Enterobacteriales

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Enterobacteriales

The Enterobacterales order — Enterobacterales is an order of bacteria that contains seven groups (ie, families) of gram-negative bacilli. Bacteria within the Enterobacterales families include several clinically relevant bacteria that commonly cause infections. The most clinically relevant families within the Enterobacterales order include the following:

- **Enterobacteriaceae family** – This family includes at least 33 genera of bacteria, some of which cause human disease. The most notable are *Escherichia* (eg, *Escherichia coli*), *Klebsiella*, *Enterobacter*, *Citrobacter*, *Salmonella*, and *Shigella*.
- Morganellacaeae family – Clinically relevant genera in this family include Proteus, Morganella, and Providencia.
- Other families include genera such as Serratia, Hafnia, and Yersinia

Table 1 | Taxonomy and treatment of infection with common pathogenic Gram negative bacteria

Phylum	Family	Example genus	Antibiotic classes active*	Commonly used antibiotics*
Proteobacteria	Enterobacteriales	*Escherichia, Klebsiella*	Penicillins, cephalosporins	Ampicillin, piperacillin, cephazolin, ceftriaxone
		Enterobacter, Citrobacter, Serratia	Carbapenems, aminoglycosides, fluoroquinolones	Meropenem, gentamicin, ciprofloxacin
	Pseudomonales	Pseudomonas	Penicillins, carbapenems, aminoglycosides, fluoroquinolones	Piperacillin, meropenem, gentamicin, ciprofloxacin
	Moraxellaceae	Acinetobacter	Penicillins, carbapenems	Piperacillin, meropenem
Bacteroidetes	Bacteroidaceae	Bacteroides	Nitroimidazoles, penicillins	Metronidazole, piperacillin

*Examples of most commonly used agents, in the absence of specific resistance. A β lactam inhibitor (such as tazobactam) is typically combined with piperacillin to overcome common β lactamases.

Enterobacteriaceae

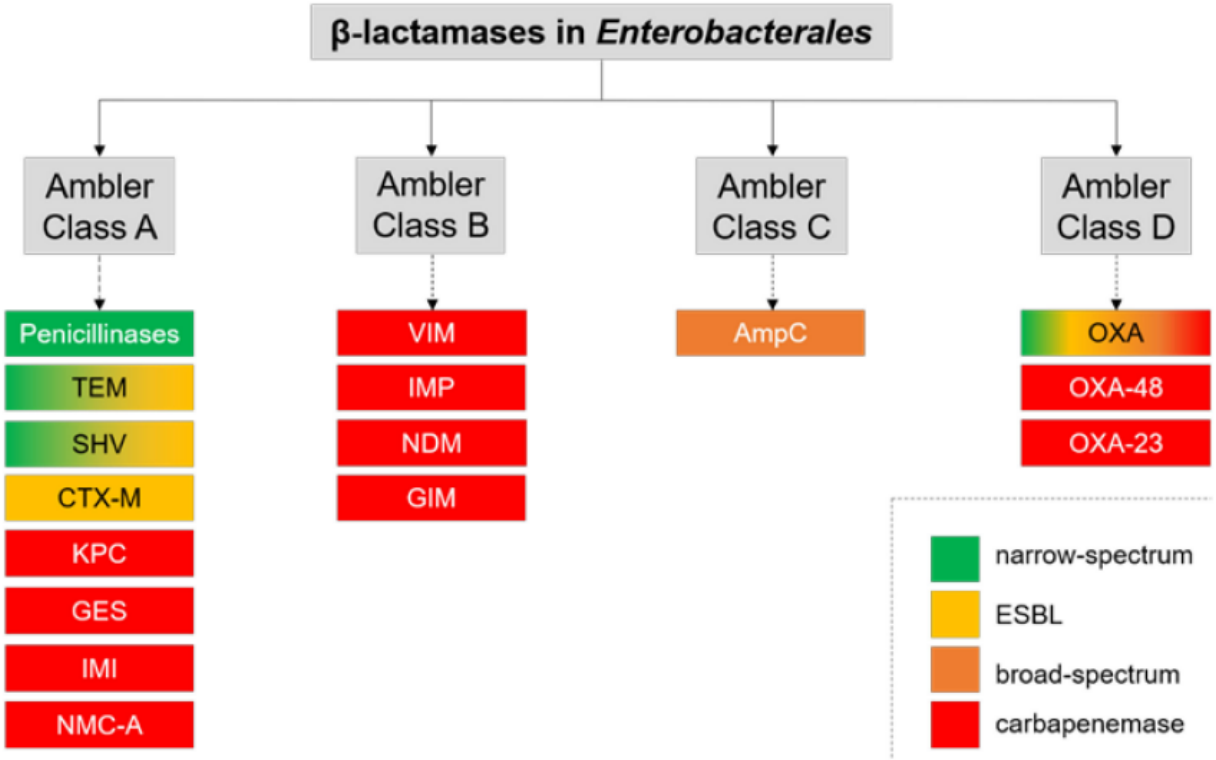


Figure 1. Ambler's classification with examples of main β-lactamases in *Enterobacterales*.

Noster, J.; Thelen, P.; Hamprecht, A. Detection of Multidrug-Resistant Enterobacterales—From ESBLs toCarbapenemases. Antibiotics 2021, 10,1140. https://doi.org/10.3390/antibiotics10091140

ESBL

Indicator agents:
Cefotaxime
Ceftazidime
Cefepime

If I oR to any third generation or fourth generation oxyimino-cephalosporin they are often ESBL

ESBL s are enzymes that can show different substrate affinity
Not all enzymes inactivate in the same way substrate drugs
Some enzymes hydrolyze more ceftazidime (TEM and SHV), others more cefotaxime (CTX-M). So both drugs should be used in susceptibility tests.

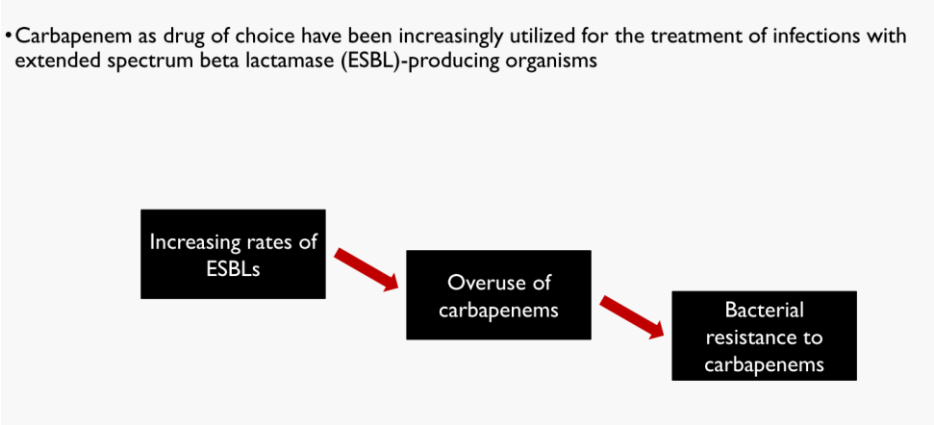
AmpC cephalosporinases

Indicator agents:
Cefotaxime
Ceftazidime
Cefoxitin: EUCAST reccomends to use cefoxitin MIC for screening only so it not reported in antibiogram usualy)

