Antibiotic stewardship sau folosirea judicioasă a antibioticelor în cazul infecțiilor produse de germeni Gram-negativi rezistenți

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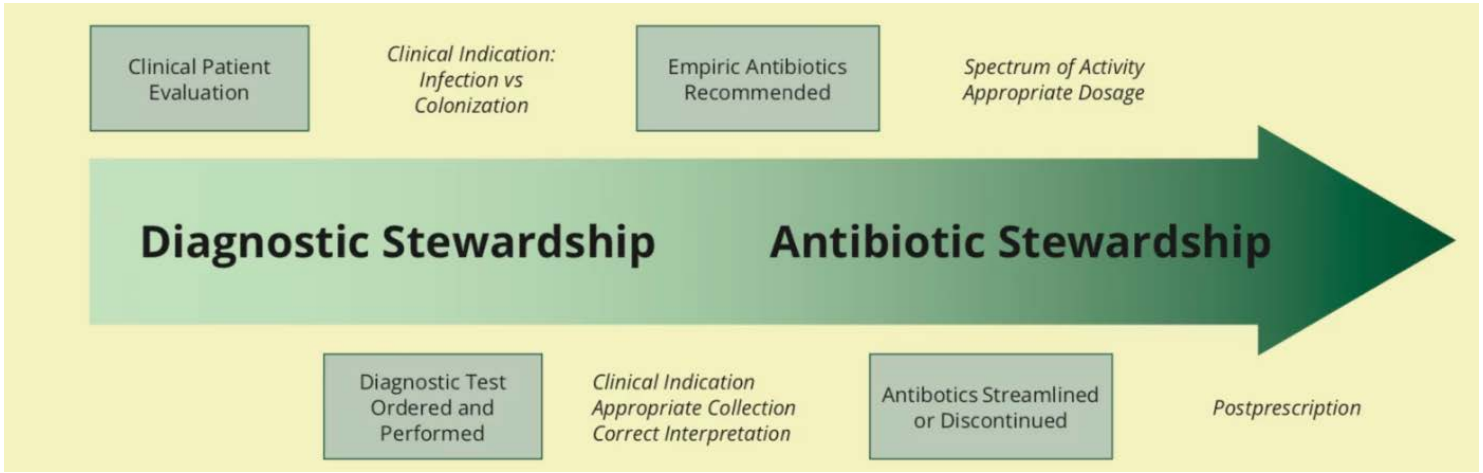
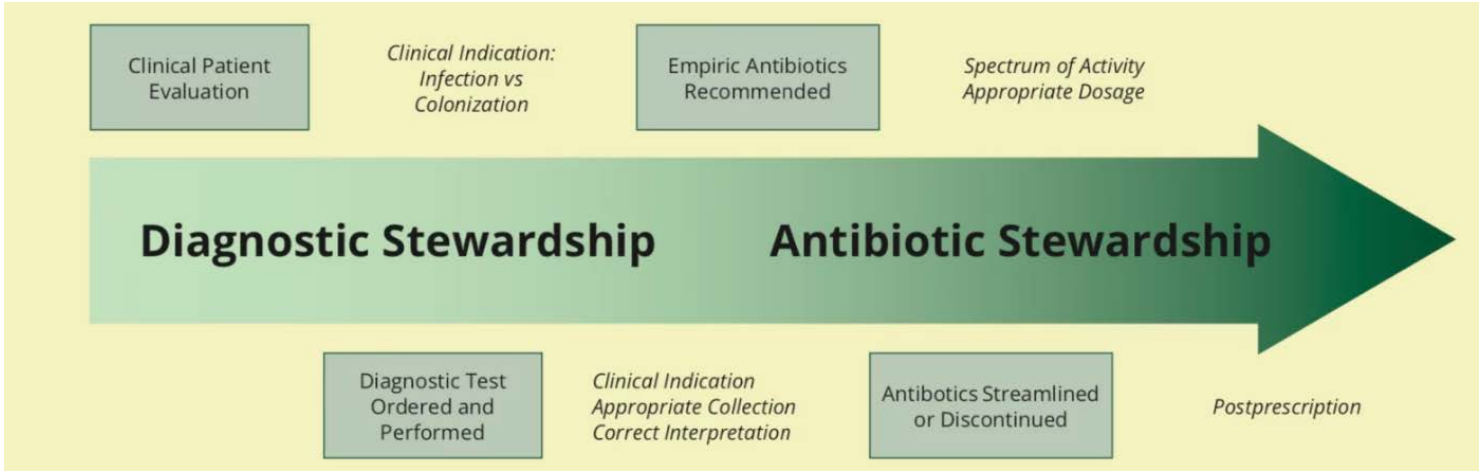
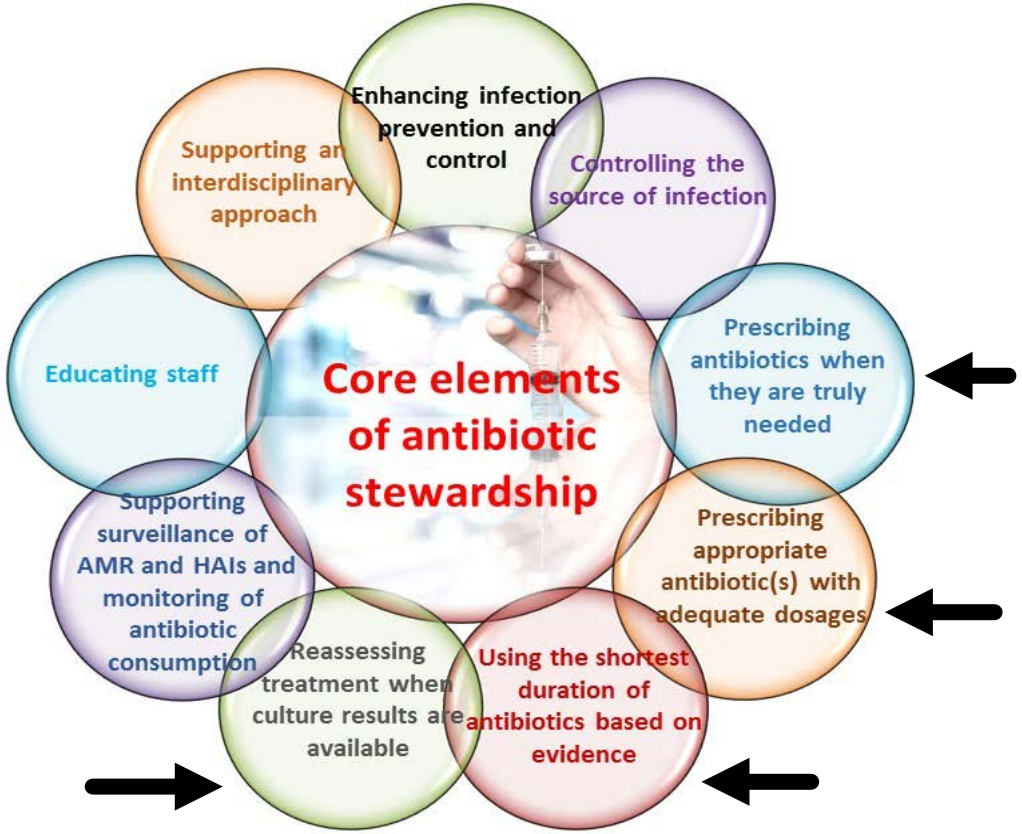
Antibiotic stewardship



Antibiotic stewardship

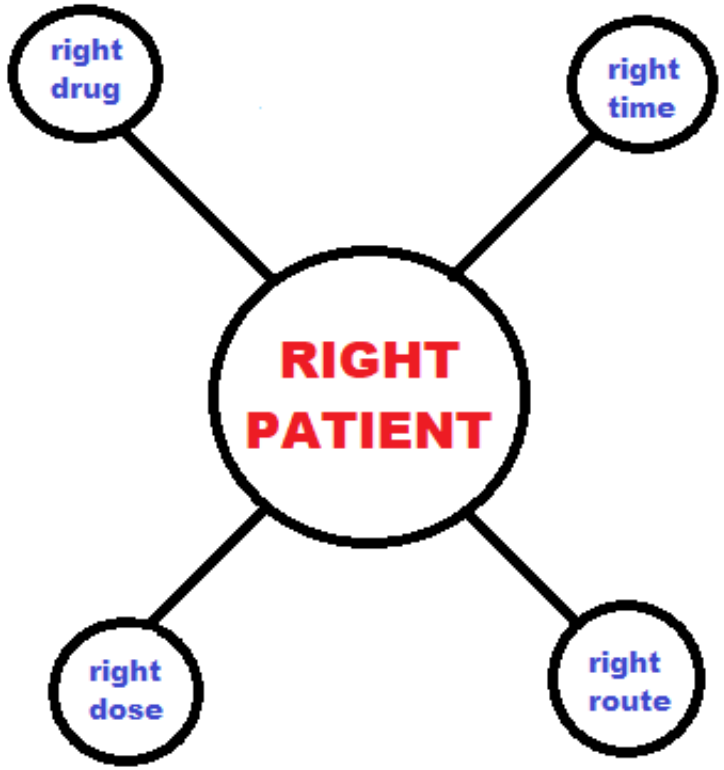




Agenda

- *Right drug, right patient*

Practical recommendations from IDSA and ESCMID Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections



- *Right dose, right time, right route*

Ceftazidime-Avibactam in the treatment of infections due to CRE and MDR *P. aeruginosa*: **evaluation in adults, in real-world settings**

Current clinical indications/approval for new BLs

Antibiotic	FDA	EMA
Ceftazidime/avibactam	cUTI, cIAI and HAP and VAP	cUTI, cIAI, HAP and VAP, **treatment Gram-negative infections in patients with limited treatment options**
Ceftolozane/tazobactam	cUTI, cIAI and HAP and VAP	cUTI, cIAI and HAP and VAP,
Imipenem/relebactam	cUTI and cIAI	HAP and VAP and for BSI with a suspected respiratory source, and for **the treatment Gram-negative infections in patients with limited treatment options**
Meropenem/vaborbactam	cUTI	cUTI, **HAP and VAP,** and for the treatment Gram-negative infections in patients with limited treatment options
Cefiderocol	cUTI, HAP and VAP	for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options
Tigecycline	cSSTI and IAI, CAP	cSSTI and IAI,

cUTI=complicated urinary tract infections; cIAI=complicated intra-abdominal infections; HAP=hospital acquired pneumonia;

VAP=ventilator associated pneumonia; cSSTI= complicated skin and soft tissue infections

M. Paul et al. ESCMID Guidelines Clinical Microbiology and Infection 28 (2022) 521e547

New beta-lactams for MDR Gram-negatives

In vitro beta-lactam spectrum of activity against beta-lactamases and resistant Gram-negative organisms

	KPC	NDM (MBL)	**AmpC**			
Agent	Class A	Class B	Class C	Class D	MDR *P. aeruginosa*	*Acinetobacter* spp.
CAZ-AVI	Yes	No	Yes	OXA-48	Yes	No
C/T	No	No	Yes	No	Yes	No
IMI-REL	Yes	No	Yes	No	Yes	No
Cefiderocol	Yes	Yes	Yes	Yes	Yes	Yes

CAZ-AVI=ceftazidime avibactam C/T=ceftolozane/tazobactam; IMI-REL=imipenem/relebactam

Adapted from Noval M et al, Current Infectious Disease Reports (2020) 22: 1
https://doi.org/10.1007/s11908-020-0710-9
Zavicefta, Summary of Product Characteristics, EMA

Carbapenemase-producing *Klebsiella pneumoniae* in Romania: a six-month survey

Hospitals from Bucharest, Bacău and Iaşi

Total number of isolates collected during survey period			Hospital	Number carbapenems- non-susceptible	Number carbapenemase producers	Type of carbapenemase			
NS (%)	S[b] (%)	NS + S				OXA-48	NDM	KPC	VIM
30 (16)	152 (84)	182	H1	10	8	6	2	-	-
5 (8)	57 (92)	62	H2	5	5	4	1	-	-
42 (19)	178 (81)	220	H3	10	8	4	2	2	-
22 (21)	83 (79)	105	H4	9	8	7	-	1	-
12 (13)	80 (87)	92	H5	7	6	5	-	1	-
48 (18)	212 (82)	260	H6	10	9	9	-	-	-
52 (23)	172 (77)	224	H7	12	10	8	-	-	2
62 (26)	180 (74)	242	H8	12	11	8	3	-	-
273	**1114**	**1387**	Total	75	65	51	8	4	2

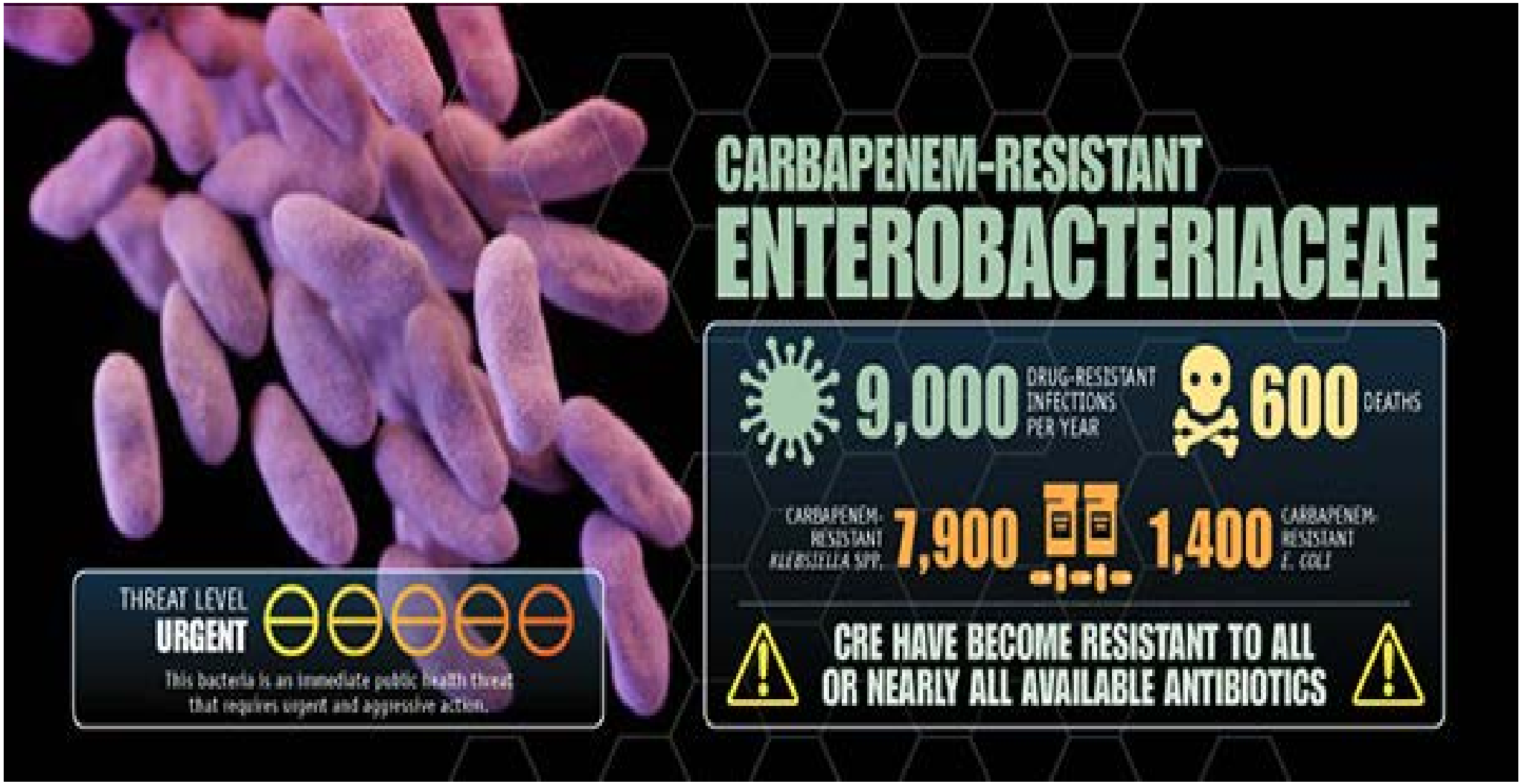
- 20% of total isolates are NS
- Out of the analyzed strains (n=75), 65 are carbapenemase producers
- 10 strains were NDM or VIM !

Lixandru BE, Cotar AI, Straut M, Usein CR, Cristea D, Ciontea S, et al. (2015) *Carbapenemase-Producing Klebsiella pneumoniae in Romania: A Six-Month Survey.* PLoS ONE 10(11): e0143214. doi:10.1371/journal.pone.0143214

Agent	KPC-producer	NDM-producer	OXA-48-like-producer	Carbapenem-resistant *Pseudomonas aeruginosa*	Carbapenem-resistant *Acinetobacter baumannii*	*Stenotrophomonas maltophilia*
Aztreonam-avibactam						
Cefiderocol						
Ceftazidime-avibactam[1]						
Ceftolozane-tazobactam[1]						
Eravacycline[1,2]						
Fosfomycin (intravenous)						
Imipenem-relebactam[3]						
Meropenem-vaborbactam[1]						
Plazomicin[1,4]						
Polymyxin B[1,5] or Colistin[1,5]						
Tigecycline[1,2]						

Figure 1. Select antibiotics with activity against carbapenem-resistant organisms. Green, susceptibility anticipated to be >80%; yellow, susceptibility anticipated to be 30% to 80%; red, intrinsic resistance or susceptibility anticipated to be <30%. [1], US Food and Drug Administration–approved agent; [2], synthetic tetracycline derivative; [3], imipenem-cilastatin–relebactam; [4], synthetic aminoglycoside; [5], polymyxin class. Abbreviations: KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase.

Carbapenem-resistant Enterobacteriaceae (CRE)



CRE – Practical recommendation

IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 1.0, 3/7/2022

What are the preferred antibiotics for the treatment of infections outside of the urinary tract caused by CRE if carbapenemase production is present?

