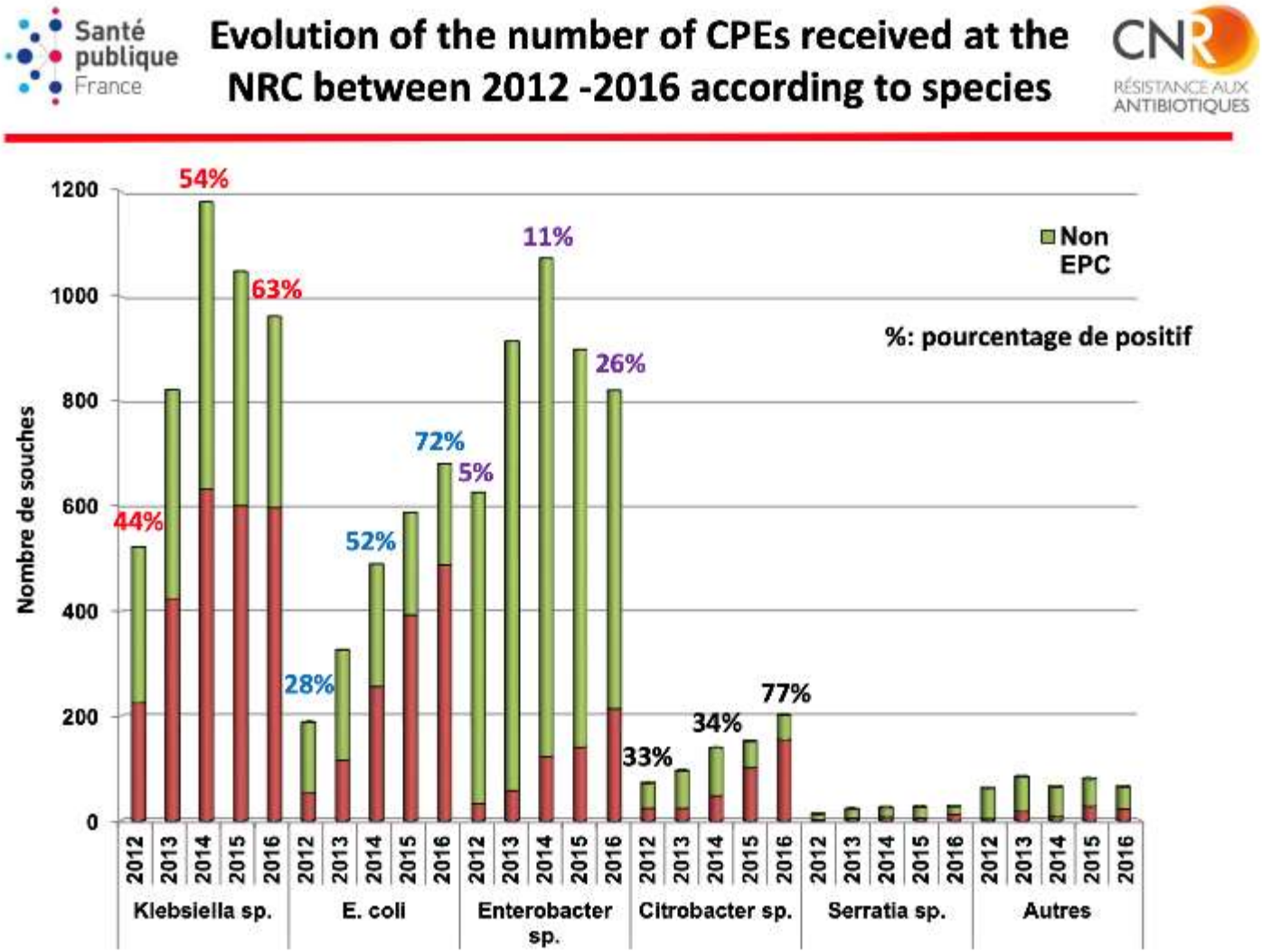


Important in terms of treatment issues, but no epidemic dissemination,

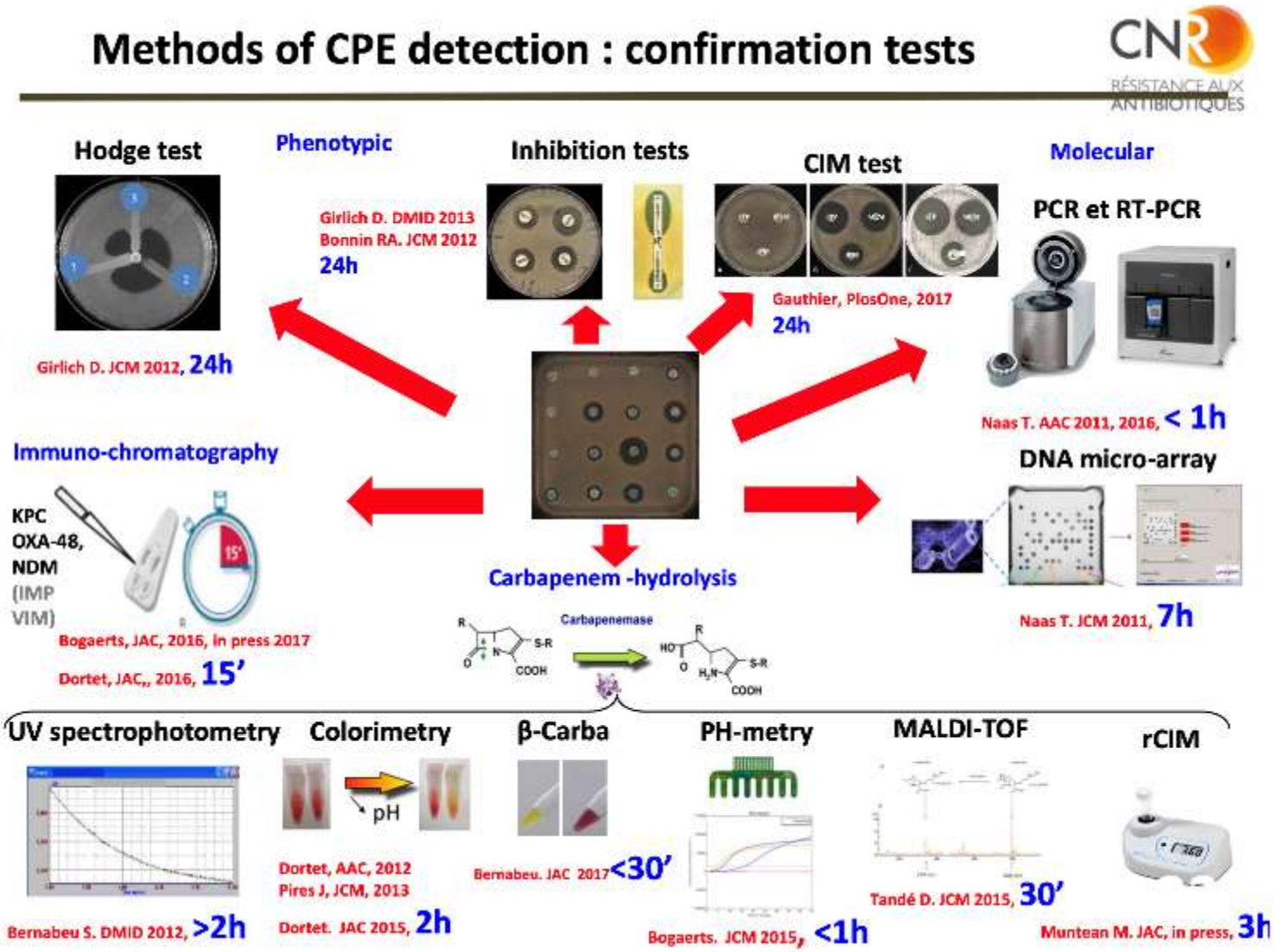
=> chromosomal mutations with important fitness cost

Plus fréquent groupe 3.
Enterobacter , Citrobacter

Résistance aux carbapénèmes avec ou sans carbapénèmase



Parmi les nombreuses méthodes de détection des Carbapénèmases



Tests rapides de confirmation

- **Tests enzymatiques**
  - Détectent toutes les carbapénémases mais ne permetten pas de les typer
- **Biologie moléculaire :**
  - Détection le plus souvent de OXA-48 (et OXA-48 like), KPC, VIM, IMP-1, NDM
  - Ne détecte pas toujours OXA-23
- **Bandelettes d'immunochromatographie**
  - Anticorps monoclonaux
  - OXA-48 (et ses variants), OXA-163, OXA-23
  - NDM, VIM, KPC, IMP

Evaluations faites par les CNR
de la résistance aux antibiotiques

Résistance aux carbapénèmes chez *P. aeruginosa*

Study	Year	# Hospitals	Strains			% ESBLs		% Carbapenemases	
			Number	Origin	Selection	In collection	France estimate	In collection	France estimate
GESPA	1999-2004	6	120	Bacteremias	non redundant	0	< 1%	0	< 1%
ONERBA	2007	85	140	Diagnostic samples non CF	non redundant CAZ^R (>32mg/L)	7.9%	1%	2.9%	0.4%
GESPAR	2010	26	109	ICU	non redundant $IPM^{I/R}$ (>4mg/L)	3.7%	0.7%	6.4%	1.2%
GERPA	2015	36	420	Diagnostic samples non CF	non redundant CAZ^R (8mg/L) +/- $IPM^{I/R}$ (>4mg/L)	2.9%	0.55%	3.1%	0.86%

***

CNR RÉSISTANCE AUX ANTIBIOTIQUES

2020: *n*= 47 958 souches

- **CAZ^R = 18.2%**
- **IMP^R = 19.0%**
- **MER^R = 17.3%**

Santé publique France

RéPiDS

Mission SPARES, rapport 2022

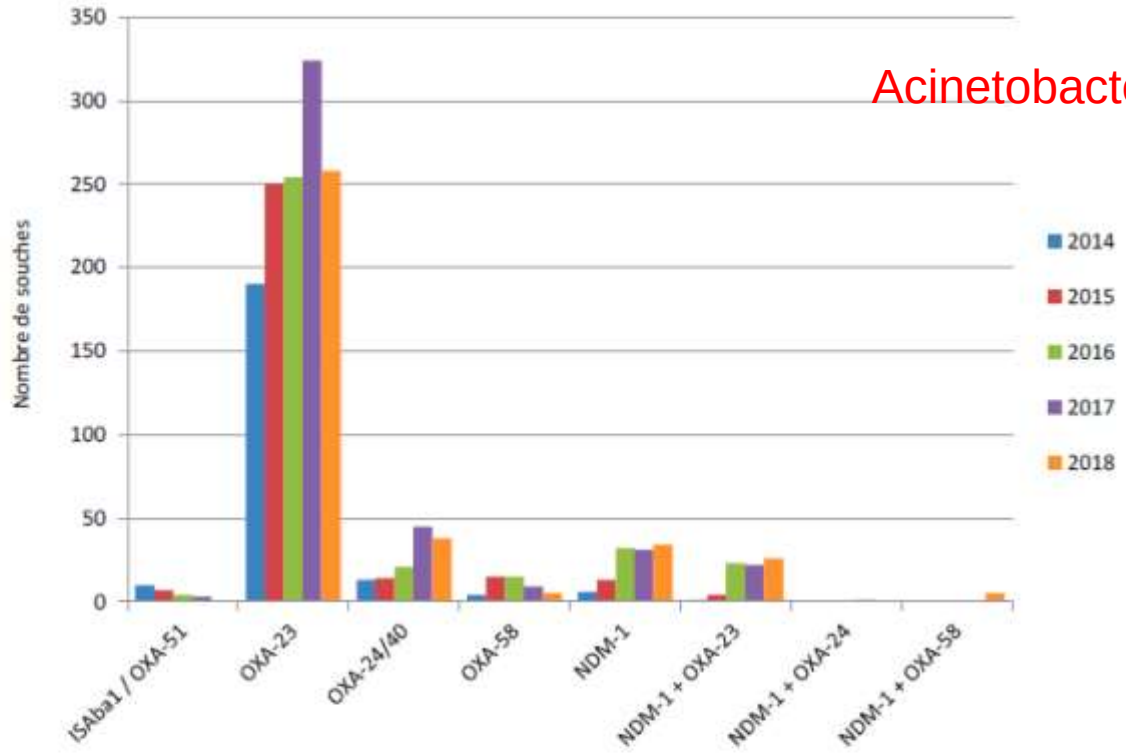
✸ **>85%** des souches résistantes aux carbapénèmes par altération de la porine OprD

2020: *n*= 47 958 souches

- **CAZ^R = 18.2%**
- **IMP^R = 19.0%**
- **MER^R = 17.3%**

Mutants ampC ++ : 95% des souches CAZ^R
Mutants oprD- : 95% des souches imp^R

Epidémiologie nationale
CNR BGN non fermentaires



Carbapénèmases identifiées chez *A. baumannii* sur la période 2014-2018.

