Place des nouvelles bêta-lactamines +/- inhibiteurs en soins critiques

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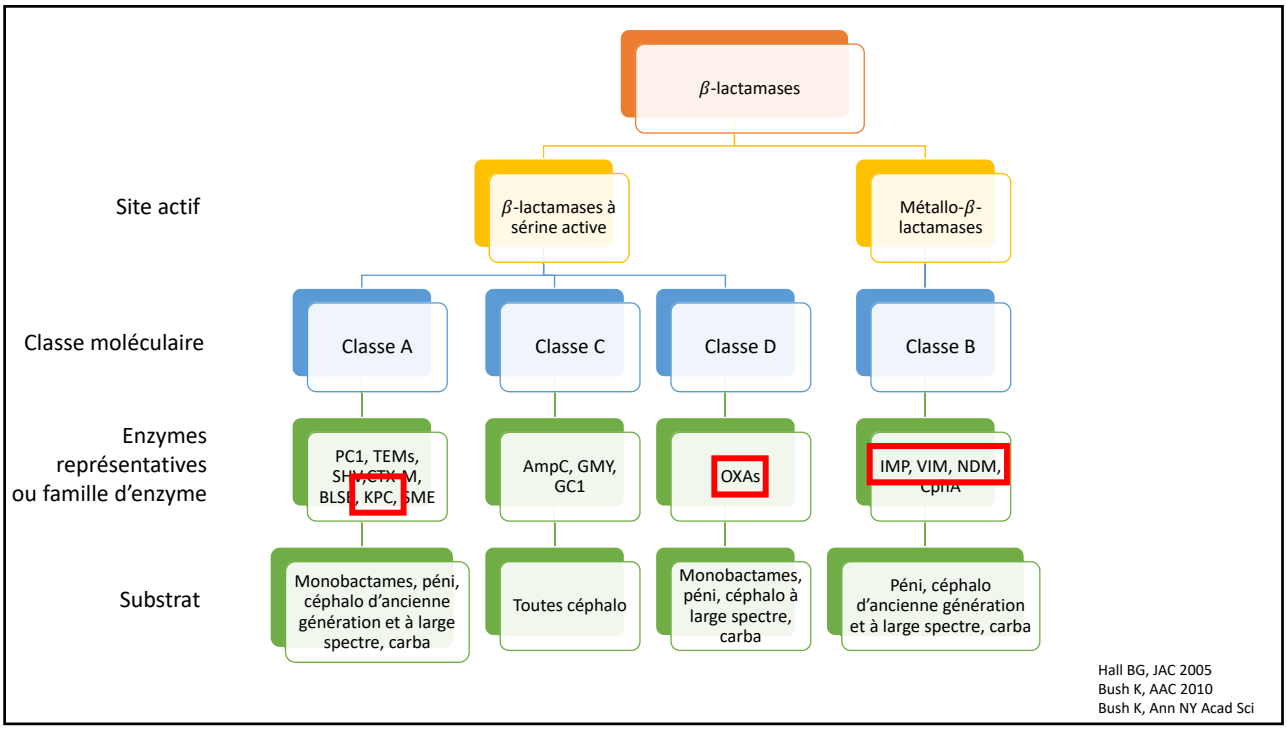
Infectiologie : approche diagnostique et thérapeutique
en Soins Critiques Avril 2022

Plan

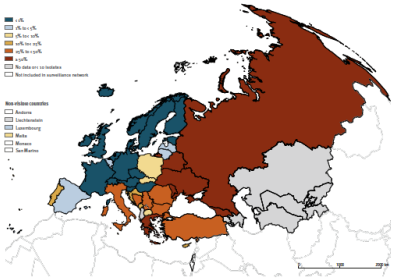
- Introduction
- Epidémiologie
- Nouvelles bêta-lactamines +/- inhibiteurs
- Recommandations ESCMID
- Exemples de résistance
- Conclusion ouvertures

Introduction

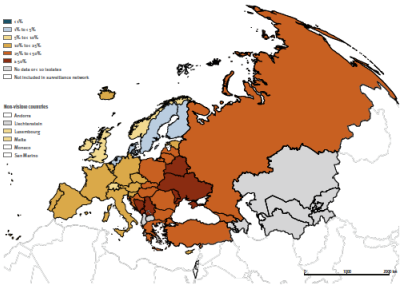


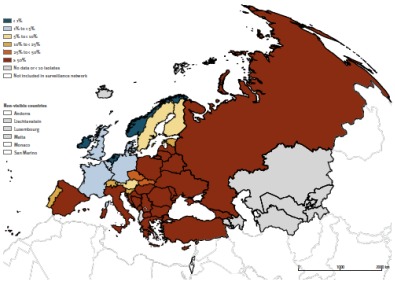
Hall BG, JAC 2005
Bush K, AAC 2010
Bush K, Ann NY Acad Sci