- Meropenem-vaborbactam, **ceftazidime-avibactam, and imipenem-cilastatin-relebactam** are preferred treatment options for KPC-producing infections outside of the urinary tract.
- **Ceftazidime-avibactam in combination with aztreonam, or** cefiderocol **as monotherapy, are preferred treatment options for NDM and other metallo-β-lactamase-producing infections.**
- **Ceftazidime-avibactam is the preferred treatment option for OXA-48-like-producing infections.**

https://www.idsociety.org/practice-guideline/amr-guidance/#toc-5

Clinical Microbiology and Infection 28 (2022) 521–547

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Guidelines

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

Mical Paul [1, 2, §], Elena Carrara [3, §], Pilar Retamar [4, 5], Thomas Tängdén [6], Roni Bitterman [1, 2], 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, §]

CRE - ESCMID Guidelines

- For patients with **severe infections due to CRE:** meropenem-vaborbactam or ceftazidime-avibactam if active in vitro.
- There is **no evidence to recommend for or against the use of** imipenem-relebactam and fosfomycin monotherapies for CRE at the time of writing.
- **Severe infections** caused by **CRE carrying metallo-beta-lactamases** and/or resistant to new antibiotic monotherapies, we suggest aztreonam plus ceftazidime-avibactam combination therapy.
- For patients with **severe infections due to CRE carrying metallo-beta-lactamases and/or resistant to all other antibiotics**, including ceftazidime-avibactam and meropenem-vaborbactam: cefiderocol.

- For patients with **non-severe infections due to CRE**, under the consideration of antibiotic stewardship: use of an old antibiotic, chosen from among the in vitro active on an individual basis and according to the source of infection, as good clinical practice. For patients with **cUTI, we suggest aminoglycosides, including plazomicin, over tigecycline**.
- We suggest that **tigecycline NOT be used for BSI and HAP/VAP**; if necessary, in patients with pneumonia, clinicians may use high-dose tigecycline.

M. Paul et al. ESCMID Guidelines Clinical Microbiology and Infection 28 (2022) 521e547

CRE – Practical recommendation

IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 1.0, 3/7/2022

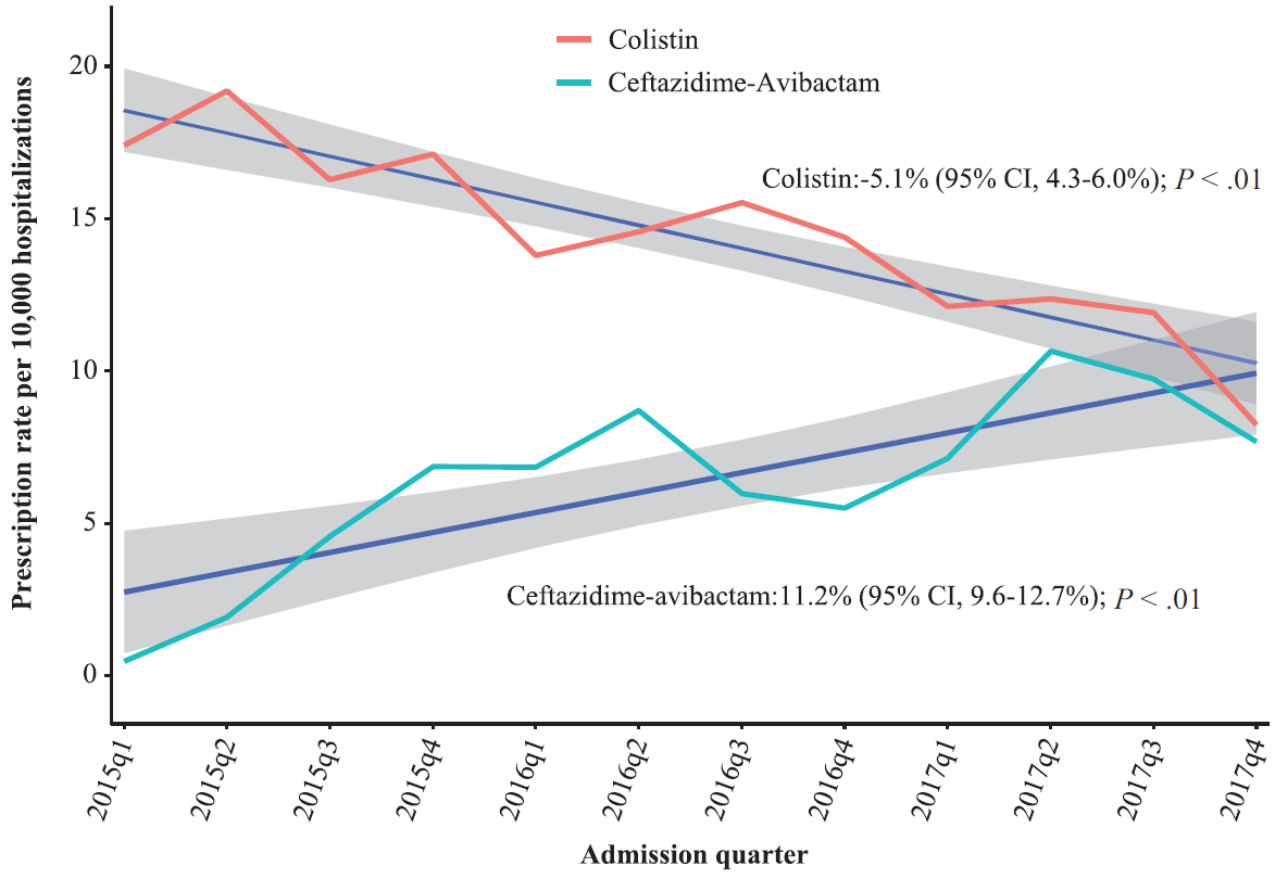
Role of polymyxins and combination antibiotic therapy (BL plus FQ/AG/polymyxin) for the treatment of infections caused by CRE

Polymyxin B and colistin should be avoided for the treatment of infections caused by CRE. Colistin can be considered as an alternative agent for uncomplicated CRE cystitis

Combination antibiotic therapy (i.e., the use of a β-lactam agent in combination with an aminoglycoside, fluoroquinolone, or polymyxin) is not routinely recommended for the treatment of infections caused by CRE.

https://www.idsociety.org/practice-guideline/amr-guidance/#toc-5

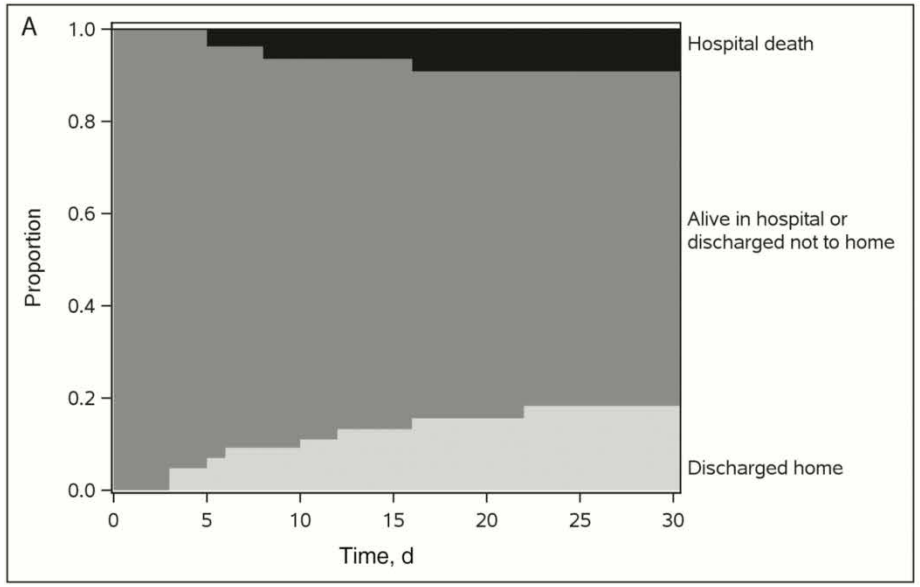
Usage of CAZ-AVI vs Colistin in 210 US hospitals (2015-2017)



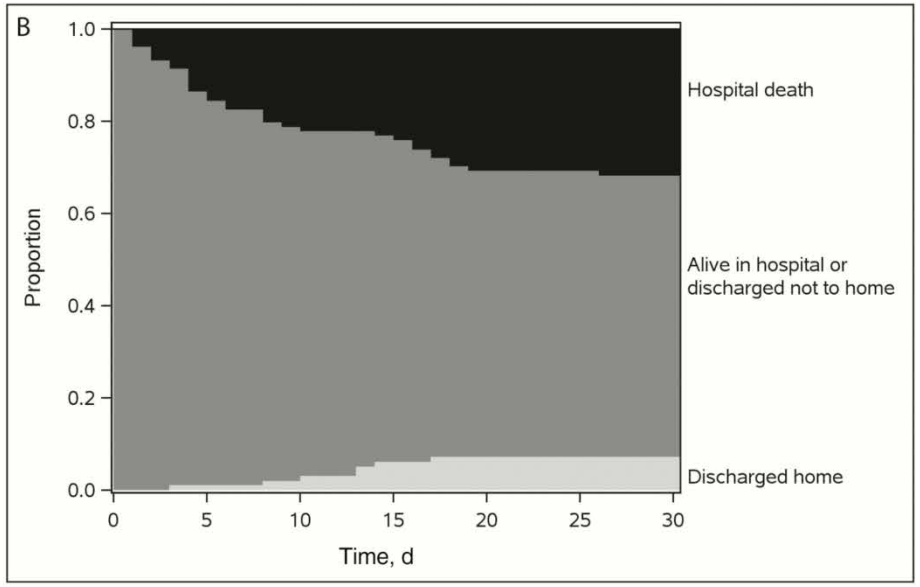
Strich JR, et al. Clinical Infectious Diseases® 2021;72(4):611–21 DOI: 10.1093/cid/ciaa061

