

41^e

RÉUNION INTERDISCIPLINAIRE DE
CHIMIOTHÉRAPIE ANTI-INFECTIEUSE

LUNDI 13 & MARDI 14
DÉCEMBRE 2021

PALAIS DES CONGRÈS • PARIS



Imipénème/relebactam; meropénème/vaborbactam et cefidéracol

Spectre d'activité et résistances



UNI
FR
UNIVERSITÉ DE FRIBOURG
UNIVERSITÄT FREIBURG



CHUV Centre hospitalier
universitaire vaudois

Unil
UNIL | Université de Lausanne



Nationales Referenzlaboratorium zur Früherkennung
neuer Antibiotikaresistenzen und Resistenzmechanismen

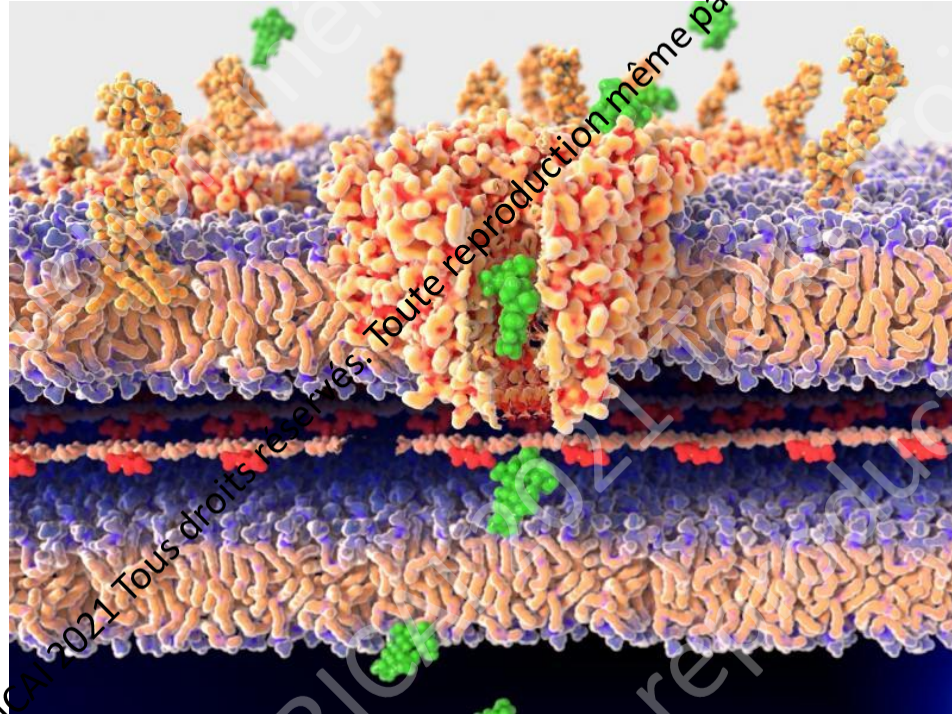
Prof. Patrice Nordmann

Institut
thématisés
Inserm
Institut national
de la santé et de la recherche médicale

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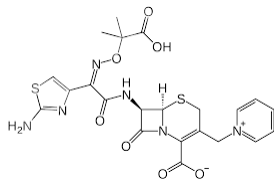
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Novel antibiotics against Gram negatives

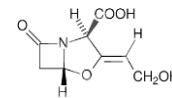


β -Lactams and inhibitors

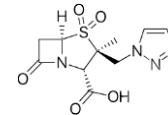
Ceftazidime



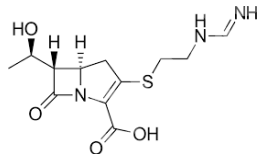
Acide clavulanique



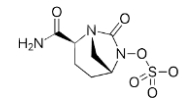
Tazobactam



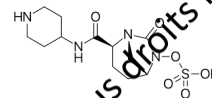
Impipénème cilastatine



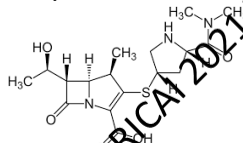
Avibactam



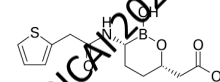
Relebactam



Méropénème



Vaborbactam



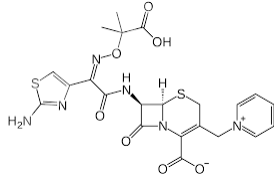
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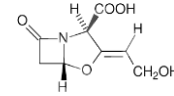
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β -Lactams and inhibitors

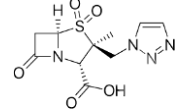
Ceftazidime



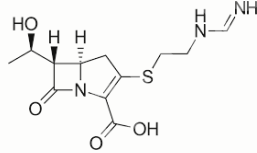
Acide clavulanique



Tazobactam

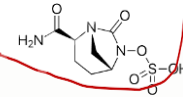


Impipénème cilastatine

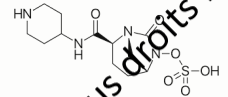


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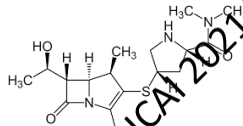
Avibactam



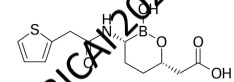
Relebactam



Méropénème



Vaborbactam

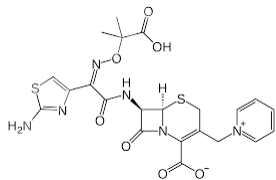


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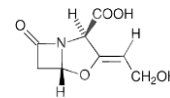
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β -Lactams and inhibitors