Epidémiologie



K.p. C-R
France 0.5%
(2019 1%)





A.b. C-R
France: 3.3%
(2019: 13.3%)

P.a. C-R
France: 12.6%
(2019: 12.7%)

2022,
données 2020

CARACTÉRISTIQUES ET ÉVOLUTION DES SOUCHES D'ENTÉROBACTÉRIES PRODUCTRICES DE CARBAPÉNÉMASES (EPC) ISOLÉES EN FRANCE, 2012-2020

// CHARACTERISTICS AND EVOLUTION OF CARBAPENEMASE-PRODUCING ENTEROBACTERALES IN FRANCE, 2012-2020

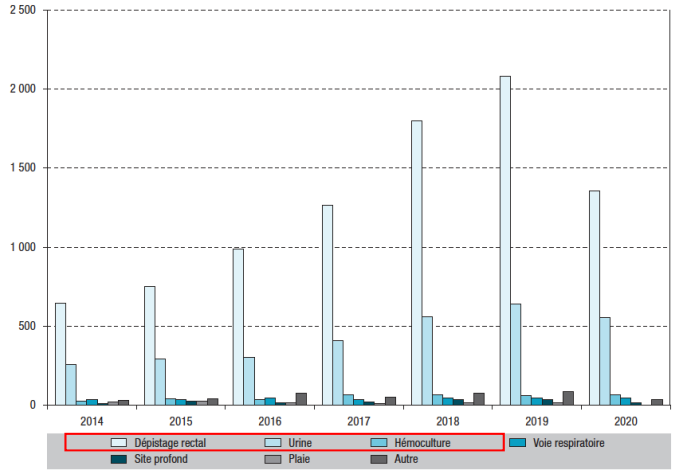
Agnès B. Jousset[1,2,3], Cécile Emeraud[1,2,3], Rémy A. Bonnin[1,2], Thierry Naas[1,2,3], Laurent Dortet[1,2,3] (laurent.dortet@aphp.fr)

[1] Centre national de référence de la résistance aux antibiotiques : entérobactéries productrices de carbapénémases, Hôpital de Bicêtre, AP-HP, Le Kremlin-Bicêtre

SPF 2021

Figure 2

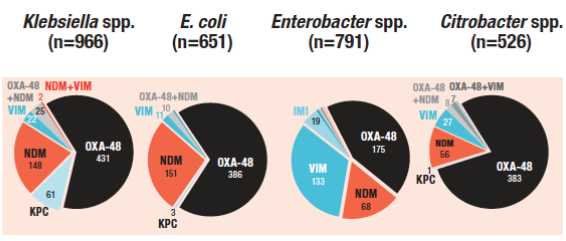
Origine des sites de prélèvements d'entérobactéries productrices de carbapénémases de 2014 à 2020, France



Distribution des carbapénémases identifiées au CNR* en 2020, France

Classe de Ambler	Type de carbapénémase	Nombre de souches	%
Classe A	KPC	65	2,9
	GES-5	1	0,05
	IMI	20	0,9
	NMC-A	2	0,1
Classe B	NDM	443	20,1
	VIM	204	9,2
	NDM + VIM	6	0,3
Classe D	OXA-48-like	1 398	63,3
	OXA-23	11	0,5
Classe A + Classe D	KPC + OXA-48-like	1	0,05
Classe B + Classe D	NDM + OXA-48-like	46	2,1
	VIM+ OXA-48-like	10	0,5
	NDM + VIM+ OXA-48-like	1	0,05
TOTAL		2 208	100

Mécanismes de résistances aux carbapénèmes en 2020 en fonction du genre bactérien



GHT : carbapénémases hors colonisation

	2020	2021	2022
CHi Fréjus-Saint-Raphaël	2 OXA-48	1 NDM 1 IMP15	0
Cannes	2 OXA-48	2 OXA-48	1 KPC
Antibes (EB)	-	1 OXA-48 2 OXA-48 NDM	-

Enjeux cliniques

Mortality due to KPC carbapenemase-producing *Klebsiella pneumoniae* infections: Systematic review and meta-analysis
Mortality due to KPC *Klebsiella pneumoniae* infections

