Key Takeaways 讓AI整理出Take home message

CRE	KPC: MEV (preferred) > CAZ-AVI > IMI-REL | NDM/MBL: CAZ-AVI + ATM or cefiderocol | OXA-48-like: CAZ-AVI Polymyxins NOT recommended | Combination therapy NOT required once β-lactam confirmed active
DTR Pa	Non-MBL: C/T, CAZ-AVI, or IMI-REL (preferred) | MBL-producing: cefiderocol (monotherapy) High cross-resistance C/T ↔ CAZ-AVI → switch to IMI-REL or cefiderocol on recurrence | No combination therapy
CRAB	PREFERRED: SUL-DUR + carbapenem | ALTERNATIVE: High-dose amp-sulbactam (9g SUL/day) + partner agent Cefiderocol = last resort, always combine | Do NOT use: carbapenem alone, rifampin, polymyxin monotherapy, nebulized antibiotics

Always consult an ID specialist for AMR infections. | www.idsociety.org/practice-guideline/amr-guidance/

CAZ-AVI = Ceftazidime-avibactam | MEV = Meropenem-vaborbactam | IMI-REL = Imipenem-cilastatin-relebactam | C/T = Ceftolozane-tazobactam | ATM = Aztreonam | SUL-DUR = Sulbactam-durlobactam | TMP-SMX = Trimethoprim-sulfamethoxazole | MBL = Metallo-β-lactamase | BSI = Bloodstream infection | UTI = Urinary tract infection | IAI = Intra-abdominal infection

Current treatment for MBLs

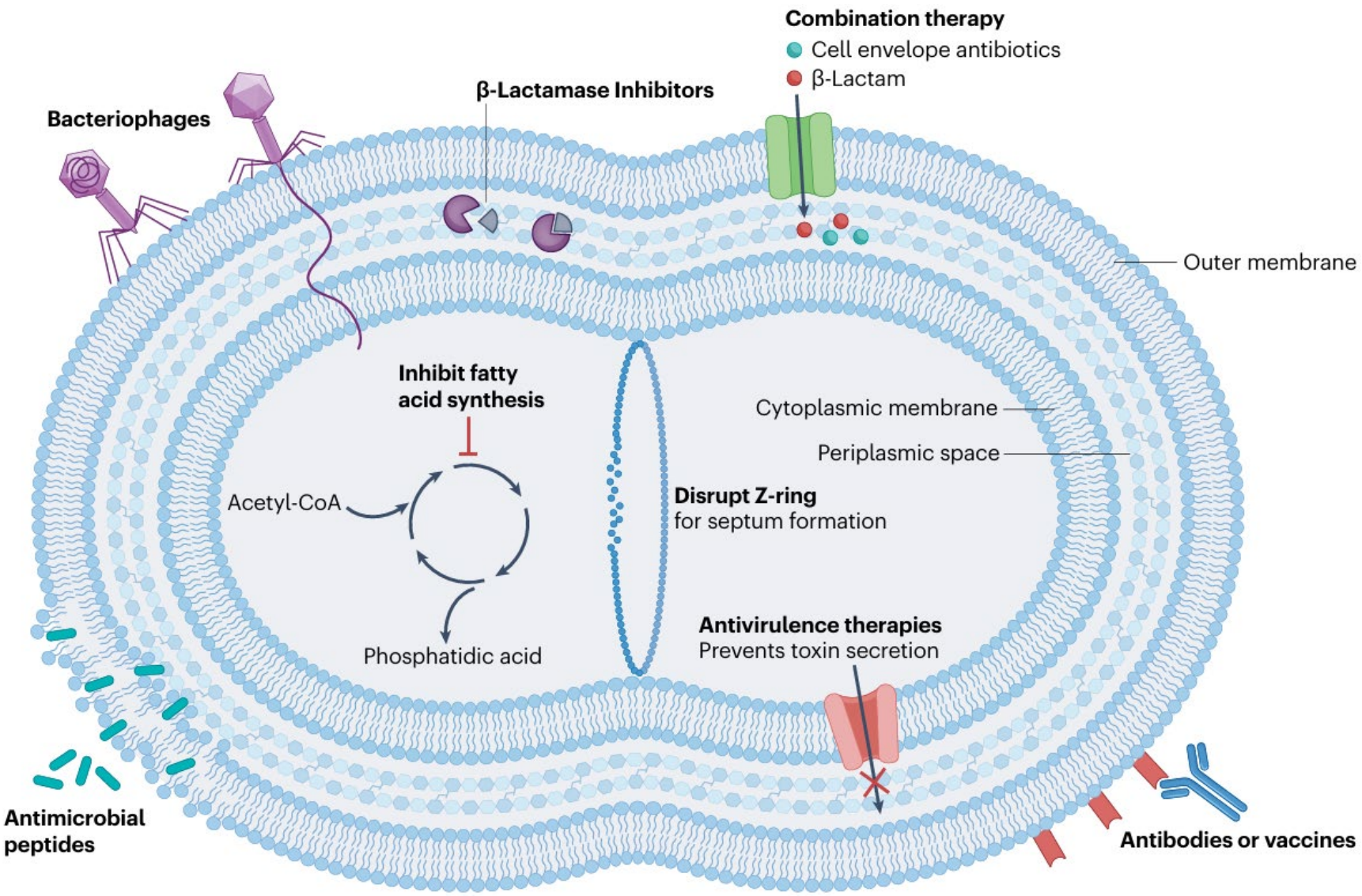
- Cefiderocol
- Aztreonam-avibactam (aztreonam + ceftazidime/avibactam)
- Cefepime / Taniborbactam
- Tigecycline / eravacycline

Challenges for the development of MBL inhibitors

- Active site in a shallow groove
- Structural diversity
- Superfamily of metalloproteins

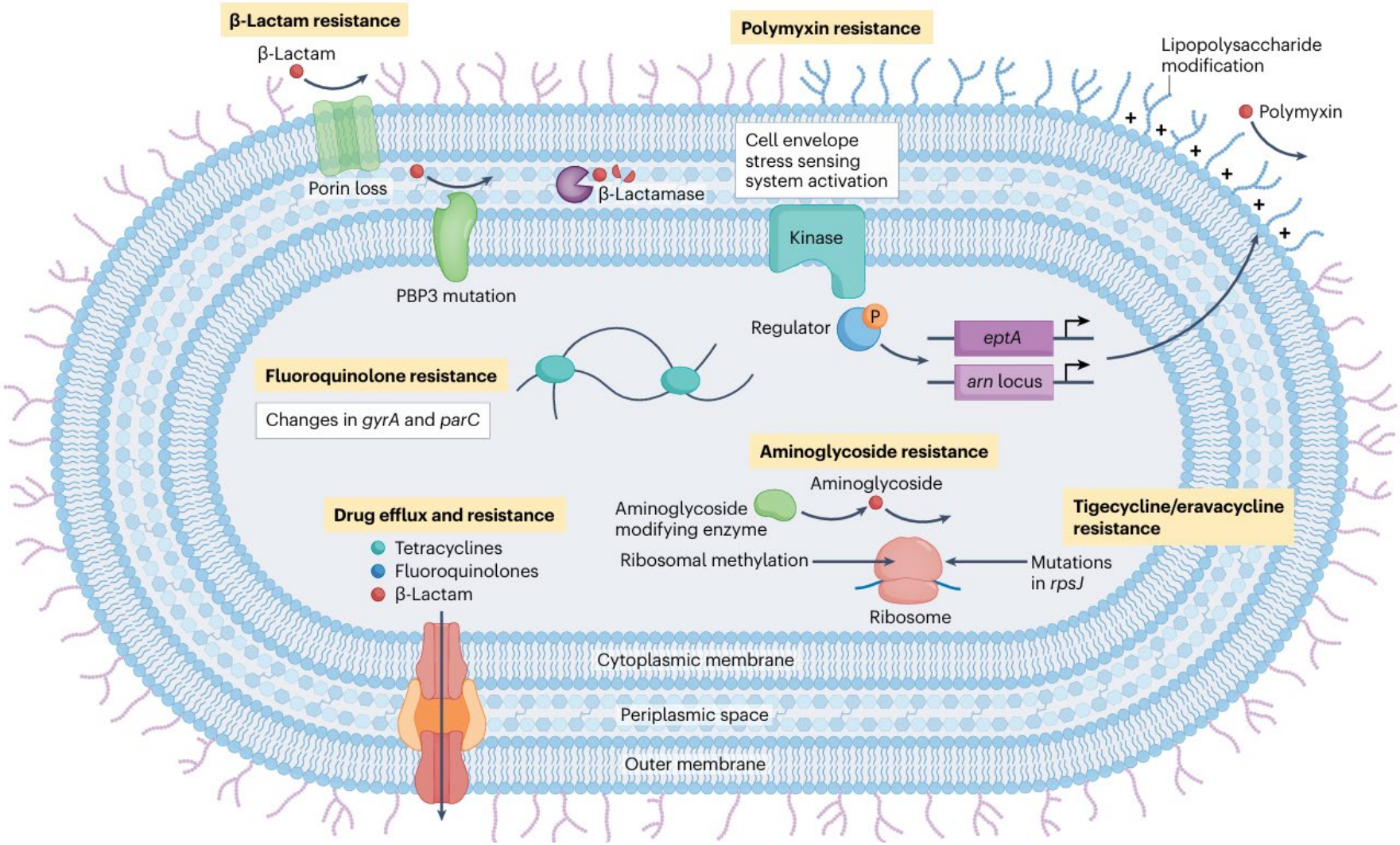
Lancet Infect Dis. 2022 Jan;22(1):e28-e34.

Novel treatment approaches for ESKAPE pathogens



Nat Rev Microbiol.2024 Oct;22(10):598-6

Emerging mechanisms of resistance in Gram-negative pathogens



Nat Rev Microbiol.2024 Oct;22(10):598-6

Genotypic testing for CRE identification

Main characteristics of the rapid molecular tools so far available for the detection and characterization of the antibiotic resistance genes in multidrug-resistant Enterobacteriaceae (MDR-*Ent*).

Molecular tool				
Single PCR coupl standard DNA				
Next-generation methodologies				oratories
Multiplex end-p				
Hyplex platforms (commercial)				
Real-time PCR				
NucliSENS EasyQ platform (com				
Multiplex real-ti				
Check-Points (co				
LAMP				
Microarray				ications
Check-Points (commercial k				
Identibac (comm				
MALDI-TOF MS (f of catalytic acti				ns of isolates g
MALDI-TOF MS (f of atomic mass				s can be
MALDI-TOF MS (for mini-sequ				d more rapid
PCR/ESI-MS (PLEX-ID, commercial)	4–6 h (starting from sample)	++++	(Clinical)/ Research	Excellent for clinical applications. However, so far available only for research

BioFire® FilmArray®

Pneumonia Panel *plus*

健保點13, 800
自費:~18, 000

18 (15+3) bacteria, 10 virus, 7 resistance genes

BACTERIA
Semi-Quantitative Bacteria
Acinetobacter calcoaceticus-baumannii complex
Enterobacter cloacae complex
Escherichia coli
Haemophilus influenzae
Klebsiella aerogenes
Klebsiella oxytoca
Klebsiella pneumoniae group
Mora
Prote
Pseu
Serra
Staph
Strep
Streptococcus pneumoniae
Streptococcus pyogenes

ATYPICAL BACTERIA
Qualitative Bacteria
Chlamydia pneumoniae
Legionella pneumophila
Mycoplasma pneumoniae

VIRUSES
Adenovirus
Parainfluenza Virus
Respiratory Syncytial Virus

ANTIMICROBIAL RESISTANCE GENES
Carbapenemases
IMP
KPC
NDM
OXA-48-like
VIM

ESBL

Genotypic testing: gold standard, but high cost and inability to detect new carbapenemase genes (high specificity of the primer sets)

=> **Phenotypic testing**

Diagn Microbiol Infect Dis. 2013 Nov;77(3):179-94.

Phenotypic testing for CRE identification

Modified carbapenem inactivation method

TABLE 1 Select phenotypic tests for carbapenemase detection in clinical isolates[a]

Test parameter	Modified Hodge test (10,18–24)	Carba NP test and variants (10, 24–29, 32)	mCIM (7, 10, 32, 43)	Lateral flow immunoassays (11–16)	Targeted carbapenemase assays (47–53)	MALDI-TOF MS hydrolysis approach (28, 54–61)
Carbapenem-resistant organisms	*Enterobacteriaceae*	*Enterobacteriaceae*, *Pseudomonas aeruginosa*	*Enterobacteriaceae*, *P. aeruginosa*	*Enterobacteriaceae*	Generally *Enterobacteriaceae*	*Enterobacteriaceae*, *P. aeruginosa*, *A. baumannii*
Accuracy	For *Enterobacteriaceae*, sensitivity, ~95% and	For *Enterobacteriaceae*, sensitivity, ~84% and specificity, ~100%;	For *Enterobacteriaceae*, sensitivity, 97% and specificity, 99%; for	For *Enterobacteriaceae*, sensitivity, 100%	Accuracy varies by test, e.g., OXA-48 disk test sensitivity,	For *Enterobacteriaceae*, sensitivities, 77%–100% and
Ease of use						
Interpretation results						
Total time to test						
Turnaround ti						
Estimated cost	<$1.00	For manual versions, ≥$2.00; cost increases if imipenem-based	<$1.00	Prices have not yet been established	Varies by test; ranges from <$1.00–$6.00; MBL gradient	<$1.00 if MALDI-TOF MS instrument already available
Regulatory status		*aeruginosa*; manual Carba NP is CLSI endorsed				

[a]IP, imipenem; IPI, imipenem inhibitor (imipenem plus EDTA); RUO, research use only; LDT, laboratory-developed test. Table modified from reference 10.