Plus de 1000 ß-lactamases décrites à ce jour

Class A

TEM Temoniera

SHV Suylfhydril reagent variable

BLSE Plus de 350 types dont:

TEM3-TEM >180

SHV2- SHV > 130

SFO Serratia fonticola ß-lactamase

TLE Tem-like ß-lactamase

PER Pseudomonas extended resistant ß-lactamase

GES Guyana ß-lactamase

CTXM Cefotaxime hydrolizing ß-lactamase

Carbapénèmase

KPC Klebsiella carbapenemase,

Nmc-A non metallo carbapénèmase

IMI Imipenemase,

SME Serratia marcencens ß-lactamase,

GES

Classe B

NDM New Dehli ß-lactamase	29 variants
VIM Verona imipenemase	69 variants
IMP Imipenem resistant Pseudomonas	85 variants

ccrA = cfiA Bacteroides fragilis II groupe homology

Classe C ampC genes >50

CMY	cefamycin hydrolysing ß-lactamase
ACT-1	ampC type ß lactamase
MOX	Moxalactam hydrolysing ß-lactamase
FOX	cefoxitin hydrolysing ß lactamase
DHA-1	Dharan Hospital Saudi arabia ß-lactamase
ACC	Ambler C Class ß lactamase
CFE	Citrobacter freudii ß-lactamase
ADC	Acinetobacter derived cephalosporinase

Classe D oxacillininase > 250 enzymes

DU infectiologie 2025

Carbapénèmases et

Inhibiteurs de carbapénèmases

L. Dubreuil

Un nouvel inhibiteur de BLSE qui n'est pas un inhibiteur de carbapénèmase

Enmetazobactam. Breakpoint CFP + ENM. 4/4 Enterobacterales
CFT+ tazo. 2/2. et 4=4 Pyo

BLSE, mais pas KPC, actif sur C et quelques D dont OXA 48

Entérobactérales

Ampc +++. DHA1 > CFT-TAZO

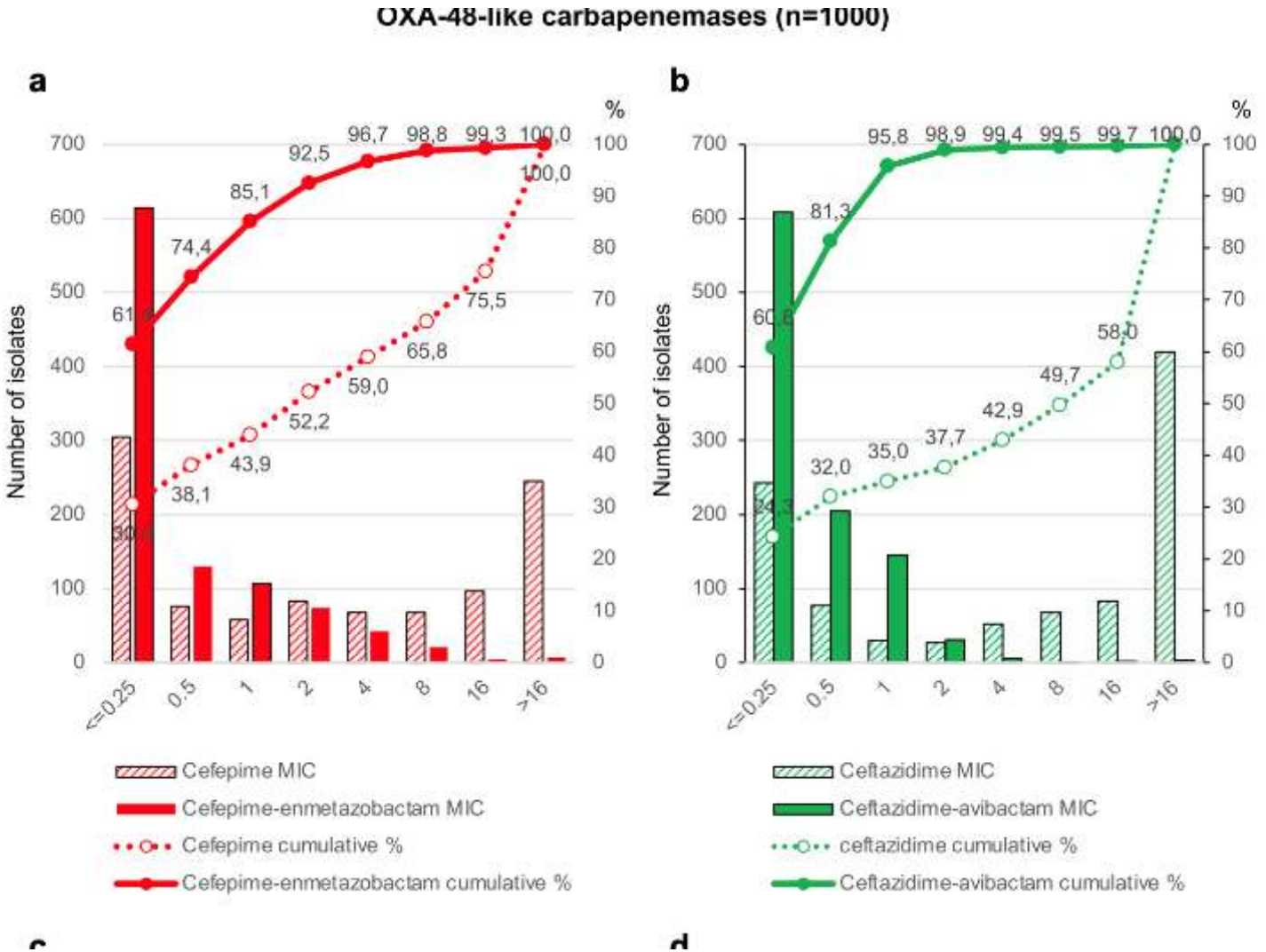
BLSE .+++. CTXM, SHV,

Défaut de porine non affecté comme CFT

Oxa si CAZ S +++ si CAZ R Variable.
Dans les 2 cas. >> CFP + ENM = CAZ-AVI

KPC variable <50%. < CAZ + Avi.

MBL non



Contrairement à IMI + Rel. ou Mero-Vabor

R.A. Bonnin et al. / Clinical Microbiology and Infection xxx (xxxx)

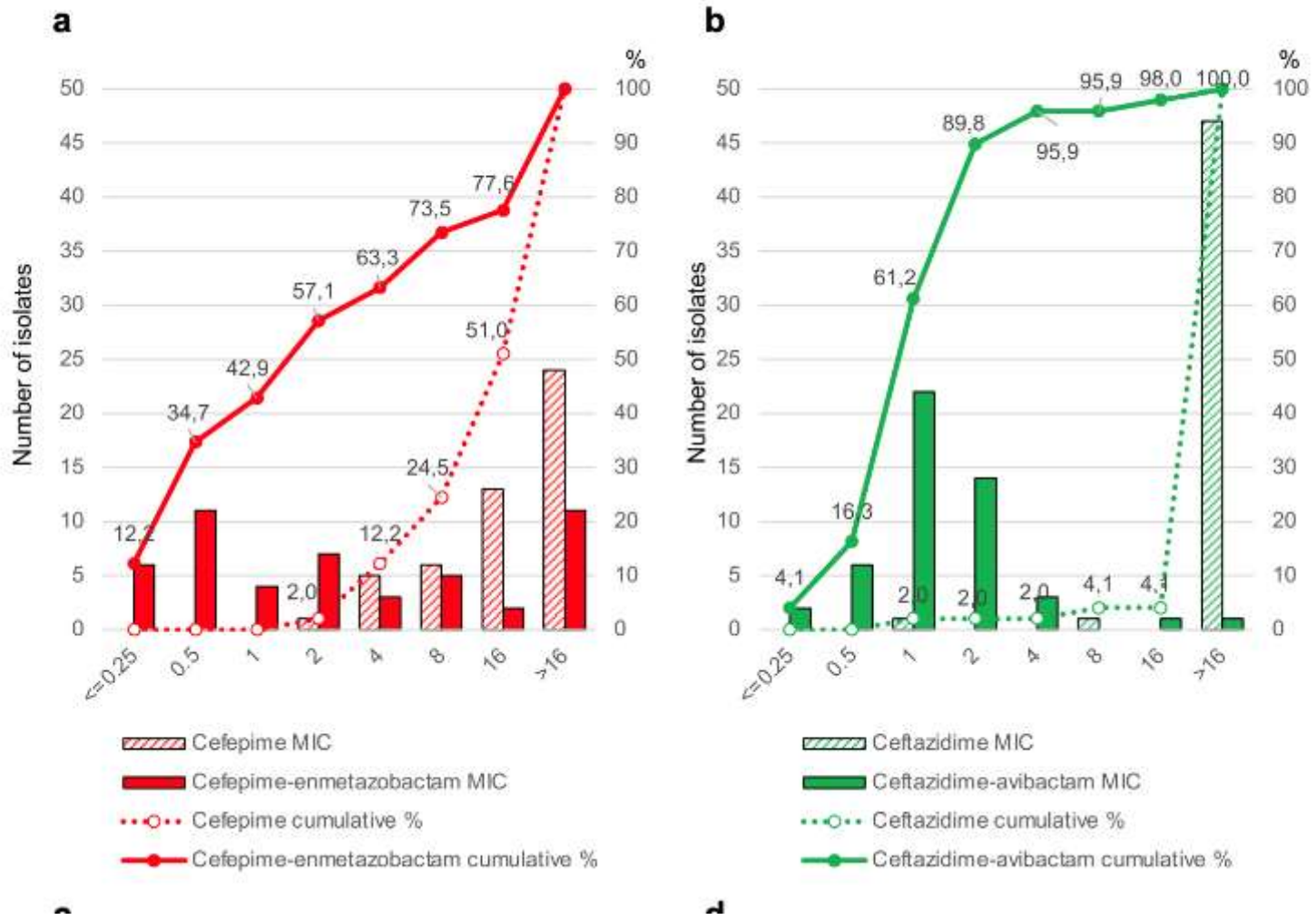

KPC carbapenemases (n=49)
a
b
Number of isolates
%
<=0.25
0.5
1
2
4
8
16
>16
12,2
34,7
42,9
57,1
63,3
73,5
77,6
2,0
12,2
24,5
51,0
4,1
16,3
61,2
89,8
95,9
95,9
98,0
100,0
2,0
2,0
2,0
4,1
4,1
Cefepime MIC
Cefepime-enmetazobactam MIC
Cefepime cumulative %
Cefepime-enmetazobactam cumulative %
Ceftazidime MIC
Ceftazidime-avibactam MIC
Ceftazidime cumulative %
Ceftazidime-avibactam cumulative %

Table 2
Cumulative rate of susceptibility of carbapenem-resistant Enterobacterales that do not produce a carbapenemase.

Antimicrobial	MIC (mg/L)								MIC_{50}	MIC_{90}
	≤0.25	0.5	1	2	4	8	16	>16		
Cefepime	0.8%	5.0%	6.6%	13.2%	24.8%	35.5%	50.4%	100.0%	16	>16
Cefepime-enmetazobactam	9.9%	21.5%	41.3%	53.7%	66.9%	78.5%	87.6%	100.0%	2	>16
Ceftazidime	0.0%	0.0%	0.8%	2.5%	5.0%	5.8%	11.6%	100.0%	>16	>16
Ceftazidime-avibactam	10.7%	22.3%	52.9%	76.9%	92.6%	96.7%	100.0%	100.0%	1	4
Imipenem	24.0%	41.3%	69.4%	76.9%	87.6%	93.4%	96.7%	100.0%	1	8
Imipenem-relebactam	54.9%	77.9%	89.3%	93.4%	96.7%	100.0%	100.0%	100.0%	≤0.25	2
Meropenem	28.3%	37.5%	49.2%	66.7%	80.8%	92.5%	95.8%	100.0%	2	8
Meropenem-relebactam	47.1%	57.9%	70.2%	86.0%	90.9%	95.9%	99.2%	100.0%	0.5	4
Ertapenem	2.5%	5.8%	22.3%	33.9%	40.5%	57.0%	71.9%	100.0%	8	>16

Colors correspond to clinical categorization according to EUCAST guideline: green for "Susceptible at standard dosage"; yellow for "Susceptible upon increased exposure" and red for "Resistant"

66% de sensibilité souches ne produisant pas de carbapénèmase mais résistante aux carbapénèmes

Morissey

1696 Enterobactérales 92,6% inhibées à 0,25 mg/L

Klebsiella BLSE 92% à 1 mg/L pour céfépime enmetazobactam vs 8mg/l pour cefepime tazobactam

In vitro activity of cefepime-enmetazobactam on carbapenem-resistant gram negatives

Remy A. Bonnin 1, 2, 3, Katy Jeannot 4, 5, Anne Santerre Henriksen 6, Juan Quevedo 7, Laurent Dortet 1, 2, 3, *

https://doi.org/10.1016/j.cmi.2024.09.031
CMI 2024

Cefepime-enmetazobactam treatment of OXA-48 producers- related infections **might help to limit the usage of ceftazidime-avibactam which is now considered as the reference for the treatment of infection caused by OXA-48 producers**

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Généralités

Tous les nouveaux inhibiteurs autres que acide clavulanique, tazobactam, enmetazobactam, sulbactam sont actifs sur :

classes A dont les KPC

Et

Class C

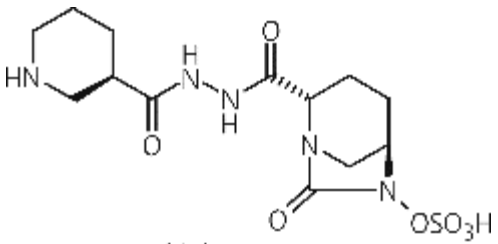
Céphalosporinases (Cases) chromosomiques ou plasmidiques y compris les hyperproducteurs de Cases