Journal of Infection

Ramos-Casraneda et al. 2018

37 études, 2005-2015 Am. Sud – Asie – Grèce –Italie, 5124 patients, qualité médiocre des études

28% de bactériémie

KPC-KP infection was mainly studied in non-critical hospitalized patients, 62.7%, followed by critically ill, 23.5%, oncology, 5.9% and transplant patients, 5.9%

Overall mortality was 41.0% (95%CI 37.0–44.0), with the highest mortality rates being observed in oncology patients, 56.0% (95%CI 38.1–73.0), and Brazil, 51.3% (95%CI 43.0–60.0)

Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study

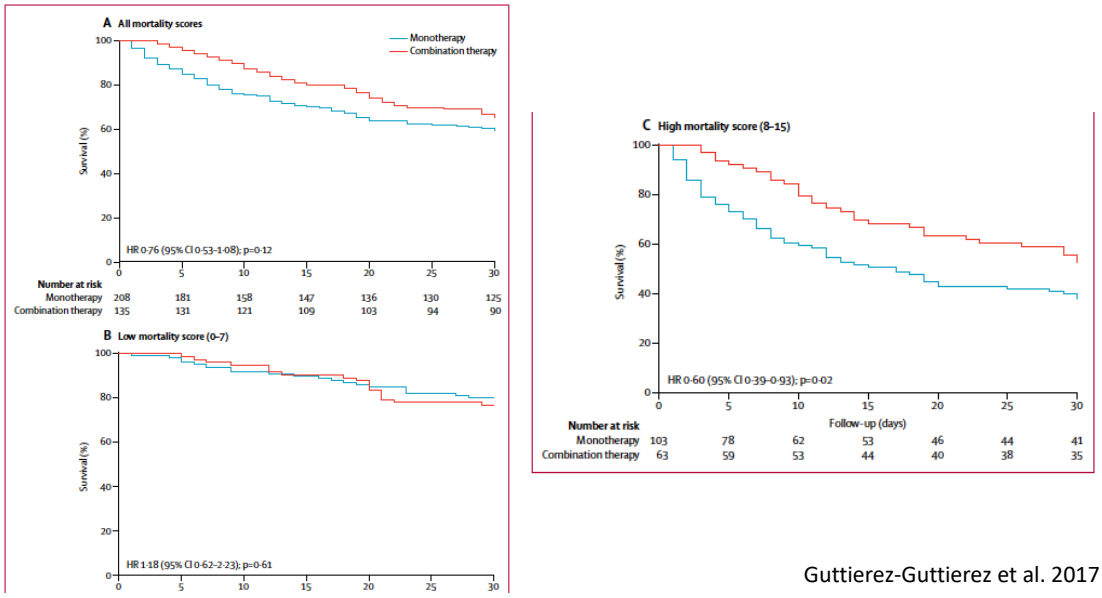
Lancet Infect Dis 2017; 17: 726-34

Guttierez-Guttierez et al. 2017

Rétrospectif multicentrique 2004-2013
437 patients
K. pneumoniae: 86%

30d Mortality:
Appropriate therapy (started in ≤5 days after infection)
HR = 0.45 (0.33–0.62) <0.0001

	Appropriate therapy (n=343)	Inappropriate therapy (n=94)
30 day mortality	132 (38%)	57 (61%)
Type of carbapenemase	..	..
OXA-48	57 (17%)	12 (13%)
KPC	253 (74%)	76 (81%)
Metallo-β-lactamases	33 (10%)	6 (6%)
VIM	30 (9%)	6 (6%)
Other	3 (1%)	0
Source other than urinary or biliary tract	272 (79%)	76 (81%)



Guttierez-Guttierez et al. 2017

Infections caused by KPC-producing *Klebsiella pneumoniae*: differences in therapy and mortality in a multicentre study

Journal of Antimicrobial Chemotherapy

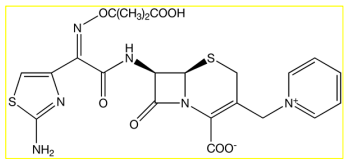
Tumbarello et al. 2015

661 patients dont 447 bactériémiques
14d Mortality 34.1%

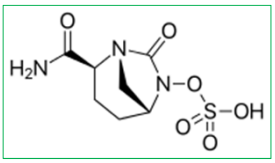
Table 5. Multivariate analysis of risk factors for 14 day mortality in patients with infections caused by KPC-Kp