Many strains belonging to the Enterobacteriacceae family have one or more AmpC genes, which, however, are expressed mainly in strains of Enterobacter spp. (on chromosome)Proteus spp. (on plasmid).
Microrganisms under the acronim «**SPICE**» (Serratia, Pseudomonas,Indole positive Proteus, Citrobacter and Enterobacter) have chromosomal AmpC genes usually not expressed. Higher production can be induced under antibiotic therapy

Carbapenemases

- Indicator agents:
- Meropenem
- Imipenem
- Ertapenem



- The United States Centers for Disease Control and Prevention (CDC) defines carbapenem-resistant Enterobacterales (CRE) as bacteria within the Enterobacterales order that are resistant to at least one carbapenem (ie, ertapenem, meropenem, doripenem, or imipenem) or that produce a carbapenemase enzyme

KPC (class A),
IMP, VIM, NDM (class B),
OXA 48 (class D),
Enzymes that hydrolyze most penicillins and cephalosporins ,including oxyimino-beta-lactam compounds and carbapenems

Identification and screening of carbapenemase-producing *Enterobacteriaceae*

P. Nordmann[1], M. Gniadkowski[2], C. G. Giske[3], L. Poirel[1], N. Woodford[4], V. Miriagou[5] and the European Network on Carbapenemases*

1) *Service de Bactériologie-Virologie, INSERM U914 'Emerging Resistance to Antibiotics', Hôpital de Bicêtre, Assistance Publique/Hôpitaux de Paris, Faculté de Médecine et Université Paris-Sud, K.-Bicêtre, France,* 2) *Department of Molecular Microbiology National Medicine Institute, Warsaw, Poland,* 3) *Clinical Microbiology MTC, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden,* 4) *Antibiotic Resistance Monitoring and Reference Laboratory Health Protection Agency, London, UK and* 5) *Laboratory of Bacteriology, Hellenic Pasteur Institute, Athens, Greece*

TABLE 2. **Breakpoint values for carbapenems according to the US (CLSI) and European (EUCAST) guidelines, as updated June 2010 (MIC values, mg/L)**

	CLSI		EUCAST	
	S (≤)	R (≥)	S (≤)	R (>)
Imipenem	1	4	2	8
Meropenem	1	4	2	8
Ertapenem	0.5	2	0.5	1
Doripenem	1	4	2	8

TABLE 3. **Range of MICs of carbapenems for clinical *Enterobacteriaceae* expressing the main carbapenemases**

	MIC (mg/L)		
	Imipenem	Meropenem	Ertapenem
KPC	0.5 to >32	0.5 to >32	0.5 to >32
IMP/VIM/NDM	0.5 to >32	0.5 to >64	0.38 to >32
OXA-48/OXA-181	0.25 to 64	0.38 to 64	0.38 to >32

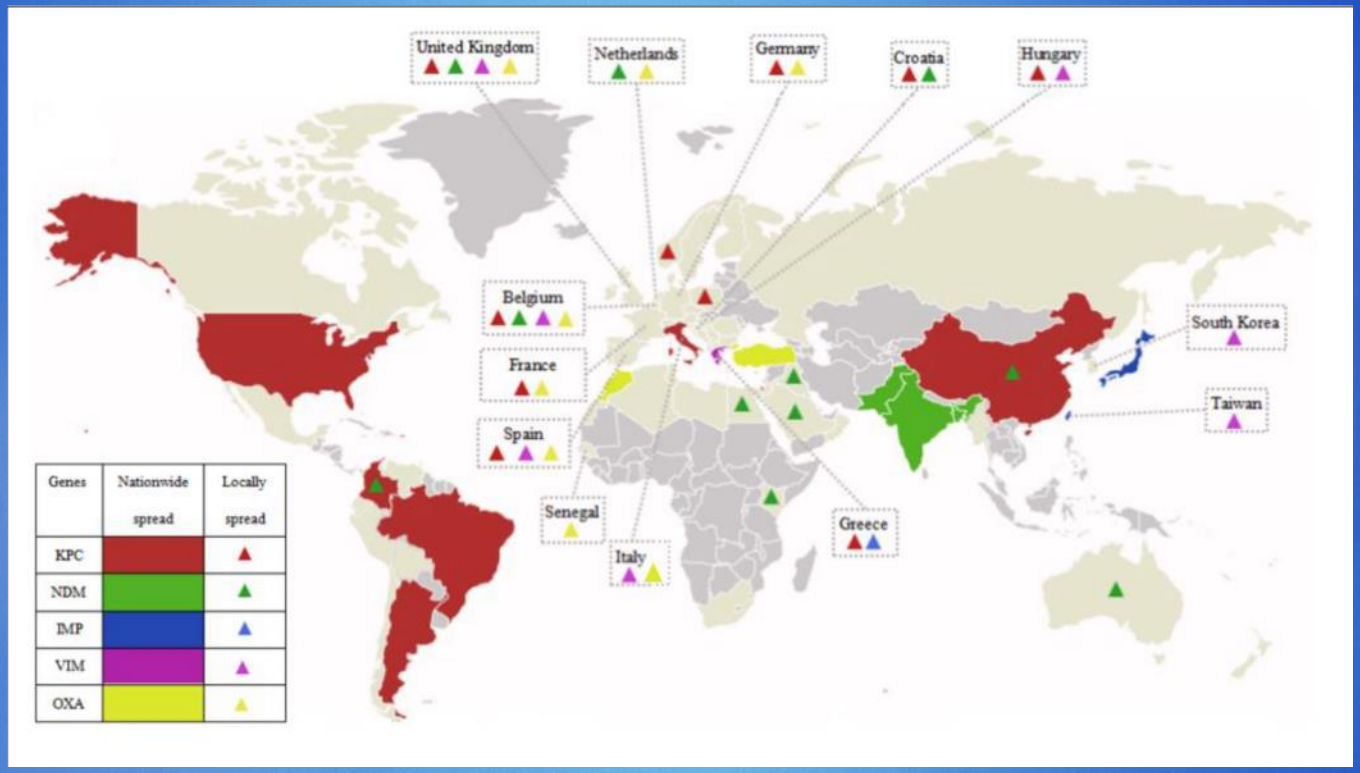
Combined resistance mechanism may also affect carbapenem susceptibility (e.g., combination of dereprerssed AmpC or ESBL and decreased permeability)

TABLE 1. **Resistance phenotypes resulting from the expression of the main carbapenemases reported in *Enterobacteriaceae* without or with extended-spectrum β-lactamases (ESBLs)**

	AMX	AMC	TZP	CTX	CAZ	IMP	ETP	MER	ATM
KPC	R	S/I	R	R	R	S/I/R	I/R	S/I/R	R
KPC + ESBL	R	I/R	R	R	R	I/R	I/R	I/R	R
IMP/VIM/NDM	R	R	I/R	R	I/R	S/I/R	I/R	S/I/R	S
IMP/VIM/NDM + ESBL	R	R	I/R	R	R	I/R	R	S/I/R	R
OXA-48/OXA-181	R	R	S/I/R	S/I	S	S/I	S/I	S/I	S
OXA-48/OXA-181 + ESBL	R	R	I/R	R	R	I/R	I/R	I/R	R

AMX, amoxycillin; AMC, amoxycillin–clavulanic acid; TZP, piperacillin–tazobactam; CTX, cefotaxime; CAZ, ceftazidime; IMP, imipenem; ETP, ertapenem; MER, meropenem; ATM, aztreonam.

