ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ
ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
ΙΑΤΡΙΚΗ ΣΧΟΛΗ
ΜΕΤΑΠΤΥΧΙΑΚΟ ΠΡΟΓΡΑΜΜΑ ΣΠΟΥΔΩΝ «ΛΟΙΜΩΞΙΟΛΟΓΙΑ»
Διευθυντής: Καθηγητής Ε. Ι. Γιαμαρέλλος-Μπουρμπούλης

Νεότεροι αναστολείς β-λακταμασών για νοσοκομειακή χρήση

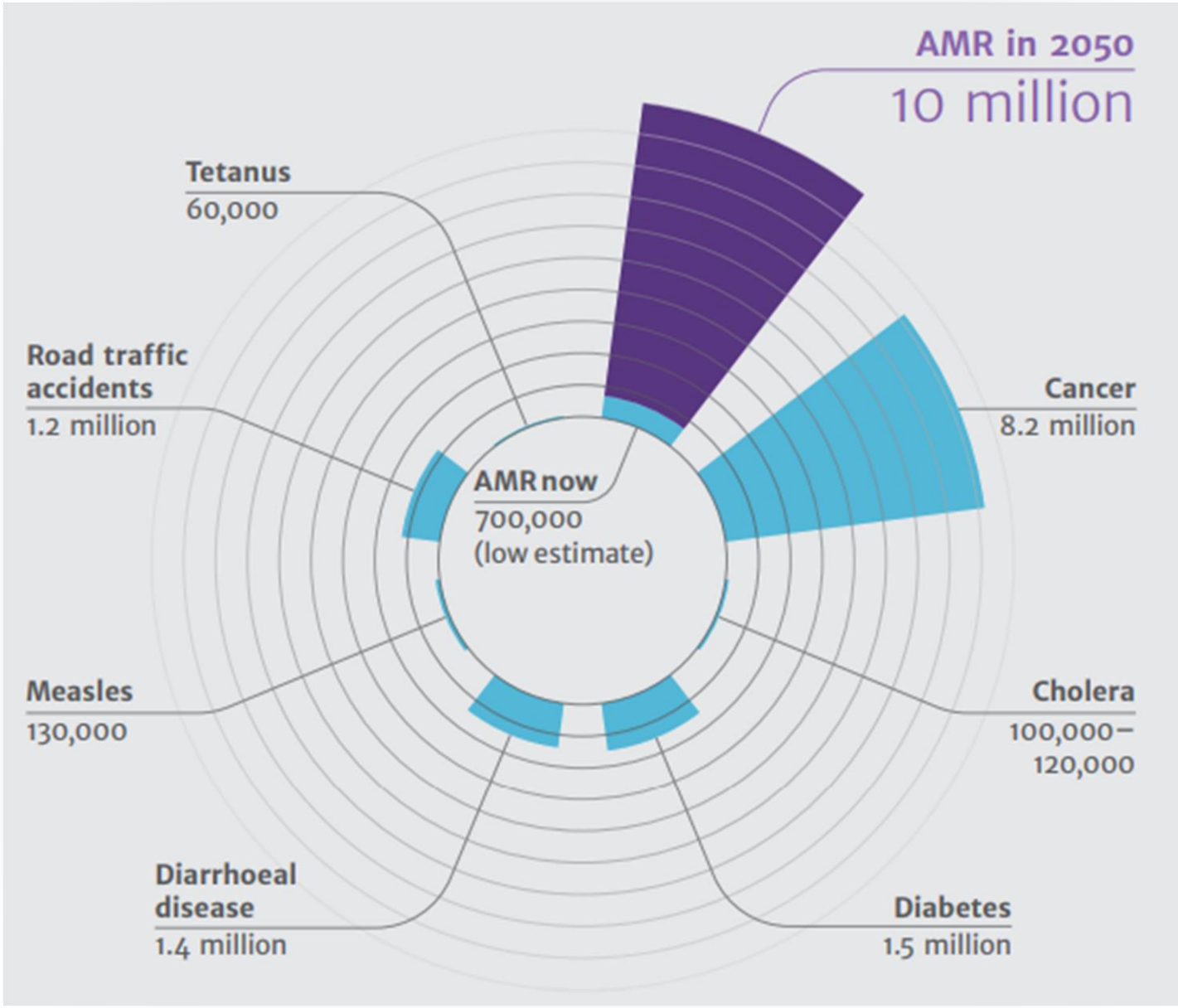
Καρολίνα Ακινόσογλου

Παθολόγος – Λοιμωξιολογος

Επικουρη Καθηγητρια Παθολογιας

Πανεπιστημίου Πατρών

Deaths attributable to antimicrobial resistance every year compared to other causes of death

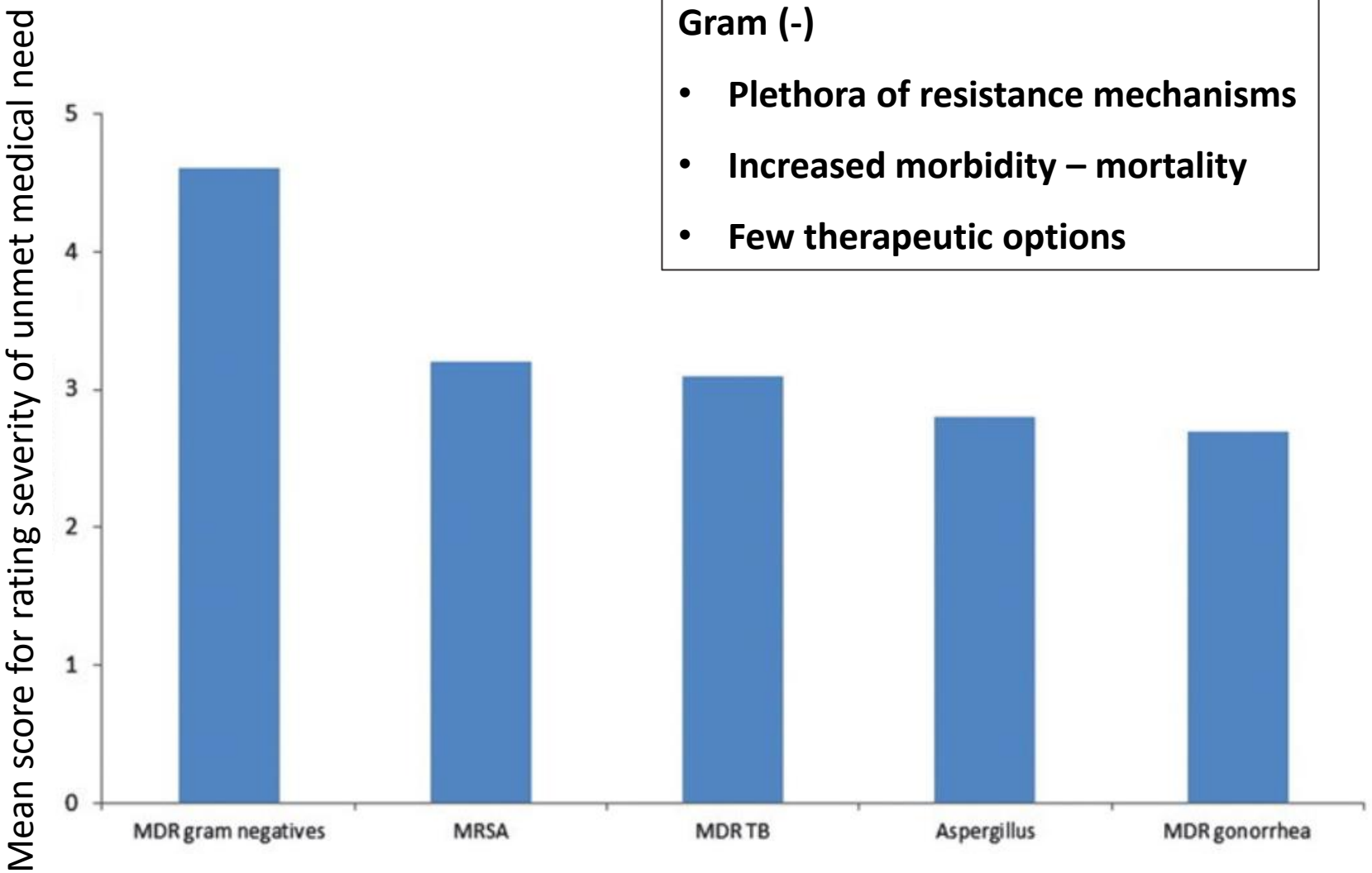


Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. http://amr-review.org/publications

Unmet Medical Need in Infectious Diseases

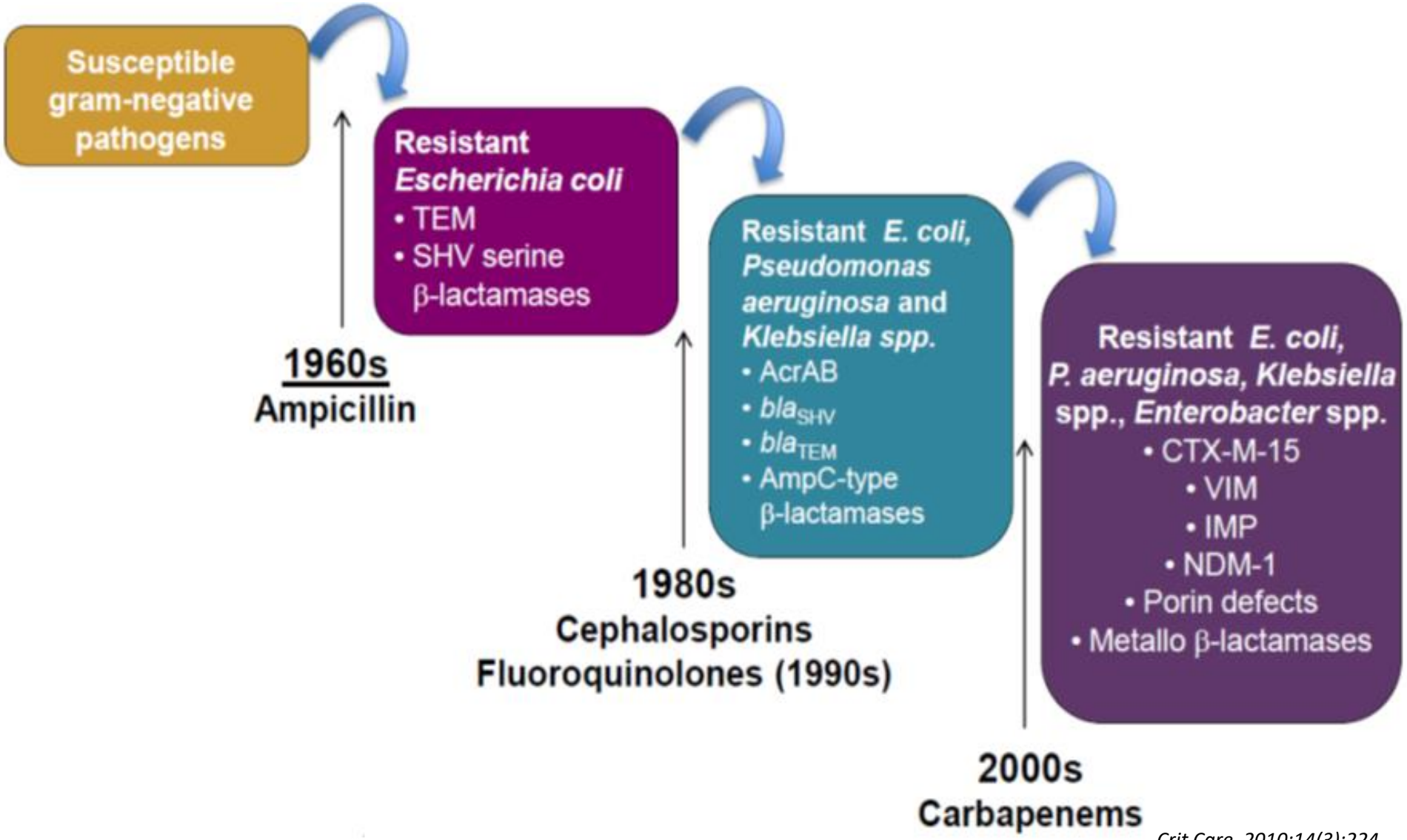
Gram (-)

- **Plethora of resistance mechanisms**
- **Increased morbidity – mortality**
- **Few therapeutic options**



Clin Infect Dis. 2012 Jun 1; 54(11): 1677–1678.

Microbial Resistance in Gram (-)



Crit Care. 2010;14(3):224.
Clin Microbiol Rev Feb 2018; 3

Ανθεκτικά Gram (-) με παραγωγή ESBL

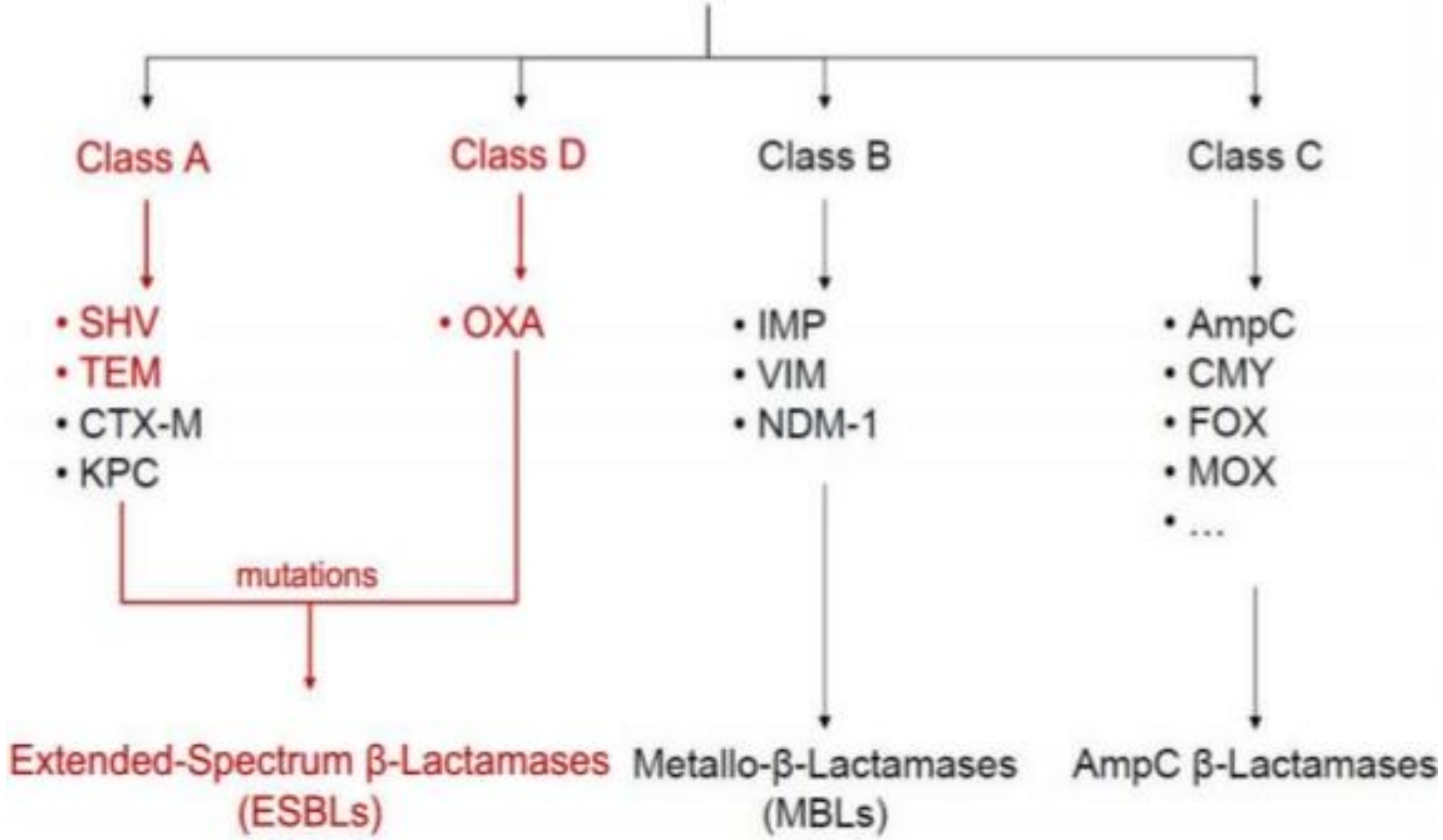
- **Beta-lactamases** are enzymes that open the beta-lactam ring, inactivating the antibiotic. The first **plasmid-mediated beta-lactamase** in gram-negative bacteria was **discovered in Greece in the 1960s (TEM)**.

