



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

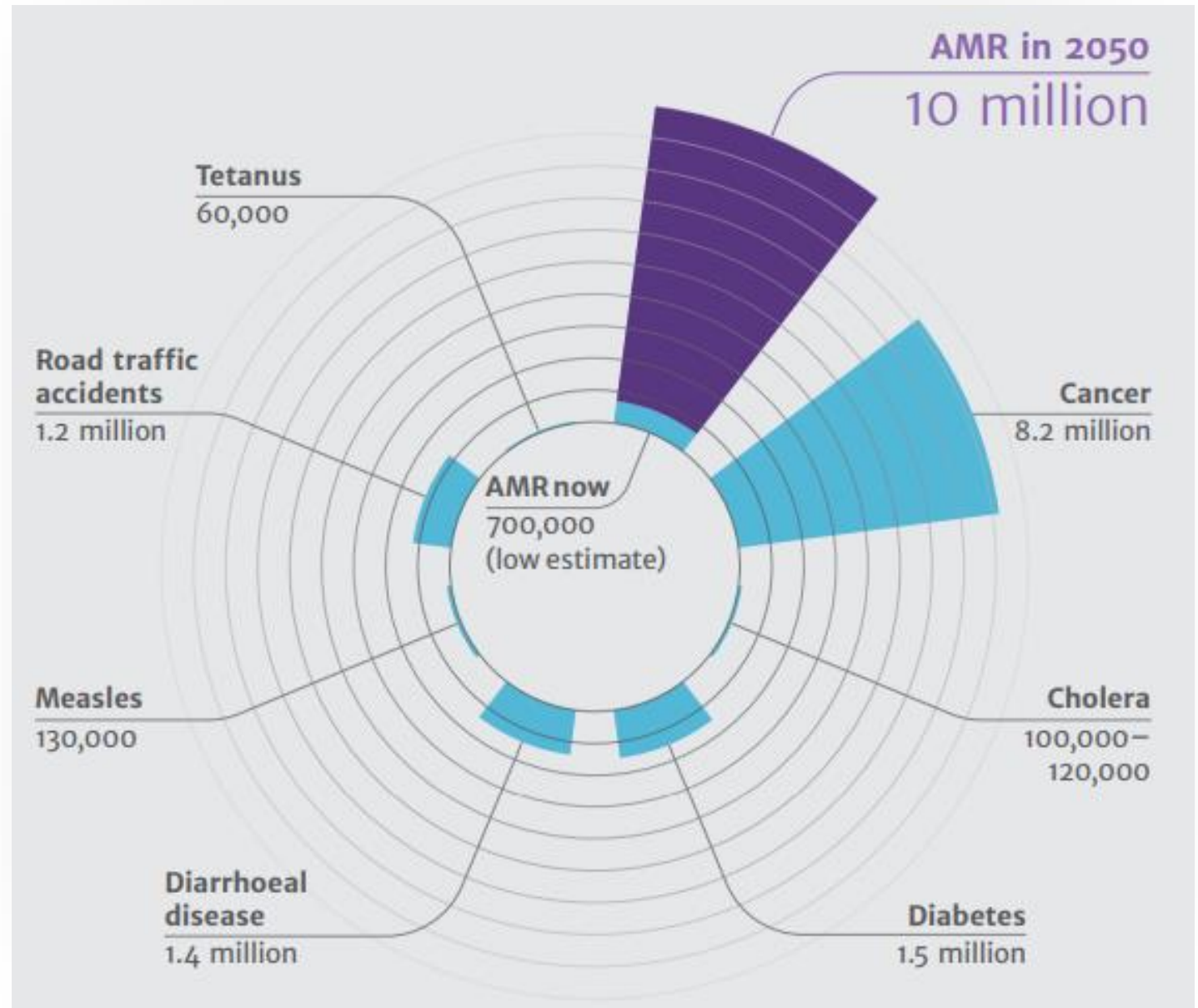
Καρολίνα Ακινόσογλου

Παθολόγος – Λοιμωξιολογος

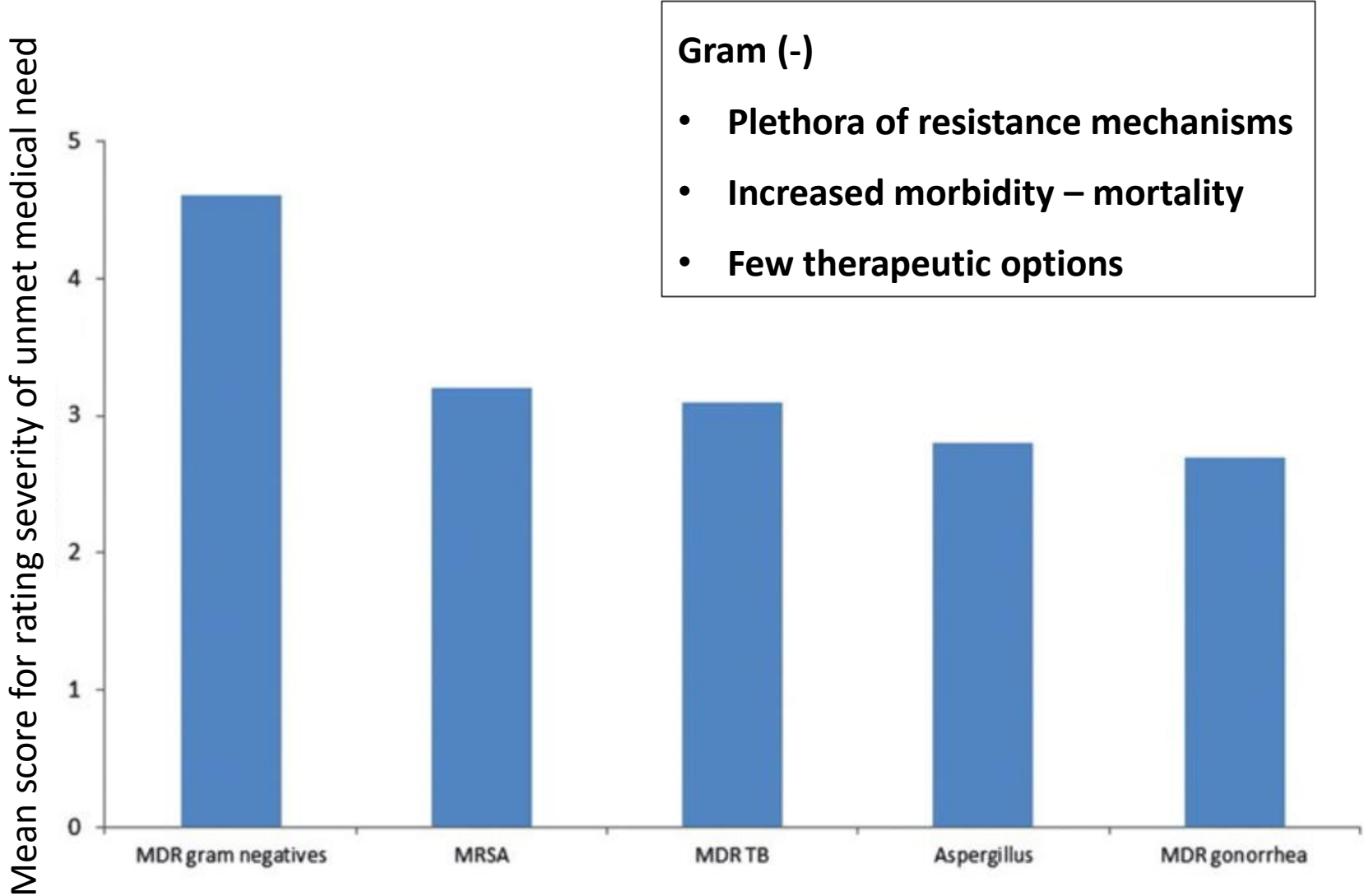
Επικουρη Καθηγητρια Παθολογιας

Πανεπιστημίου Πατρών

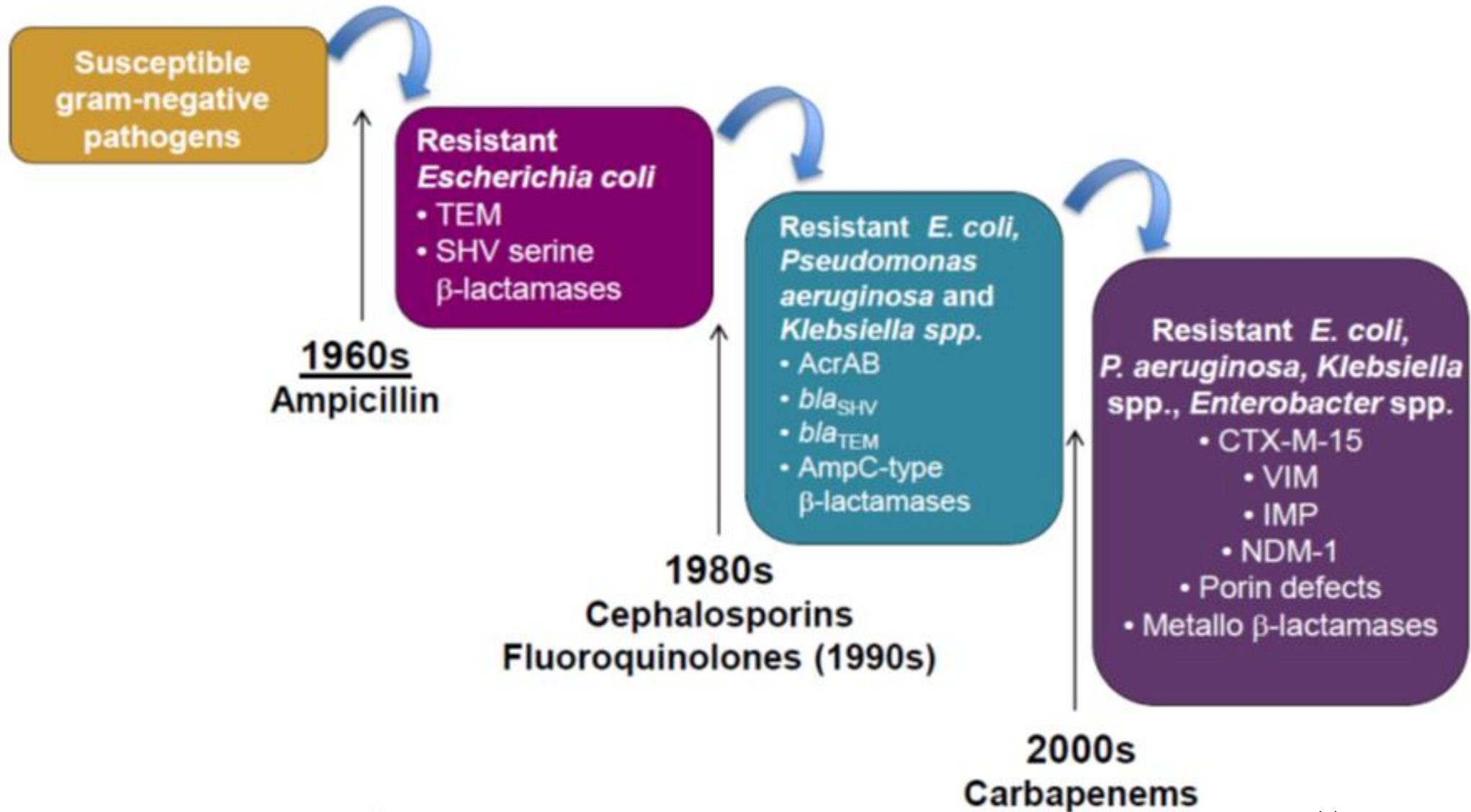
Deaths attributable to antimicrobial resistance every year compared to other causes of death



Unmet Medical Need in Infectious Diseases



Microbial Resistance in Gram (-)



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)**.

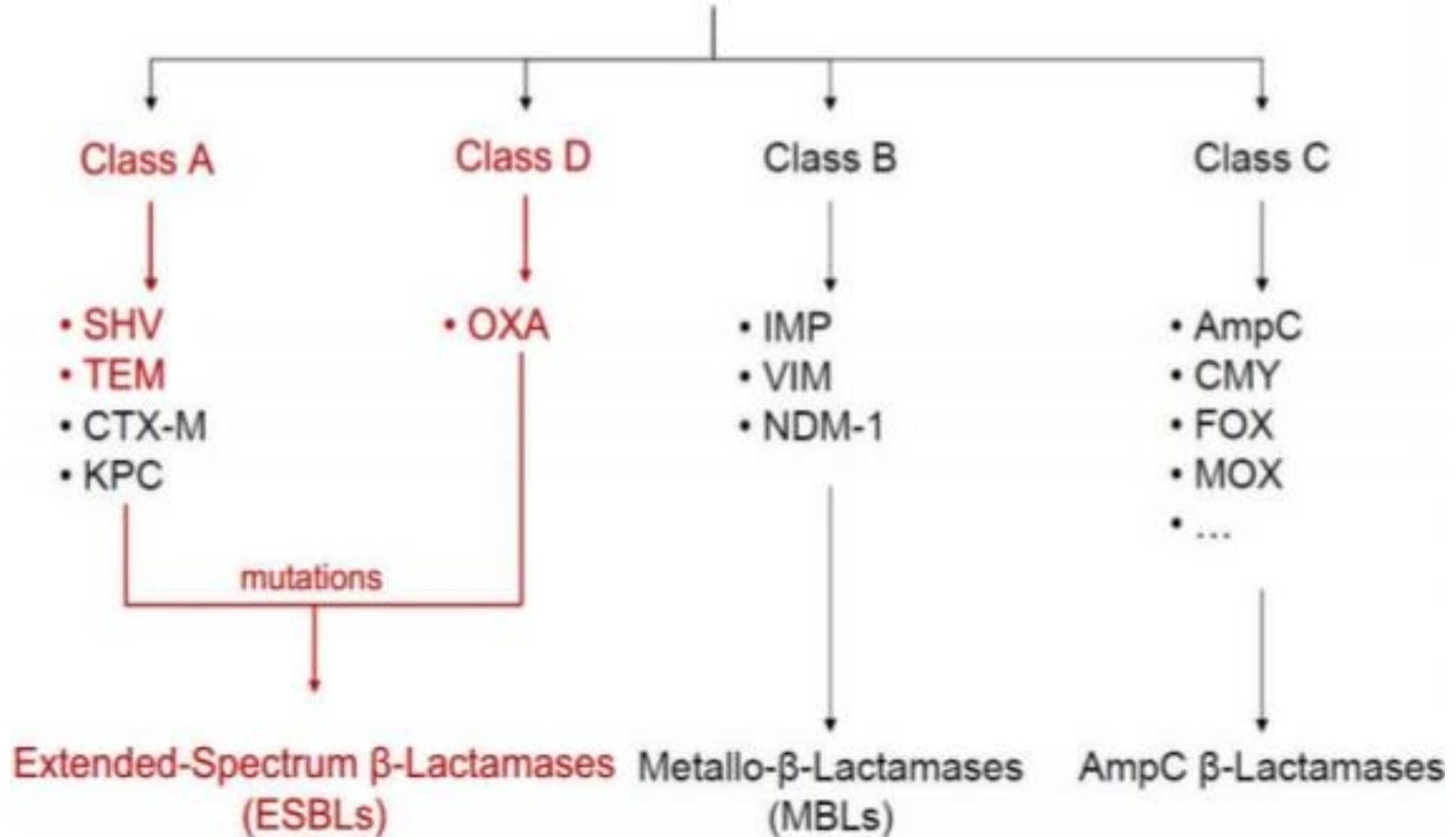


❑ Extended-spectrum beta-lactamases (ESBL) are enzymes that confer resistance to most beta-lactam antibiotics: **penicillins, cephalosporins, and the monobactam aztreonam**