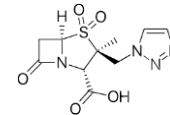
Ceftazidime



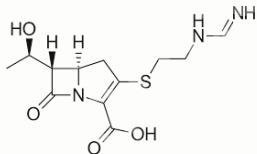
Acide clavulanique



Tazobactam

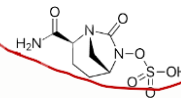


Impipénème cilastatine

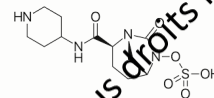


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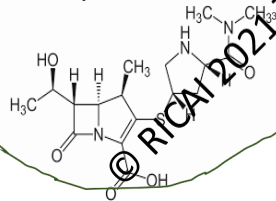
Avibactam



Relebactam

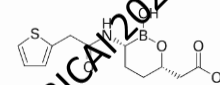


Méropénème



VABOREM

Vaborbactam



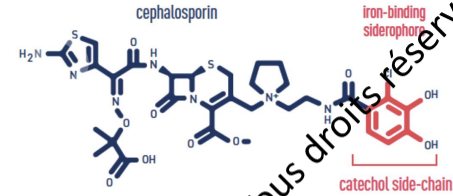
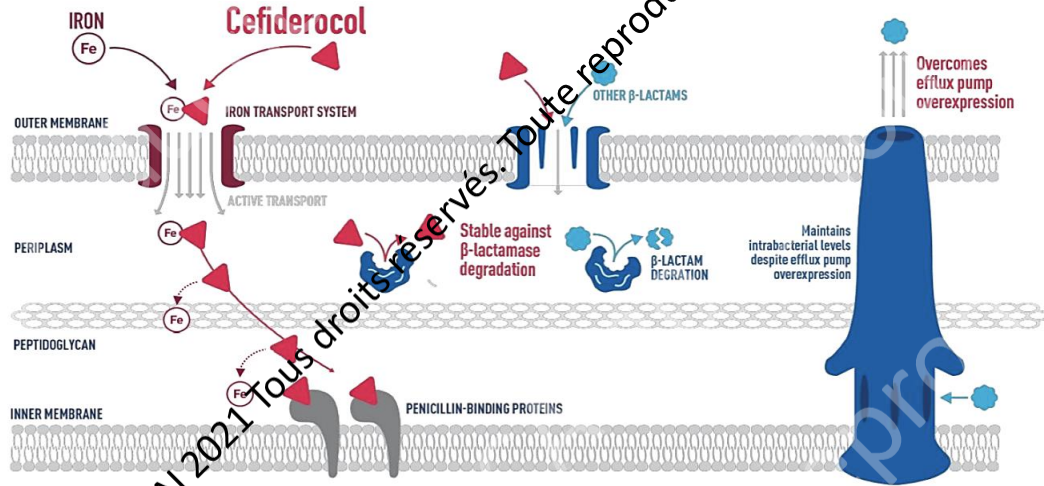
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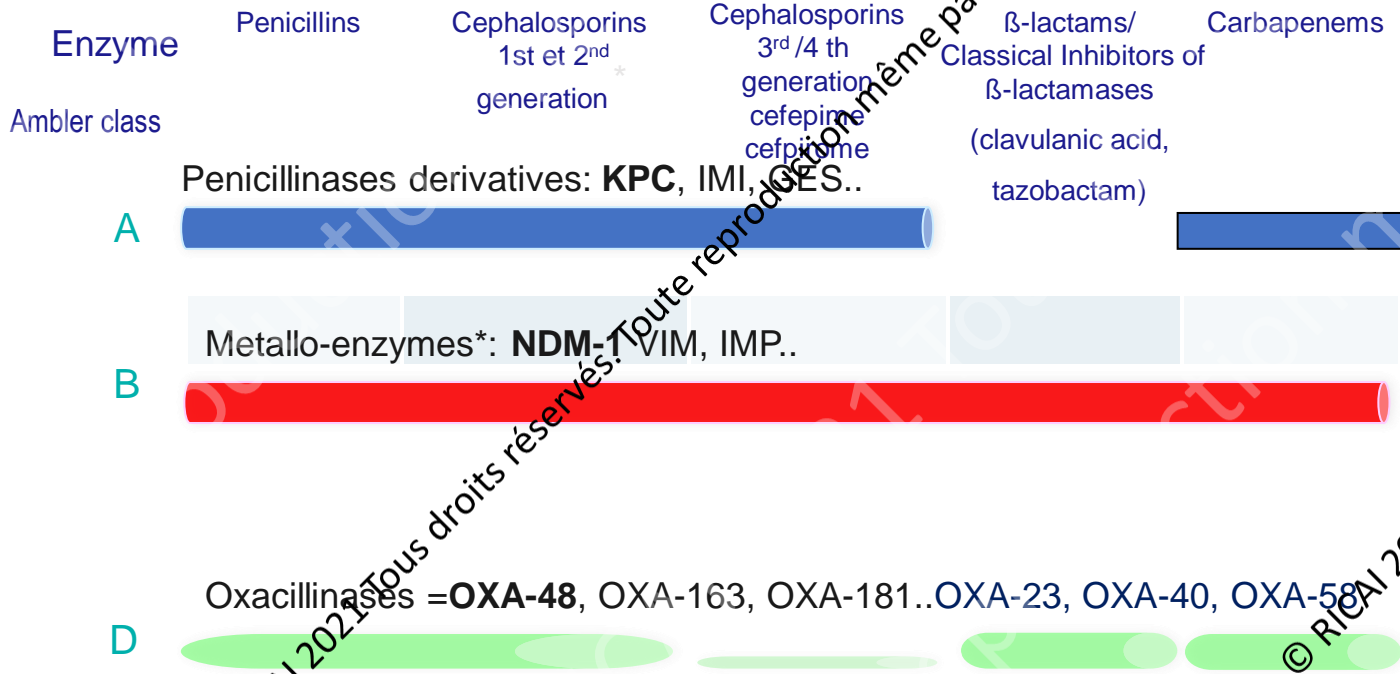
Cefidericol