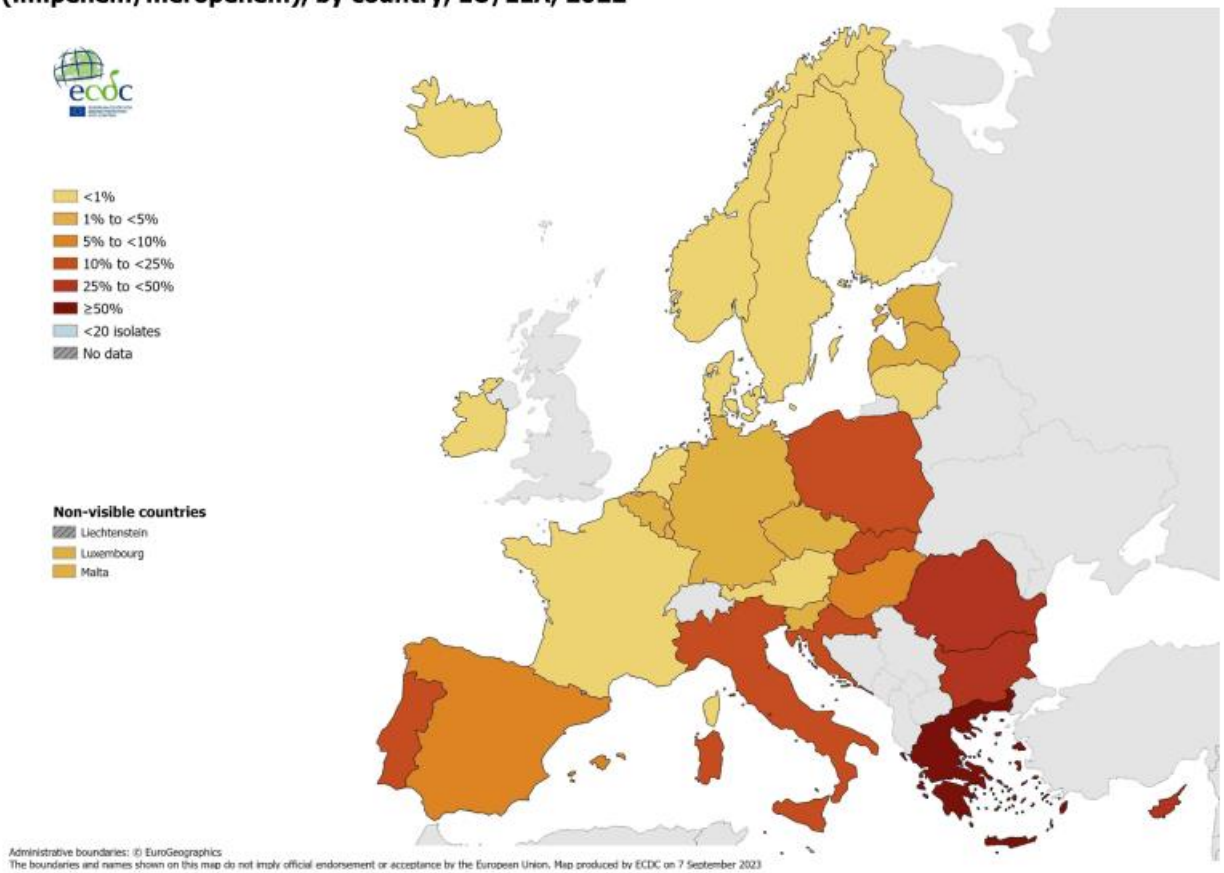
Carbapenemanse by Country



Cui X, Zhang H and Du H (2019)
Carbapenemases in Enterobacteriaceae: Detection and Antimicrobial Therapy.
Front. Microbiol. 10:1823. doi: 10.3389/fmicb.2019.01823

KPC

Figure 5. *Klebsiella pneumoniae*. **Percentage of invasive isolates resistant to carbapenems (imipenem/meropenem), by country, EU/EEA, 2022**



Between 2018 and 2022, there was a significantly increasing trend in the EU/EEA population-weighted mean percentage for carbapenem resistance, and the largest increase (+2.4%) in population-weighted mean AMR
percentage under EARS-Net surveillance during 2018−2022 occurred in carbapenem-resistant K. pneumoniae

Impact of CRE on the Risk of IET and Associated Outcomes


RESEARCH ARTICLE Open Access

Carbapenem resistance, inappropriate empiric treatment and outcomes among patients hospitalized with Enterobacteriaceae urinary tract infection, pneumonia and sepsis

Marya D. Zilberberg[1*], Brian H. Nathanson[2], Kate Sulham[3], Weihong Fan[3] and Andrew F. Shorr[4]

Retrospective analysis of databases (2009−2013) in patients with Enterobacterales infections/N=40,137 patients; CRE=1,227 (3.1%)

Compared to patients with CSE, patients with CRE:

- Had more comorbidities at baseline (P=0.009)
- Were more likely to have a healthcare-associated infection (P<0.001)
- Had a greater severity of illness at hospital day 2 (P<0.001)
- **Were 4-fold more likely to receive inappropriate empirical antibiotic therapy (P<0.001)**

IET results in: ↑ mortality by 12% ↑ LOS by 5.2 days ↑ costs by $10,312

CRE, carbapenem-resistant Enterobacterales; CSE, carbapenem-susceptible Enterobacterales; IET, inappropriate empirical treatment; LOS, length of stay

Zilberberg MD et al. BMC Infect Dis. 2017; 17(1):279

The Impact of CRE Infections in Vulnerable Patients

The global spread of CRE is an important threat to vulnerable patient populations worldwide

CRE have emerged as lethal causes of bacteraemia in neutropenic patients with haematological malignancies

Inability to rapidly identify neutropenic patients who are bacteraemic with CRE lead to a 2–3-day delay until administration of appropriate therapy

Evidence from the real-world data demonstrates increasing frequency in the rate of CRE K. pneumoniae isolates causing BSIs in patients with haematological malignancies with impact on mortality

Understanding the local distribution of pathogens and their susceptibility patterns and of patients' risk factors for CRE K. pneumoniae is urgent to improve the efficacy of therapeutic treatment protocols

Van Duin D, et al. Clin Infect Dis 2018;66:163–71; Satlin MJ, et al. J Infect 2016;73:336–45; Trecarichi EM, et al. Am J Hematol 2016;91:1076–81.
The global spread of CRE is an important threat to vulnerable patient populations worldwide

RISK FACTORS AND RISK ASSESSMENT TOOLS

Predictive Model – KPC-producing K. pneumoniae

Retrospective, matched case-control study in 5 Italian hospitals
Independent risk factors for KPC-producing K. pneumoniae infection:

- Charlson index of ≥ 3
- Indwelling CVC
- Recent surgery
- Neutropenia
- ≥ 2 recent hospitalisations
- Recent fluoroquinolone and/or carbapenem therapy

Models developed to predict isolation and infection

"This study provides information which might be useful for the clinical management of patients harboring KPC-producing K. pneumoniae and for controlling the spread of this organism."