Colistin vs. Ceftazidime-Avibactam in the treatment of infections due to CRE: efficacy profile

Ceftazime-Avibactam



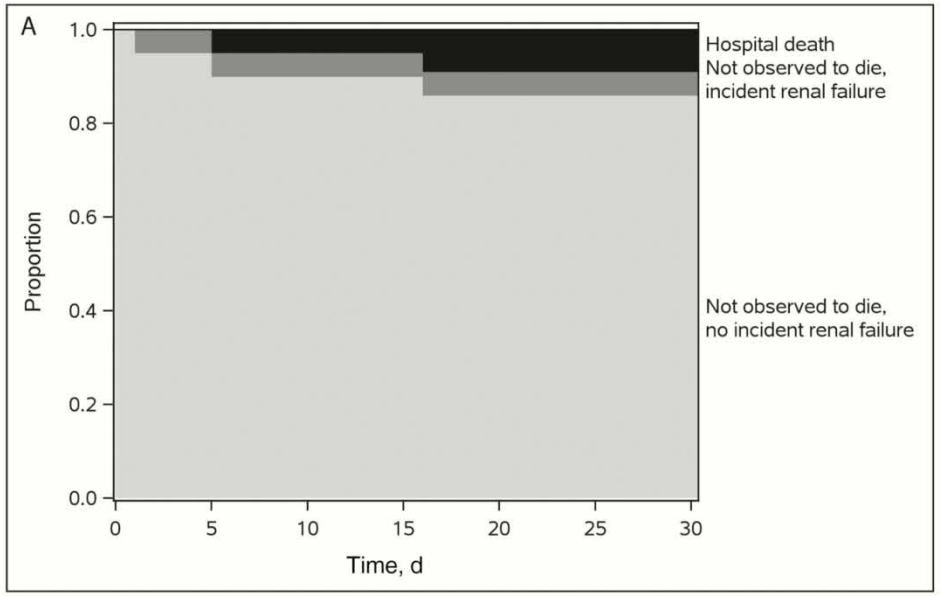
Colistin



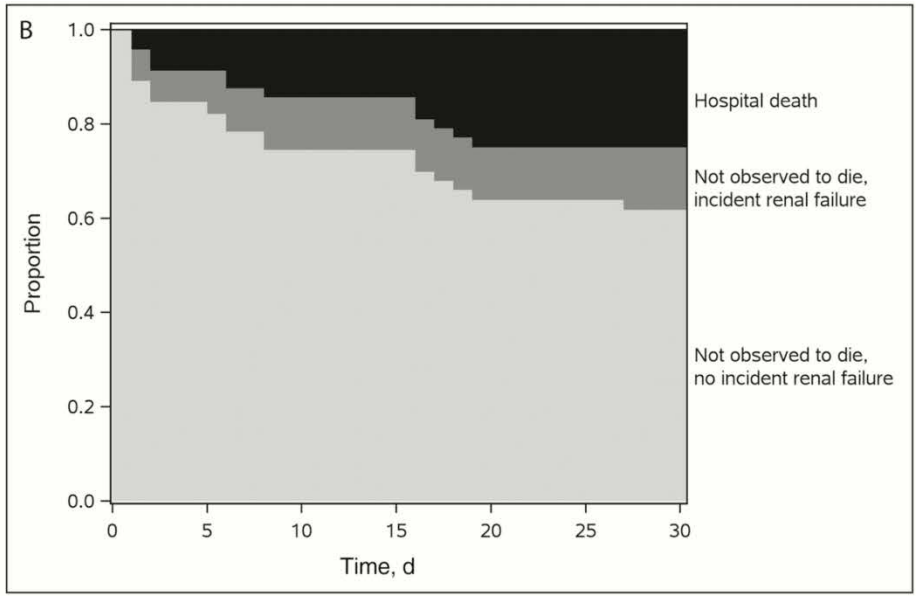
- David van Duin et al., Antibacterial Resistance Leadership Group; Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae, *Clinical Infectious Diseases*, Volume 66, Issue 2, 6 January 2018, Pages 163–171, https://doi.org/10.1093/cid/cix78

Colistin vs. Ceftazidime-Avibactam in the treatment of infections due to CRE: safety profile

Ceftazime-Avibactam



Colistin



- David van Duin et al., Antibacterial Resistance Leadership Group; Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae, *Clinical Infectious Diseases*, Volume 66, Issue 2, 6 January 2018, Pages 163–171, https://doi.org/10.1093/cid/cix783

ESCMID-Recommendations on combination therapy for CRE

- We suggest that clinicians **avoid carbapenem-based combination therapy for CRE infections**, unless the meropenem MIC is 8 mg/L, where high-dose extended-infusion meropenem may be used as part of combination therapy if the new BLBLI are not used.

- **CRE infections susceptible to and treated with ceftazidime-avibactam, meropenem-vaborbactam or cefiderocol, NO combination therapy.**

- **Severe infections caused by CRE carrying metallo-beta-lactamases and/or resistant to new antibiotic monotherapies**, we suggest **aztreonam and ceftazidime-avibactam combination therapy.**

- **Severe infections** caused by **CRE susceptible in vitro only to polymyxins, aminoglycosides, tigecycline or fosfomycin**, or in the case of non-availability of new BLBLI, we suggest treatment with **more than one drug active in vitro**. No recommendation for or against specific combinations can be provided.

- In patients with **non-severe infections** or among patients with low-risk infections, under the **consideration of antibiotic stewardship, we consider the use of monotherapy chosen from among the in vitro active old drugs**, on an individual basis and according to the source of infection as good clinical practice

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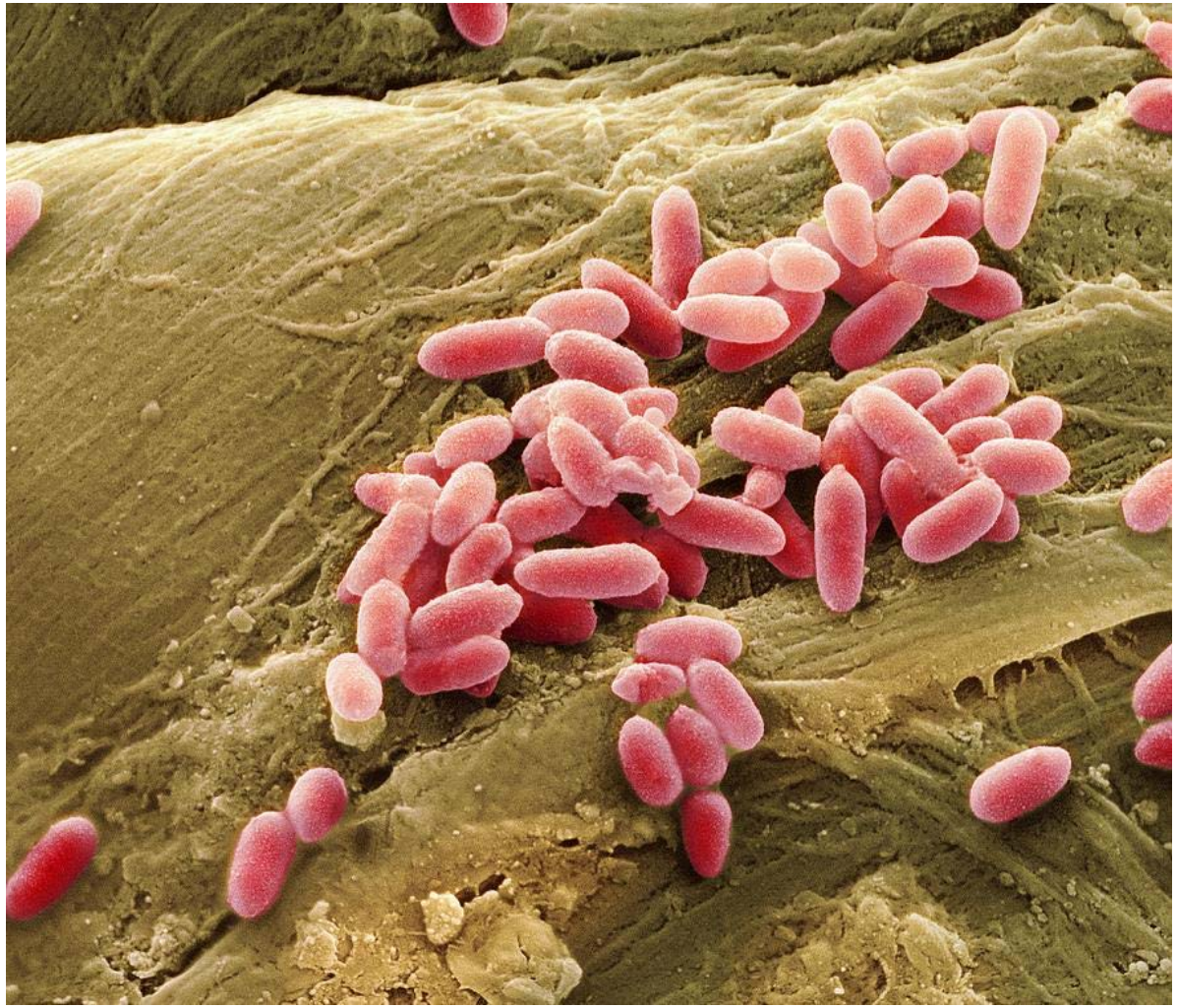
Pseudomonas aeruginosa