- **Extended-spectrum beta-lactamases (ESBL)** are enzymes that confer resistance to most beta-lactam antibiotics: **penicillins**, **cephalosporins**, and the monobactam **aztreonam**

  - **Frequently co-resistant** to **aminoglycosides, quinolones and co-trimoxazole.** Resistant **genes coding** for ESBLs and, for example, aminoglycoside-modifying or quinolone-modifying enzymes (AMEs) often **reside within the same conjugative plasmids**

  - **Quinolones co-resistance 40%**

β-lactamases Functional Classification



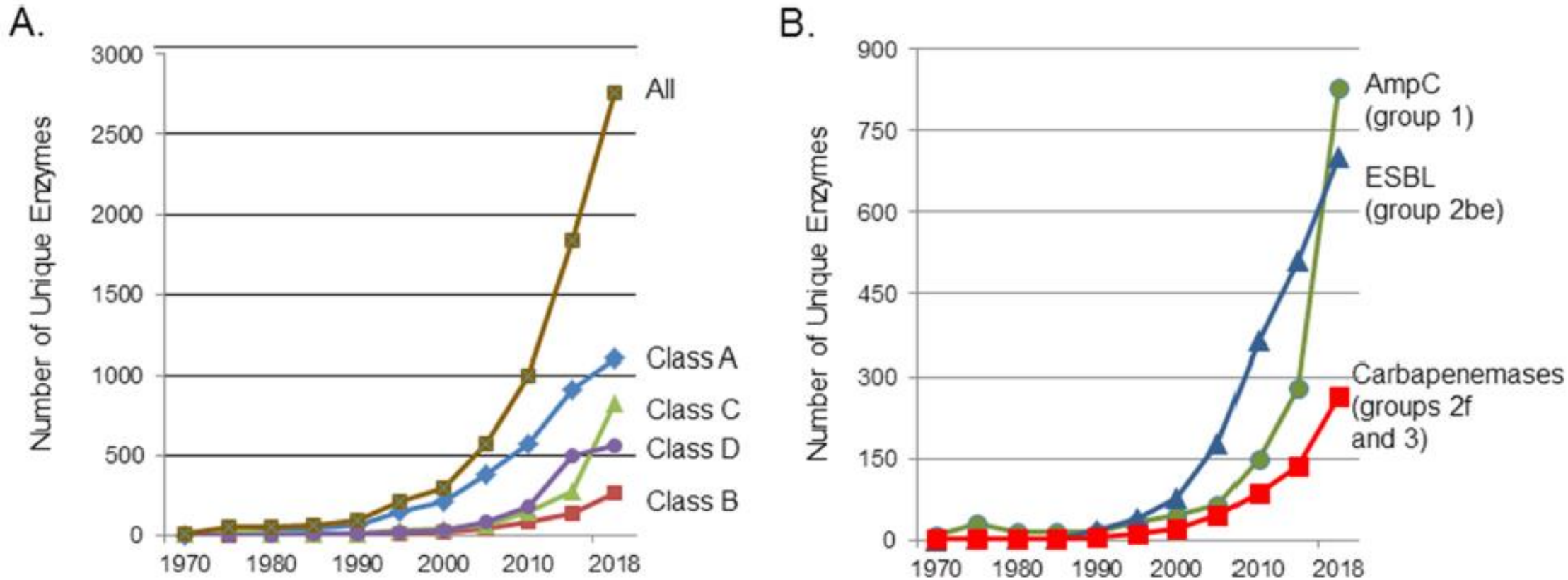
Antimicrob Agents Chemother. 2018 Sep 24;62(10)

Dates, organisms, and locations of the first of a series of -lactamase-producing isolates with long-term clinical significance

Original β-lactamase name (currently recognized name)	Yr of first verified isolation	Organism	Location
Penicillinase (chromosomal AmpC)	1940	*Bacillus coli* (*Escherichia coli*)	England
Penicillinase	1942	*Staphylococcus aureus*	England
OXA	1962	*Salmonella enterica* serovar Typhimurium, *Escherichia coli*[a]	England
TEM-1	1963	*Escherichia coli*	Greece
SHV-1	1972	*Klebsiella pneumoniae*	Unknown
Transferable ESBL (SHV-2)	Pre-1983	*K. pneumoniae*	Germany
Serine (class A, group 2f)	1982	*Serratia marcescens*	England (London)
carbapenemase (SME-1)	1985		USA (Minnesota)
Plasmid-encoded AmpC (MIR-1)	1988	*K. pneumoniae*	USA (Massachusetts)
Plasmid-encoded MBL (IMP-1)	1988	*Pseudomonas aeruginosa*	Japan
Inhibitor-resistant TEM (TEM-30)	1991	*E. coli*	France (Paris)
KPC-type (KPC-2)	1996	*K. pneumoniae*	USA (North Carolina)
NDM-1	2006	*K. pneumoniae*	India (New Delhi)

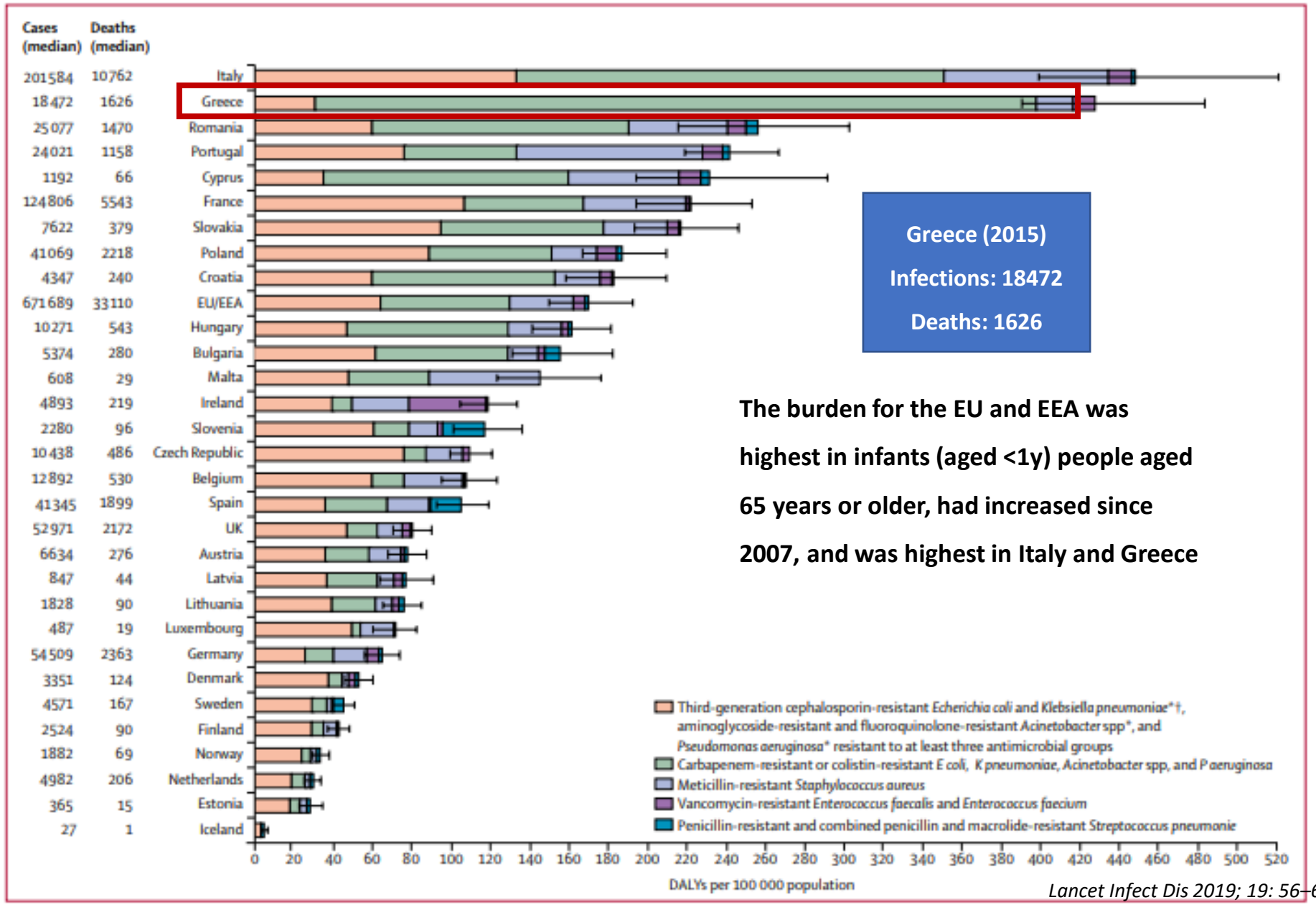
Antimicrob Agents Chemother. 2018 Sep 24;62(10)

Increase in numbers of unique, naturally occurring -lactamases



Annu Rev Microbiol 2011 65:455– 478
Antimicrob Agents Chemother. 2018 Sep 24;62(10)

European Antimicrobial Resistance Surveillance Network 2015



Greece (2015)

Infections: 18472

Deaths: 1626

The burden for the EU and EEA was highest in infants (aged <1y) people aged 65 years or older, had increased since 2007, and was highest in Italy and Greece

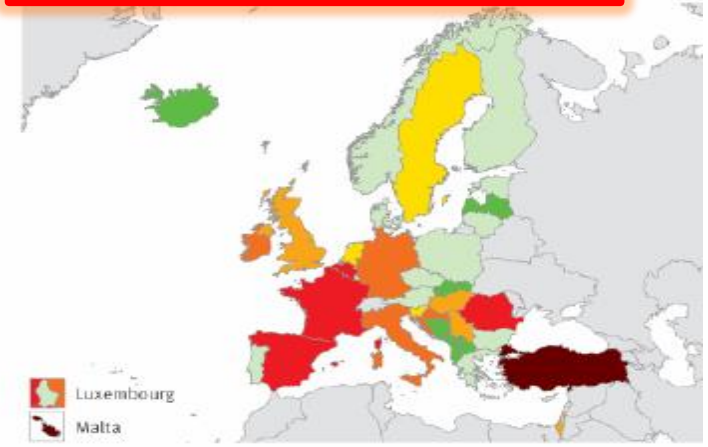
Lancet Infect Dis 2019; 19: 56–66

Geographic distribution of carbapenemase-producing Enterobacteriaceae by resistance mechanism

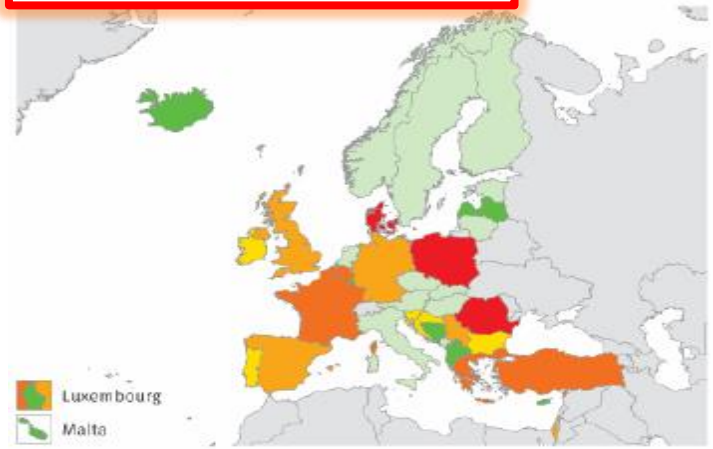
(ECDC: European Survey of Carbapenemase-Producing Enterobacteriaceae (EuSCAPE) working group, 2015)

A. KPC: Endemic situation

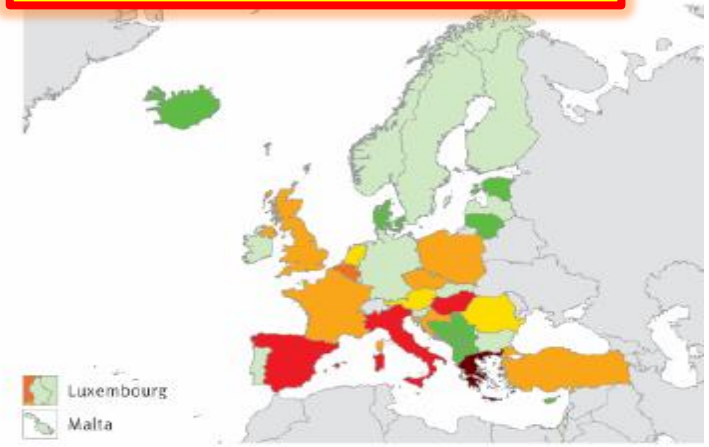
B. OXA-48: Sporadic occurrence



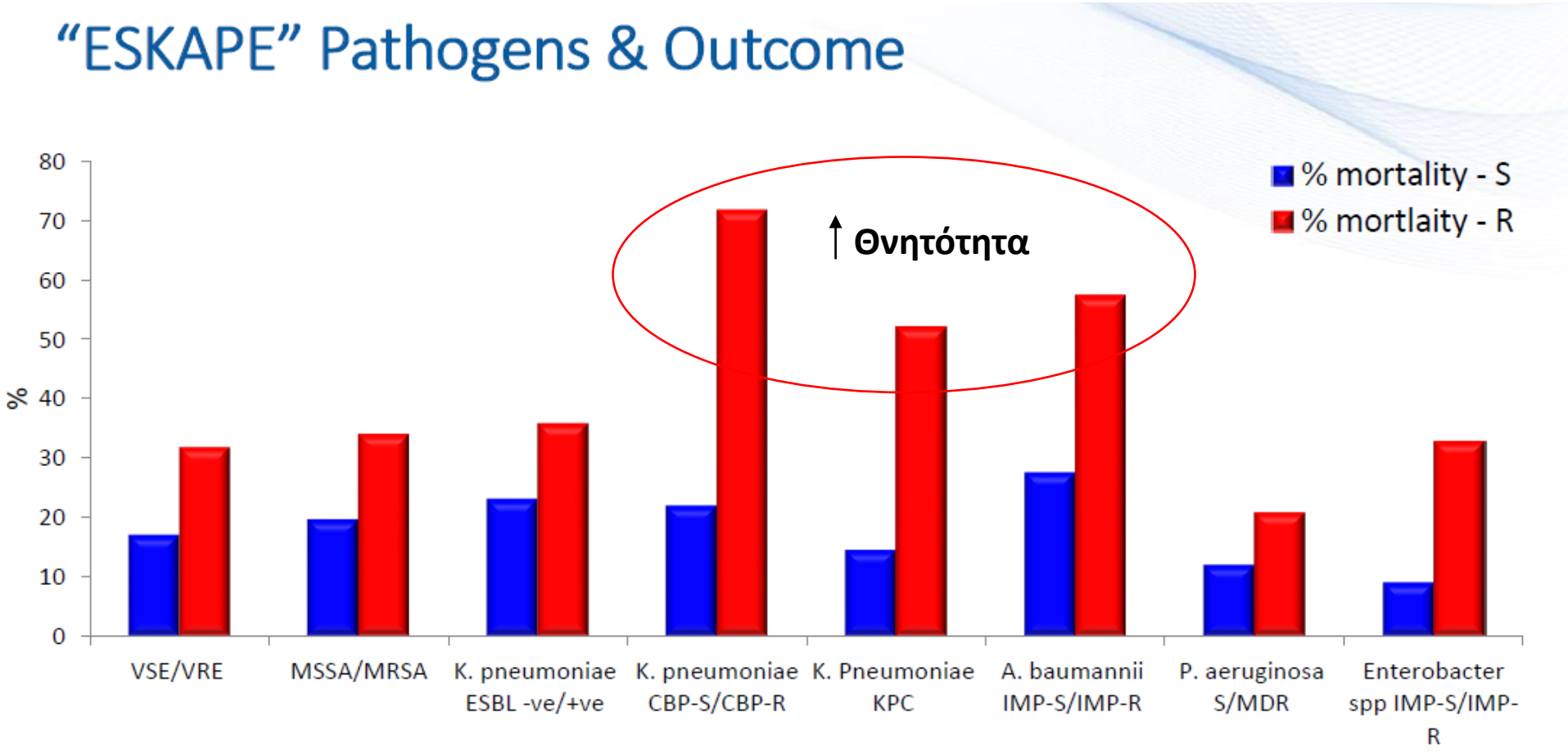
C. NDM: Regional spread



B. VIM: Endemic situation



Ανθεκτικά στις καρβαπενέμες εντεροβακτηριακά και θνητότητα



Butler et al. Infect Control Hosp Epidemiol. 2010; 31:28–35; Shurland et al. Infect Control Hosp Epidemiol. 2007;28:273-79; Borer A, et al. Infect Control Hosp Epidemiol. 2009;30:972-6; Kwon K. et al. J Antimicrob Chemother. 2007;59:525–30; Marchaim D. et al. Antimicrob Agents Chemother. 2008; 52:1413-18.Trecarichi E et al. Am J Hematol 201

Ποσοστά αντοχής σε 3ης γενιάς κεφαλοσπορίνες, Pip/Tazo, και συνδυαστικής αντοχής (*Ιουλιος – Δεκεμβριος 2018, WHONET Greece)*

	(R) Ceftazidime	(R) Pip/Tazo	MDR (Cefta/cipro/amik)
E. Coli	7-13%	5-6.6%	8-16%
Pseudomonas	16.8-25.4%	17.2-27.3%	11.2-25%
Enterobacter	26-34%	24-31%	6-9%
Klebsiella	42-68%	43-72%	37-57%
Acinetobacter	87–95%	90-97%	80-88%

- Στελέχη απομονωθέντα από 1η κ/α κλινικού δείγματος
- Τα υψηλά ποσοστά σε κάθε κατηγορία αντιστοιχούν σε ασθενείς ΜΕΘ

Cumulative Comparative Resistance Rates to Carbapenems

Jan – Jun2016 vs Jan-Jun 2018, WHONET Greece

Isolated Bacteria in Blood Cultures	Medical Wards		Surgical Wards		ICU	
	2016	2018	2016	2018	2016	2018
Klebsiella pneumoniae	53%	56%	65%	70%	88%	90%
Acinetobacter baumannii	88%	88%	94%	93%	99%	98%
Pseudomonas aeruginosa	29%	34%	55%	38%	44%	53%

WHONET GREECE, Available at: http://www.mednet.gr/whonet/ (last accessed May 2019)

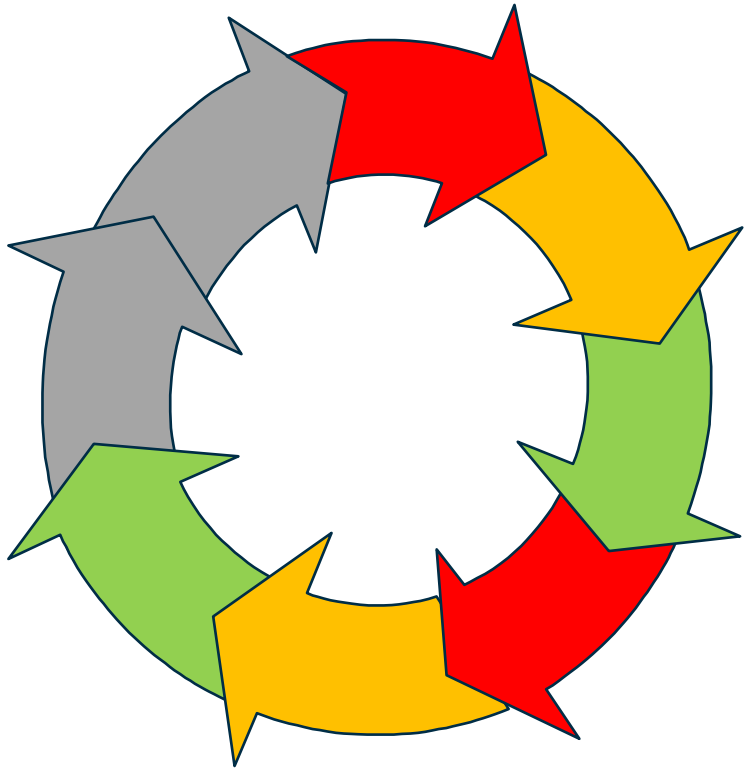
Φαύλος Κύκλος χρήσης Καρβαπενεμών

Αυξημένα ανθεκτικά στις καρβαπενέμες στελέχη

Pseudomonas aeruginosa

Acinetobacter

Εντεροβακτηριοειδή



Διασταυρούμενη μετάδοση
+
εξάπλωση της αντοχής (ESBLs)

Αυξημένη χρήση καρβαπενεμών

Επιλεγμένα ανθεκτικά στις καρβαπενέμες στελέχη

Nordmann and Poirel. J Antimicrob Chemother. 2013;68:487-9.