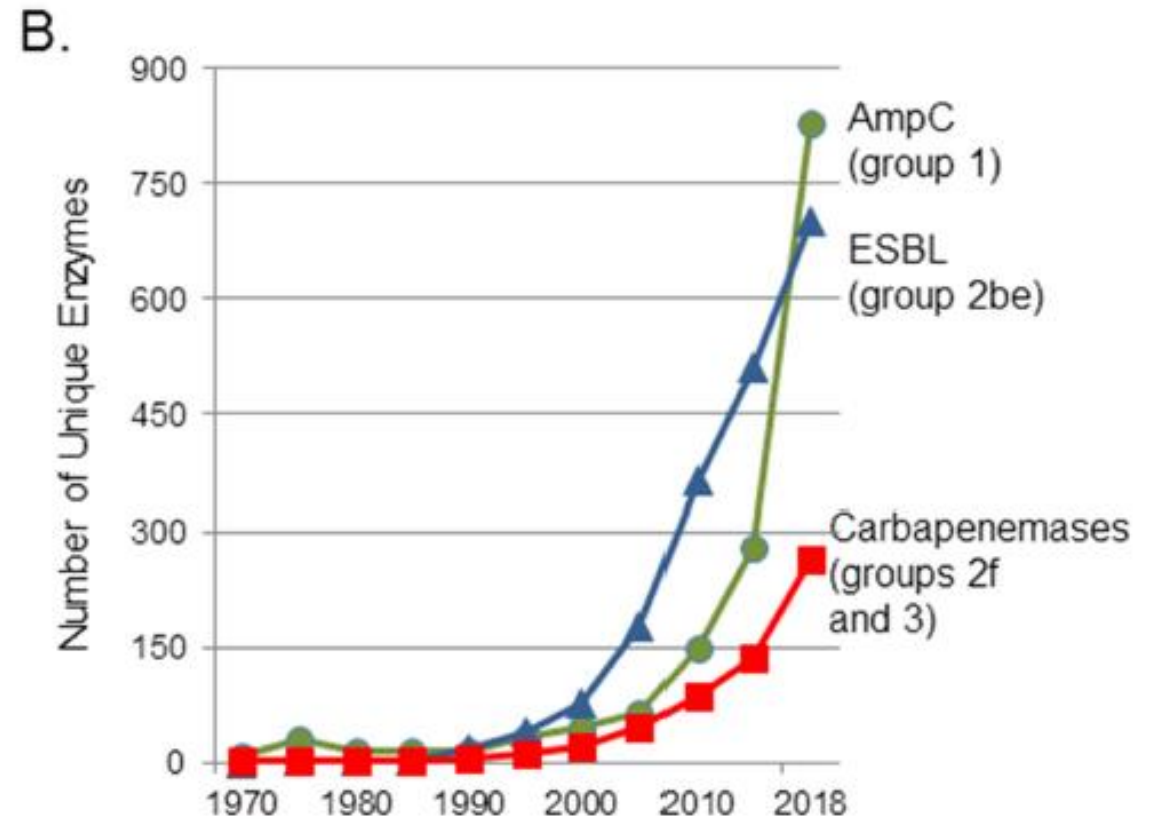
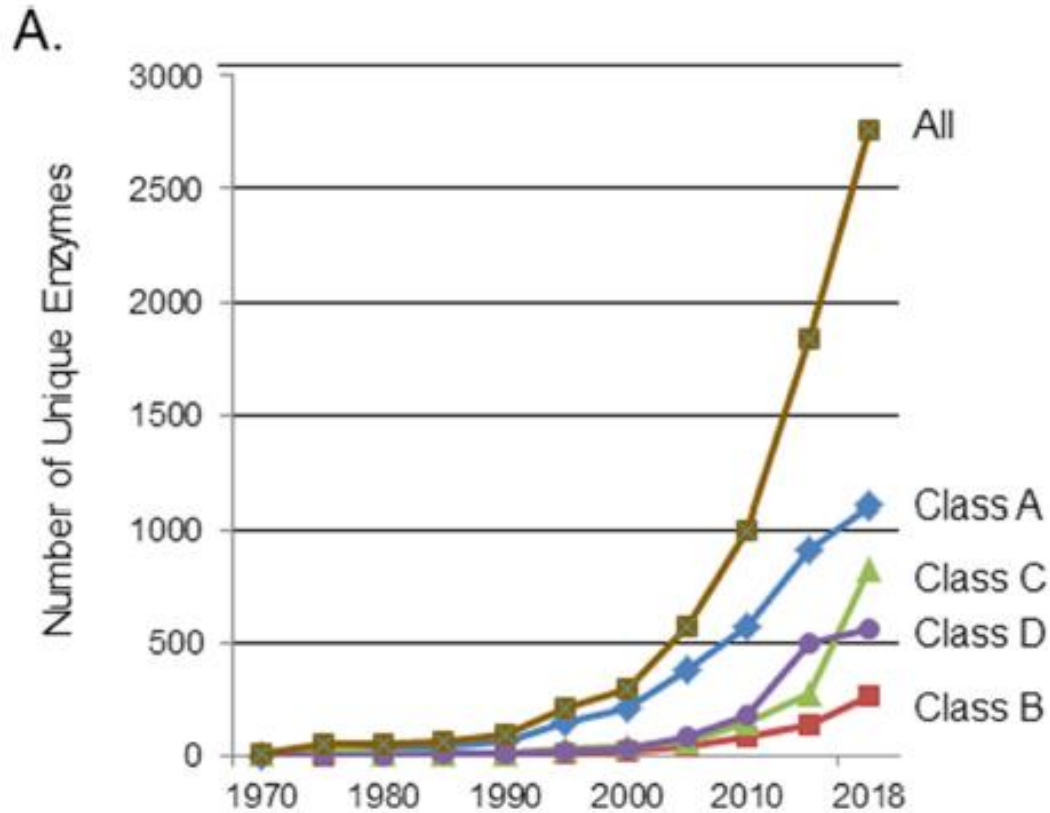
❑ **Frequently co-resistant to aminoglycosides, quinolones and co-trimoxazole.** Resistant **genes coding** for ESBLs and, for example, aminoglycoside-modifying or quinolone-modifying enzymes (AMEs) often **reside within the same conjugative plasmids**

❑ **Quinolones co-resistance 40%**

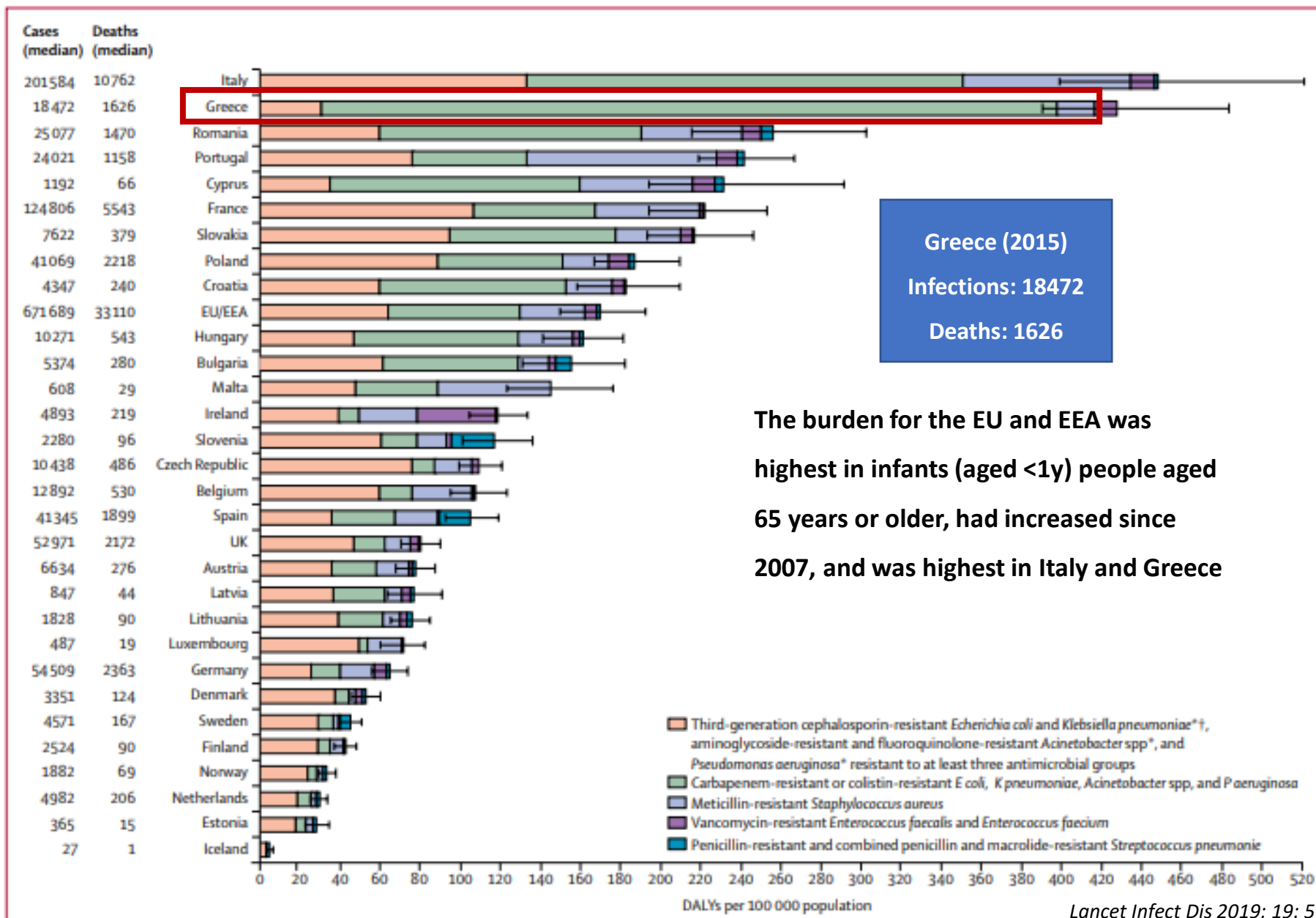
β -lactamases Functional Classification



Increase in numbers of unique, naturally occurring -lactamases



European Antimicrobial Resistance Surveillance Network 2017



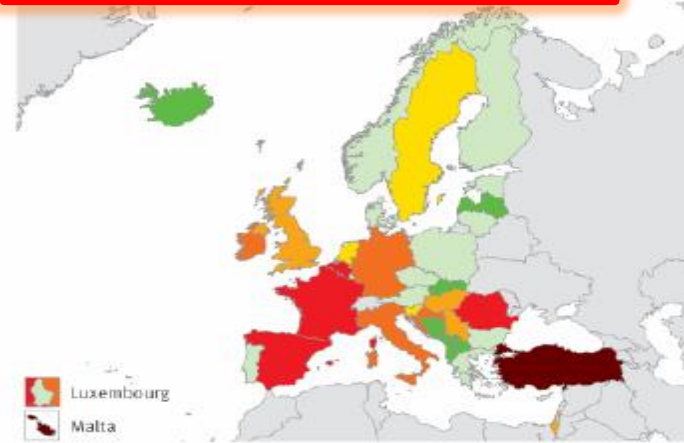
Geographic distribution of carbapenemase-producing Enterobacteriaceae by resistance mechanism