Variable	*P* value	OR (95% CI)
Combination therapy	0.001	0.52 (0.35–0.77)
BSI	<0.001	2.09 (1.34–3.29)
Septic shock at infection onset	0.001	2.45 (1.47–4.08)
APACHE III score	<0.001	1.05 (1.04–1.07)
Chronic renal failure	<0.001	2.27 (1.44–3.58)
Colistin-resistant isolate	0.001	2.18 (1.37–3.46)
Inadequate empirical antimicrobial therapy	0.04	1.48 (1.01–2.18)

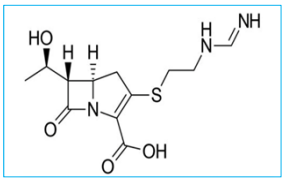
Nouvelles bêta-lactamines +/- inhibiteurs



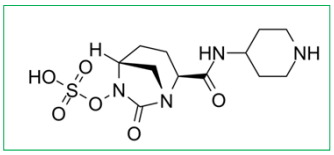
Ceftazidime



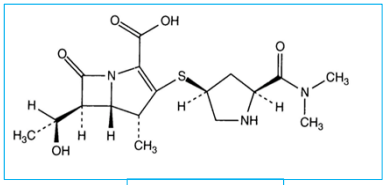
Avibactam



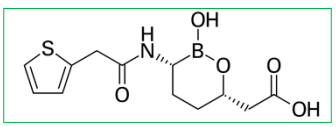
Imipénème



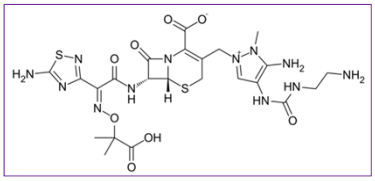
Relebactam



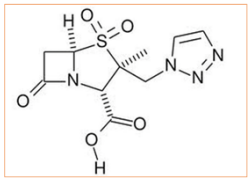
Meropénème



Vaborbactam

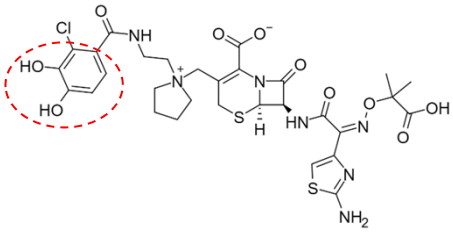


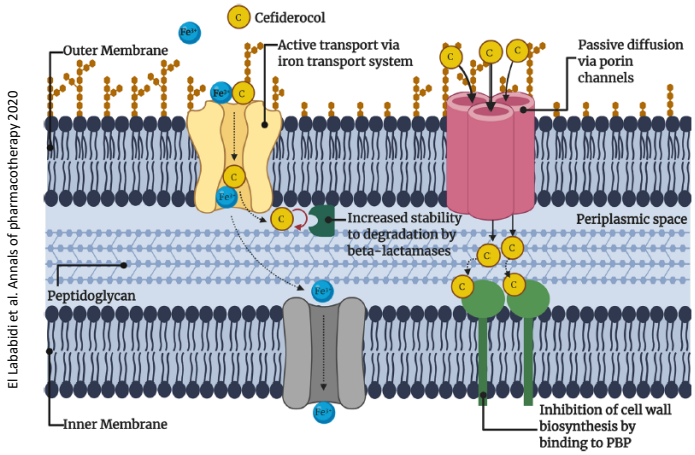
Ceftolozane



Tazobactam

Groupement catéchol





Approved treatment options for MDR Gram-negative infections in Europe

	cUTI	cIAI	HA pneumonia including VAP	Gram – with limited options	Bacteremia with or suspected to be associated with cUTI, cIAI or HAP/VAP	Paediatric pop
Cefto-Tazo	✓	✓	✓	✗	✗	✗
Cefta-Avi	✓	✓	✓	✓	✓	✓
Imi-Rele	✗	✗	✓	✓	✗	✗
Mero-Vabor	✓	✓	✓	✓	✓	✗
Cefiderocol	✗	✗	✗	✓	✗	✗

	Enterobacteriaceaea						*P. aeruginosa*					*A. baumanii*		
	ESBL	AmpC	CRE non-CP	KPC	MBL	OXA-48	AmpC	Efflux	Porine	CRPA Non-MBL	CRPA MBL	AmpC	OXA-23, 40, 58	MBL
Ceftolozane-Tazobactam														
Ceftazidime-Avibactam					+ATM						+ATM			
Meropénème-Vaborbactam														
Imipénème-Relebactam														
Cefiderocol														