(1) **Growth-based assays**: measure C-S Ecoli growth in the presence of a carbapenem, ex: **modified carbapenem inactivation method** and modified Hodge test

(2) **Hydrolysis methods**: detect carbapenem degradation products, ex: Carba NP test and MALDI-TOF MS)

(3) **Antibody-based method**: detect carbapenemase enzymes through the use of specific antibodies, ex: lateral flow immunoassays

(4) **Inhibitor-based methods**: differentiate carbapenemases by applying class-specific inhibitors, ex: targeted carbapenemase assays

Limitation of phenotypic testing: inability to identity carbapenemase type, several hours and multi-steps, limited specificity (false-positive)

J Clin Microbiol. 2018 Oct 25;56(11):e01140-18

圖中分類	可能代表的抗生素
Penicillin + BLI	**Piperacillin-tazobactam**、ampicillin-sulbactam、amoxicillin-clavulanate
Carbapenem	**Meropenem**、imipenem-cilastatin、doripenem、ertapenem
Cephalosporin + BLI	**Ceftolozane-tazobactam** 最常見；有時也可能包含 cefoperazone-sulbactam
Cephalosp + non β-lactam BLI	**Ceftazidime-avibactam** 最典型；也可能包含 ceftazidime-avibactam + aztreonam 這類策略
Siderophore cephalosporin	**Cefiderocol**，幾乎就是指這個藥
Monobactam	**Aztreonam**
Carbapenem + BLI	**Meropenem-vaborbactam**、**imipenem-cilastatin-relebactam**
Aminoglycosides	Amikacin、gentamicin、tobramycin、plazomicin
Polymyxins	Colistin、polymyxin B

Infection (2024) 52:2029–2042
https://doi.org/10.1007/s15010-024-02277-y

REVIEW

Ceftazidime-avibactam combination therapy versus monotherapy for treating carbapenem-resistant gram-negative infection: a systemic review and meta-analysis

Wei Hsu[1] · Min-Hsiang Chuang[1] · Wen-Wen Tsai[2] · Chih-Cheng Lai[3] · Hsin-Yu Lai[1] · Hung-Jen Tang[1]

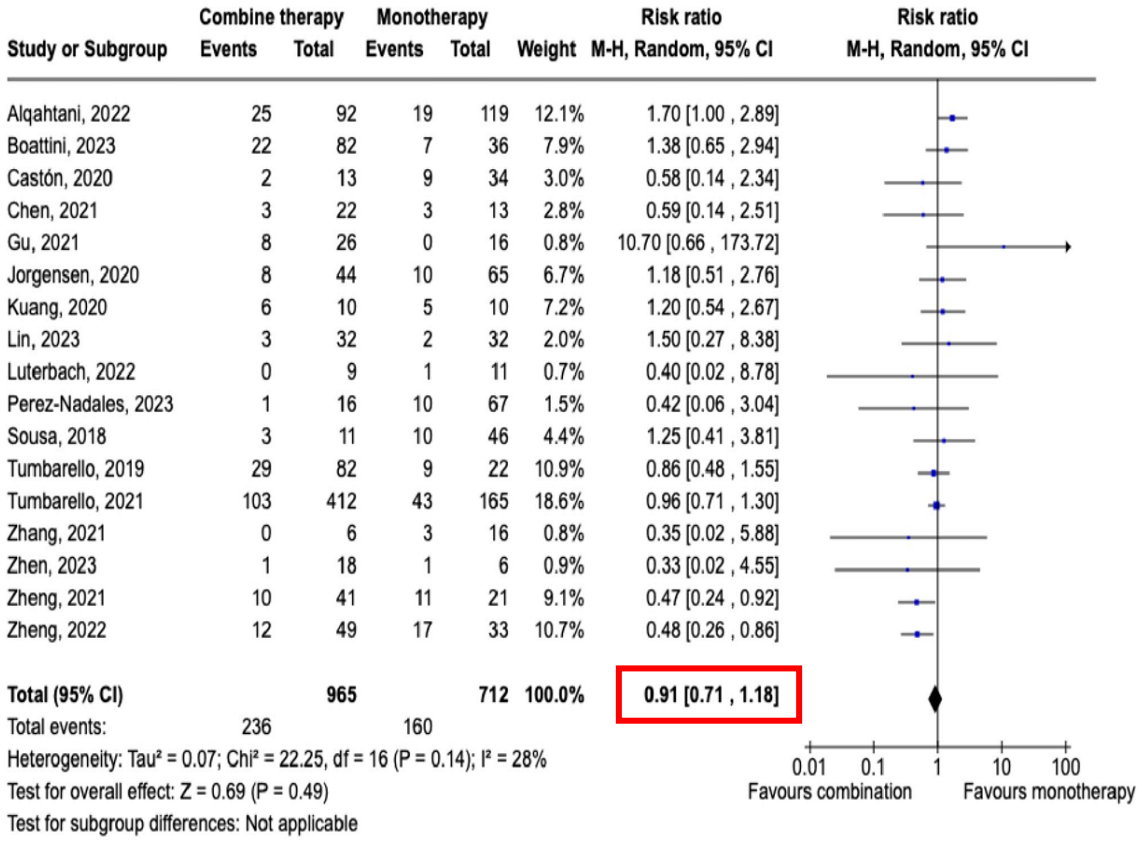
[1] Department of Internal Medicine, Division of Hospital Medicine, Chi Mei Medical Center, Tainan, Taiwan

[2] Department of Neurology, Chi Mei Medical Center, Tainan, Taiwan

[3] Department of Intensive Care Medicine, Chi Mei Medical Center, Tainan, Taiwan

Infection.2024 Oct;52(5):2029-2042.

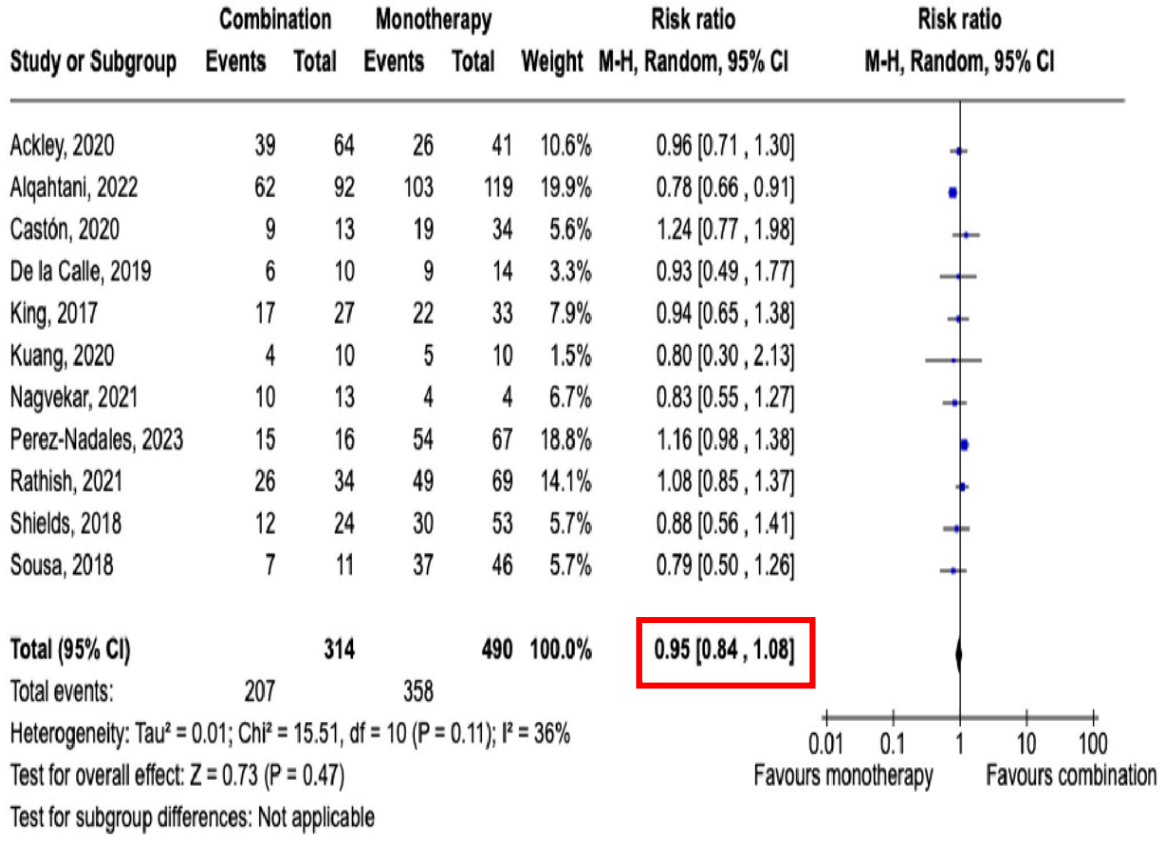
30-day mortality



Study or Subgroup	Combine therapy Events	Total	Monotherapy Events	Total	Weight	Risk ratio M-H, Random, 95% CI
Alqahtani, 2022	25	92	19	119	12.1%	1.70 [1.00 , 2.89]
Boattini, 2023	22	82	7	36	7.9%	1.38 [0.65 , 2.94]
Castón, 2020	2	13	9	34	3.0%	0.58 [0.14 , 2.34]
Chen, 2021	3	22	3	13	2.8%	0.59 [0.14 , 2.51]
Gu, 2021	8	26	0	16	0.8%	10.70 [0.66 , 173.72]
Jorgensen, 2020	8	44	10	65	6.7%	1.18 [0.51 , 2.76]
Kuang, 2020	6	10	5	10	7.2%	1.20 [0.54 , 2.67]
Lin, 2023	3	32	2	32	2.0%	1.50 [0.27 , 8.38]
Luterbach, 2022	0	9	1	11	0.7%	0.40 [0.02 , 8.78]
Perez-Nadales, 2023	1	16	10	67	1.5%	0.42 [0.06 , 3.04]
Sousa, 2018	3	11	10	46	4.4%	1.25 [0.41 , 3.81]
Tumbarello, 2019	29	82	9	22	10.9%	0.86 [0.48 , 1.55]
Tumbarello, 2021	103	412	43	165	18.6%	0.96 [0.71 , 1.30]
Zhang, 2021	0	6	3	16	0.8%	0.35 [0.02 , 5.88]
Zhen, 2023	1	18	1	6	0.9%	0.33 [0.02 , 4.55]
Zheng, 2021	10	41	11	21	9.1%	0.47 [0.24 , 0.92]
Zheng, 2022	12	49	17	33	10.7%	0.48 [0.26 , 0.86]
Total (95% CI)		**965**		**712**	**100.0%**	**0.91 [0.71 , 1.18]**
Total events:	236		160			

Heterogeneity: Tau² = 0.07; Chi² = 22.25, df = 16 (P = 0.14); I² = 28%
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable

Clinical success rate

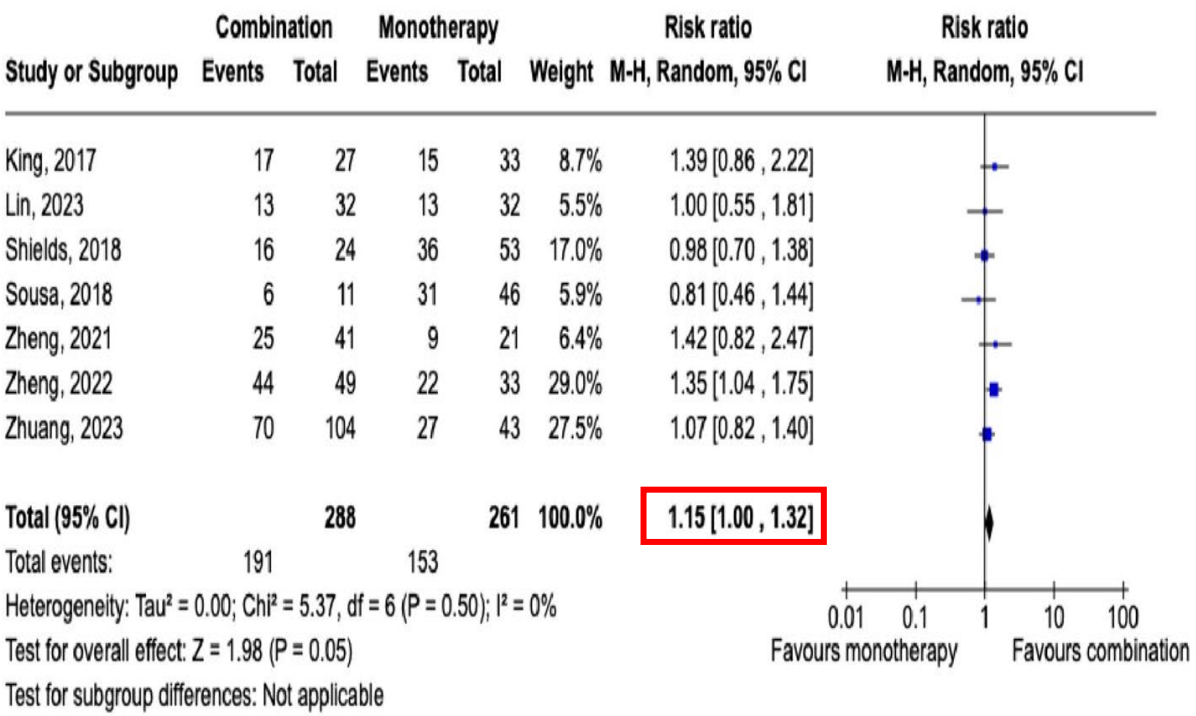


Study or Subgroup	Combination Events	Total	Monotherapy Events	Total	Weight	Risk ratio M-H, Random, 95% CI
Ackley, 2020	39	64	26	41	10.6%	0.96 [0.71 , 1.30]
Alqahtani, 2022	62	92	103	119	19.9%	0.78 [0.66 , 0.91]
Castón, 2020	9	13	19	34	5.6%	1.24 [0.77 , 1.98]
De la Calle, 2019	6	10	9	14	3.3%	0.93 [0.49 , 1.77]
King, 2017	17	27	22	33	7.9%	0.94 [0.65 , 1.38]
Kuang, 2020	4	10	5	10	1.5%	0.80 [0.30 , 2.13]
Nagvekar, 2021	10	13	4	4	6.7%	0.83 [0.55 , 1.27]
Perez-Nadales, 2023	15	16	54	67	18.8%	1.16 [0.98 , 1.38]
Rathish, 2021	26	34	49	69	14.1%	1.08 [0.85 , 1.37]
Shields, 2018	12	24	30	53	5.7%	0.88 [0.56 , 1.41]
Sousa, 2018	7	11	37	46	5.7%	0.79 [0.50 , 1.26]
Total (95% CI)		**314**		**490**	**100.0%**	**0.95 [0.84 , 1.08]**
Total events:	207		358			

Heterogeneity: Tau² = 0.01; Chi² = 15.51, df = 10 (P = 0.11); I² = 36%
Test for overall effect: Z = 0.73 (P = 0.47)
Test for subgroup differences: Not applicable

Infection.2024 Oct;52(5):2029-2042.

Microbiological eradication rate



Study or Subgroup	Combination Events	Combination Total	Monotherapy Events	Monotherapy Total	Weight	Risk ratio M-H, Random, 95% CI
King, 2017	17	27	15	33	8.7%	1.39 [0.86 , 2.22]
Lin, 2023	13	32	13	32	5.5%	1.00 [0.55 , 1.81]
Shields, 2018	16	24	36	53	17.0%	0.98 [0.70 , 1.38]
Sousa, 2018	6	11	31	46	5.9%	0.81 [0.46 , 1.44]
Zheng, 2021	25	41	9	21	6.4%	1.42 [0.82 , 2.47]
Zheng, 2022	44	49	22	33	29.0%	1.35 [1.04 , 1.75]
Zhuang, 2023	70	104	27	43	27.5%	1.07 [0.82 , 1.40]
Total (95% CI)		**288**		**261**	**100.0%**	**1.15 [1.00 , 1.32]**
Total events:	191		153			

Heterogeneity: Tau² = 0.00; Chi² = 5.37, df = 6 (P = 0.50); I² = 0%

Test for overall effect: Z = 1.98 (P = 0.05)

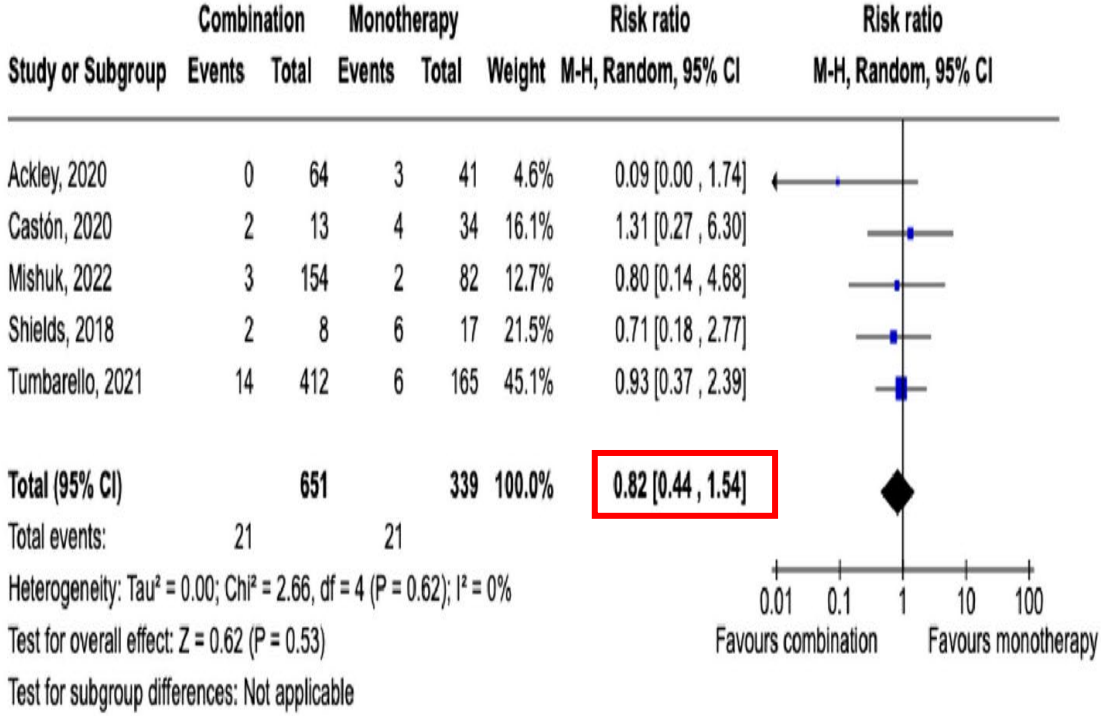
Test for subgroup differences: Not applicable