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

A. KPC: Endemic situation



B. OXA-48: Sporadic occurrence



C. NDM: Regional spread

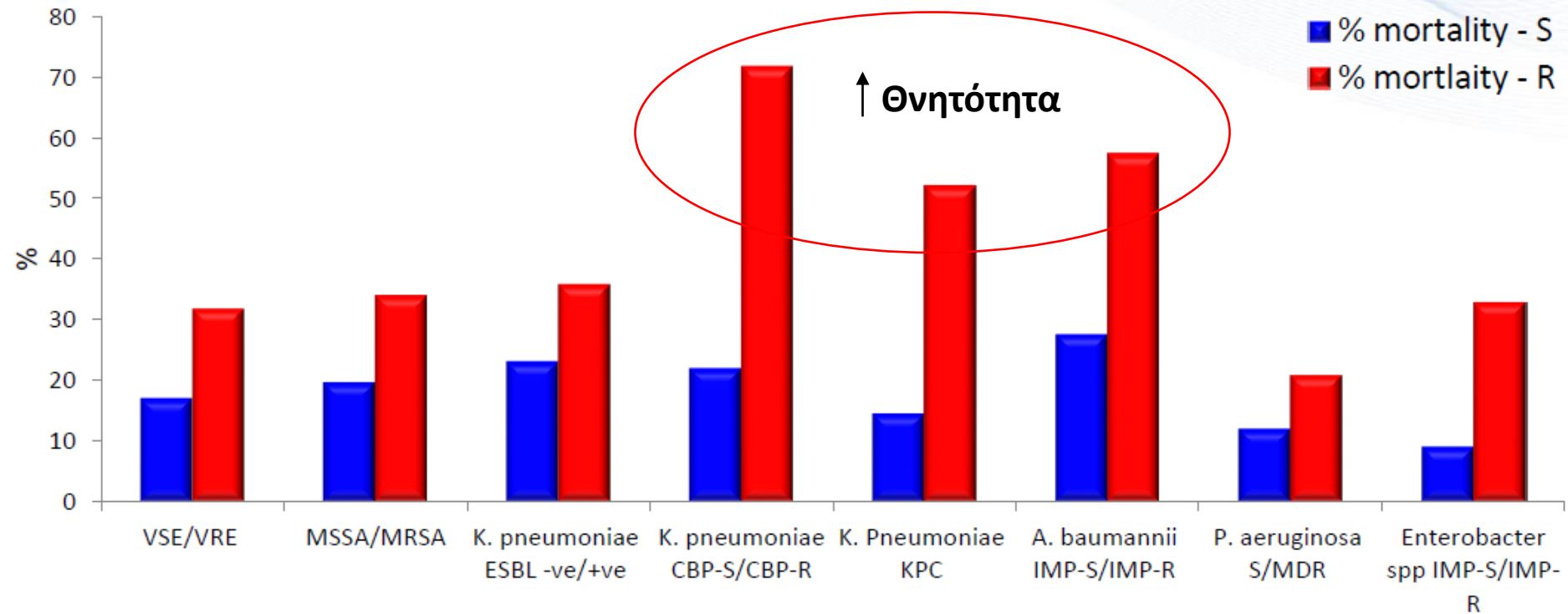


B. VIM: Endemic situation



Ανθεκτικά στις καρβαπενέμες εντεροβακτηριακά και θνητότητα

“ESKAPE” Pathogens & Outcome



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

Cumulative Comparative Resistance Rates to Carbapenems

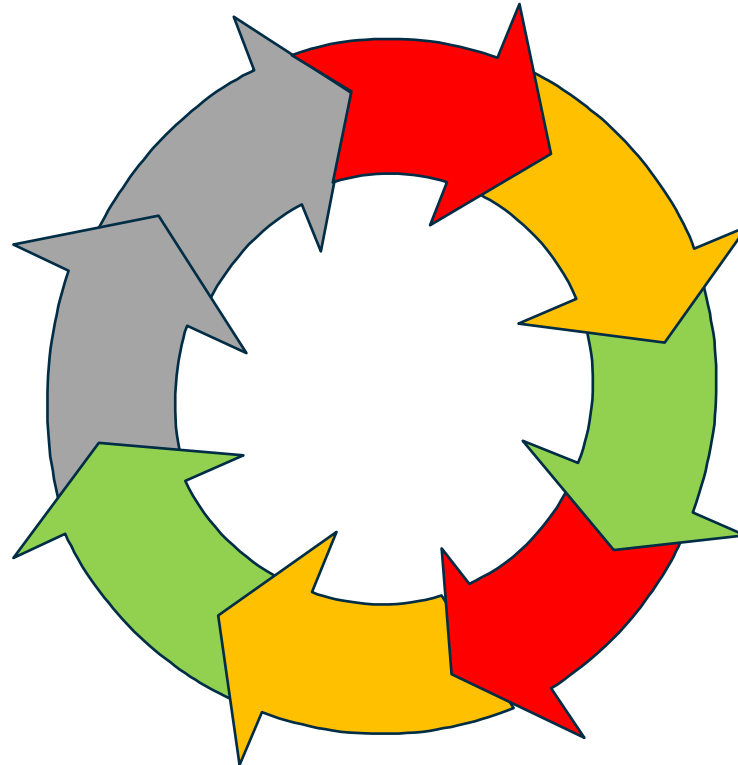
Jan – Jun 2016 vs Jul-Dec 2020, WHONET Greece

Isolated Bacteria in Blood Cultures	Medical Wards		Surgical Wards		ICU	
	2016	2020	2016	2020	2016	2020
<i>Klebsiella pneumoniae</i>	53%	43%	65%	43%	88%	76%
<i>Acinetobacter baumannii</i>	88%	94%	94%	93%	99%	98%
<i>Pseudomonas aeruginosa</i>	29%	34%	55%	23%	44%	45%

Φαύλος Κύκλος χρήσης Καρβαπενεμών

Αυξημένα ανθεκτικά στις καρβαπενέμες στελέχη

Διασταυρούμενη
μετάδοση
+
εξάπλωση της αντοχής
(ESBLs)



Pseudomonas aeruginosa

Acinetobacter

Εντεροβακτηριοειδή

Αυξημένη χρήση
καρβαπενεμών

Επιλεγμένα ανθεκτικά στις καρβαπενέμες
στελέχη

Unmet Medical Need in Infectious Diseases

WHO : List of antibiotic-resistant pathogens for which antibiotics are urgently needed¹



CRITICAL (No1 Priority)¹

- ***Acinetobacter baumannii*, Carbapenem-Resistant**
- ***Pseudomonas aeruginosa*, Carbapenem-Resistant**
- ***Enterobacteriaceae*, Carbapenem-Resistant, 3rd gen cephalosporin-Resistant**

CRO: Carbapenem-resistant organisms

ECDC 2017: Greece²

CRO

- **64.7% of *Klebsiella pneumoniae*,**
- **94.8% of *Acinetobacter baumannii***
- **39.3% of *Pseudomonas aeruginosa***

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

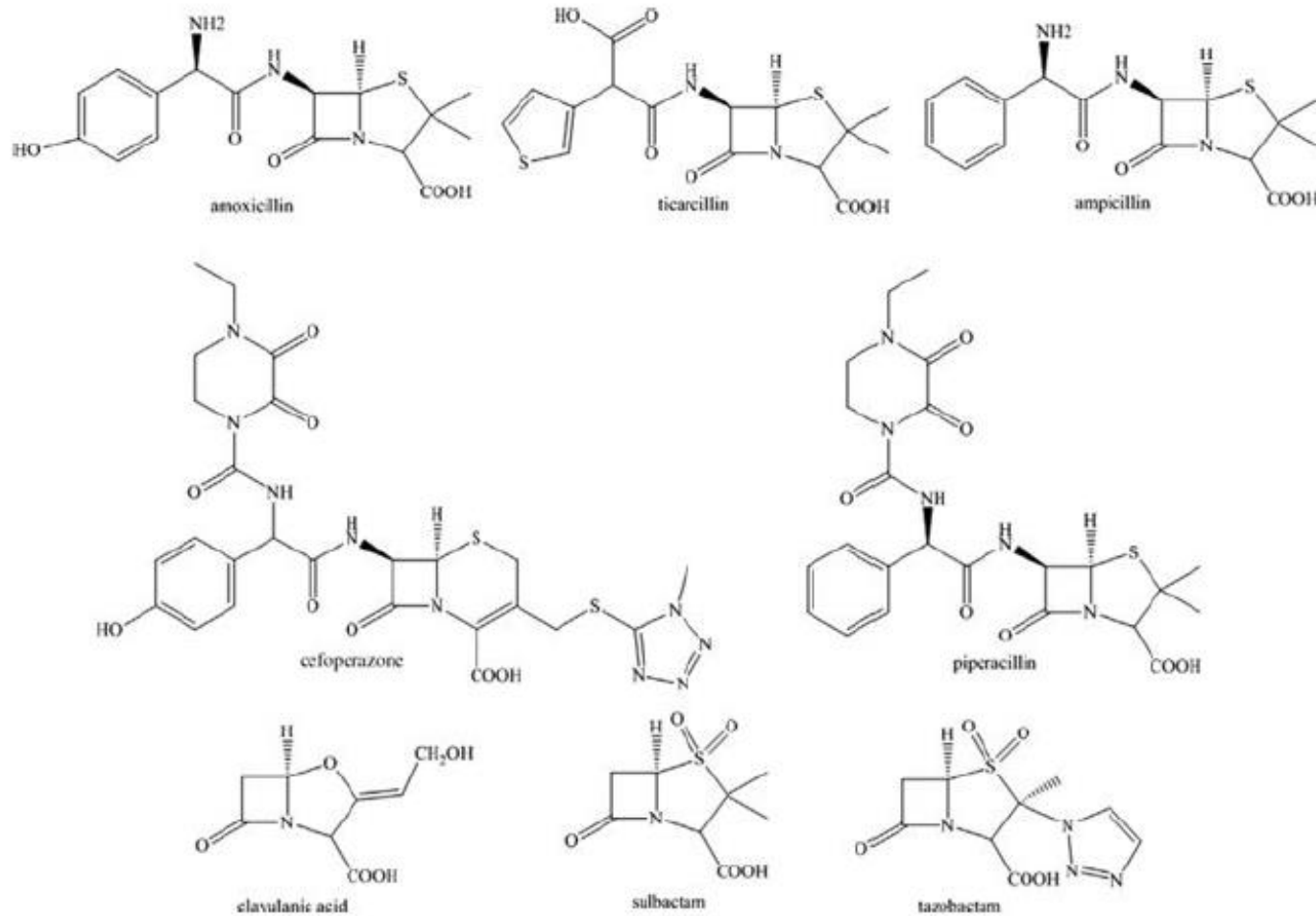
Risk factors for antimicrobial resistant Gram (-) bacteria

Baseline characteristics	Epidemiological background	Recent (<3 months) antibiotic therapy	Prior colonization	Indwelling devices
<ul style="list-style-type: none"> • Age >70 years • Diabetes mellitus • Charlson index ≥ 3 • Recurrent or obstructive UTIs • Use of corticosteroids • Immunosuppression • Trauma • Malignancy • Organ transplantation • COPD • Neutropenia • Recent surgery 	<ul style="list-style-type: none"> • Prior hospital admission (in the last 12 months) • Prolonged hospitalization • Transfer from another health-care facility • Current or prior ICU admission • Local epidemiology, outbreak • Travel from high endemic area^a 	<ul style="list-style-type: none"> • Recent aminopenicillins • Recent cephalosporins • Recent fluoroquinolones • Recent carbapenems • Recent aminoglycosides 	<ul style="list-style-type: none"> • Gut colonization with ESBL • Gut colonization with CRE • Colonization with MRSA • Colonization with <i>Acinetobacter</i> • Endotracheal colonization with <i>P. aeruginosa</i> 	<ul style="list-style-type: none"> • Urinary catheter • Gastrostomy or jejunostomy • Nasogastric tube • CVC • Mechanical ventilation • Hemodialysis

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.

^aCentral 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.

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

- Colistin
- Fosfomycin
- Aztreonam (MBL)
- Ceftolozane/tazobactam
- Ceftazidime/avibactam

Klebsiella

- Colistin
- Aminoglycosides
- Tigecycline
- Fosfomycin
- Aztreonam (MBL)
- Carbapenems (MIC<8)
- Ceftazidime/avibactam

Acinetobacter

- Colistin
- Tigecycline
- Sulbactam

Θεραπευτικές επιλογές για λοιμώξεις από ESBL / CR

• Καρβαπενέμες

Αναστολείς β-λακταμασών
(piper/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 (υψηλότερη συχνότητα σε σχέση με καρβαπενεμες)

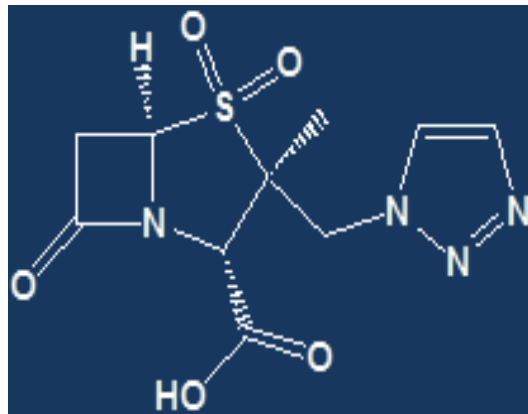
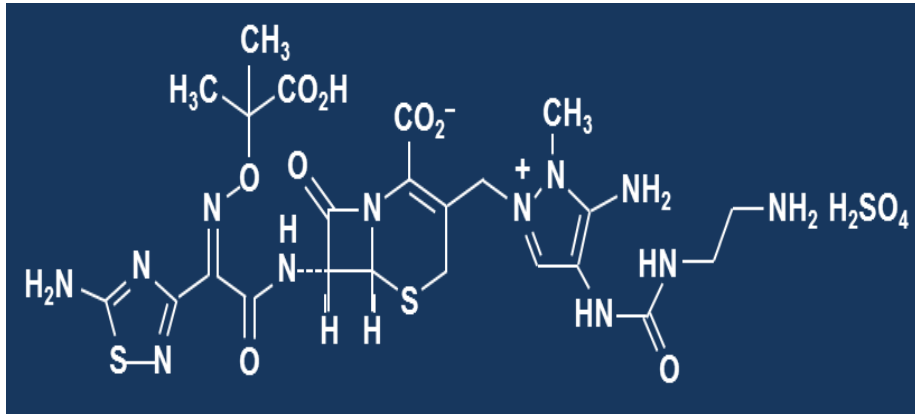
❖ **Τιγκεκυκλίνη**: σε ενδοκοιλιακές λοιμώξεις σε ασθενείς που δεν είναι βαρέως πάσχοντες (απουσία βακτηριαιμίας – όχι *Pseudomonas*, *Proteus* – black box warning)

❖ **Φωσφομυκίνη**: μόνο σε ουρολοιμώξεις σε μη βαρέως πάσχοντες ασθενείς (μονοθεραπεία αναπτυξη ανθεκτικότητας)

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

Κεφτολοζάνη/Ταζομπακτάμη

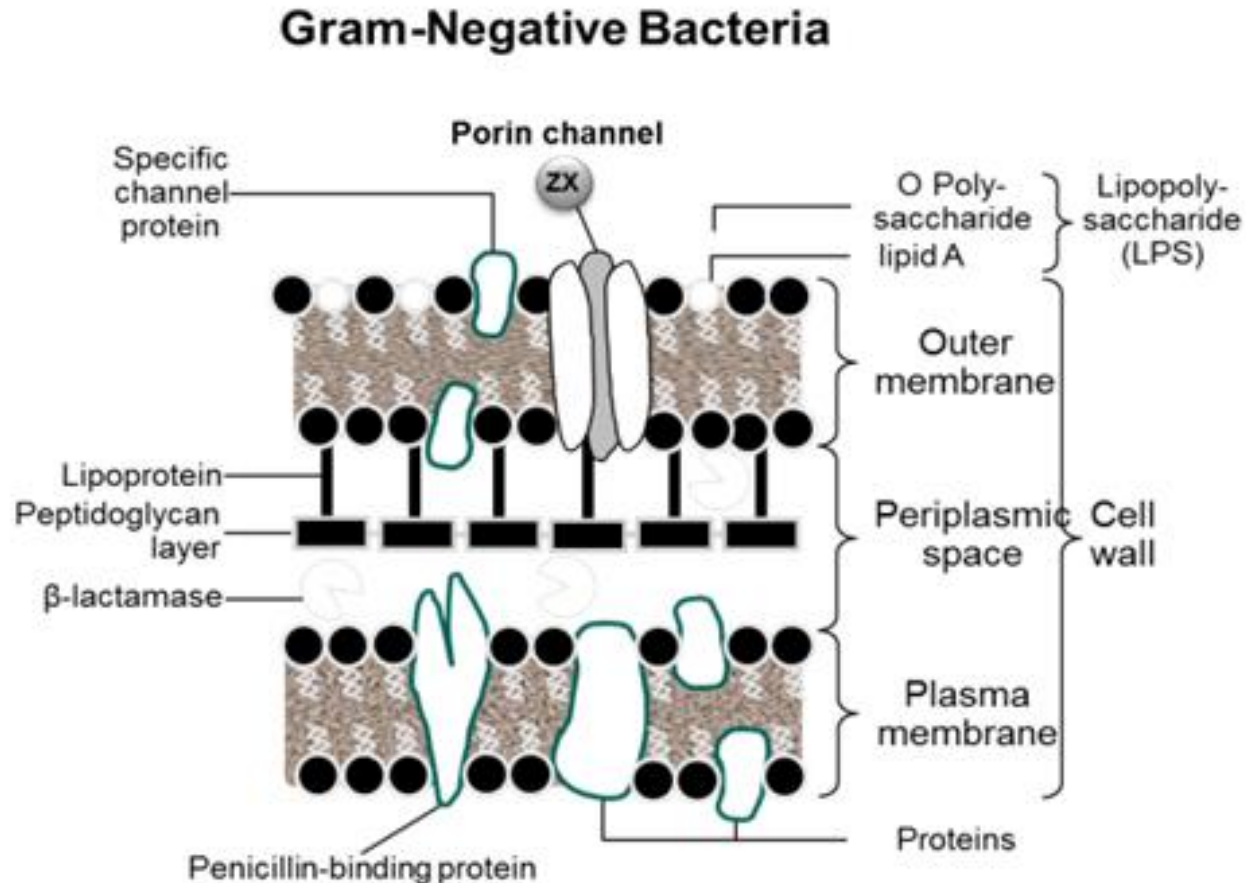
Νέα Κεφαλοσπορίνη & Παλιός Αναστολέας



Κατηγορία

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

























Μηχανισμός δράσης



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

Ευρύ φάσμα έναντι περισσότερων Enterobacteriaceae που παράγουν ESBL

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

Κεφτολοζάνη/Ταζομπακτάμη

Χαμηλή MIC₉₀ 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. Paterson², Daniel Cloutier¹, Jennifer A. Huntington¹, Benjamin Miller¹, Caleb A. Bliss¹, Judith N. Steenbergen¹, Ellie Hershberger¹, Obiamiwe Umeh¹ and Keith S. Kaye³