Tumbarello M et al. Antimicrob Agents Chemother. 2014; 58(6):3514-20
Predictive Model – KPC-producing K. pneumoniae
CVC, central venous catheter

Risk factors for infections caused by carbapenem-resistant Enterobacterales: an international matched case-control-control study (EURECA)

Salvador Pérez-Galera,[a,b,aa] Jose M. Bravo-Ferrer,[a,aa] María Paniagua,[a,z] Tomislav Kostyanev,[c,d] Marlieke E. A. de Kraker,[e] Jan Feifel,[f] Jesús Sojo-Dorado,[g] Joost Schotsman,[g] Rafael Cantón,[h,i] George L. Daikos,[j] Biljana Carevic,[k] Gorana Dragovac,[l] Lionel K. Tan,[m] Lul Raka,[n] Adriana Hristea,[o] Pierluigi Viale,[p] Murat Akova,[q] Jose María Reguera,[r] Lucía Valiente de Santis,[r] Julián Torre-Cisneros,[i,s] Ángela Cano,[s] Emmanuel Roilides,[t] Lili Radulovic,[u] Cenk Kirakli,[v] Evelyn Shaw,[i,w] Matthew E. Falagas,[x,y] Vicente Pintado,[h,i] Herman Goossens,[c] Marc J. Bonten,[f]

Risk Factors for CRE infection

	CRE vs CSE		CRE vs non-infected	
	Adjusted OR (95% CI)	p	Adjusted OR (95% CI)	p
Intrinsic features				
Age (per year)	–	–	1.03 (1.01–1.05)	0.001
Chronic renal failure (moderate or severe)	2.81 (1.40–5.64)	0.004	–	–
Epidemiological exposures				
Previous colonization/infection by CRE	6.94 (2.74–17.53)	<0.001	13.14 (3.98–43.43)	<0.001
Admission from home	0.44 (0.23–0.85)	0.014	–	–
Previous hospitalization (last 6 months)	–	–	1.84 (0.95–3.55)	0.068
Invasive procedures and therapies				
Urinary catheter (last week)	1.78 (1.03–3.07)	0.038	3.68 (1.86–7.28)	<0.001
Immunosuppressive drugs	–	–	3.38 (1.44–7.93)	0.005
Exposure to antibiotics				
MODEL A: Broad-spectrum anti-gram negative drugs	2.20 (1.25–3.88)[a]	0.006	2.89 (1.45–5.73)[b]	0.002
MODEL B: Days of broad-spectrum anti-gram negative drugs	1.04 (1.00–1.07)[c]	0.014	1.02 (0.99–1.04)[d]	0.081
MODEL C: Time of exposure to broad-spectrum drugs				
No broad spectrum anti-gram negative drugs	Ref[e]	Ref	Ref[f]	Ref
Broad spectrum anti-gram negative drugs, <6 days	1.25 (0.57–2.71)	0.56	3.00 (1.07–8.43)	0.037
Broad spectrum anti-gram negative drugs, ≥6 days	2.86 (1.56–5.26)	0.001	2.96 (1.44–6.06)	0.003
MODEL D: Number of broad-spectrum drugs				
None	Ref[g]		Ref[h]	
One	1.70 (1.00–2.90)	0.050	2.03 (1.23–3.36)	0.006
≥2	3.66 (1.77–7.58)	<0.001	2.95 (1.56–5.60)	<0.001

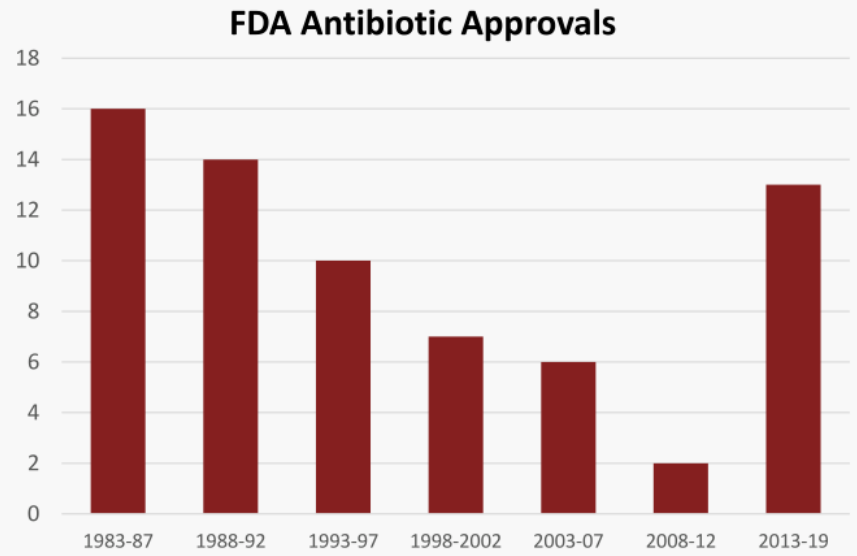
The main risk factors for CRE infections in hospitals with high incidence included previous colonization, urinary catheter and exposure to broad spectrum antibiotics.

TREATMENT OPTIONS FOR CRE INFECTION: PAST PRESENT AND FUTURE

"Older" Antimicrobial Agents for CRE Infections

Antimicrobial agents	Recommended dose for CRE infections[a]	Comments
Meropenem	2 g every 8 h by prolonged infusion for isolates with MICs of 2–8 mg/L	May not be effective for isolates with MIC > 8 mg/L
Ertapenem	Consider 2 g every 24 h	Used in double-carbapenem therapy
Colistin	Loading dose of 9 MU, followed by 9 MU/day in 2–3 divided doses	
Polymyxin B	Loading dose of 2–2.5 mg/kg, followed by 5 mg/kg/day in 2 divided doses	
Tigecycline	Loading dose of 100 mg, followed by 50 mg every 12 h	Consider loading dose of 200 mg, followed by 100 mg every 12 h for severe infections
Gentamicin Tobramycin	5–7 mg/kg/day	Used in combination therapy. Consider a higher dose of 10–15 mg/kg/day for severe infections without other options. Risk of toxicity may increase. TDM is recommended
Amikacin	15–20 mg/kg/day	Used in combination therapy. Consider a higher dose of 25–30 mg/kg/day for severe infections without other options. Risk of toxicity may increase. TDM is recommended
Fosfomycin	4 g every 6 h to 8 g every 8 h	Used in combination therapy