Mais pas tous les sur-producteurs Cases (ESACs)

Extended spectrum amp C. qui hydrolyse céfépime

B-lactamines et inhibiteurs de ß-lactamases IBL

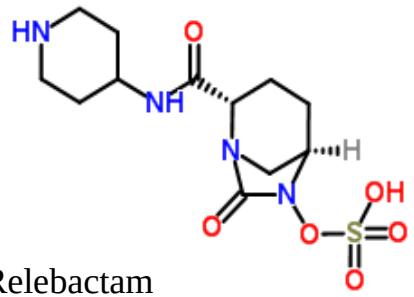
bicyclo-acyl hydrazide = BCH



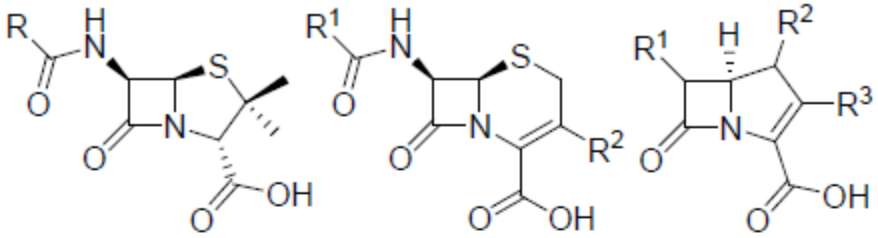
Zidebactam

diazabicyclooctanes= **DBO**

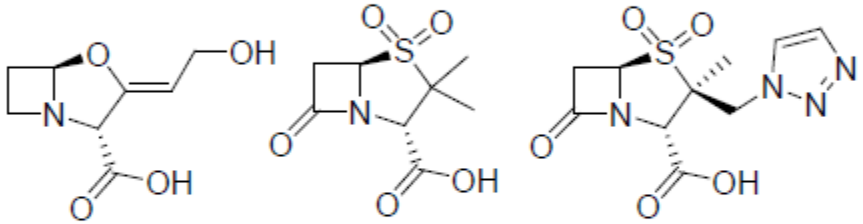
Nacubactam



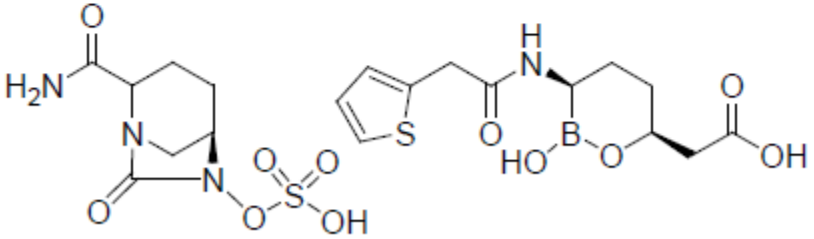
Relebactam



Penicillin Cephalosporin Carbapenem



Clavulanic acid Sulbactam Tazobactam

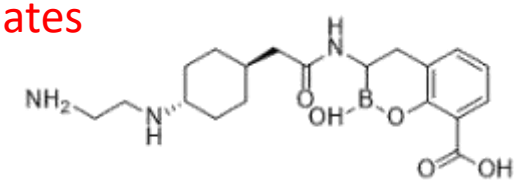


Avibactam (NXL-104) RPX-7009 = Vaborbactam

Figure 1: β-Lactam antibiotics and β-lactamase inhibitors.

Boronates

VNRX 5133=
Taniborbactam

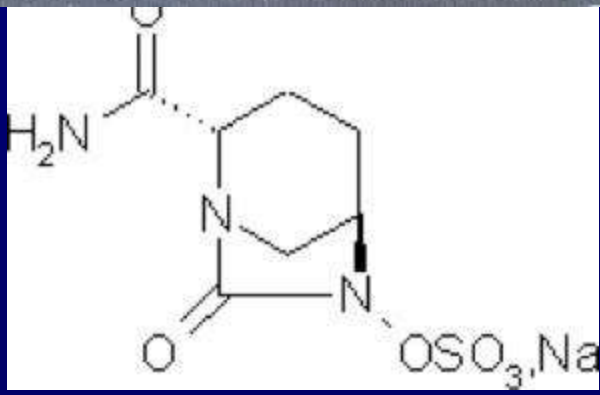


Activity of NXL104 (a new ß-lactamase inhibitor) Avibactam in Combination with ß-lactams

L. J. DUBREUIL[1], S. MAHIEUX [1], C. NEUT [1], C. MIOSSEC [2], J. PACE [2], A. BRYSKIER [3]

Abstract E188 ICCAC San Francisco, September 2009

1 Lille, 2 Novexel 3 Hoechst Marion Roussel -> Aventis



Ceftazidime- avibactam

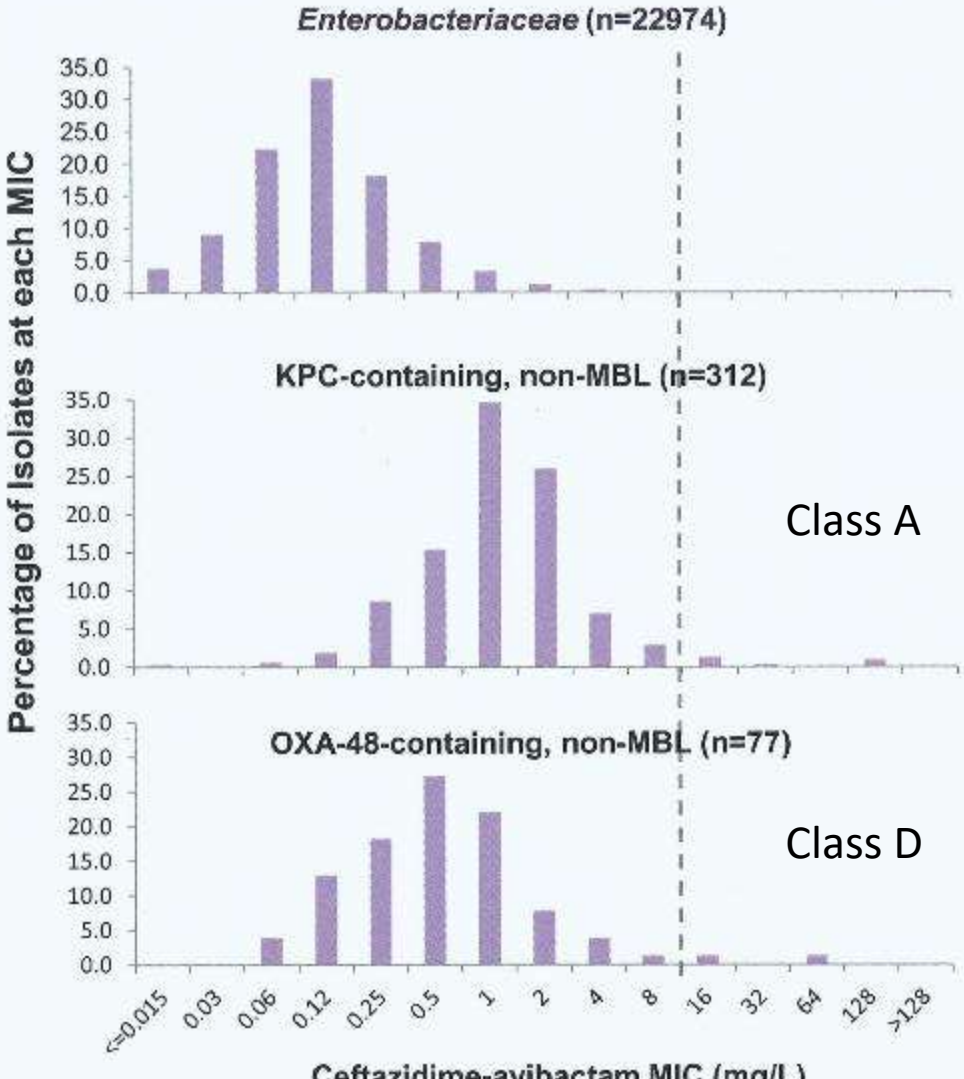
In-Vitro Activity vs KPC and OXA-48 Genotype

Enterobacteriaceae

Classes A,C,D

≤8 mg/L categorizes the majority of KPC genotype isolates as susceptible

≤8 mg/L categorizes the majority of OXA-48 genotype isolates as susceptible



Premier échec décrit en 2017

Ceftazidime-avibactam (CZA) in 2015

- Activity against serine beta-lactamases, including KPC
  - Isolate tested and found to have KPC-3
- No activity vs. class B beta-lactamases (e.g., NDM)
  - Isolate negative for MBLs (by PCR and by WGS)
- So… should work, right?

First case of KPC-producer resistant to CZA
Isolated 1 month prior to CZA FDA-approval

* MIC confirmed resistance, 16 – 32 ug/mL

Antimicrob. Agents Chemother. **2017** vol. 61 e00537-17

Mutations !!

prevent avibactam from binding to and inhibiting the ß-lactamase.

Resistance to CAZ-AVI by KPC-2 Variants

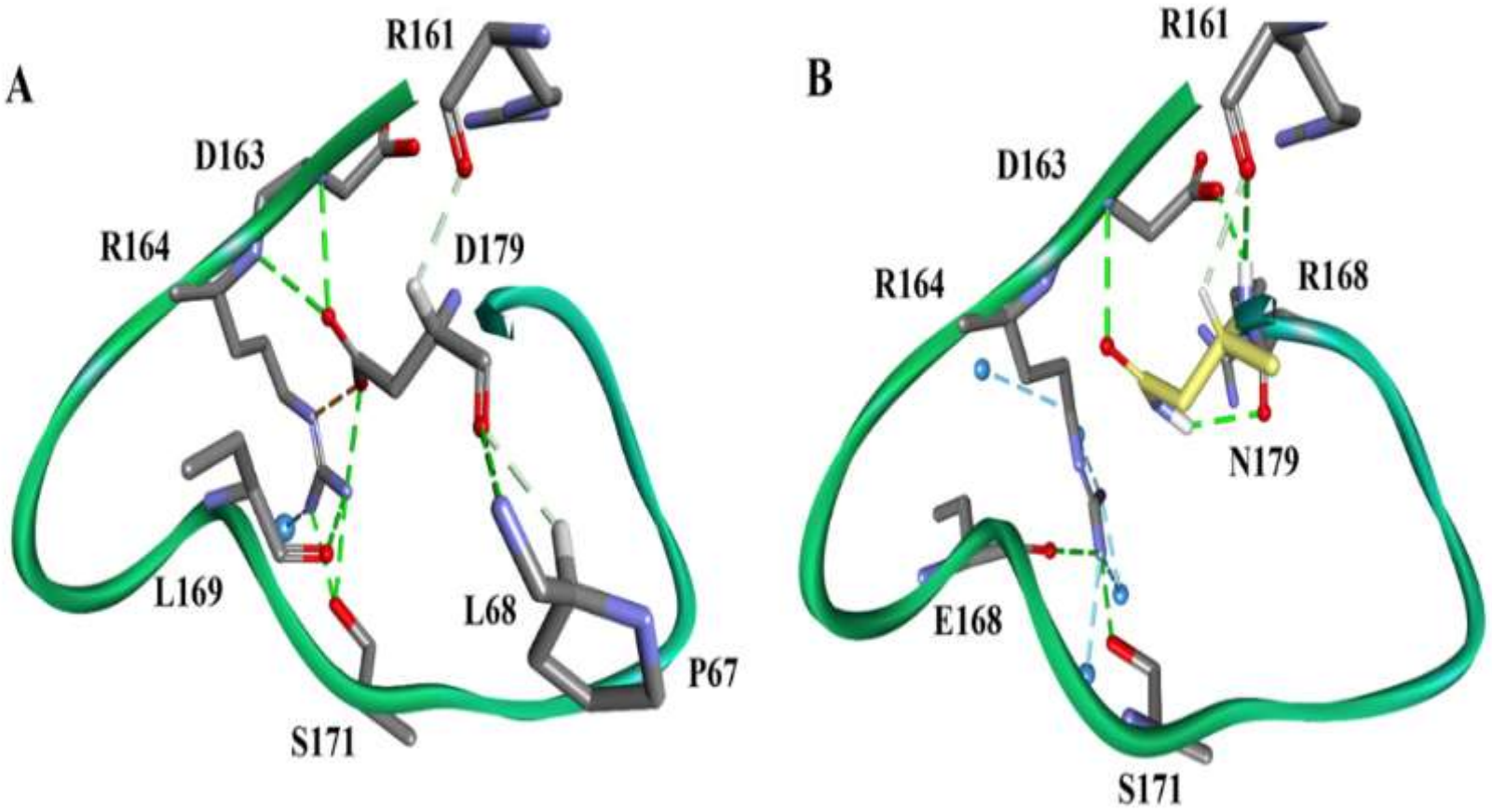


FIG 1 Ω-Loop hydrogen bond networking changes due to the aspartate (D)-to-asparagine (N) substitution at Ambler position 179 in KPC-2. (A) KPC-2. (B) Asp179Asn (D179N) variant.