Unmet Medical Need in Infectious Diseases

WHO : List of antibiotic-resistant pathogens for which antibiotics are urgently needed[1]

CRITICAL (No1 Priority)[1]	ECDC 2017: Greece[2]
• ***Acinetobacter baumannii*, Carbapenem-Resistant** • ***Pseudomonas aeruginosa*, Carbapenem-Resistant** • ***Enterobacteriaceae*, Carbapenem-Resistant, 3rd gen cephalosporin-Resistant**	**CRO** • **64.7% of *Klebsiella pneumoniae*,** • **94.8% of *Acinetobacter baumanii*** • **39.3% of *Pseudomonas aeruginosa***

CRO: Carbapenem-resistant organisms

1. WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf. Accessed March 2017 2. European Centre for Disease Prevention and Control (ECDC). Surveillance of antimicrobial resistance in Europe Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2017. Available at https://ecdc.europa.eu, last accessed May 2019

Risk factors for antimicrobial resistant Gram (-) bacteria

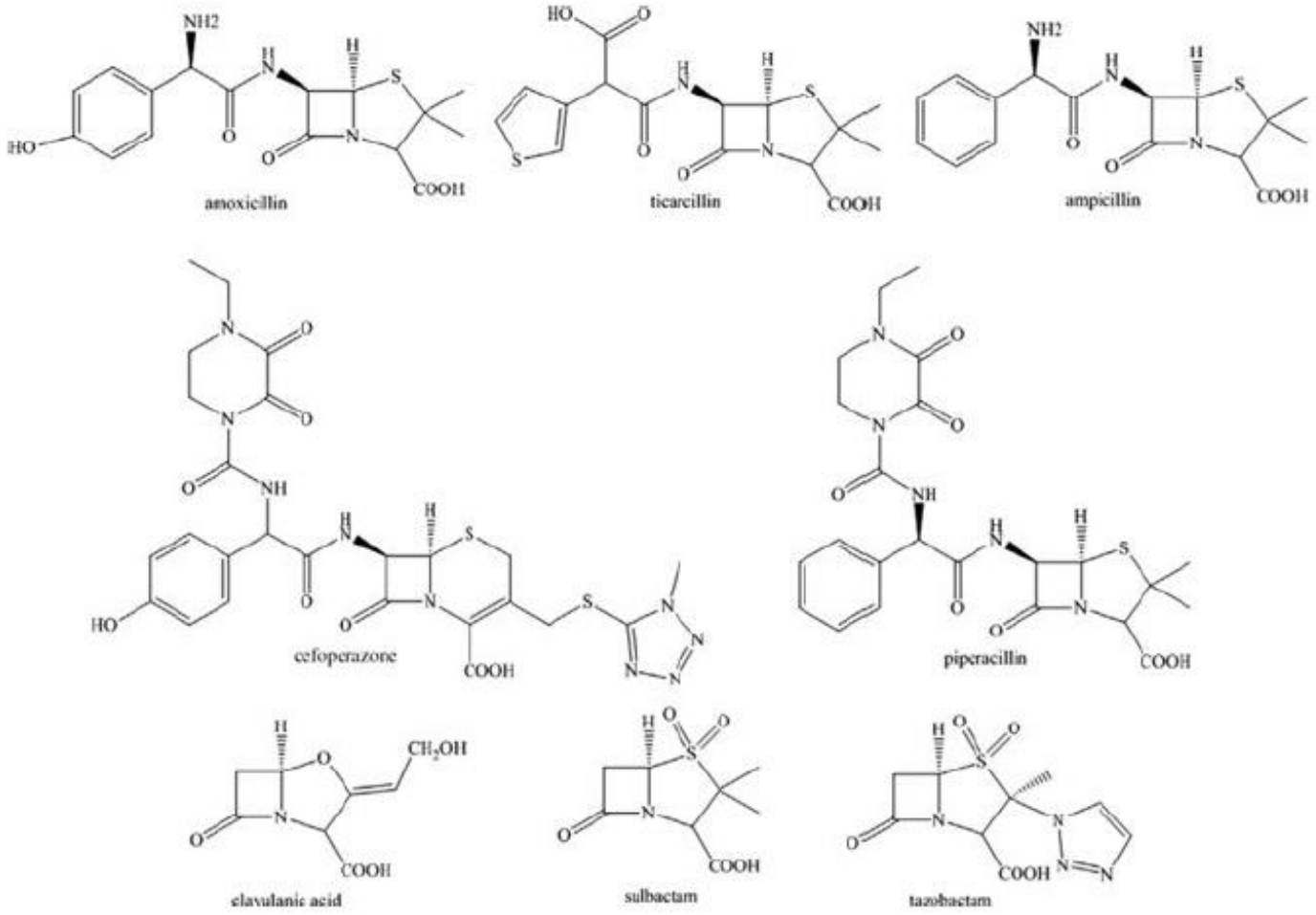
Baseline characteristics	Epidemiological background	Recent (<3 months) antibiotic therapy	Prior colonization	Indwelling devices
• Age >70 years	• Prior hospital admission (in the last 12 months)	• Recent aminopenicillins	• Gut colonization with ESBL	• Urinary catheter
• Diabetes mellitus	• Prolonged hospitalization	• Recent cephalosporins	• Gut colonization with CRE	• Gastrostomy or jejunostomy
• Charlson index ≥3	• Transfer from another health-care facility	• Recent fluoroquinolones	• Colonization with MRSA	• Nasogastric tube
• Recurrent or obstructive UTIs	• Current or prior ICU admission	• Recent carbapenems	• Colonization with *Acinetobacter*	• CVC
• Use of corticosteroids	• Local epidemiology, outbreak	• Recent aminoglycosides	• Endotracheal colonization with *P. aeruginosa*	• Mechanical ventilation
• Immunosuppression	• Travel from high endemic area[a]			• Hemodialysis
• Trauma				
• Malignancy				
• Organ transplantation				
• COPD				
• Neutropenia				
• Recent surgery				

CVC: central venous catheter; COPD: chronic obstructive pulmonary disease; CRE: carbapenemase-resistant *Enterobacteriaceae*; ESBL: extended-spectrum beta-lactamase; ICU: intensive care unit; MRSA: methicillin-resistant staphylococcus aureus; UTIs: urinary tract infections; VIM: verona integron-encoded metallo-beta-lactamase.

[a]Central and western Asia for ESBL; USA, Italy, Greece, and Israel for *K. pneumoniae* carbapenemases; Greece for VIMs; Turkey for OXA-48; and the Indian subcontinent for New Delhi metallo-beta-lactamases.

Bassetti M et al. Expert Rev Anti Infect Ther. 2017

β-Lactamase inhibitors of the past and their β-lactam partners



the β-lactamase inhibitor targeted the β-lactamase inactivating it, so that the partner β-lactam could inactivate the penicillin binding protein (PBP) target, eventually resulting in bacterial cell death

β-Lactamase inhibitors of the past (clavulanic acid, sulbactam, and tazobactam) **and their β-lactam partners : Problem**

- Target only class A serine β-lactamases, thus metallo-β-lactamases (MBLs) of class B, AmpCs serine β-lactamases belonging to class C, and OXAs serine β-lactamases of class D, ➔ resistant to inhibition

- Variants of class A β-lactamases (eg, TEM-1 and SHV-1) evolved single amino acid substitutions (eg, S130G, K234R) ➔ resistant to inhibition

- New class A β-lactamases, such as KPC-2, evolved (circa 1996) with the ability to hydrolyze clavulanic acid, sulbactam, and tazobactam

Major obstacles in β-lactamase inhibitor development

- Mechanisms by which β-lactamases are resistant to clavulanic acid, tazobactam and/or sulbactam, are different even within the same class of β-lactamase
- MDR Gram-negatives possess more than one of these β-lactamases (MBLs : Zn2+-mediated noncovalent mechanism, OXA : heterogeneous >500 different variants; OXA β-lactam hydrolytic mechanism different and not like the other serine-based mechanisms)

A single “magic bullet” β-lactam-β-lactamase inhibitor combination that targets all clinically important β-lactamases (eg, KPC-2, OXA-24/40, AmpC, and NDM-1) Is unlikely

Θεραπευτικές επιλογές για MDR-GNB λοιμώξεις

Pseudomonas	Klebsiella	Acinetobacter
• Colistin • Fosfomycin • Aztreonam (MBL) • Ceftolozane/tazobactam • Ceftazidime/avibactam	• Colistin • Aminoglycosides • Tigecycline • Fosfomycin • Aztreonam (MBL) • Carbapenems (MIC<8) • Ceftazidime/avibactam	• Colistin • Tigecycline • Sulbactam

Θεραπευτικές επιλογές για λοιμώξεις από ESBL / CR

- **Καρβαπενέμες**

Αναστολείς β-λακταμασών (pip/tazo)

- Κεφεπίμη
- Τιγκεκυκλίνη
- Φωσφομυκίνη
- Αμινογλυκοσίδες

- **Κεφτολοζάνη/ταζομπακτάμη**
- **Κεφταζιδίμη/αβιμπακτάμη**

❖ **Pip/Tazo:** επιλογή σε ασθενείς που δεν είναι βαρέως πάσχοντες (απουσία βακτηριαιμίας vs μεροπενεμης)

❖ **Κεφεπίμη:** δεν είναι αποτελεσματική και ασφαλής επιλογή (υψηλοτερη συχνοτητα σε σχεση με καρβαπενεμες)

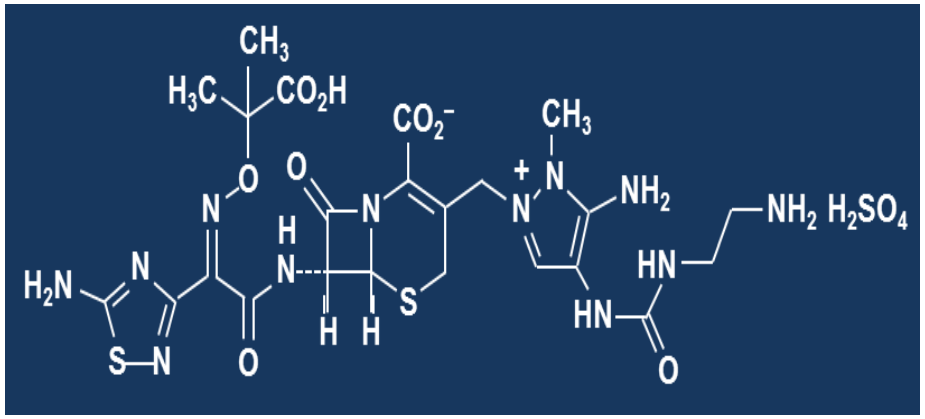
❖ **Τιγκεκυκλίνη:** σε ενδοκοιλιακές λοιμώξεις σε ασθενείς που δεν είναι βαρέως πάσχοντες (απουσία βακτηριαιμίας – όχι *Pseudomonas, Proteus* – black box warning)

❖ **Φωσφομυκίνη:** μόνο σε ουρολοιμώξεις σε μη βαρέως πάσχοντες ασθενείς (μονοθεραπεια αναπτυξη ανθεκτικοτητας)

❖ **Αμινογλυκοσίδες:** ως συμπληρωματική θεραπεία (σε σοβαρές λοιμώξεις), ως μονοθεραπεία μόνο σε ουρολοιμώξεις σε μη βαρέως πάσχοντες ασθενείς

Κεφτολοζάνη/Ταζομπακτάμη

Νέα Κεφαλοσπορίνη & **Παλιός Αναστολέας**



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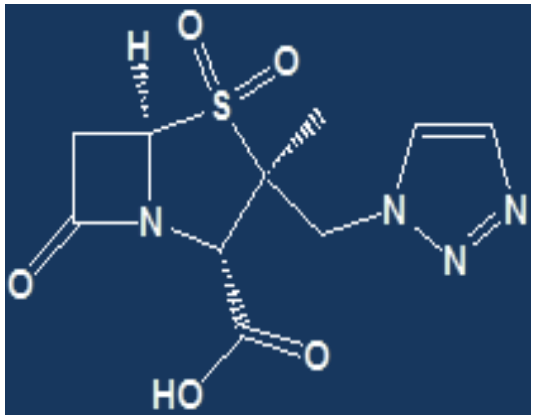
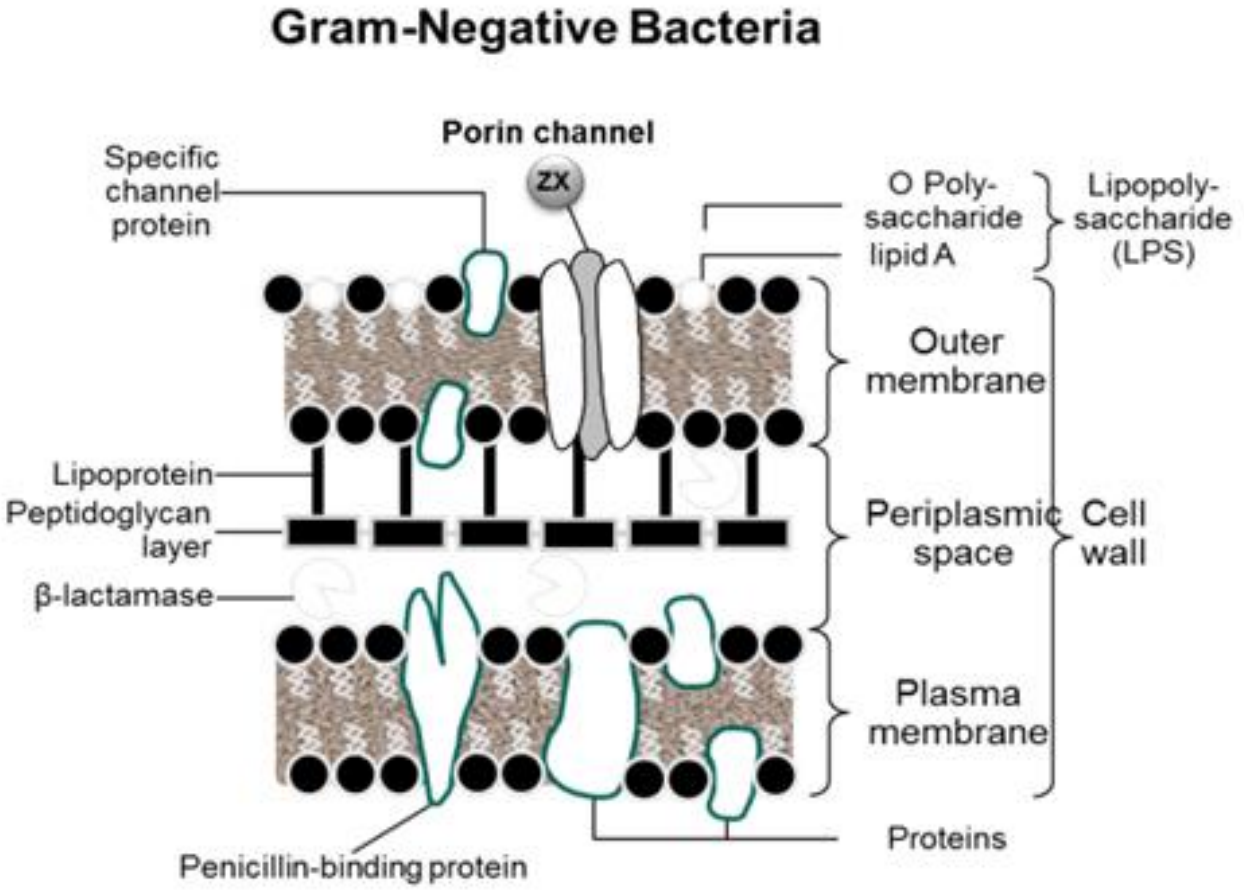


Κατηγορία

- Αντιψευδομοναδική Κεφαλοσπορίνη + αναστολέας β-λακταμάσης
- Αναλογία 2:1

Zhanel et al. Drugs. 2014;74:31-51. Ceftolozane/Tazobactam, SmPC 2017

Μηχανισμός δράσης



- **<u>Ταχέως βακτηριοκτόνο</u>**
- Αναστέλλει τη σύνθεση του κυτταρικού τοιχώματος
- **Δραστική έναντι *<u>Pseudomonas aeruginosa</u>* με ανεπάρκειες πορινών και μεταλλάξεις**
- Αναστέλλει τη παραγωγή β-λακταμασών

Ευρύ φάσμα έναντι περισσοτέρων **<u>Enterobacteriaceae που παράγουν ESBL</u>**

Δεν επηρεάζεται από τους μηχανισμούς αντοχής της P. aeruginosa

Resistance Mechanisms	Outer Membrane Porin Loss OprD	β-lactamase Enzyme AmpC	Efflux Pump MexXY	Efflux Pump MexAB
Ceftolozane	●	●	●	●
Ceftazidime	◐	○	●	○
Cefepime	●	○	○	○
Piperacillin/tazobactam	●	○	●	○
Imipenem	○	●	●	●
Meropenem	◐	●	○	◐

○ Activity greatly decreased >> ● Retains activity

Table adapted from Castanheira M, *et al.* 2014

1. Takeda et al. Antimicrob Agents Chemother. 2007;51:826-30. 2. Crandon et al. Antimicrob Agents Chemother. 2012;56:6137-46. 3. Davies et al. J Antimicrob Chemother. 2011;66:2298-2307. 4. Livermore. Clin Infect Dis. 2002;34:634-40. 5. Riera et al. J Antimicrob Chemother. 2011;66:2022-7. 6. Zhanel et al. Drugs. 2007;67:1027-52.