Risk ratio M-H, Random, 95% CI

0.01 0.1 1 10 100

Favours monotherapy Favours combination

Post-treatment emergent resistance



Study or Subgroup	Combination Events	Combination Total	Monotherapy Events	Monotherapy Total	Weight	Risk ratio M-H, Random, 95% CI
Ackley, 2020	0	64	3	41	4.6%	0.09 [0.00 , 1.74]
Castón, 2020	2	13	4	34	16.1%	1.31 [0.27 , 6.30]
Mishuk, 2022	3	154	2	82	12.7%	0.80 [0.14 , 4.68]
Shields, 2018	2	8	6	17	21.5%	0.71 [0.18 , 2.77]
Tumbarello, 2021	14	412	6	165	45.1%	0.93 [0.37 , 2.39]
Total (95% CI)		**651**		**339**	**100.0%**	**0.82 [0.44 , 1.54]**
Total events:	21		21			

Heterogeneity: Tau² = 0.00; Chi² = 2.66, df = 4 (P = 0.62); I² = 0%

Test for overall effect: Z = 0.62 (P = 0.53)

Test for subgroup differences: Not applicable

Risk ratio M-H, Random, 95% CI

0.01 0.1 1 10 100

Favours combination Favours monotherapy

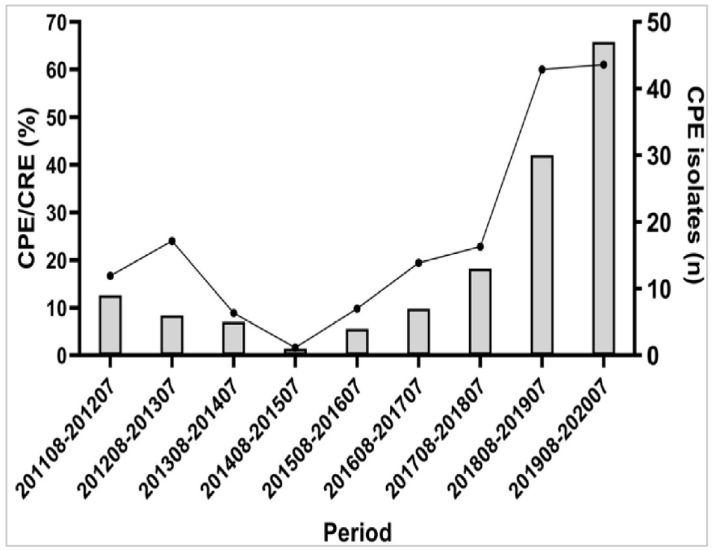
Activity of new agents against GNB pathogens

	Enterobacterales					
	Class A Carbapenemase (*e.g.* KPC)	Class B Carbapenemase (*e.g.* NDM)	Class D Carbapenemase (*e.g.* OXA-48)	*Pseudomonas aeruginosa*	*Acinetobacter baumannii*	*Stenotrophomonas maltophilia*
Ceftobiprole						
(Zerbaxa) Ceftolozane-tazobactam						
(Zavicefta) Ceftazidime-avibactam						
Cefiderecol						
Meropenem-vaborbactam						
(Recarbrio) Imipenem-relebactam						
(Emblaveo) Aztreonam-avibactam						
Plazomicin						
Eravacycline						

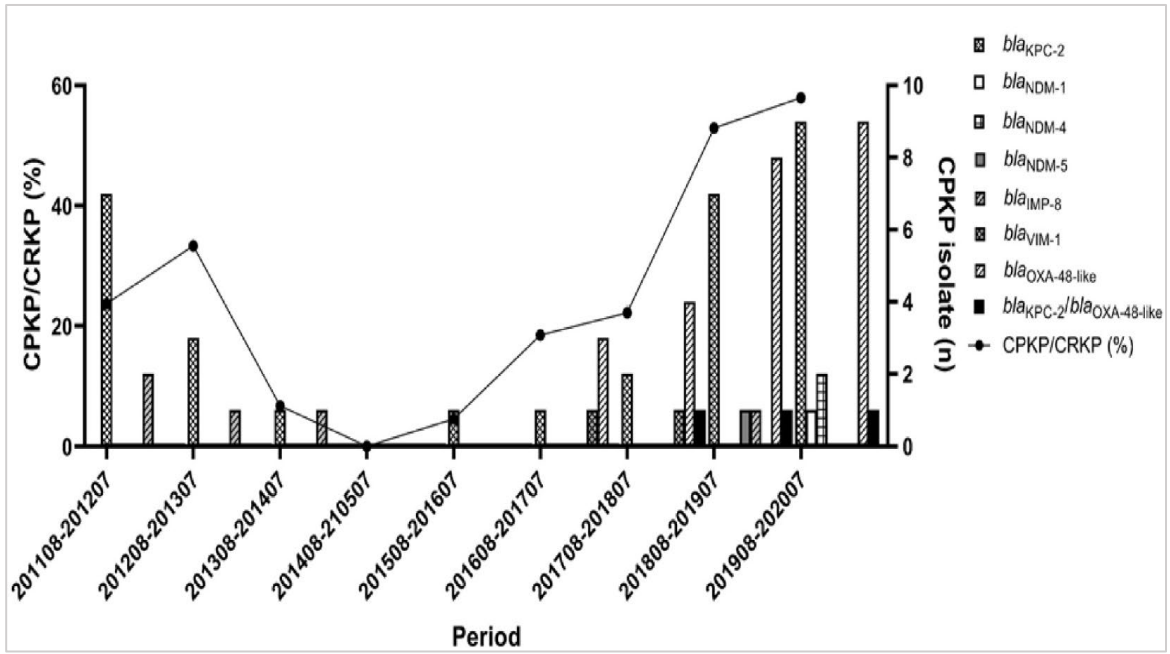
Eur Respir Rev. 2022 Dec 21;31(166):220119

Types of carbapenemase producers in CRKP

455 CRE isolates, En Chu Kong Hospital, between 2011 to 2020



CPE/CRE increasing

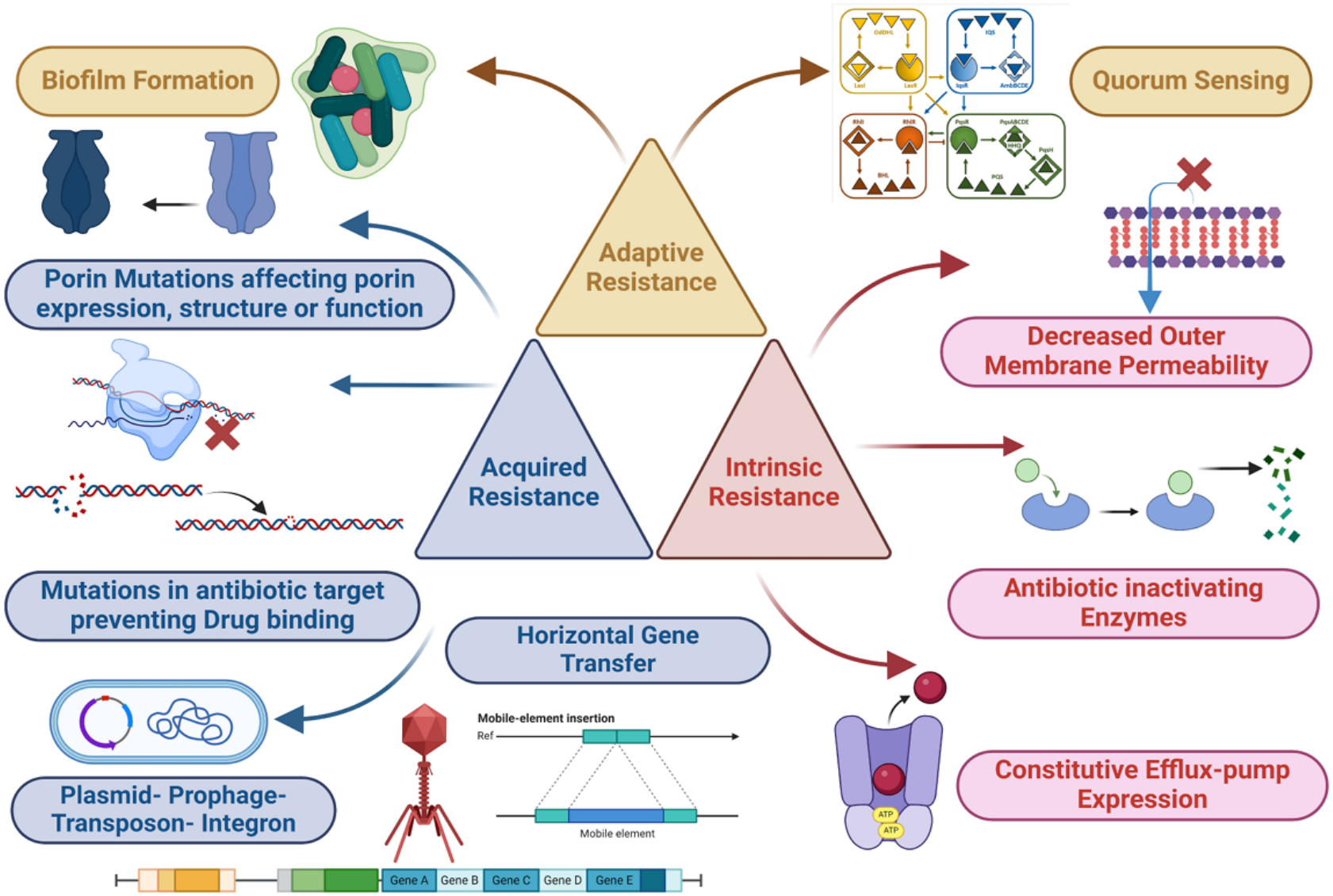


KPC and OXA-48 predominant
MBLs increasing

CPE: Carbapenemase-producing Enterobacteriaceae

Front Microbiol. 2022 Mar 11:13:703113.

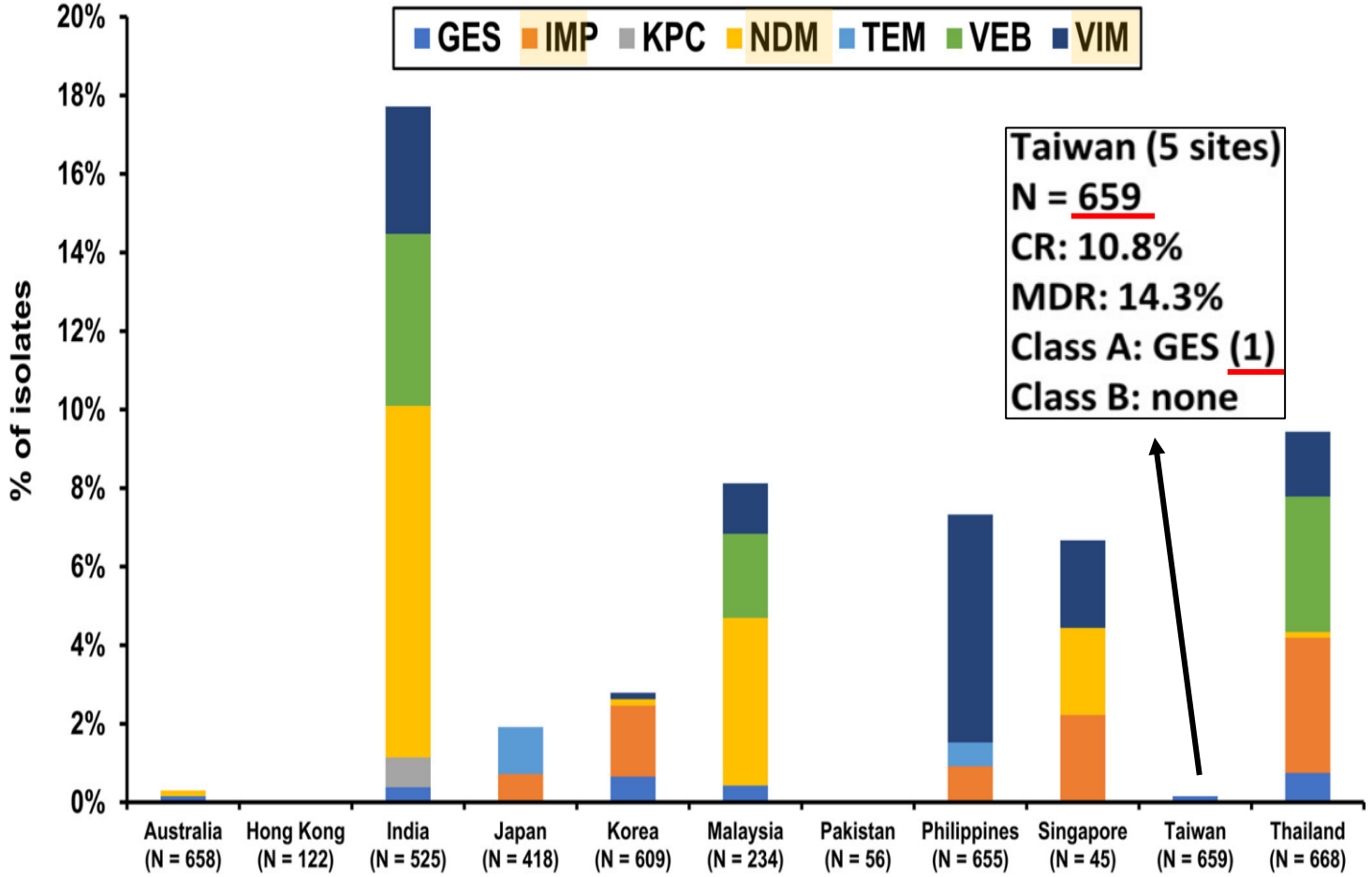
Mechanism of antimicrobial resistance of *P. aeruginosa*



Elfadadny et al. Front Microbiol.2024 Apr 5:15:1374466.

Proportion of *B*-lactamase genes for *P. aeruginosa* in the Asia-Pacific region from 2015 to 2019, ATLAS program

(total, n =6,349)



- For 747 of the CRPA that were available for gene screening, *B*-lactamase genes were detected in 245 **(32.8%)** isolates.
- The most common b-lactamase genes were **VIM** (29.0%), followed by **NDM** (24.9%), VEB (20.8%), IMP (18.0%), GES (5.7%), TEM (3.3%), and KPC (1.6%).

China were not available for multiplex PCR

Lee et al. Antimicrob Agents Chemother.2022 Feb 15;66(2):e0200021.