Phénomène de mutations : Fréquent et rapide (deux semaines de traitement)

Shields novel ST258, clade II sublineage, which are not hypermutators

Ceftazidime-avibactam resistance

10% of patients (8/77) treated for CRE infections developed ceftazidime-avibactam resistance

14% of patients (8/59) treated for CR-Kp infections developed ceftazidime-avibactam resistance

Patient	Days of C-A	Infection Type	Location	Treatment regimen	RRT*	Outcome at 30 days
1	10	PNA	MICU	Monotherapy	No	Failure
2	19	IAI	SICU	Monotherapy	CRRT	Failure
3	15	PNA	SICU	Monotherapy	No	Success w/ relapse
4	15	PNA	CTICU	+ inhaled gent	CRRT	Failure
5	15	PNA	MICU	Monotherapy	HD	Failure
6	7	PNA	MICU	Monotherapy	No	Failure
7	25	PNA	10G	Monotherapy	HD	Failure
8	31	PNA	CTICU	+ inhaled/IV gent	CRRT	Failure

* Independent risk factor for resistance (OR: 11.70, 95% CI: 1.79 – 76.0; *P*=0.003)

Open Forum Infectious Diseases

ID CASE

Emergence of Ceftazidime-Avibactam Resistance and Restoration of Carbapenem Susceptibility in *Klebsiella pneumoniae* Carbapenemase-Producing *K pneumoniae*: A Case Report and Review of Literature

Ryan K. Shields,[1,2] M. Hong Nguyen,[1,2] Ellen G. Press,[1] Liang Chen,[3] Barry N. Kreiswirth,[3] and Cornelius J. Clancy[1,2,4]

Isolate 4-A:
Meropenem-resistant
Ceftazidime-avibactam susceptible

Isolate 4-C:
Meropenem-susceptible
Ceftazidime-avibactam resistant

KPC Variant A177E, D179Y

Effet Paradoxal

Mécanismes de résistance acquise à ceftazidime –avibactam

Variants de SHV-1 et KPC-2; cause : une seule mutation isolée

Mutations en 164 ou 179 sur KPC2 empêche la fixation (binding) de l'inhibiteur sur la ß-lactamase

Plasmide de KPC3 variant apparaissant après 10 à 19j de traitement de KPC

Association imperméabilité et surproduction AmpC (ESACs)

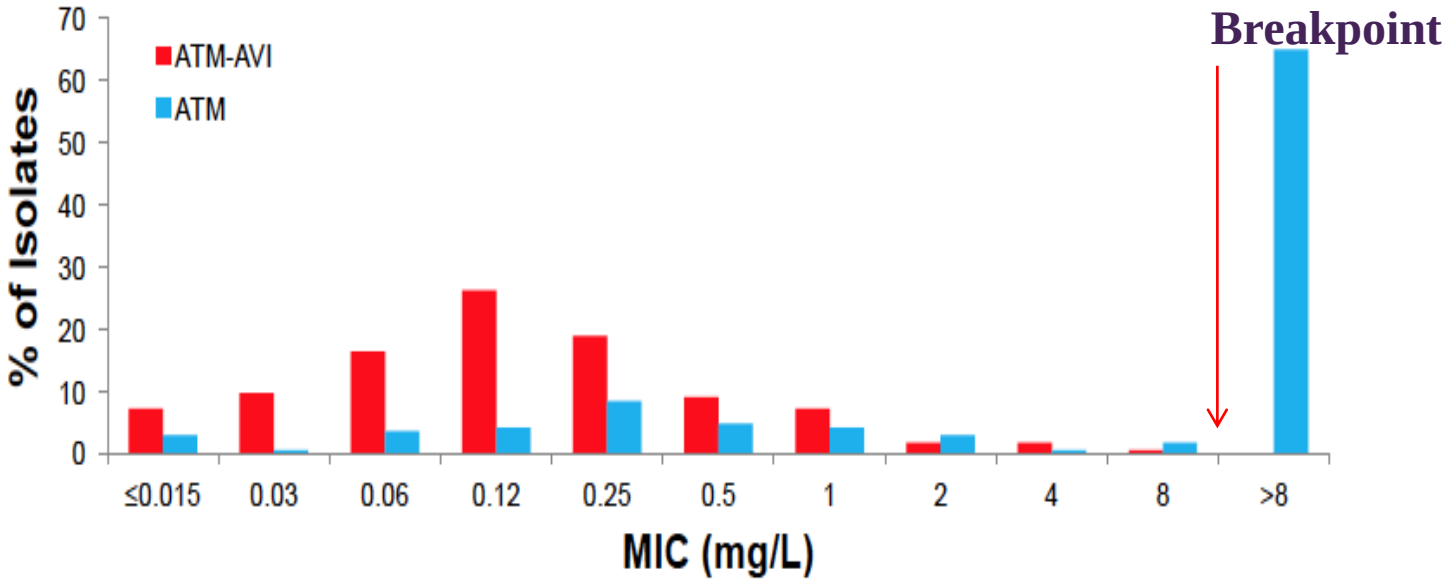
Que faire si ß lactamase classe B chez Entérobactérales ?

Microbiological Activity

MBL-Producing *Enterobacteriaceae*

Aztréonam + avibactam

MIC Distribution of ATM and ATM-AVI (at constant 4 mg/L AVI) for MBL-producing *Enterobacteriaceae* (n=163), collected from global surveillance studies (2012-2014)



- Avibactam potentiates the activity of aztreonam against MBL-producing *Enterobacteriaceae* (MIC_{90} decreases from >128 to 1 mg/L; 8 mg/L highest MIC observed)

MBL Enterobacterales
May The A+A Force Be With You!

Aztréonam + avibactam

Loading dose of 500 mg aztreonam/137 mg avibactam infused over 30 minutes, followed by 1500 mg aztreonam/410 mg avibactam every 6 hours infused over 3 hours

Table 1. Susceptibility and β-lactamase content of clinical isolates

			MIC (mg/L)	
Pathogen	Strain	β-Lactamases	ATM	ATM/AVI[a]
K. pneumoniae	ARC3803	NDM-1, CTX-M-15, OXA-1, SHV-1, TEM-1	256	0.25
	ARC3602	NDM-1, TEM-1, CTX-M-15, SHV-11, CMY-6	256	0.5
	ARC3802	NDM-1, TEM-1, CTX-M-15, SHV-2a, SHV-11	128	0.125
E. coli	ARC3805	NDM-1, TEM-208, OXA-1, OXA-2, CTX-M-15, CMY-4	>256	4
	ARC3807	NDM-1, TEM-1, SHV-12, OXA-9, CMY-42	>256	8
	ARC3600	NDM-1, OXA-1, CMY-6	16	0.125

ATM, aztreonam; AVI, avibactam.
[a]Avibactam at 4 mg/L.

J Antimicrob Chemother 2015; **70**: 2618–2626

Successful use of avibactam and aztreonam combination for a multiresistant *Stenotrophomonas maltophilia* bloodstream infection in a patient with idiopathic medullary aplasia

A.Diarra, L.Pascal, B.Carpentier, N. Baclet, P. Cabaret
A.F.Georgel, L.Dubreuil, P. Weyrich

Infectious Diseases Now
2021, 51, 7, 637-638

Antibiotique	Catégorization cliniquel	CMI en mg/L
Ticarcilline + acide - clavulanique	R	> 256
Ceftazidime	R	> 256
Ceftazidime + avibactam	R	> 256
Lévofloxacine	R	8
Cotrimoxazole	R	> 4
Colimycine	R	64

Aztreonam-avibactam may not replace ceftazidime/avibactam: the case of KPC-21 carbapenemase and penicillin-binding protein 3 with four extra amino acids

Ke Ma[a], Yu Feng[b], Zhiyong Zong[a,b,c,*]

Paradoxal

Table 1
Minimum inhibitory concentrations (MICs) of avibactam-based combinations and carbapenems against strains in this study.[a]

Strain	MIC (mg/L) ATM	ATM-AVI [b]	CAZ	CAZ-AVI	IPM	MEM
035166 [c]	**>1024**	2/4	**>1024**	4/4	**256**	**128**
035166R [c]	**>1024**	**512/4**	**>1024**	4/4	**16**	**16**
BL21	≤0.03	≤0.03/4	≤0.03	≤0.03/4	0.03	≤0.03
BL21::pET-28	≤0.03	≤0.03/4	≤0.03	≤0.03/4	0.03	≤0.03
BL21::KPC-2	**>1024**	≤0.03/4	**128**	≤0.03/4	**256**	**128**
BL21::KPC-21	**>1024**	1/4	**16**	≤0.03/4	**16**	**16**
035125ΔpCMY42 [d]	4	2/4	4	2/4	0.25	0.03
035125ΔpCMY42::pET-28	4	2/4	4	2/4	0.25	0.03
035125ΔpCMY42::KPC-2	**>1024**	4/4	**>1024**	8/4	**512**	**256**
035125ΔpCMY42::KPC-21	**>1024**	**256/4**	**>1024**	8/4	**32**	**32**

ATM, aztreonam; ATM-AVI, aztreonam/avibactam; CAZ, ceftazidime; CAZ-AVI, ceftazidime/avibactam; IPM, imipenem; MEM, meropenem; PBP3, penicillin-binding protein 3.

[a] MICs that reached the Clinical and Laboratory Standards Institute (CLSI) breakpoints to define resistance are highlighted in bold.

[b] Breakpoints of ATM were applied for ATM-AVI.

[c] Both 035166 and 035166R have a YRIN insertion in PBP3.

[d] 035125ΔpCMY42 is a plasmid-cured variant (losing the plasmid carrying bla_{CMY-42}) of strain 035125 with the YRIK insertion in PBP3, which has been described in our previous study [11].

an amino acid substitution of tryptophan to arginine at Ambler position 105 (Trp105Arg, W105R). This KPC-2 variant has been named KPC-21,
Ceftazidime/avibactam-susceptible but exhibit high-level resistance to aztreonam/avibactam.

Association : Aztreonam + ceftazidime -avibactam

TABLE 2 MICs and categorization according to CLSI breakpoints for antimicrobials on MBL-producing *Enterobacteriaceae*, MBL-producing *P. aeruginosa*, and *S. maltophilia*

Enterobacteriaceae sp.	β-Lactamases	MICs (mg/liter) by treatment[a]						
		ATM	CZA	C/T	AMC	ATM+ CZA	ATM+ C/T	ATM+ AMC
E. coli	NDM-1 + OXA-1 + OXA-10 + CMY-16 + TEM-1	32	>256	>256	16	0.125	24	8
E. coli	NDM-1 + CTX-M-15 + TEM-1	>256	>256	>256	12	1	>256	2
E. coli	NDM-1 + OXA-1 + OXA-2 + CTX-M-15 + TEM-1	>256	>256	>256	24	2	>256	8
E. coli	NDM-1 + CTX-M-15 + TEM-1	>256	>256	>256	32	6	>256	8
E. coli	NDM-4 + CTX-M-15 + OXA-1	>256	>256	>256	96	6	>256	4
E. coli	NDM-4 + CTX-M-15 + CMY-6	>256	>256	>256	>256	6	>256	24
E. coli	NDM-5 + TEM-1 + CTX-M-15	>256	>256	>256	96	8	>256	64
E. coli	NDM-6 + CTX-M-15 + OXA-1	>256	>256	>256	16	1	>256	2
E. coli	NDM-7 + ESBL	>256	>256	>256	96	4	>256	32
K. pneumoniae	NDM-1 + CTX-M-15 + SHV-11 + OXA-1	>256	>256	>256	12	0.125	24	0.38
K. pneumoniae	NDM-1 + CTX-M-15 + CMY-4 + OXA-1	>256	>256	>256	32	0.75	>256	16
K. pneumoniae	NDM-1 + CTX-M-15 + OXA-1 + OXA-9 + TEM-1 + SHV-28 + SHV-11	>256	>256	>256	32	0.25	>256	3
K. pneumoniae	NDM-1 + OXA-1 + SHV-11	>256	>256	>256	12	0.047	0.094	0.094
K. pneumoniae	NDM-1 + OXA-1 + CTX-M-15 + TEM-1 + SHV-28 +	>256	>256	>256	16	0.047	3	0.25
S. maltophilia		>256	>256	>256	32	2	128	2
S. maltophilia		>256	>256	6	96	1.5	6	2
S. maltophilia		>256	>256	>256	>256	4	>256	4
S. maltophilia		>256	16	72	16	1	8	2
S. maltophilia		>256	>256	>256	>256	0.75	24	0.75
P. aeruginosa	VIM-2 + overexpressed cephalosporinase	16	24	>256	>256	8	12	16
P. aeruginosa	IMP-2 + overexpressed cephalosporinase	12	>256	>256	>256	6	12	24
Enterobacter cloacae	VIM-1 + SHV-70	256	128	>256	48	0.094	0.25	0.19
E. cloacae	VIM-4 + CTX-M-15 + TEM-1 + SHV-31	64	>256	>256	64	1	64	32
Citrobacter freundii	VIM-2 + TEM-1 + ESBL	16	16	>256	32	0.25	2	24
C. freundii	VIM-2 + TEM-1 + OXA-9 + OXA-10	32	24	>256	32	1.5	16	24
E. coli	IMP-8 + SHV-12	128	>256	>256	24	0.19	2	0.38
K. pneumoniae	IMP-8 + SHV-12	>256	48	>256	12	0.094	32	0.25
E. cloacae	IMP-8 + SHV-12	12	>256	>256	24	0.032	0.064	0.094
E. cloacae	GIM-1 + ESBL	12	>256	48	24	0.5	8	16
Enterobacter hormaechei	TMB-1 + overexpressed Case[b]	64	64	32	32	0.5	12	12
C. freundii	TMB-1 + overexpressed Case	64	96	32	12	0.125	12	12

Meropenem + vaborbactam

Meropenem vaborbactam Designed for KPC

Classes A, C

Actif sur BLSE, KPC +++
Non actif sur classe B (VIM et NDM)
très peu actif sur classe D (OXA 48 et OXA 163)

Pas d'apport du vaborbactam sur les souches Mero S,

Ni sur *Acinetobacter, Stenotro*phomonas et les anaérobies stricts.