Ταζομπακτάμη

Δραστικότητα έναντι ESBLs

Ανασταλτική δράση αναστολέων β-λακταμασών έναντι διαφόρων β-λακταμασών

	Ένζυμο β-λακταμάσης					
	AmpC	CTX-M	SHV	TEM	KPC	MBL
Σουλμπακτάμη[3]	-/+[a]	+	+	+	-	-
Κλαβουλανικό οξύ[4,5]	-	+	+	+	-	-
Ταζομπακτάμη[3,6]	-	+	+	+	-	-
Αβιβακτάμη[7]	+	+	+	+	+	-

1. Livermore et al. J Antimicrob Chemother. 2010;65:1972-4. 2. Titelman et al. Diag Microbiol Infect Dis. 2011;70:137-41. 3. Drawz and Bonomo. Clin Microbiol Rev. 2010;23:160-201. 4. Jacoby and Munoz-Price. N Engl J Med. 2005;352:380-91. 5. Shadid et al. Crit Rev Microbiol. 2009;35:81-108. 6. Ceftolozane/Tazobactam SmPC 2017. 7. Zhanel et al. Drugs. 2013;73:159-77.

Κεφτολοζάνη/Ταζομπακτάμη

Χαμηλή MIC_{90} έναντι ESBLs (συγκεντρωτικά δεδομένα)

Efficacy of ceftolozane/tazobactam against urinary tract and intra-abdominal infections caused by ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae*: a pooled analysis of Phase 3 clinical trials

Myra W. Popejoy[1]*, David L. Paterson[2], Daniel Cloutier[1], Jennifer A. Huntington[1], Benjamin Miller[1], Caleb A. Bliss[1], Judith N. Steenbergen[1], Ellie Hershberger[1], Obiamiwe Umeh[1] and Keith S. Kaye[3]

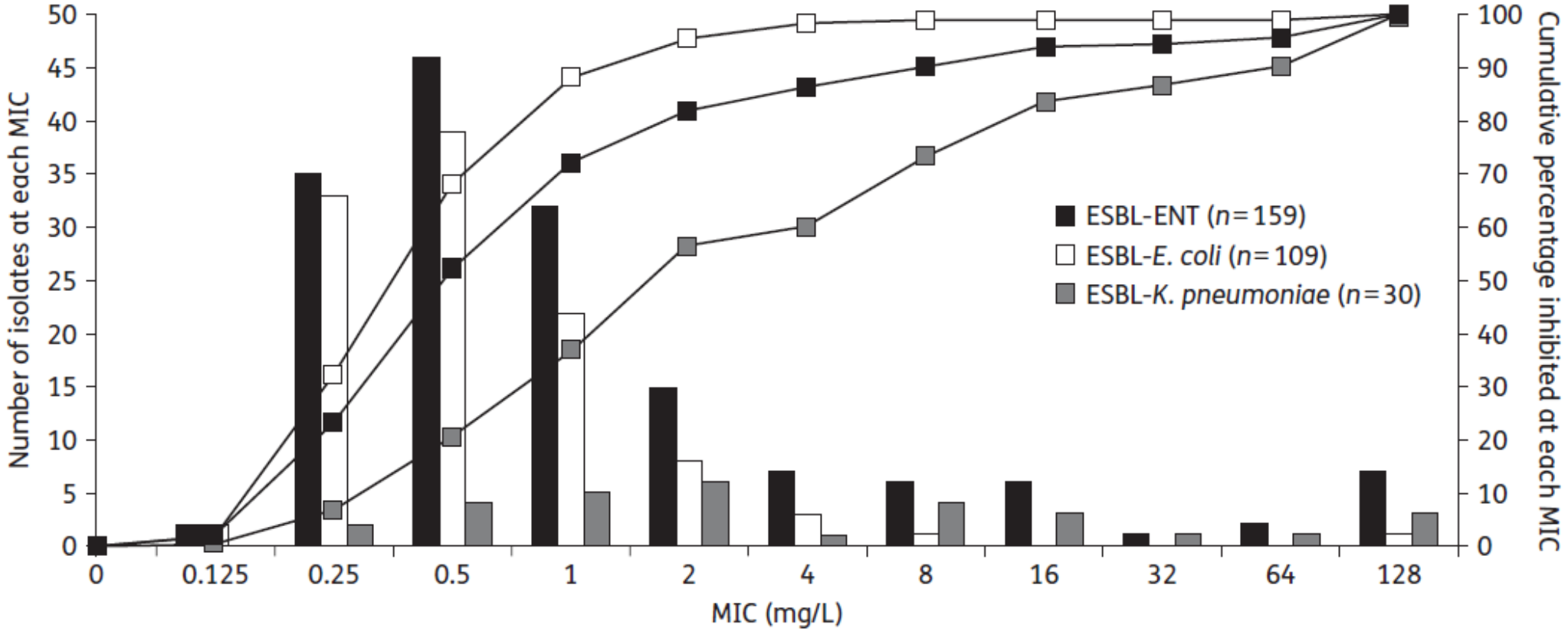


Figure 1. Distribution of ceftolozane/tazobactam MICs for ESBL-ENT (pooled ME population).

Journal of Antimicrobial Chemotherapy Advance Access published October 5, 2016

Κεφτολοζάνη/Ταζομπακτάμη

In vitro activity

Pseudomonas aeruginosa, including drug-resistant strains

Escherichia coli, including ESBL-positive strains

Klebsiella pneumoniae, including ESBL-positive strains

Minimal activity against Gram-positive bacteria

Limited activity against anaerobes No activity against KPC, MBL

Development

cUTI, cIAI, nosomial pneumonia

In vivo efficacy

Activity in mouse models of sepsis, pneumonia, uti, burn wound infection, thigh infection

Pharmacokinetics

- Linear PK
- Lung penetration
- Rapid tissue distribution
- Minimal accumulation
- Extensive renal excretion
- Low protein binding
- Minimal CYP450 drug-drug interactions

Ceftolozane/Tazobactam Plus Metronidazole for Complicated Intra-abdominal Infections in an Era of Multidrug Resistance: Results From a Randomized, Double-Blind, Phase 3 Trial (ASPECT-cIAI)

Joseph Solomkin,[1] Ellie Hershberger,[2] Benjamin Miller,[2] Myra Popejoy,[2] Ian Friedland,[2,a] Judith Steenbergen,[2] Minjung Yoon,[2] Sylva Collins,[2] Guojun Yuan,[2] Philip S. Barie,[3] and Christian Eckmann[4]

[1]Department of Surgery, University of Cincinnati College of Medicine, Cincinnati, Ohio; [2]Cubist Pharmaceuticals, Lexington, Massachusetts; [3]Departments of Surgery and Medicine, Weill Cornell Medical College, New York, New York; and [4]Department of General, Visceral and Thoracic Surgery, Academic Hospital of Medical University Hannover, Peine, Germany

Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI)

Florian M Wagenlehner, Obiamiwe Umeh, Judith Steenbergen, Guojun Yuan, Rabih O Darouiche

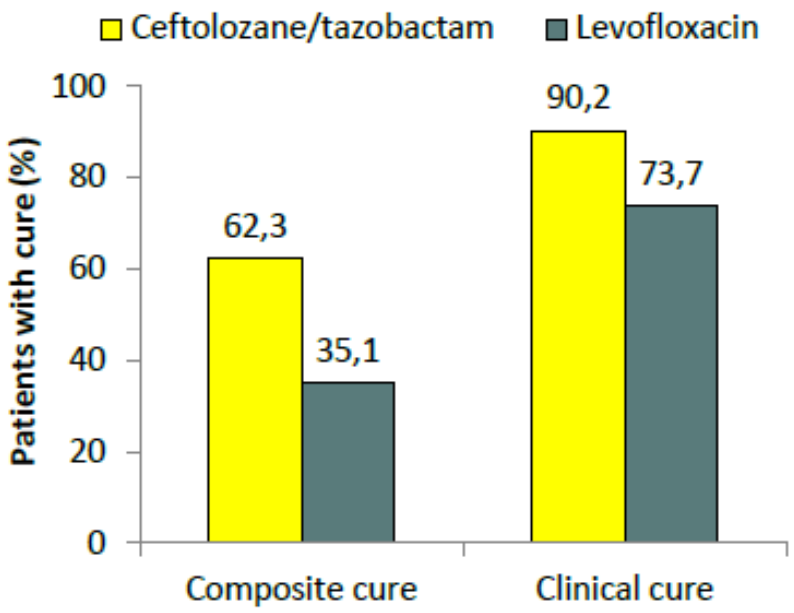
Ceftolozane–tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial

Marin H Kollef, Martin Nováček, Ülo Kivistik, Álvaro Réa-Neto, Nobuaki Shime, Ignacio Martin-Loeches, Jean-François Timsit, Richard G Wunderink, Christopher J Bruno, Jennifer A Huntington, Gina Lin, Brian Yu, Joan R Butterton, Elizabeth G Rhee

Εγκριτικές μελέτες

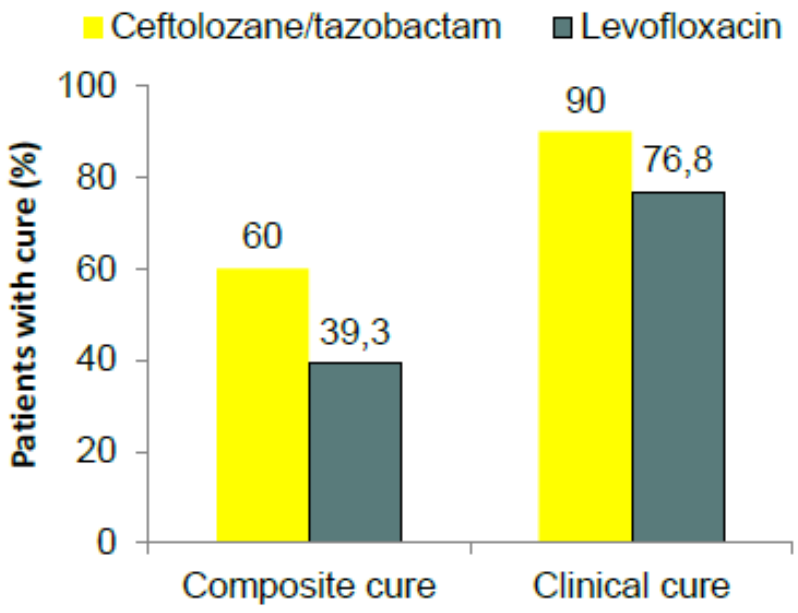
ASPECT-cUTI
Outcomes in Key Subgroups (mMITT at TOC)

ESBL-producing pathogens



	Ceftolozane/ Tazobactam	Levofloxacin	95% CI
Composite cure	38/61 (62.3%)	20/57 (35.1%)	9.2 to 42.9
Clinical cure	55/61 (90.2%)	42/57 (73.7%)	2.6 to 30.2

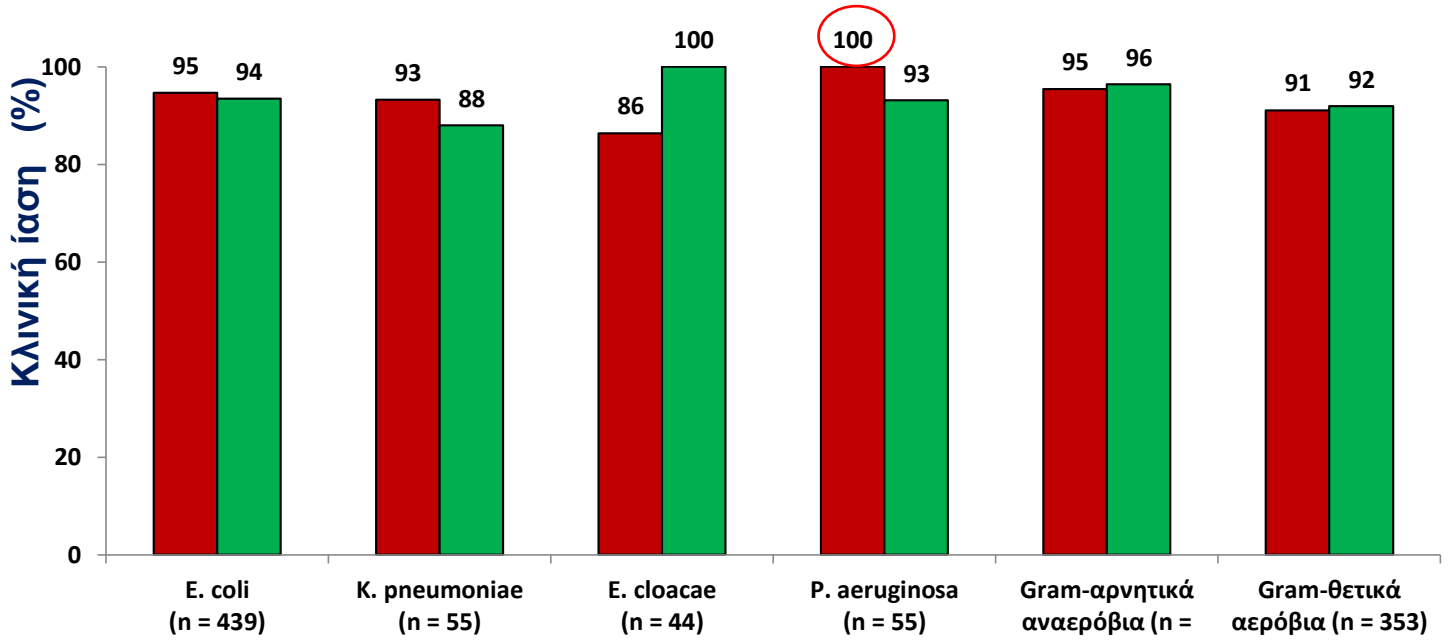
Levofloxacin-resistant pathogens



	Ceftolozane/ Tazobactam	Levofloxacin	95% CI
Composite cure	60/100 (60.0%)	44/112 (39.3%)	7.2 to 33.2
Clinical cure	90/100 (90.0%)	86/112 (76.8%)	3.1 to 22.9

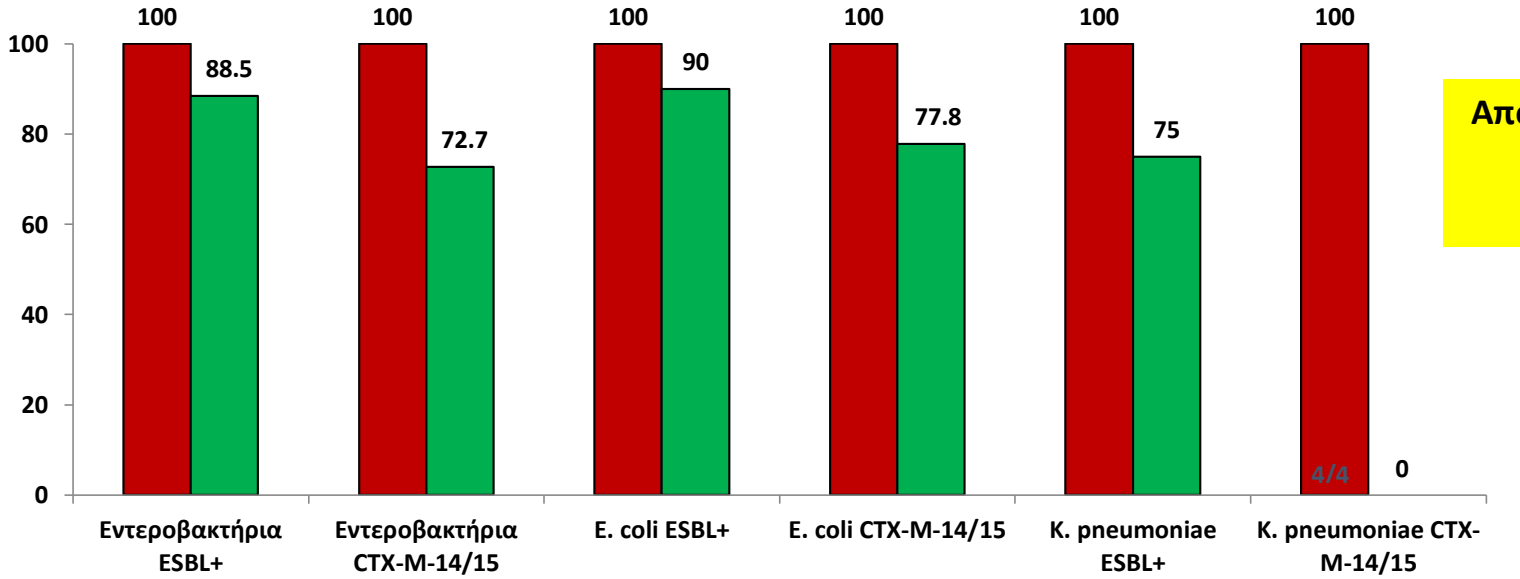
Wagenlehner et al. ECCMID 2014. Poster eP449.