Susceptibility of ceftolozane/tazobactam for CRPA in Taiwan

Group/region of Taiwan	Ward[a]	Year Percent susceptible to ceftolozane/tazobactam (no. of isolates)					
		2016	2017	2018	2019	2020	2021
All *P. aeruginosa*							
All regions	ICU	96.6 (116)	92.7 (109)	96.8 (93)	93.7 (111)	99.2 (125)	97.6 (127)
	non-ICU	96.7 (244)	95.2 (294)	98.4 (250)	98.1 (268)	99.2 (266)	97.1 (243)
Northern	ICU	95.2 (21)	83.3 (12)	90.9 (22)	95.0 (20)	100 (13)	96.2 (26)
	non-ICU	94.0 (67)	94.0 (50)	97.2 (72)	98.5 (66)	100 (70)	88.4 (43)
Central	ICU	94.1 (51)	90.6 (53)	97.1 (35)	97.9 (48)	98.2 (55)	98.1 (52)
	non-ICU	100 (53)	96.3 (81)	98.8 (85)	96.5 (57)	98.5 (65)	98.6 (74)
Southern	ICU	100 (44)	97.7 (44)	100 (36)	88.4 (43)	100 (57)	98.0 (49)
	non-ICU	96.8 (124)	95.1 (163)	98.9 (93)	98.6 (145)	99.2 (131)	99.2 (126)
Carbapenem-resistant *P. aeruginosa*[b]							
All regions	ICU	87.0 (23)	77.8 (18)	92.6 (27)	87.1 (31)	100 (31)	94.9 (39)
	non-ICU	93.8 (32)	82.5 (40)	92.9 (42)	93.2 (44)	98.3 (58)	88.2 (34)
Northern	All[c]	89.5 (19)	60.0 (20)	83.3 (24)	92.0 (25)	100 (22)	77.3 (22)
Central	All[c]	80.0 (10)	90.5 (21)	100 (22)	92.0 (25)	95.0 (20)	100 (19)
Southern	All[c]	96.3 (27)	85.2 (27)	96.3 (27)	88.0 (25)	100 (49)	96.9 (32)

[a] The ward source of 2.7% (82/3013) of all *P. aeruginosa* and 3.7% (19/520) of CRPA isolates were not recorded.
[b] Carbapenem-resistant *P. aeruginosa* was defined by an isolate testing resistant to either imipenem or meropenem (meropenem was not tested from 2012 to 2015).
[c] Owing to the relatively small number of CRPA identified in some years, the totals from all wards were combined.

ceftolozane/tazobactam cover inherit resistance => increasing acquired resistance in northern region?

J Glob Antimicrob Resist.2023 Sep:34:106-112.

Activity of new agents against GNB pathogens

	Enterobacterales					
	Class A Carbapenemase (*e.g.* KPC)	Class B Carbapenemase (*e.g.* NDM)	Class D Carbapenemase (*e.g.* OXA-48)	*Pseudomonas aeruginosa*	*Acinetobacter baumannii*	*Stenotrophomonas maltophilia*
Ceftobiprole						
(Zerbaxa) Ceftolozane-tazobactam						
(Zavicefta) Ceftazidime-avibactam						
Cefiderecol						
Meropenem-vaborbactam						
Imipenem-relebactam						
Aztreonam-avibactam						
Plazomicin						
Eravacycline						

Bassetti et al. Eur Respir Rev. 2022 Dec 21;31(166):220119

Treatment options for CRPA according to mechanism of resistance

		(Zerbaxa) C/T	(Zavicefta) CAZ/AVI	IMI/REL	Cefiderocol	Pazomicin	Fosfomycin	Colistin
PCR	Carbapenemase							
	Class A	No	Yes	Yes	Yes	Yes	Yes	Yes
	Class B	No	No	No	Yes	Variable	Yes	Yes
	Class D	No	Yes	No	Yes	Yes	Yes	Yes
?	(porin) OprD	Yes	Yes	Yes	Yes			
	(efflux) MexAB	Yes	No	Yes	Yes			
	(efflux) MexXY	Yes	No	Yes	Yes			

Zakhour et al. Antibiotics (Basel).2022 Oct 18;11(10):1432.

Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by CRGBN (CREDIBLE-CR)

- multicenter, phase 3 RCT, CR-GNB, nosocomial pneumonia, BSI, cUTI, others

	Nosocomial pneumonia	
	Cefiderocol (n=40)	Best available therapy (n=19)
Clinical outcomes		
End of treatment		
Clinical cure	24 (60%; 43·3–75·1)	12 (63%; 38·4–83·7)
Clinical failure	13 (33%)	7 (37%)
Indeterminate	3 (8%)	0
Test of cure		
Clinical cure*	20 (50%; 33·8–66·2)	10 (53%; 28·9–75·6)
Clinical failure	16 (40%)	6 (32%)
Indeterminate	4 (10%)	3 (16%)

	Cefiderocol (n=101)	Best available therapy (n=49)
Acinetobacter spp*	21/42 (50%)	3/17 (18%)
Acinetobacter baumannii	19/39 (49%)	3/17 (18%)
Klebsiella pneumoniae	8/34 (24%)	4/16 (25%)
Without *Acinetobacter* spp	6/28 (21%)	4/15 (27%)
Pseudomonas aeruginosa	6/17 (35%)	2/12 (17%)
Without *Acinetobacter* spp	2/11 (18%)	2/11 (18%)
Escherichia coli	1/6 (17%)	0/3
Without *Acinetobacter* spp	0/3	0/1
Stenotrophomonas maltophilia	4/5 (80%)	NA
Without *Acinetobacter* spp	2/3 (67%)	NA

Data are n/N (%). NA=not available. *Includes *Acinetobacter baumannii* (for 39 patients assigned cefiderocol and 17 assigned best available therapy), *Acinetobacter nosocomialis* (for two patients assigned cefiderocol), and *Acinetobacter radioresistens* (for one patient assigned cefiderocol).

***Table 6:* All-cause mortality at the end of study by most frequent baseline pathogen in the safety population**

polymicrobial infections

Bassetti et al. Lancet Infect Dis.2021 Feb;21(2):226-240

What Are Preferred Antibiotics for the Treatment of DTR *P. aeruginosa* that Produce Metallo-β-Lactamase Enzymes?

- For patients infected with DTR PA isolates that are MBL-producing, the preferred treatment is cefiderocol.

- **Clinical data** on the use of cefiderocol as a treatment for MBL-producing PA are **limited**.

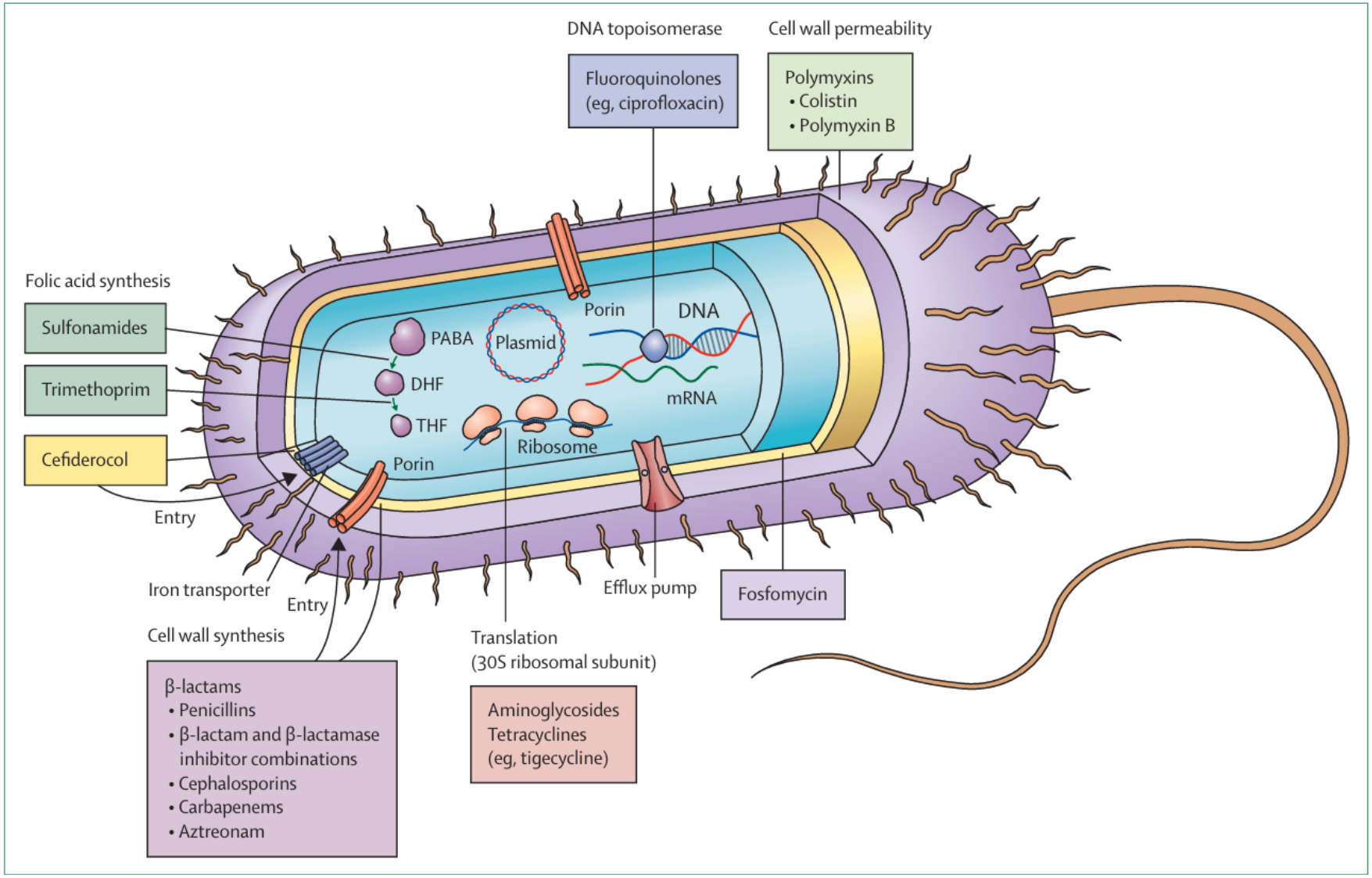
In vitro activity of Cefiderocol against CRPA with Metallo-β-Lactamase

SIDERO-WT Surveillance Studies, in north America and Europe from 2014 to 2019

Genotype (no. of isolates)	Antimicrobial agent	MIC (mg/L)			CLSI MIC interpretation		
		Range	MIC_{50}	MIC_{90}	% Susceptible	% Intermediate	% Resistant
MBL (227)[a]	Cefiderocol	0.008–4	0.25	2	100	0	0
	Aztreonam–avibactam ($n=76$)[d]	0.25–>8	>8	>8	NA[f]	NA	NA
	Cefepime	2–>64	32	>64	2.6	21.6	75.8
	Ceftazidime–avibactam	2–>64	32	>64	1.8	NA	98.2
	Ceftolozane–tazobactam	0.5–>64	>64	>64	0.9	0.0	99.1
	Ciprofloxacin	≤0.12–>8	>8	>8	1.8	2.2	96.0
	Colistin	≤0.25–4	1	2	0	98.7	1.3
	Meropenem	4–>64	64	>64	0	3.1	96.9
VIM (200)[a]	Cefiderocol	0.008–4	0.25	1	100	0	0
	Aztreonam–avibactam ($n=65$)[d]	0.25–>8	>8	>8	NA	NA	NA
	Cefepime	2–>64	32	>64	3.0	24.5	72.5
	Ceftazidime–avibactam	2–>64	32	>64	2.0	NA	98.0
	Ceftolozane–tazobactam	0.5–>64	>64	>64	1.0	0	99.0
	Ciprofloxacin	≤0.12–>8	>8	>8	2.0	2.5	95.5
	Colistin	≤0.25–4	1	2	0	98.5	1.5
	Meropenem	4–>64	64	>64	0	3.5	96.5
IMP (25)[a]	Cefiderocol	0.12–4	2	4	100	0	0
	Aztreonam–avibactam ($n=9$)[d]	8–>8	ND[e]	ND	NA	NA	NA
	Cefepime	>16–>64	>64	>64	0	0	100
	Ceftazidime–avibactam	>16–>64	>64	>64	0	NA	100
	Ceftolozane–tazobactam	>16–>64	>64	>64	0	0	100
	Ciprofloxacin	>8–>8	>8	>8	0	0	100
	Colistin	0.5–2	1	2	0	100	0
	Meropenem	8–>64	>64	>64	0	0	100

Wise et al. Microb Drug Resist.2023 Aug;29(8):360-370.

Mechanisms of action of key antibiotics for the treatment of multidrug-resistant GNB infections



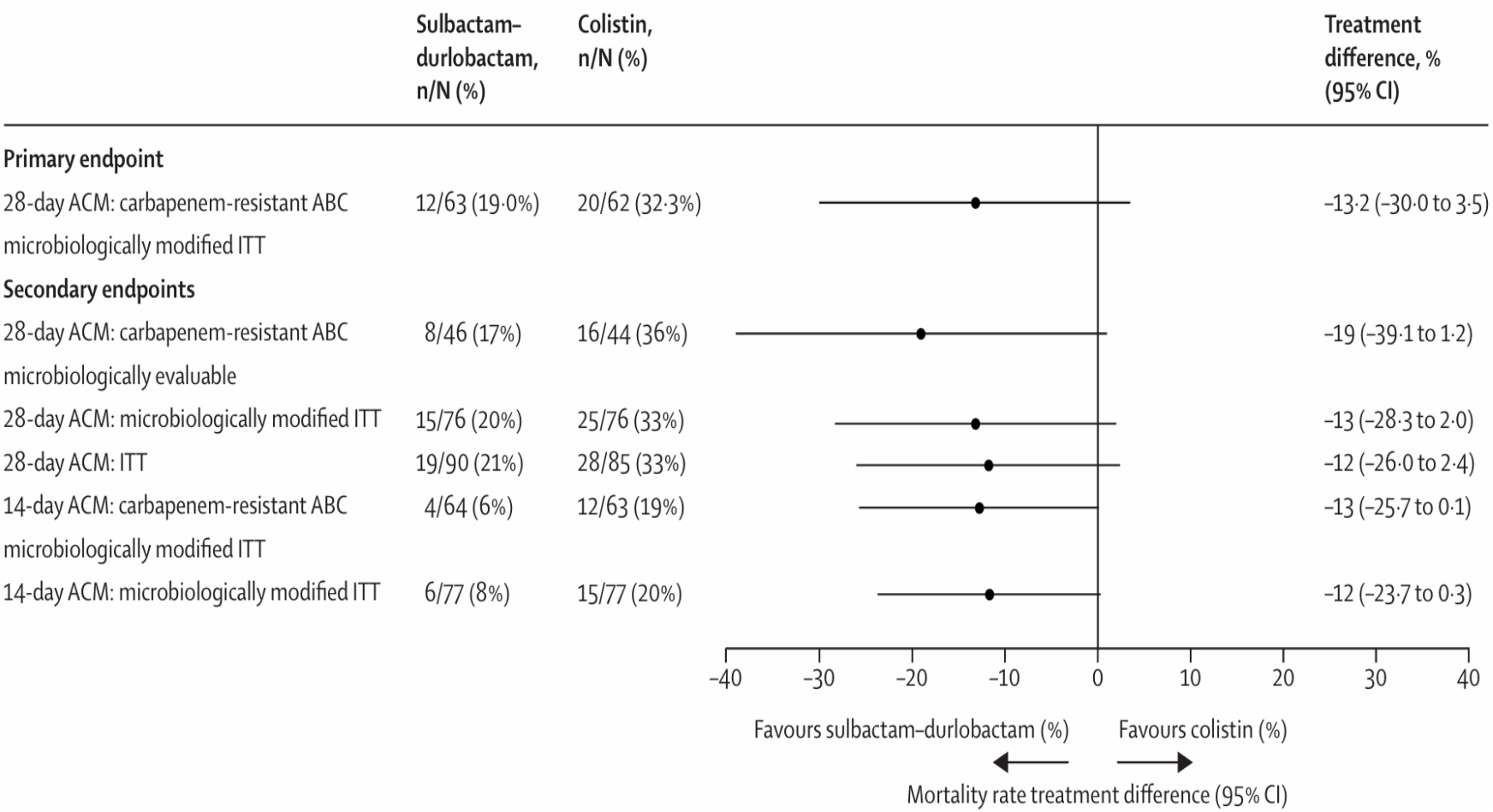
Lancet.2025 Jan 18;405(10474):257-272

Efficacy and safety of sulbactam–durlobactam versus colistin for the treatment of patients with serious infections caused by *Acinetobacter baumannii–calcoaceticus* complex: a multicentre, randomised, active-controlled, phase 3, non-inferiority clinical trial (ATTACK)