Activité association = activité du méropenem seul sur *Acinetobacter, Stenotrophomonas,Pseudomonas*

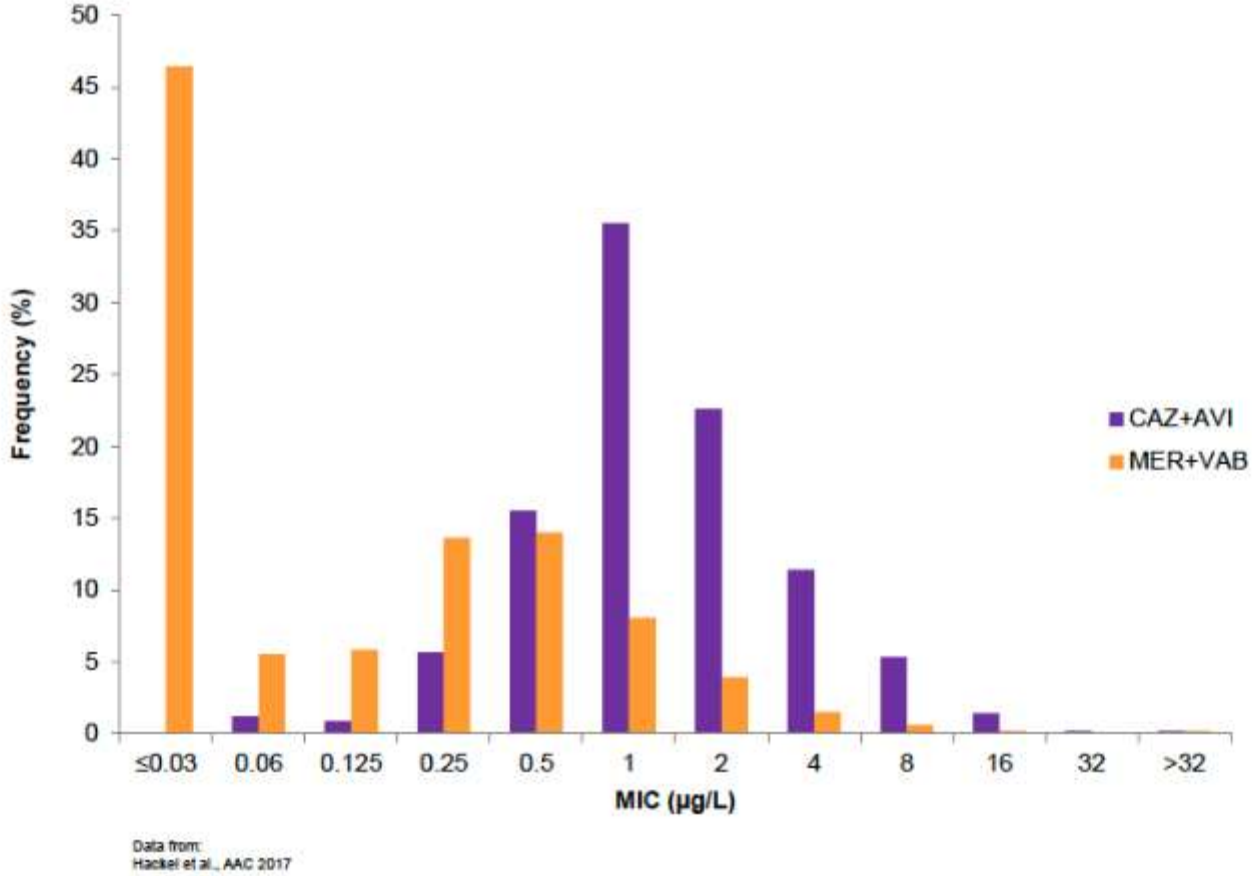
Résistance si perte porine OmpK36 et ompK35

En présence de KPC, la diminution des CMI des ß-lactamines associées est plus importante quand le vaborbactam est associé aux carbapénèmes par rapport aux autres ß- lactamines, d'où l'association retenue au final

M/V plus actif que CAZ-AVI sur les KPC

KPC producing ENT: 991 strain panel
Higher Potency of M/V Compared to C/A

Summary of In Vitro Activities of Meropenem-Vaborbactam and Ceftazidime-Avibactam Tested against 991 KPC-Producing Enterobacteriaceae



Antimicrobial Activity of Ceftazidime-Avibactam and Comparators against Pathogens Harboring OXA-48 and AmpC Alone or in Combination with Other β-Lactamases Collected from Phase 3 Clinical Trials and an International Surveillance Program

Antimicrobial Agents and Chemotherapy March 2022 Volume 66 Issue 3 e01985-21

Lynn-Yao Lin,[a] Dmitri Debabov,[a] William Chang,[a] Gregory Stone,[b] Todd Riccobene[c]

	CAZ/AVI 16	Mero/vabor 8/8
Enterobacterales OXA 48 producing	100%	80,5%
Entérobactérales ampC overproducing	100	98,7
P. aeruginosa ampC overproducing	100	64,2

Mero/vabor devrait être réservé aux KPC

Compared to currently available antibiotics, meropenem-vaborbactam demonstrated lower MIC values against both clinical and engineered isolates, including engineered E. coli strains that had KPC,BLSE : SHV and TEM enzymes.

Lower potential for resistance to develop. Infect Dis Ther (2020) 9:757–767

Meropenem/Vaborbactam:

Drugs (2018) 78:1259–1270 Dhillon

- **En cours de traitement par Ceftazidime/avibactam, l'émergence de souches résistantes à cette association est due à divers mécanismes incluant des adaptations du gène bla_{KPC-2}, ou des mutations sur le plasmide portant bla_{KPC3}**

  (e.g. D179Y substitution de protéine).

- **Le Vaborbactam n'est pas affecté par ces KPC-2 ou variants de KPC-3 contenant l'amino-substitution D179Y, qui se traduit par une plus grande efficacité catalytique de l'hydrolyse de la ceftazidime et la résistance à l'avibactam**

Meropenem/Vaborbactam et ceftazidime avibactam, résistances croisées ?

- **Dans l'étude de Hackel et al. sur 991 souches d'Entérobactérales produisant KPC, mais OXA-48 et MBL negatives,**

  14 souches sur 18 sont ceftazidime/avibactam-resistantes (MIC_{90} ≥ 16 µg/mL) et sensibles à meropenem/vaborbactam (MIC_{90} ≤ 4 µg/mL)

  et 6 souches sur 10 sont meropenem/vaborbactam résistantes (MIC_{90} ≥ 8 µg/mL) sont sensibles à ceftazidime/avibactam (MIC_{90} ≤ 8 µg/mL)

- **La résistance croisée entre meropenem/vaborbactam et ceftazidime/avibactam survient dans 20.8% (5 of 24) des souches résistants à l'un des deux agents**

Hackel et al. AAC 2018; 62: 1-10 Dhillon et al. **Drugs (2018) 78:1259–1270**

Résistance KPC au méropénème-vaborbactam

- **Retenir**
- **Dans les études cliniques sont décrites fréquemment des variants des souches de *K. pneumoniae* ayant une duplication de deux acides aminés Gly134 et Asp135 (GD repeat) pour la porine OmpK36.**

- **Du fait de la duplication de deux acides aminés dans la boucle L3 de la porine, il apparaît que OmpK36 en dépit de son canal rétréci conserve son activité quoiqu'elle diminue la pénétration du méropénème**

- **Multiplicité des mécanismes**

CMI de M/V > 8/8 mg/L si:

- **GD repeat et 3 à 7 copies de bla_{KPC}**
- **ou/et**
- **Mutations porines ompK35 et ompk36 par IS (promoteur)**

J Antimicrob Chemother 2019; **74**: 1457–1459
doi:10.1093/jac/dky557
Advance Access publication 11 January 2019

Association possible sur KPC
CAZ /AVI + Mero/vaborbactam

In vitro synergistic activity of meropenem/vaborbactam in combination with ceftazidime/avibactam against KPC-producing *Klebsiella pneumoniae*

Paolo Gaibani [1]*, Simone Ambretti[1], PierLuigi Viale[2,3] and Maria Carla Re[1,3]

Table 1. Antimicrobial susceptibility and synergy testing results of KPC-Kp clinical isolates

	MIC (mg/L)						∑FIC, MEM/VAB in association with:			
Isolate	CAZ	MEM	IPM	MEM/VAB	CAZ/AVI	GEN	CAZ/AVI	CAZ	IPM	GEN
Kp1	256	256	256	2	1	2	0.285	0.25	0.25	0.52
Kp2	256	256	256	1.5	1	2	0.41	0.83	0.41	0.83
Kp3	256	256	256	0.5	1	256	0.63	0.375	0.313	1.13
Kp4	256	16	16	0.064	1	0.5	0.42	0.7	0.59	0.98
Kp5	256	16	32	0.064	0.5	2	0.375	0.43	0.34	0.85
Kp6	256	16	32	0.064	1	2	0.25	0.43	0.5	1.18
Kp7	256	16	32	0.064	2	2	0.72	0.59	0.43	1.123
Kp8	256	16	32	0.125	1	2	0.5	0.295	0.235	0.84
Kp9	256	256	256	64	4	2	0.25	0.83	0.83	0.75
Kp10	256	2	0.25	0.5	256	2	1.035	1.66	1.26	1.16
Kp11	256	256	256	256	4	2	0.155	2	0.62	0.62
Kp12	256	8	8	0.5	256	2	1.26	1.5	0.5	0.69
Kp13	256	256	256	256	32	2	0.215	2	1.5	1.25
Kp14	256	256	256	256	8	2	0.185	2	2	1.125
Kp15	256	32	16	0.25	64	1	0.5	1	0.5	1
Kp16	256	256	256	256	16	2	0.12	0.12	0.3	0.5
Kp17	256	256	256	1	16	3	0.66	0.7	0.37	0.91
Kp18	256	256	256	256	4	2	0.347	2	1.5	0.32

CAZ, ceftazidime; MEM, meropenem; IPM, imipenem; MEM/VAB, meropenem/vaborbactam; CAZ/AVI, ceftazidime/avibactam; GEN, gentamicin; ∑FIC, total fractional inhibitory concentration.
Light grey shading indicates resistance and dark grey shading indicates synergy.

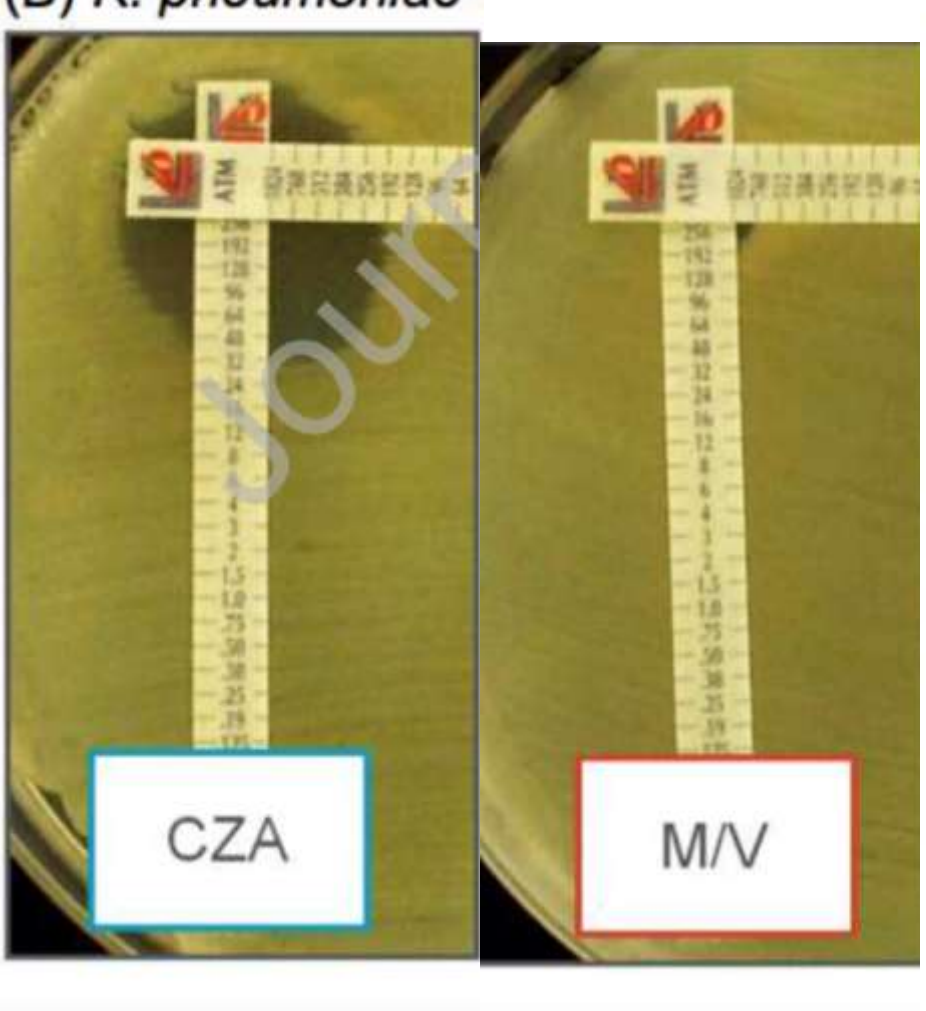
Si plusieurs ß lactamases dont classe B associer aztréonam

Les 2 souches sont résistantes CZA et M/V

Fig. 2.

