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

Νεώτεροι αναστολείς β-λακταμασών για νοσοκομειακή χρήση

Καρολίνα Ακινόσογλου

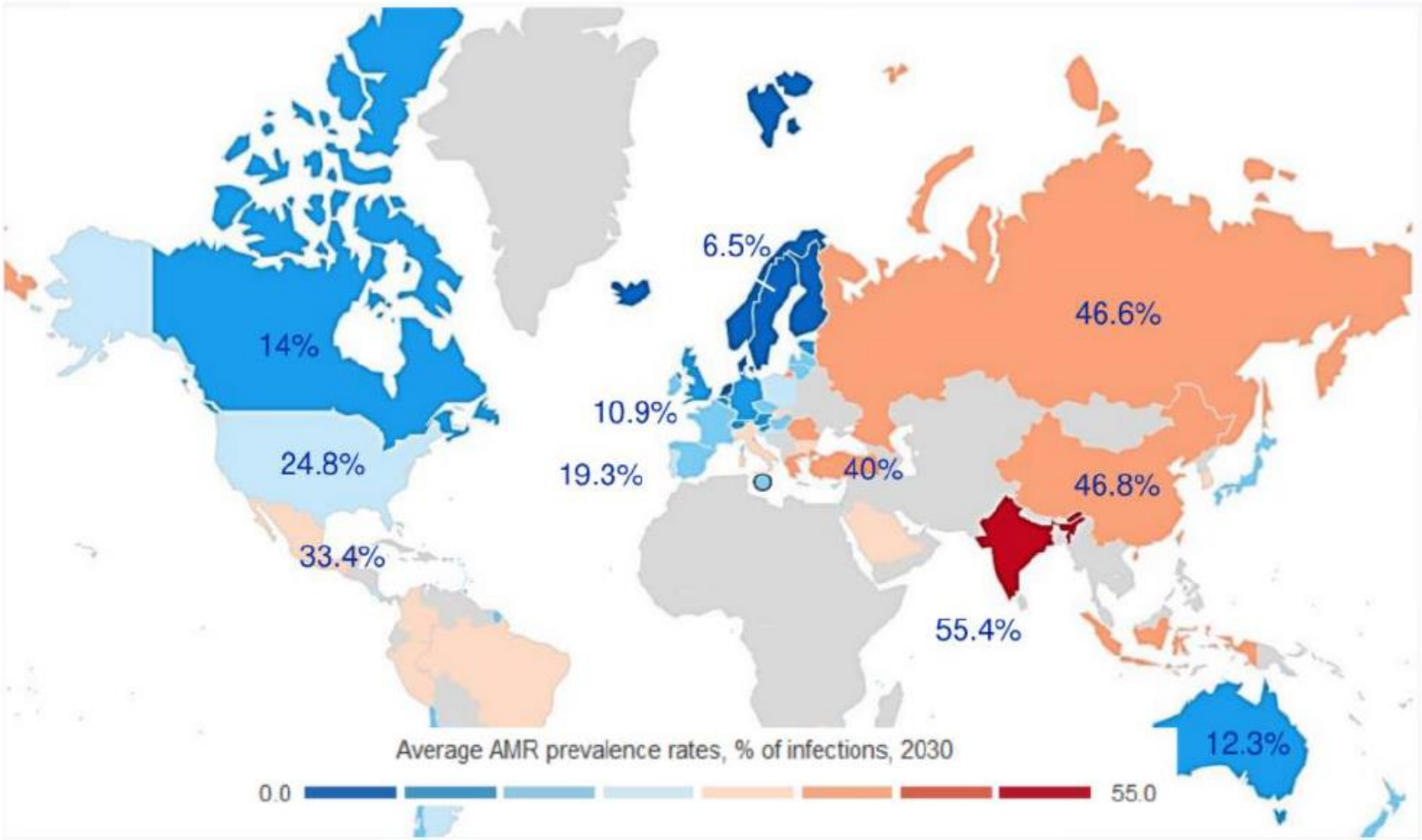
Παθολόγος-Λοιμωξιολόγος

Αναπληρωτρια Καθηγήτρια Παθολογιας

Ιατρικού Τμήματος, Παν/μίου Πατρών

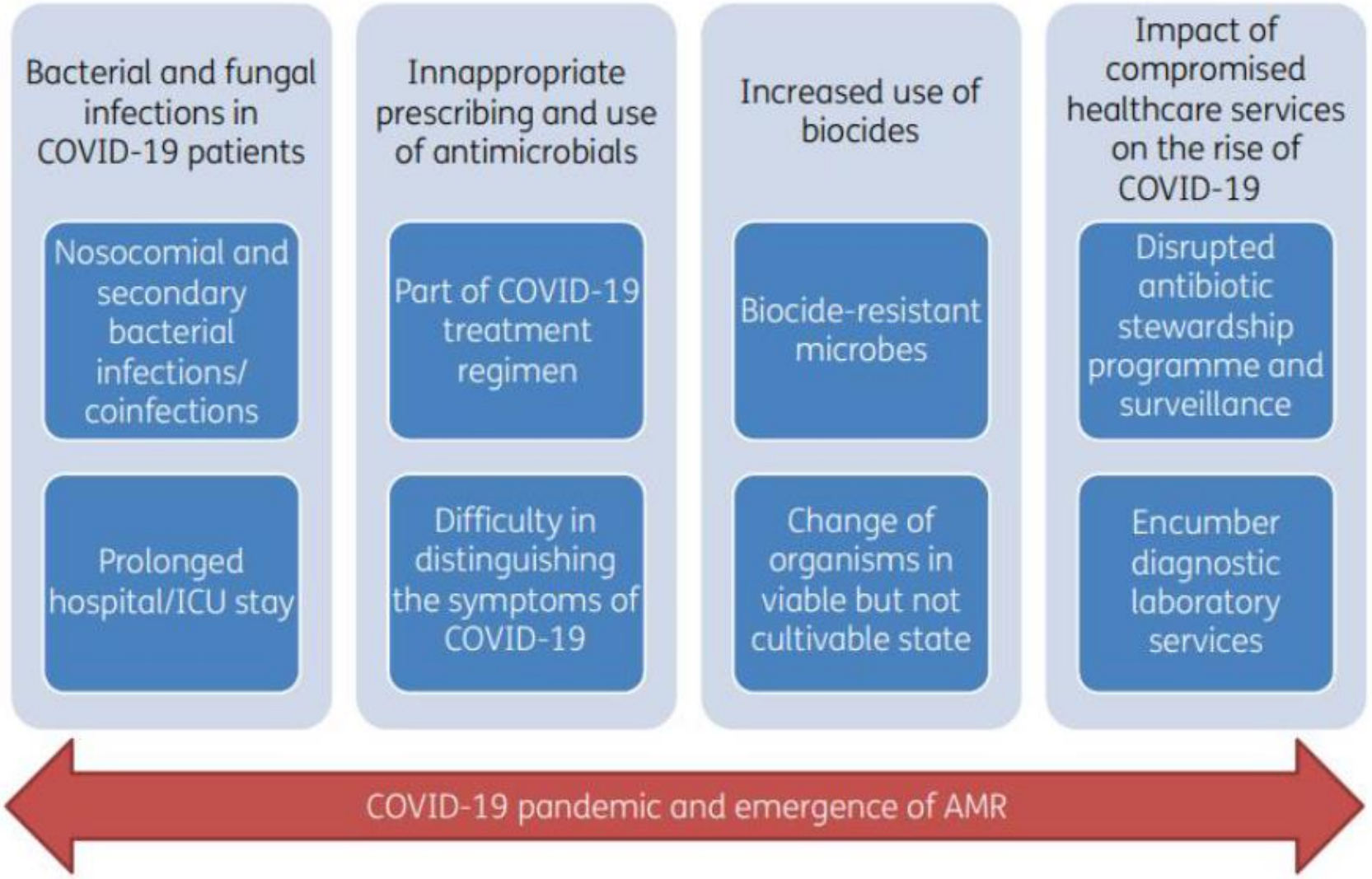
So, lets put things into context

Predicted trends of antimicrobial resistance in 2030



AMR, antimicrobial resistance.Organisationfor Economic Co-operation and Development (OECD). Compare your country. In: Stemming the Superbug Tide: Just A Few Dollars More. OECD Health Policy Studies, OECD Publishing: Paris; 2018. https://www.oecd.org/health/stemming-the-superbug-tide-9789264307599-en.htm(Accessed December 2021).

Relevant predictors of the development of AMR during COVID-19



AMR, antimicrobial resistance; ICU, intensive care unit.Ansari S, et al. JAC Antimicrob Resist2021;3(2):dlab038. doi:10.1093/jacamr/dlab038.

Mortality rates with multidrug-resistant Gram-negative infections

- Mortality rate from bacteraemia caused by *P. aeruginosa* of 20–39%, reaching 44% in patients with VAP (Spain)[1]
- 28-day all-cause mortality rate of 40% in patients with carbapenemase-producing *K. pneumoniae* (Greece)[2]
- INCREMENT: 30-day mortality rate of 33.7% in patients with infections caused by ESBL *K. pneumoniae* & 17.4% *E. coli*[3]
- Mortality rate of 41.0% in patients with infections caused by KPC-producing *K. pneumoniae* (meta-analysis)[4]
- 30-day mortality rate of 50% in patients with infections caused by OXA-48-producing Enterobacterales (Spain)[5]

ESBL, extended-spectrum β-lactamase; KPC, Klebsiella pneumoniaecarbapenemase; OXA, oxacillinase; VAP, ventilator-associated pneumonia.1. Mensa J, et al. Rev Esp Quimioter 2018;31:78–100; 2. Daikos GL, et al. Antimicrob Agents Chemother2014;58:2322–8; 3. Scheuerman O, et al. Infect Control Hosp Epidemiol 2018;39:660–7; 4. Ramos-CastañedaJA, et al. J Infect2018;76:438–48.; 5. Navarro-San Francisco C, et al. Clin Microbiol Infect 2013;19:72–9.

Economic burden of serious MDR Gram-negative infections

Infections due to **MDR bacteria** cost at least €1.5 billion each year in EU[1]

AMR has an economic & societal burden through lost productivity[2,3]

- In the US, AMR is associated with more than $20 billion in direct healthcare-related costs, with an additional $35 billion attributed to lost productivity[3]
- By 2050, AMR could cause the annual global GDP to fall by 3.8% and an additional 28 million people to fall into poverty[4]

Resistant Gram-negative infections are associated with a significant economic burden[5]

- MDR Gram-negative bacteria are associated with ~2.5 times higher hospital costs compared with infections with sensitive Gram-negative bacteria[5]

AMR, antimicrobial resistance; GDP, gross domestic product; MDR, multidrug-resistant.1. European Centre for Disease Prevention and Control (ECDC)/European Medicines Agency. The Bacterial Challenge: Time to React. Stockholm: ECDC; 2009; 2. Naylor NR, et al. Antimicrob Resist Infect Control 2018;7:58; 3. Kaye KS and Pogue JM. Pharmacotherapy2015;35:949–62; 4. The World Bank. Drug-Resistant Infections: A Threat to Our Economic Future. 2017. https://documents1.worldbank.org/curated/en/323311493396993758/pdf/final-report.pdf(Accessed February 2022); 5. Evans HL, et al. Crit Care Med 2007;35:89–95.

β-lactamases

Serine Enzymes

Class A

Older TEM & SHV,
ESBLs: new**TEM**, **SHV**, **CTX-M**

KPC

Class C

AmpC

Class D

OXA-48 like

Metallo enzymes (MBLs)

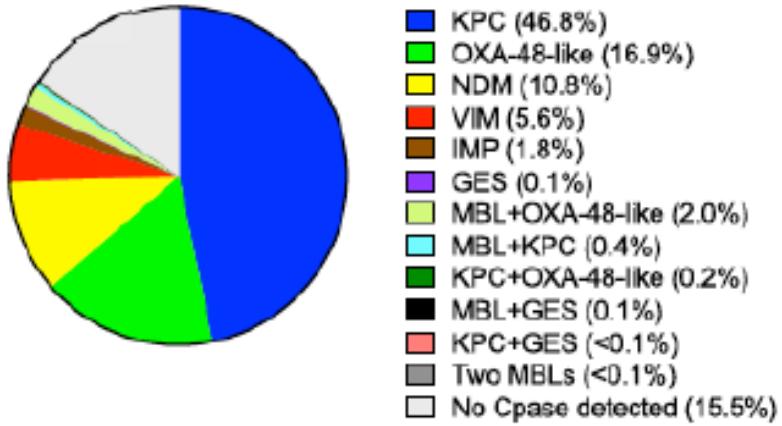
Class B

IMP, NDM-1
VIM-1

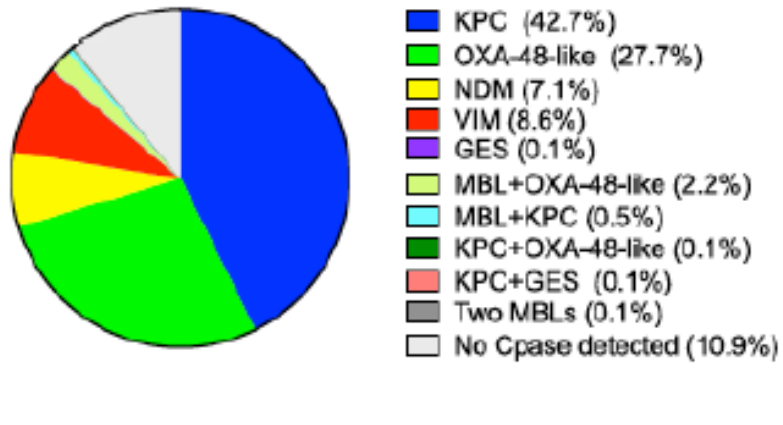
TEM: *temoneira;* ***SHV:*** *sulfhydryl variable;* ***ESBLs:*** *Extended spectrum b-lactamases* ***CTX-M:*** *cefotaxime-β-lactamases* ***KPC****: Klebsiella pneumoniae carbapenemase,* ***IMP****, imipenemase-type carbapenemase,* ***VIM****: Verona integron-encoded metallo-β-lactamase,* ***NDM:***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

Distribution of carbapenem resistance mechanisms identified in meropenem-nonsusceptible Enterobacterales isolates by geographic region

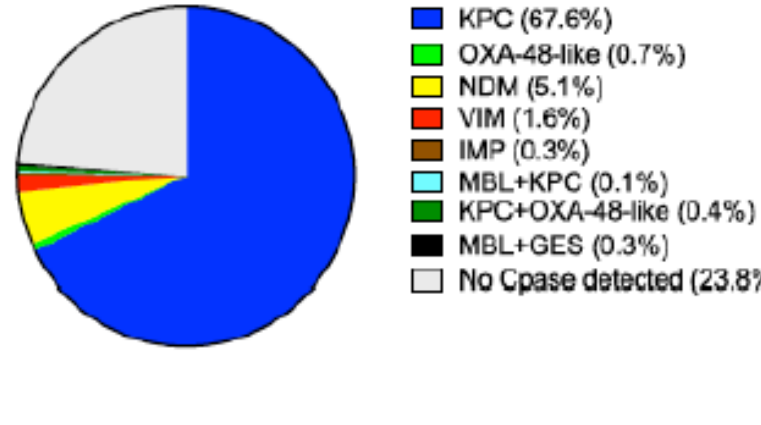
Global (n=2,666)