Difficult to treat resistant (DTR)
P. aeruginosa

According to IDSA and ESCMID guidelines, **DTR *P. aeruginosa*** are those strains **non-susceptible** to:

- piperacillin/tazobactam,
- ceftazidime,
- cefepime,
- aztreonam,
- meropenem, imipenem,
- ciprofloxacin and levofloxacin.

Difficult to treat resistant (DTR) *P. aeruginosa* – Practical recommendation

IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 1.0, 3/7/2022

What are preferred antibiotics for the treatment of infections caused by MDR P. aeruginosa?

- **When P. aeruginosa isolates test susceptible to traditional non-carbapenem β-lactam agents (i.e., piperacillin-tazobactam, ceftazidime, cefepime, aztreonam), they are preferred over carbapenem therapy.**
- **For infections caused by P. aeruginosa isolates not susceptible to any carbapenem agents but susceptible to traditional β-lactams, the administration of a traditional agent as high-dose extended-infusion therapy is suggested, after antibiotic susceptibility testing results are confirmed.**
- **For patients with moderate to severe disease or poor source control with *P. aeruginosa* isolates resistant to carbapenems but susceptible to traditional β-lactams, use of a novel β-lactam agent that tests susceptible (e.g., ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam) is also a reasonable treatment option**

https://www.idsociety.org/practice-guideline/amr-guidance/#toc-5

DTR *P. aeruginosa* – Practical recommendation

IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 1.0, 3/7/2022

What is the likelihood of the emergence of resistance of DTR-P. aeruginosa isolates to the newer β-lactam agents when used to treat DTR-P. aeruginosa infections?

In the largest retrospective cohort study, reported by **Tumbarello, et al. (2021)** (which included 577 patients with KPC-producing *K. pneumoniae*), **the rate of resistance development was low (3%)**

The emergence of resistance is a concern with all of the novel β-lactams used to treat DTR-P. aeruginosa infections, but the frequency appears to be the highest for ceftolozane-tazobactam and ceftazidime-avibactam.

What is the role of combination antibiotic therapy for the treatment of infections caused by DTR-P. aeruginosa?

Combination antibiotic therapy is not routinely recommended for infections caused by DTR-P. aeruginosa if in vitro susceptibility to a first-line antibiotic (i.e., ceftolozane-tazobactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam) has been confirmed

https://www.idsociety.org/practice-guideline/amr-guidance/#toc-5

Combination therapy to increase permeability or prevent efflux (for *P. aeruginosa*)

Colistin + CAZ-AVI

Fosfomycin + CAZ-AVI

Isolate	MIC (mg/liter)[a]		
	CAZ-AVI-COL	FOS	FOS-CAZ-AVI
E. coli			
DH10B	–	32	–
DH10B bla_{PDC-3}	–	32	<0.06
P. aeruginosa			
PAO1	0.5	64	1
CL232	32	32	4
696	8	128	1
715	32	8	8
716	4–8	128	64
776	2	128	4
795	128	128	4
834	8	64	4
835	2–4	64	4
839	8–16	>128	4
851	–	>128	8

- Winkler ML, Papp-Wallace KM, Hujer AM, Domitrovic TN, Hujer KM, Hurless KN, Tuohy M, Hall G, Bonomo RA. **2015**. Unexpected challenges in treating multidrug-resistant gram-negative bacteria: resistance to ceftazidime-avibactam in archived isolates of *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 59:1020 –1029. doi:10.1128/AAC.04238-14.

ESCMID Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA)

- In patients with **severe infections** due to difficult to treat CRPA, we suggest therapy with ceftolozane-tazobactam if active in vitro. Insufficient evidence is available for imipenem-relebactam, cefiderocol and ceftazidime-avibactam (monotherapy) at this time.

- In patients with **non-severe or low-risk CRPA infections**, under the consideration of antibiotic stewardship, we consider it good clinical practice to use the old antibiotics, chosen from among the in vitro active antibiotics on an individual basis and according to the source of infection.

- Lacking evidence, **we cannot recommend for or against the use of combination therapy** with the new BLBLI (ceftazidime-avibactam and ceftolozane-tazobactam) or cefiderocol for CRPA infections**.**

- When treating **severe infections caused by CRPA** with polymyxins, aminoglycosides, or fosfomycin, we suggest treatment with **two in vitro active drugs**. No recommendation for or against specific combinations can be provided.

- In patients with **non-severe or low-risk CRPA infections**, under the consideration of antibiotic stewardship, we consider it good clinical practice to use monotherapy chosen from among the drugs active in vitro, on an individual basis and according to the source of infection.

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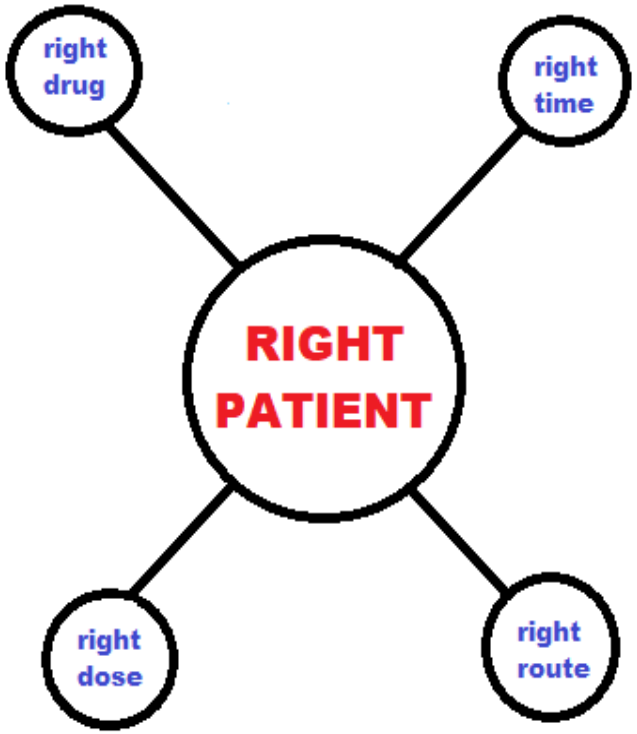
Right dose, right time, right route

Agenda

- *Right drug, right patient*

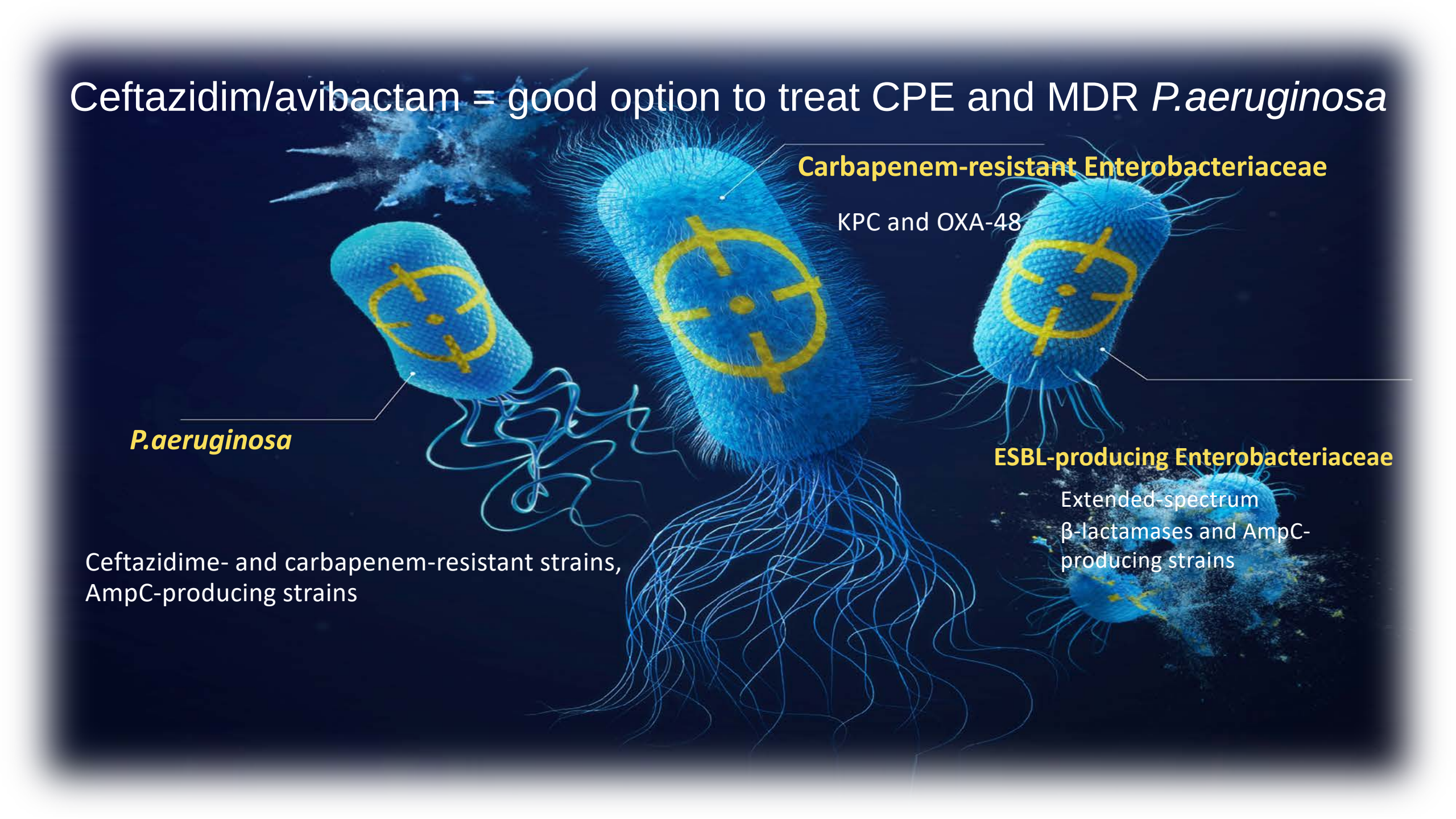
Practical recommendations from IDSA and ESCMID Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections



- *Right dose, right time, right route*

Ceftazidime-Avibactam in the treatment of infections due to CRE and MDR *P. aeruginosa*: **evaluation in adults, in real-world settings**

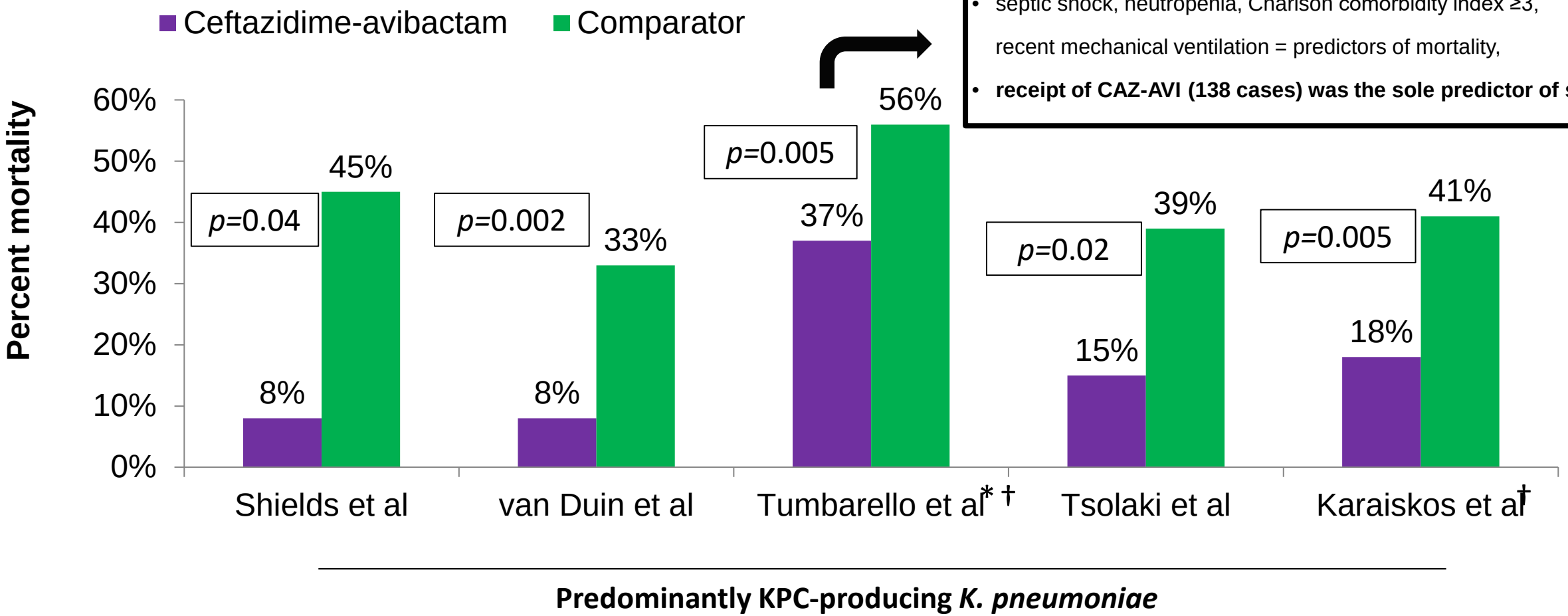
Ceftazidim/avibactam = good option to treat CPE and MDR *P.aeruginosa*



Ceftazidime-avibactam: observational clinical data

208 cases of KPC-Kp bacteremia:

- septic shock, neutropenia, Charlson comorbidity index ≥3, recent mechanical ventilation = predictors of mortality,
- **receipt of CAZ-AVI (138 cases) was the sole predictor of survival.**



*Ceftazidime-avibactam was used as salvage therapy; † propensity-score matched analysis of patients with bloodstream infections

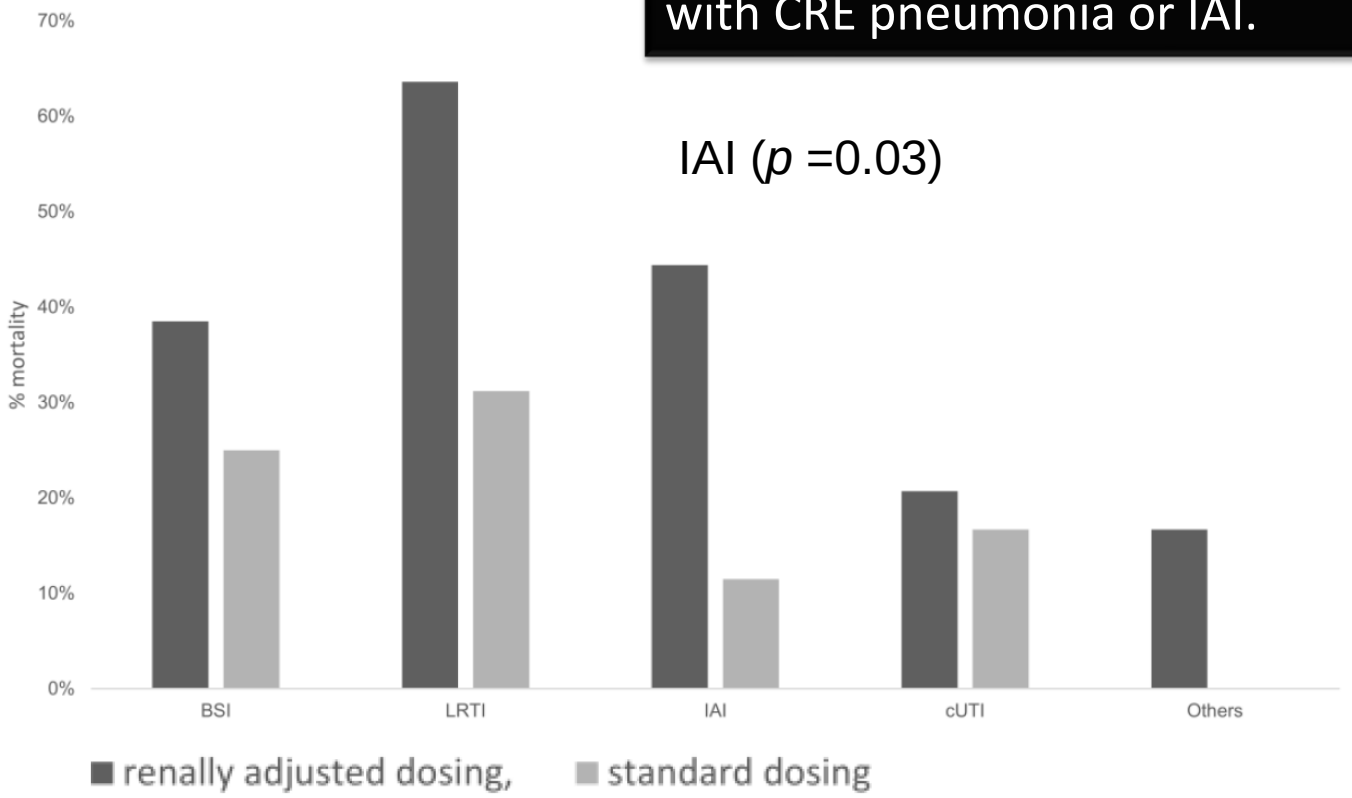
Shields RK, *et al. Antimicrob Agents Chemother.* 2017;61(8):e00883-17; van Duin D, *et al. Clin Infect Dis.* 2018;66(2):163–71; Tumbarello M, *et al. Clin Infect Dis.* 2019;68:355–64; Tsolaki V, et al, *Antimicrob Agents Chemother* 2020;64(03):e02320—19. Karaiskos I, et al. *J Antimicrob Chemother* 2021;76:775.