Cefidericol

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The carbapenemases



* Aztreonam excluded

β-Lactamases

Inhibitors of β-lactamases	ESBL	AmpC Enterobacterales	AmpC P. aer	Carbapenemases			
				KPC	NDM, VIM, IMP	OXA-48 like	OXA-23 OXA-40 OXA-58
Dérivés de β-lactamines							
Clavulanic acid							
Tazobactam							
Diazabicyclooctanes							
Avibactam							
Relebactam							
Boronic acid derivative							
Vaborbactam							
<u>Cefidericol</u>							

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Recommended antibiotic treatment options for carbapenem-resistant Enterobacterales (CRE), assuming *in vitro* susceptibility to agents in , for URINARY TRACT INFECTIONS

Source of Infection	Preferred Treatment	Alternative Treatment (first-line options not available or tolerated)
Cystitis	Oral drug Single-dose of an aminoglycoside Meropenem (standard-infusion): only if ertapenem resistant, meropenem susceptible, AND carbapenemase testing results are either not available or negative.	Ceftazidime-avibactam Meropenem-vaborbactam Imipenem-cilastatin-relebactam, Cefiderocol Colistin (only when no alternative options are available)
Pyelonephritis or cUTI	Ceftazidime-avibactam Meropenem-vaborbactam Imipenem-cilastatin-relebactam, Cefiderocol Meropenem (extended-infusion): only if ertapenem resistant, meropenem susceptible, AND carbapenemase testing results are either not available or negative.	Once-daily aminoglycosides

Recommended antibiotic treatment options for carbapenem-resistant Enterobacterales (CRE), assuming *in vitro* susceptibility to agents, for OTHER INFECTIONS

Source of Infection	Preferred Treatment	Alternative Treatment (first-line options not available or tolerated)
Infections outside of the urinary tract Resistant to ertapenem, susceptible to meropenem, AND carbapenemase testing results are either not available or negative	Meropenem ¹ (extended-infusion)	Ceftazidime-avibactam
Infections outside of the urinary tract Resistant to ertapenem, meropenem , AND carbapenemase testing results are either not available or negative	Ceftazidime-avibactam Meropenem-vaborbactam Imipenem-cilastatin-relebactam	Cefiderocol Tigecycline, eravacycline (IAI)
KPC identified (Or carbapenemase positive but identity of carbapenemase unknown ³)	Ceftazidime-avibactam Meropenem-vaborbactam Imipenem-cilastatin-relebactam	Cefiderocol Tigecycline, eravacycline (IAI)
Metallo-β-lactamase (i.e., NDM, VIM, or IMP) carbapenemase identified	Ceftazidime-avibactam + aztreonam Cefiderocol	Tigecycline, eravacycline (IAI)
OXA-48-like carbapenemase identified	Ceftazidime-avibactam	Cefiderocol Tigecycline, eravacycline (IAI)

Recommended antibiotic treatment options for difficult-to-treat (DTR) *Pseudomonas aeruginosa*, assuming *in vitro* susceptibility to agents

Source of Infection	Preferred Treatment	Alternative Treatment (when first-line options not available/tolerated)
Cystitis	<p>Ceftolozane-tazobactam Ceftazidime-avibactam Imipenem-relebactam Cefiderocol</p> <p>or a single-dose of an aminoglycoside</p>	Colistin
Pyelonephritis or cUTI	<p>Ceftolozane-tazobactam Ceftazidime-avibactam Imipenem-cilastatin-relebactam Cefiderocol</p>	Once-daily aminoglycosides
Infections outside of the urinary tract	<p>Ceftolozane-tazobactam Ceftazidime-avibactam Imipenem-cilastatin-relebactam</p>	<p>Cefiderocol</p> <p>Aminoglycoside monotherapy: limited to uncomplicated bloodstream infections with complete source control²</p>

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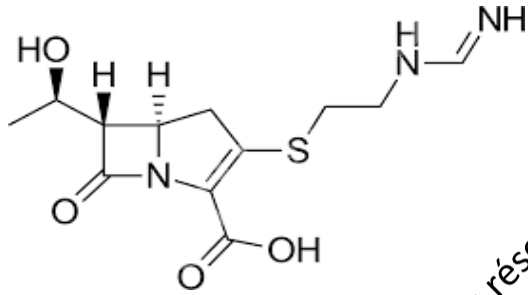
Resistances