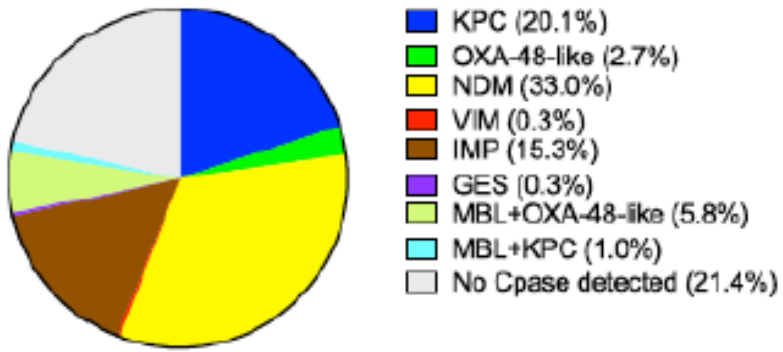
Europe (n=1,441)



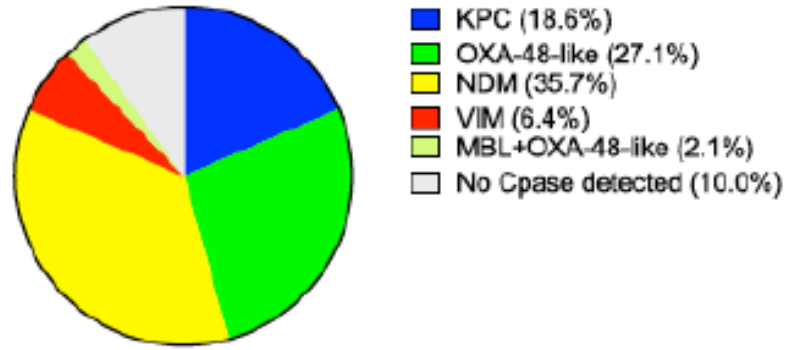
Latin America (n=689)



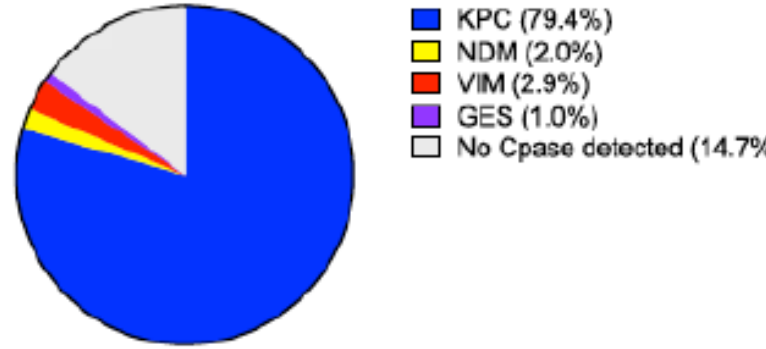
Asia/South Pacific (n=294)



Middle East/Africa (n=140)



North America (n=102)*



*2012 to 2016 only.

Cpase, carbapenemase; GES, Guiana extended-spectrum β-lactamase; IMP, imipenemase; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; VIM, Verona integron-encoded metallo-β-lactamase.

Kazmierczak KM, et al. *Antimicrob Agents Chemother* 2021;65:e0200020.

P.aeruginosa : Difficult to treat and antibiotic resistance mechanisms

Chromosomally encoded
Class C β-lactamase, AmpC
HYPEREXPRESSED[1-3]

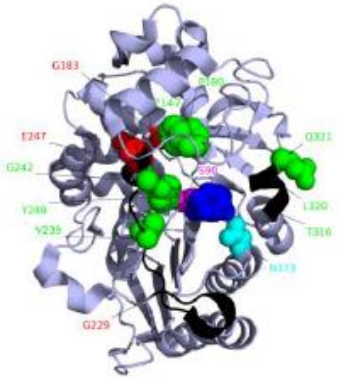
Ceftazidime/cefepime	✗
Aztreonam	✗
Piperacillin–tazobactam	✗
Imipenem–relebactam	✓
Ceftolozane–tazobactam	✓
Ceftazidime–avibactam	✓

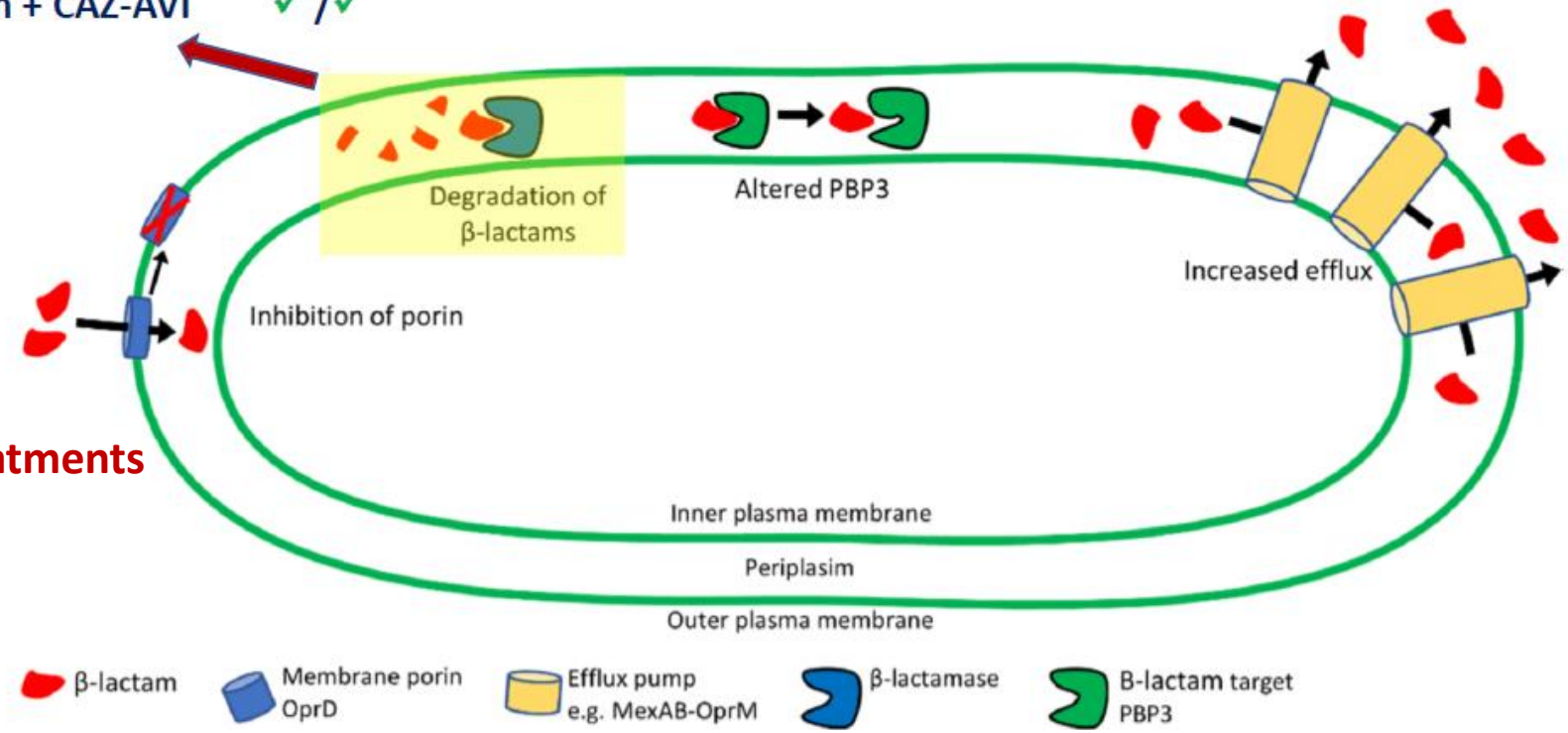
HGT-acquired carbapenemases
VIM, IMP / KPC, OXA[1-4]

Imipenem–relebactam	✗ / ✗
Ceftolozane–tazobactam	✗ / ✗
Ceftazidime–avibactam	✗ / ✓
Aztreonam + CAZ-AVI	✓ / ✓

Mutated AmpC[1,3]

Ceftolozane–tazobactam	✗
Ceftazidime–avibactam	✗





Inherent resistance to many drug classes

Capacity to form biofilm

Quickly acquires resistance to ongoing treatments

*Pfizer has data on combination therapy of ZAVICEFTA along with metronidazole, aminoglycosides, vancomycin and linezolid based only on Phase III trials and in vitro studies. Beyond this, Pfizer has no data to recommend combination therapy. When reviewing data from real-world studies, please note that there are limitations of real-world data analyses. The interpretations from non-randomised real-world data analyses are limited by potential selection bias and unknown confounding factors.[5]

1.Glen KA, Lamont IL. Pathogens 2021;10:1638; 2. Daikos GL, et al. Antibiotics (Basel) 2021;10:1126; 3. Kunz Coyne AJ, et al. 2022; doi: 10.1007/s40121-022-00591-2 (Epub ahead of print) ; 4. Lee M, et al. Diagn Microbiol Infect Dis 2021;99:115227; 5. Alemayehu D, et al. J Manag Care Pharm 2011;17(9 Suppl A):S22–S26.

Newer Expanded Spectrum β-lactamases

MDR pathogen	Mechanism	Ceftazidime–avibactam	Ceftolozane–tazobactam	Meropenem–vaborbactam	Imipenem–relebactam	Cefiderocol
ESBL	SHV/TEM	✓	✓	✓	✓	✓
	CTX-M	✓	✓	✓	✓	✓
Enterobacterales	AmpC	✓	✗	✓	✓	✓
P. aeruginosa	AmpC	✓	✓	✓	✓	✓
CRE	KPC	✓	✗	✓	✓	✓
	OXA-48	✓	✗	✗	✗	✓
	MBL	✗	✗	✗	✗	✓
P. aeruginosa	Carbapenem-resistant	✓	✓	✗	✓	✓
	MDR	✓	✓	✗	✓	✓
Acinetobacter spp.	Carbapenem-resistant	✗	✗	✗	✗	✓

AmpC, ampicillin class C; CRE, carbapenem-resistant Enterobacterales; CTX-M, cefotaximase; ESBL, extended-spectrum β-lactamase; KPC, Klebsiella pneumoniaecarbapenemase; MBL, metallo-β-lactamase; MDR, multidrug-resistant; OXA, oxacillinase; SHV, sulfhydryl-variable β-lactamase; TEM, Temoneira β-lactamase.1. Lagacé-Wiens P, et al. Core Evid2014;9:13–25; 2. ZAVICEFTA®(ceftazidime–avibactam) Summary of Product Characteristics. Pfizer, 2021; 3. Liscio JL, et al. Int J Antimicrob Agents 2015;46:266–71; 4. Bush K. Int J Antimicrob Agents 2015;46:483–93; 5. Zhanel GG, et al. Drugs2013;73:159–77; 6. Wright H, et al. Clin Microbiol Infect 2017;23:704–12; 7. Munita JH, et al. Clin Infect Dis 2017;65:158–61; 8. ZERBAXA®(ceftolozane–tazobactam) Summary of Product Characteristics. Merck, 2019; 9. Sader HS, et al. Diagn Microbiol Infect Dis 2015;83:389–94; 10. Walkty A, et al. Antimicrob Agents Chemother 2011;55:2992–4; 11. Lomovskaya O, et al. Antimicrob Agents Chemother 2017;61:e01443-17; 12. RECARBRIO®(imipenem+cilastatin/relebactam) Summary of Product Characteristics. Merck, 2021; 13. Bush K and Jacoby GA. Antimicrob Agents Chemother 2010;54:969–76; 14. VABOREM®(meropenem–vaborbactam) Summary of Product Characteristics. Menarini International, 2021; 15. Noval M, et al. Curr Infect Dis Rep 2020;22:1; 16. FETROJA®(cefiderocol) US Prescribing Information. Shionogi, 2020.

Comparison of recently-approved treatment options in adults for MDR Gram-negative infections in Europe

Agent*	Complicated urinary tract infection (cUTI), including pyelonephritis	Complicated intra-abdominal infection (cIAI)	Hospital-acquired pneumonia, including ventilator-associated pneumonia (HAP/VAP)	Infections due to aerobic Gram-negative organisms in patients with limited treatment options†	Bacteraemia that occurs in association with, or is suspected to be associated with cUTI, cIAI or HAP/VAP	Indications approved in paediatric population (3 months and older)?
Ceftazidime–avibactam[1,‡]	✓	✓	✓	✓	✓	✓
Imipenem/cilastatin–relebactam[3]	✗	✗	✓	✓	✗	✗
Meropenem–vaborbactam[4]	✓	✓	✓	✓	✓	✗
Cefiderocol[5]	✗	✗	✗	✓	✗	✗

Ceftolozane–tazobactam has been omitted because it does not cover CRE.[2]

*Launched in at least one major market; † Data support the use of ZAVICEFTA in adult patients with limited treatment options, including in primary bacteraemia, cSSTI, BJI, meningitis, febrile neutropenia, cystic fibrosis, post-transplant patients due to KPC and OXA-48 resistance mechanisms, and MDR *Pseudomonas*[6–20]; ‡ Bacteraemia that occurs in association with, or is suspected to be associated with, CUTI, CIAI or HAP/VAP are approved only for use in adults.[1]

BJI, bone and joint infections; cIAI, complicated intra-abdominal infection; cSSTI, complicated skin and soft tissue infection; cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; KPC, *Klebsiella pneumoniae* carbapenemase; MDR, multidrug-resistan
OXA, oxacillinase; VAP, ventilator-associated pneumonia.

1. ZAVICEFTA® (ceftazidime–avibactam) Summary of Product Characteristics. Pfizer, 2021; 2. ZERBAXA® (ceftolozane–tazobactam) Summary of Product Characteristics. Merck, 2021; 3. RECARBRIO® (imipenem+cilastatin/relebactam) Summary of Product Characteristics. Merck, 2021; 4. VABOREM® (meropenem–vaborbactam) Summary of Product Characteristics. Menarini International Operations, 2021; 5. FETCROJA® (cefiderocol) Summary of Product Characteristics. Shionogi, 2022; 6. Sousa A, et al. *J Antimicrob Chemother* 2018;73:3170
5; 7. Shields RK, et al. *Antimicrob Agents Chemother* 2017;61:e00883-17; 8. Temkin E, et al. *Antimicrob Agents Chemother* 2017;61:e01964-16; 9. Castón JJ, et al. *Int J Infect Dis* 2017;59:118–23; 10. van Duin D, et al. *Clin Infect Dis* 2018;66:163–71; 11. Tumbarello M, et al. *Cli*
Infect Dis 2019;68:355–64; 12. Tumbarello M, et al. *Clin Infect Dis* 2021;73:1664–76; 13. Tsolaki V, et al. *Antimicrob Agents Chemother* 2020;64:e02320-19; 14. Rathish B, et al. *Cureus* 2021;13:e13081; 15. Jabbour JF, et al. *Curr Opin Infect Dis* 2020;33:146–54; 16. Chen W, et
al. *Ann Transl Med* 2020;8:39; 17. Atkin SD, et al. *Infect Drug Resist* 2018;11:1499–510; 18. Aguado JM, et al. *Transplant Rev (Orlando)* 2018;32:36–57; 19. Soriano A, et al. *Infect Dis Ther* 2021;10:1989-2034; 20. Mazuski JE, et al. *Infect Dis Ther* 2021;10:2399–414.