Κεφτολοζάνη/Ταζομπακτάμη vs. Μεροπενέμης



Κλινική ίαση ανά παθογόνο

Cefto/tazo
Meropenem



Αποτελεσματικότητα έναντι ESBLs

Solomkin et al. Clin Infect Dis. 2015;60(10):1462-71.

Ceftolozane/tazobactam 3-gram dose regimen is an efficacious and well-tolerated treatment option for critically ill patients with ventilated, gram-negative nosocomial pneumonia

	Ceftolozane–tazobactam group	Meropenem group	% difference (95% CI)*
28-day all-cause mortality (ITT population)†			
Overall	87/362 (24·0%)	92/364 (25·3%)	1·1 (–5·1 to 7·4)‡
Ventilator-associated pneumonia	63/263 (24·0%)	52/256 (20·3%)	–3·6 (–10·7 to 3·5)§
Ventilated hospital-acquired pneumonia	24/99 (24·2%)	40/108 (37·0%)	12·8 (0·2 to 24·8)§
28-day all-cause mortality (microbiological ITT population)†	53/264 (20·1%)	63/247 (25·5%)	4·4 (–2·8 to 11·8)‡
Clinical cure at test of cure (ITT population)†			
Overall	197/362 (54·4%)	194/364 (53·3%)	1·1 (–6·2 to 8·3)‡
Ventilator-associated pneumonia	147/263 (55·9%)	146/256 (57·0%)	–1·1 (–9·6 to 7·4)§
Ventilated hospital-acquired pneumonia	50/99 (50·5%)	48/108 (44·4%)	6·1 (–7·4 to 19·3)§
Clinical cure at test of cure (clinically evaluable population)¶			
Overall	139/218 (63·8%)	143/221 (64·7%)	–1·3 (–10·2 to 7·7)‡
Ventilator-associated pneumonia	105/159 (66·0%)	111/172 (64·5%)	1·5 (–8·7 to 11·6)§
Ventilated hospital-acquired pneumonia	34/59 (57·6%)	32/49 (65·3%)	–7·7 (–25·0 to 10·6)§
Microbiological eradication at test of cure (microbiological ITT population)†	193/264 (73·1%)	168/247 (68·0%)	4·5 (–3·4 to 12·5)‡

Lancet Infect Dis. 2019 Sep 25

Συμπερασματικά : Κεφτολοζάνη / ταζομπακτάμη

Τάξη	**Μηχανισμός δράσης**	**In vitro δραστικότητα**	**Ενδείξεις**
•Αντιψευδομοναδική κεφαλοσπορίνη + αναστολέας β-λακταμάσης • Σταθερή αναλογία 2:1	• Ταχέως βακτηριοκτόνος • Αναστολή σύνθεσης κυτταρικού τοιχώματος • Ενεργός έναντι *P. aeruginosa* με ανεπάρκειες ή μεταλλάξεις πορίνης	• Εντεροβακτηριακά (*E. Coli, Klebsiella* που παράγουν **ESBL, AmpC** • Ανώτερη **αντιψευδομοναδική** δράση σε σχέση με κεφταζιδίμη (πολλαπλοί μηχανισμοί αντοχής) • **Όχι δραστική έναντι στελεχών που παράγουν KPC, MBLs**	• Επιπλεγμένες ενδοκοιλιακές λοιμώξεις (με μετρονιδαζόλη) • Επιπλεγμένες λοιμώξεις ουροποιητικού (πυελονεφρίτιδα) • Νοσοκ πνευμονια

David van Duin, Robert A. Bonomo. CID 2016:63 63(2):234–41

The management of intra-abdominal infections from a global perspective: 2017 WSES guidelines for management of intra-abdominal infections

Appendix 4

Empiric antimicrobial regimens for critically ill patients with healthcare-associated IAIs. Normal renal function

Healthcare-associated IAIs

Critically ill patients

Meropenem 1 g 8-hourly

or

Doripenem 500 mg 8-hourly

or

Imipenem/Cilastatin 1 g 8-hourly

or

As a carbapenem-sparing regimen

Ceftolozane /Tazobactam 1.5 g 8-hourly + Metronidazole 500 mg 6-hourly

or

Ceftazidime/Avibactam 2.5 g 8-hourly + Metronidazole 500 mg 6-hourly

+

Vancomycin 25–30 mg/kg loading dose then 15–20 mg/kg/dose 8-hourly

or

Teicoplanin 12 mg/kg 12-hourly times 3 loading dose then 12 mg/kg 24-hourly

or

In patients at risk for infection with vancomycin-resistant enterococci (VRE) including patients with previous enterococcal infection or colonization, immunocompromised patients, patients with long ICU stay, or recent Vancomycin exposure

Linezolid 600 mg 12-hourly

or

Daptomycin 6 mg/kg 24-hourly

+-

In patients at high risk for invasive candidiasis

Echinocandins: caspofungin (70 mg LD, then 50 mg daily), anidulafungin (200 mg LD, then 100 mg daily), micafungin (100 mg daily) or Amphotericin B Liposomal 3 mg/kg/dose 24-hourly

In patients with suspected or proven infection with MDR (non-metallo-beta-lactamase-producing) Pseudomonas aeruginosa consider use of antibiotic combinations with **Ceftolozane /Tazobactam**

In patients with suspected or proven infection with carbapenemase-producing Klebsiella pneumoniae consider use of antibiotic combinations with **Ceftazidime/Avibactam**

In patients with documented beta-lactam allergy consider use of antibiotic combinations with **Amikacin 15–20 mg/kg 24-hourly**

Συμπεριλήφθηκε στις Διεθνείς Κατευθυντήριες Οδηγίες 2017 για τις Επιπλεγμένες Ενδο-κοιλιακές Λοιμώξεις

Εμπειρική Θεραπεία: Σύσταση 2A

Empiric Therapy Recommendation	Ceftolozane/Tazobactam + Metronidazole
Empiric Therapy (general)	**2A** Use primarily for higher-risk patients with IAI suspected or proven to be **caused by ESBL-producing Enterobacteriaceae and resistant strains of P. aeruginosa** for which other agents are not suitable
Resistant P. aeruginosa	2C
MDR, XDR, PDR P. aeruginosa	**2B**
ESBL-producing Enterobacteriaceae	**2B**
KPC-producing Enterobacteriaceae	No recommendations
AmpC-β-lactamase-producing Enterobacteriaceae	No recommendations
Carbapenem-resistant Enterobacteriaceae	No recommendations

Συμπεριλήφθηκε στις Διεθνείς Κατευθυντήριες Οδηγίες 2017 για τις Επιπλεγμένες Λοιμώξεις του Ουροποιητικού Συστήματος

European Association of Urology

Urosepsis

Urosepsis is a systemic, deleterious host response to infection originating from the urinary tract and/or male genital organs. Urosepsis is accompanied by signs of systemic inflammation, presence of symptoms of organ dysfunction and persistent hypotension associated with tissue anoxia.

Recommendations for parenteral antimicrobial therapy of urosepsis				
Anti-microbials	**Daily dose**	**LE**	**GR**	**Comments**
Cefotaxime	2 g t.i.d	2	A*	Not studied as monotherapy in acute uncomplicated pyelonephritis.
Ceftazidime	1-2 g t.i.d	2	A*	
Ceftriaxone	1-2 g q.d	1b	A*	Lower dose studied, but higher dose recommended. Same protocol for acute uncomplicated pyelonephritis and complicated UTI (stratification not always possible).
Cefepime	1-2 g b.i.d	1b	B	
Piperacillin/tazobactam	2.5-4.5 g t.i.d	1b	A*	
Ceftolozane/tazobactam	1.5 g t.i.d	1b	B	
Ceftazidime/avibactam	2.5 g t.i.d	1b	B	
Gentamicin	5 mg/kg q.d	1b	B	Not studied as monotherapy in acute uncomplicated pyelonephritis.
Amikacin	15 mg/kg q.d	1b	B	
Ertapenem	1 g q.d	1b	B	Same protocol for acute uncomplicated pyelonephritis and complicated UTI (stratification not always possible).
Imipenem/cilastatin	0.5/0.5 g t.i.d	1b	B	
Meropenem	1 g t.i.d	2	B	
Doripenem	0.5 g t.i.d	1b	B	

* *Upgraded based on panel consensus.*

Κεφτολοζάνη / ταζομπακτάμη: σε ποιο ασθενή?

- Η κεφτολοζάνη-ταζομπακτάμη νέα επιλογή για κάλυψη ανθεκτικών gram (-) [ESBL, AmpC]
- Ισχυρή αντιψευδομοναδική δράση (πολλαπλοί μηχανισμοί αντοχής)
- Δεν έχει δράση σε πολυανθεκτικά Gram (-) που παράγουν καρβαπενεμάσες (CRE)

Στοχευμένη: ασθενείς με επιπλεγμένη ενδοκοιλιακή λοίμωξη ή ουροποιητικού από ESBL ή από (R) pseudomonas

Εμπειρική: ασθενείς με επιπλεγμένη ενδοκοιλιακή λοίμωξη ή ουροποιητικού + **παράγοντες κινδύνου για ESBL**

Κεφτολοζάνη/ ταζομπακτάμη

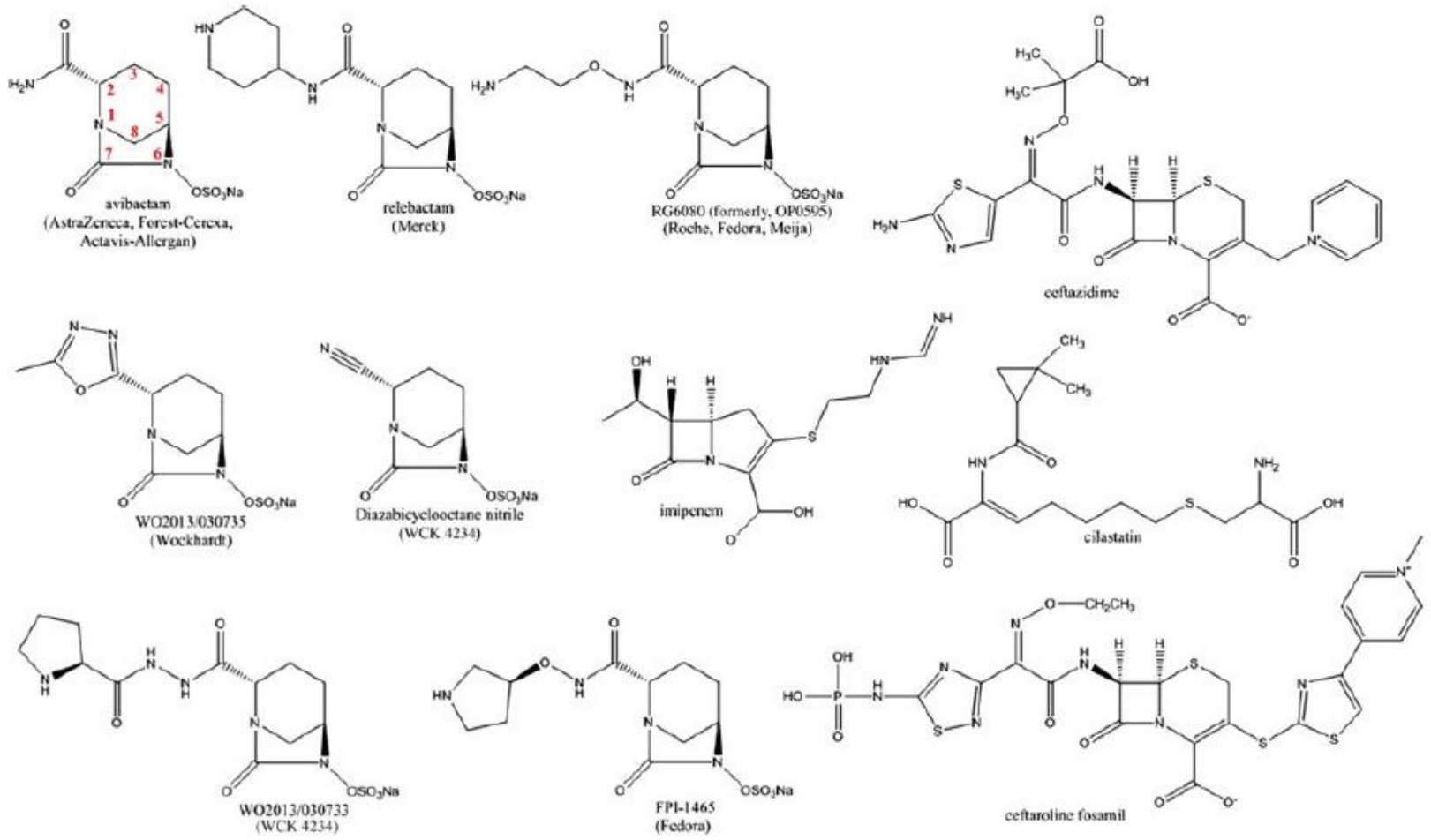
Αποφυγή καρβαπενεμών

Αποκλιμάκωση αντοχών σε καρβαπενέμες

- **Ηλικία >70**
- **Σακχ. Διαβήτης**
- **Charlson index >3**
- **Πρόσφατη νοσηλεία (εντός 3 μηνών)**
- **Πρόσφατα αντιβιοτικά (εντός 3 μηνών)**
- **Διαμονή σε οίκο ευγηρίας**
- **Ουροκαθετήρας**

Diazabicyclooctanones : Avibactam

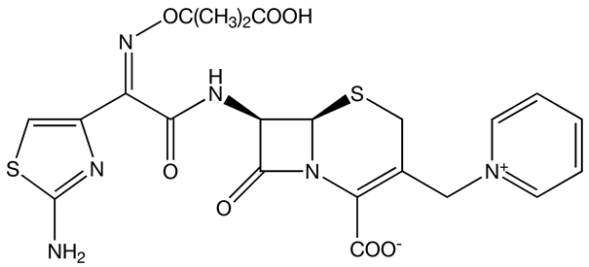
Ceftazidime – Avibactam : Old Cephalosporin & New Inhibitor



Ceftazidime-Avibactam: Old Cephalosporin & New Inhibitor

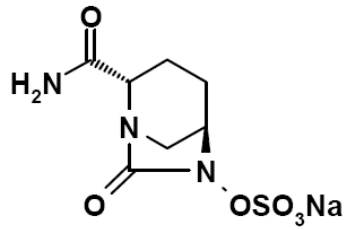
Ceftazidime

- **Extended-spectrum cephalosporin** with activity against **Enterobacteriaceae** and **P. aeruginosa**[1]
- Binds PBPs, leading to bacterial cell lysis[1]



Avibactam

- **Novel non-β-lactam β-lactamase inhibitor** with a unique mode of action[2]
- High binding affinity for Class A, C and some Class D β-lactamases (**ESBLs, KPCs and AmpC**), some of which are resistant to current agents (e.g. KPCs)[3]



1. Extended b-lactamase spectrum

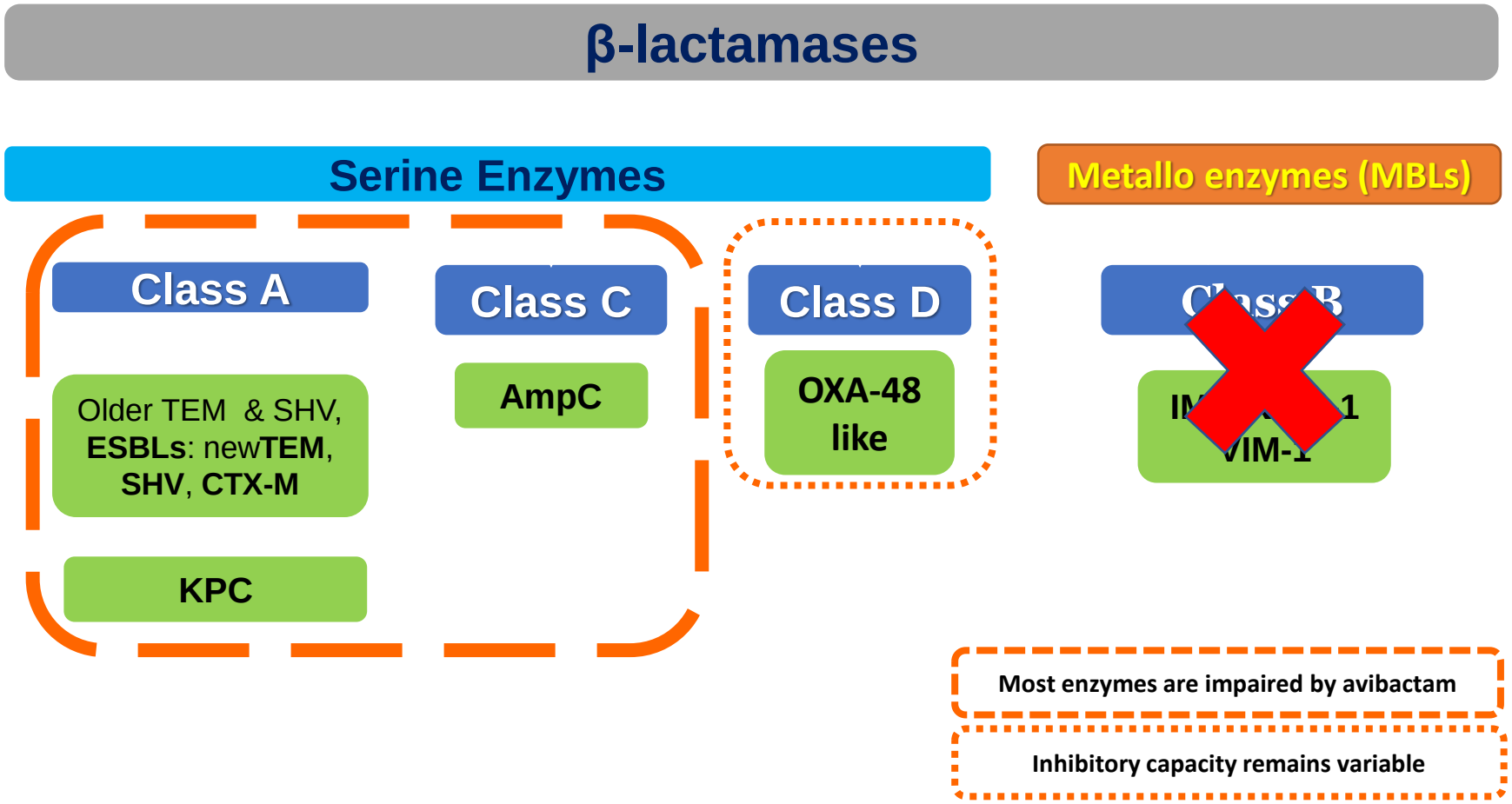
2. Reversible inhibition: Recycling

3. No b-lactamic back bone – no induction of b-lactamases

Ceftazidime-avibactam is the first BL/BLI to retain activity against KPC-producing isolates, along with ESBLs, Ampc, and OXA-48