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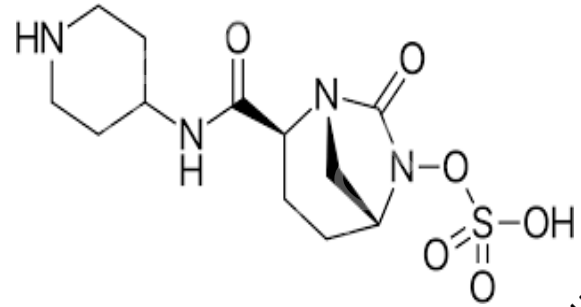
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Imipenem Relebactam

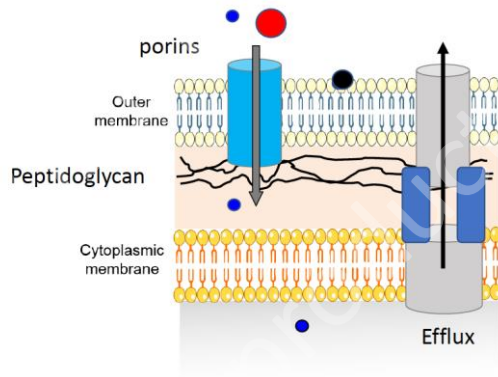


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Imipenem Relebactam



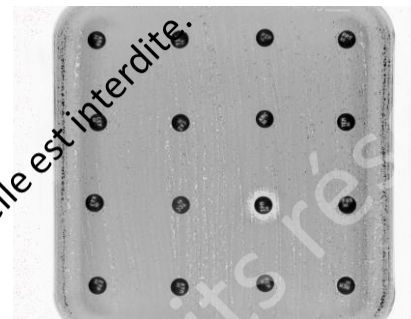
- Inactivation OprD/ MexAB-Opr M + mutation PBP 1 a (*P. aeruginosa*; Gomis-Font et al. 2020).
- Mutations in OmpK35/36 (*K. pneumoniae*; Balabanian et al. 2018; Haidar et al. 2017)
- contribution of GES to a given level of resistance to inhibitory effect of relebactam in *P. aeruginosa* ? (Young et al, 2019; Loo et al. 2019, Fraile-Ribot et al. 2020)

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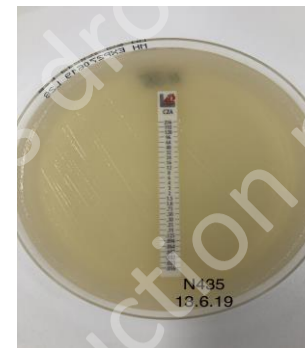


Phenotypic, Biochemical, and Genetic Analysis of KPC-41, a KPC-3 Variant Conferring Resistance to Ceftazidime-Avibactam and Exhibiting Reduced Carbapenemase Activity

Linda Mueller,^{a,b,c} Amandine Masseron,^a Guy Prod'Hom,^c Tatiana Galperine,^d Gilbert Greub,^c Laurent Poirel,^{a,b} Patrice Nordmann^{a,b,c,e}



β-Lactam ^a	MIC (μg/ml)	
	UM (KPC-41)	FF (KPC-3)
Amoxicillin	>128	>128
Amoxicillin + CLA	>128	>128
Ticarcillin	>128	>128
Ticarcillin + CLA	>128	>128
Piperacillin	>128	>128
Piperacillin + TZB	>128	>128
Cephalothin	>128	>128
Cefotaxime	32	>128
Ceftazidime	1,024	1,024
Ceftazidime + AVI	>128	4
Ceftaroline	>256	>256
Cefepime	16	28
Ceftolozane + TZB	>256	64
Cefoxitin	32	32
Astreonom	>128	>128
Imipenem	8	8
Meropenem	8	8
Ertapenem	4	16



Ceftazidime/avibactam

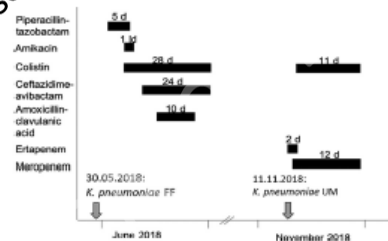


FIG 1 Timetable of antimicrobial treatments and isolation of the *K. pneumoniae* strains FF and UM. Black bars represent antimicrobial treatments, with numbers representing treatment length in days (d) or the loading dose (kd). Gray arrows indicate the dates of isolation of *K. pneumoniae* isolates FF and UM.

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Imipenem - Relebactam

	Enterobacterales					Pseudomonas spp.				Acinetobacter spp.
	ESBL	AmpC	KPC	OXA-48	MBLs	Efflux	AmpC	MBLs	OprD loss	
	Active	Active	Active	Potential resistance	Inactive	Active	Active	Inactive	Active	Partial/unreliable activity