LET'S
TALK
ABOUT IT

Newer Expanded Spectrum β-lactamases

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ESBL	SHV/TEM	✓	✓	✓	✓	✓
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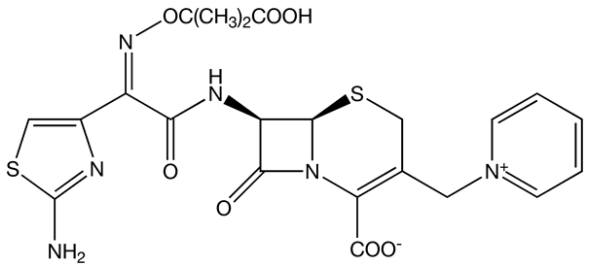
	OXA-48	✓	✗	✗	✗	✓
	MBL	✗	✗	✗	✗	✓
P. aeruginosa	Carbapenem-resistant	✓	✓	✗	✓	✓
	MDR	✓	✓	✗	✓	✓
Acinetobacter spp.	Carbapenem-resistant	✗	✗	✗	✗	✓

AmpC, ampicillin class C; CRE, carbapenem-resistant Enterobacterales; CTX-M, cefotaximase; ESBL, extended-spectrum β-lactamase; KPC, Klebsiella pneumoniaecarbapenemase; MBL, metallo-β-lactamase; MDR, multidrug-resistant; OXA, oxacillinase; SHV, sulfhydryl-variable β-lactamase; TEM, Temoneira β-lactamase.1. Lagacé-Wiens P, et al. Core Evid2014;9:13–25; 2. ZAVICEFTA®(ceftazidime–avibactam) Summary of Product Characteristics. Pfizer, 2021; 3. Liscio JL, et al. Int J Antimicrob Agents 2015;46:266–71; 4. Bush K. Int J Antimicrob Agents 2015;46:483–93; 5. Zhanel GG, et al. Drugs2013;73:159–77; 6. Wright H, et al. Clin Microbiol Infect 2017;23:704–12; 7. Munita JH, et al. Clin Infect Dis 2017;65:158–61; 8. ZERBAXA®(ceftolozane–tazobactam) Summary of Product Characteristics. Merck, 2019; 9. Sader HS, et al. Diagn Microbiol Infect Dis 2015;83:389–94; 10. Walkty A, et al. Antimicrob Agents Chemother 2011;55:2992–4; 11. Lomovskaya O, et al. Antimicrob Agents Chemother 2017;61:e01443-17; 12. RECARBRIO®(imipenem+cilastatin/relebactam) Summary of Product Characteristics. Merck, 2021; 13. Bush K and Jacoby GA. Antimicrob Agents Chemother 2010;54:969–76; 14. VABOREM®(meropenem–vaborbactam) Summary of Product Characteristics. Menarini International, 2021; 15. Noval M, et al. Curr Infect Dis Rep 2020;22:1; 16. FETROJA®(cefiderocol) US Prescribing Information. Shionogi, 2020.

Ceftazidime-Avibactam: Old Cephalosporin & New Inhibitor

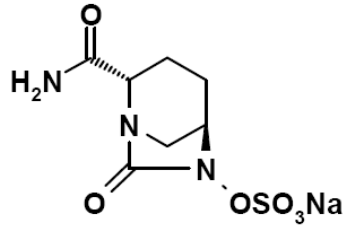
Ceftazidime

- **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.*

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

Πρόγραμμα κλινικών δοκιμών φάσης III του Zavicefta[1,2,3,4,5]

Επτά προοπτικές, διεθνείς, πολυκεντρικές, τυχαιοποιημένες μελέτες φάσης III

RECLAIM 1, 2 και 3: Ενήλικες με cIAIs *1.507 ασθενείς*[1,2]

- Διπλά τυφλή τυχαιοποίηση (1:1)
  - **CAZ 2000 mg+AVI 500 mg**+μετρονιδαζόλη 500 mg IV x3 ή
  - **MER 1000 mg** IV+εικονικό φάρμακο x3
- **Πρωτεύον στόχος:**
  Μη κατωτερότητα της CAZ–AVI
  - **RECLAIM** 1 & 2 (TOC στον mMITT, CE)
  - **RECLAIM** 3 (TOC visit στον CE)

RECAPTURE 1 και 2: Ενήλικες με cUTIs *1.033 ασθενείς*[3]

- Διπλά τυφλή τυχαιοποίηση (1:1)
  - **CAZ 2000 mg+AVI 500 mg x3 IV** ή
  - **DOR 500 mg**+εικονικό φάρμακο x3 IV
- **Πρωτεύων στόχος**
  - Εκτίμηση της μη κατωτερότητας της CAZ-AVI στα συμπρωτεύοντα τελικά σημεία στην ομάδα ανάλυσης mMITT:
  - Υποχώρηση των συμπτωμάτων ουρολοίμωξης
  - Υποχώρηση/βελτίωση του λαγόνιου πόνου
  - Μικροβιολογική εκρίζωση και υποχώρηση των συμπτωμάτων ανά ασθενή

REPRISE: Ενήλικες με CAZ-R παθογόνα 333 ασθενείς[4]

- Ανοιχτή τυχαιοποίηση (1:1)
  - **CAZ 2000 mg+AVI 500** mg+ μετρονιδαζόλη 500 mg x3 IV ή
  - **Βέλτιστη διαθέσιμη θεραπεία (BAT)**
- **Πρωτεύων στόχος**
  - Εκτίμηση της κλινικής ανταπόκρισης στην CAZ-AVI & στην βέλτιστη διαθέσιμη θεραπεία (BAT) ανά ασθενή κατά την επίσκεψη TOC σε cUTIs και cIAIs προκαλούμενες από Gram-αρνητικά παθογόνα ανθεκτικά στην CAZ

BAT: Καρβαπενέμες (97%)

REPROVE: Ενήλικες με HAP (συμπ. VAP) 817 ασθενείς[5]

- Διπλά τυφλή τυχαιοποίηση (1:1)
  - **CAZ 2000 mg+AVI 500 mg x3 IV** ή
  - **MER 1000** mg+ εικονικό φάρμακο x3
  Συν ανοιχτή εμπειρική θεραπεία με λινεζολίδη+ αμινογλυκοσίδη
- **Πρωτεύων στόχος**
  - Εκτίμηση της μη κατωτερότητας της CAZ-AVI στο ποσοστό κλινικής ίασης κατά την επίσκεψη TOC στους πληθυσμούς cMITT και CE

AVI: avibactam, **BAT**, best available therapy, **CAZ**, ceftazidime, **CE**, clinically evaluable, **cIAIs**, complicated intra-abdominal infections, **cMITT**, clinically modified intent-to-treat, **cUTIs**, complicated urinary tract infections, **DOR:** Ντοριπενέμη, **IV:** ενδοφλέβια, **MER:** meropenem, **mMITT**, microbiological modified intent-to-treat, **HAP: νοσοκομειακή πνευμονία**, **TOC**, test of cure, **VAP**, ventilator-associated pneumonia

1. Mazuski JE et al. *Clin Infect Dis*. 2016;62:1380–1389 2. *X. Qin et al. International Journal of Antimicrobial Agents 49 (2017) 579–588. 3. Wagenlehner F, et al. Clin Infect Dis 2016;63:754-62. 4. Carmeli Y et al, Lancet Infect Dis 2016;16: 661–73. 5. Torres A, et al. Lancet Infect Dis. 2017 Dec 15*

Κεφταζιντίμη-Αβιμπακτάμη (CAZ-AVI) : Προφίλ Ασφάλειας και Ανοχής[1,2]

- Σε επτά κλινικές μελέτες Φάσης 2 και Φάσης 3, 2.024 ενήλικοι ασθενείς έλαβαν θεραπεία με κεφταζιντίμη-αβιμπακτάμη[1]
- Οι πιο συχνές ανεπιθύμητες ενέργειες που εμφανίστηκαν σε ≥5% των ασθενών υπό θεραπεία με CAZ-AVI ήταν η θετική άμεση δοκιμασία Coombs, η ναυτία και η διάρροια[1]
- Η ναυτία και η διάρροια ήταν συνήθως ήπιας ή μέτριας έντασης[1]

Αναφερόμενες Ανεπιθύμητες ενέργειες (ΑΕ) σε τέσσερις κλινικές δοκιμές Φάσης 3[2,3]

Ανεπιθύμητες ενέργειες (ΑΕ) (%)	RECLAIM 1 & 2		RECAPTURE 1 & 2	
	CAZ-AVI + μετρονιδαζόλη*	Μεροπενέμη	CAZ-AVI‡	Ντοριπενέμη
Οποιαδήποτε ΑΕ	**45.9**	**42.9**	**36.2**	**31.0**
Σοβαρή ΑΕ	**7.9**	**7.6**	**4.1**	**2.4**
Διακοπή της θεραπείας λόγω ΑΕ	**2.6**	**1.3**	**1.4**	**1.2**

Οι συχνότερα αναφερόμενες ΑΕ στο σκέλος του CAZ-AVI ήταν διάρροια (7,6%), ναυτία (6,8%), έμετοι (4,5%) και πυρεξία (4,5%)
.‡ Οι συχνότερα αναφερόμενες ΑΕ στο σκέλος του CAZ-AVI ήταν κεφαλαλγία (7,4%), ναυτία (2,9%), διάρροια (2,7%) και δυσκοιλιότητα (2,2%)
ΑΕ: Ανεπιθύμητες ενέργειες, CAZ-AVI: κεφταζιντίμη-αβιμπακτάμη
1. Περίληψη Χαρακτηριστικών Προϊόντος Zavicefta, 10/2018. 2. Mazuski JE, et al. Clin Infect Dis 2016;62:1380–9; 3. Wagenlehner F, et al. Clin Infect Dis 2016;63:754–62.

The real world evidence…

Real-world evidence: 42 studies with 4753 patients

Single-centre, retrospective cohort studies[1–23]

- 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
- Algwizani A, et al. 2018
- Rodríguez-Núñez O, et al. 2018
- De la Calle C, et al. 2019
- Alraddadi BM, et al. 2019
- Katchanov J, et al. 2018
- Recio R, et al. 2018
- Spoletini G, et al. 2019
- Iannaccone M, et al. 2020
- Chen W, et al. 2020
- Rathish B, et al. 2021
- Atkin SD, et al. 2018
- Shi Y, et al. 2021
- Chen J, et al. 2022
- Wang Q, et al. 2022
- Gu J, et al. 2021
- Zhang F, et al. 2021
- Corbella et al. 2022

Multicentre, retrospective cohort studies[24–38]

- Temkin E, et al. 2017
- Castón JJ, et al. 2017
- King M, et al. 2017
- Jorgensen SCJ, et al. 2019
- Bassetti M, et al. 2019
- Tsolaki V, et al. 2020
- Jorgensen SC, et al. 2020
- Ackley R, et al. 2020
- Strich JR, et al. 2021
- Vena A, et al. 2020
- Tumbarello M, et al. 2021
- Castón JJ, et al. 2022
- Almangour TA, et al. 2022
- Balandín B, et al. 2022
- Falcone M, et al. 2020
- Tumbarello M, et al. 2019

Single-centre, prospective, observational or multicentre case–control studies[39–41]

- Sousa A, et al. 2018
- Guimarães T, et al. 2019

Multicentre, prospective, observational cohort studies[42]

- van Duin D, et al. 2018

**Pfizer hasdata on combination therapy of Zaviceftaalong with metronidazole, aminoglycosides, vancomycinand linezolid based only on Phase III trialsand in vitro studies. Beyond this, Pfizer has no data to recommend combination therapy. Limitations of real-world data analyses: the interpretations from non-randomisedreal-world data analyses are limited by potential selection bias and unknown confounding factors.*

431. Aitken SL, et al. Clin Infect Dis 2016;63:954–8; 2. Shields RK, et al. Clin Infect Dis 2016;63:1615–8; 3. KrappF, et al. Int J AntimicrobAgents 2017;49:770–3; 4. Shields RK, et al. AntimicrobAgents Chemother 2017;61:e00883-17; 5. SantevecchiBA, et al. Int J AntimicrobAgents 2018;51:629–35; 6. Shields RK, et al. AntimicrobAgents Chemother 2018;62:e02497-18; 7. AlgwizaniA, et al. J Infect Public Health 2018;11:793–5; 8. Rodríguez-NúñezO, et al. J Glob AntimicrobResist 2018;15:136–9; 9. De la Calle C, et al. Int J AntimicrobAgents 2019;53:520–4; 10. AlraddadiBM, et al. BMC Infect Dis 2019;19:772; 11. KatchanovJ, et al. PLoSOne 2018;13:e0195757; 12. RecioR, et al. Int J AntimicrobAgents 2018;52:172–9; 13. SpoletiniG, et al. J AntimicrobChemother 2019;74:1425–9; 14. IannacconeM, et al. J Chemother 2020;32:160–2; 15. Chen W, et al. Ann TranslMed 2020;8:39–51; 16.Rathish B, et al. Cureus2021;13:e13081; 17. Atkin SD, et al Infect Drug Resist 2018;11:1499–1510; 18. Shi Y et al. Infect Dis Ther2021; doi: 10.1007/s40121-021-00542-3 (Epubahead of print); 19. Chen J, et al. Infect Drug Resist2022;15:655–67; 20. Wang Q, et al. J Infect Public Health2022; doi: 10.1016/j.jiph.2022.02.003 (Epubahead of print); 21. Gu J, et al. JGlob AntimicrobResist 2021;26:20–5; 22. Zhang F, et al. Infect Drug Resist 2021;14:5165–74; 23.CorbellaL, et al. Int J AntimicrobAgents 2022;59:106517; 24. Temkin E, et al. AntimicrobAgents Chemother 2017;61:e01964-16; 25. CastónJJ, et al. Int J Infect Dis 2017;59:118–23; 26. King M, et al. AntimicrobAgents Chemother 2017;61:e00449-17; 27. Jorgensen SCJ, et al. Open Forum Infect Dis 2019;6:ofz522; 28. BassettiM, et al. J Glob AntimicrobResist 2019;17:109–11; 29. TsolakiV, et al. AntimicrobAgents Chemother2020;64:e02320-19; 30. Jorgensen SC, et al. Infect Dis Ther2020;9:291–304; 31. Ackley R, et al. AntimicrobAgents Chemother 2020;64:e02313-19; 32. StrichJR, et al. Clin Infect Dis 2021;72:611–21; 33. Vena A, et al. Antibiotics (Basel) 2020;9:71; 34. TumbarelloM, et al. Clin Infect Dis2021;73:1664–76; 35. CastonJJ, et al. JAntimicrobChemother2022; doi: 10.1093/jac/dkac049 (Epubahead of print); 36. AlmangourTA, et al. Infect Drug Resist2022;15:211–21; 37. BalandínB, et al. Int J AntimicrobAgents 2022; doi: 10.1016/j.ijantimicag.2022.106536 (Epubahead of print); 38. Falcone M, et al. Crit Care 2020;24:29–41; 39. TumbarelloM, et al. Clin Infect Dis 2019;68:355–64;40. Sousa A, et al. J AntimicrobChemother 2018;73:3170–5; 41.GuimarãesT, et al. AntimicrobAgents Chemother 2019;63:pii:e00528-19; 42. van DuinD, et al. Clin Infect Dis 2018;66:163–71; 43. Alemayehu D, et al. J ManagCare Pharm 2011;17(9 SupplA):S22–S26.