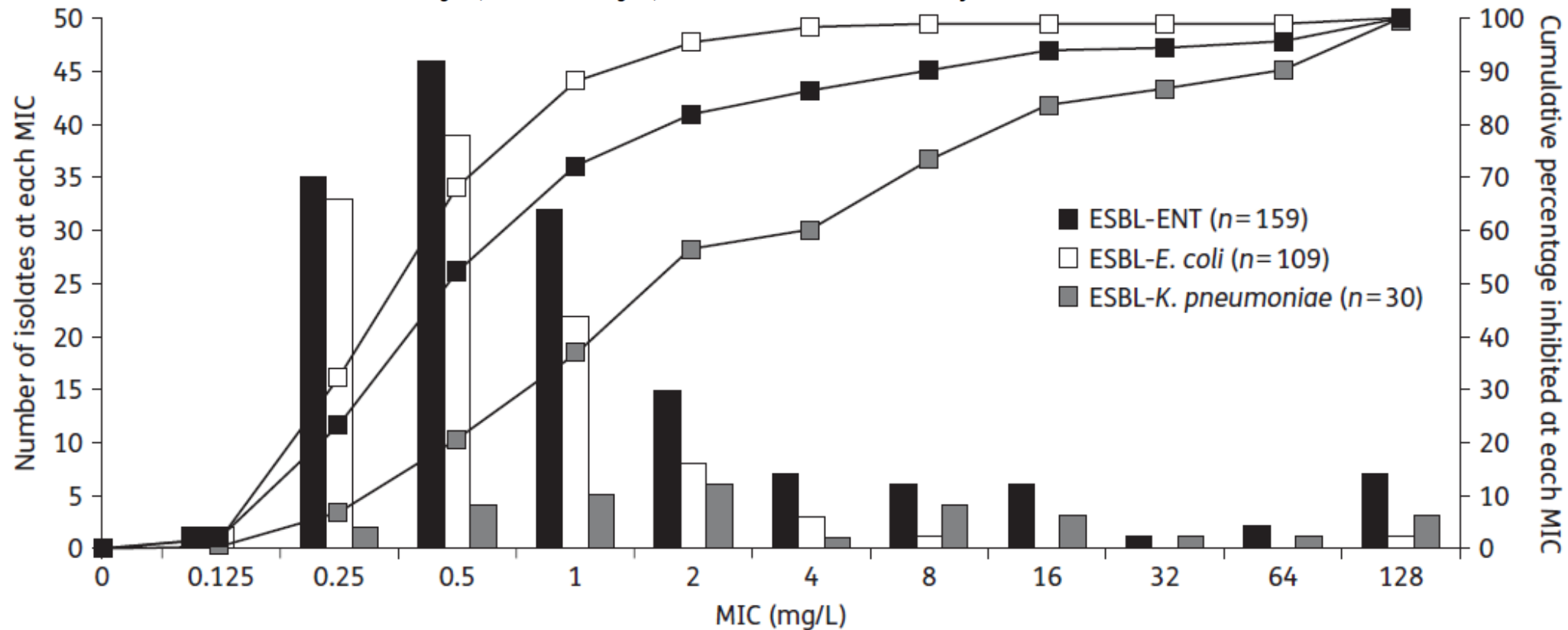


Figure 1. Distribution of ceftolozane/tazobactam MICs for ESBL-ENT (pooled ME population). Journal of Antimicrobial Chemotherapy Advance Access published October 5, 2016

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 Eckmann⁴

¹Department of Surgery, University of Cincinnati College of Medicine, Cincinnati, Ohio; ²Cubist Pharmaceuticals, Lexington, Massachusetts; ³Departments of Surgery and Medicine, Weill Cornell Medical College, New York, New York; and ⁴Department 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

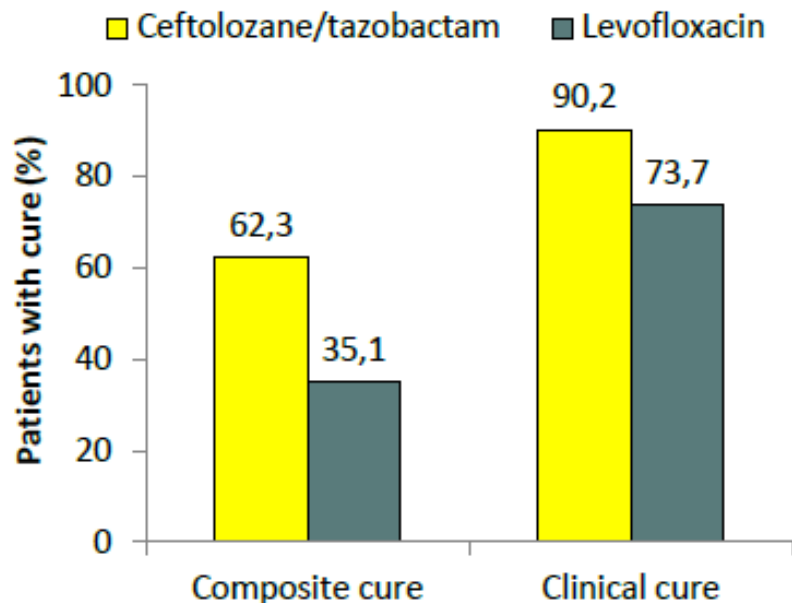
Marin H Kollef, Martin Nováček, Ůlo Kivistik, Álvaro Réa-Neto, Nobuaki Shime, Ignacio Martin-Loeches, Jean-François Timsit, Richard G Wunderink, Christopher J Bruno, Jennifer A Huntington, Gina Lin, Brian Yu, Joan R Butterson, Elizabeth G Rhee

Εγκριτικές μελέτες

ASPECT-cUTI

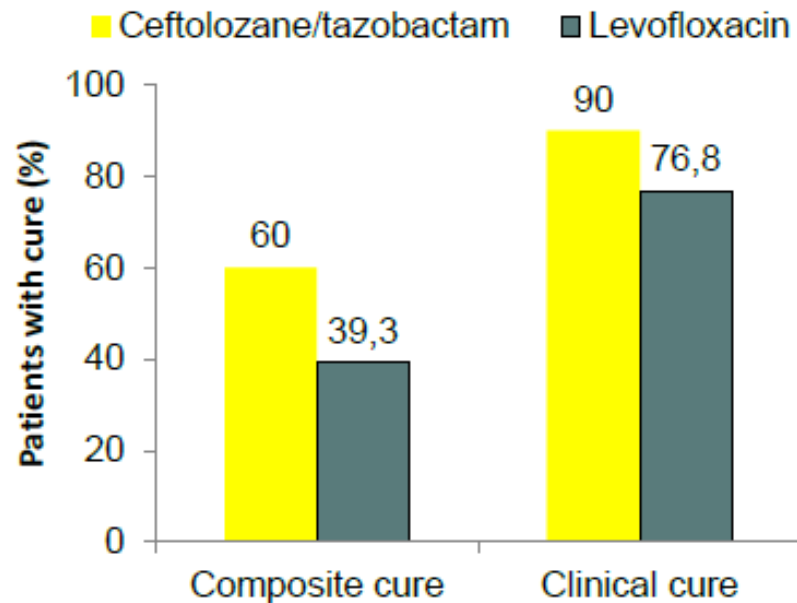
Outcomes in Key Subgroups (mMITT at TOC)

ESBL-producing pathogens



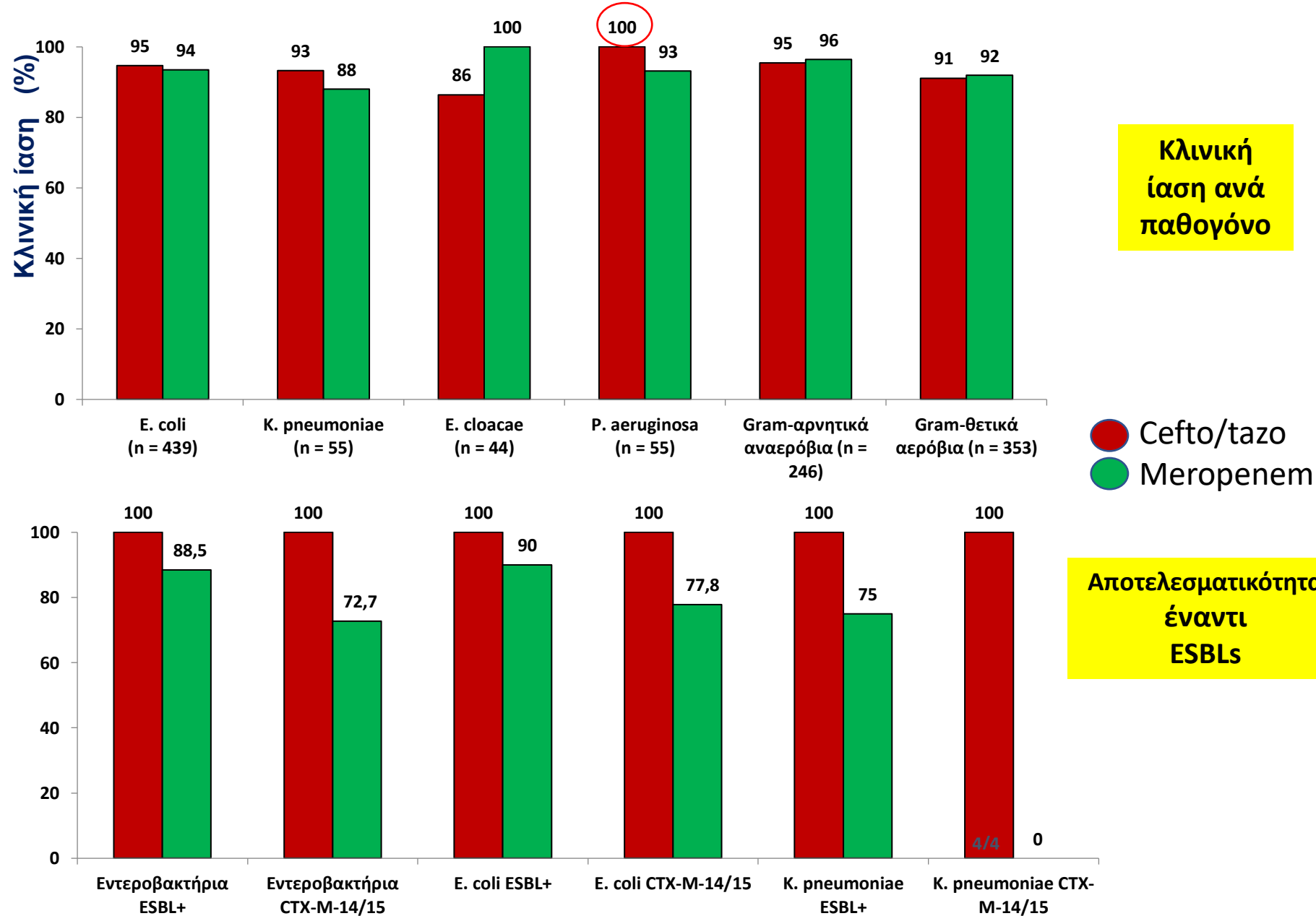
	Ceftolozane/ Tazobactam	Levofloxacin	95% CI
Composite cure	38/61 (62.3%)	20/57 (35.1%)	9.2 to 42.9
Clinical cure	55/61 (90.2%)	42/57 (73.7%)	2.6 to 30.2

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

Κεφτολοζάνη/Ταζομπακτάμη vs. Μεροπενέμης



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)‡

Συμπερασματικά : Κεφτολοζάνη / ταζομπακτάμη

Τάξη

- Αντιψευδομοναδική ή κεφαλοσπορίνη + αναστολέας β-λακταμάσης
- Σταθερή αναλογία 2:1

Μηχανισμός δράσης

- Ταχέως βακτηριοκτόνος
- Αναστολή σύνθεσης κυτταρικού τοιχώματος
- Ενεργός έναντι *P. aeruginosa* με ανεπάρκειες ή μεταλλάξεις πορίνης

In vitro δραστηριότητα

- 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**

Ενδείξεις

- Επιλεγμένες ενδοκοιλιακές λοιμώξεις (με μετρονιδαζόλη)
- Επιλεγμένες λοιμώξεις ουροποιητικού (πυελονεφρίτιδα)
- Νοσοκ πνευμονία

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 IAs. Normal renal function

Healthcare-associated IAs

Critically ill patients

Meropenem 1 g 8-hourly

or

Doripenem 500 mg 8-hourly

or

Imipenem/Glastatin 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

<u>Empiric Therapy Recommendation</u>	<u>Ceftolozane/Tazobactam + Metronidazole</u>
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
Επιλεγμένες Λοιμώξεις του
Ουροποιητικού Συστήματος