Keith S Kaye, Andrew F Shorr, Richard G Wunderink, Bin Du, Gabrielle E Poirier, Khurram Rana, Alita Miller, Drew Lewis, John O'Donnell, Lan Chen, Harald Reinhart, Subasree Srinivasan, Robin Isaacs, David Altarac

Lancet Infect Dis.2023 Sep;23(9):1072-1084

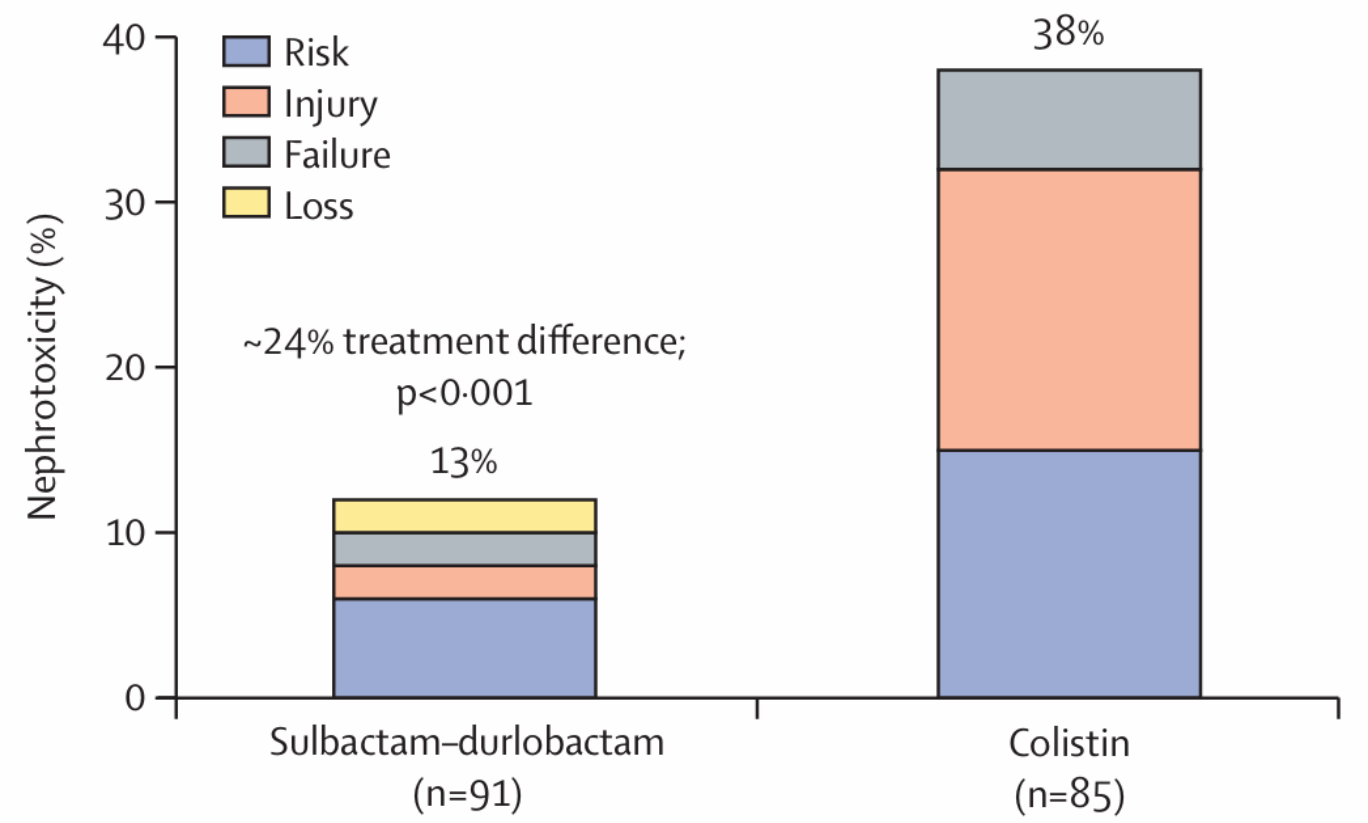
Sulbactam–durlobactam + imipenem–cilastatin VS **Colistin** + imipenem–cilastatin



- 59 clinical sites in 16 countries
- non-inferiority study (treatment difference was less than +20%)

Lancet Infect Dis.2023 Sep;23(9):1072-1084

Sulbactam–durlobactam + imipenem–cilastatin VS **Colistin** + imipenem–cilastatin



Incidence of nephrotoxicity measured by modified RIFLE criteria

Lancet Infect Dis.2023 Sep;23(9):1072-1084

Colistin Monotherapy versus Combination Therapy for Carbapenem-Resistant Organisms

OVERCOME study: international, randomized, double-blind, placebo-controlled trial
Colistin + placebo (n=210) vs colistin + meropenem (n=213)
Pneumonia (70%), bacteremia (30%); CRAB (78%), CRE (16%), CRPA (11%)

Table 3. Twenty-Eight–Day Mortality.*

Cause of Mortality	Colistin plus Placebo	Colistin plus Meropenem	Difference (95% CI)†	P Value

Table 4. Secondary Outcomes.*

Outcome	Colistin plus Placebo	Colistin plus Meropenem	Difference (95% CI)† or P Value
Clinical failure‡			
Overall	119/184 (65)	110/190 (58)	6.8 (–3.1 to 16.6)
Death by 7 days' posttreatment	52/184 (28)	39/190 (21)	7.7 (–0.9 to 16.4)
Need for rescue therapy	44/184 (24)	42/190 (22)	1.8 (–6.7 to 10.3)
Discontinue due to adverse event	12/184 (7)	21/190 (11)	–4.5 (–10.2 to 1.2)
BSI >5 days§	4/59 (7)	2/67 (3)	3.8 (–3.8 to 11.4)
Oxygenation failure¶	72/123 (59)	53/117 (46)	12.9 (0.3–25.4)
Pneumonia	96/132 (73)	87/134 (65)	7.8 (–3.3 to 18.9)
Bloodstream infection	23/52 (44)	23/56 (41)	3.2 (–15.5 to 21.8)
Acinetobacter baumannii	95/140 (68)	88/146 (60)	7.6 (–3.5 to 18.7)
CRE	18/32 (56)	16/33 (48)	7.8 (–16.4 to 32.0)
Pseudomonas aeruginosa	12/20 (60)	11/19 (58)	2.1 (–28.8 to 33.0)
Microbiologic cure‖			
Overall	106/163 (65)	103/171 (60)	4.8 (–5.6 to 15.2)
Pneumonia	59/114 (52)	48/115 (42)	10.0 (–2.8 to 22.9)
BSI	47/49 (96)	55/56 (98)	–2.3 (–8.8 to 4.2)
A. baumannii	76/121 (63)	74/130 (57)	4.9 (–7.2 to 17.0)
CRE	23/29 (79)	24/32 (75)	4.3 (–16.7 to 25.3)
P. aeruginosa	9/19 (47)	6/17 (35)	12.1 (–19.9 to 44.0)

NEJM Evid. 2023Jan;2(1):10.1056/evidoa2200131.

Antimicrobials commonly tested against CRE

Antimicrobial	EUCAST MIC breakpoint indicating resistance	Prevalence[a] of susceptible isolates	Remarks
Ceftazidime	>4	<3%	Resistance usually associated with concurrent expression of ESBL or AmpC β-lactamases
Cefepime	>4	<5%	
Aztreonam		<5%	Susceptibility or low-level resistance may be expected in case of metallo-β-lactamase carbapenemase expression. Resistance is the rule when other carbapenemases (KPC, OXA-48, etc.) or extended spectrum β-lactamases are co-expressed
Piperacillin-tazobactam	>16	<5%	Resistance usually associated with high-level expression of extended spectrum β-lactamases
Ceftazidime-avibactam **(Zavicefta)**	>8	>90%	Susceptibility expected in case of KPC or OXA-48 carbapenemase expression. Resistance is the rule when metallo-enzymes (NDM, IMP, VIM, etc.) are expressed
Imipenem	>8	<5%	Variable degrees of resistance may occur according to level of carbapenemase expression and concurrent presence of other mechanisms of carbapenem resistance
Meropenem	>8	<5%	
Doripenem	>2	<5%	
Amikacin	>16	50%	Cross resistance not the rule depending on actual subtype of modifying enzyme expressed
Gentamicin	>4	40%	
Ciprofloxacin	>0.5	<5%	Very low rates of susceptibility expected in endemic settings of carbapenem-resistant *Enterobacteriaceae* prevalence
Trimethoprim-sulphamethoxazole	>4	<5%	Sparse data available
Fosfomycin	>32	50%	Variable results according to the susceptibility method used
Tigecycline	>2	85%	Consistent susceptibility data across multiple studies and settings
Colistin	>2	80%	Broth microdilution recommended to avoid major errors

[a] Conservative estimates based on literature data (average rates) and the author's personal experience.

Clin Microbiol Infect. 2019 Aug;25(8):943-950

Cefiderocol Non-Inferior but Not Superior to Standard of Care (GAME CHANGER)

Cefiderocol vs standard of care for hospital-acquired / health-care–associated Gram-negative bloodstream infection

Open-label, parallel-group RCT · 17 tertiary hospitals / 6 countries · Nov 2019–Oct 2023 · cefiderocol 2 g IV q8h (3-h infusion) vs clinician-chosen SOC

POPULATION

504 main analysis (250 cefiderocol / 254 SOC) · 127 (25%) carbapenem-resistant

DESIGN

Open-label RCT · non-inferiority (10% margin) then superiority test

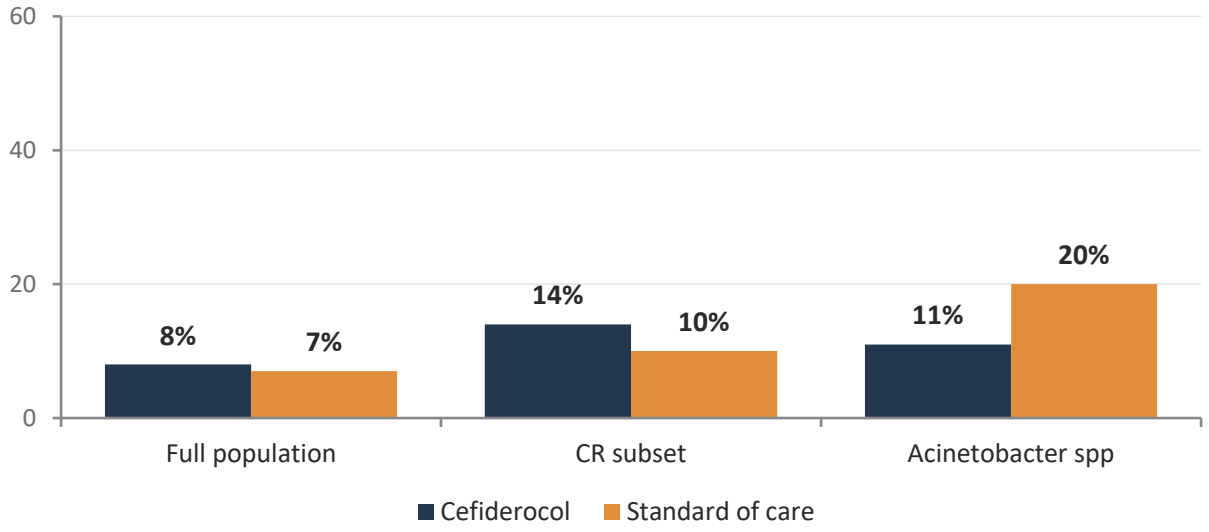
COMPARISON

Cefiderocol 2 g q8h vs standard of care (up to 3 active agents)

PRIMARY ENDPOINT

14-day all-cause mortality (main analysis population)

14-day all-cause mortality: cefiderocol vs standard of care (%)



Key results — non-inferior, not superior

8% vs 7%

14-day mortality (primary)

Full population · ARD 1% (95% CI −3 to 6) · non-inferior

14% vs 10%

Carbapenem-resistant subset

14-day mortality · ARD 5% (−7 to 16) · superiority not shown

50% vs 18%

MBL-producing Enterobacterales

30-day mortality (8/16 vs 2/11) · cefiderocol safety signal

- **Cefiderocol was non-inferior but NOT superior to standard of care — including the carbapenem-resistant subset.**
- **A higher mortality signal with MBL-producing Enterobacterales urges caution and combination strategies; *Acinetobacter* outcomes were reassuring.**

Lancet Infect Dis 2026;26(2):148–59 · GAME CHANGER trial (NCT03869437)

Antimicrobials commonly tested against CRE

Antimicrobial	EUCAST MIC breakpoint indicating resistance	Prevalence[a] of susceptible isolates	Remarks
Ceftazidime	>4	<3%	Resistance usually associated with concurrent expression of ESBL or AmpC β-lactamases
Cefepime	>4	<5%	
Aztreonam		<5%	Susceptibility or low-level resistance may be expected in case of metallo-β-lactamase carbapenemase expression. Resistance is the rule when other carbapenemases (KPC, OXA-48, etc.) or extended spectrum β-lactamases are co-expressed
Piperacillin-tazobactam	>16	<5%	Resistance usually associated with high-level expression of extended spectrum β-lactamases
Ceftazidime-avibactam **(Zavicefta)**	>8	>90%	Susceptibility expected in case of KPC or OXA-48 carbapenemase expression. Resistance is the rule when metallo-enzymes (NDM, IMP, VIM, etc.) are expressed
Imipenem	>8	<5%	Variable degrees of resistance may occur according to level of carbapenemase expression and concurrent presence of other mechanisms of carbapenem resistance
Meropenem	>8	<5%	
Doripenem	>2	<5%	
Amikacin	>16	50%	Cross resistance not the rule depending on actual subtype of modifying enzyme expressed
Gentamicin	>4	40%	
Ciprofloxacin	>0.5	<5%	Very low rates of susceptibility expected in endemic settings of carbapenem-resistant *Enterobacteriaceae* prevalence
Trimethoprim-sulphamethoxazole	>4	<5%	Sparse data available
Fosfomycin	>32	50%	Variable results according to the susceptibility method used
Tigecycline	>2	85%	Consistent susceptibility data across multiple studies and settings
Colistin	>2	80%	Broth microdilution recommended to avoid major errors

[a] Conservative estimates based on literature data (average rates) and the author's personal experience.