J Antimicrob Chemother
https://doi.org/10.1093/jac/dkac049

Journal of Antimicrobial Chemotherapy

Impact of ceftazidime/avibactam versus best available therapy on mortality from infections caused by carbapenemase-producing Enterobacterales (CAVICOR study)[*,1]

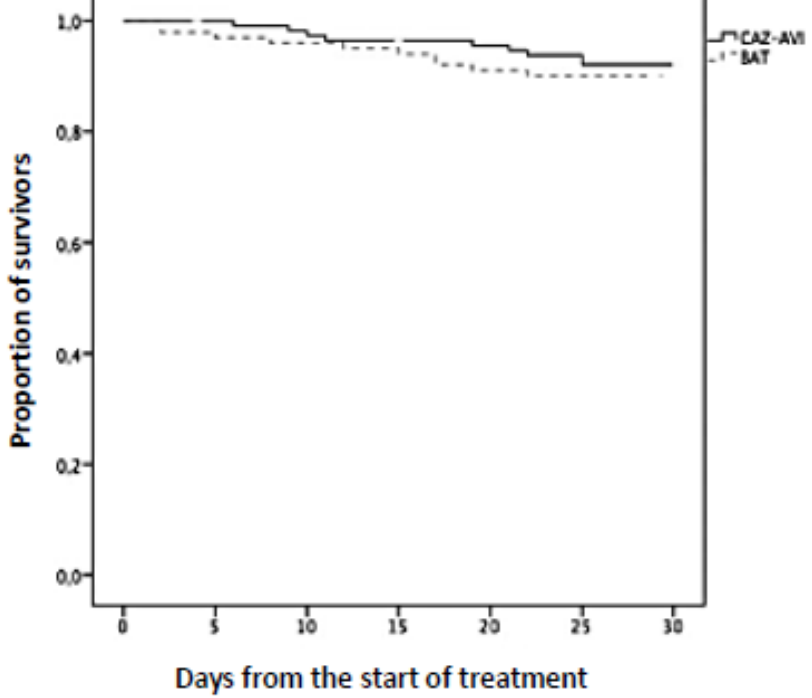
Juan José Castón[1,2,3,4*], Angela Cano[1,2,3,4], Inés Pérez-Camacho[5], Jose M. Aguado[4,6,7], Jordi Carratalá[4,8,9], Fernando Ramasco[10], Alex Soriano[4,11], Vicente Pintado[12], Laura Castelo-Corral[13], Adrian Sousa[14], María Carmen Fariñas[4,15,16], Patricia Muñoz[4,17,18,19,20], Vicente Abril López De Medrano[21], Óscar Sanz-Peláez[22], Ibai Los-Arcos[4,23,24], Irene Gracia-Ahufinger[3,25], Elena Pérez-Nadales[1,2,3], Elisa Vidal[1,2,3,4], Antonio Doblas[1], Clara Natera[1,2], Luis Martínez-Martínez[3,4,25,26] and Julian Torre-Cisneros[1,2,3,4]

Variable*	Ceftazidime–avibactam (n=189)	Best available therapy (n=150)	P value
21-day clinical cure, n (%)	169 (89.4)	119 (79.3)	0.01
Microbiological response, n (%)	100 (52.9)	50 (33.3)	<0.001
Infection relapse, n (%)	24 (12.7)	13 (8.6)	0.24
Crude mortality (30 days), n (%)	26 (13.7)	33 (22)	0.04

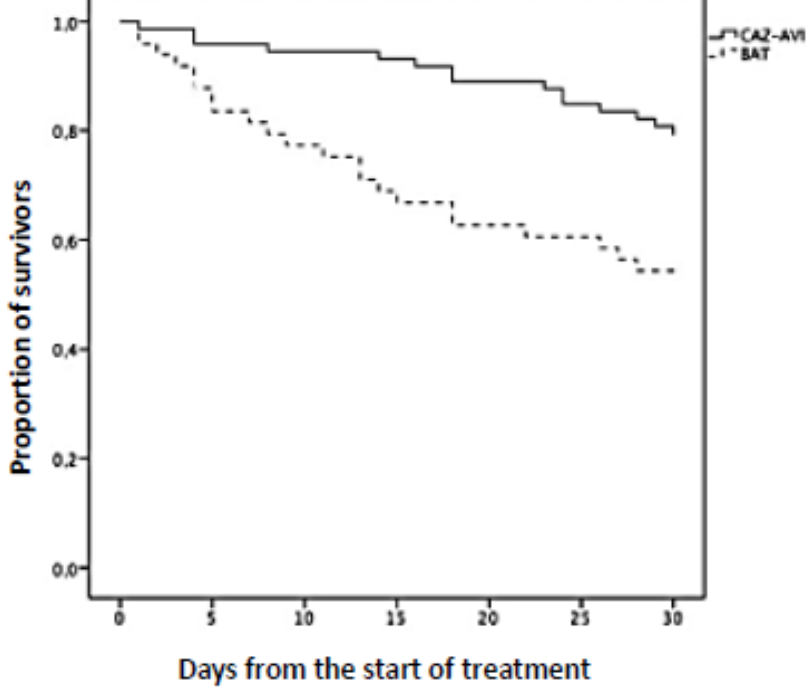
**Limitations of real-world data analyses: the interpretations from non-randomisedreal-world data analyses are limited by potential selection bias and unknown confounding factors.21. CastónJJ, et al. J Antimicrob Chemother 2022;dkac049. doi:10.1093/jac/dkac049. Online ahead of print; 2. Alemayehu D, et al. J Manag Care Pharm 2011;17(9 Suppl A):S22–S26.*

CAVICOR: Survival outcomes in patients treated with CAZ–AVI vs BAT for infections caused by CPE*[1]

Survival in patients with INCREMENT-CPE score of ≤7 points (log rank 0.73)



Survival in patients with INCREMENT-CPE score of >7 points (log rank 0.004)



**Limitations of real-world data analyses: the interpretations from non-randomisedreal-world data analyses are limited by potential selection bias and unknown confounding factors.2BAT, best available therapy; CAZ–AVI, ceftazidime–avibactam; CPE, carbapenemase-producing Enterobacterales. 1. Castón JJ, et al. J Antimicrob Chemother 2022;dkac049. doi:10.1093/jac/dkac049. Online ahead of print; 2. Alemayehu D, et al. J Manag Care Pharm 2011;17(9 Suppl A):S22–S26.*

Ceftazidime–avibactam vs other regimens in the treatment of CRE

Observational studies*,**,†

- **van Duin D, et al. *Clin Infect Dis* 2018**

CAZ–AVI-based (n=38) vs colistin-based (n=99) therapy. IPTW-adjusted all-cause hospital mortality 30 days after starting treatment was **9% (CAZ–AVI) versus 32% (colistin-based)‡,**[1]

- **Tsolaki V, et. al *Antimicrob Agents Chemother* 2020**

Of 77 ICU patients with serious infections, 41 received CAZ–AVI and 36 other therapy. **CAZ–AVI-containing regimens were an independent predictor of survival and clinical cure**[3]

- **Tumbarello M, et al. *Clin Infect Dis* 2019**

Of 154 patients with CR-GNB infections treated with CAZ–AVI, 104 had KPC BSIs and were compared with a matched cohort treated with other drugs (n=104).§ **Treatment with CAZ–AVI-containing regimens was the sole independent predictor for 30-day survival**[2]

- **Ackley R, et al. *Antimicrob Agents Chemother* 2020**

CAZ–AVI (n=105, the majority in combination with another agent) vs meropenem–vaborbactam (n=26, 4 received combination). Composite endpoint; no significant difference in clinical success; 3 isolates in CAZ–AVI group developed resistance, none in the meropenem–vaborbactam group[4]

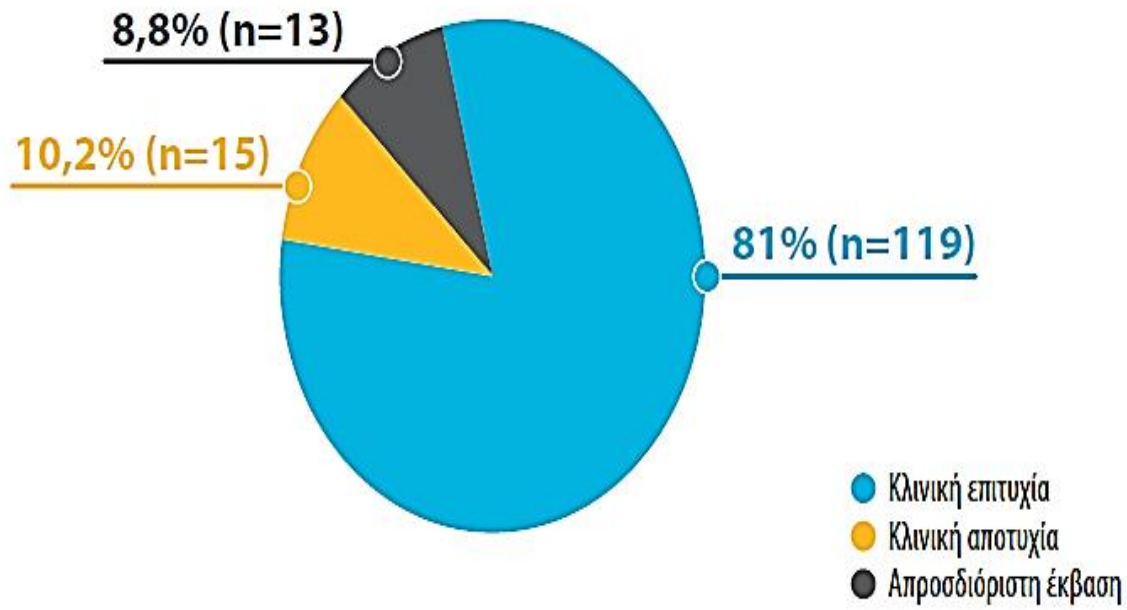
Pfizer has data on combination therapy of ZAVICEFTA along with metronidazole, aminoglycosides, vancomycin and linezolid based only on Phase III trials and *in vitro* studies. Beyond this, Pfizer has no data to recommend combination therapy; ** When reviewing data from real-world studies, please note that there are limitations of real-world data analyses. The interpretations from non-randomised real-world data analyses are limited by potential selection bias and unknown confounding factors;5 † Data support the use of ZAVICEFTA in adult patients with limited treatment options, including in primary bacteraemia, cSSTI, BJI, meningitis, febrile neutropenia, cystic fibrosis, post-transplant patients due to KPC and OXA-48 resistance mechanisms, and MDR *Pseudomonas;*1-3,6-17 ‡ IPTW-adjusted estimates; adjustment for confounding by indication was performed using inverse probability of treatment weighting (IPTW)1; § Patients treated for KPC-Kp infections between 1 April 2016 and 31 December 2017; Approximately 75% were bacteraemic and approximately 25% were non-bacteraemic infections involving (in order of decreasing frequency) the lower respiratory tract, intra-abdominal structures, the urinary tract, or other sites.2

BJI, bone and joint infection; BSI, bloodstream infections; CAZ–AVI, ceftazidime–avibactam; CRE, carbapenem-resistant Enterobacteriaceae; CR-GNB, carbapenem-resistant Gram-negative bacteria; cSSTI, complicated skin and soft tissue infection; ICI, intensive care unit; IPTW, inverse probability of treatment weighting; KPC, *Klebsiella pneumoniae* carbapenemase; MDR, multidrug-resistant; OXA, oxacillinase.

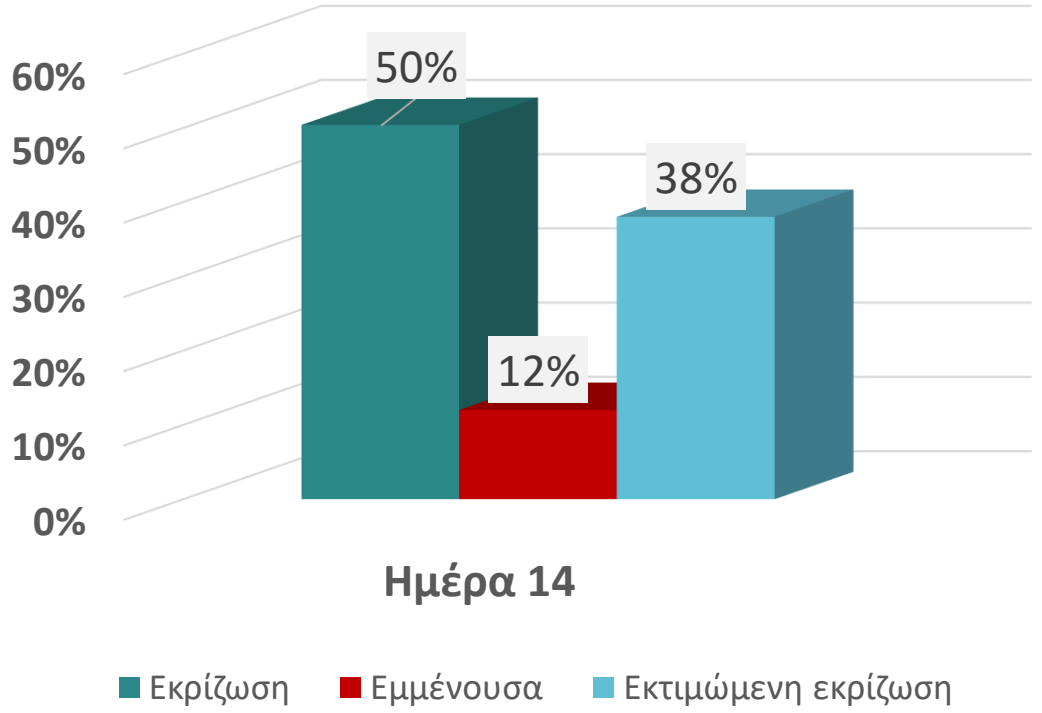
1. van Duin D, et al. *Clin Infect Dis* 2018;66:163–71; 2. Tumbarello M, et al. *Clin Infect Dis* 2019;68:355–64; 3. Tsolaki V, et al. *Antimicrob Agents Chemother* 2020;64:e02320-19; 4. Ackley R, et al. *Antimicrob Agents Chemother* 2020;64:e02313-19; 5. Alemayehu D, et al. *J Manag Care Pharm* 2011;17(9 Suppl A):S22–S26; 6. Sousa A, et al. *J Antimicrob Chemother* 2018;73:3170–5; 7. Shields RK, et al. *Antimicrob Agents Chemother* 2017;61:e00883-17; 8. Temkin E, et al. *Antimicrob Agents Chemother* 2017;61:e01964-16; 9. Castón JJ, et al. *Int J Infect Dis* 2017;59:118–23; 10. Tumbarello M, et al. *Clin Infect Dis* 2021;73:1664–76; 11. Rathish B, et al. *Cureus* 2021;13:e13081; 12. Jabbour JF, et al. *Curr Opin Infect Dis* 2020;33:146–54; 13. Chen W, et al. *Ann Transl Med*;2020;8:39; 14. Atkin SD, et al. *Infect Drug Resist* 2018;11:1499–510; 15. Aguado JM, et al. *Transplant Rev (Orlando)* 2018;32:36–57; 16. Soriano A, et al. *Infect Dis Ther* 2021;10:1989-2034; 17. Mazuski JE, et al. *Infect Dis Ther* 2021;10:2399–414.