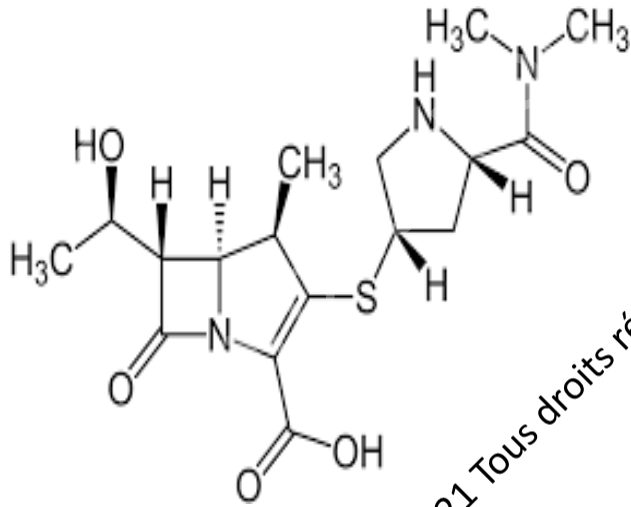
- Active
- Partial/unreliable activity
- Inactive
- Potential resistance

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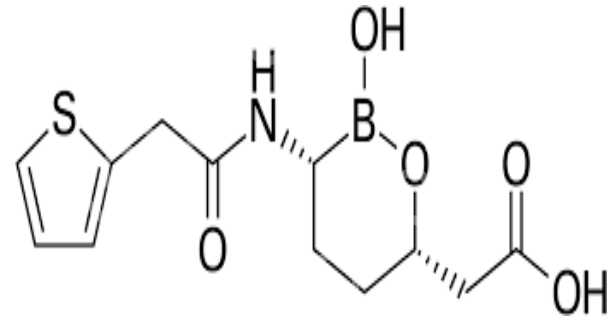
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Meropenem-Vaborbactam

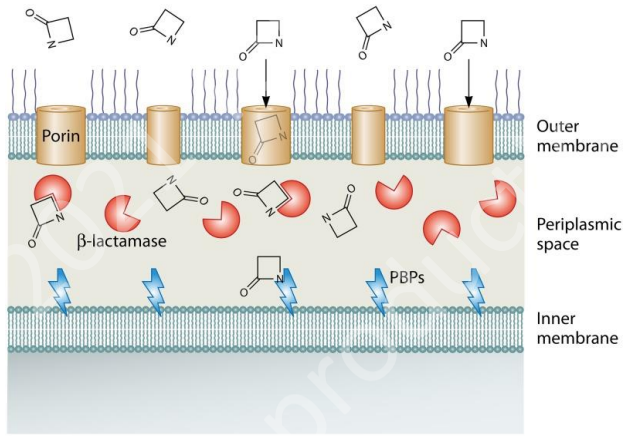


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Meropenem Vaborbactam



- Emergence of resistance in vivo OmpK35/36 + overexpression KPC (*K. pneumoniae*, Sun et al. 2017)
- Mutations in Omp proteins and efflux systems (**Enterobacterales**; Hecker et al. 2015; Lapuebla et al. 2015; Bush 2015; Hackel et al. 2017)

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Meropenem-Vaborbactam

Meropenem Meropenem-Vaborbactam (MIC)

Strain ID	Species	Antibiotic	Meropenem MIC	Meropenem-Vaborbactam MIC
N1006	<i>Escherichia coli</i>	KPC-3	32	0,5
N1113	<i>Escherichia coli</i>	KPC-3	0,125	0,125
N897	<i>Escherichia coli</i>	NDM-5	2	2
N898	<i>Escherichia coli</i>	NDM-5	>32	>64
N901	<i>Escherichia coli</i>	NDM-5	4	6
N935	<i>Escherichia coli</i>	NDM-5	24	12
N1014	<i>Escherichia coli</i>	NDM-5	>32	>64
N1071	<i>Escherichia coli</i>	NDM-5	4	4
N1076	<i>Escherichia coli</i>	NDM-5	24	12
N1081	<i>Escherichia coli</i>	NDM-5	>32	>64
N1097	<i>Escherichia coli</i>	NDM-5	1	1,5
N1115	<i>Escherichia coli</i>	NDM-5	>32	>64
N1146	<i>Escherichia coli</i>	NDM-5	>32	>64
N1153	<i>Escherichia coli</i>	NDM-5	>32	>64
N1235	<i>Escherichia coli</i>	NDM-5	12	12
N1239	<i>Escherichia coli</i>	NDM-5	>32	>64
N1255	<i>Escherichia coli</i>	NDM-5	>32	>64
N385	<i>Escherichia coli</i>	OXA-181	0,5	0,38
N591	<i>Escherichia coli</i>	OXA-181	0,19	0,19
N1067	<i>Escherichia coli</i>	OXA-181	0,19	0,125
N1152	<i>Escherichia coli</i>	OXA-181	0,75	0,75
N1229	<i>Escherichia coli</i>	OXA-181	1	1
N229	<i>Escherichia coli</i>	OXA-244	0,25	0,5
N481	<i>Escherichia coli</i>	OXA-244	0,25	0,38
N511	<i>Escherichia coli</i>	OXA-244	0,5	1
N574	<i>Escherichia coli</i>	OXA-244	0,094	0,38
N658	<i>Escherichia coli</i>	OXA-244	0,38	0,38
N846	<i>Escherichia coli</i>	OXA-244	0,064	0,064
N961	<i>Escherichia coli</i>	OXA-244	0,064	0,094
N974	<i>Escherichia coli</i>	OXA-244	1	1
N1004	<i>Escherichia coli</i>	OXA-244	0,38	1
N1036	<i>Escherichia coli</i>	OXA-244	0,125	0,094
N1066	<i>Escherichia coli</i>	OXA-244	0,125	0,094
N1074	<i>Escherichia coli</i>	OXA-244	0,064	0,094
N1085	<i>Escherichia coli</i>	OXA-244	0,125	0,094
N244	<i>Escherichia coli</i>	OXA-48	1	0,38
N446	<i>Escherichia coli</i>	OXA-48	0,25	0,38
N642	<i>Escherichia coli</i>	OXA-48	2	2