The Antibiotic Pipeline is Delivering



2014 Ceftolozane-tazobactam

2015 Ceftazidime-avibactam

2017 Delafloxacin

2017 Meropenem-vaborbactam

2018 Plazomicin

2018 Eravacycline

2018 Omadacycline

2019 Imipenem-relebactam

2019 Lefamulin

2019 Cefiderocol

FDA, Food and Drug Administration

Adapted from Talbot GH, *et al. Clin Infect Dis.* 2019;69(1):1-11

New Antimicrobial Agents Active Against Carbapenemases

Yes
Limited
No

Antimicrobial agents	Approved for	KPC	NDM	IMP	VIM	OXA-48
Ceftazidime/ avibactam	UTI, cIAI					
Meropenem/vaborbactam	UTI including pyelonephritis					
Imipenem cilastatin/relebactam	UTI including pyelonephritis					
Cefiderocol	UTI including pyelonephritis					
Aztreonam/ Avibactam	Phase III					
Eravacycline	cIAI					
Plazomicin	cUTI					

cUTI, complicated urinary tract infection; cIAI, complicated intra-abdominal infection; HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia
Adapted from Kanj SS, et al. Int J Antimicrob):1066Agents. 2022 ;60(333

Mortality of Treatment of CRE Infections

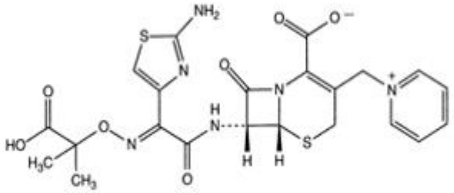
Study	Treatment	Mortality
Borer, 2009	Not known	50%
Trecarichi, 2016 (haematol. pts)	Not known	52.2%
Tzouvelekis, 2012	Inappropriate therapy	50%
Tzouvelekis, 2012	Colistin monotherapy	45%
Tzouvelekis, 2012	Combination therapy	30%
Gutierrez-Gutierrez, 2017	Monotherapy vs combination therapy	41% vs 35%
Shields, 2017	Ceftazidime/avibactam (mono or combo)	8%
Wunderink RG, 2018	Meropenem/vaborbactam	15.6%
Motsch, 2020	Imipenem/relabactam	9.5%

Borer A, et al. Infect Control Hospital Epid. 2009;30:10; Gutierrez-Gutierrez, et al. BMJ Open. 2017:7:e015365;
Trecarichi EM, et al. Virulence. 2017; 8(4):470-484; Shields RK, et al. Antimicrob Agents Chemother. 2017;
61(8):e00883-17; Tzouvelekis LS, et al. Clin Microbiol Infect. 2014; 20(9):862-72; Wunderink RG, et al. Infect
Dis Ther. 2018; 7(4): 439–455; Motsch J, et al. Clin Infect Dis. 2020; 70(9):1799-1808

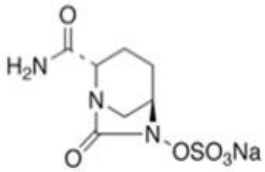
CEFTAZIDIME-AVIBACTAM

Avibactam is a DBO β-lactamase inhibitor

- FDA approved for cUTI, cIAI, HAP/VAP
- EMA approved for cUTI/AP, cIAI, HAP/VAP
- Bacterial infections due to Gram-negative organisms with limited treatment options
- 7 randomized controlled studies
- Real-world indications include CRE infections



Ceftazidime



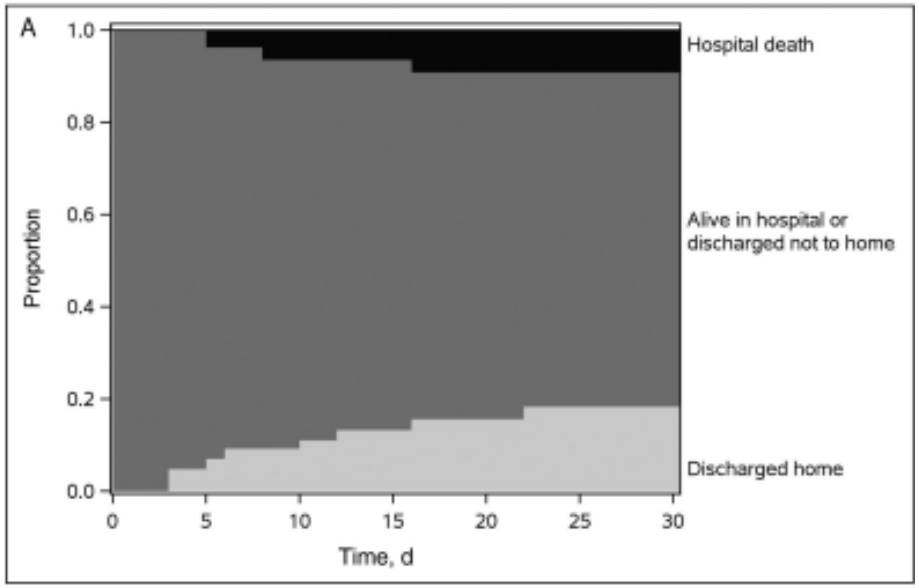
Avibactam

KPC	NDM	OXA-48	AmpC + porin

Baseline resistance due to MBL-producing CRE. Rarely nonfunctional porins plus ↑ bla KPC copy number

CAZ-AVI Compared to Colistin in the Treatment of CRE

Real-world prospective observational study in 18 US hospitals from 2011–2016 in 137 patients with documented CRE infections (bloodstream [46%], respiratory tract [22%], and urinary tract infections [14%])



CAZ-AVI group (n=38)

Clinical Infectious Diseases
MAJOR ARTICLE

Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae

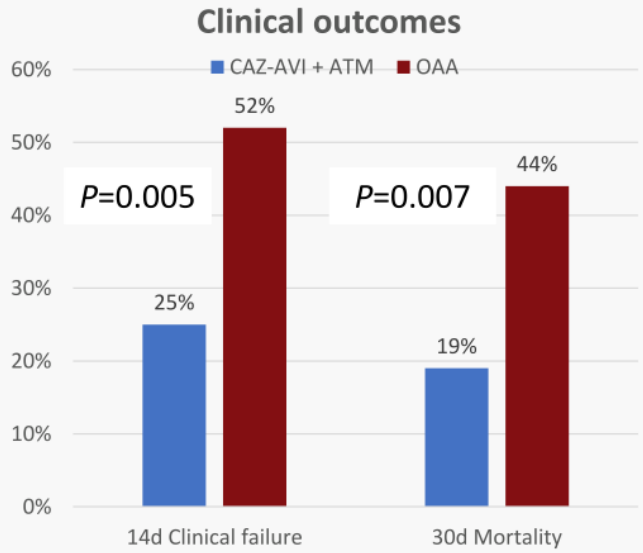
David van Duin,[1] Judith J. Lok,[2] Michelle Earley,[2] Eric Cober,[3] Sandra S. Richter,[4] Federico Perez,[5,6] Robert A. Salata,[6] Robert C. Kalayjian,[7] Richard R. Watkins,[8,9] Yohei Doi,[10] Keith S. Kaye,[11] Vance G. Fowler Jr,[12,13] David L. Paterson,[14] Robert A. Bonomo,[5,6,15,16] and Scott Evans[2];

Compared to colistin, patients treated with CAZ-AVI were
1) Less likely to die
2) More likely to be discharged from hospital within 30 days of starting treatment
3) More likely to experience an overall better outcome, including less renal failure