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

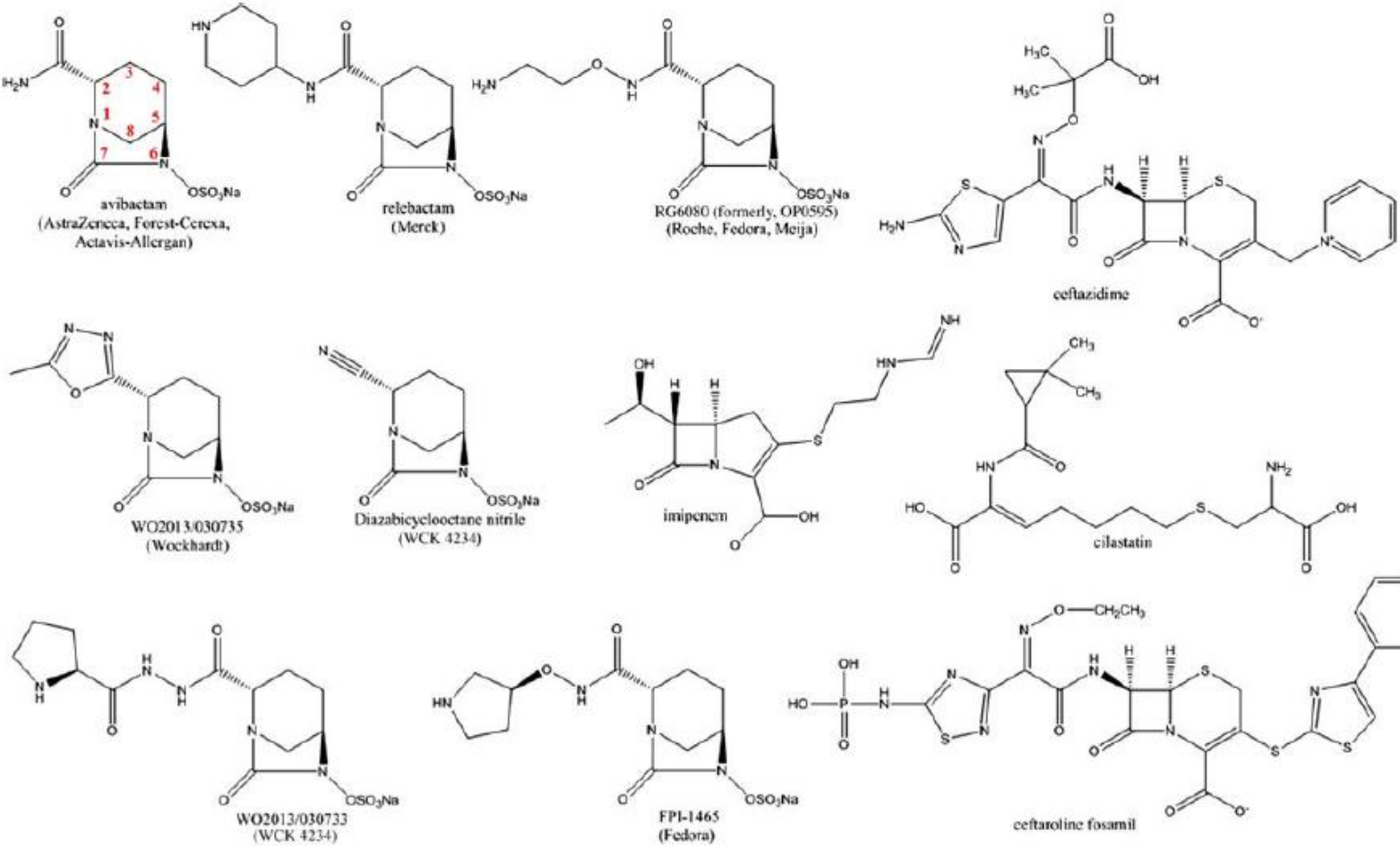
-
Αποφυγή
καρβαπενεμών

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

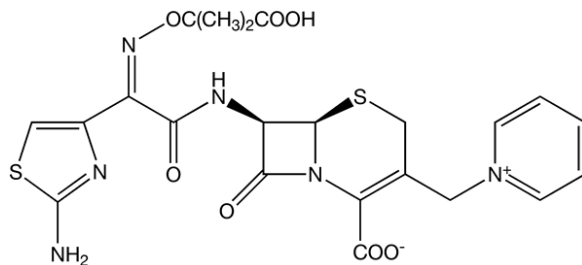
Ceftazidime – Avibactam : Old Cephalosporin & New Inhibitor



Ceftazidime-Avibactam: Old Cephalosporin & New Inhibitor

Ceftazidime

- **Extended-spectrum cephalosporin** with activity against **Enterobacteriaceae** and **P. aeruginosa**¹
- Binds PBPs, leading to bacterial cell lysis¹



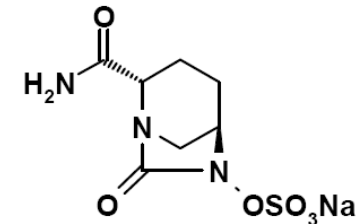
1. **Extended b-lactamase spectrum**

2. **Reversible inhibition: Recycling**

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

Avibactam

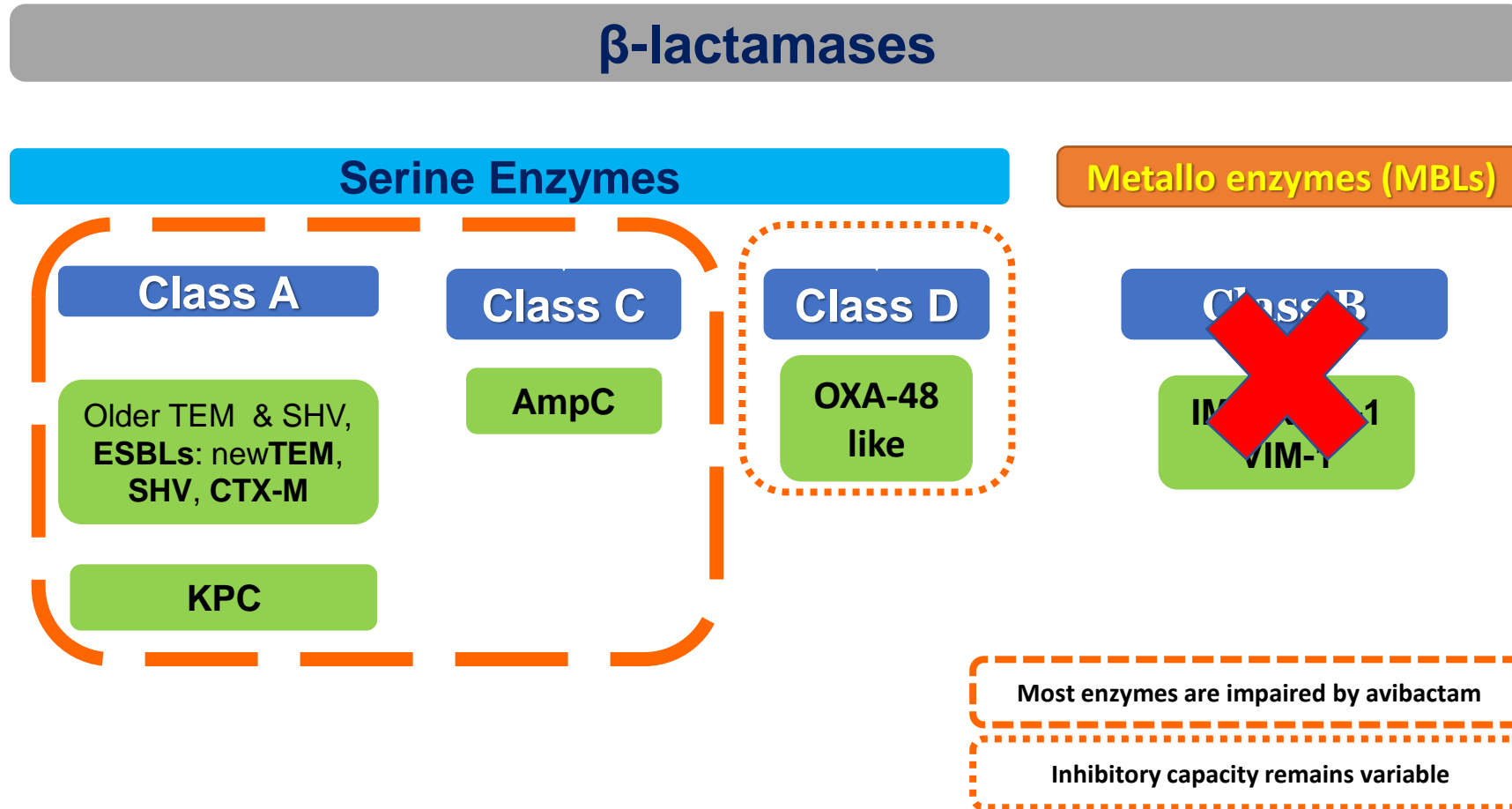
- **Novel non-β-lactam β-lactamase inhibitor** with a unique mode of action²
- High binding affinity for Class A, C and some Class D β-lactamases (**ESBLs, KPCs and AmpC**), some of which are resistant to current agents (e.g. KPCs)³



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-*b*-lactamases *KPC*: *Klebsiella pneumoniae* carbapenemase, *IMP*, imipenemase-type carbapenemase, *VIM*: Verona integron-encoded metallo-*b*-lactamase, *NDM*: New Delhi metallo-*b*-lactamase, *OXA*: oxacillinase-type carbapenemases, 1. *Antimicrob Chemother* 2016; 71: 2713–2722..

Αβιμπακτάμη

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.

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**

Ceftazidime-Avibactam Microbiological Spectrum

Gram (-) bacteria	cAIs	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

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
<i>Pseudomonas aeruginosa</i>	≤8	≥8	≤17	≥17	≤ 8/4	≥ 16/4	≥ 21	≤ 20

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

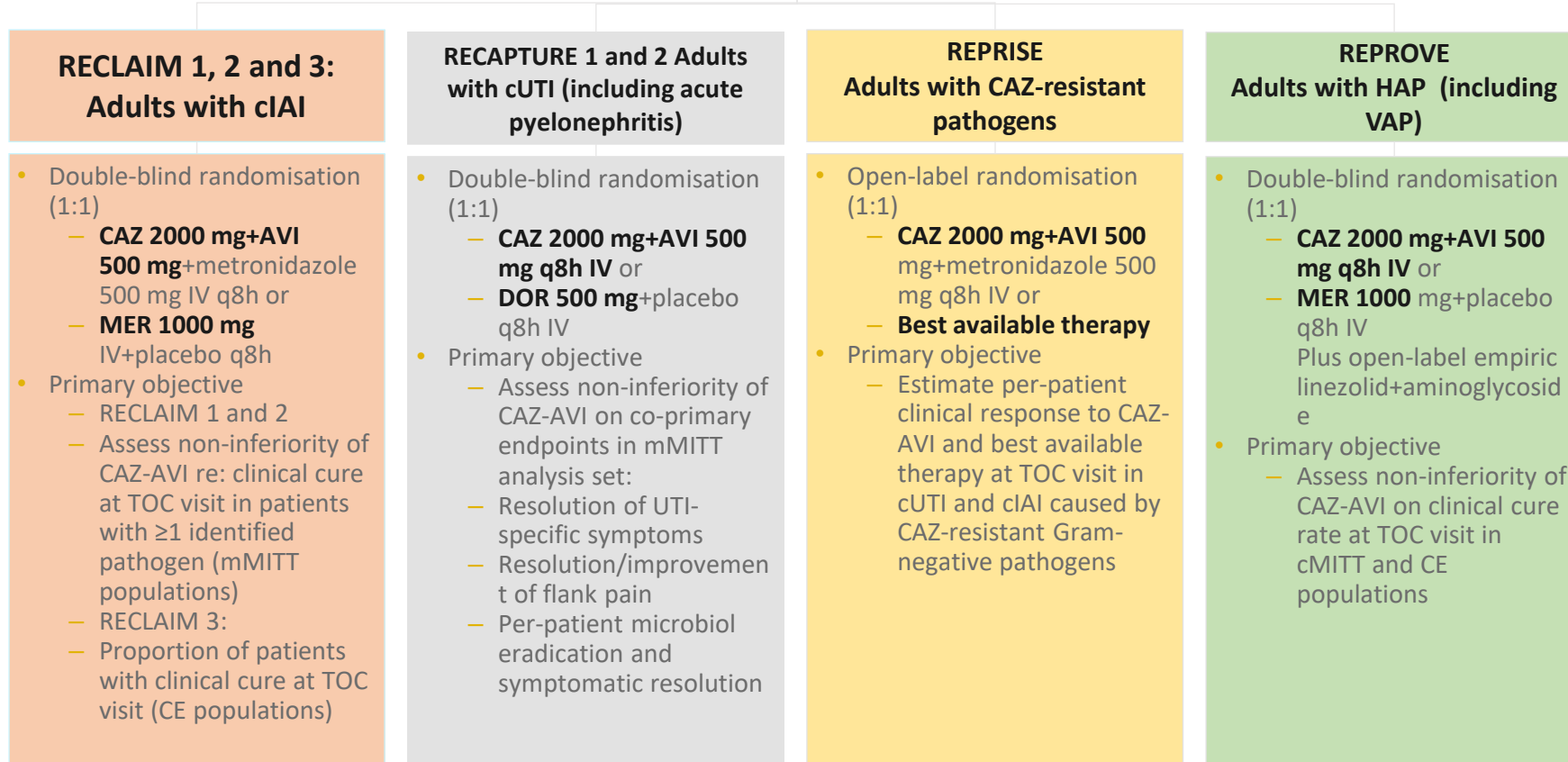
- DD overestimates resistance to caz-avi and is less concordant (72%) than e-test (96%) to BMD (p=0.0003)