(B) *K. pneumoniae*

(A) *E. coli* 542



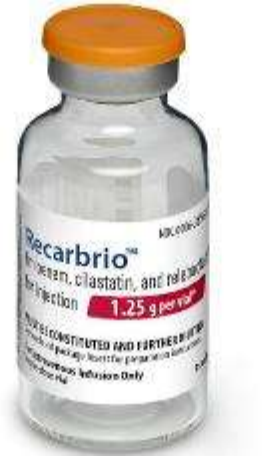
NDM1 + OXA 232 + CTX-M-15

ATM + CZA seul synergique

NDM CZA et M/V –R

Synergie des 2 avec AZT

Lindsay M. Avery , Elias M. Mullane , David P. Nicolau. International Journal of Antimicrobial Agents 55 (2020) 105863



Relebactam
Designed for *Pseudomonas aeruginosa*

Imipenem + cilastatine+ relebactam

Actif classes A et C (ESBLs, AmpC, KPC)
Plus stable à l 'hydrolyse par KPC2 que avibactam

Contrairement à Meropenem/vaborbactam intérêt +++ pour IMI /REL sur le pycocyanique

Relebactam pas d'induction de ampC à la différence de l'avibactam

In P. aeruginosa, there was an MIC reduction in OprD-deficient strains from 16–64 mg/L to 1–4 mg/L.

Inactivation of the porin protein OmpK36 in *K. pneumoniae* has been reported to confer resistance to both imipenem–relebactam and meropenem–vaborbactam.

IMI/REL compared to MERO/VABOR

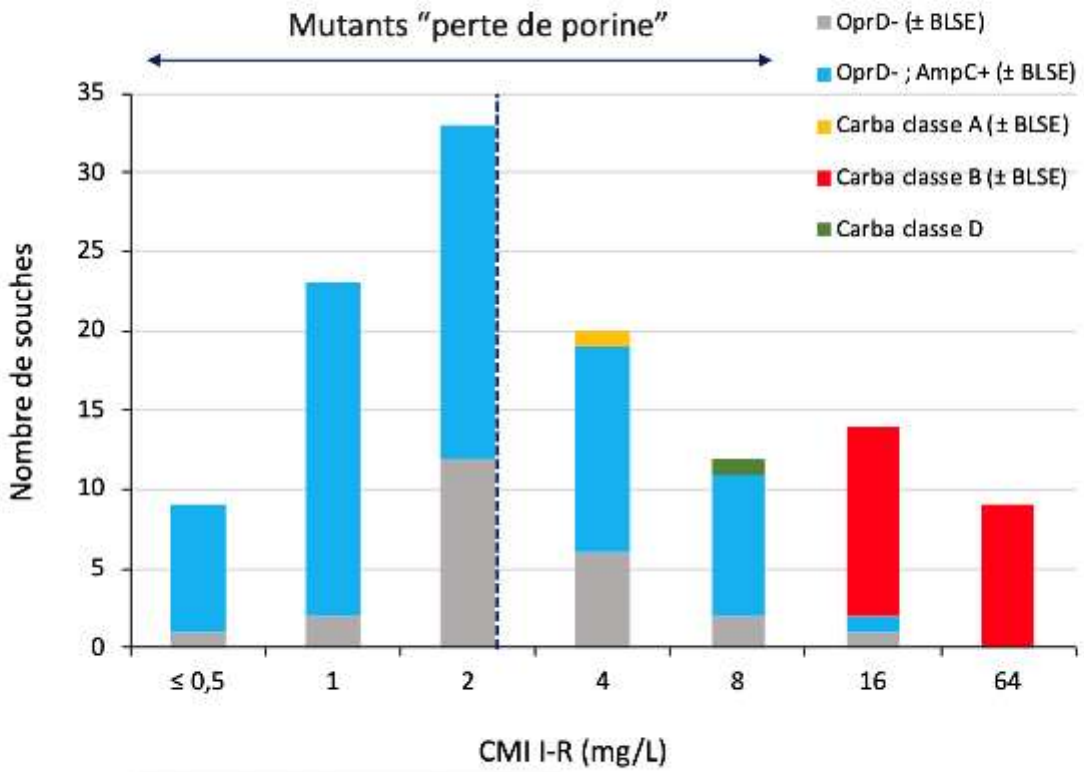
- Clinical isolates from 11 Queens and Brooklyn hospitals
- Carbapenems tested at 2-fold dilutions, with 4 ug/ml REL or 8 ug/ml VABOR
- Against KPC *K. pneumoniae* relebactam and vaborbactam restored imipenem or meropenem susceptibility, respectively, to all isolates
- Against resistant *P. aeruginosa*
  - relebactam restored IMI susceptibility to all isolates; IMI MIC $_{50/90}$ 1/2 ug/ml in the presence of REL
  - vaborbactam did not restore MERO susceptibility to MERO resistant *isolates;* MERO MIC $_{50/90}$ 8/32 ug/ml in the presence of VABOR

	MIC 50/90 ug/ml				MIC 50/90 ug/ml	
Organism (n)	**Imipenem**	**Imi + Rel (REL 4ug/ml)**		**Organism (n)**	**Meropenem**	**Mero + Vabor (VABOR 8 ug/ml)**
K. pneumoniae **KPC (111)**	**16 / >16**	**0.25 / 1**		***K. pneumoniae*** KPC (121)	**>16 / >16**	**0.03 / 0.5**
P. aeruginosa IMI-R (144)	**8 / >16**	**1 / 2**		***P. aeruginosa*** MERO-R (98)	**8 / 32**	**8 / 32**

Lapuebla et al AAC 2015 59; 4856; Lapuebla et al AAC 2015 59: 5029

Le relebactam ne récupère pas toutes les souches oprD-

Imipénème/Relebactam et Mutants OprD⁻



http://www.cnr-resistance-antibiotiques.fr/index.html

Données CNR sur n=120 souches résistantes à l'imipénème (CMI > 4 mg/L)

Pseudomonas oprD- et efflux → resistance croisée IMI/Rel et Mer/V

KPC-2 vs. KPC-3 Activity

KPC Producing K. pneumoniae (n=62)	Imipenem-Relebactam Median MIC (range)		Ceftazidime-Avibactam Median MIC (range)	
	Median MIC (range)	P-value	Median MIC (range)	P-value*
KPC-3 variant	0.25 (0.125-0.5)	0.31	128 (16-512)	0.0001
No KPC-3 variant	0.5 (0.125-4)		2 (0.25-16)	

*p<0.0001 by multivariate analysis

1. Humphries et al AAC 2015; 59:6605. 2. Humphries et al AAC 2017; 61:e00537. 3. Nelson et al AAC 2017; 61:e00989. 4. Shields et al, AAC 2017; 61:e2097. 5. Haidar et al AAC2017; 61:e2534. 6. Haidar et al. AAC 2017; 61: e00642-17.

Letter to the Editor

In vitro activity of imipenem-relebactam against KPC-producing *Klebsiella pneumoniae* resistant to ceftazidime-avibactam and/or meropenem-vaborbactam

Donatella Lombardo, Simone Ambretti, Tiziana Lazzarotto, Paolo Gaibani*

Operative Unit of Clinical Microbiology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

Activités comparées des inhibiteurs de ß-lactamases

* Entérobactérales ***

Agent Classes de Ambler	KPC A	MBL B	ampC C	Oxa D	Pseudomonas aeruginosa MDR	Acinetobacter baumannii MDR
Avibactam-ceftazidime	X	N	X	v	X	N
Aztreonam-Avibactam	X	X*	X		N	N
Relebactam-imipenem	**X**		X		**X**	N
Vaborbactam-Meropenem	**X**	N	X	N	N	N
N= inactif V = variable						
IBL de choix en rouge						

L. Dubreuil 2018

Nacubactam is a DBO inhibitor with in vitro activity against class A, class C, and some class D β-lactamases. Lab :Roche

Nacubactam (NAC, RG6080, OP0595) is a novel dual action diazabicyclooctane having both a ß- lactamase inhibitor activity and a direct antibacterial activity that can additionally translate to an "enhancer" effect when partnered with beta-lactams.

Activité > DBO sur MDL, also inhibit enterobacterial PBP2, achieving antibacterial activity and potentiating PBP3- targeted β-lactams; this can allow activity against strains with enzymes not inhibited by DBOs, including MBLs.

Isolate group:		NAC	MEM:NAC [1:1][1]	MEM:NAC [2:1][1]	MEM:NAC [2][2]	MEM:NAC [4][2]	MEM
All (n=1553)	MIC_{50}	2	0.12	0.25	≤ 0.004	≤ 0.004	0.5
	MIC_{90}	> 32	2	4	0.5	0.25	128
Class A (n= 577)	MIC_{50}	2	0.03	0.03	≤ 0.004	≤ 0.004	0.03
	MIC_{90}	> 32	0.06	0.06	0.015	0.015	0.12
Class B (n= 123)	MIC_{50}	4	2	4	0.008	≤ 0.004	32
	MIC_{90}	> 32	32	32	64	64	> 256
Class C (n= 254)	MIC_{50}	2	0.06	0.06	≤ 0.004	≤ 0.004	0.12
	MIC_{90}	> 32	0.25	0.25	0.06	0.015	0.5
Class D (n= 212)	MIC_{50}	32	1	2	0.25	0.12	4
	MIC_{90}	> 32	4	8	8	4	64
KPC (n= 381)	MIC_{50}	4	1	1	0.008	≤ 0.004	64
	MIC_{90}	> 32	2	4	0.5	0.25	256
GES (n=6)[3]	MIC range	1 - > 32	0.12 - 4	0.12 - 8	≤ 0.004 - 8	≤ 0.004 - 1	0.12 - 256

NAC, nacubactam; MEM; meropenem

[1]Fixed MEM:NAC ratio; [2]Fixed NAC concentration (mg/L); [3]GES-6 or GES-20 carbapenemase-positive

Nacubactam (RG6080) alone and in combination against metallo-beta-lactamase (MBL)-producing Enterobacteriaceae

D. Livermore

Activité > DBO sur MDL

2 populations MIC 1-8 mg/L (85%) ou >32mg/L (*Proteae*)

ACTIVITY ON MBLs

309 Enterobacteriaceae: 158 NDM,52 VIM,99 MBL

8+4 mg/L aztreonam-nacubactam inhibited	308
8+4 mg/l aztreonam + avibactam	303
8+4 mg/l cefepime + nacubactam	278
8+4 mg/l Cefepime+ avibactam	68
4+4 mg/l meropenem +nacubactam	262
8+4 mg/l meropenem + avibactam	85

Zidebactam

Zidebactam (ZID) is the first described Gram-negative ß-lactam enhancers belonging to the bicyclo-acyl hydrazide (BCH) series.

ZID in combination with cefepime (FEP) MDR Gram-negative organisms, including *P. aeruginosa* and *Acinetobacter baumannii.*

BCHs were designed with the objective of augmenting PBP2 binding in P. aeruginosa and A. baumannii rather than the conventional approach of optimizing the ß-lactamase inhibitory activity of the compound.

Avibactam, the first example of a DBO,in contrast possessed weak PBP2 affinity in Enterobacteriaceae

On the other hand, cefepime showed potent PBP1a and PBP3 inhibition, while meropenem inhibited PBP2, PBP3, and PBP4.