CAZ-AVI + Aztreonam for MBL

102 patients with bloodstream infections due to MBL

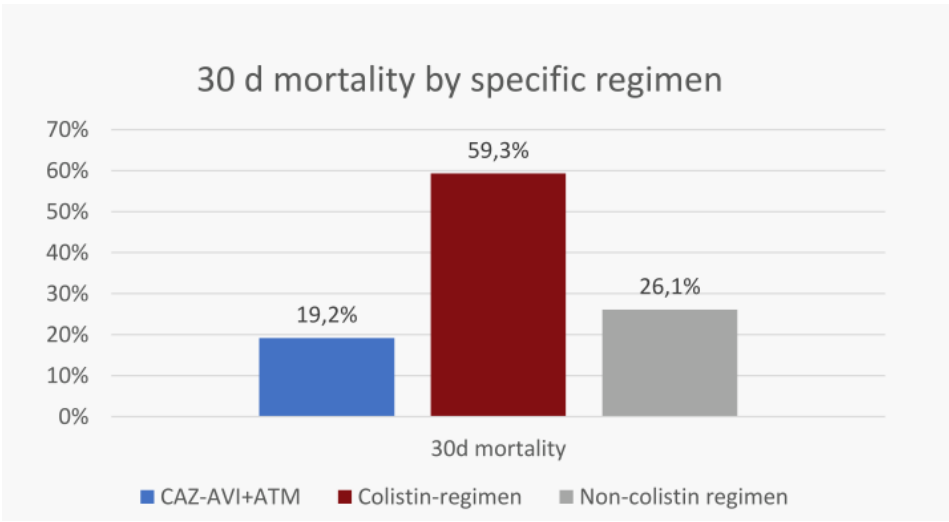
- 82 NDM, 20 VIM
- 91% *K. pneumoniae*



Clinical Infectious Diseases
MAJOR ARTICLE

Efficacy of Ceftazidime-avibactam Plus Aztreonam in Patients With Bloodstream Infections Caused by Metallo-β-lactamase–Producing Enterobacterales

Marco Falcone,[1] George L. Daikos,[2] Giusy Tiseo,[1] Dimitrios Bassoulis,[2] Cesira Giordano,[3] Valentina Galfo,[1] Alessandro Leonildi,[3] Enrico Tagliaferri,[1] Simona Barnini,[3] Spartaco Sani,[4] Alessio Farcomeni,[5] Lorenzo Ghiadoni,[5] and Francesco Menichetti[1]



Meropenem-Vaborbactam

FDA approved in 2017 for cUTI
EMA approved in 2018 for cUTI, HAP, VAP, secondary bacteremia
• Treatment of infections due to Gram-negative organisms with limited treatment options
Vaborbactam is a boronic acid β-lactamase inhibitor
• Inhibits other class A (KPC, CTX-M, SHV, TEM)
• Minimal impact against non-KPC-producing CRE

KPC	NDM	OXA-48	AmpC + porin

Imipenem-Cilastatin- Relebactam

Combination of the carbapenem imipenem, the renal dehydropeptidase-I inhibitor cilastatin, and the novel β-lactamase inhibitor relebactam

• Approved in the USA and EU for the treatment of adults with HABP, VABP, cUTIs including pyelonephritis and cIAIs in adults with limited or no alternative treatment options

• Potent in vitro activity against KPC-producing Enterobacterales

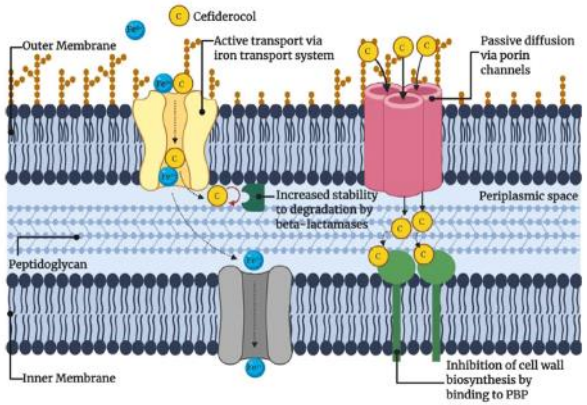
KPC	NDM	OXA-48	AmpC + porin

Cefiderocol: In Vitro Activity

Novel siderophore cephalosporin

- In vitro activity against all carbapenemase-producing Enterobacterales
- FDA approved in 2019
- Indicated for the treatment of cUTI, HAP/VAP

KPC	NDM	OXA-48	AmpC + porin



Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial

Richard G Wunderink, Yuko Matsunaga, Mari Ariyasu, Philippe Clevenbergh, Roger Echols, Keith S Kaye, Marin Kollef, Anju Menon, Jason M Pogue, Andrew F Shorr, Jean-Francois Timsit, Markus Zeitlinger, Tsutae D Nagata

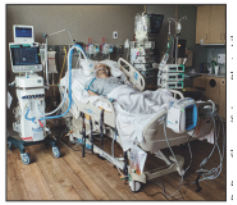
Results: similar clinical and microbiological efficacy to BAT.
Numerically more death occurred in the cefiderocol group, primarily in the patient subset with A baumannii infections.

Mortality at day 14 was higher in patients treated with cefiderocol compared to BAT for pulmonary infections (25% vs 11%) and BSI (22% vs 7%), but not in patients with complicated UTI (12% vs 40%)

- Mortality differences persisted at day 28 and at the end of the study

Cefiderocol: the Trojan horse has arrived but will Troy fall?

The global public health crisis of multidrug-resistant Gram-negative organisms underscores the need for antibiotics with novel bacterial targets. Cefiderocol, the first siderophore-conjugated antibiotic to progress beyond phase 1 human trials, was designed to overcome challenges presented by common carbapenem-resistance mechanisms. The drug enters bacterial cells using (given as described for the APEKS-NP study[1]) or best available therapy, 66% of which consisted of colistin-based regimens. 78 (47%) of 150 patients were in the ICU at randomisation, 67 (45%) had pneumonia, 47 (31%) had bloodstream infection (BSI). A high frequency of patients had non-fermenting organisms and 142 (95%) had recently received antibiotics. Clinical

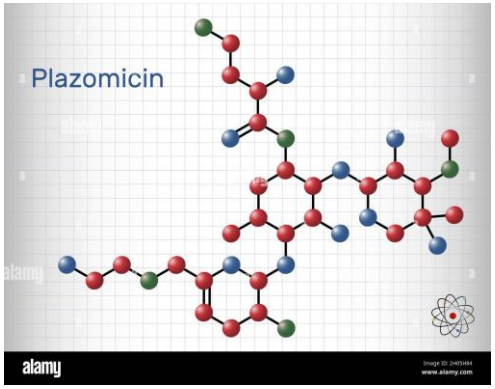


Lancet Infect Dis 2020

"The best interpretation of cefiderocol that can be gleaned from these studies is that it is as good as comparator agents that are frankly suboptimal for the treatment of infections caused by carbapenem-resistant organisms"

Plazomicin

A next-generation semi-synthetic aminoglycoside
Approved by the FDA in 2018 for cUTI



KPC	NDM	OXA-48	AmpC + porin

Eravacycline

- A novel antibiotic of the tetracycline class
- Broad-spectrum of activity, including multi-drug resistant organisms
- Approved by the FDA for the treatment of cIAI in 2018 following IGNITE-1 and IGNITE-4 trials