Clin Microbiol Infect. 2019 Aug;25(8):943-950

Efficacy and Safety of Imipenem-Relebactam vs Colistin Plus Imipenem in Patients With Imipenem-nonsusceptible Bacterial Infections

Phase 3, RCT, double-blind,, UTI (52%), pneumonia (38%), IAI (10%)
Pseudomonas aeruginosa (77%), *Klebsiella* spp. (16%), other *Enterobacteriaceae* (6%)

	IMI/REL (n = 21)		Colistin + IMI (n = 10)		Unadjusted Difference	Adjusted Difference[a]	
Endpoint	n	% (95% CI)[b]	n	% (95% CI)[a]	%	%	90% CI
Primary endpoint							
Favorable overall response[c]	15	71.4 (49.8, 86.4)	7	70.0 (39.2, 89.7)	1.4	–7.3	(–27.5, 21.4)
Hospital-acquired bacterial pneumonia/ ventilator-associated bacterial pneumonia	7/8	87.5 (50.8, 99.9)	2/3	66.7		20.8	
Complicated intraabdominal infection	0/2[d]	0.0	0/2[e]	0.0		0.0	
Complicated urinary tract infection	8/11	72.7 (42.9, 90.8)	5/5	100.0 (51.1, 100.0)		–27.3 (–52.8, 12.8)	
Secondary endpoints							
Favorable clinical response (day 28)	15[f]	71.4 (49.8, 86.4)	4[g]	40.0 (16.7, 68.8)	31.4	26.3	(1.3, 51.5)
28-day all-cause mortality	2	9.5 (1.4, 30.1)	3	30.0 (10.3, 60.8)	–20.5	–17.3	(–46.4, 6.7)
Treatment-emergent nephrotoxicity[h]	3/29	10.3 (2.8, 27.2)	9/16	56.3 (33.2, 76.9)		–45.9 (–69.1, –18.4)	

[c] Overall response defined as hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (HAP/VAP), survival through day 28; complicated intraabdominal infection (cIAI), clinical response at day 28; complicated urinary tract infection (cUTI), composite clinical and microbiological response 5–9 days after the end of therapy (EOT).

IMI/REL may be preferable to colistin-based therapy for treating carbapenem-nonsusceptible infections, given that IMI/REL had comparable efficacy but significantly less nephrotoxicity and other AEs.

Clin Infect Dis. 2020 Apr 15;70(9):1799-1808

Meropenem-Vaborbactam versus Ceftazidime-Avibactam for Treatment of CRE Infections

Multicenter, retrospective cohort study in USA from 2015 to 2018
40 % bacteremia, 30 % pneumonia

TABLE 6 *Post hoc* subgroup analysis[a]

	CZA monotherapy group (*n* = 41)	CZA combination therapy group (*n* = 64)	MVB monotherapy group (n = 22)	*P* value
No. of clinical successes (%)	26 (63.4)	39 (60.9)	15 (68.2)	0.83
No. of 90-day mortalities (%)	9 (22.0)	20 (31.2)	6 (27.3)	0.58
No. of recurrences of CRE infection (%) (→ within 90 days)	9 (22.0)	6 (9.4)	3 (13.6)	0.20
No. of increases in study drug MIC in mg/liter (%)	5 (12.2)	1 (1.6)	0	0.03
No. of emergences of study drug resistance (%)	3 (7.3)	0	0	0.07

TABLE 7 CZA monotherapy MIC increase and emergence of resistance[a]

Initial infection MIC (mg/liter)	Recurrent infection MIC (mg/liter)	Emergence of resistance?	Duration of CZA (days)	Source of infection	Baseline RRT?
0.25	0.75	No	10.6	Intra-abdominal	No
0.75	1.5	No	7.6	Respiratory	No
0.75	12	Yes	10.3	Respiratory	Yes
4	12	Yes	13.2	Respiratory	Yes
2	32	Yes	4.4	Respiratory	Yes

[a]CZA, ceftazidime-avibactam; RRT, renal replacement therapy.

Emergence of resistance after clinical exposure:
ceftazidime-avibactam: 10% to 20%, meropenem-vaborbactam 3%

Antimicrob Agents Chemother. 2020 Apr 21;64(5):e02313-19; Clin Infect Dis. 2023 Jul 18:ciad428.

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

Prospective observational study, 3 hospitals in Italy and Greece

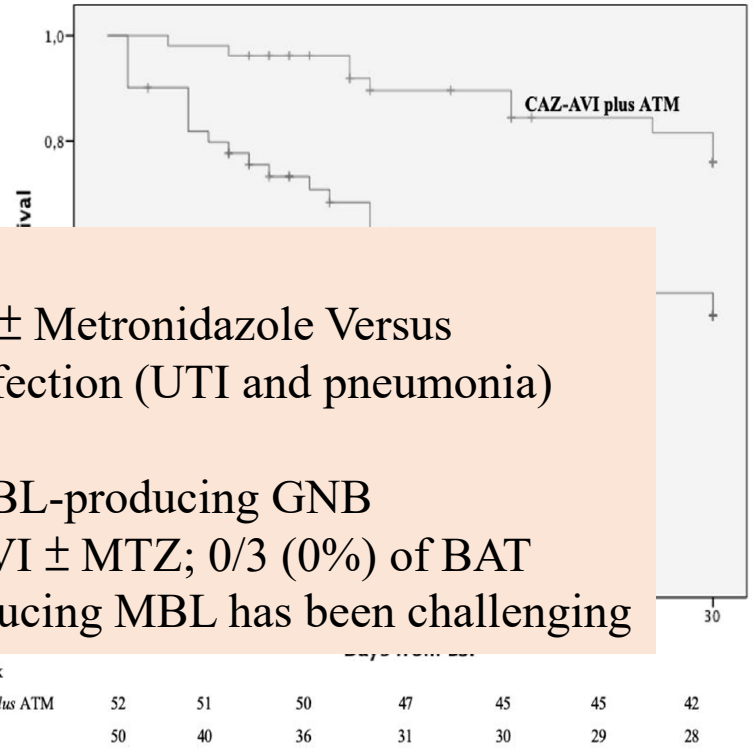
Table 2. Targeted Antibiotic Regimens Administered in 102 Bloodstream Infections Due to Metallo-β-Lactamase–Producing Enterobacterales

Antibiotic Regimen	No. (%) (N = 102)	Mortality, No. (%)
CAZ-AVI + ATM[a]	52 (51)	10/52 (19.2)
OAAs		
Colistin-containing regimens	27 (26.5)	16/27 (59.3)
Colistin + fosfomycin + tigecycline	7	6/7
Colistin + fosfomycin	7	5/7
Colistin + meropenem	5	3/5
Colistin + ATM + piperacillin-tazo		
Colistin + genta		
Colistin + cotrin		
Colistin alone		
Regimens not containing colis		
Tigecycline + ar		
Fosfomycin + a		
Tigecycline + fo		
Tigecycline + meropenem	1	0/1
ATM + aminoglycosides	4	1/4
ATM + fosfomycin	1	0/1
ATM alone	2	1/2

Abbreviations: ATM, aztreonam; CAZ-AVI, ceftazidime-avibactam; OAAs, other active antibiotics.
[a]In vitro activity is supported by in vitro synergistic tests.

Mortality: 30-day all-cause

30- day Kaplan-Meier survival curves



Phase III Aztreonam-Avibactam study:

1. REVISIT study: Aztreonam-Avibactam ± Metronidazole Versus Meropenem ± Colistin for severe GNB infection (UTI and pneumonia)

2. ASSEMBLE study : Infection due to MBL-producing GNB
Clinical cure: 5/12 (41.7%) of the ATM-AVI ± MTZ; 0/3 (0%) of BAT
=> TERMINATE => recruit bacteria producing MBL has been challenging

Clin Infect Dis. 2021 Jun 1;72(11):1871-1878.

Cefiderocol for the Treatment of Infections Due to MBL-Producing Pathogens in the CREDIBLE-CR and APEKS-NP Phase 3 Randomized Studies

CREDIBLE-CR: Cefiderocol (N = 16) vs. BAT (N = 7)
APEKS-NP: Cefiderocol (N = 8) vs. Meropenem (N = 3)

	Clinical Cure at TOC		Eradication at EOT		ACM Day 28	
CREDIBLE-CR + APEKS-NP[e]	Cefiderocol (N = 24)	All Comparators[f] (N = 10)[a]	Cefiderocol (N = 24)	All Comparators[f] (N = 10)[a]	Cefiderocol (N = 24)	All Comparators[f] (N = 10)[a]
Overall	70.8 (17/24)	40.0 (4/10)	58.3 (14/24)	30.0 (3/10)	12.5 (3/24)	50.0 (5/10)
Type of infection						
Pneumonia	71.4 (10/14)	50.0 (3/6)	42.9 (6/14)	33.3 (2/6)	21.4 (3/14)	33.3 (2/6)
Other diagnoses[b]	70.0 (7/10)	25.0 (1/4)	80.0 (8/10)	25.0 (1/4)	0 (0/10)	75.0 (3/4)
MBL type						
NDM	56.3 (9/16)	33.3 (2/6[a])	62.5 (10/16)	16.7 (1/6[a])	18.8 (3/16)	50.0 (3/6[a])
Non-NDM	100 (8/8)	40.0 (2/5[a])	50.0 (4/8)	40.0 (2/5[a])	0 (0/8)	40.0 (2/5[a])
Pathogen type						
Enterobacterales	73.3 (11/15)	20.0 (1/5)	66.7 (10/15)	20.0 (1/5)	13.3 (2/15)	60.0 (3/5)
Non-fermenters	66.7 (6/9)	60.0 (3/5)	44.4 (4/9)	40.0 (2/5)	11.1 (1/9)	40.0 (2/5)

ACM, all-cause mortality; EOT, end of treatment; TOC, test of cure.

Clin Infect Dis. 2022 Sep 29;75(6):1081-1084

Ceftolozane/Tazobactam vs Polymyxin or Aminoglycoside-based regimens for MDR or XDR *P. aeruginosa* infection

A retrospective, multicenter, observational cohort study in America

Covariate	Ceftolozane/ Tazobactam (N = 100)	Polymyxin/ Aminoglycoside (N = 100)	*P* Value
Severity of illness and infection-related variables			
Intensive care unit at infection onset	70	68	.76
No sepsis	14	11	.67
Sepsis	48	43	.57
Severe sepsis	15	23	.21
Septic shock	23	23	1.00
Severe sepsis or septic shock	38	46	.22
Vasopressors during therapy	30	34	.54
SOFA (sequential organ failure assessment) score[a]	8 (6–10) (n = 54)[b]	8 (5–10) (n = 63)[b]	.48
Polymicrobial infection	40	46	.39
Site of infection			
Ventilator-associated pneumonia	52	51	1
Hospital-acquired pneumonia	12	24	.04
Urinary tract	16	11	.41
Wound	13	8	.36
Other	7	6	
Presence of bacteremia	6	8	.58
Treatment-related variables			
Infectious diseases consult	100	92	.004
Time to active therapy (hours)[a]	55.5 (23–80.25)	43.5 (4.2–72.3)	.10
Time to study drug (hours)[a]	63.5 (45.3–92)	53.3 (5–93)	.08
Combination therapy	15	72	<.001

Outcome	Ceftolozane/ Tazobactam (N = 100)	Polymyxin/Aminoglycoside (N = 100)	*P* Value
Clinical cure	81	61	.002
In-hospital mortality	20	25	.40
Acute kidney injury	6	34	<.001
Risk			
Injury			
Failure			
Renal re			
Hypersensitivity reaction	0	1	.32
Neuropathies	0	2	.16
Seizures	0	0	N/A
Clostridium difficile on therapy	4	5	.73
C. difficile after therapy before discharge	2	3	.65
C. difficile on readmission	1	2	.46
Discharge status			
Home	26	14	.15
Skilled nursing facility/long-term acute care facility/Other hospital	54	61	
30-day readmission[b]	21 (26)	18 (24)	.59
30-day readmission due to infection[b]	12 (15)	11 (15)	.82
30-day recurrence[b]	11 (14)	12 (16)	1.0
90-day recurrence[b]	13 (16)	12 (16)	1.0
Length of stay from onset of bacteremia (days)[c]	14.5 (9–26)	14 (9–24.5)	.65
Intensive care unit length of stay (days)[c]	16 (9–25)	13 (7–23)	.22
Mechanical ventilation duration (days)[c]	11 (4–18)	11 (4–22)	.96

NNT for a clinical cure with ceftolozane/tazobactam: **5**
NNH with AKI with a polymyxin/aminoglycoside: **4**

Pogue et al. Clin Infect Dis.2020 Jul 11;71(2):304-310

Ceftolozane-Tazobactam versus Ceftazidime-Avibactam for MDR *P. aeruginosa* infection

- A retrospective and multicenter cohort study in Saudi Arabia
- 40% received combination therapy, 50% polymicrobial infections, <50% bacteremia or pneumonia

Outcome[a]	C-T (*n* = 100)	CAZ-AVI (*n* = 100)	*P* Value	Odds Ratio (95% CI)	Adjusted Odds[b] Ratio (95% CI)
Clinical cure	61	66	0.463	0.81 (0.43 to 1.49)	0.92 (0.41 to 2.05)
In-hospital mortality	44	37	0.314	1.34 (0.76 to 2.36)	1.13 (0.52 to 2.48)
30-day mortality	27	23	0.514	1.24 (0.65 to 2.35)	1.20 (0.48 to 3.00)
Infection-related mortality	25	19	0.307	1.42 (0.72 to 2.79)	1.00 (0.40 to 2.52)
Microbiologic outcome[c]					
Eradication	46	43	0.843	0.94 (0.46 to 1.89)	
Persistence	32	28			
30-day readmission[d]	11	14	0.73		
30-day readmission due to infection[d]	5	8	0.511		
30-day recurrence[d]	8	13	0.364		
90-day recurrence[d]	14	16	0.96		
Length of hospital stay from onset of infection (days)	30 (20 to 75)	32 (17 to 66)	0.61		
Length of ICU stay from onset of infection (days)[e]	25 (9 to 44)	24 (14 to 40)	0.829		
Duration of mechanical ventilation (days)[f]	23 (7 to 45)	21 (8 to 42)	0.874		
Acute kidney injury	23	17	0.289	1.46 (0.69 to 3.14)	1.74 (0.66 to 4.59)
Risk	6	8			
Injury	7	1			
Failure	6	7			
RRT	4	1			
Acute liver injury	3	1			

C-T, ceftolozane tazobactam; CAZ-AVI, ceftazidime-avibactam

Almangour et al. Antimicrob Agents Chemother.2023 Aug 17;67(8):e0040523.

Imipenem/Relebactam vs Colistin + Imipenem in Patients with Imipenem-nonsusceptible Bacterial Infections

- Randomized, controlled, double-blind, phase 3 trial; HAP/VAP, cIAI, or cUTI

Table S12: Favorable overall response by baseline pathogen

	IMI/REL (N=21)		Colistin + IMI (N=10)		Unadjusted difference	Adjusted difference[b]	
	n/N	% (95% CI)[a]	n/N	% (95% CI)[a]	%	%	90% CI
Citrobacter freundii	0/1	0.0	0/0	-	NC	NC	NC
Enterobacter cloacae	1/1	100.0	0/0	-	NC	NC	NC
Klebsiella oxytoca	0/0	-	1/1	100.0	NC	NC	NC
Klebsiella pneumoniae	1/3	33.3	1/1	100.0	-66.7	-66.7	NC
KPC-positive Enterobacteriaceae[c]	1/4[d]	25.0[d] (3.4, 71.1)	1/1	100.0	-75.0	-66.7	NC
Pseudomonas aeruginosa	13/16	81.3 (56.2, 94.2)	5/8	62.5 (30.4, 86.5)	18.8	3.1	-19.8, 38.2

IMI, imipenem/cilastatin; IMI/REL, imipenem/cilastatin plus relebactam

Although not achieving statistical significance, potentially due to the small sample size, the numerical differences suggest improved outcomes with use of imipenem-cilastatin-relebactam over colistin-based regimens.