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NARA

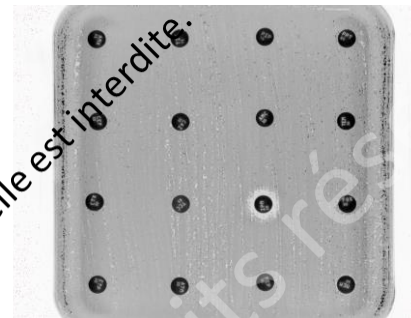
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Phenotypic, Biochemical, and Genetic Analysis of KPC-41, a KPC-3 Variant Conferring Resistance to Ceftazidime-Avibactam and Exhibiting Reduced Carbapenemase Activity

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Ceftazidime/avibactam

β-Lactam ^a	MIC (μg/ml)	
	UM (KPC-41)	FF (KPC-3)
Amoxicillin	>128	>128
Amoxicillin + CLA	>128	>128
Ticarcillin	>128	>128
Ticarcillin + CLA	>128	>128
Piperacillin	>128	>128
Piperacillin + TZB	>128	>128
Cephalothin	>128	>128
Cefotaxime	32	>128
Ceftazidime	1,024	1,024
Ceftazidime + AVI	>128	4
Ceftaroline	>256	>256
Cefepime	16	28
Ceftolozane + TZB	>256	64
Cefoxitin	32	32
Astreonom	>128	>128
Imipenem	8	8
Meropenem	8	8
Ertapenem	4	16

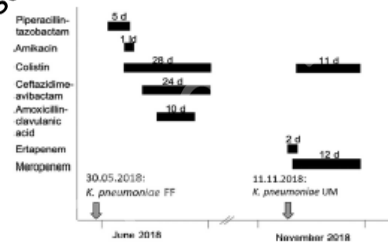


FIG 1 Timetable of antimicrobial treatments and isolation of the *K. pneumoniae* strains FF and UM. Black bars represent antimicrobial treatments, with numbers representing treatment length in days (d) or the loading dose (kd). Gray arrows indicate the dates of isolation of *K. pneumoniae* isolates FF and UM.

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Meropenem - Vaborbactam

	Enterobacterales					Pseudomonas spp.				Acinetobacter spp.
	ESBL	AmpC	KPC	OXA-48	MBLs	Efflux	AmpC	MBLs	OprD loss	
	Active	Active	Active	Potential resistance	Inactive	Inactive	Active	Inactive	Inactive	Partial/unreliable activity
	K. pneumoniae OmpK36 porin mutation, non-functional OmpK39-37									

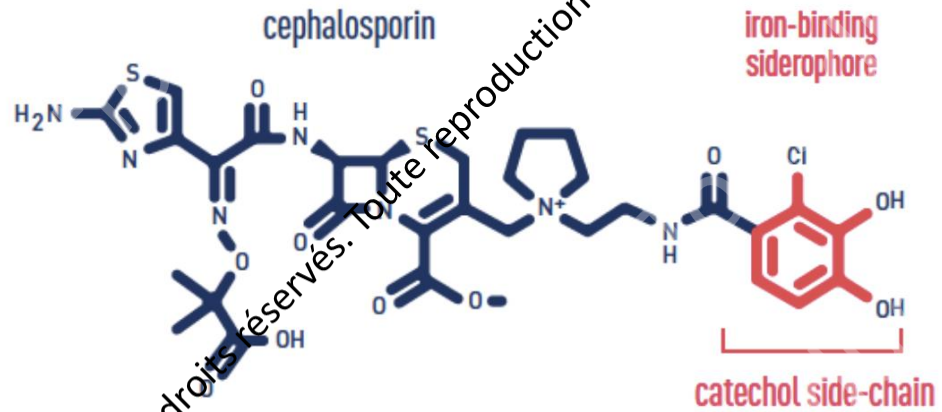
- Active
- Inactive
- Partial/unreliable activity
- Potential resistance