KPC	NDM	OXA-48	AmpC + porin

Resistance to New Antibiotics

Resistance to ceftazidime/avibactam in infections and colonisations by KPC-producing Enterobacterales: a systematic review of observational clinical studies

Stefano Di Bella[a,*], Daniele Roberto Giacobbe[b], Alberto Enrico Maraolo[c], Valentina Viaggi[d], Roberto Luzzati[a], Matteo Bassetti[b,e], Francesco Luzzaro[d], Luigi Principe[d,1]

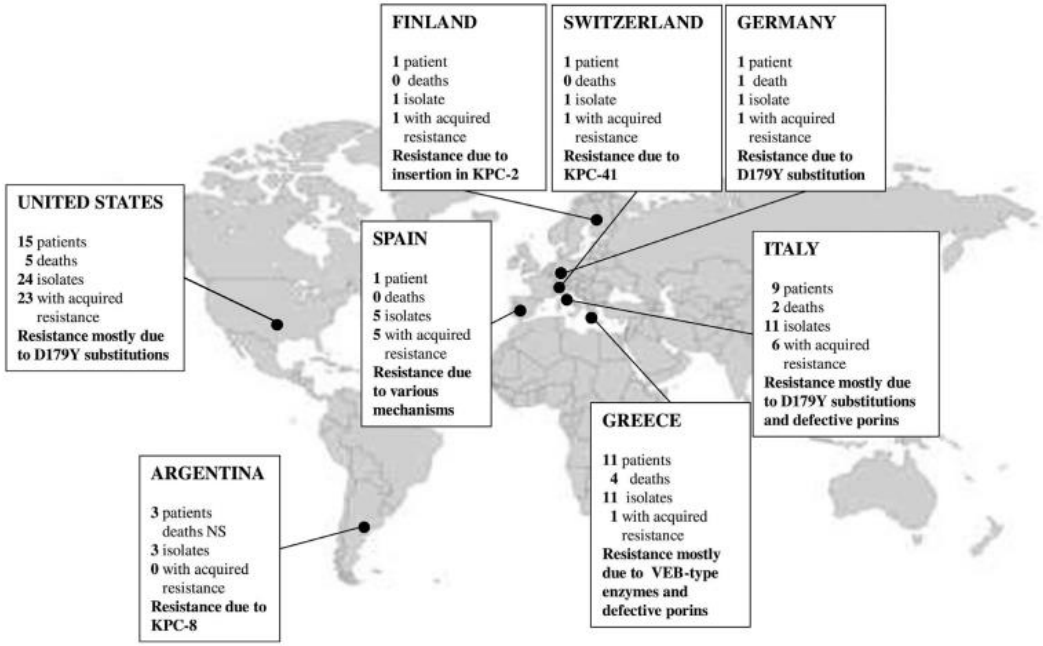


Fig. 2. Country-wise distribution of ceftazidime/avibactam-resistant cases and most relevant features.

antibiotics MDPI

Article

Epidemiology of Meropenem/Vaborbactam Resistance in KPC-Producing *Klebsiella pneumoniae* Causing Bloodstream Infections in Northern Italy, 2018

Paolo Gaibani [1,*], Donatella Lombardo [1], Linda Bussini [2], Federica Bovo [1], Beatrice Munari [1], Maddalena Giannella [2], Michele Bartoletti [2], Pierluigi Viale [2], Tiziana Lazzarotto [1] and Simone Ambretti [1]

antibiotics

Article

In Vitro Activity of Cefiderocol on Multiresistant Bact Strains and Genomic Analysis of Two Cefiderocol Resistant Strains

Michela Padovani [†], Anna Bertelli [†], Silvia Corbellini, Giorgio Piccinelli, Francesca Gurrieri and Maria Antonia De Francesco [*]

WHAT IS NEW IN THE FUTURE FOR CRE?

Beta-lactamase inhibitor	Structure	Type of inhibition	Spectrum of activity	Important organisms covered (with resistance pattern)	Clinical use	References
Avibactam*	Non-beta-lactam beta-lactamase inhibitor (DBO)	Reversible beta-lactamase inhibition	Class A, C beta-lactamases (except class C beta-lactamase in *Enterobacter cloacae*) and D (OXA-48, lesser extent) Activity against class B when combined with aztreonam	CRE (including CAZ-resistant strains) CRPA	cUTI, cIAI, VAP, HAP (in combination with ceftazidime)	[14–16]
Relebactam	Non-beta-lactam beta-lactamase inhibitor (DBO)	Irreversible beta-lactamase inhibition	Class A and C beta-lactamases	CRE XDR *P. aeruginosa* CRPA MSSA *Enterococcus faecalis* *Bacteroides spp.*	cUTI, cIAI, HAP, VAP (in combination with imipenem-cilastatin)	[14,15]
Vaborbactam	Non-beta-lactam beta-lactamase inhibitor (cyclic boronate inhibitor)	Reversible beta-lactamase inhibition	Class A and C beta-lactamases Weak activity against class D beta-lactamases (OXA-48)	MDR Enterobacterales CRE	cUTI, cIAI, HAP, VAP, BSI (in combination with meropenem)	[14–16]
Taniborbactam*	Non-beta-lactam beta-lactamase inhibitor (cyclic boronate inhibitor)	Reversible beta-lactamase inhibition	Class A, B, C and D beta-lactamases	CRE CRPA	cUTI, HAP, VAP (in combination with cefepime)	[14,16]
Xeruborbactam* (QPX7728)	Non-beta-lactam beta-lactamase inhibitor (cyclic boronate inhibitor)	Reversible beta-lactamase inhibition	Class A, B and D beta-lactamases Weak activity against IMP-1 and OXA-48	CRAB CRE CRPA	Clinical trials underway (in combination with ceftazidime)	[14,16,17]
Tazobactam	Beta-lactam derived beta-lactamase inhibitor	Irreversible beta-lactamase inhibition	Class A (except KPC), C beta-lactamases	MDR and XDR *Pseudomonas aeruginosa*	cUTI, cIAI, HAP, VAP (when combined with ceftolozane)	[14,15]
Enmetazobactam	Beta-lactam derived beta-lactamase inhibitor (Cyclic boronate inhibitor) (N-methylated derivative of tazobactam)	Irreversible beta-lactamase inhibition	Class A, C and D beta-lactamases (no activity against OXA-24/40)	CRE *Pseudomonas aeruginosa*	cUTI (in combination with cefepime)	[14,16]
Durlobactam	Non-beta lactam beta-lactamase inhibitor (DBO)	Reversible beta-lactamase inhibition	Class A, C and D beta-lactamases	XDR *Acinetobacter baumannii* (including carbapenem-resistant isolates)	cUTI (when combined with Sulbactam)	[14,16]
Zidebactam	Non-beta lactam beta-lactamase inhibitor (DBO)	Reversible beta-lactamase inhibition	Class A, C and D beta-lactamases	CRE MDR *Pseudomonas aeruginosa* CRPA *Stenotrophomonas maltophilia*	cUTI (in combination with cefepime)	[14,16]

*effective against metallo-beta-lactamases.
DBO, diazabicyclooctane; CRE, carbapenem-resistant Enterobacterales; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; cUTI, complicated urinary tract infection; cIAI, complicated intra-abdominal infection; HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; MDR, multi-drug resistant; XDR, extensively drug-resistant; MSSA, methicillin-susceptible *Staphylococcus aureus*, BSI; bloodstream infection; CRAB, carbapenem-resistant *Acinetobacter baumannii*; IMP, imipenemase.