Motsch et al. Clin Infect Dis.2020 Apr 15;70(9):1799-1808

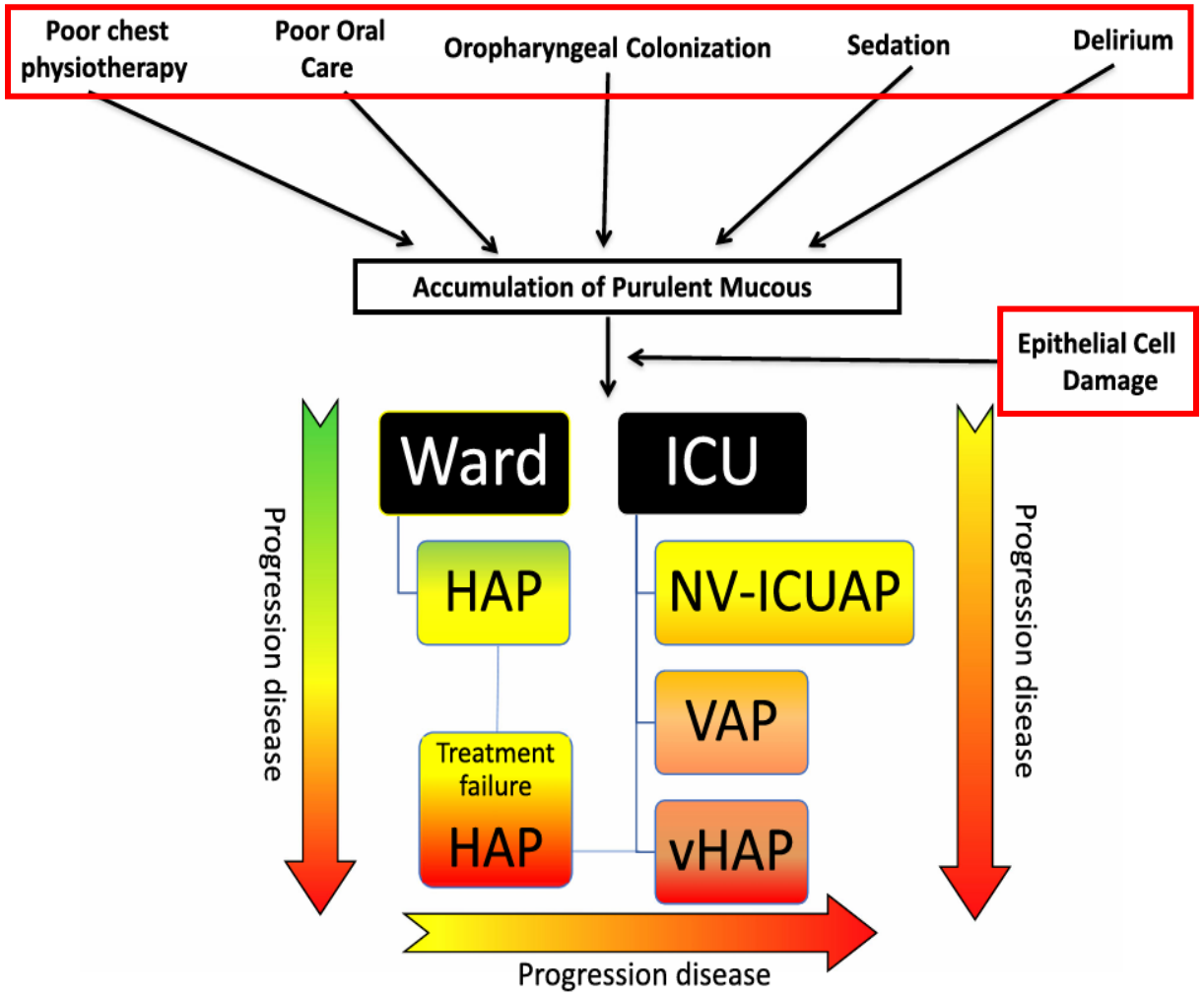
Resistant mechanism of DTR *P. aeruginosa* to newer β-Lactam Agents

- Ceftolozane-tazobactam and ceftazidime-avibactam: amino acid substitutions, insertions, or deletions in *Pseudomonas*-derived cephlosporinase (AmpC variants)
- Imipenem-relebactam: loss of OprD (porin) and overexpression of efflux pumps
- Cefiderocol: mutations in the TonB-dependent iron transport system, amino acid changes in PDCs, modifications in the PBP3 target

- Cross-resistance: ceftolozane-tazobactam <=> ceftazidime-avibactam (30-86%); ceftolozane-tazobactam => cefiderocol (21%)

Tamma et al. Clin Infect Dis.2021 Dec 6;73(11):e4599-e4606; Tamma et al. Clin Infect Dis.2024 Aug 7:ciae403; Hareza et al. Antimicrob Agents Chemother.2024 Oct 8;68(10):e0090724

Prevention => identify risk factors => Treatment

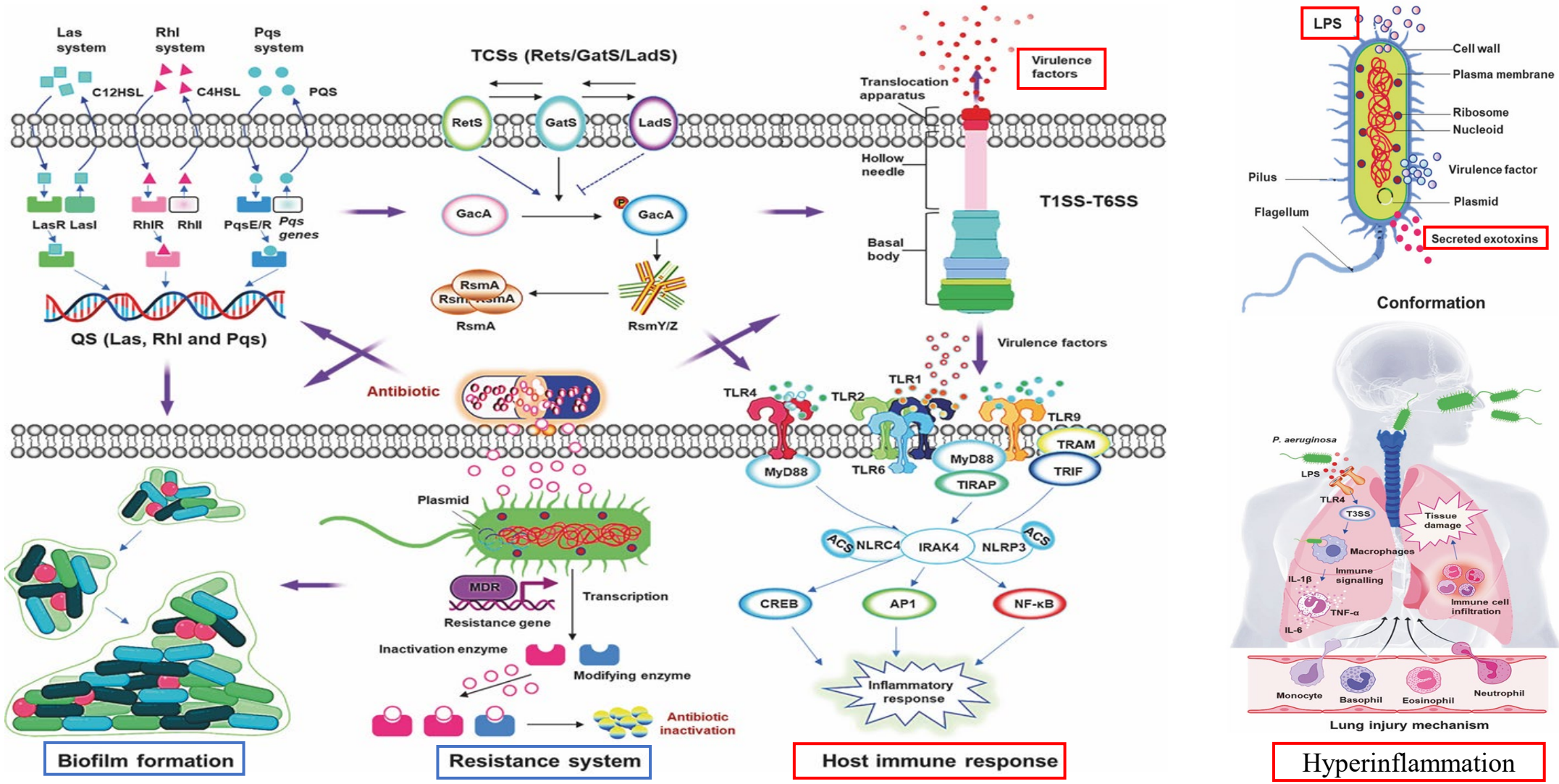


Risk factor for MDR PA nosocomial pneumonia

- Prior airway colonization by *P. aeruginosa*
- Previous antibiotic treatment
- Solid cancer
- Shock
- Alcohol abuse
- Pleural effusion
- Chronic liver disease
- Prior use of carbapenems
- Prior use of fluoroquinolones
- Duration of therapy
- APACHE II score

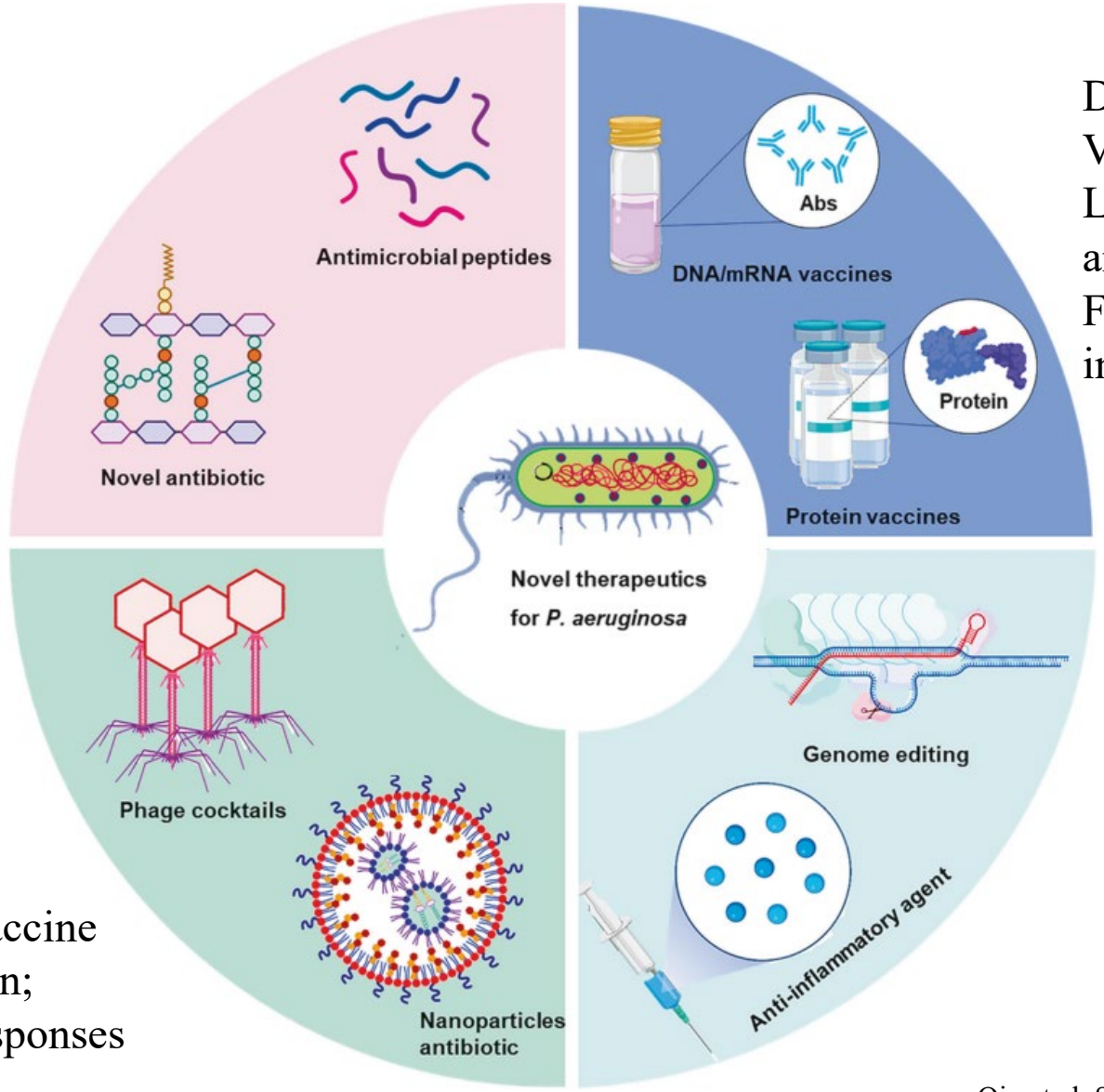
Zaragoza et al. Crit Care.2020 Jun 29;24(1):383

Interlinked and mechanistic regulatory network in *P. aeruginosa*



Qin et al. Signal Transduct Target Ther.2022 Jun 25;7(1):199.

Promising novel therapeutics for *P. aeruginosa*



Development of vaccines is slow
Vaccine targets:
LPS, OMP: high rates of variations and mutations
Flagella: toward motile bacteria instead of biofilms-forming strains

Phage neutralizing antibodies and exotoxins during phage preparations

CRISPR systems for editing genes of host and bacteria

Good for drug, gene and vaccine delivery, biofilm penetration; drawback: host immune responses

Qin et al. Signal Transduct Target Ther.2022 Jun 25;7(1):199.

TAKE HOME MESSAGE

- Versatile mechanisms of antimicrobial resistance in *P. aeruginosa* include intrinsic, acquired and adaptive resistance.

- Monitor the prevalence and class of carbapenemase in *P. aeruginosa* could be important for DTR-PA infection in the future. (AST is indicated nowadays)

- Ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem--relebactam are preferred for DTR-PA pneumonia; cefiderocol is an alternative treatment option.

- Issues for newer β-lactam agents: empirical treatment, exchange between newer agents, frequency of resistance, cross-resistance…

Colistin Monotherapy versus Combination Therapy for Carbapenem-Resistant Organisms

OVERCOME study: international, randomized, double-blind, placebo-controlled trial
Colistin + placebo (n=210) vs colistin + meropenem (n=213)
Pneumonia (70%), bacteremia (30%); CRAB (78%), CRE (16%), CRPA (11%)

Table 3. Twenty-Eight–Day Mortality.*

Cause of Mortality	Colistin plus Placebo	Colistin plus Meropenem	Difference (95% CI)†	P Value

Table 4. Secondary Outcomes.*

Outcome	Colistin plus Placebo	Colistin plus Meropenem	Difference (95% CI)† or P Value
Clinical failure‡			
Overall	119/184 (65)	110/190 (58)	6.8 (–3.1 to 16.6)
Death by 7 days' posttreatment	52/184 (28)	39/190 (21)	7.7 (–0.9 to 16.4)
Need for rescue therapy	44/184 (24)	42/190 (22)	1.8 (–6.7 to 10.3)
Discontinue due to adverse event	12/184 (7)	21/190 (11)	–4.5 (–10.2 to 1.2)
BSI >5 days§	4/59 (7)	2/67 (3)	3.8 (–3.8 to 11.4)
Oxygenation failure¶	72/123 (59)	53/117 (46)	12.9 (0.3–25.4)
Pneumonia	96/132 (73)	87/134 (65)	7.8 (–3.3 to 18.9)
Bloodstream infection	23/52 (44)	23/56 (41)	3.2 (–15.5 to 21.8)
Acinetobacter baumannii	95/140 (68)	88/146 (60)	7.6 (–3.5 to 18.7)
CRE	18/32 (56)	16/33 (48)	7.8 (–16.4 to 32.0)
Pseudomonas aeruginosa	12/20 (60)	11/19 (58)	2.1 (–28.8 to 33.0)
Microbiologic cure‖			
Overall	106/163 (65)	103/171 (60)	4.8 (–5.6 to 15.2)
Pneumonia	59/114 (52)	48/115 (42)	10.0 (–2.8 to 22.9)
BSI	47/49 (96)	55/56 (98)	–2.3 (–8.8 to 4.2)
A. baumannii	76/121 (63)	74/130 (57)	4.9 (–7.2 to 17.0)
CRE	23/29 (79)	24/32 (75)	4.3 (–16.7 to 25.3)
P. aeruginosa	9/19 (47)	6/17 (35)	12.1 (–19.9 to 44.0)

NEJM Evid. 2023Jan;2(1):10.1056/evidoa2200131.