D'après Chaïbi K et al. *Antibiotics* 2022
et ESCMID guidelines 2022

Recommandations ESCMID 2022

Guidelines

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)

Mica P et al. 2022

3GCephRE	Strength of Reco.	Level of evidence
Among **all patients** with 3GCephRE infections the new BLBLI **are reserved antibiotics for extensively resistant bacteria** and therefore, we consider it good clinical practice to **avoid their use** for infections caused by 3GCephRE, due to antibiotic stewardship considerations.	Good practice statement	Expert opinion

Guidelines

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)

Mica P et al. 2022

Carbapenem-resistant Enterobacterales (CRE)	Strength of Reco.	Level of evidence
Severe inf. : we suggest mero-vabor or cefta-avi if active in vitro	Conditionnal	Moderate/low
Severe inf. : due to CRE carrying **MBL** and/or resistant to all other antibiotics, including cefta-avi and mero-vabor, we conditionally recommend treatment with cefiderocol.	Conditionnal	Low
Non severe inf. : under the consideration of antibiotic stewardship, we consider the use of an **old antibiotic**, as good clinical practice. Ag over Tige for cUTI	Good practice statement/conditional	Expert opinion / low
We suggest that Tige not be used for BSI and HAP/VAP; if necessary, in patients with pneumonia, clinicians may use high-dose Tige	Conditionnal	Low
There is **no evidence** to recommend **for or against** the use of imi-rele and fosfo monotherapies for CRE at the time of writing.	No reco.	

Guidelines

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)

Mica P et al. 2022

Recommendations on combination therapy for CRE	Strength of Reco.	Level of evidence
For CRE infections treated with ceftaz-avi, mero-vabor or cefiderocol, **we do not recommend combination therapy**	Strong	Low
For patients with **severe infections** caused by CRE carrying **MBL** and/or resistant to new antibiotic monotherapies, we suggest atm and cefta-avi combination therapy	Conditionnal	Moderate
For **severe infections** caused by CRE susceptible in vitro only to polymyxins, aminoglycosides, tigecycline or fosfomycin, or in the case of non-availability of new BLBLI, we suggest treatment with more than one drug active in vitro. No recommendation for or against specific combinations can be provided.	Conditionnal	Moderate
Avoid carba-based combination therapy for CRE, unless the mero MIC is **≤8 mg/L**, where high-dose extended-infusion mero may be used **as part of** combination therapy if new BLBLI not used.	Conditionnal	Low
In patients with **non-severe** infections, under the consideration of antibiotic stewardship, we consider the use of monotherapy chosen from among the in vitro active **old drugs**, on an **individual basis** and according to the source of infection as good clinical practice	Good practice statement	Expert opinion

Guidelines

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)

Mica P et al. 2022

Carbapenem-resistant *P. aeruginosa* (CRPA)	Strength of Reco.	Level of evidence
In **severe infections** due to difficult to treat CRPA, we suggest therapy with cefto-tazo if active in vitro. Insufficient evidence is available for imi-rele, cefiderocol and cefta-avi at this time.	Conditionnal	Very Low
In **non-severe** or low-risk CRPA infections, under the consideration of antibiotic stewardship, we consider it good clinical practice to use the old antibiotics, chosen from among the in vitro active antibiotics on an individual basis and according to the source of infection.	Good practice statement	Expert opinion

Guidelines

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)

Mica P et al. 2022

Recommendations on combination therapy for CRPA	Strength of Reco.	Level of evidence
Lacking evidence, we cannot recommend for or against the use of combination therapy with the new BLBLI (cefta-avi and cefto-tazo) or cefiderocol for CRPA infections.	No recommandation	
When treating **severe infections** caused by CRPA with polymyxins, aminoglycosides, or fosfomycin, we suggest treatment with **two** in vitro active drugs. No recommendation for or against specific combinations can be provided.	Conditionnal	Very Low
In patients with **non-severe or low-risk** CRPA infections, under the consideration of antibiotic stewardship, we consider it good clinical practice to use monotherapy chosen from among the drugs active in vitro, on an individual basis and according to the source of infection.	Good practice statement	Expert opinion

Guidelines

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)

Mica P et al. 2022

CRAB	Strength of Reco.	Level of evidence
For patients with CRAB susceptible to sulbactam and HAP/VAP, we suggest ampicillin-sulbactam.	Conditionnal	Low
For patients with CRAB resistant to sulbactam, a polymyxin or high-dose tigecycline can be used if active in vitro. We cannot recommend on the preferred antibiotic.	No recommandation	
We conditionally recommend **against** cefiderocol for the treatment of infections caused by CRAB.	Conditionnal	Low