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**

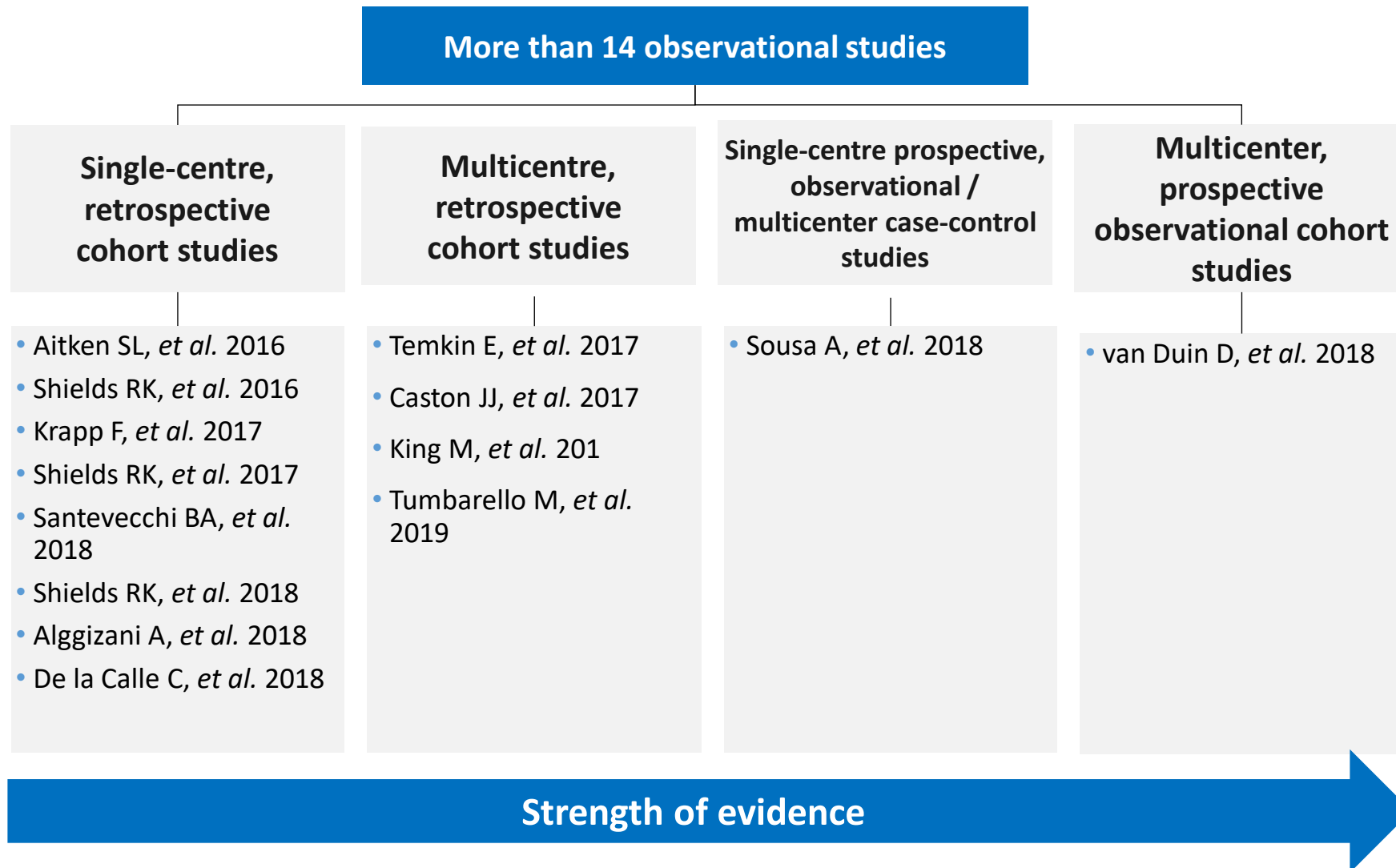
Ceftazidime-avibactam : Clinical trial programme

Seven prospective, international, multicentre, randomised Phase III studies



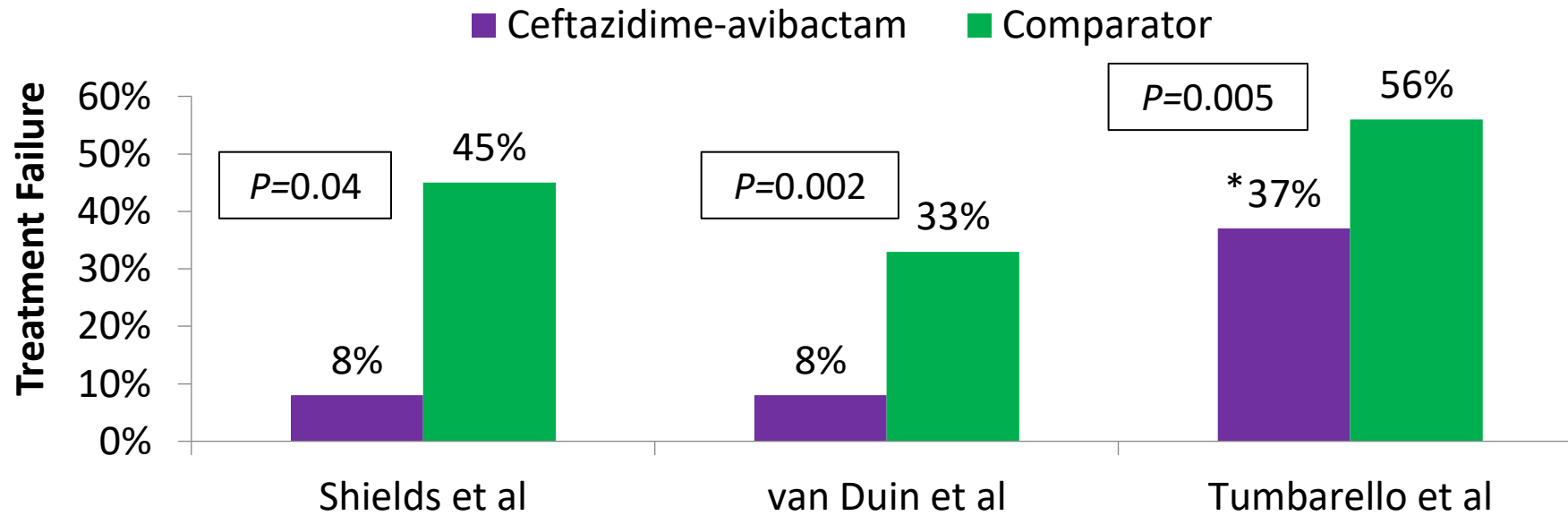
Clin Infect Dis. 2016;62:1380–9
Clin Infect Dis 2016 Sep 15;63(6):754-62
Lancet Infect Dis. 2016 Jun;16(6):661-67
Lancet Infect Dis. 2018 Mar;18(3):285-295.

Ceftazidime–avibactam: real-world data



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.

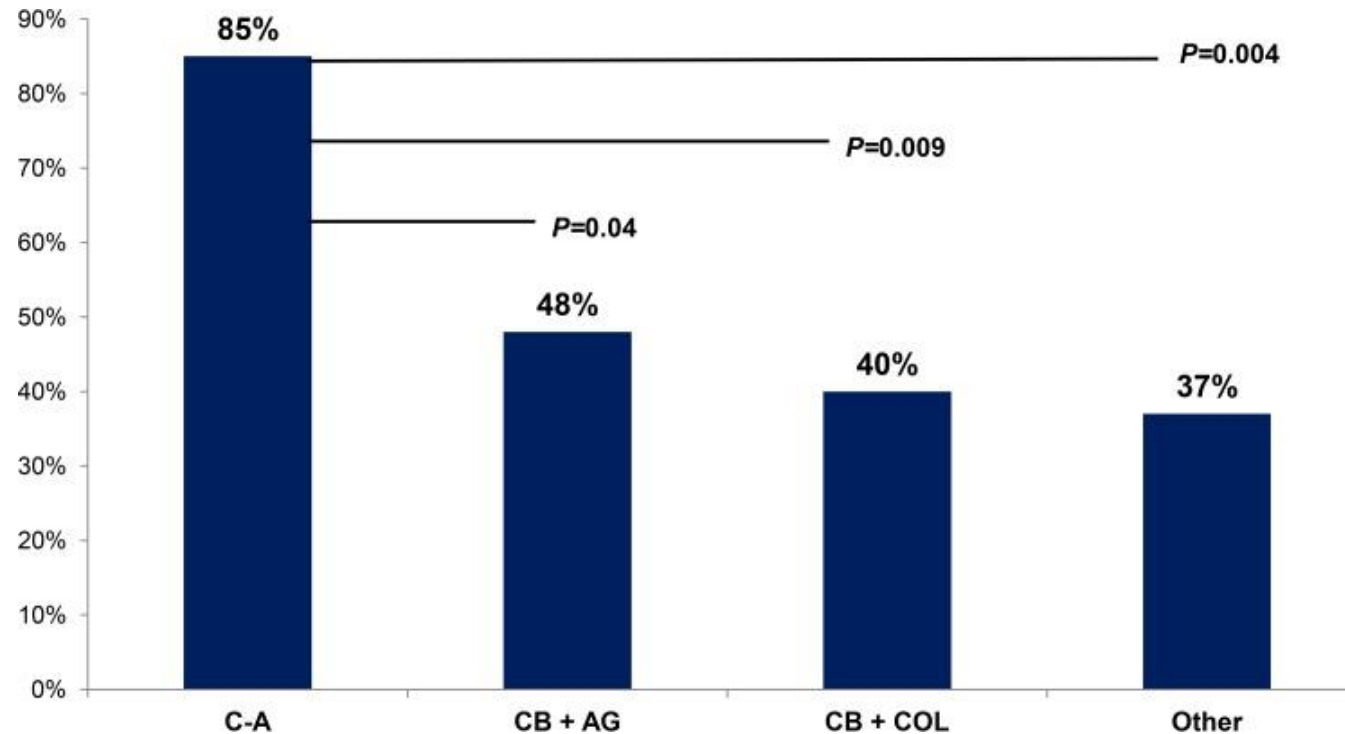
Ceftazidime–avibactam treatment: impact on survival



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

^a Used as salvage therapy

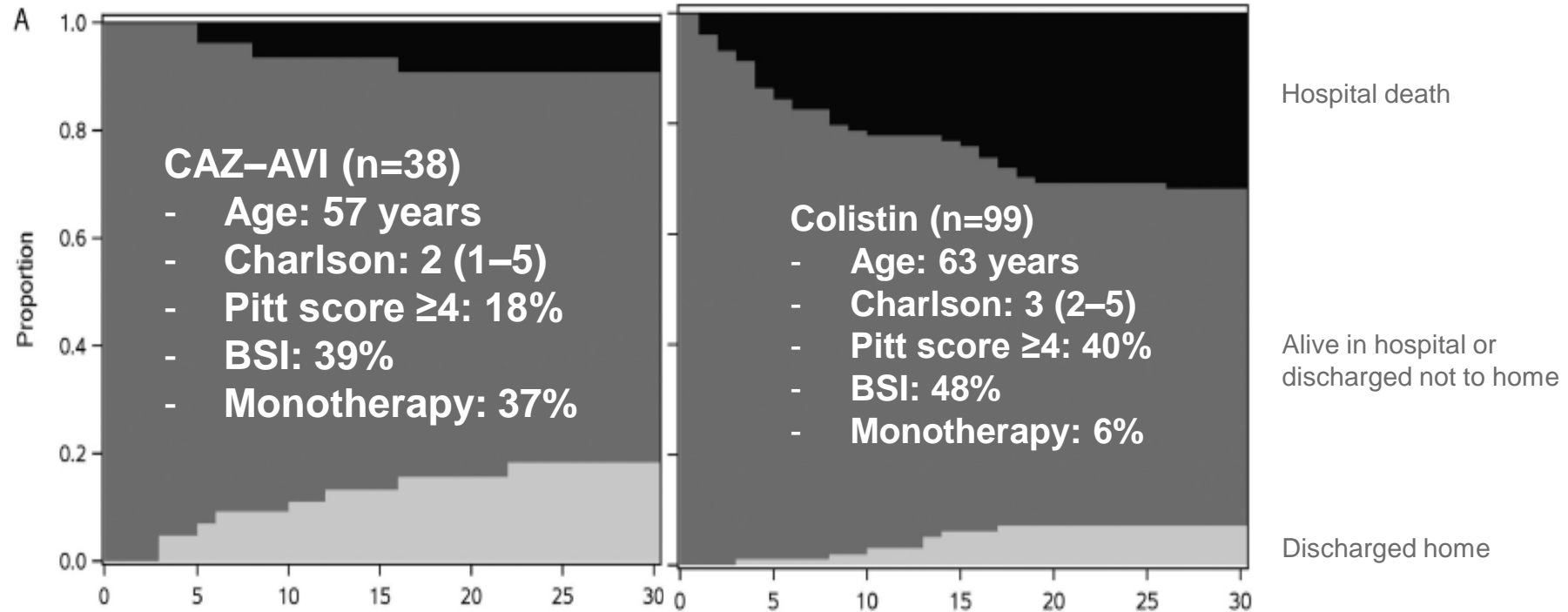
Caz-Avi & Carbapenem-Resistant *K. pneumoniae* Bacteremia



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**

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

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

Variables	Without propensity score adjustment		Adjusted for the propensity score for therapy with CAZ-AVI	
	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)

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, Michela Ansuinelli¹, Clara Minotti¹, Claudio Cartoni¹, Silvia Maria Trisolini¹, Saveria Capria¹, Walter Barberi¹, Stefania Santilli², Alessandra Giordano², Giuseppe Gentile¹

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

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**

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.

- **Στοχευμένη Θεραπεία:**

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,

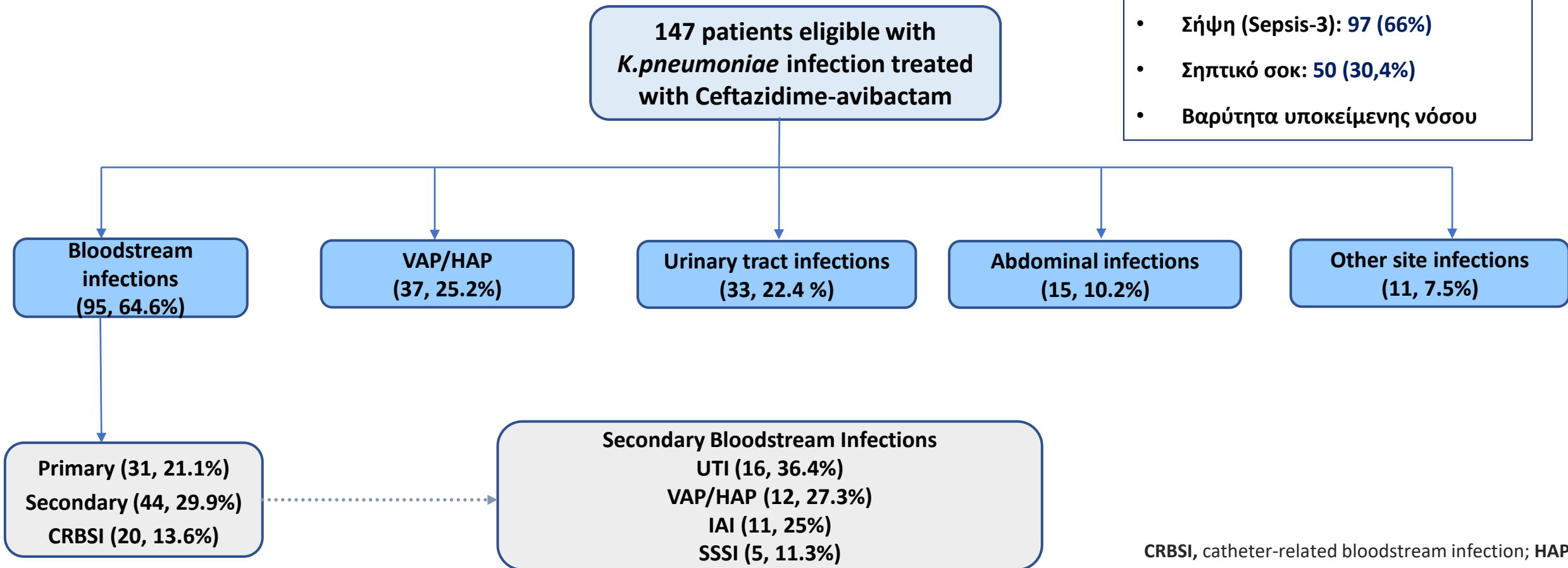
β) σε ήπιες λοιμώξεις που οφείλονται σε εντεροβακτηριακά που παράγουν KPC ή OXA-48, είναι προτιμότερο να χρησιμοποιείται ένα από τα 3 παλαιότερα φάρμακα αν το παθογόνο έχει in vitro ευαισθησία σε αυτά (π.χ. γενταμικίνη, κολιστίνη ή φωσφομυκίνη για UTIs, τιγκεκυκλίνη για λοίμωξη χειρουργικού τραύματος).