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Cefidericol

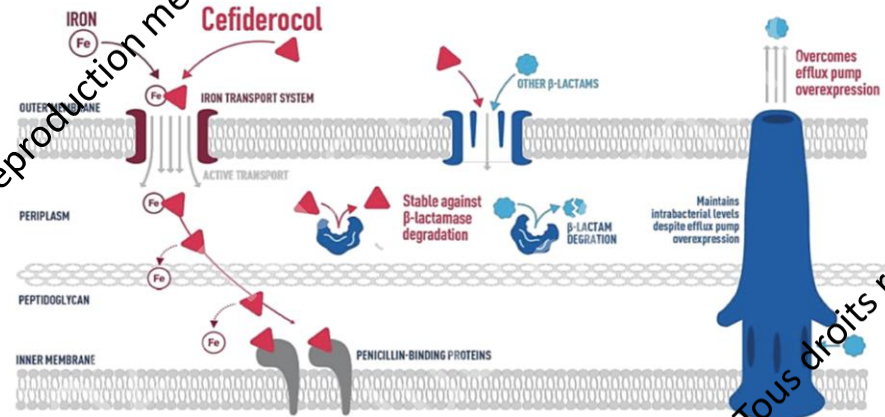


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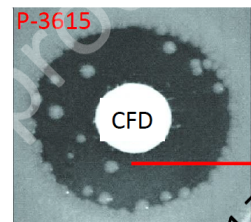
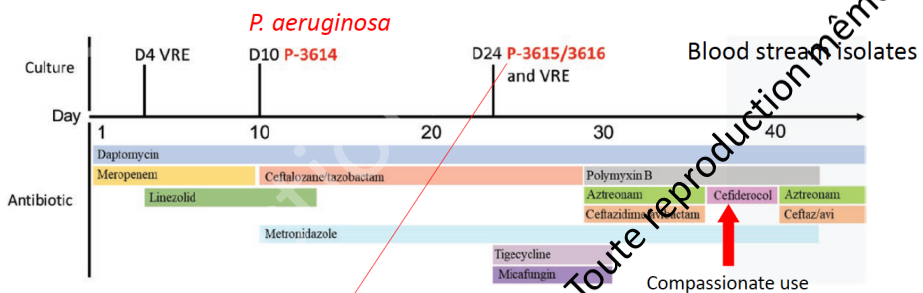
Target	Organism(s)	Function
<i>tonB</i>	<i>Escherichia coli</i>	Component of inner membrane protein complex providing energy to TonB-dependent transporters
<i>cirA</i>	<i>E. coli</i> , <i>Enterobacter cloacae</i>	Encodes receptor which preferentially transports catechololate siderophores
<i>fiu</i>	<i>E. coli</i>	Encodes receptor that preferentially transports catechololate siderophores
<i>baeS</i>	<i>Klebsiella pneumoniae</i>	Encodes a sensor kinase protein of the two-component BaeSR signal transduction system reported to affect a variety of envelope stress response pathways.
<i>exbD</i>	<i>K. pneumoniae</i>	TonB-dependent energy transduction system reported to affect the function of iron transporters
<i>envZ</i>	<i>K. pneumoniae</i>	Two-component transcriptional regulator reported to affect the expression of iron transporters
<i>ompR</i>	<i>K. pneumoniae</i>	Two-component transcriptional regulator reported to affect the expression of iron transporters
<i>yicM</i>	<i>K. pneumoniae</i>	Unknown function
<i>ampC</i>	<i>E. cloacae</i> complex	Chromosomal β -lactamase gene



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Emergence of non-susceptibility to cefiderocol in *P. aeruginosa*

Case report of patient without prior exposure to cefiderocol



P. aeruginosa isolate before cefiderocol treatment

Genetic variants
OR
Phenotypic variants
Heteroresistance

	MIC (mg/L)				
	CEF	CAZ/Avib	MER	CFD	Colistin
P-3614	16	8	>16	2	ND
P-3615	>16	>16	>8	ND	2
P-3616	>16	>16	>8	8	2

Progressive Development of Cefiderocol Resistance in *Escherichia coli* During Therapy is Associated With an Increase in *bla*_{NDM-5} Copy Number and Gene Expression

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Background. As cefiderocol is increasingly being prescribed in clinical practice, it is critical that we understand key mechanisms contributing to acquired resistance to this agent.

Methods. We describe a patient with acute lymphoblastic leukemia and a New Delhi metallo- β -lactamase (NDM)-5–producing *Escherichia coli* intra-abdominal infection in whom resistance to cefiderocol evolved approximately 2 weeks after the start of treatment. Through whole-genome sequencing (WGS), messenger RNA expression studies, and ethylenediaminetetraacetic acid inhibition analysis, we investigated the role of increased *bla*_{NDM-5} production and genetic mutations contributing to the development of cefiderocol resistance, using 5 sequential clinical *E. coli* isolates obtained from the patient.

Results. In all 5 isolates, *bla*_{NDM-5} genes were identified. The minimum inhibitory concentrations for cefiderocol were 2, 4, and >32 $\mu\text{g}/\text{mL}$ for isolates 1–2, 3, and 4–5, respectively. WGS showed that isolates 1–3 contained a single copy of the *bla*_{NDM-5} gene, whereas isolates 4 and 5 had 5 and 10 copies of the *bla*_{NDM-5} gene, respectively, on an IncFIA/FIB/IncFII plasmid. These findings were correlated with those of *bla*_{NDM-5} messenger RNA expression analysis, in which isolates 4 and 5 expressed *bla*_{NDM-5} 1.7- and 2.8-fold, respectively, compared to, isolate 1. Synergy testing with the combination of ceftazidime-avibactam and aztreonam demonstrated expansion of the zone of inhibition between the disks for all isolates. The patient was successfully treated with this combination and remained infection free 1 year later.

Conclusions. The findings in our patient suggest that increased copy numbers of *bla*_{NDM} genes through translocation events are used by Enterobacteriales to evade cefiderocol-mediated cell death. The frequency of increased *bla*_{NDM-5} expression in contributing to cefiderocol resistance needs investigation.

Keywords. NDM; cefiderocol, antimicrobial resistance; *Escherichia coli*.