Zidébactam

- **Activité intrinsèque** **A,B,C**
- **60% des Entérobactérales à 4 mg/L**
- **E. coli, Enterobacter 0,06-0,25 mg/L**
- **Klebsiella 0,12 >128 mg/L**
- **Proteae Serratia >> 128 mg/L**

- **+ céfépime :** Entérobactérales et Pyo
- **BLSE, AmpC, KPC, MBLs metallo-ß-lactamases (including VIM, IMP and NDM)**
- **Actif sur E. coli CAZ-AVI-R, AZT-AVI-R, IMI-Rel –R**

- **Pyo actif sur MBL 91% à 8 mg/L (VIM and IMP)**;
- **Acinetobacter NDM**
- **Peu actif sur OXA**
- **Cefepime/zidebactam activité modérée sur OXA-23/24/58 Acinetobacter baumannii**
- **Résistance insertion PLP3**
- Helio S. Sader* J Antimicrob Chemother 2017; 72: 1696–170

Céfépime+ Taniborbactam

Inhibiteur A, B (sauf IMP), C, D

Acineto MDL NDM ++ 100%. OXA70%
Pyo peu d'intérêt
Stenotrophomonas +++

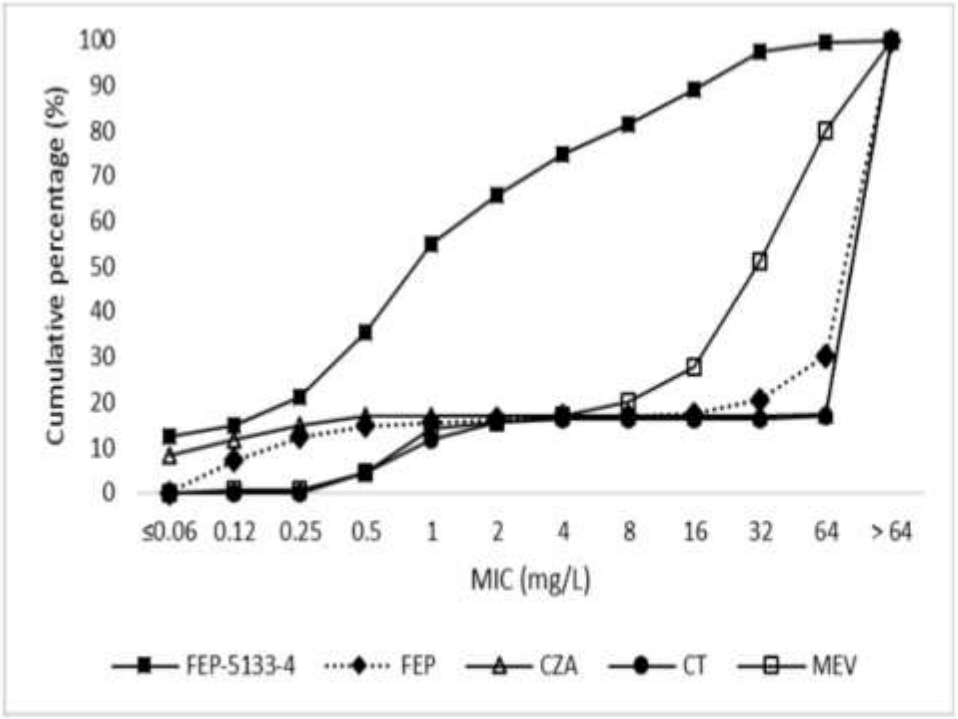
A four-amino acid 'INYR' or 'YRIN' insertion, with or without a one/two-amino acid mutation in PBP3, may have caused cefepime/taniborbactam MICs >8mg/L among 96.6% (28/29) of the NDM-5-producing E.coli

Taniborbactam inhibits some metallo ß lactamases, but it lacks inihibitory activity against OXA carbapenemases from Acinetobacter

Échec par perte de porines fonctionnelles
Insertion gène de la PLP3
IMP

The combination of Cefepime and Taniborbactam (VNRX-5133)

155 **Enterobacteriaceae** (130 NDM-producers, 25 OXA-producers), and 50 VIM-producing **P. aeruginosa** were included in this analysis. MICs of cefepime + tanoborbactam at a fixed concentration of 4 mg/L (FEP/ tanoborbactam)



81% of isolates were inhibited at the susceptible breakpoint of 8 mg/L, and a total of 89% were inhibited at 16 mg/L.

In comparison, susceptibility was 17% for ceftazidime-avibactam, 16% for ceftolozane-tazobactam,17% for meropenem-vaborbactam

N=155 Enterobacteriaceae (130 NDM, 25 OXA-48); FEP-5133-4, cefepime tested in combination with VNRX-5133 at 4 mg/l; FEP, cefepime; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEV, meropenem-vaborbactam

In Vitro Activity of Cefepime-Taniborbactam against Carbapenemase-Producing *Enterobacterales* and *Pseudomonas aeruginosa* Isolates Recovered in Spain

Antimicrobial Agents and Chemotherapy , March 2022 Volume 66 Issue 3 e02161-21

Marta Hernández-García,[a,b] María García-Castillo,[a,b] Patricia Ruiz-Garbajosa,[a,b] Germán Bou,[b,c] María Siller-Ruiz,[d] Cristina Pitart,[e] Irene Gracia-Ahufinger,[f] Xavier Mulet,[b,g] Álvaro Pascual,[b,h,i,j] Nuria Tormo,[k] Rafael Cantón[a,b]

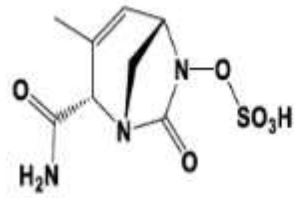
FTB was the most active agent in both Enterobacterales (97.6% MIC_{FTB}, ≤8/4 mg/L) and *Pseudomonas* (67.1% MIC_{FTB}, ≤8/4 mg/L) populations.

Résistance %										
Entérobacterales	**CTB 2,4**		**MEV**	**10,9**	**CZA**	**19,4**		**IMR**	**28,3**	
Klebsiella	**1,6**		**7**		**11,8**		**19,9**			
Sensibilité %									**C/T**	
P. aeruginosa		**67,5**		**33,7**		**63,2**			**38,7**	**36**

CTB Cefépime + taniborbactam
C/T ceftolozane/ tazobactam

Durlobactam + sulbactam

Extended spectrum DBO BLI



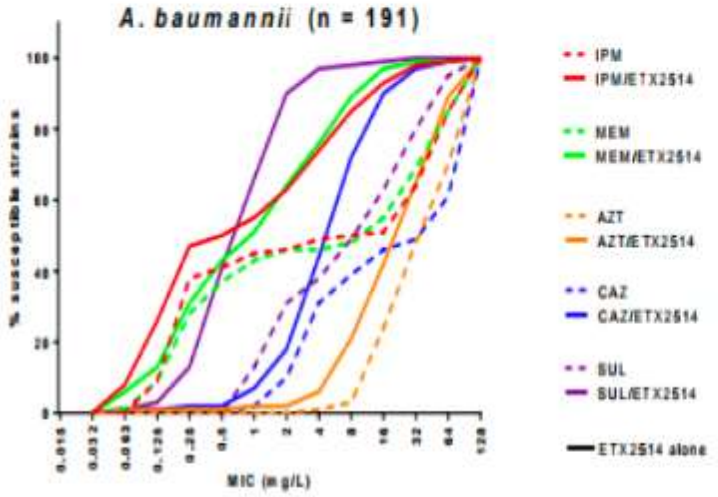
Designed Acinetobacter

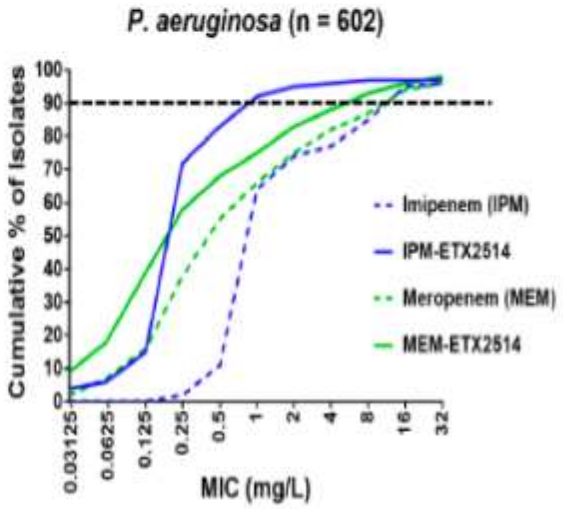
Lab: Entasis Durlobactam

ETX2514 – Class A √
Class C √
Class D √

Inactif classe B

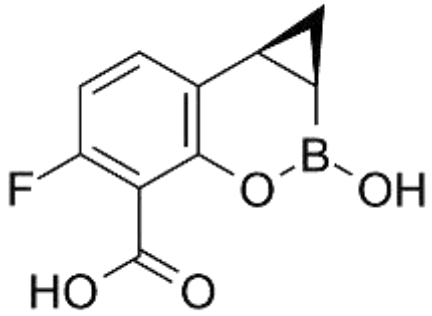
- Covalent reactivity increased due to strain
- Combination w/ sulbactam against *A. baumannii*
- Phase 1 (Entasis Therapeutics from AstraZeneca)





Durant-Reville et al. *Nat. Microbiol.* 2(9), 2017, 17104

Xeruborbactam = QXP7728



Class A, B, C, D inhibited at fixed concentration 4 µg/ml

First time against *A baumannii* Oxa*23 OXA -24/40 and OXA 58

is also a potent inhibitor of many class B metallo-beta-lactamases (NDM, VIM, CcrA, IMP, and GIM but not SPM or L1).

Nelson et al.

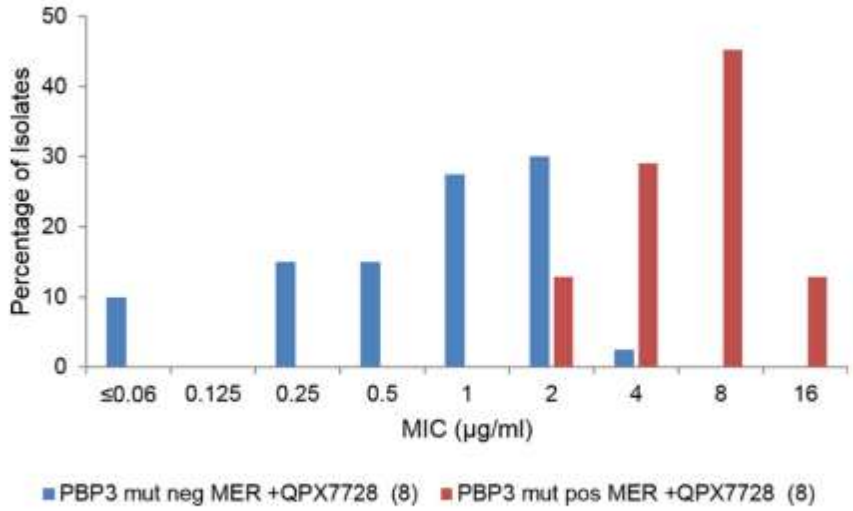


FIG 2 Distributions of meropenem-QPX7728 (8 µg/ml) MICs against OXA-23-producing strains ($n = 71$) based on the presence of an A515V or A515T mutation in PBP3. PBP3 mut pos, presence of an A515V or A515T mutation ($n = 31$); PBP3 mut neg, absence of these mutations.

Mutation PLP 3
OXA23

Pas toujours résistant

Activités comparées des inhibiteurs de ß-lactamases

* Entérobactérales

Agent Classes de Ambler	KPC A	MBL B	ampC C	Oxa D	Pseudomonas aeruginosa MDR	Acinetobacter baumannii MDR
Avibactam-ceftazidime	X	N	X	v	X	N
Aztreonam-Avibactam	X	X*	X		N	N
Relebactam-imipenem	**X**		X		**X**	N
Vaborbactam-Meropenem	**X**	N	X	N	N	N
Taniborbactam-Céfépime	X	X	X	Xf	X	N
Zidebactam--Céfépime	X	X	X	Xf	X	Xf
Nacubactam-Méropenem	X	X	X	v	X	X
Durlobactam- Sulbactam	X		X	X	N	X
Xeruborbactam	X	X	X	X	X	X

L. Dubreuil 2023

Voie orale pour l'urinaire

J Antimicrob Chemother 2020; **75**: 2384–2393
doi:10.1093/jac/dkaa183 Advance Access publication 22 May 2020

Journal of Antimicrobial Chemotherapy

Oral cephalosporin and β-lactamase inhibitor combinations for ESBL-producing Enterobacteriaceae urinary tract infections

Adam G. Stewart [1,2], Patrick N. A. Harris [1,3], Andrew Henderson[1,4], Mark A. Schembri [5,6] and David L. Paterson[1,2]*

Table 3. *In vitro* activity of oral cephalosporins with or without β-lactamase inhibitors against ESBL-producing Enterobacteriaceae

Oral cephalosporin ± β-lactamase inhibitor	Reference(s)	Total no. of isolates tested across all studies	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Range (mg/L)	Susceptibility (%)
Cefixime	78, 81	214	6	>64	0.5 to >64	7–8.6
Cefpodoxime	85, 87, 98	386	>16 to >64	>16 to >64	0.5 to >64	0–1.2
Ceftibuten	12, 85, 98, 99	1044	2–8	16 to >64	NA	1–56.9
Cefpodoxime/clavulanate	73, 75–77, 81	1144	0.5–1	0.5 to >32	≤0.06 to >32	58.8–75
Ceftibuten/clavulanate	91	4	0.125–1	0.125–1	NA	NA
Cefixime/clavulanate	78, 79, 81	276	0.25	0.75	0.09–24	86.3–90
Cefpodoxime/QPX7728	84, 85	NA	0.5	4	NA	NA
Ceftibuten/QPX7728	84, 85	NA	≤0.06	1	NA	NA
Cefpodoxime/ETX0282	87, 100	937	≤0.015–0.5	0.03–1	0.12–2	NA
Ceftibuten/VNRX7145	88, 89, 99, 101	884	0.06 to <1	0.12–1	NA	96.9–100

NA, data not available.