Ceftazidime/avibactam in the era of carbapenemase-producing *Klebsiella pneumoniae*: experience from a national registry study

I. Karaiskos^{1*}†, G. L. Daikos²†, A. Gkoufa², G. Adamis³, A. Stefanos⁴, S. Symbardi⁵, G. Chrysos⁶, E. Filiou⁷, D. Basoulis², E. Mouloudi⁸, L. Galani¹, K. Akinosoglou⁹, K. Arvaniti¹⁰, A. Masgala¹¹, M. Petraki¹², E. Papadimitriou¹³, I. Galani¹⁴, G. Poulakou¹⁵, C. Routsis¹⁶ and H. Giamarellou¹ on behalf of the Hellenic Ceftazidime/Avibactam Registry Study Group‡

- Ηλικία : 60,9 έτη (17,1)
- Άνδρες: 109 (74,1%)
- CCI: 2 (1-5)
- APACHE II: 16,5 (7,6)
- SOFA : 6,7 (4,2))
- Νοσηλεία σε ΜΕΘ: 74 (50,3%)
- Σήψη (Sepsis-3): 97 (66%)
- Σηπτικό σοκ: 50 (30,4%)
- Βαρύτητα υποκείμενης νόσου

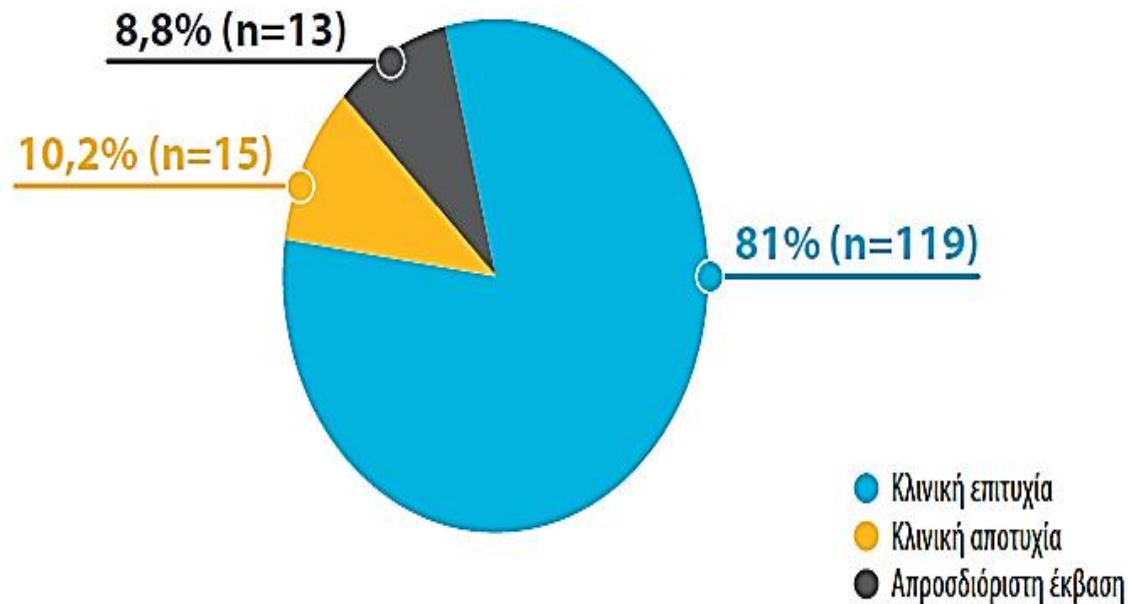


CRBSI, catheter-related bloodstream infection; HAP, hospital-acquired pneumonia; VAP, ventilated associated pneumonia

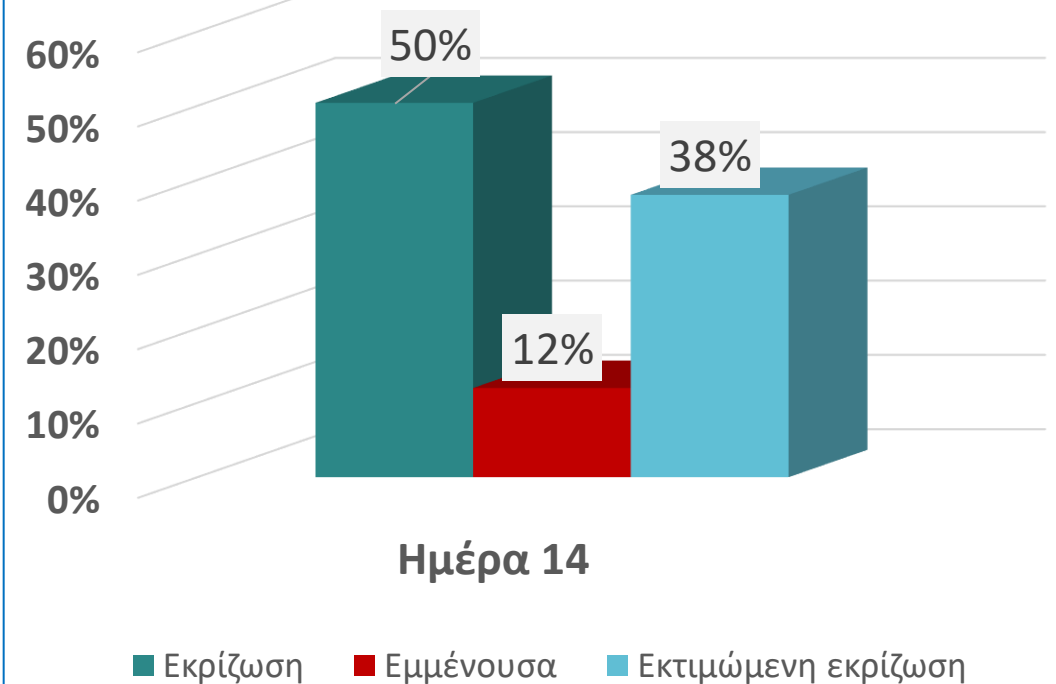


Ceftazidime/avibactam in the era of carbapenemase-producing *Klebsiella pneumoniae*: experience from a national registry study

Κλινική ανταπόκριση την ημέρα 14



Μικροβιολογική ανταπόκριση την ημέρα 14



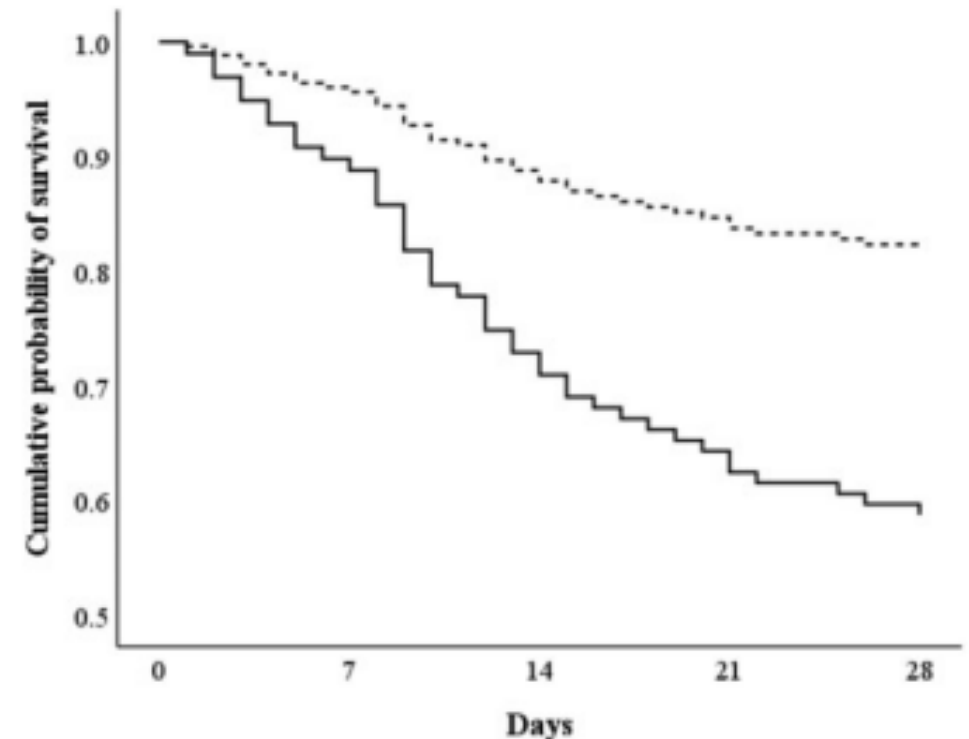
- Εμφάνιση αντοχής στην CAZ-AVI κατά τη διάρκεια της θεραπείας: **2 ασθενείς (1,4%)**
- Υποτροπή της λοίμωξης μετά τη διακοπή της θεραπείας με CAZ-AVI κατά τη διάρκεια της νοσηλείας: **6 ασθενείς (4,1%)** - 4 ασθενείς με KPC + MBL *K. pneumoniae*

Treatment with ceftazidime/avibactam-containing regimens [HR = 0.37 (95% CI = 0.19–0.71); P = 0.003] remained an independent predictor of survival

28-day mortality was lower in KPC-Kp bacteraemia patients that received CAZ/AVI vs other agents (18.3% έναντι 40.8%; P = 0.005)

Table 4. Cox proportional hazards model of factors associated with all-cause 28 day mortality in 142 patients with KPC-Kp bloodstream infections

Variable	HR (95% CI)	P
Severity of underlying disease		
ultimately fatal/non-fatal	2.25 (1.08–4.70)	0.03
rapidly fatal/non-fatal	6.4 (2.0–20.5)	0.001
Charlson comorbidity index ≥ 2	2.44 (1.08–5.52)	0.032
Septic shock/sepsis	1.67 (0.90–3.12)	0.100
Ceftazidime/avibactam-based therapy/other antimicrobials	0.37 (0.19–0.71)	0.003

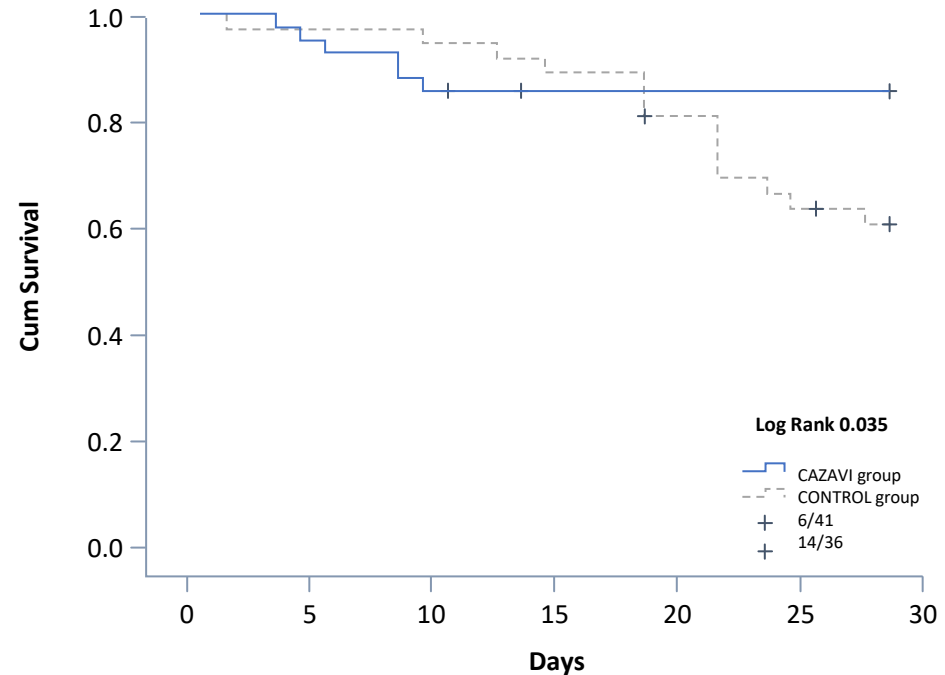
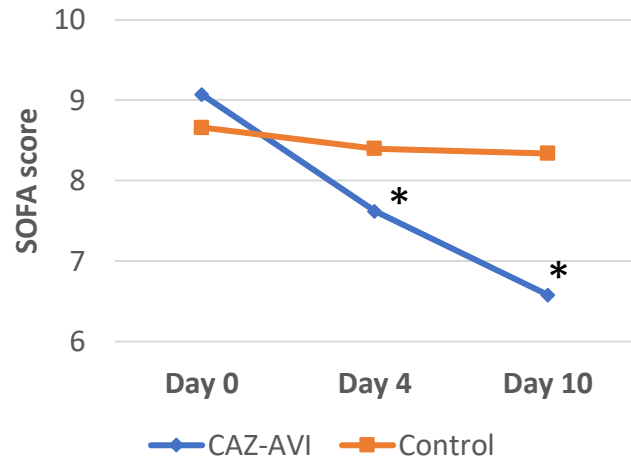


The all-cause 28-day mortality rate was rather low (calculated at around 20%)

CAZ–AVI to treat life-threatening infections by carbapenem-resistant pathogens in critically ill mechanically ventilated patients

The most significant predictor of clinical cure was an antibiotic regimen containing CAZ–AVI

- Improvement in SOFA score on Day 4 and 10 in the CAZ–AVI group compared with the control group



- Clinical cure was observed in 33/41 (80.5%) patients in the CAZ–AVI group vs 19/36 (52.8%) patients in the control group
- Microbiological eradication was achieved in 33/35 (94.3%) patients in CAZ–AVI group vs 21/31 (67.7%) patients in the control group

- ICU cumulative survival was 61% in the CAZ–AVI group and 41.7% in the control group
- The ICU LOS for patients that were discharged did not differ between the two groups