***ESBLs**: extended-spectrum β-lactamases, **KPC**: Klebsiella pneumoniae carbapenemase, **OXA**: oxacillinase1. J Antimicrob Chemother. 1983;12:119–126 2.Proc Natl Acad Sci. 2012;29:11663–11668. 3. Drugs (2013) 73:159–177. 4 Int J Antimicrob Agents 2015;46:483–93.5. J Antimicrob Chemother 2016; 71: 2713–2722.*

Activity of Ceftazidime-Avibactam



TEM: *temoneira;* ***SHV:*** *sulfhydryl variable;* ***ESBLs:*** *Extended spectrum b-lactamases* ***CTX-M:*** *cefotaxime-ß-lactamases* ***KPC****: Klebsiella pneumoniae carbapenemase,* ***IMP****, imipenemase-type carbapenemase,* ***VIM****: Verona integron-encoded metallo-ß-lactamase,* ***NDM:*** *New Delhi metallo-ß-lactamase,* ***OXA:*** *oxacillinase-type carbapenemases,* ***1. Antimicrob Chemother 2016; 71: 2713–2722****..*

Ceftazidime-avibactam PK/PD data

- **No drug–drug interaction between ceftazidime and avibactam**
- **Ceftazidime and avibactam undergo renal elimination**
- **No dose adjustments necessary based on age or gender**
- **Ceftazidime-avibactam penetrates well into lung ELF; drug levels proportional to those in plasma**
- **Dose adjustments necessary in patients with moderate to severe renal impairment; dose adjustments simple due to linear PK**
- **Ceftazidime-avibactam 2000–500 mg q8h infused over 2 h provides adequate exposure against clinically relevant Gram-negative pathogens**

1. Edeki T et al. ICAAC 2013; Poster A-1019 2. Merdjan H et al. Clin Drug Investig. 2015;35:307–317 3. Tarral A, Merdjan H. Clin Ther. 2015;37(4):877–886 4. Nicolau D et al. ICAAC 2013; Poster A-1027 5. Crandon JL et al. Antimicrob Agents Chemother 2012;56:6137–6146 6. Das S et al. ECCMID 2015; Abstract

Ceftazidime-Avibactam Microbiological Spectrum

Gram (-) bacteria	cIAIs	cUTIs	HAP , VAP
Citrobacter freundii	✓	×	×
Enterobacter cloacae	✓	✓	✓
Escherichia coli	✓	✓	✓
Klebsiella oxytoca	✓	×	×
Klebsiella pneumoniae	✓	✓	✓
Proteus mirabilis	×	✓	✓
Pseudomonas aeruginosa	✓	✓	✓
Serratia marcescens	×	×	✓

× *In vitro* sensitivity but not enough data to justify use

Zavicefta SPC 2019

Caz-Avi: Breakpoints

Table 1. EUCAST and CLSI/FDA breakpoints for ceftazidime-avibactam (CAZ-AVI)

	EUCAST				CLSI/FDA			
	Broth microdilution		**Disk diffusion** Disk potency CAZ/AVI 10/4 µg		**Broth microdilution**		**Disk diffusion** Disk potency CAZ/AVI 30/20 µg	
	MICs (mg/L)		Zone diameters (mm)		MICs (mg/L)		Zone diameters (mm)	
	S	R	S	R	S	R	S	R
Enterobacteriaceae	≤8	≥8	≤13	≥13	≤ 8/4	≥ 16/4	≥ 21	≤ 20
Pseudomonas aeruginosa	≤8	≥8	≤17	≥17	≤ 8/4	≥ 16/4	≥ 21	≤ 20

MIC, minimum inhibitory concentration; S, susceptible; R, resistant.

- **DD <u>overestimates</u> resistance to caz-avi and is less concordant (72%) than e-test (96%) to BMD (p=0.0003)**

J Clin Microbiol 56:e01093-17
Zavicefta SPC 2018

Caz-Avi Indications

- **Complicated intra-abdominal infection (cIAI)**
- **Complicated urinary tract infection (cUTI), including pyelonephritis**
- **Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP)**
- **Caz-Avi is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adult patients with limited treatment options**

Zavicefta spc 2019

Ceftazidime-avibactam : Clinical trial programme

Seven prospective, international, multicentre, randomised Phase III studies

RECLAIM 1, 2 and 3: Adults with cIAI

- Double-blind randomisation (1:1)
  - **CAZ 2000 mg+AVI 500 mg**+metronidazole 500 mg IV q8h or
  - **MER 1000 mg** IV+placebo q8h
- Primary objective
  - RECLAIM 1 and 2
  - Assess non-inferiority of CAZ-AVI re: clinical cure at TOC visit in patients with ≥1 identified pathogen (mMITT populations)
  - RECLAIM 3:
  - Proportion of patients with clinical cure at TOC visit (CE populations)

RECAPTURE 1 and 2 Adults with cUTI (including acute pyelonephritis)

- Double-blind randomisation (1:1)
  - **CAZ 2000 mg+AVI 500 mg q8h IV** or
  - **DOR 500 mg**+placebo q8h IV
- Primary objective
  - Assess non-inferiority of CAZ-AVI on co-primary endpoints in mMITT analysis set:
  - Resolution of UTI-specific symptoms
  - Resolution/improvement of flank pain
  - Per-patient microbiol eradication and symptomatic resolution

REPRISE Adults with CAZ-resistant pathogens

- Open-label randomisation (1:1)
  - **CAZ 2000 mg+AVI 500** mg+metronidazole 500 mg q8h IV or
  - **Best available therapy**
- Primary objective
  - Estimate per-patient clinical response to CAZ-AVI and best available therapy at TOC visit in cUTI and cIAI caused by CAZ-resistant Gram-negative pathogens

REPROVE Adults with HAP (including VAP)

- Double-blind randomisation (1:1)
  - **CAZ 2000 mg+AVI 500 mg q8h IV** or
  - **MER 1000** mg+placebo q8h IV
  Plus open-label empiric linezolid+aminoglycoside
- Primary objective
  - Assess non-inferiority of CAZ-AVI on clinical cure rate at TOC visit in cMITT and CE populations

Clin Infect Dis. 2016;62:1380–9
Clin Infect Dis 2016 Sep 15;63(6):754-62
Lancet Infect Dis. 2016 Jun;16(6):661-67
Lancet Infect Dis. 2018 Mar;18(3):285-295.

Ceftazidime–avibactam: real-world data

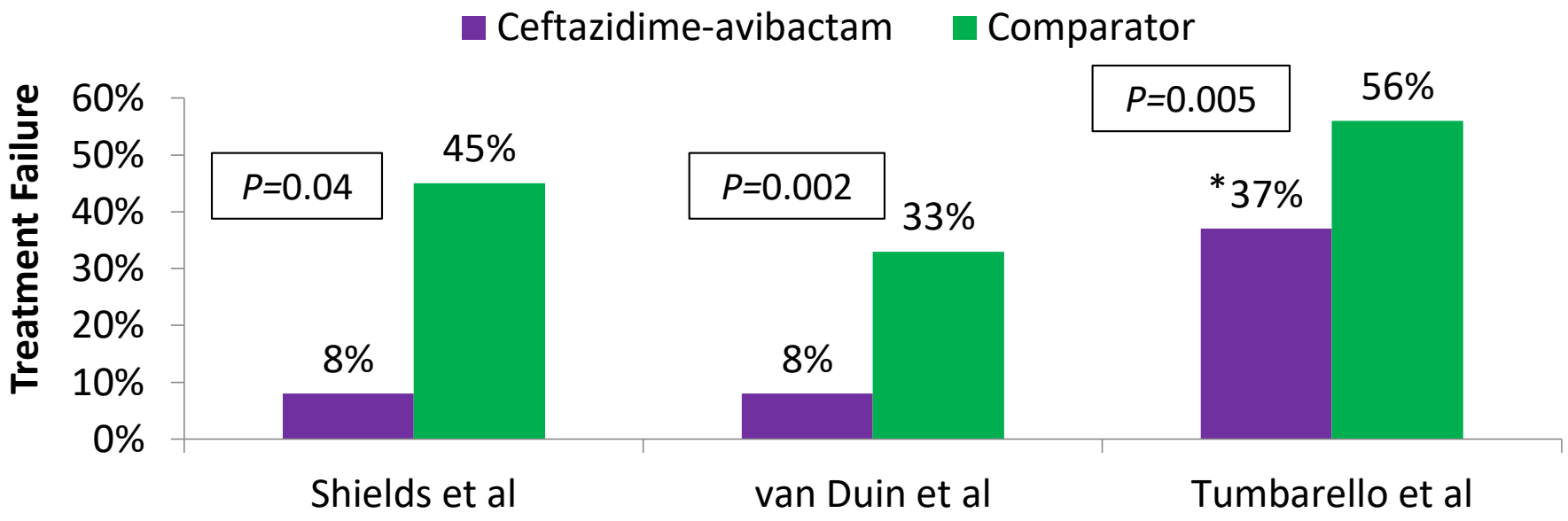
More than 14 observational studies

Single-centre, retrospective cohort studies	Multicentre, retrospective cohort studies	Single-centre prospective, observational / multicenter case-control studies	Multicenter, prospective observational cohort studies
• Aitken SL, *et al.* 2016 • Shields RK, *et al.* 2016 • Krapp F, *et al.* 2017 • Shields RK, *et al.* 2017 • Santevecchi BA, *et al.* 2018 • Shields RK, *et al.* 2018 • Alggizani A, *et al.* 2018 • De la Calle C, *et al.* 2018	• Temkin E, *et al.* 2017 • Caston JJ, *et al.* 2017 • King M, *et al.* 201 • Tumbarello M, *et al.* 2019	• Sousa A, *et al.* 2018	• van Duin D, *et al.* 2018

Strength of evidence

Aitken SL, et al. Clin Infect Dis. 2016;63:954–8; Shields RK, et al. Clin Infect Dis. 2016;63:1615–8; Krapp F, et al. IJAA. 2017;49:770–3; Shields RK, et al. Antimicrob Agents Chemother. 2017;61:e00883-17; Santevecchi BA, et al. Int J Antimicrob Agents. 2018;51:629–35; Shields RK, et al. Antimicrob Agents Chemother. 2018;62:e02497-18; Alggizani A, et al. J Infect Public Health. 2018;11:793–5; De la Calle C, et al. IJAA. 2018. [Epub ahead of print]; Temkin E, et al. Antimicrob Agents Chemother. 2017;61:e01964-17; Caston JJ, et al. Int J Infect Dis. 2017;59:118–23; King M, et al. Antimicrob Agents Chemother. 2017;61:e00449-17; Sousa A, et al. J Antimicrob Chemother. 2018;73:3170–5; Tumbarello M, et al. Clin Infect Dis. 2019;68:355–64; van Duin D, et al. Clin Infect Dis. 2018;66(2):163–71.

Ceftazidime–avibactam treatment: impact on survival

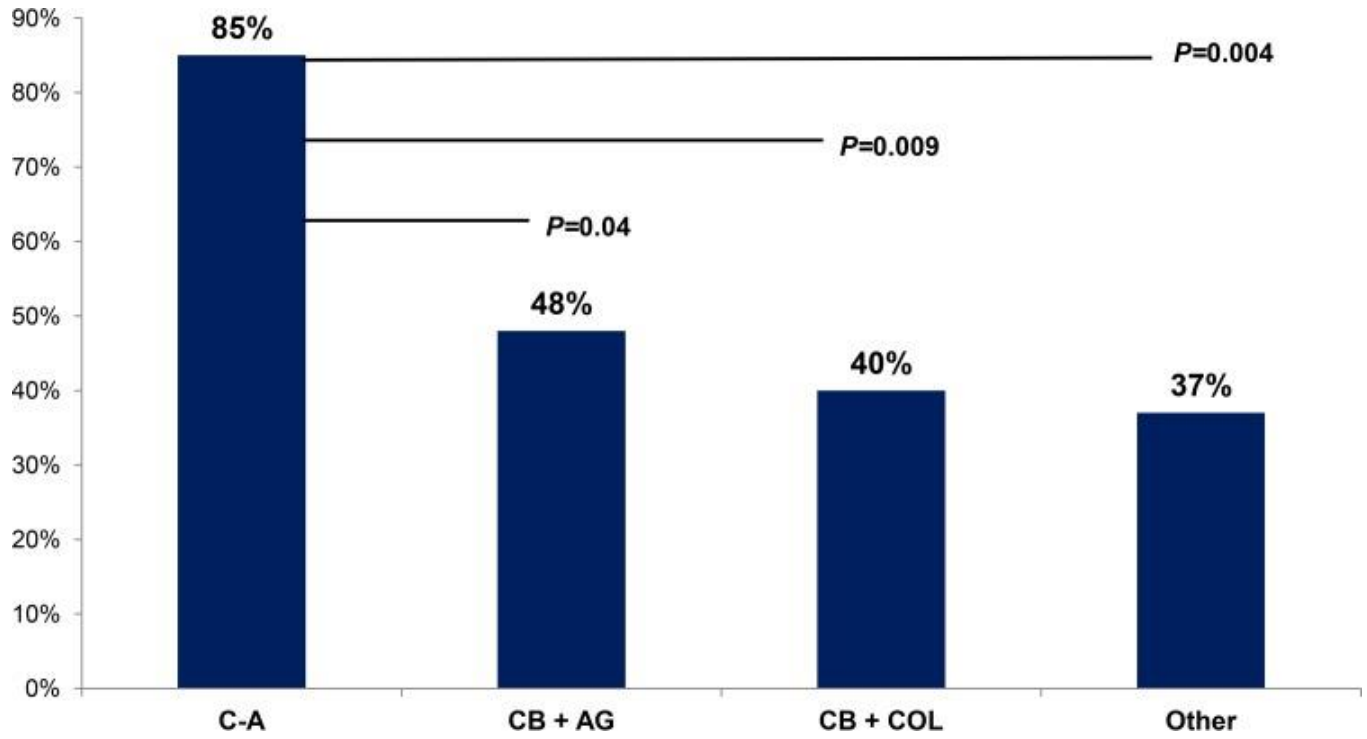


Data are almost exclusively against KPC-producing *K. pneumoniae*!

[a] Used as salvage therapy

Antimicrob Agents Chemother. 2017;61(8):e00883-17;
Clin Infect Dis. 2018;66(2):163–71;.
Clin Infect Dis. 2019;68:355–64.