La Commissione Europea approva aztreonam-avibactam per i pazienti con infezioni da batteri multiresistenti

Martedi 23 Aprile 2024 Redazione

Therapeutic Bacteriophages for Gram-Negative Bacterial Infections in Animals and Humans

AUTHORS
Panagiotis Zagaliotis[1,5], Jordyn Michalik-Provasek[2], Jason J. Gill[2], and Thomas J. Walsh[1,3,4]

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Review

Phage–Antibiotic Therapy as a Promising Strategy to Combat Multidrug-Resistant Infections and to Enhance Antimicrobial Efficiency

Chengxi Liu †, Qixuan Hong †, Rachel Yoon Kyung Chang, Philip Chi Lip Kwok and Hak-Kim Chan *

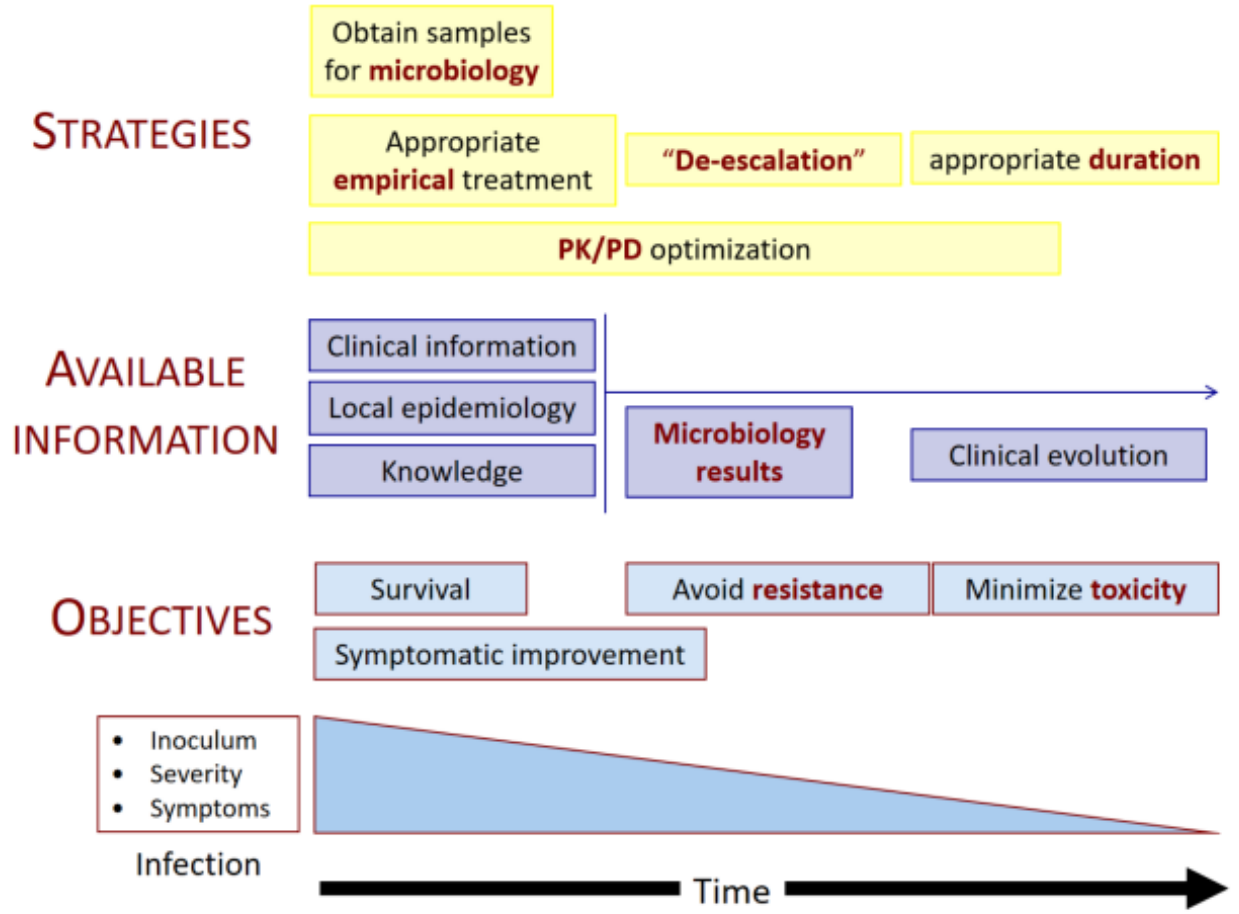


Figure 1 | Therapeutic strategies according to the time of infection evolution. Adapted from J. Cobo.

Assess your patient carefully before prescribing antibiotics

In severe infections, start FAST.

Choose empiric therapy considering local epidemiology and patients' individual factors

Dosing matters, too

Get the bug

indication and expected duration

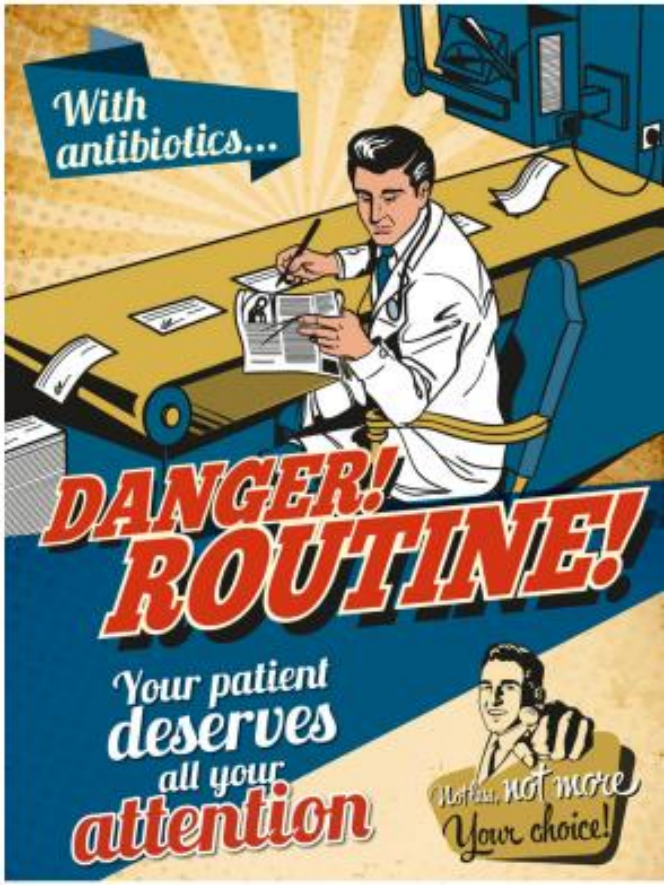
Reassess (and adjust) antibiotic therapy periodically

Target antimicrobial therapy when possible

Switch to po (oral route) when possible.

Don't go overtime with antibiotic duration.

Conclusions



GRAZIE PER L'ATTENZIONE