Contribution of PER-Type and NDM-Type β -Lactamases to Cefiderocol Resistance in *Acinetobacter baumannii*

Laurent Poirel,^{a,b,c} Mustafa Sadek,^{a,d} Patrice Nordmann^{a,b,c,e}

TABLE 1 Susceptibility testing of cefiderocol nonsusceptible *Acinetobacter baumannii* isolates and *A. baumannii* or *E. coli* recombinant strains

Species or strain	Resistance determinant	MIC ($\mu\text{g/ml}$) ^a
		FDC (EUMPROXF [CMP1SHIH panel]) ^b
<i>A. baumannii</i>	OXA-23+PER-7	>8 (>16)
	OXA-23+PER-7	>8 (>16)
	OXA-23+PER-7	>8 (>32)
	OXA-23+PER-1	>8 (16)
	OXA-23+PER-1	>8 (32)
	OXA-23+PER-1	>8 (>32)
	OXA-23+PER-7	>8 (>32)
	OXA-23+PER-7	>8 (>32)
	NDM-1	2
	NDM-1	8
	NDM-1	4
	NDM-1	(>8) 16
	NDM-1	2
	NDM-1	4
	NDM-5	8
NDM-9	(>8) 16	



Contribution of PER-Type and NDM-Type β -Lactamases to Cefiderocol Resistance in *Acinetobacter baumannii*

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Species or strain	Resistance determinant	MIC (μ g/ml) ^a
		FDC (EUMDROXF [CMP1SHIH panel]) ^f
<i>A. baumannii</i>	OXA-23+PER-7	>8 (>16)
	OXA-23+PER-7	>8 (>16)
	OXA-23+PER-7	>8 (>32)
	OXA-23+PER-1	>8 (16)
	OXA-23+PER-1	>8 (>16)
	OXA-23+PER-1	>8 (>32)
	OXA-23+PER-7	>8 (>32)
	OXA-23+PER-7	>8 (>32)
	NDM-1	2
	NDM-1	8
	NDM-1	4
	NDM-1	(>8) 16
	NDM-1	2
	NDM-1	4
	NDM-5	8
	NDM-9	(>8) 16
	<i>A. baumannii</i> CIP70.10	PER-1
NDM-1		1
NDM-5		0.5
NDM-9		1
OXA-23		\leq 0.125
OXA-40		\leq 0.125
OXA-48		\leq 0.125
OXA-58		\leq 0.125
CTX-M-2		\leq 0.125

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Contribution of PER-Type and NDM-Type β -Lactamases to Cefiderocol Resistance in *Acinetobacter baumannii*

Laurent Poirel^{a,b,c} Mustafa Sadek^{a,d} Patrice Nordmann^{a,b,c,e}

Enzyme	Specific activity ($\mu\text{mol}\cdot\text{min}^{-1}\cdot\text{mg}^{-1}$)	
	Benzylpenicillin	Cefiderocol
PER-1	6.72	2.14
NDM-1	13.60	0.28
CTXM-2	6.28	NH
VEB-1	19.07	NH
VIM-2	8.5	NH
CTX-M-15	2.65	NH

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Contribution of PER-Type and NDM-Type β -Lactamases to Cefiderocol Resistance in *Acinetobacter baumannii*

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Species or strain	Resistance determinant	MIC ($\mu\text{g/ml}$) ^a	
		FDC (EUMDROXF [CMP15H], panel) ^b	FDC-AV1c
<i>A. baumannii</i>	OXA-23+PER-7	>8 (>16)	0.5
	OXA-23+PER-7	>8 (>16)	0.25
	OXA-23+PER-7	>8 (>32)	0.5
	OXA-23+PER-1	>8 (16)	0.5
	OXA-23+PER-1	>8 (32)	0.5
	OXA-23+PER-1	>8 (>32)	0.25
	OXA-23+PER-7	>8 (>32)	0.25
	OXA-23+PER-7	>8 (>32)	2
	NDM-1	2	ND
	NDM-1	8	ND
	NDM-1	4	ND
	NDM-1	(>8) 16	ND
	NDM-1	2	ND
	NDM-1	4	ND
	NDM-5	8	ND
	NDM-9	(>8) 16	ND
	<i>A. baumannii</i> CIP70.10	PER-1	2
NDM-1		1	ND
NDM-5		0.5	ND
NDM-9		1	ND
OXA-23		≤ 0.125	≤ 0.125
OXA-40		≤ 0.125	≤ 0.125
OXA-48		≤ 0.125	≤ 0.125
OXA-58		≤ 0.125	≤ 0.125
CTX-M-2	≤ 0.125	≤ 0.125	



Interesting combination

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Cefiderocol

	Enterobacterales					Pseudomonas spp.				Acinetobacter spp.
	ESBL	AmpC	KPC	OXA-48	MBLs	Efflux	AmpC	MBLs	OprD loss	
						<div style="border: 1px solid #ccc; padding: 5px; background-color: #e0f0ff;"> <i>P. aeruginosa</i> Overexpression of FecA (ferric citrate transporter)/AmpC mutations </div>				

PER and NDM may potentially contribute to cefiderocol resistance

- Active
- Partial/unreliable activity
- Inactive
- Potential resistance

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Take home message

- Novel antibiotics are either being already available against MDR Gram negatives
- Acquired resistance to novel molecules is increasingly reported but depending of the couple molecule/bacterial species
- Still difficult to treat bacterial infections ; metallo-enzymes producers (++ NDM) in Enterobacterales and multidrug resistant *A.baumannii*