Guidelines

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)

Mica P et al. 2022

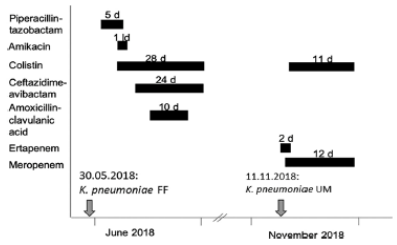
Recommendations on combination therapy for CRAB	Strength of Reco.	Level of evidence
For all patients with CRAB infections, **we do not recommend** polymyxin-meropenem combination therapy or polymyxin-rifampin combination therapy	Strong	High/moderate
For patients with **severe and high-risk CRAB infections**, we suggest combination therapy including **two in vitro active antibiotics** among the available antibiotics (polymyxin, aminoglycoside, tigecycline, sulbactam combinations).	Conditionnal	Very Low
For patients with CRAB infections with a meropenem MIC ≤8 mg/L, we **consider carbapenem combination therapy**, using high-dose extended-infusion carbapenem dosing, as good clinical practice.	Good practice statement	Expert opinion

Exemples de résistance

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

Antimicrobial Agents and Chemotherapy®

Mueller L et al. 2019



Souches de portage

β-Lactam[a]	MIC (μg/ml) *K. pneumoniae* 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	128
Ceftolozane + TZB	>256	64
Cefoxitin	32	32
Aztreonam	>128	>128
Imipenem	4	8
Meropenem	1	8
Ertapenem	4	16

Defining Baseline Mechanisms of Cefiderocol Resistance in the Enterobacterales

MICROBIAL DRUG RESISTANCE

Simner et al. 2021

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

Clinical Infectious Diseases BRIEF REPORT

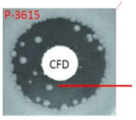
Rapid Development of Cefiderocol Resistance in Carbapenem-resistant *Enterobacter cloacae* During Therapy Is Associated With Heterogeneous Mutations in the Catecholate Siderophore Receptor *cirA*

Klein S et al. 2022

Clinical Infectious Diseases BRIEF REPORT

Evolution of Cefiderocol Non-Susceptibility in *Pseudomonas aeruginosa* in a Patient Without Previous Exposure to the Antibiotic

Sterling AP et al. 2021



Interestingly, there were SNPs identified in genes belonging to TonB dependent receptors (TBDRs), associated with iron acquisition, and in the chromosomal *ampC* β-lactamase gene.

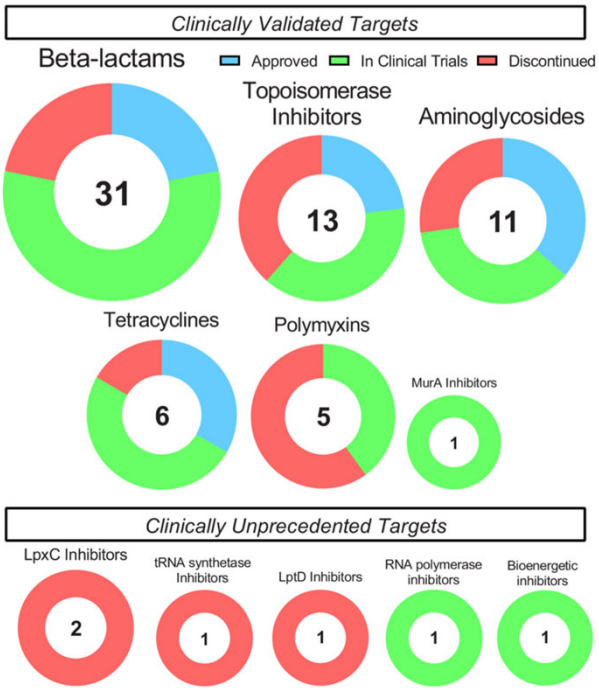
Antimicrobial Agents and Chemotherapy

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

Poirel et al. 2021

OXA23 + PER

Conclusion / ouvertures



Prasad et al. AAC 2022

- Solutions pour des impasses
- Usage ponctuel: difficultés à « s'approprier » ces molécules
- Gestion des données de sensibilité (techniques rapides, choix des panels)
- Rationnel au monitoring pharmacologique en soins critiques
- Situation caricaturale d'une collaboration nécessaire