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*

CAZ–AVI, ceftazidime–avibactam; MBL: Metallo-b-lactamases

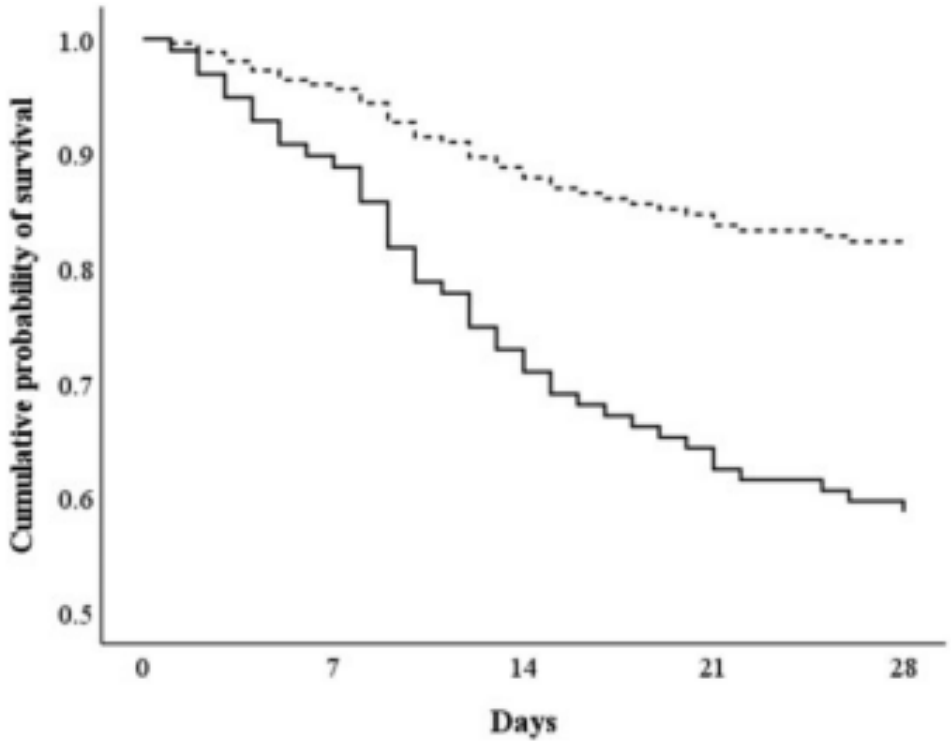
Karaiskos et al J Antimicrob Chemother. 2021

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%)

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Ceftazidime–avibactam for patients with serious Gram-negative infections and limited treatment options*: Studies and patient populations[1†]

73 publications (including 10 congress abstracts)

- 1,926 CAZ–AVI-treated patients
- 1,114 comparator-treated patients
- 2 prospective observational studies, 12 retrospective comparative/case–control studies, 16 retrospective cohort/chart review studies, 17 case series, 26 case reports

Studies were from:

- Europe (34; 47%), North America (29; 40%), China (5; 7%), Latin America (2; 3%) and the Middle East (2; 3%), Europe + Australia (1; 1%)

Most common infections:

- Pneumonia, bacteraemia, SSTIs, UTIs, abdominal infections

Most common organisms:

- CRE or carbapenemase-producing Enterobacterales (n=1,718)
- MDR and XDR *Pseudomonas aeruginosa* (n=150)

Many search results included complex patients:

Patient type	Publications (n)	Patients (n)
Haematology/ oncology	5 publications	44 patients
Solid organ transplant	7 publications	35 patients
Cystic fibrosis-related bronchopulmonary infection	6 publications	14 patients
Surgical and trauma	10 case studies	10 patients

All patients were hospitalised for serious illness
Most patients had multiple comorbidities

*Data support the use of ZAVICEFTA in adult patients with limited treatment options, including in primary bacteraemia, cSSTI, BJI, meningitis, febrile neutropenia, cystic fibrosis, post-transplant patients due to KPC and OXA-48 resistance mechanisms, and MDR *Pseudomonas*;[1–15] †Limitations of real-world data analyses: the interpretations from non-randomised real-world data analyses are limited by potential selection bias and unknown confounding factors.[16]

BJI, bone and joint infection; CAZ–AVI, ceftazidime–avibactam; CRE, carbapenem-resistant Enterobacterales; cSSTI, complicated skin and soft tissue infection; KPC, *Klebsiella pneumoniae* carbapenemase; MDR, multidrug-resistant; OXA, oxacillinase; SSTI, skin and soft tissue infection; UTI, urinary tract infection; XDR, extensively drug-resistant.

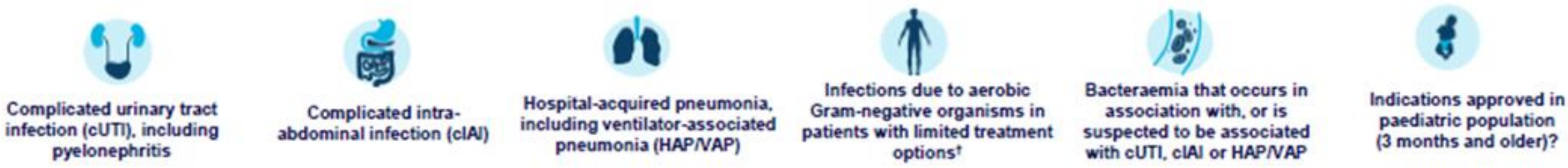
1. Soriano A, et al. *Infect Dis Ther* 2021;10:1989–2034; 2. Castón JJ, et al. *Int J Infect Dis* 2017;59:118–23; 3. van Duin D, et al. *Clin Infect Dis* 2018;66:163–71; 4. Sousa A, et al. *J Antimicrob Chemother* 2018;73:3170–5; 5. Temkin E, et al. *Antimicrob Agents Chemother* 2017;61:e01964-16; 6. Shields RK, et al. *Antimicrob Agents Chemother* 2017;61:e00883-17; 7. Tumbarello M, et al. *Clin Infect Dis* 2019;68:355–64; 8. Tumbarello M, et al. *Clin Infect Dis* 2021;ciab176; 9. Tsolaki V, et al. *Antimicrob Agents Chemother* 2020;64:e02320-19; 10. Rathish B, et al. *Cureus* 2021;13:e13081; 11. Jabbour J-F, et al. *Curr Opin Infect Dis* 2020;33:146–54; 12. Chen W, et al. *Ann Transl Med* 2020;8:39; 13. Atkin SD, et al. *Infect Drug Resist* 2018;11:1499–510; 14. Aguado JM, et al. *Transplant Rev (Orlando)* 2018;32:36–57; 15. Mazuski JE, et al. *Infect Dis Ther* 2021; 10:2399–414; 16. Alemayehu D, et al. *J Manag Care Pharm* 2011;17(9 Suppl A):S22–S26.

Συστάσεις για τη χορήγηση του συνδυασμού Κεφταζιντίμη-Αβιμπακτάμη[1]

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.

Σημείωση: 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 παλαιότερα φάρμακα αν το παθογόνο έχει *in vitro* ευαισθησία σε αυτά (π.χ. γενταμικίνη, κολιστίνη ή φωσφομυκίνη γιά UTIs, τιγκεκυκλίνη γιά λοίμωξη χειρουργικού τραύματος).



1. Οδηγίες της Εθνικής Επιτροπής Αντιβιογράμματος αναφορικά με την Zaficefta (ceftazidime/avibactam) και Zerbaxa (Ceftolozane / tazobactam). Available at: http://www.moh.gov.gr/articles/kentriko-symboylio-ygeias-ndash-kesy/apofaseis-ethnikhs-epitrophs-antibiogrammatos/5639-odhies-gia-thn-zaficefta-ceftazidime-avibactam-kai-zerbaxa-ceftolozane-tazobactam/(last accessed January 2019).

IMP, imipenemase-type carbapenemase, KPC: Klebsiella pneumoniae carbapenemase, ,NDM: New Delhi metallo-β-lactamase, OXA: oxacillinase-type carbapenemases, UTI: λοίμωξη ουροποιητικού, VIM: Verona integron-encoded metallo-β-lactamase

Συστάσεις για τη χορήγηση του συνδυασμού Κεφταζιντίμη-Αβιμπακτάμη (Οδηγίες της Εθνικής Επιτροπής Αντιβιογράμματος)

Εμπειρική Θεραπεία

Μπορεί να χορηγηθεί επί **κλινικής υποψίας** λοίμωξης, σε ασθενείς με παράγοντες κινδύνου για λοίμωξη από CPE, όπως:

- Α. Προηγούμενη λοίμωξη ή αποικισμό από CPE που παράγει KPC ή OXA-48
- Β. Νοσηλεία σε ΜΕΘ το τελευταίο εξάμηνο
- Γ. Νοσηλεία στον ίδιο θάλαμο με γνωστούς φορείς των μικροβίων αυτών

Και έχοντες τουλάχιστον ένα από τα παρακάτω:

- **Κατάσταση του ξενιστή**: Βαρέως πάσχοντες, ασθενείς ΜΕΘ, ανοσοκατεσταλμένοι ασθενείς
- **Βαρύτητα της λοίμωξης**: Ασθενείς με σοβαρή σήψη, σηπτική καταπληξία

CPE: Carbapenemase-producing *Enterobacteriaceae*, **KPC:** *Klebsiella pneumoniae* carbapenemase

Οδηγίες της Εθνικής Επιτροπής Αντιβιογράμματος αναφορικά με το Zaficefta (ceftazidime/avibactam) και το Zerbaxa (Ceftolozane / tazobactam). Available at: http://www.moh.gov.gr/articles/kentrikosymboylioygeias-ndash-kesy/apofaseis-ethnikhs-epitrophs-antibiogrammatos/5639-odhies-gia-thn-zaficefta-ceftazidime-avibactam-kaizerbaxa-ceftolozane-tazobactam/ (last accessed February 2020).

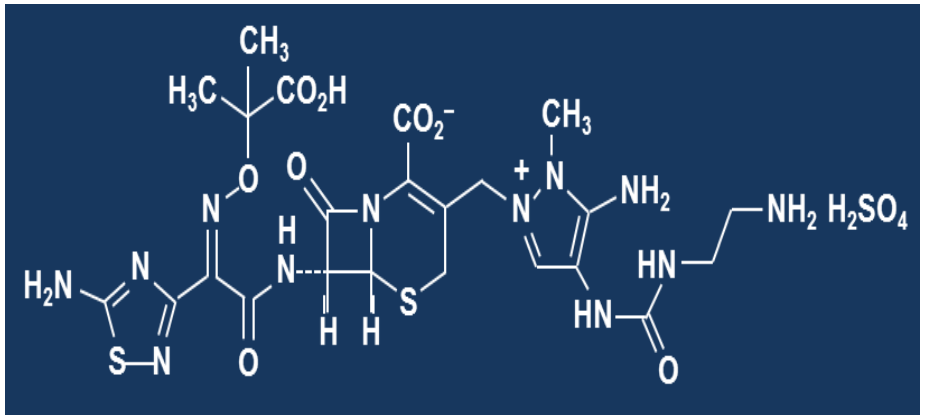
Newer Expanded Spectrum β-lactamases

MDR pathogen	Mechanism	Ceftazidime–avibactam	Ceftolozane–tazobactam	Meropenem–vaborbactam	Imipenem–relebactam	Cefiderocol
ESBL	SHV/TEM	✓	✓	✓	✓	✓
	CTX-M	✓	✓	✓	✓	✓
Enterobacterales	AmpC	✓	✗	✓	✓	✓
P. aeruginosa	AmpC	✓	✓	✓	✓	✓
CRE	KPC	✓	✗	✓	✓	✓
	OXA-48	✓	✗	✗	✗	✓
	MBL	✗	✗	✗	✗	✓
P. aeruginosa	Carbapenem-resistant	✓	✓	✗	✓	✓
	MDR	✓	✓	✗	✓	✓
Acinetobacter spp.	Carbapenem-resistant	✗	✗	✗	✗	✓

AmpC, ampicillin class C; CRE, carbapenem-resistant Enterobacterales; CTX-M, cefotaximase; ESBL, extended-spectrum β-lactamase; KPC, Klebsiella pneumoniaecarbapenemase; MBL, metallo-β-lactamase; MDR, multidrug-resistant; OXA, oxacillinase; SHV, sulfhydryl-variable β-lactamase; TEM, Temoneira β-lactamase.1. Lagacé-Wiens P, et al. Core Evid2014;9:13–25; 2. ZAVICEFTA®(ceftazidime–avibactam) Summary of Product Characteristics. Pfizer, 2021; 3. Liscio JL, et al. Int J Antimicrob Agents 2015;46:266–71; 4. Bush K. Int J Antimicrob Agents 2015;46:483–93; 5. Zhanel GG, et al. Drugs2013;73:159–77; 6. Wright H, et al. Clin Microbiol Infect 2017;23:704–12; 7. Munita JH, et al. Clin Infect Dis 2017;65:158–61; 8. ZERBAXA®(ceftolozane–tazobactam) Summary of Product Characteristics. Merck, 2019; 9. Sader HS, et al. Diagn Microbiol Infect Dis 2015;83:389–94; 10. Walkty A, et al. Antimicrob Agents Chemother 2011;55:2992–4; 11. Lomovskaya O, et al. Antimicrob Agents Chemother 2017;61:e01443-17; 12. RECARBRIO®(imipenem+cilastatin/relebactam) Summary of Product Characteristics. Merck, 2021; 13. Bush K and Jacoby GA. Antimicrob Agents Chemother 2010;54:969–76; 14. VABOREM®(meropenem–vaborbactam) Summary of Product Characteristics. Menarini International, 2021; 15. Noval M, et al. Curr Infect Dis Rep 2020;22:1; 16. FETROJA®(cefiderocol) US Prescribing Information. Shionogi, 2020.

Κεφτολοζάνη/Ταζομπακτάμη

Νέα Κεφαλοσπορίνη & **Παλιός Αναστολέας**



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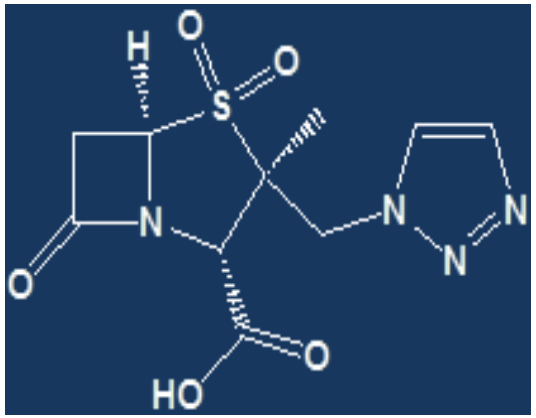


Κατηγορία

- Αντιψευδομοναδική Κεφαλοσπορίνη

  + αναστολέας β-λακταμάσης

- Αναλογία 2:1

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

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.