Impact on 30-day mortality rates of renally adjusted CAZ-AVI dosing

Potentially negative impact on outcome of CAZ-AVI dose adjustments for impaired renal function, especially in patients with CRE pneumonia or IAI.

LRTI (p=0.04)

IAI (p =0.03)



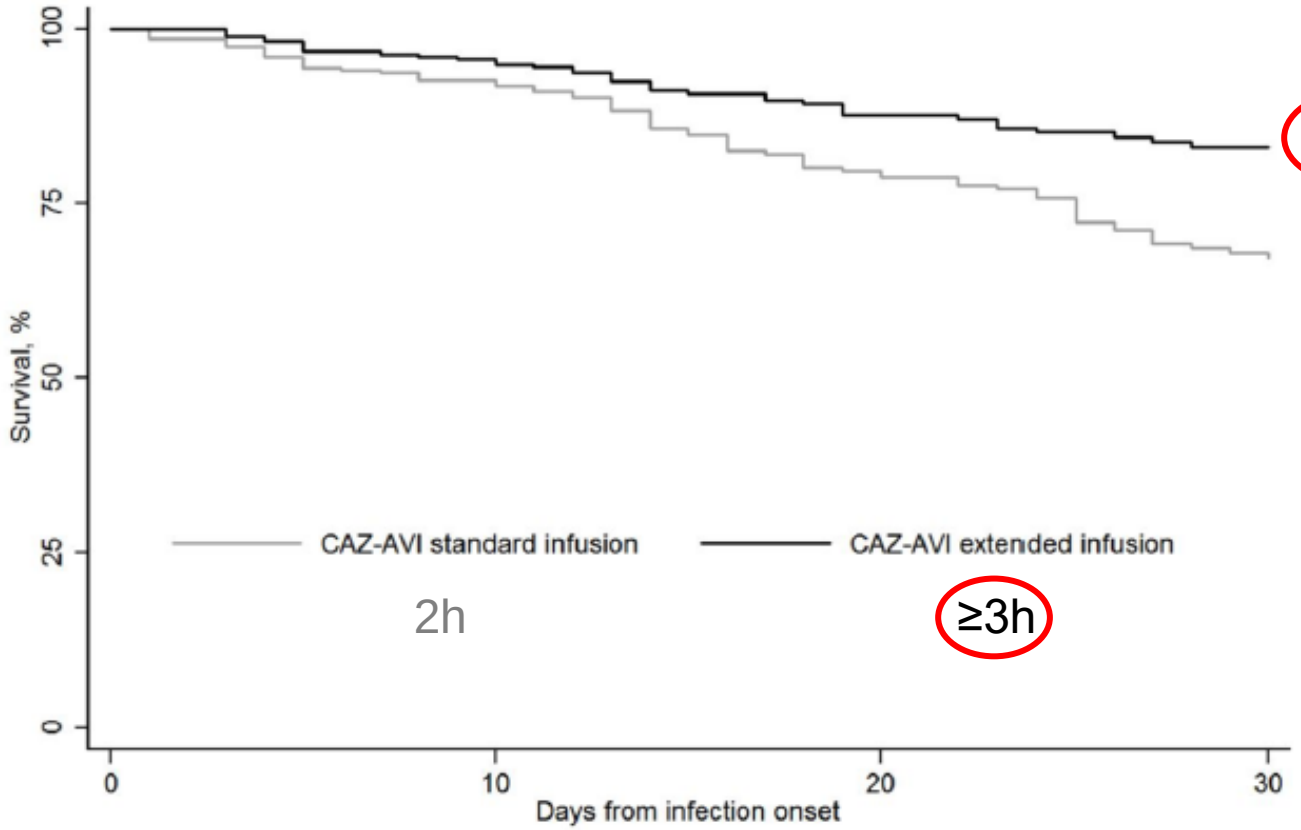
Mortality was positively associated with:

- presence at infection onset of septic shock (P = .002),
- neutropenia (P < .001), an INCREMENT score ≥8 (P = .01);
- lower respiratory tract infection (LRTI) (P = .04);
- **CAZ-AVI dose adjustment for renal function (P = .01)**

Estimated CrCl (mL/min)*	Dose regimen†	Frequency
31-50	1 g/0.25 g	Every 8 hours
16-30	0.75 g/0.1875 g	Every 12 hours
6-15	0.75 g/0.1875 g	Every 24 hours
ESRD including on haemodialysis‡	0.75 g/0.1875 g	Every 48 hours

Tumbarello M, et al. Clinical Infectious Diseases, 22 Feb 2021 https://doi.org/10.1093/cid/ciab176

Impact of CAZ-AVI infusion times on 30-day survival



30-day all-cause mortality:

20.7%

28.7%

$p < 0.001$

Tumbarello M, et al. Clinical Infectious Diseases, 22 Feb 2021 https://doi.org/10.1093/cid/ciab176

Antibiotic treatment options for *P. aeruginosa* infection outside of the urinary tract

	First-Line Treatment	Other Options
ESBL *P. aeruginosa*	Meropenem 1–2 g q8h (3 h-infusion)	Ceftolozane/tazobactam 1.5 g q8h (for infection other than pneumonia); 3 g q8h (for pneumonia) Ceftazidime/avibactam 2.5 g q8h Imipenem/relebactam 1 g q6h
DTR *P. aeruginosa* (not MBL-producer)	Ceftolozane/tazobactam 3 g q8h (3 h-infusion) Ceftazidime/avibactam 2.5 g/qh (3 h-infusion) Imipenem/relebactam 1.25 g q6h (30 min-infusion)	Cefiderocol 2 g q8h (3 h-infusion)
DTR *P. aeruginosa* (not MBL-producer; resistant to ceftolozane/tazobactam)	Ceftazidime/avibactam 2.5 g q8h (3 h-infusion)	Cefiderocol 2 g q8h (3 h-infusion) Ceftazidime/avibactam 2.5 g q8h (3 h-infusion) + Fosfomycin 12–24 g per day
DTR *P. aeruginosa* (MBL-producer) *	Cefiderocol 2 g q8h (3 h-infusion) Colistin 9 × 10^6 IU per day Cefiderocol 2 g q8h (3 h-infusion) + inhaled colistin 0.5–2 × 10^6 q12h	Ceftazidime/avibactam 2.5 g q8h + aztreonam 2 g q8h (3 h-infusion) Colistin + fosfomycin + aminoglycoside Bacteriophage therapy

DTR: difficult-to treat resistance; ESBL: extended spectrum beta-lactamase; MBL: metallo-beta-lactamase.
* Optimal treatment is unknown; infectious disease consultation is strongly recommended.

According to IDSA and ESCMID guidelines, **DTR P. aeruginosa** are those strains non-susceptible to piperacillin/tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem, ciprofloxacin, and levofloxacin.

L van den Bogaart, O Manuel Antibiotics 2022, 11, 612. https://doi.org/10.3390/antibiotics11050612

CAVICOR Study

J Antimicrob Chemother
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Journal of Antimicrobial Chemotherapy

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

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Best available treatments (BAT)