Caz-Avi & Carbapenem-Resistant *K. pneumoniae* Bacteremia

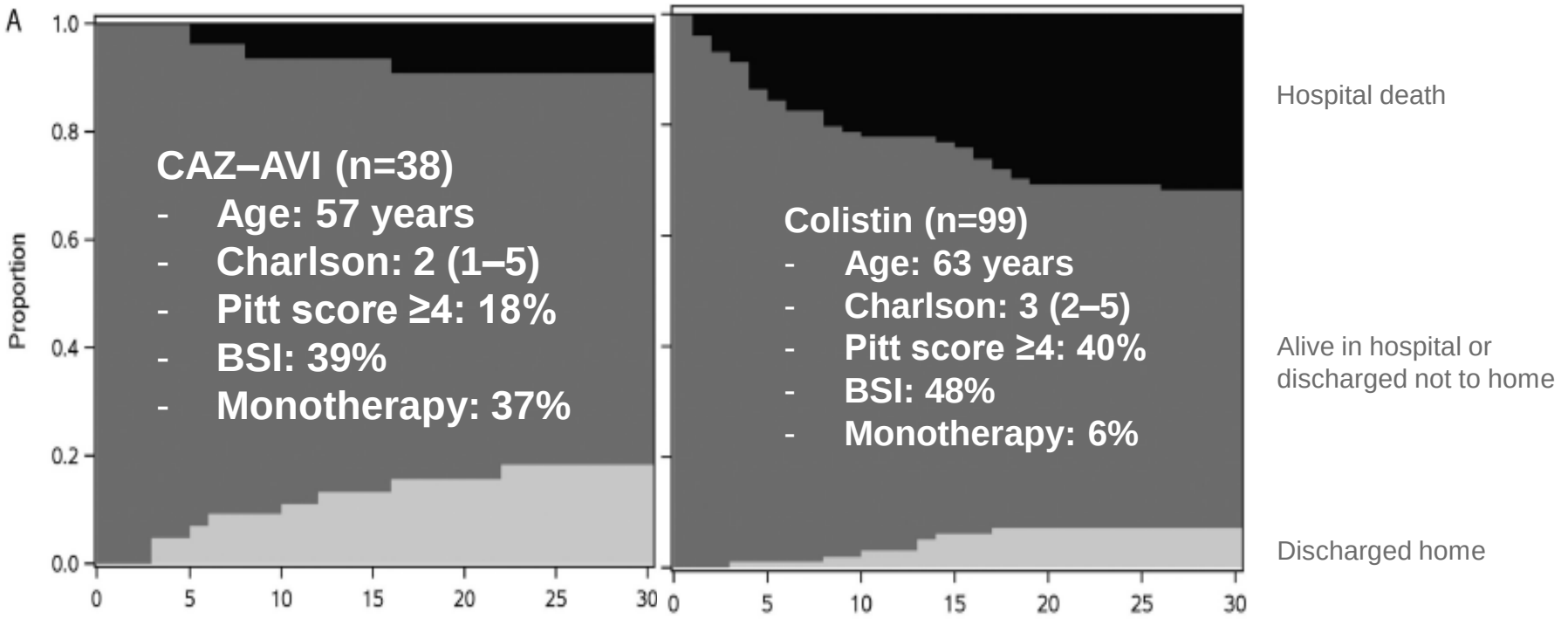


Rates of 30-day clinical success across treatment regimens

By multivariable logistic regression, primary bacteremia (OR, 4.50; 95% CI, 1.53 to 13.21; *P* = 0.006) and **receipt of C-A (OR, 8.64; 95% CI, 1.61 to 43.39; *P* = 0.01) were independent predictors of clinical success**

*Antimicrob Agents Chemother 2017. Jul 25;**61**(8) e00883-17*

Colistin vs. Caz-Avi in the Treatment of Infections due to CRE



- Incident renal failure was 5% for CAZ–AVI versus 13% for colistin
- IPTW-adjusted all-cause mortality at 30 days was 9% for CAZ–AVI vs 32% for colistin
- CAZ–AVI had an IPTW-adjusted 64% probability of a better outcome versus colistin

Clin Infect Dis. 2018;66:163–71.

CAV–AVI as salvage therapy in infections caused by carbapenemase-producing *K. pneumoniae* (Italy)

Multivariate analysis of factors associated with 30-day mortality in the 208 patients with *K. pneumoniae* carbapenemase-producing bacteraemia

	Without propensity score adjustment		Adjusted for the propensity score for therapy with CAZ-AVI	
Variables	*P* value	OR (95% CI)	*P* value	OR (95% CI)
Mechanical ventilation	<0.001	4.25 (1.99-9.09)	<0.001	4.31 (1.99-9.33)
Charlson comorbidity index >3	0.001	3.31 (1.61-6.77)	0.001	3.30 (1.61-6.77)
Neutropenia	0.01	3.22 (1.25-8.29)	0.03	3.36 (1.25-8.75)
Septic shock	0.002	2.95 (1.46-5.94)	0.003	2.94 (1.46-5.92)
Any regimen that included CAZ-AVI	<0.001	0.25 (0.13-0.51)	0.001	0.27 (0.13-0.57)

Clin Infect Dis. 2019 Jan 18;68(3):355-364

CAV–AVI : Real life experience in haematological patients

Int J Infect Dis. 2017 Jun;59:118-123. doi: 10.1016/j.ijid.2017.03.021. Epub 2017 Apr 6.

Clinical efficacy of ceftazidime/avibactam versus other active agents for the treatment of bacteremia due to carbapenemase-producing Enterobacteriaceae in hematologic patients.

Castón JJ[1], Lacort-Peralta I[2], Martín-Dávila P[3], Loeches B[4], Tabares S[5], Temkin L[6], Torre-Cisneros J[7], Paño-Pardo JR[8].

28th ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Madrid, Spain
21 – 24 April 2018

P0681 **Ceftazidime-avibactam as empiric therapy in febrile neutropenic high-risk haematological patients, HMpts, colonized with carbapenem-resistant Klebsiella pneumoniae (CRKP)**

Alessandra Micozzi*[1 1], Michela Ansuinelli[1], Clara Minotti[1], Claudio Cartoni[1], Silvia Maria Trisolini[1], Saveria Capria[1], Walter Barberi[1], Stefania Santilli[2], Alessandra Giordano[2], Giuseppe Gentile[1]

[1]Hematology, Cellular Biotechnologies and Hematology Sapienza University of Rome, [2]Microbiology, Dipartimento di Sanità pubblica e Malattie Infettive Sapienza Università di Roma

Int J Infect Dis. 2017 Jun;59:118-123

Caz-Avi as salvage therapy for infections due to OXA-48 carbapenemase-producing Enterobacteriaceae

Table 3. Comparison of patients receiving monotherapy versus combination treatment with ceftazidime/avibactam

Variable	Monotherapy ($n = 46$)	Combination ($n = 11$)	*P* value
Age, years median (IQR)	69 (30–82)	58 (33–78)	0.21
Male sex, *n* (%)	35 (76)	9 (82)	0.68
Charlson index >2, *n* (%)	27 (59)	6 (55)	0.80
Hospital-acquired, *n* (%)	39 (85)	10 (91)	0.59
INCREMENT-CPE score >7, *n* (%)	19 (41)	4 (36)	0.76
Vasopressor use, *n* (%)	16 (35)	4 (36)	0.42
APACHE-II score, median (IQR)	20 (8–40)	23 (9–45)	0.13
CAZ/AVI started owing to previous treatment failure, *n* (%)	22 (48)	7 (64)	0.34
Source of infection, *n* (%)			
pulmonary	9 (20)	6 (54)	0.02
urinary	13 (28)	1 (9)	0.18
intra-abdominal	10 (22)	4 (36)	0.31
Source control procedure, *n* (%)	7 (15)	2 (18)	0.18
Time to start of treatment with CAZ/AVI, days, median (IQR)	2 (0–15)	4 (2–17)	0.11
14 day mortality, *n* (%)	7 (15)	1 (9)	0.42
30 day mortality, *n* (%)	10 (22)	3 (27)	0.69
90 day recurrence, *n* (%)	4 (9)	2 (18)	0.35
Clinical cure, *n* (%)	37 (80)	7 (64)	0.44
Microbiological cure, *n* (%)	31 (67)	6 (54)	0.58

- Observational study of a prospectively collected cohort, 57 patients
- Intra-abdominal (28%), respiratory (26%), urinary (25%), 54% severe infection, 81% caz-avi as monotherapy, median duration of treatment: 13 day

- **Ceftazidime–avibactam shows promising results, for the treatment of patients with severe infections due to OXA-48-producing Enterobacteriaceae**
- **The emergence of resistance to ceftazidime–avibactam was not observed**

Antimicrob Chemother. 2018 Aug 7. doi: 10.1093/jac/dky295.

Caz-Avi Targeted - Therapy

Προκειμένου να διασφαλιστεί η ορθολογική χρήση του ανωτέρω σκευάσματος, η Εθνική Επιτροπή Αντιβιογράμματος προτείνει τα κάτωθι:

- Για κάθε περίπτωση χορήγησης Zavicefta θα πρέπει να προηγείται συνεργασία με Λοιμωξιολόγο ή Κλινικό Ιατρό ή Βιοπαθολόγο με εμπειρία στις λοιμώξεις.

- **<u>Στοχευμένη Θεραπεία:</u>**

1. Σε λοιμώξεις από εντεροβακτηριακά που παράγουν καρβαπενεμάση (CPE) τύπου KPC ή OXA-48 με in vitro ευαισθησία στο εν λόγω φάρμακο.
2. Σε λοιμώξεις από ψευδομονάδα με in vitro ευαισθησία στο εν λόγω φάρμακο, όταν δεν υπάρχει άλλη αποτελεσματική θεραπεία.

α) Εάν το Zavicefta θα χορηγηθεί μόνο του ή σε συνδυασμό με άλλο δραστικό φάρμακο εναπόκειται στην κρίση του θεράποντος ιατρού,
β) σε ήπιες λοιμώξεις που οφείλονται σε εντεροβακτηριακά που παράγουν KPC ή OXA-48, είναι προτιμότερο να χρησιμοποιείται ένα από τα 3 παλαιότερα φάρμακα αν το παθογόνο έχει in vitro ευαισθησία σε αυτά (π.χ. γενταμικίνη, κολιστίνη ή φωσφομυκίνη γιά UTIs, τιγκεκυκλίνη γιά λοίμωξη χειρουργικού τραύματος).

Η πρώτη προοπτικη καταγραφή της χορήγησης Κεφταζιντίμης-Αβιμπακτάμης σε 15 Ελληνικά Τριτοβάθμια Νοσοκομεία:

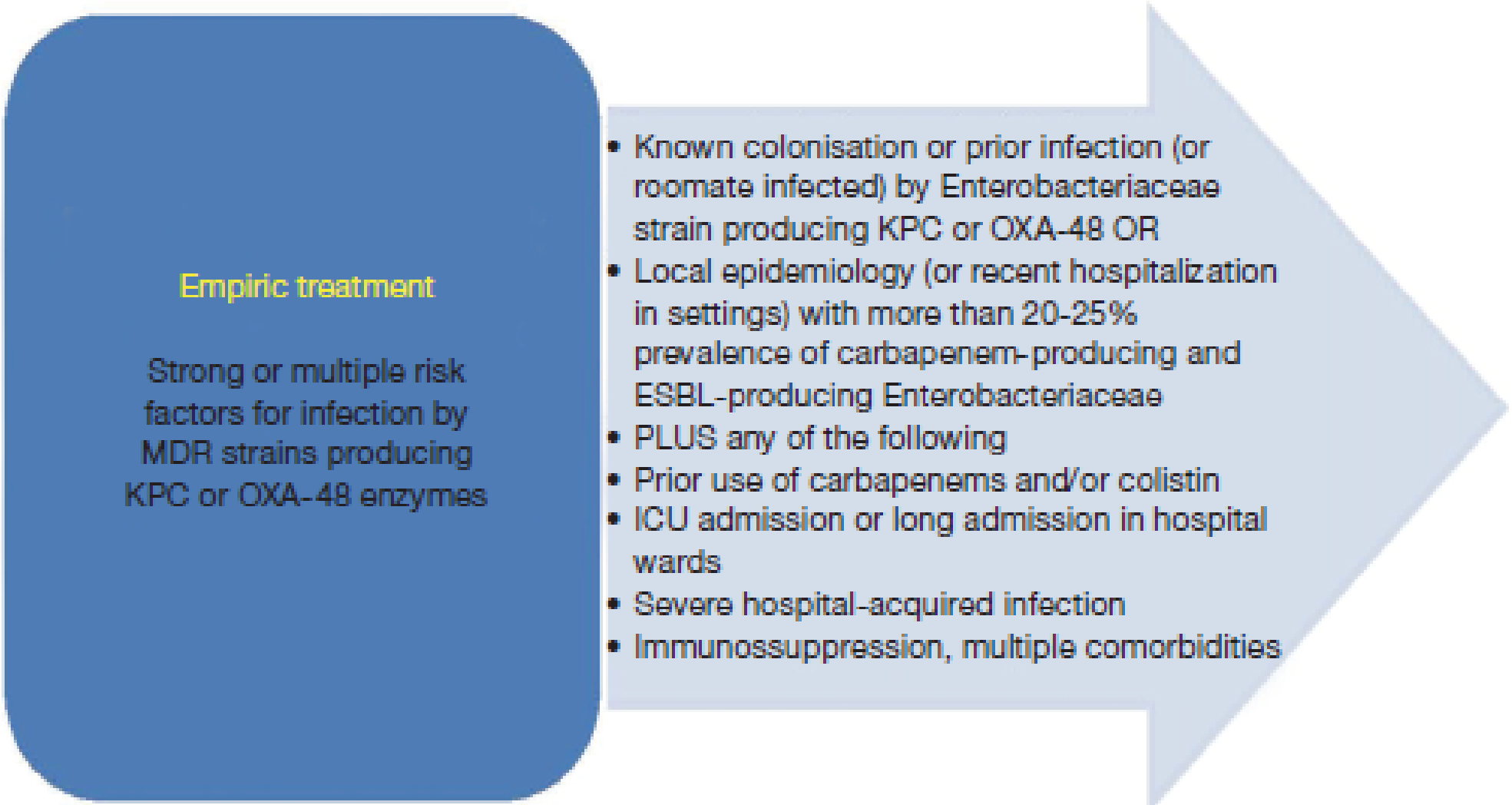
The Greek CAZ-AVI Registry (Φεβρουάριος 2018 – Μάρτιος 2019)
Οργάνωση: Ελληνική Εταιρεία Χημειοθεραπείας

*** Με ολοκλήρωση καταγραφής**

- **Αριθμός ασθενών: 110* (σύνολο 160)**
- **Βακτηριαιμίες: 75 (70%)**
- **VAP: 20 (19%)**
- **Μονοθεραπεία: 32%**
- **Θνητότητα: 14%**
- **Επιτυχής κλινική ανταπόκριση: 85%**
- **Ανάπτυξη αντοχής: 2.7% (3 ασθενείς)**

H Giamarellou, Personal Communication

Potential indications of ceftazidime-avibactam, as empiric treatment



Ann Transl Med 2018;6(21):423

Diazabicyclooctanones : Avibactam

- ## Aztreonam – Avibactam

ATM against MBL but not ESBL, AmpC, serine carbapenameses ➔ achievable with Avi

- A Study to Determine the Efficacy, Safety and Tolerability of Aztreonam-Avibactam (ATM-AVI) ± Metronidazole (MTZ) Versus Meropenem (MER) ± Colistin (COL) for the Treatment of Serious Infections Due to Gram Negative Bacteria. (REVISIT) -NCT03329092)

- Efficacy, Safety, and Tolerability of ATM-AVI in the Treatment of Serious Infection Due to MBL-producing Gram-negative Bacteria - NCT03580044

- ## Ceftaroline - Avibactam

CPT : fifth gen cephalosporin but not ESBL, AmpC, *Acinetobacter, Pseudomonas*

New β-lactam-β-lactamase inhibitor combinations in the clinic or in development

Combination	Company	Type of β-Lactamase Inhibitor	Development Phase	US Clinical Trial Numbers (Status)
Ceftolozane-tazobactam	Merck/Cubist Pharmaceuticals	Sulfone	FDA approved (2014)	NCT01147640 (completed); NCT01853982 (terminated); NCT02266706, NCT02070757, and NCT02387372 (recruiting); NCT02508753 (completed); NCT02421120 (recruiting); NCT02620774 (not open yet)
Ceftazidime-avibactam	AstraZeneca Pharmaceuticals, Forest-Cerexa, Actavis-Allergan	DBO	FDA approved (2014)	NCT01395420, NCT01430910, NCT01290900, NCT01644643, NCT01291602, NCT00752219, NCT00690378, NCT01599806, NCT01595438, NCT01893346, NCT01499290, NCT01500239, NCT01920399, NCT01534247, and NCT01789528 (completed); NCT01726023 (completed); and NCT01808092 (completed); NCT02475733 and NCT02497781 (recruiting)
Ceftaroline-avibactam	AstraZeneca Pharmaceuticals, Forest-Cerexa, Actavis-Allergan	DBO	Phase 2	NCT01624246, NCT01281462, NCT01290900, and NCT01789528 (completed)
Aztreonam-avibactam	AstraZeneca Pharmaceuticals, Forest-Cerexa, Actavis-Allergan	DBO	Phase 1	NCT01689207 (completed); NCT02655419 (not open yet)
Imipenem-relebactam	Merck Sharp & Dohme Corporation	DBO	Phase 2	NCT01275170 and NCT01506271 (completed); and NCT01505634 (completed); NCT02452047 and NCT02493764 (recruiting)
RG6080 (formerly OP0595)	Meiji Seika Pharma Co, Ltd, Roche, and Fedora	DBO	Phase 1	NCT02134834 (completed)
Meropenem-RPX7009	Rempex Pharmaceuticals (The Medicines Company)	Boronate	Phase 3	NCT01897779, NCT02020434, and NCT02073812 (completed); and NTC02168946 and NCT02166476 (recruiting); NCT01751269 (completed); NCT02687906 (not open yet)
Biapenem-RPX7009	Rempex Pharmaceuticals (The Medicines Company)	Boronate	Phase 1	NCT01772836 (completed)
S-649266	Shionogi	Cephalosporin	Phase 2	NCT02321800 (recruiting); NCT02714595 (not open yet)

Diazabicyclooctanones : Relebactam and OP0595 (RG6080)

- **Relebactam** + imipenem – cilastatin
- Lacks activity against MBLs and most OXAs
- Improves activity against most species of *Enterobacteriaceae* (reduces ↓ MIC x2-128) and against some imipenem-nonsusceptible *P. aeruginosa* (↓ MIC x8)
- <u>FDA approved for cUTI and cIAI</u>