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, *Acinetobacter, Stenotrophomonas, Enterococcus spp*

Complicated urinary tract infection (cUTI), including pyelonephritis

Complicated intra-abdominal infection (cIAI)

Hospital-acquired pneumonia, including ventilator-associated pneumonia (HAP/VAP)

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

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**

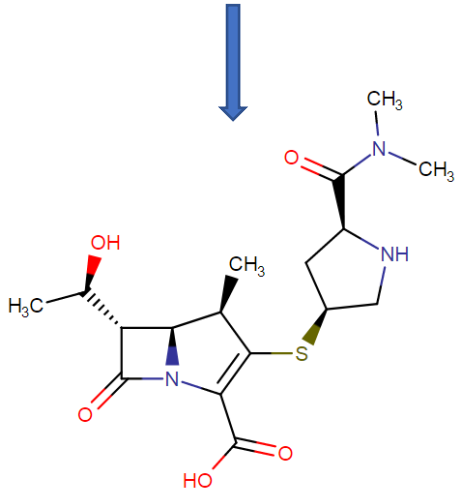
Newer Expanded Spectrum β-lactamases

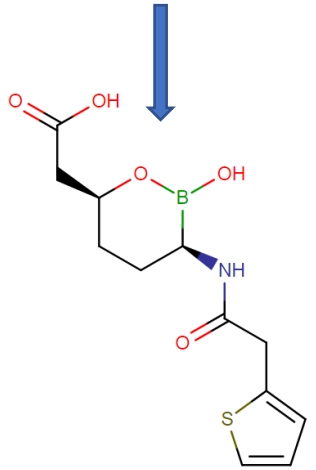
MDR pathogen	Mechanism	Ceftazidime–avibactam	Ceftolozane–tazobactam	Meropenem–vaborbactam	Imipenem–relebactam	Cefiderocol
ESBL	SHV/TEM	✓	✓	✓	✓	✓
	CTX-M	✓	✓	✓	✓	✓
Enterobacterales	AmpC	✓	✗	✓	✓	✓
P. aeruginosa	AmpC	✓	✓	✓	✓	✓
CRE	KPC	✓	✗	✓	✓	✓
	OXA-48	✓	✗	✗	✗	✓
	MBL	✗	✗	✗	✗	✓
P. aeruginosa	Carbapenem-resistant	✓	✓	✗	✓	✓
	MDR	✓	✓	✗	✓	✓
Acinetobacter spp.	Carbapenem-resistant	✗	✗	✗	✗	✓

*AmpC, ampicillin class C; CRE, carbapenem-resistant Enterobacterales; CTX-M, cefotaximase; ESBL, extended-spectrum β-lactamase; KPC, Klebsiella pneumoniaecarbapenemase; MBL, metallo-β-lactamase; MDR, multidrug-resistant; OXA, oxacillinase; SHV, sulfhydryl-variable β-lactamase; TEM, Temoneira β-lactamase.**1. Lagacé-Wiens P, et al. Core Evid2014;9:13–25; 2. ZAVICEFTA®(ceftazidime–avibactam) Summary of Product Characteristics. Pfizer, 2021; 3. Liscio JL, et al. Int J Antimicrob Agents 2015;46:266–71; 4. Bush K. Int J Antimicrob Agents 2015;46:483–93; 5. Zhanel GG, et al. Drugs2013;73:159–77; 6. Wright H, et al. Clin Microbiol Infect 2017;23:704–12; 7. Munita JH, et al. Clin Infect Dis 2017;65:158–61; 8. ZERBAXA®(ceftolozane–tazobactam) Summary of Product Characteristics. Merck, 2019; 9. Sader HS, et al. Diagn Microbiol Infect Dis 2015;83:389–94; 10. Walkty A, et al. Antimicrob Agents Chemother 2011;55:2992–4; 11. Lomovskaya O, et al. Antimicrob Agents Chemother 2017;61:e01443-17; 12. RECARBRIO®(imipenem+cilastatin/relebactam) Summary of Product Characteristics. Merck, 2021; 13. Bush K and Jacoby GA. Antimicrob Agents Chemother 2010;54:969–76; 14. VABOREM®(meropenem–vaborbactam) Summary of Product Characteristics. Menarini International, 2021; 15. Noval M, et al. Curr Infect Dis Rep 2020;22:1; 16. FETROJA®(cefiderocol) US Prescribing Information. Shionogi, 2020.*

Vaborem (EU) ή Vabomere (US)

(Μεροπενέμη / Βαμπορβακτάμη)





«Μια καρβαπενέμη και ένας καινοτόμος μη-β-λακταμικός κυκλικός αναστολέας β-λακταμασών περιέχων βορονικό οξύ»

Φάσμα δραστικότητας

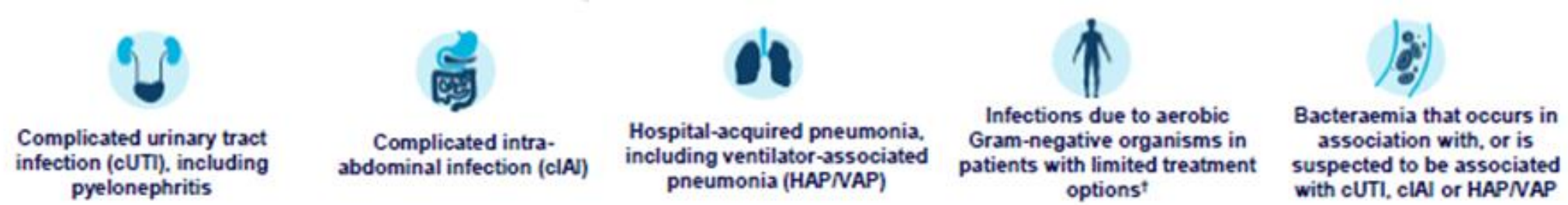
Κλινική αποτελεσματικότητα έναντι ειδικών παθογόνων

Η αποτελεσματικότητα **έχει καταδειχτεί** σε κλινικές μελέτες έναντι των ακόλουθων παθογόνων τα οποία ήταν ευαίσθητα σε μεροπενέμη/βαμπορβακτάμη *in vitro*.

Επιπλεγμένες λοιμώξεις της ουροφόρου οδού, συμπεριλαμβανομένης της πυελονεφρίτιδας

Gram-αρνητικοί μικροοργανισμοί:

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Enterobacter cloacae*



Vaborem (meropenem-vaborbactam). Summary of Product Characteristics, Menarini International, Dec 2021

Εγκριτικές Μελέτες

Μελέτη	Τύπος σχεδιασμού	Πληθυσμός	Παρέμβαση	Συμπέρασμα
TANGO-I	Phase 3, multicenter, multinational, randomized clinical	In patients with complicated Urinary Tract Infection (**UTI**), including acute pyelonephritis	Eligible patients were randomized 1:1 to receive **meropenem-vaborbactam (2g/2g over 3 hours; n = 274)** or **piperacillin-tazobactam (4g/0.5g over 30 minutes; n = 276)** every 8 hours. After 15 or more doses, patients could be switched to oral levofloxacin if they met prespecified criteria for improvement, to complete 10 days of total treatment.	Among patients with complicated UTI, including acute pyelonephritis and growth of a baseline pathogen, meropenem-vaborbactamvs piperacillin-tazobactam resulted in a **composite outcome of complete resolution or improvement of symptoms along with microbial eradication that met the noninferiority criterion**. Further research is needed to understand the spectrum of patients in whom meropenem-vaborbactam offers a clinical advantage.
TANGO-II	Phase 3, multinational, open-label, randomized controlled trial	In patients with confirmed/suspected CRE infection (**bacteremia, HABP/VABP, cIAI, cUTI/acute pyelonephritis**)	Eligible patients were randomized 2:1 to **meropenem-vaborbactam (2g/2g over 3 h, q8h for 7-14 days)** or **BAT (mono/combination therapy with polymyxins, carbapenems, aminoglycosides, tigecycline; or ceftazidime-avibactam alone)**.	Monotherapy with meropenem-vaborbactam for CRE infection was associated with **increased clinical cure, decreased mortality, and reduced nephrotoxicity compared with BAT**.

JAMA. 2018;319(8):788-799. doi:10.1001/jama.2018.0438
Infect Dis Ther. 2018;7(4):439-455. doi:10.1007/s40121-018-0214-1

Newer Expanded Spectrum β-lactamases

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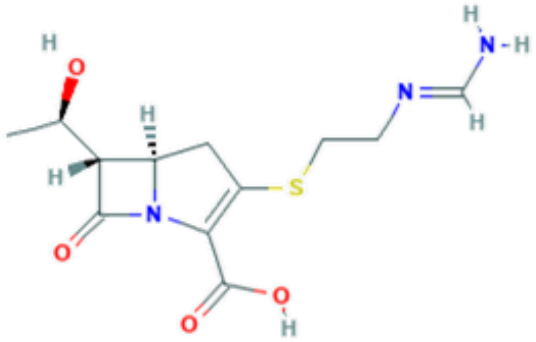
CRE	KPC	✓	✗	✓	✓	✓
	OXA-48	✓	✗	✗	✗	✓
	MBL	✗	✗	✗	✗	✓
P. aeruginosa	Carbapenem-resistant	✓	✓	✗	✓	✓
	MDR	✓	✓	✗	✓	✓
Acinetobacter spp.	Carbapenem-resistant	✗	✗	✗	✗	✓

*AmpC, ampicillin class C; CRE, carbapenem-resistant Enterobacterales; CTX-M, cefotaximase; ESBL, extended-spectrum β-lactamase; KPC, Klebsiella pneumoniaecarbapenemase; MBL, metallo-β-lactamase; MDR, multidrug-resistant; OXA, oxacillinase; SHV, sulfhydryl-variable β-lactamase; TEM, Temoneira β-lactamase.**1. Lagacé-Wiens P, et al. Core Evid2014;9:13–25; 2. ZAVICEFTA®(ceftazidime–avibactam) Summary of Product Characteristics. Pfizer, 2021; 3. Liscio JL, et al. Int J Antimicrob Agents 2015;46:266–71; 4. Bush K. Int J Antimicrob Agents 2015;46:483–93; 5. Zhanel GG, et al. Drugs2013;73:159–77; 6. Wright H, et al. Clin Microbiol Infect 2017;23:704–12; 7. Munita JH, et al. Clin Infect Dis 2017;65:158–61; 8. ZERBAXA®(ceftolozane–tazobactam) Summary of Product Characteristics. Merck, 2019; 9. Sader HS, et al. Diagn Microbiol Infect Dis 2015;83:389–94; 10. Walkty A, et al. Antimicrob Agents Chemother 2011;55:2992–4; 11. Lomovskaya O, et al. Antimicrob Agents Chemother 2017;61:e01443-17; 12. RECARBRIO®(imipenem+cilastatin/relebactam) Summary of Product Characteristics. Merck, 2021; 13. Bush K and Jacoby GA. Antimicrob Agents Chemother 2010;54:969–76; 14. VABOREM®(meropenem–vaborbactam) Summary of Product Characteristics. Menarini International, 2021; 15. Noval M, et al. Curr Infect Dis Rep 2020;22:1; 16. FETROJA®(cefiderocol) US Prescribing Information. Shionogi, 2020.*

Χημική δομή του Recarbrio

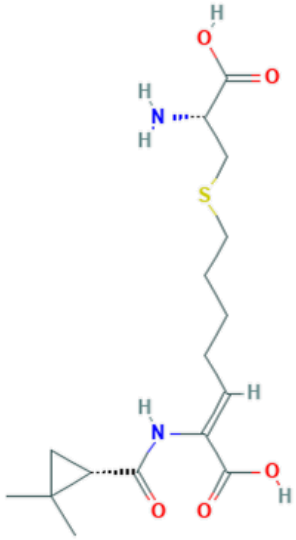
- Συνδυασμός ιμιπενέμης, μιας καρβαπενέμης, σιλαστατίνης, ενός αναστολέα νεφρικής δεϋδροπεπτιδάσης, και ρελεμπακτάμης, ενός αναστολέα β-λακταμασών

Ιμιπενέμη



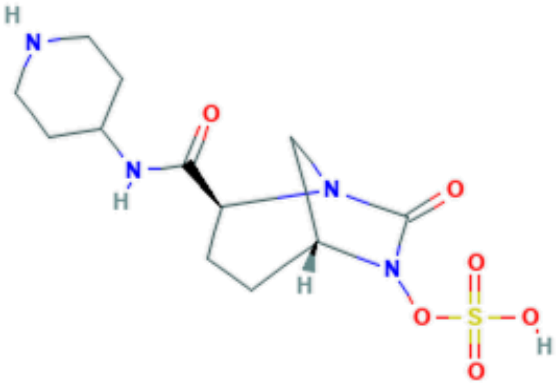
Ιμιπενέμη: αναστολή των πρωτεϊνών σύνδεσης πενικιλίνης (PBPs) που οδηγούν σε αναστολή της σύνθεσης κυτταρικών τοιχωμάτων της πεπτιδογλυκάνης.

Σιλαστατίνη



Σιλαστατίνη: περιορίζει τον νεφρικό μεταβολισμό της ιμιπενέμης και δεν έχει αντιβακτηριακή δράση.

Ρελεμπακτάμη



Ρελεμπακτάμη: μη βήτα-λακταμικός αναστολέας των Ambler κλάσης A και C βήτα-λακταμασών, συμπεριλ **KPC** και **ESBLs**, και **AmpC-τύπου** βήτα-λακταμάσες, συμπεριλ. Κεφαλοσπορινάσης που προέρχεται από Ψευδομονάδα (**PDC**). Η ρελεμπακτάμη δεν αναστέλλει τα MBL ή τις καρβαπενεμάσες κλάσης D. Η ρελεμπακτάμη δεν έχει αντιβακτηριακή δράση.

Γιατί η ρελεμπακτάμη είναι κατάλληλη για την προσθήκη στην ιμιπενέμη-σιλαστατίνη;

- Αναστέλλοντας την AmpC συχνά αποκαθίσταται η ευαισθησία της Pseudomonas στην ιμιπενέμη (όχι σε άλλες καρβαπενέμες)
- Κανείς από τους 2 παράγοντες δεν χάνει τη δραστικότητά του από efflux μηχανισμούς
- Τα φαρμακοκινητικά /φαρμακοδυναμικά προφίλ τους είναι παρόμοια
- Η ρελεμπακταμη ΔΕΝ αποκαθιστα δραστικοτητα ιμιπενεμης αν υπαρχει μηχανισμος αντοχης που οφειλεται σε πορινες
- MIC≤2

Hospital-acquired pneumonia, including ventilator-associated pneumonia (HAP/VAP)

Infections due to aerobic Gram-negative organisms in patients with limited treatment options†

Αντιμικροβιακο φασμα

- Acinetobacter calcoaceticus baumannii σύμπλεγμα
- Citrobacter spp. (συμπεριλαμβανομένων C. freundii και C. koseri)
- Enterobacter spp. (συμπεριλαμβανόμενων E. asburiae και E. cloacae)
- Escherichia coli
- Klebsiella spp. (συμπεριλαμβανομένων K. aerogenes, K. oxytoca και K. pneumoniae)
- Pseudomonas aeruginosa
- Serratia marcescens

- Bacteroides spp. (συμπεριλαμβανόμενου του B. fragilis)
- Fusobacterium spp. (συμπεριλαμβανόμενου του F. nucleatum και του F. necrophorum)
- Prevotella spp. (συμπεριλαμβανόμενου του P. melaninogenica, P. bivia, και P. buccae)

- Enterococcus faecalis
- Staphylococcus aureus (μόνο ευαίσθητα στη methicillin στελέχη)
- Viridans group streptococci (συμπεριλαμβανόμενου του S. anginosus και του S. constellatus)

ΔΕΝ ΚΑΛΥΠΤΕΙ:

- Legionella spp.
- Stenotrophomonas maltophilia

Δέσμευση από πρωτεΐνες πλάσματος

- Η δέσμευση της ιμιπενέμης και της σιλαστατίνης στις πρωτεΐνες του ανθρώπινου πλάσματος είναι περίπου 20% και 40%, αντίστοιχα. Η σύνδεση της ρελεμπακτάμης με τις πρωτεΐνες του ανθρώπινου πλάσματος είναι περίπου 22% και είναι ανεξάρτητη από τη συγκέντρωση

Διείσδυση στο ELF

- Η διείσδυση στο υγρό της πνευμονικής επιθηλιακής επένδυσης (ELF) εκφρασμένο ως ο συνολικός λόγος έκθεσης στο ELF προς μη δεσμευμένο πλάσμα ποσοστό ήταν 55% και 54% για την ιμιπενέμη και την ρελεμπακτάμη, αντίστοιχα.