QXP = Xeruborbactam, VNRX-7145 prodrogue taniborbactam
ETXO82 = analogue durlobactam

Ceftibuten-Ledaborbactam (VNRX5236)

TABLE 3 Impact of key Ambler class A, B, C, and D enzymes on activity of CTB/VNRX-5236 and comparators in isogenic strains of *E. coli*[a]

		Fold increase in MIC compared to vector control for:[b]						
β-lactamase	β-lactamase class	CTB	CTB/VNRX-5236 (4)	CTB/CLA	AMX	AMX/CLA	Tebipenem	Sulopenem
TEM-10	A	4	2	4	≥128	8	4	2
CTX-M-15	A	64	0.5	1	≥128	4	4	4
GES-5	A	8	0.5	4	≥128	≥128	512	256
SHV-5	A	128	0.5	1	≥128	8	4	8
SHV-12	A	256	1	1	≥128	8	4	4
VEB-9	A	≥1,024	2	1	≥128	1	2	4
KPC-2	A	16	0.25	16	≥128	≥128	2,048	2,048
KPC-3	A	16	0.25	16	≥128	≥128	2,048	2,048
KPC-3 D179Y	A	32	2	2	4	4	8	16
PER-1	A	1,024	2	2	128	1	4	8
CMY-2	C	1,024	2	1,024	128	≥128	4	8
P99/AmpC	C	≥1,024	4	≥1,024	≥128	≥128	8	16
ACT-17	C	1,024	4	≥1,024	128	≥128	4	8
CMY-42	C	≥1,024	4	1,024	128	≥128	16	16
OXA-23	D	2	0.5	2	≥128	≥128	128	64
OXA-48	D	4	1	4	≥128	≥128	256	512
OXA-163	D	32	0.5	32	≥128	≥128	32	8
OXA-181	D	2	0.5	2	≥128	≥128	256	1,024
NDM-1	B	≥1,024	≥1,024	≥1,024	≥128	≥128	2,048	1,024

[a]CTB, ceftibuten; CTB/VNRX-5236 (4), ceftibuten with VNRX-5236 fixed at 4 μg/ml; CLA, clavulanic acid; AMX, amoxicillin; AMX/CLA, amoxicillin with clavulanic acid fixed at 4 μg/ml.

[b]MIC increases of ≤8-fold from vector control are shaded in gray and are based on modal MIC testing across 4 replicates. Vector control MICs were CTB, 1 μg/ml; CTB/VNRX-5236, 0.25 μg/ml; CTB/CLA, 1 μg/ml; AMX, 8 μg/ml; AMX/CLA, 8 μg/ml; tebipenem, 0.016 μg/ml; sulopenem, 0.06 μg/ml.

ARX 1796 = Avibactam produg QXP = Xeruborbactam

Oral Antibiotics in Clinical Development for Community-Acquired Urinary Tract Infections

Balaji Veeraraghavan . Yamuna Devi Bakthavatchalam . Rani Diana Sahni

Table 2 Spectrum of activity of oral antibiotics against Gram-negative pathogens causing community-acquired urinary tract infections

Oral antibiotics	Activity spectrum				
	ESBLs	ampC	CRE		
			KPC	MBL	OXA-48-like
Tebipenem pivoxil hydrobromide	✔	✔	X	X	X
Sulopenem-etzadroxil/probenecid	✔	✔	X	X	X
Cefpodoxime/ETX0282	✔	✔	✔	X	✔
Ceftibuten/VNRX-7145 ledaborbactam	✔	✔	✔	X	✔
Ceftibuten/ARX1796	✔	✔	✔	X	✔
Ceftibuten/ QPX7728	✔	✔	✔	✔	✔

✔ active, *X* not active, *ESBL* extended-spectrum β-lactamases, *ampC* class C cephalosporinase, *KPC K. pneumoniae* carbapanemases, *MBL* metallo β-lactamases, *OXA-48* oxacillinase, *CRE* carbapenem-resistant Enterobacterales, *CRPA* carbapenem-resistant *P. aeruginosa*, *CRAB* carbapenem-resistant *A. baumannii*

ARX 1796 = Avibactam prodrug

QXP = Xeruborbactam

ETX 0282 prodrogue de ETX 1317 analogue du Durlobactam

Le début de la multi-résistance aux inhibiteurs ?

Klebsiella pneumoniae Mutants Resistant to Ceftazidime-Avibactam Plus Aztreonam, Imipenem-Relebactam, Meropenem-Vaborbactam, and Cefepime-Taniborbactam

Naphat Satapoomin,[a] Punyawee Dulyayangkul,[a] Matthew B. Avison[a]

AAC April 2022 Volume 66 Issue 4

Klebsiella pneumoniae variant that is resistant to ceftazidime-avibactam plus meropenem-vaborbactam, has a ramR plus **ompK36 mutation**, and produces the V239G **variant KPC-3** exhibits resistance to ceftazidime-avibactam plus aztreonam and imipenem-relebactam but not cefepime-taniborbactam.

Additional mutation of **ompK35** and production of the OXA-48-like carbapenemase **OXA-232** were required to confer **cefepime-taniborbactam resistance.**

Molécules récentes et à venir concurrentes

Taniborbactam et inhibiteurs de carbapénèmases

Échec par perte de **porines** fonctionnelles — Castanheira et al. Int. J. Antimicrob agents 56 (2020)

Mutations des ß-lactamases — Sun et al. Antimicrob. Agents Chemother 2017; 61 / Shields et al. Clin Infect Dis. Apr 1 2020)

Insertion gène de la **PLP3** — Wang et al. Antimicrob. Agents Chemother. 2020; 75: 1850–1858

Céfidérocol

Insertion délétion rendant les **transporteurs inefficaces**

Pas de résistance croisée avec les associations IBL/ ß-lactamines par un mécanisme d'insertion ou de délétion dans les gènes rendant les transporteurs inefficaces.

Akinobu Ito, et al. Antimicrob. Agents Chemother. 2016,60:7396

PLP3 ?

Associations étudiées à ce jour

Ceftazidime avibactam + aztréonam

Meropénème –vaborbactam + aztréonam

Céfédéricol + Ceftazidime avibactam

Difficultés avec ses inhibiteurs de ß lactamases

Multiplicité et diversité des ß lactamases

KPC1. KPC 130
Oxa 48. oxa 244. Oxa 1186. NDM 30 VIM83

Spectre : inhibition classe B oui mais toujours une exception cf tableau ci dessous : les IMP pour Taniborbactam IMP10 uniquement pour Xeruborbactam

Association des mécanismes de résistance

Perméabilité (perte de porine ompk36),mutations des ß lactamases PLP3 et efflux
Xeruborbactam le plus large spectre en 2024 mais moins bon que taniborbactam si efflux associé

TABLE 4 Determination of the kinetic inhibition parameters of metallo-β-lactamase inhibitors against NDM-1, VIM-2, IMP-1, and IMP-10

	K_i (μM)[a]			
Inhibitor	**NDM-1**	**VIM-2**	**IMP-1**	**IMP-10**
Taniborbactam	0.016	0.01	>20	>20
Xeruborbactam	0.08	0.002	0.3	11.3

[a]K_i corresponds to a relative k_{off}/k_{on} to the inhibitor for the enzyme.

Conclusions d'un expert sur les IBL

***

Affecter et privilégier les inhibiteurs selon les espèces, les ß-lactamases et les mécanismes de résistance:

Pseudomonas	Imipenem/ relebactam
Acinetobacter	Durlobactam-sulbactam
Entérobactérales:	
MDL	Aztréonam –avibactam
KPC	**Mero/varbobactam**
OXA 48	Ceftazidime –avibactam

Synergie M-V et CAZ-AVI sur KPC

Devant la multiplicité des mécanismes de résistance associées dans une même bactérie seul l'antibiogramme réalisée sur chaque association ß-lactamine + IBL permet de guider le clinicien.

Mono vs. combo regimens with novel beta-lactam/beta-lactamase inhibitor combinations for the treatment of infections due to carbapenemase-producing *Enterobacterales*: insights from the literature

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Aminoglycosides could be useful in case of **bloodstream and severe urinary infections.**

Pneumonia is a risk factor for CZA resistance emergence: **fosfomycin**, due to favorable lung pharmacokinetics/ pharmacodynamics, could represent an interesting partner; fosfomycin could be added also for **osteomyelitis**.

Tigecycline could be preferred for intrabdominal and skin-soft tissue infections.

Due to nephrotoxicity and lack of in vitro synergy, the association CZA/**colistin** seems **not optimal**. MVB and I–R were mostly used as monotherapies.

Currently, there is no definitive evidence whether combinations are more effective than monotherapies; further studies are warranted, and to date only personal opinions can be provided.

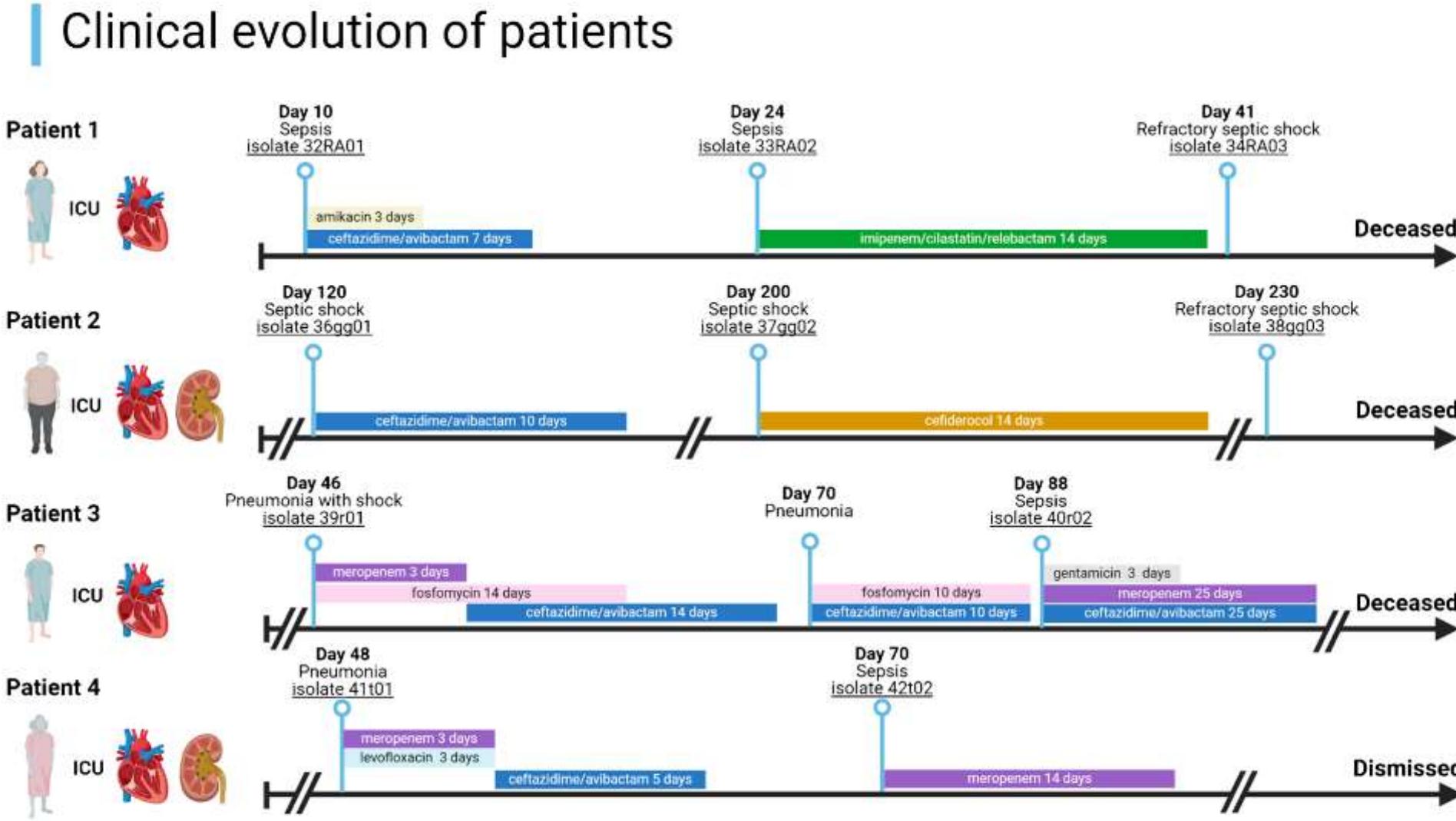

Fig. 1 Clinical evolution of the patients included in the study (Created in BioRender. Boattini, M. (2024) BioRender.com/n78m272)

TT CZA

Table 2 Antimicrobial susceptibility profiles of **KPC**-producing Klebsiella pneumoniae strains included in the study

Patient	KPC-Kp isolate	MIC (mg/L)							
		MEM	IPM	CAZ/AVI	AZT/AVI	MEV	IMR	CFDC	
1	32RA01	>32	>8	0.5	0.25	1.5	0.5	0.5	KPC2
	33RA02	4	1	>256	0.75	1	0.25	2	KPC33
	34RA03	>32	>8	≤2	1	>64	>32	2	KPC2 + efflux
2	36gg01	>32	>8	0.5	0.38	1	0.25	0.5	KPC2
	37gg02	>32	>8	2	1.5	1.5	0.12	0.25	
	38gg03	4	1	>256	8	2	0.5	16	KPC14
3	39r01	32	>8	3	0.38	1	0.25	1	KPC3
	40r02	32	>8	>256	>256	0.25	0.12	4	KPC3 + porine*
4	41t01	32	>8	2	1	1	0.5	0.5	KPC2
	42t02	2	1	>256	12	0.25	0.25	4	KPC14

I/R

CFD

CZA +MER

MER

Grey shading indicated drug-resistant strain according to EUCAST clinical breakpoints (v. 14.0)

KPC-Kp KPC-producing Klebsiella pneumoniae, *MEM* meropenem, *IPM* imipenem, *CAZ/AVI* ceftazidime/avibactam, *AZT/AVI* aztreonam/avibactam, *MEV* meropenem/avibactam, *IMR* imipenem/relebactam, *CFDC* cefiderocol

* OmpK36 with an inserion of GD at position 135