Infect Dis Clin North Am. 2016 June ; 30(2): 441–464

New β-lactam-β-lactamase inhibitor combinations in the clinic or in development

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Ceftolozane-tazobactam	Merck/Cubist Pharmaceuticals	Sulfone	FDA approved (2014)	NCT01147640 (completed); NCT01853982 (terminated); NCT02266706, NCT02070757, and NCT02387372 (recruiting); NCT02508753 (completed); NCT02421120 (recruiting); NCT02620774 (not open yet)
Ceftazidime-avibactam	AstraZeneca Pharmaceuticals, Forest-Cereva, Actavis-Allergan	DBO	FDA approved (2014)	NCT01395420, NCT01430910, NCT01290900, NCT01644643, NCT01291602, NCT00752219, NCT00690378, NCT01599806, NCT01595438, NCT01893346, NCT01499290, NCT01500239, NCT01920399, NCT01534247, and NCT01789528 (completed); NCT01726023 (completed); and NCT01808092 (completed); NCT02475733 and NCT02497781 (recruiting)
Ceftaroline-avibactam	AstraZeneca Pharmaceuticals, Forest-Cereva, Actavis-Allergan	DBO	Phase 2	NCT01624246, NCT01281462, NCT01290900, and NCT01789528 (completed)
Aztreonam-avibactam	AstraZeneca Pharmaceuticals, Forest-Cereva, Actavis-Allergan	DBO	Phase 1	NCT01689207 (completed); NCT02655419 (not open yet)
Imipenem-relebactam	Merck Sharp & Dohme Corporation	DBO	Phase 2	NCT01275170 and NCT01506271 (completed); and NCT01505634 (completed); NCT02452047 and NCT02493764 (recruiting)
RG6080 (formerly OP0595)	Meiji Seika Pharma Co, Ltd, Roche, and Fedora	DBO	Phase 1	NCT02134834 (completed)
Meropenem-RPX7009	Rempex Pharmaceuticals (The Medicines Company)	Boronate	Phase 3	NCT01897779, NCT02020434, and NCT02073812 (completed); and NTC02168946 and NCT02166476 (recruiting); NCT01751269 (completed); NCT02687906 (not open yet)
Biapenem-RPX7009	Rempex Pharmaceuticals (The Medicines Company)	Boronate	Phase 1	NCT01772836 (completed)
S-649266	Shionogi	Cephalosporin	Phase 2	NCT02321800 (recruiting); NCT02714595 (not open yet)

Diazabicyclooctanones : Relebactam and OP0595 (RG6080)

- **RG6080** : inhibits Class A and C, but also PBP-2 ➔ does not need a β-lactam partner for antimicrobial activity

Infect Dis Clin North Am. 2016 June ; 30(2): 441–464

Promising new β-lactams or β-lactamase inhibitors in preclinical development

β-Lactamase Inhibitor Name	Partner β-Lactam	Company	Type of β-Lactamase Inhibitor
FPI-1465	Aztreonam or ceftazidime	Fedora	DBO (also inhibits PBP activity)
WCK 4234	Meropenem	Wockhardt, Ltd	DBO
WO2013/030735	Not necessary?	Wockhardt, Ltd	DBO (also inhibits PBP activity)
WCK 5153	Not necessary?	Wockhardt, Ltd	DBO (also inhibits PBP activity)
Benzo(b)thiophene-2-boronic acid	Ceftazidime	Tharabor and Regents of the University of California	Boronate
Sulfonamide boronates (CR161, compound 4, and compound 9)	Ceftazidime or cefotaxime	Tharabor and Regents of the University of California	Boronate
S02030	Cefepime	Case Western Reserve University and Universita degli Studi di Modena e Reggio Emilia	Boronate
3,4-dihydro-2H-benzo[e][1,2] oxaborinine-8-carboxylic acids	Ceftazidime or meropenem	VenatoRx Pharmaceuticals	Boronate
α-Aminoboronic acids	Ceftazidime	VenatoRx Pharmaceuticals	Boronate
3,4-Dihydro-2H-benzo[e][1,2] oxaborinine-8-carboxylic acids	Carbapenem	Rempex Pharmaceuticals (The Medicines Company)	Boronate
AA101	Cefepime	Allecra Therapeutics	Sulfone
Sulfone derivatives	Meropenem or imipenem	Orchid Pharmaceuticals	Sulfone
Sulfone derivatives	Meropenem or imipenem	Dr John D. Buynak (Southern Methodist University)	Sulfone
Clavam derivatives	Ceftazidime	Nabriva Therapeutics	Clavam
MG96077	Imipenem	Mirati Therapeutics	Phosphonate
BAL30072	Meropenem or no β-lactam required	Basilea Pharmaceuticals	Siderophore monobactam
BAL30376 (BAL19764, BAL29880, & clavulanic acid)	No β-lactam required	Basilea Pharmaceuticals	Siderophore monobactam, bridged monobactam, and a clavam
MK-8712	Imipenem	Merck Sharp & Dohme Corporation	Bridged monobactam
Siderophore monobactams	Aztreonam or meropenem	Pfizer	Siderophore monobactam
Syn2190	Ceftazidime	Taiho Pharmaceuticals Co	Siderophore monobactam
3′-Thiobenzoyl cephalosporins	Meropenem	University of Waterloo, Wilfrid Laurier University	β-Lactam
FSI-1686 and FSI-1671	No β-lactam required	FOB Synthesis Inc	β-Lactam
BTZs	Imipenem	Universidad de la Republica, Montevideo, Uruguay	Bisthiazolidine
ME1071	Ceftazidime or biapenem	Meiji Seika Kaisha Ltd	Malaic acid derivative

Diazabicyclooctanones in preclinical - development

- **Boronic acid (Vaborbactam)**

- Main role: treatment of KPC-producing *Enterobaceriaceae.*

- Reduced MICs

- Did not potentiate the activity of carbapenems against *P.aeruginosa* and *A.baumanii*

- **Meropenem/Vaborbactam** approved for UTI (not active against class B or D carbapenemases (ie, metallo-beta-lactamases and OXA-type enzymes)

Infect Dis Clin North Am. 2016 June ; 30(2): 441–464

Promising new β-lactams or β-lactamase inhibitors in preclinical development

β-Lactamase Inhibitor Name	Partner β-Lactam	Company	Type of β-Lactamase Inhibitor
FPI-1465	Aztreonam or ceftazidime	Fedora	DBO (also inhibits PBP activity)
WCK 4234	Meropenem	Wockhardt, Ltd	DBO
WO2013/030735	Not necessary?	Wockhardt, Ltd	DBO (also inhibits PBP activity)
WCK 5153	Not necessary?	Wockhardt, Ltd	DBO (also inhibits PBP activity)
Benzo(b)thiophene-2-boronic acid	Ceftazidime	Tharabor and Regents of the University of California	Boronate
Sulfonamide boronates (CR161, compound 4, and compound 9)	Ceftazidime or cefotaxime	Tharabor and Regents of the University of California	Boronate
S02030	Cefepime	Case Western Reserve University and Universita degli Studi di Modena e Reggio Emilia	Boronate
3,4-dihydro-2H-benzo[e][1,2] oxaborinine-8-carboxylic acids	Ceftazidime or meropenem	VenatoRx Pharmaceuticals	Boronate
α-Aminoboronic acids	Ceftazidime	VenatoRx Pharmaceuticals	Boronate
3,4-Dihydro-2H-benzo[e][1,2] oxaborinine-8-carboxylic acids	Carbapenem	Rempex Pharmaceuticals (The Medicines Company)	Boronate
AA101	Cefepime	Allecra Therapeutics	Sulfone
Sulfone derivatives	Meropenem or imipenem	Orchid Pharmaceuticals	Sulfone
Sulfone derivatives	Meropenem or imipenem	Dr John D. Buynak (Southern Methodist University)	Sulfone
Clavam derivatives	Ceftazidime	Nabriva Therapeutics	Clavam
MG96077	Imipenem	Mirati Therapeutics	Phosphonate
BAL30072	Meropenem or no β-lactam required	Basilea Pharmaceuticals	Siderophore monobactam
BAL30376 (BAL19764, BAL29880, & clavulanic acid)	No β-lactam required	Basilea Pharmaceuticals	Siderophore monobactam, bridged monobactam, and a clavam
MK-8712	Imipenem	Merck Sharp & Dohme Corporation	Bridged monobactam
Siderophore monobactams	Aztreonam or meropenem	Pfizer	Siderophore monobactam
Syn2190	Ceftazidime	Taiho Pharmaceuticals Co	Siderophore monobactam
3′-Thiobenzoyl cephalosporins	Meropenem	University of Waterloo, Wilfrid Laurier University	β-Lactam
FSI-1686 and FSI-1671	No β-lactam required	FOB Synthesis Inc	β-Lactam
BTZs	Imipenem	Universidad de la Republica, Montevideo, Uruguay	Bisthiazolidine
ME1071	Ceftazidime or biapenem	Meiji Seika Kaisha Ltd	Maleic acid derivative

Diazabicyclooctanones in preclinical - development

- Sulfons
- Clavams
- Phosphonates
- Ciderophore cephalosporin, Monobactams, Novel 3’ Thiobenzoyl cephalosporins, novel carbapenems (as evaders of β-lactamases)
- MBL inhibitors : Bisthiazolidines
- Maleic acid derivatives

Infect Dis Clin North Am. 2016 June ; 30(2): 441–464

TO CONCLUDE…IN PRACTICE

Table 1: Classification of β-lactamase inhibitors and its properties

Clavulanic acid/ sulbactam/tazobactam	DBOs (DBO - Second generation of - βLI)				Vaborbactam
First generation BLI	Avibactam (First generation DBO)	Relebactam (First gen DBO)	Zidebactam (Second generation DBO)	Nacubactam (Second gen DBO)	New generation βLI
β-lactam β-lactamase inhibitor	Non-β-lactam/β-lactamase inhibitor				
Derived from β-lactam scaffolds	Derived from DBO heterocyclic core structure				Boronic acid derivative
-	Irreversible binding				-
Cover only the class A β-lactamases (inactive against class C/D)	Potent inhibitor of class A, C, D (OXA-48 producers, KPC)		Increased activity to class C β-lactamase than avibactam and relebactam		Potent inhibitor of class A (KPC) and C β-lactamase
Only sulbactam has intrinsic activity against *A. baumannii*	No useful intrinsic antibacterial activity		Intrinsic activity against *P. aeruginosa* and *A. baumannii*		-
-	Not effective against *Acinetobacter sp.*, producing OXA type carbapenemases		Potent in activators of *P. aeruginosa* PBP2 and *A. baumannii* PBP2 (unique about 2nd gen DBO)		-
-	No activity against MBL producers		-		-

DBOs: Diazabicyclooctanes, βLI: β-lactamase inhibitors, *P. aeruginosa*: *Pseudomonas aeruginosa*, *A. baumannii*: *Acinetobacter baumannii*, MBL: Metallo β-lactamase

Clin Microbiol Rev 2010;23:160-201
Cold Spring Harb Perspect Med 2016;6.

TO CONCLUDE…IN PRACTICE

New β-lactam/β-lactamase inhibitor and its spectrum of activity against multi-drug resistant *Enterobacteriaceae*, *Pseudomonas spp*. and multi-drug resistant *Acinetobacter spp*.

βL/βLI	*Enterobacteriaceae*										*Pseudomonas spp.*					*Acinetobacter spp.*
	ESBL	AmpC	ESBL + AmpC	bla_{KPC}	bla_{NDM}	bla_{OXA-48}	bla_{KPC} + ESBL + AmpC	MBL + ESBL + AmpC	bla_{OXA-48} + ESBL	ompK35/ ompK36 mutant*	ESBL	AmpC	Efflux	oprD mutant	bla_{VIM}/ bla_{NDM}	
Ceftazidime/avibactam	✓	✓	✓	✓[a]	×	✓	✓	×	✓	NA	✓	✓	±	NA	×	×
Ceftolozane/tazobactam	✓	±[b]	±	×	×	×	×	×	×	NA	✓	✓	✓	✓	×	×
Aztreonam/avibactam	✓	✓	✓	✓	✓	✓	✓	✓	✓	NA	✓	±	×	NA	✓	×
Imipenem/relebactam	✓	✓	✓	✓[c]	×	×	✓	×	×	×	✓	✓	✓	✓	×	±
Meropenem/Vaborbactam	✓	✓	✓	✓[d]	×	×	✓	×	×	×	✓	✓	×	×	×	×

✓: Active, ×: Not active, ±: May or may not be, [a]Ceftazidime/avibactam not effective against bla_{KPC-3} and bla_{KPC} producing ST258, [b]Ceftolozane/tazobactam is not active against de-repressed AmpC producing *Enterobacter spp*, but active against Chromosomal AmpC, [c]Imipenem-relebactam active against bla_{KPC}, except $bla_{KPC-2,3}$ variant, dMeropenem-Vaborbactam active against $bla_{KPC-2,3}$. Except KPC producing *K. pneumoniae* ST11, *For *K.pneumoniae*. MDR: Multi-drug resistant, βLI: β-lactamase inhibitor, NA: Not available, βL: β-lactam, ESBL: Extended spectrum β-lactamases

TO CONCLUDE…IN PRACTICE

Clinical interpretative criteria of newer β-lactam/β-lactamase inhibitors from Clinical and Laboratory Standards Institute guideline 2018

	Ceftazidime/avibactam	Ceftolozane/tazobactam
Disc diffusion		
Enterobacteriaceae	≥21/≤20 mm (S/R)	≥21/18-20/≤17 mm (S/I/R)
Pseudomonas spp.	≥21/≤20 mm (S/R)	≥21/17-20/≤16 mm (S/I/R)
MIC		
Enterobacteriaceae	≤8/4/≥16/4 μg/ml (S/R)	≤2/4/4/4/≥16/4 μg/ml (S/I/R)
Pseudomonas spp.	≤8/4/≥16/4 μg/ml (S/R)	≤4/4/8/4/≥16/4 μg/ml (S/I/R)

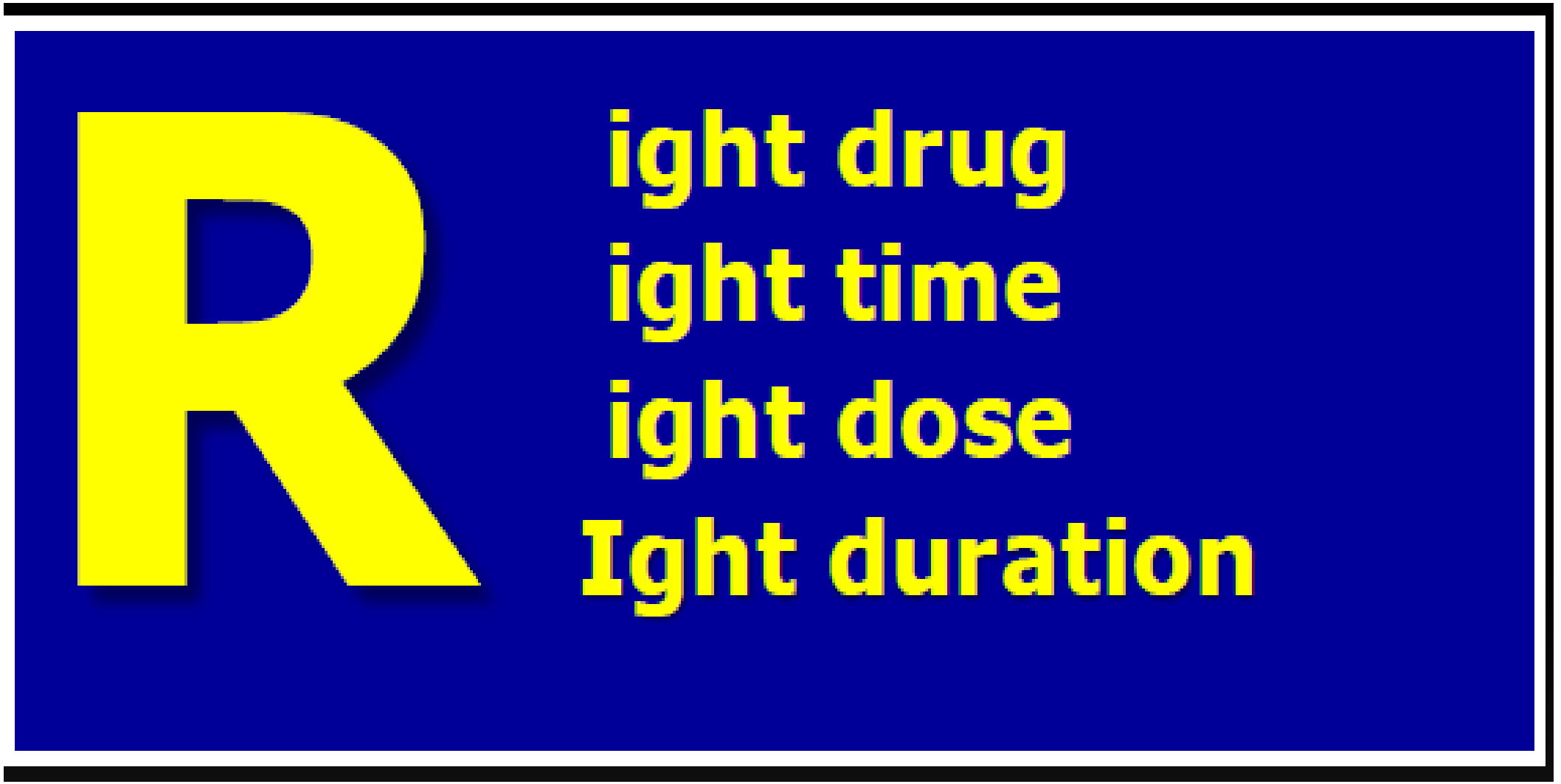
MIC: Minimum inhibitory concentration

Αντιβιοτικά που αναμένουμε για gram (-)

	ESBL	CRE	MDR *P.aeruginosa*	MDR Acinetobacter
Cefiderocol	YES	KPC and NDM-1	YES	YES
Ceftolozane- Tazobactam	YES	NO	YES	NO
Ceftazidime-avibactam	YES	KPCs and OXA-48 (not active against MBLs)	YES	NO
Ceftaroline fosamil-avibactam	YES	KPCs and OXA-48 (not active against MBLs)	NO	NO
Aztreonam-avibactam	YES	MBLs such as NDM	YES	NO
Meropenem/vaborbactam	YES	KPCs	NO^	NO
Imipenem/cilastatin-relebactam	YES	KPCs and OXA-48 (not active against MBLs)	NO^	NO

BE SPARING but NOT STINGY, when other options available to keep it useful !!!

DE-ESCALATE



Thank you for your patience !