Αποβολή

- Ιμιπενέμη, σιλαστατίνη και ρελεμπακτάμη απεκκρίνονται κυρίως από τους νεφρούς

Γραμμικότητα

- Φαρμακοκινητική της ρελεμπακτάμης είναι γραμμική
- Ελάχιστη συσσώρευση ιμιπενέμης, σιλαστατίνης ή ρελεμπακτάμης μετά από πολλαπλές ενδοφλέβιες εγχύσεις ρελεμπακτάμης 30 λεπτών (50 έως 625 mg) συγχορηγούμενα με 500 mg ιμιπενέμη/500 mg σιλαστατίνης κάθε 6 ώρες έως 7 ημέρες σε υγιή ενήλικα αρσενικά με φυσιολογική νεφρική λειτουργία.

Imipenem + cilastatin–relebactam: επισκόπηση κλινικών δοκιμών

Clinical trials

RESTORE-IMI 1:[1]

- I/R έναντι imipenem + colistin για λοιμώξεις από μη ευαίσθητα στην ιμιπενέμη στελέχη (HAP/VAP, cUTI, cIAI), τυχαιοποίηση 2:1. Κύριο τελικό σημείο αποτελεσματικότητας: συνολική ανταπόκριση (πληθυσμός mMITT)
- Αποτελέσματα:
  - N=31 (n=21 για την I/R και n=10 για το σκέλος imipenem + colistin) στον πληθυσμό mMITT
    - 11 HAP/VAP, 16 cUTI, και 4 cIAI; 29% APACHE II score > 15, 35% ≥ 65 έτη, 77% *P. aeruginosa*, 16% *Klebsiella spp*, 6% άλλα Enterobacteriaceae, οι β-λακταμάσες που ανευρέθηκαν περιλάμβαναν AmpC (84% των ασθενών mMITT), ESBLs (35%), KPC (16%), και OXA-48 (3%)
  - **Ευνοϊκή συνολική ανταπόκριση: 71,4% για την I/R έναντι 70% για το σκέλος colistine + imipenem** Τάσεις υπέρ της I/R για δευτερεύοντα τελικά σημεία (καλύτερη κλινική ανταπόκριση την ημέρα 28, θνητότητα από κάθε αίτιο την ημέρα 28)
  - Ασφάλεια: AE σχετιζόμενα με φάρμακο 16,1% I/R έναντι 31,3% για colistine + imipenem
    - Αναδυόμενη νεφροτοξικότητα: 10,3% για την I/R και 56,3% για colistine + imipenem (p = 0.002)
    - Κλινικά σχετικές αυξήσεις ηπατικών τρανσαμινασών: 0% για την I/R έναντι 13% για colistine + imipenem (p=0,047)

I/R, imipenem/relebactam; P/T, piperacillin tazobactam: CMY, cephamycinase; CTX-M, cefotaximase-Munich; cIAI, complicatedintraabdominal infections; cUTI, complicated urinary tract infection; DHA, docosahexaenoic acid; ESBL, extended-spectrum β-lactamase; HAP, hospital-acquired pneumonia; KPC, *K. pneumoniae carbapenemase*; MBL, metallo-β-lactamase; OXA, oxacillinase; PBP, penicillin-binding protein; q6h, every 6 hours; SHV, sulphydral variable β-lactamase; TEM, Temoniera β-lactamase; VAP, ventilator-associated pneumonia; mMITT, modified microbiologic intent-to-treat; MITT, modified intent-to-treat.

1. Motsch J, et al. *Clin Infect Dis* 2020;70:1799–808; 2. Titov I, et al. *Clin Infect Dis* 2020;doi:10.1093/cid/ciaa803. Epub ahead of print.

Imipenem + cilastatin–relebactam: επισκόπηση κλινικών δοκιμών

Clinical trials

RESTORE-IMI 2:[2]

- I/R έναντι piperacillin-tazobactam (P/T) για ασθενείς με HAP/VAP. Κύριο τελικό σημείο αποτελεσματικότητας: θνητότητα από κάθε αίτιο την ημέρα 28 (πληθυσμός MITT)
- Αποτελεσματικότητα
  - N=531 (n=264 για την I/R και n=267 για P/T)
    - 47,5% APACHE II score ≥ 15, 42,9% > 65 έτη
    - 25.6% *K. pneumoniae*, 18.9% *P. aeruginosa*, 15.5% *E. coli*
  - **θνητότητα από κάθε αίτιο την ημέρα 28: 15.9% για την I/R έναντι 21.3% για την P/T** (προσαρμοσμένη διαφορά θεραπείας, −5.3% [95% CI, −11.9% έως 1.2%]; μη κατωτερότητα *p*<.001)
    - Χαμηλότερη θνητότητα με την I/R έναντι της P/T για ασθενείς με HAP/VAP υπό μηχανικό αερισμό και σε ασθενείς με APACHE II score ≥ 15
  - Ασφάλεια: συγκρίσιμη μεταξύ I/R και P/T. Η I/R ήταν καλώς ανεκτή με λίγα σοβαρά AE ή διακοπές της θεραπείας

I/R, imipenem/relebactam; P/T, piperacillin tazobactam: CMY, cephamycinase; CTX-M, cefotaximase-Munich; cIAI, complicatedintraabdominal infections; cUTI, complicated urinary tract infection; DHA, docosahexaenoic acid; ESBL, extended-spectrum β-lactamase; HAP, hospital-acquired pneumonia; KPC, *K. pneumoniae carbapenemase*; MBL, metallo-β-lactamase; OXA, oxacillinase; PBP, penicillin-binding protein; q6h, every 6 hours; SHV, sulphydral variable β-lactamase; TEM, Temoniera β-lactamase; VAP, ventilator-associated pneumonia; mMITT, modified microbiologic intent-to-treat; MITT, modified intent-to-treat.

1. Motsch J, et al. *Clin Infect Dis* 2020;70:1799–808; 2. Titov I, et al. *Clin Infect Dis* 2020;doi:10.1093/cid/ciaa803. Epub ahead of print.

Comparative activity of newer β-lactam/β-lactamase inhibitor combinations against Pseudomonas aeruginosa from patients hospitalized with pneumonia in European medical centers in 2020

Helio S. Sader[1] · Cecilia G. Carvalhaes[1] · Dee Shortridge[1] · Mariana Castanheira[1]

- Pseudomonas aeruginosa isolates were consecutively collected from patients with pneumonia in 29 medical centers in 2020 and susceptibility tested by broth microdilution method
- 583 P. aeruginosa isolates were evaluated in this study.
  - **Ceftazidime-avibactam** (95.5% susceptible),
  - **imipenem-relebactam** (94.3% susceptible),
  - **ceftolozane-tazobactam** (93.3% susceptible)
  - **colistin** (99.5% susceptible).

Sader HS et al. Eur J Clin Microbiol Infect Dis. 2022 Feb;41(2):319-324

International Guidelines

Clinical Microbiology and Infection 28 (2022) 521–547

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journal homepage: www.clinicalmicrobiologyandinfection.com

Guidelines

European Society of Clinical Microbiology and Infectious Disease (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by Europea society of intensive care medicine)

Mical Paul [1, 2, §], Elena Carrara [3, §], Pilar Retamar [4, 5], Thomas Tängdén [6], Roni Bittern
Robert A. Bonomo [7, 8, 9], Jan de Waele [10], George L. Daikos [11], Murat Akova [12],
Stephan Harbarth [13], Celine Pulcini [14, 15], José Garnacho-Montero [16], Katja Seme [17],
Mario Tumbarello [18], Paul Christoffer Lindemann [19], Sumanth Gandra [20],
Yunsong Yu [21, 22, 23], Matteo Bassetti [24, 25], Johan W. Mouton [26, †],
Evelina Tacconelli [3, 27, 28, *, §], Jesús Rodríguez-Baño [4, 5, §]

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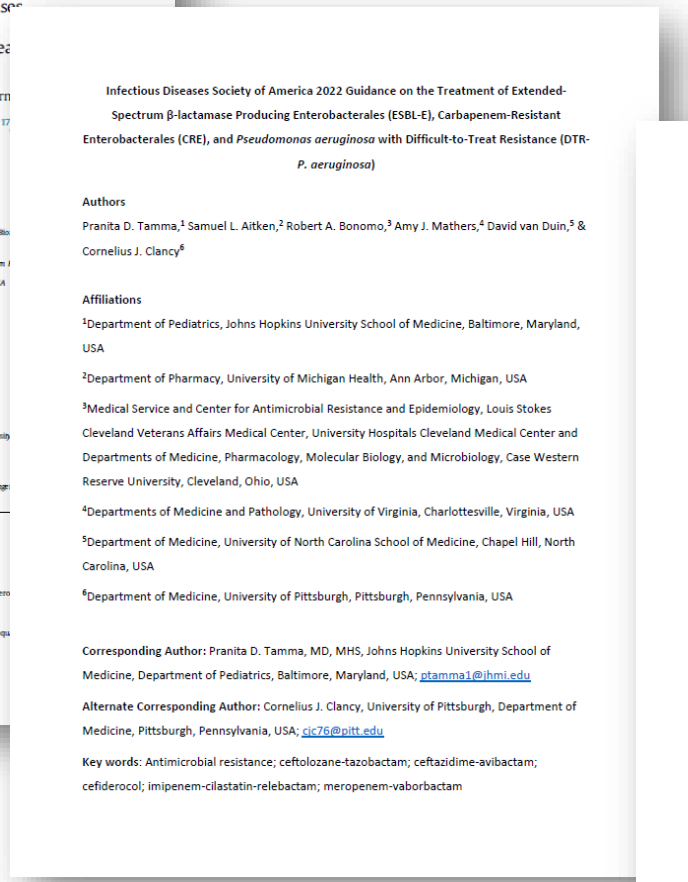
† Deceased.
§ Mical Paul and Elena Carrara made equal contributions to these guidelines; Evelina Tacconelli and Jesús Rodríguez-Baño made equ

https://doi.org/10.1016/j.cmi.2021.11.025

ESCMID



Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*)

Authors

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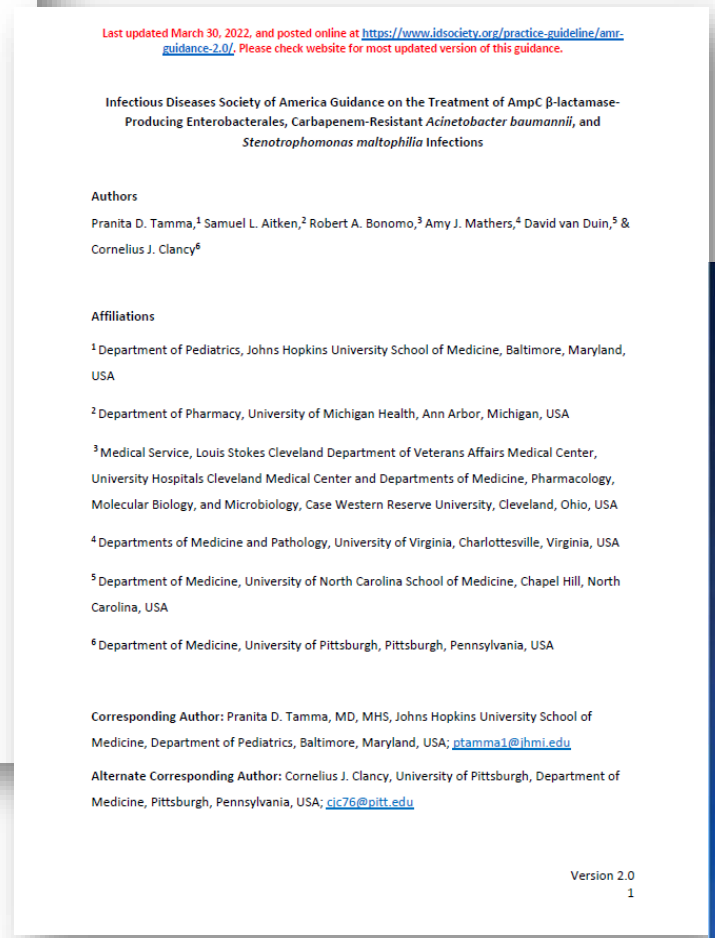
Key words: Antimicrobial resistance; ceftolozane-tazobactam; ceftazidime-avibactam; cefiderocol; imipenem-cilastatin-relebactam; meropenem-vaborbactam

IDSA
Infectious Diseases Society of America



Last updated March 30, 2022, and posted online at https://www.idsociety.org/practice-guideline/amr-guidance-2.0/. Please check website for most updated version of this guidance.

Infectious Diseases Society of America Guidance on the Treatment of AmpC β-lactamase-Producing Enterobacterales, Carbapenem-Resistant *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* Infections

Authors

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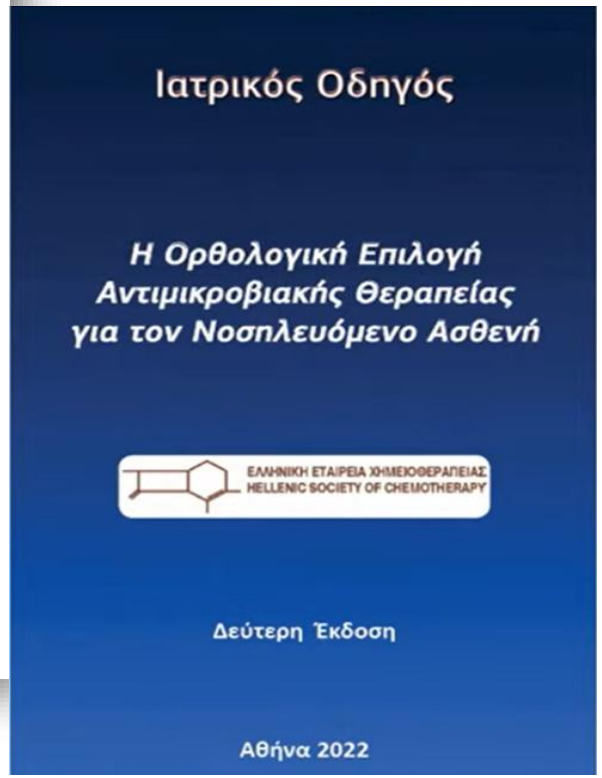


IDSA

Mild infections

- infections of the urinary tract,
- skin and soft tissue infections
- Tracheitis

without evidence of hemodynamic instability

Moderate infections

Severe infections

ESCMID

Low risk (for mortality) infections

- infections (including bloodstream infections (BSI)) originating from a urinary tract source of infection or biliary infections

after source control

High-risk infections

- All other

Severe infections:

- sepsis or septic shock

Εμπειρικό θεραπευτικό σχήμα

Παράγοντες που καθοδηγούν την επιλογή εμπειρικής αγωγής

- τα πιθανά παθογόνα,
- Βαρύτητα της νόσου
- Πιθανή εστία της λοίμωξης
- Τοπικά δεδομένα ευαισθησίας/αντοχής για τα πιθανολογούμενα παθογόνα