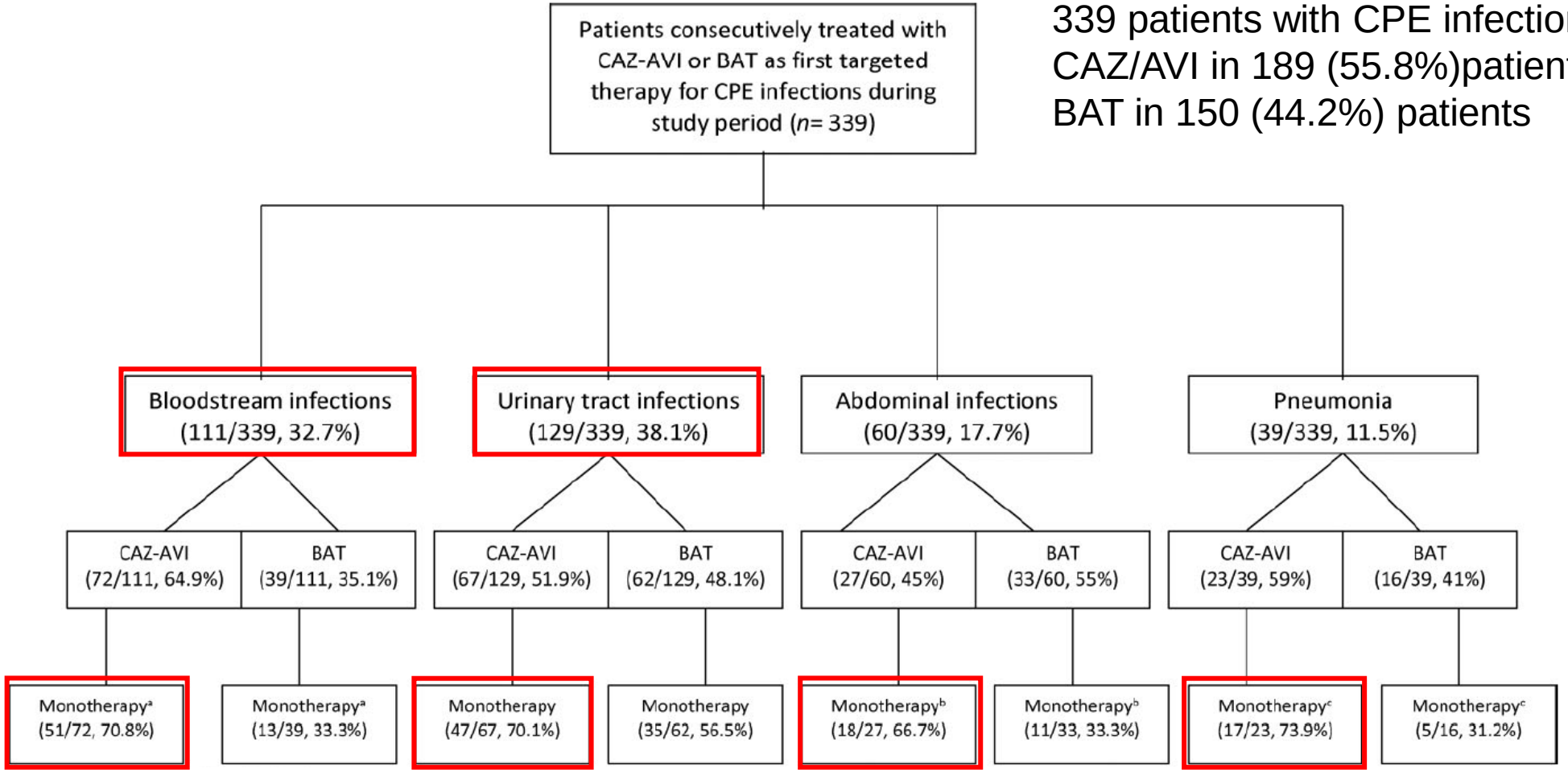
Antibiotic regimens	Total, n (%)
Monotherapy	
Meropenem	17 (11.3)
Gentamicin	12 /7.3)
Amikacin	7 (4.6)
Tigecycline	5 (4.6)
Fosfomycin	7 (4)
Colistin	3 (3.3)
Combination therapy	
Tigecycline plus gentamicin	13 (9.3)
Imipenem plus colistin	11 (6.6)
Meropenem plus amikacin	10 (5.3)
Fosfomycin plus gentamicin	6 (4)
Meropenem plus tigecycline	10 (3.3)
Tygecycline plus amikacin	7 (3.3)
Tigecycline plus gentamicin plus fosfomycin	4 (2.6)
Colistin plus gentamicin	3 (2)
Other combinations including meropenem[1]	8 (5.3)
Other combinations including imipenem[2]	8 (5.3)
Other combinations including colistin[3]	4 (2.6)
Other combinations including tigecycline[4]	2 (1.3)
Others[5]	13 (10)

38% carbapenem monotherapy/combination

Castón JJ, et al. *J Antimicrob Chemother* 2022;dkac049. doi:10.1093/jac/dkac049.

CAVICOR: Patient enrolment*[1]

339 patients with CPE infections.
CAZ/AVI in 189 (55.8%)patients
BAT in 150 (44.2%) patients



[a]P<0.001; [b]P=0.01; [c]P=0.01.

*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.[2]

BAT, 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.

CAVICOR: Outcomes

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
Crude mortality (30 days), n (%)	26 (13.7)	33 (22)	0.04

Primary →

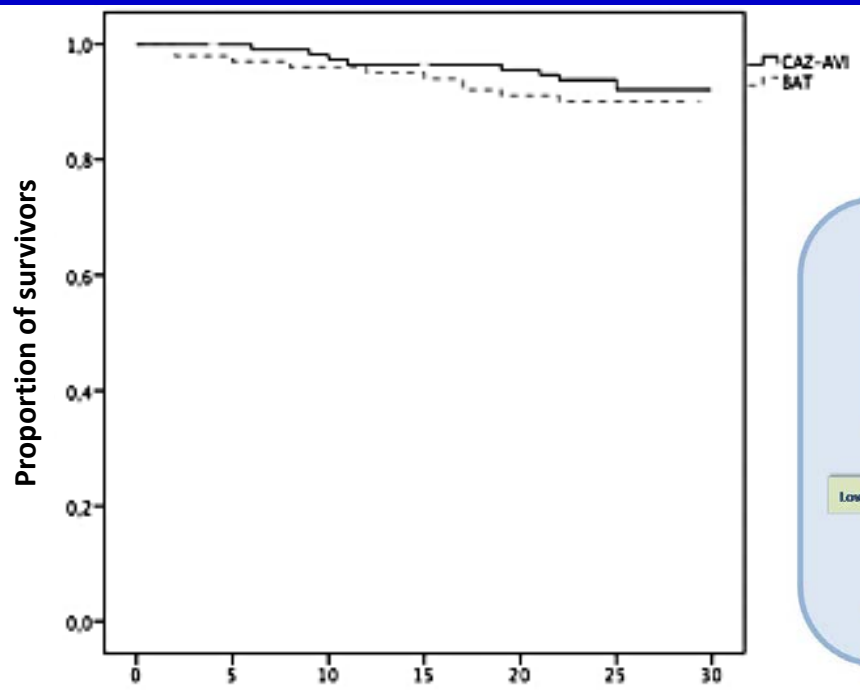
A multivariate logistic regression model was used to identify factors predictive of 30 day crude mortality

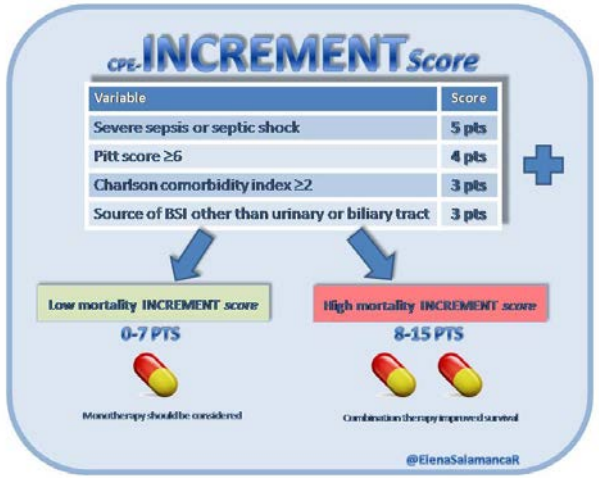
*Limitations of real-world data analyses: the interpretations from non-randomised real-world data analyses are limited by potential selection bias and unknown confounding factors.[2]

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.

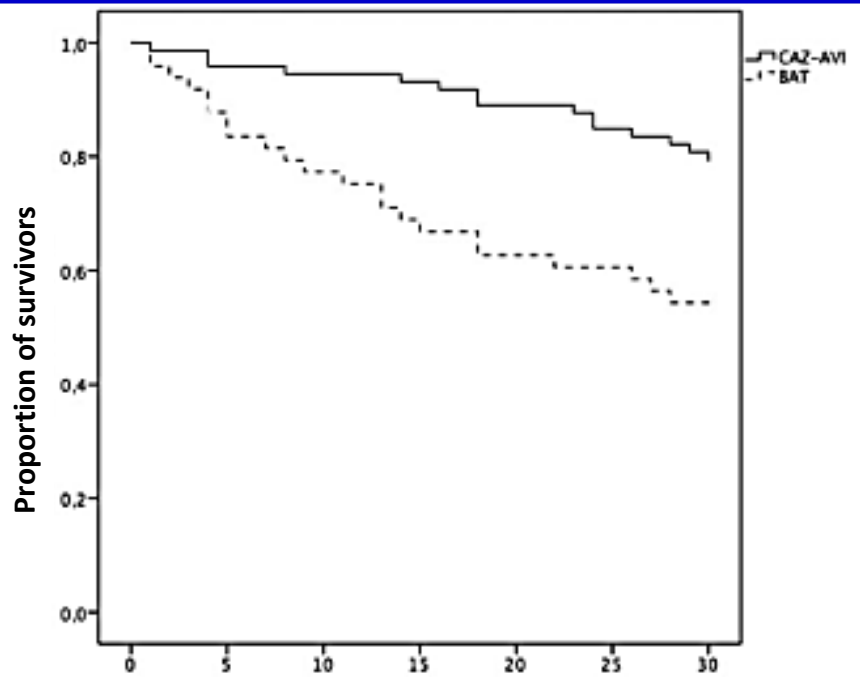
CAVICOR: Survival outcomes in patients treated with CAZ–AVI vs BAT for infections caused by CPE*[1]

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)



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BAT, best available therapy; CAZ–AVI, ceftazidime–avibactam; CPE, carbapenemase-producing Enterobacterales.

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