Ceftazidime–avibactam use for KPC–Kp infections: a retrospective observational multicenter study

Mario Tumbarello ^{1 2 3}, Francesca Raffaelli ¹, Maddalena Giannella ⁴, Elisabetta Mantengoli ⁵,
Alessandra Mularoni ⁶, Mario Venditti ⁷, Francesco Giuseppe De Rosa ⁸, Loredana Sarmati ⁹,

Table 3. Patient subgroups treated with CAZ-AVI monotherapy vs. CAZ-AVI combination therapy

	Combination therapy (n=412)	Monotherapy (n=165)	<i>P</i> value
Outcomes ^b			
30-day all-cause mortality	103 (25.0)	43 (26.1)	0.79
Infection relapse ^c	50 (12.1)	13 (7.9)	0.14
Development of resistance	14 (3.4)	6 (3.6)	0.89
Adverse reactions	15 (3.6)	5 (3.0)	0.70

Mortality was negatively associated with CAZ-AVI administration

Potential indications of ceftazidime-avibactam, as empiric treatment

Empiric treatment

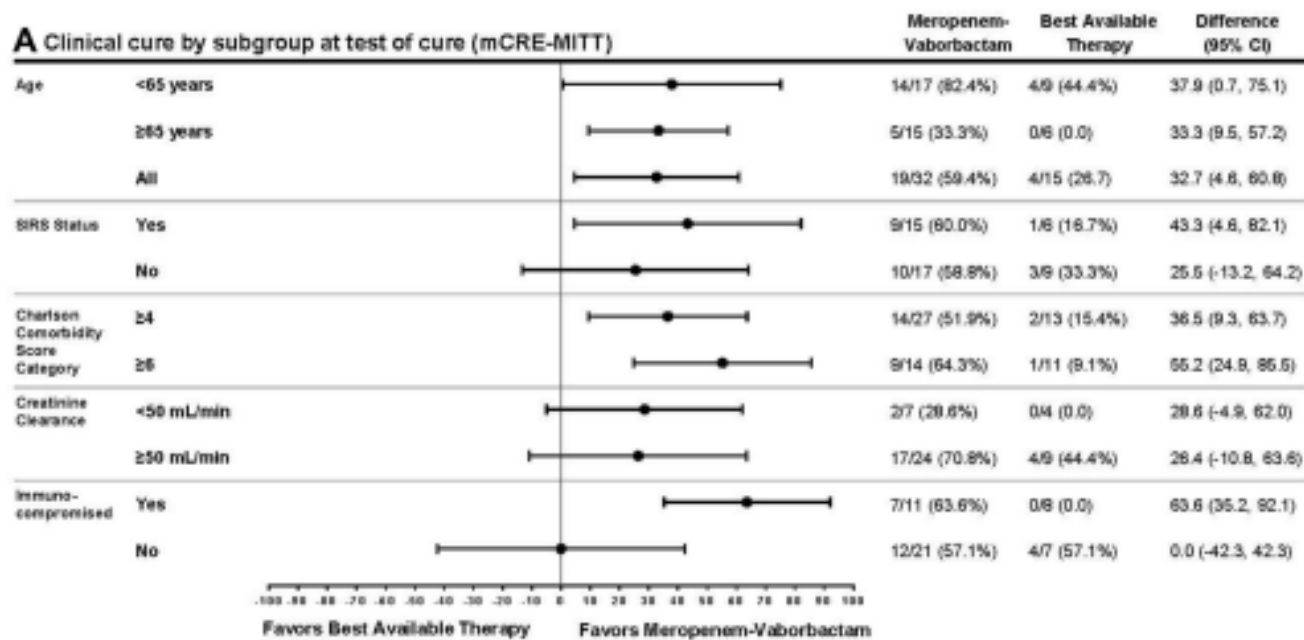
Strong or multiple risk factors for infection by MDR strains producing KPC or OXA-48 enzymes

- Known colonisation or prior infection (or roommate infected) by Enterobacteriaceae strain producing KPC or OXA-48 OR
- Local epidemiology (or recent hospitalization in settings) with more than 20-25% prevalence of carbapenem-producing and ESBL-producing Enterobacteriaceae
- PLUS any of the following
- Prior use of carbapenems and/or colistin
- ICU admission or long admission in hospital wards
- Severe hospital-acquired infection
- Immunossuppression, multiple comorbidities

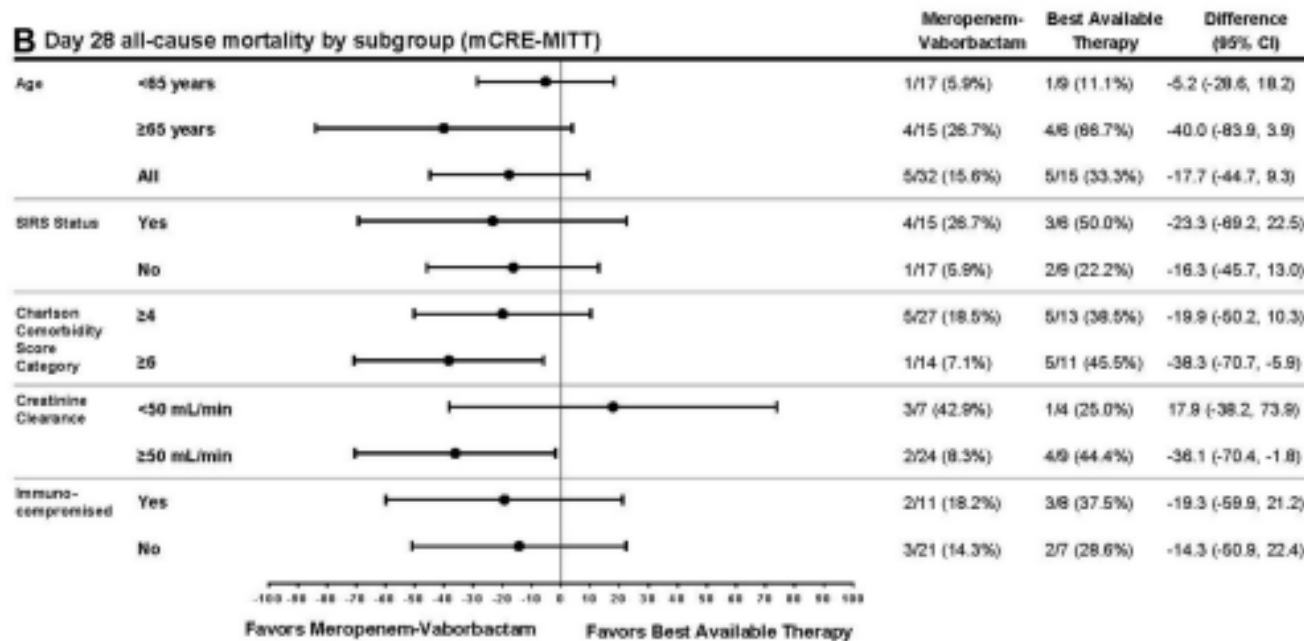
Diazabicyclooctanones in development

- **Boronic acid (Vaborbactam)**
 - Main role: treatment of KPC-producing *Enterobacteriaceae*.
 - Reduced MICs
 - Did not potentiate the activity of carbapenems against *P.aeruginosa* and *A.baumannii*
 - **Meropenem/Vaborbactam** approved for UTI (not active against class B or D carbapenemases (ie, metallo-beta-lactamases and OXA-type enzymes))
 - TANGO I and II trials

A Clinical cure by subgroup at test of cure (mCRE-MITT)



B Day 28 all-cause mortality by subgroup (mCRE-MITT)



Improvement in clinical cure and potentially an improved tolerability compared with standard therapies.

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-Ceresa, 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-Ceresa, Actavis-Allergan	DBO	Phase 2	NCT01624246, NCT01281462, NCT01290900, and NCT01789528 (completed)
Aztreonam-avibactam	AstraZeneca Pharmaceuticals, Forest-Ceresa, 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 NCT02168946 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

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

A Randomized, Double-blind, Multicenter Trial Comparing Efficacy and Safety of Imipenem/Cilastatin/Relebactam Versus Piperacillin/Tazobactam in Adults With Hospital-acquired or Ventilator-associated Bacterial Pneumonia (RESTORE-IMI 2 Study)

Ivan Titov,¹ Richard G. Wunderink,² Antoine Roquilly,³ Daniel Rodriguez Gonzalez,⁴ Aileen David-Wang,⁵ Helen W. Boucher,⁶ Keith S. Kaye,⁷ Maria C. Losada,⁸ Jiejun Du,⁹ Robert Tipping,¹ Matthew L. Rizk,¹ Munjal Patel,¹ Michelle L. Brown,¹ Katherine Young,¹ Nicholas A. Kartsonis,¹ Joan R. Butters,¹ Amanda Paschke,¹ and Luke F. Chen¹

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Background. Imipenem combined with the β -lactamase inhibitor relebactam has broad antibacterial activity, including against carbapenem-resistant gram-negative pathogens. We evaluated efficacy and safety of imipenem/cilastatin/relebactam in treating hospital-acquired/ventilator-associated bacterial pneumonia (HABP/VABP).

Methods. This was a randomized, controlled, double-blind phase 3 trial. Adults with HABP/VABP were randomized 1:1 to imipenem/cilastatin/relebactam 500 mg/500 mg/250 mg or piperacillin/tazobactam 4 g/500 mg, intravenously every 6 hours for 7–14 days. The primary endpoint was day 28 all-cause mortality in the modified intent-to-treat (MITT) population (patients who received study therapy, excluding those with only gram-positive cocci at baseline). The key secondary endpoint was clinical response 7–14 days after completing therapy in the MITT population.

Results. Of 537 randomized patients (from 113 hospitals in 27 countries), the MITT population comprised 264 imipenem/cilastatin/relebactam and 267 piperacillin/tazobactam patients; 48.6% had ventilated HABP/VABP, 47.5% APACHE II score ≥ 15 , 24.7% moderate/severe renal impairment, 42.9% were ≥ 65 years old, and 66.1% were in the intensive care unit. The most common baseline pathogens were *Klebsiella pneumoniae* (25.6%) and *Pseudomonas aeruginosa* (18.9%). Imipenem/cilastatin/relebactam was noninferior ($P < .001$) to piperacillin/tazobactam for both endpoints: day 28 all-cause mortality was 15.9% with imipenem/cilastatin/relebactam and 21.3% with piperacillin/tazobactam (difference, -5.3% [95% confidence interval (CI), -11.9% to 1.2%]), and favorable clinical response at early follow-up was 61.0% and 55.8%, respectively (difference, 5.0% [95% CI, -3.2% to 13.2%]). Serious adverse events (AEs) occurred in 26.7% of imipenem/cilastatin/relebactam and 32.0% of piperacillin/tazobactam patients; AEs leading to treatment discontinuation in 5.6% and 8.2%, respectively; and drug-related AEs (none fatal) in 11.7% and 9.7%, respectively.

Conclusions. Imipenem/cilastatin/relebactam is an appropriate treatment option for gram-negative HABP/VABP, including in critically ill, high-risk patients.

Clinical Trials Registration. NCT02493764.

Diazabicyclooctanones : Avibactam

- **Aztreonam – Avibactam**

ATM against MBL but not ESBL, AmpC, serine carbapenemaseses → 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-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)
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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 NCT02168946 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 : OP0595 (RG6080)

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

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

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)thiophane-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	Casa 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	Rampex Pharmaceuticals (The Medicines Company)	Boronate
AA101	Cefepime	Allegra Therapeutics	Sulfone
Sulfone derivatives	Meropenem or imipenem	Orchid Pharmaceuticals	Sulfone
Sulfone derivatives	Meropenem or imipenem	Dr John D. Burnak (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, BAL29680, & 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 bispenem	Meiji Seika Kaisha Ltd	Maleic acid derivative

TO CONCLUDE...IN PRACTICE

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

Clavulanic acid/ sulbactam/tazobactam	DBOs (DBO - Second generation of - β LI)				Vaborbactam
	First generation BLI	Avibactam (First generation DBO)	Relebactam (First gen DBO)	Zidebactam (Second generation DBO)	Nacubactam (Second gen DBO)
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 <i>A. baumannii</i>	No useful intrinsic antibacterial activity		Intrinsic activity against <i>P. aeruginosa</i> and <i>A. baumannii</i>		-
-	Not effective against <i>Acinetobacter sp.</i> , producing OXA type carbapenemases		Potent in activators of <i>P. aeruginosa</i> PBP2 and <i>A. baumannii</i> PBP2 (unique about 2 nd gen DBO)		-
-	No activity against MBL producers		-		-

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

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.*

β L/ β LI	<i>Enterobacteriaceae</i>										<i>Pseudomonas spp.</i>					<i>Acinetobacter spp.</i>
	ESBL	AmpC	ESBL + AmpC	<i>bla</i> _{KPC}	<i>bla</i> _{NDM}	<i>bla</i> _{OXA-48}	<i>bla</i> _{KPC} + ESBL + AmpC	MBL + ESBL + AmpC	<i>bla</i> _{OXA-48} + ESBL	ompK35/ompK36 mutant*	ESBL	AmpC	Efflux	oprD mutant	<i>bla</i> _{VIM} / <i>bla</i> _{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, ^aCeftazidime/avibactam not effective against *bla*_{KPC-3} and *bla*_{KPC} producing ST258, ^bCeftolozane/tazobactam is not active against de-repressed AmpC producing *Enterobacter spp.*, but active against Chromosomal AmpC, ^cImipenem-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, β LI: β -lactamase inhibitor, NA: Not available, β L: 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		
<i>Enterobacteriaceae</i>	$\geq 21 / \leq 20$ mm (S/R)	$\geq 21 / 18-20 / \leq 17$ mm (S/I/R)
<i>Pseudomonas spp.</i>	$\geq 21 / \leq 20$ mm (S/R)	$\geq 21 / 17-20 / \leq 16$ mm (S/I/R)
MIC		
<i>Enterobacteriaceae</i>	$\leq 8 / 4 / \geq 16 / 4$ $\mu\text{g/ml}$ (S/R)	$\leq 2 / 4 / 4 / 4 / \geq 16 / 4$ $\mu\text{g/ml}$ (S/I/R)
<i>Pseudomonas spp.</i>	$\leq 8 / 4 / \geq 16 / 4$ $\mu\text{g/ml}$ (S/R)	$\leq 4 / 4 / 8 / 4 / \geq 16 / 4$ $\mu\text{g/ml}$ (S/I/R)

MIC: Minimum inhibitory concentration

Αντιβιοτικά που αναμένουμε για gram (-)

	ESBL	CRE	MDR <i>P.aeruginosa</i>	MDR Acinetobacter
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
↓

R

**right drug
right time
right dose
Right duration**

Thank you for your patience !