- Άλλοι παράγοντες σχετιζόμενοι με τον ασθενή
- Παθογόνα που απομονώθηκαν στον ασθενή το τελευταίο 6μηνο και ευαισθησία σε αντιμικροβιακά
- Έκθεση σε αντιβιοτικά το προηγούμενο διάστημα (30 ημέρες)

https://www.idsociety.org/practice-guideline/amrguidance-2.0/, March 30, 2022

Παράγοντες κινδύνου για λοίμωξη από πολυανθεκτικά Gram αρνητικά στελέχη

Α. Παράγοντες κινδύνου για αποικισμό και λοίμωξη από Εντεροβακτηριακά ανθεκτικά στις καρβαπενέμες (στελέχη XDR)

- Λήψη αντιβιοτικών (κυρίως καρβαπενεμών και φθοριοκινολονών) και αθροιστική λήψη πολλαπλών σχημάτων αντιμικροβιακής αγωγής τις προηγούμενες 90 ημέρες
- Νοσηλεία σε ΜΕΘ ≥2 ημέρες τις προηγούμενες 90 ημέρες
- Γνωστός αποικισμός ή προηγηθείσα λοίμωξη με παθογόνο που παράγει καρβαπενεμάση
- Νοσηλεία στον ίδιο θάλαμο με ασθενή φορέα ή πάσχοντα από λοίμωξη από βακτηρίδιο που παράγει καρβαπενεμάση
- Διαμονή σε Οίκο Ευγηρίας ή Κέντρο Αποκατάστασης
- Σηπτική καταπληξία
- Ανοσοκαταστολή: αιματολογική νόσος, ουδετεροπενία, μεταμόσχευση, συμπαγής όγκος υπό χημειοθεραπεία, λήψη ανοσοκατασταλτικών με άλλη ένδειξη, χρόνια λήψη κορτικοειδών (>10mg πρεδνιζόνης ημερησίως ή >700mg αθροιστική δόση), μεταμόσχευση μυελού των οστών ή συμπαγούς οργάνου

Παράγοντες κινδύνου για λοίμωξη από Gram-αρνητικά βακτηρίδια που παράγουν ESBL
Πρόσφατη νοσηλεία (< 1 μήνας)
Πρόσφατη έκθεση σε αντιβιοτικά (≤ 6 μήνες)
Αιμοδιάλυση
Παρουσία κεντρικού iv καθετήρα
Πρόσφατο ταξίδι στην Ασία (τελευταίος χρόνος)
Διαμονή σε Οίκο Ευγηρίας ή Κέντρο Αποκατάστασης

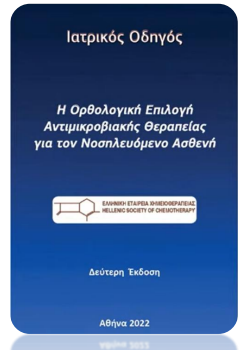
ΕΕΧ, Η Ορθολογική Επιλογή Αντιμικροβιακής Θεραπείας για τον Νοσηλευόμενο Ασθενή, 2022

Προτεινόμενα αντιμικροβιακά για την αντιμετώπιση λοιμώξεων από Εντεροβακτηριακά που παράγουν ESBL

Κυστίτιδα	Nitrofurantoin and trimethoprim-sulfamethoxazole
	Amoxicillin-clavulanate (caution), single-dose aminoglycosides, and oral fosfomycin (for E. coli only)
Πυελονεφρίτιδα/ Επιπλεγμένες Λοιμώξεις Ουροποιητικού	Ertapenem, **Meropenem**, **Imipenem-cilastatin**, Ciprofloxacin, Levofloxacin, or Trimethoprim-Sulfamethoxazole
	once-daily aminoglycosides for a full treatment course **Ceftolozane/Tazobactam**
Λοιμώξεις εκτός του Ουροποιητικού	**Carbapenem**
	oral fluoroquinolones or trimethoprim-sulfamethoxazole should be considered, after clinical response **Ceftolozane/Tazobactam**

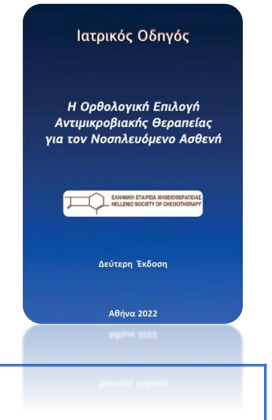
Προσαρμογή από: www.idsociety.org/practiceguideline/amr-guidance/v1.1
Η Ορθολογική Επιλογή Αντιμικροβιακής Θεραπείας για τον Νοσηλευόμενο Ασθενή, 2022

Οδηγίες για θεραπεία λοιμώξεων από CRE



Εστία Λοίμωξης		1η επιλογή	2η επιλογή
Κυστίτιδα		Αμινογλυκοσίδη	Φωσφομυκίνη ή Κολιστινη ή Κεφταζιδιμη/Αβιμπακτάμη
Πυελονεφρίτιδα Επιπλεγμένη ουρολοίμωξη	KPC ή OXA-48	**Κεφταζιδίμη/Αβιμπακτάμη**	Αμινογλυκοσίδη ή Κολιστίνη ± Φωσφομυκίνη ή Μεροπενέμη εάν MIC ≤ 8 mg/L
	VIM ή NDM	**Κεφταζιδίμη/Αβιμπακτάμη + Αζτρεονάμη**	
	VIM ή NDM σε συνδυασμό με KPC ή OXA-48	**Κεφταζιδίμη/Αβιμπακτάμη + Αζτρεονάμη**	

Οδηγίες για θεραπεία λοιμώξεων από CRE



Εστία λοίμωξης		1η επιλογή	2η επιλογή
Λοιμώξεις εκτός ουροποιητικού	KPC ή OXA-48	Κεφταζιδίμη/Αβιμπακτάμη ± Αμινογλυκοσίδη ή Κολιστίνη	**Συνδυασμός <u>δύο εκ των κάτωθι</u>** αντιμικροβιακών παραγόντων ανάλογα με το είδος της λοίμωξης: Φωσφομυκίνη, Αμινογλυκοσίδη, Κολιστίνη, Τιγεκυκλίνη ή Μεροπενέμη εάν MIC ≤ 8mg/L (Η Τιγεκυκλίνη προτιμάται σε ενδοκοιλιακές λοιμώξεις και λοιμώξεις δέρματος και μαλακών μορίων)
	VIM ή NDM	Κεφταζιδίμη/Αβιμπακτάμη + Αζτρεονάμη ± Αμινογλυκοσίδη ή Κολιστίνη	
	VIM ή NDM σε συνδυασμό με KPC ή OXA-48	Κεφταζιδίμη/Αβιμπακτάμη + Αζτρεονάμη ± Αμινογλυκοσίδη ή Κολιστίνη	

IDSA guidance 2022: Treatment options for CRE* (1/2)

	Preferred treatment	Alternative treatment (when preferred options are not available/tolerated)
Cystitis	• Ciprofloxacin, levofloxacin, trimethoprim–sulfamethoxazole, nitrofurantoin, or a single dose of an aminoglycoside • Meropenem (standard infusion)†‡	• **Ceftazidime–avibactam**, meropenem–vaborbactam, imipenem–cilastatin–relebactam, and cefiderocol • Colistin (only when no alternative options are available)
Pyelonephritis or cUTI§	• Ciprofloxacin, levofloxacin, and trimethoprim–sulfamethoxazole • **Ceftazidime–avibactam**, meropenem–vaborbactam, imipenem–cilastatin–relebactam, and cefiderocol\\ • Meropenem (extended-infusion)†‡	• Once-daily aminoglycosides
Infections outside the urinary tract (if Erta-R; Mero-S)¶	• Meropenem (extended-infusion)†	• **Ceftazidime–avibactam** (if resistant to <u>all</u> carbapenems)
Infections outside the urinary tract (if Erta-R; Mero-R)¶	• **Ceftazidime–avibactam**, meropenem–vaborbactam, and imipenem–cilastatin–relebactam	• Cefiderocol • Tigecycline, eravacycline (uncomplicated IAIs only)

Ceftazidime–avibactam is recommended by the IDSA guidance as a preferred treatment option for KPC-producing infections,\\ with improved clinical outcomes and reduced toxicity compared with polymyxin-based regimens

*Assuming *in vitro* susceptibility to agents in table; † The majority of infections caused by CRE resistant to ertapenem but susceptible to meropenem are caused by organisms that do not produce carbapenemases; ‡ Only if ertapenem-resistant, meropenem-susceptible and carbapenemase testing results are either not available or negative; § A cUTI is defined as a UTI that occurs in association with a structural or functional abnormality of the genitourinary tract or any UTI in an adolescent or adult male patient; ¶ Carbapenemase testing results are either not available or negative; \\ Resistant to both ertapenem and meropenem.

CRE, carbapenem-resistant Enterobacterales; cUTI, complicated urinary tract infection; Erta-R, ertapenem-resistant; IAI, intra-abdominal infection; IDSA, Infectious Diseases Society of America; Mero-R, meropenem-resistant; Mero-S, meropenem-susceptible; UTI, urinary tract infection.

Tamma PD, et al. Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended- Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*). www.idsociety.org/globalassets/idsa/practice-guidelines/amr-guidance/1.0/idsa-amr-guidance-v1.1.pdf (Accessed March 2022).

IDSA guidance 2022: Treatment options for CRE* (2/2)

	Preferred treatment	Alternative treatment (when preferred options are not available/tolerated)
KPC identified†	• **Ceftazidime–avibactam**, meropenem–vaborbactam, and imipenem–cilastatin–relebactam	• Cefiderocol • Tigecycline, eravacycline (uncomplicated IAIs only)
OXA-48-like carbapenemase identified	• **Ceftazidime–avibactam**	• Cefiderocol • Tigecycline, eravacycline (uncomplicated IAIs only)

Ceftazidime–avibactam is recommended by the IDSA guidance as a preferred treatment option§ for KPC-producing infections¶ and as the only preferred treatment option for OXA-48-producing CRE infections

*Assuming *in vitro* susceptibility to agents in table; † The vast majority of carbapenemase-producing Enterobacterales infections in the US are due to bacteria that produce KPC. If a disease-causing Enterobacterales is carbapenemase-producing but the specific carbapenemase enzyme is unknown, it is reasonable to treat as if the strain is a KPC producer. If a patient is infected with a CRE strain with an unknown carbapenemase status and the patient has recently travelled from an area where MBLs are endemic, treatment with ceftazidime–avibactam plus aztreonam or cefiderocol monotherapy is recommended. Ceftazidime-avibactam in combination with aztreonam, or cefiderocol as monotherapy, are preferred treatment options for NDM and other metallo-β-lactamase-producing infections; § Meropenem–vaborbactam and imipenem/cilastatin–relebactam are also preferred treatment options; ¶Or carbapenemase- positive but identity of carbapenemase unknown.

CRE, carbapenem-resistant Enterobacterales; IAI, intra-abdominal infection; IDSA, Infectious Diseases Society of America; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; OXA, oxacillinase.

Tamma PD, et al. Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended- Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*). https://www.idsociety.org/globalassets/idsa/practice-guidelines/amr-guidance/1.0/idsa-amr-guidance-v1.1.pdf (Accessed March 2022).

IDSA guidance 2020: treatment options for DTR *P. aeruginosa**

	Preferred treatment	Alternative treatment (when first-line options are not available/tolerated)
Pyelonephritis or cUTI†	• **Ceftolozane–tazobactam, ceftazidime–avibactam, imipenem/cilastatin–relebactam and cefiderocol**	• **Once-daily aminoglycosides**
Infections outside the urinary tract	• **Ceftolozane–tazobactam**, **ceftazidime–avibactam or imipenem/cilastatin–relebactam**	• **Cefiderocol** (reserved only for when preferred agents are not tolerated or active or available) • ***If no preferred agent demonstrates activity against DTR P. aeruginosa, an aminoglycoside (if susceptibility is demonstrated) can be considered in combination***

Tamma P, et al. Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with Difficult-to-Treat Resistance (DTR-P. aeruginosa), Accessed: April 2022

Analysis of the Clinical Pipeline of Treatments for Drug-Resistant Bacterial Infections: Despite Progress, More Action Is Needed

TABLE 3 Traditional antibacterial agents and combinations in NDA and phase 3 clinical development against WHO priority pathogens

Name (synonym)	Phase	Antibacterial class	Route of administration	Developer	Expected activity against priority pathogens[a]				Innovation[b]			
					CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
Solithromycin (T-4288)	NDA[c]	Macrolide	i.v. & oral	iFUJIFILM Toyama Chemical	NA	NA	NA	●[d]	—	—	—	—
Sulopenem, Sulopenem etzadroxil/probenecid	NDA[e]	β-Lactam (penem)	i.v. & oral	Iterum	○	○	○[f]	NA	—	—	—	—
Durlobactam (ETX-2514) + sulbactam	3	DBO-BLI/PBP2 binder + β-lactam-BLI/PBP1,3 binder	i.v.	Entasis	●	○	○	NA	—	—	—	—
Taniborbactam (VNRX-5133) + cefepime	3	Boronate BLI + β-lactam (cephalosporin)	i.v.	VenatoRx/GARDP	○	●	●	NA	?	✓	—	—
Enmetazobactam (AAI-101) + cefepime	3	BLI + β-lactam (cephalosporin)	i.v.	Allecra	○	○	○[g]	NA	—	—	—	—
Zoliflodacin	3	Spiropyrimidenetrione (topoisomerase inhibitor)	Oral	Entasis/GARDP	NA	NA	NA	●[d]	✓	✓	—	✓
Gepotidacin	3	Triazaacenaphthylene (topoisomerase inhibitor)	i.v. & oral	GSK	NA	NA	NA	●[d]	?	✓/?[h]	—	✓
Nafithromycin (WCK-4873)	3	Macrolide	Oral	Wockhardt	NA	NA	NA	●[d]	—	—	—	—
Benapenem	2/3	β-Lactam (carbapenem)	i.v.	Sichuan Pharmaceutical	○	○	○	NA	—	—	—	—

[a]Pathogen activity: ●, active; ?, possibly active; ○, not or insufficiently active; NA, activity not assessed, as the antibiotic is focused and developed for only either Gram-positive cocci or Gram-negative rods. Agents not active against critical-priority pathogens were assessed for activity against OPP, which includes the high and medium WHO priority pathogens.

[b]Innovation assessment: ✓, criterion fulfilled; ?, inconclusive data; —, criterion not fulfilled. CC, chemical class; MOA, new mode of action; NCR, no cross-resistance; T, new target.

[c]Solithromycin NDA for otorhinolaryngological infections submitted in Japan in April 2019.

[d]OPP target pathogens: solithromycin, *S. pneumoniae*; nafithromycin, *S. aureus* and *S. pneumoniae*; gepotidacin, *N. gonorrhoeae* and *E. coli*; zoliflodacin, *N. gonorrhoeae*.

[e]Sulopenem etzadroxil NDA submitted in USA for uncomplicated UTI (uUTI) in November 2020.

[f]Active against ESBL-producing cephalosporin-resistant but not carbapenem-resistant *Enterobacterales*.

[g]Active against ESBL-producing cephalosporin-resistant and some KPC-producing CRE.

[h]Gepotidacin is being tested in two distinct phase 3 programs: gonorrhea (NCR ✓) and uUTI (NCR ?).

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Shorten time of exposure in order to save both pt and drug, for future pts

Go for early diagnosis & colonization

Thank you for your attention