Clinical Infectious Diseases

MAJOR ARTICLE

The Impact of Synergistic Therapy Between Colistin and Meropenem on Outcomes of People With Pneumonia or Bloodstream Infection Due to Carbapenem-Resistant Gram-Negative Pathogens

Mariya Huralska,[1,a] Jason M. Pogue,[2,a] Michael Rybak,[3] Jacinda C. Abdul-Mutakabbir,[4] Kyle Stamper,[3] Dror Marchaim,[5] Visanu Thamlikitkul,[6] Yehuda Carmeli,[7] Cheng-Hsun Chiu,[8] George Daikos,[9] Sorabh Dhar,[10] Emanuele Durante-Mangoni,[11] Achilles Gikas,[12] Anastasia Kotanidou,[9] Mical Paul,[13] Emmanuel Roilides,[14] Michael Samarkos,[15] Matthew Sims,[16] Dora Tancheva,[17] Sotirios Tsiodras,[18] Daniel H. Kett,[19] Gopi Patel,[20] David P. Calfee,[21] Leonard Leibovici,[22] Laura Power,[23] Silvia Munoz-Price,[24] Hamadullah Shaikh,[1] Laura Susick,[25] Katie Latack,[25] Christine Chiou,[26] George Divine,[25] Varduhi Ghazyaran,[26] and Keith S. Kaye[1]

OVERCOME TRIAL · SECONDARY ANALYSIS

Colistin + Meropenem Synergy & CRGNB Infection Outcomes

Carbapenem-resistant Gram-negative bacilli — pneumonia / bloodstream

Study Design

407 critically ill patients Synergistic combination therapy 146 vs. functional monotherapy 261

24-hour time-kill analysis Synergy = ≥ 2-log CFU/mL reduction vs. the most active single agent

Cohort: Pneumonia 70% · CR Acinetobacter baumannii 79% · ICU 69%

Key Results

Overall clinical failure

55.3% vs 64.3%

aOR 0.62 · P = .049

Synergy vs monotherapy (adjusted, significant)

Pneumonia subgroup

62.6% vs 71.8%

aOR 0.55 · P = .04

Significantly lower failure

28-day mortality

38.3% vs 41.4%

Not significant

Similar (study underpowered)

Conclusion

Synergistic colistin + meropenem therapy was associated with lower clinical failure than non-synergistic colistin-based therapy, most notably in pneumonia and A. baumannii infection. Since synergy was present in >80% of A. baumannii isolates, adding meropenem may be considered when treating severe A. baumannii infection with polymyxin-based therapy.

Clin Infect Dis · 2026;82(3):391–8 · Huralska, Pogue et al.

2016至2025年第3季醫學中心加護病房不分部位常見之醫療照護相關感染菌種排名

表 1：2016 至 2025 年第 3 季醫學中心加護病房不分部位常見之醫療照護相關感染菌種排名

	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025Q3
菌種	排名	排名	排名	排名	排名	排名	排名	排名	排名	排名
Enterococcus faecium	2	3	3	2	3	2	1	1	1	1
Klebsiella pneumoniae	3	2	1	1	1	1	2	2	2	2
Escherichia coli	1	1	2	3	2	4	4	4	3	3
Candida albicans	4	4	4	4	4	3	3	3	4	4
Pseudomonas aeruginosa	5	6	4	5	5	5	5	5	5	5
Yeast-like	7	4	7	6	6	6	7	6	6	6
Acinetobacter baumannii	6	7	6	7	7	7	6	7	7	8
Enterococcus faecalis	9	9	9	9	8	10	9	9	8	7
Coagulase negative staphylococci	11	11	11	12	9	9	11	11	9	9
Enterobacter species	8	8	8	10	12	8	13	10	10	12

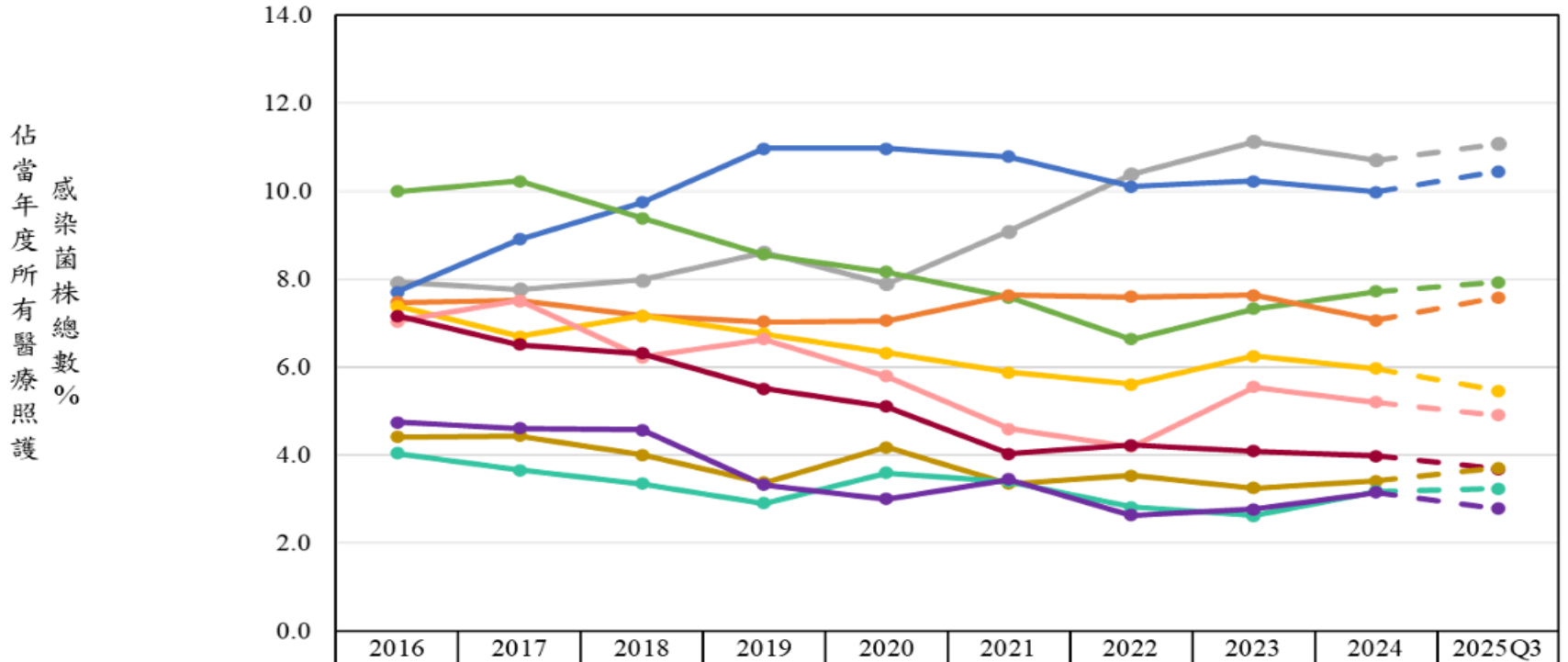
註：1.「菌種」欄位之優先順序為依據最近年度（2024 年）之醫療照護感染菌株總數排名結果。其中 *Enterococcus* species（即：*E. faecium* 及 *E. faecalis* 以外的 *Enterococcus*）、*Staphylococcus* species、*Acinetobacter* species、*Corynebacterium* species、*Candida* species 列入總菌株數計算，但不參與排名；

2.菌株總數計算方式為單一感染部位分離相同菌種以 1 次計算，分離不同種類菌種則分次計算；

3.NOS：not otherwise specified；

4.相同株數之菌種排名相同。

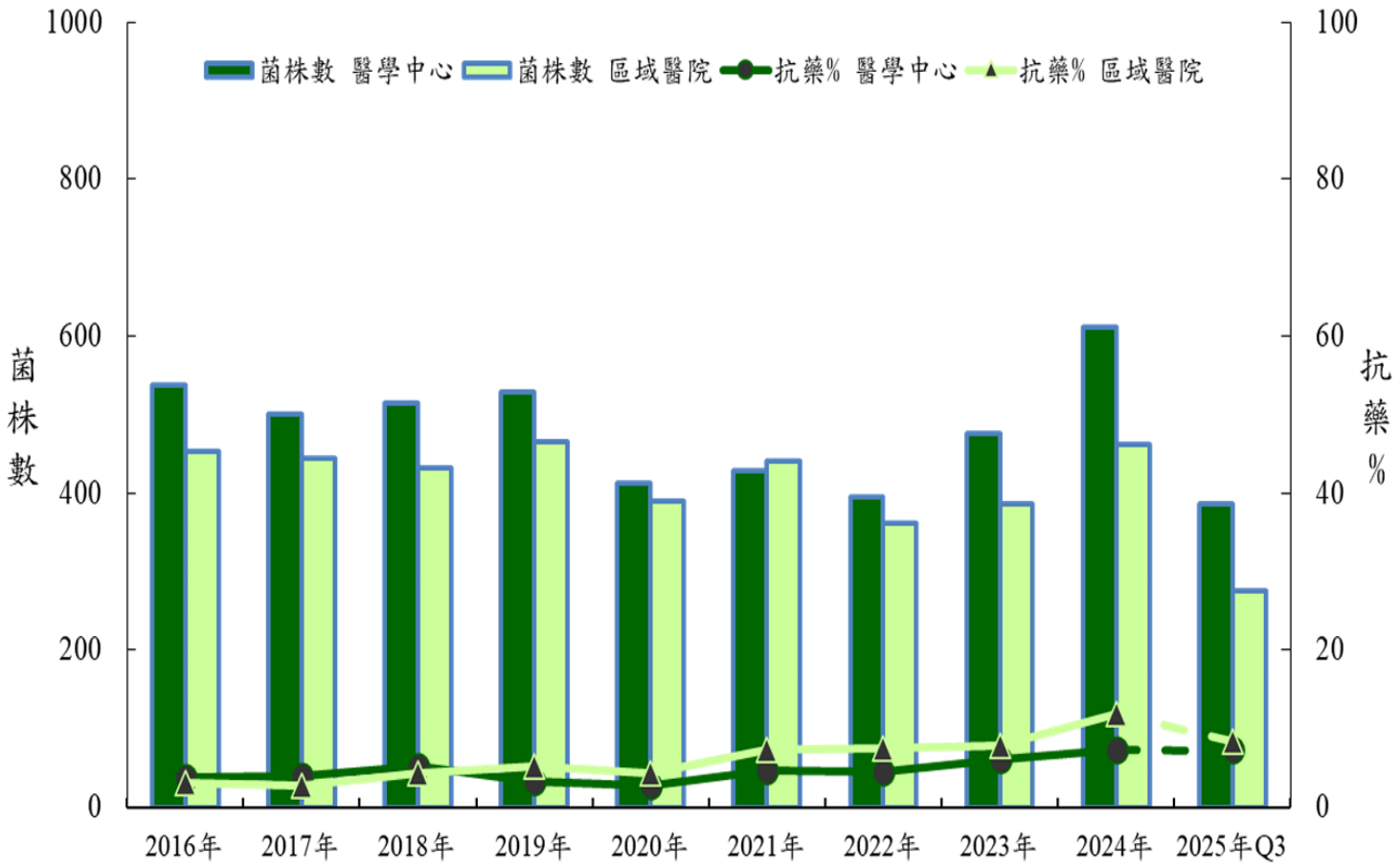
圖 3：2016至2025年第3季醫學中心加護病房常見醫療照護相關感染菌種佔當年度所有醫療照護相關感染株數比率

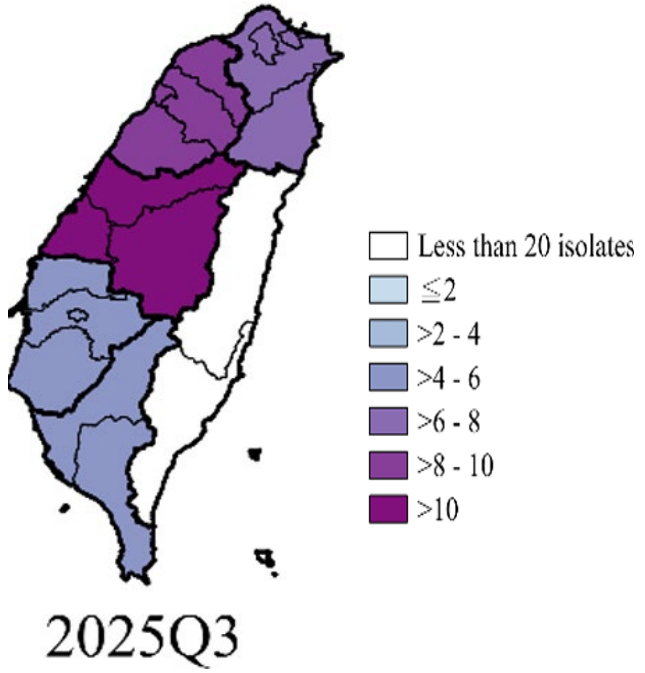


	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025Q3
Enterococcus faecium	7.9	7.8	8.0	8.6	7.9	9.1	10.4	11.1	10.7	11.1
Klebsiella pneumoniae	7.7	8.9	9.7	11.0	11.0	10.8	10.1	10.2	10.0	10.5
Escherichia coli	10.0	10.2	9.4	8.6	8.2	7.6	6.6	7.3	7.7	7.9
Candida albicans	7.5	7.5	7.2	7.0	7.1	7.6	7.6	7.6	7.1	7.6
Pseudomonas aeruginosa	7.4	6.7	7.2	6.8	6.3	5.9	5.6	6.3	6.0	5.5
Yeast-like	7.0	7.5	6.2	6.6	5.8	4.6	4.2	5.5	5.2	4.9
Acinetobacter baumannii	7.2	6.5	6.3	5.5	5.1	4.0	4.2	4.1	4.0	3.7
Enterococcus faecalis	4.4	4.4	4.0	3.4	4.2	3.4	3.5	3.3	3.4	3.7
Coagulase negative staphylococci	4.0	3.7	3.4	2.9	3.6	3.4	2.8	2.6	3.2	3.2
Enterobacter species	4.8	4.6	4.6	3.3	3.0	3.5	2.6	2.8	3.2	2.8

台灣醫療照護相關感染與抗藥性監測季報

2016至2025年第3季醫學中心及區域醫院加護病房醫療照護相關感染E. coli 菌株總數與CR E. coli 百分比





中區（13.3%）
北區（9.6%）

CR E. coli：對 carbapenem 類中的 imipenem、meropenem、ertapenem 或 doripenem 任一抗生素具抗藥性之E. coli

Underlying characteristics and demographic data of the 48 patients infected with carbapenem-resistant Enterobacterales or carbapenem-resistant *Pseudomonas* species.

Characteristic	No. (%) of patients infected with indicated isolates		
	All isolates (n = 48)	Enterobacterales (n = 34)	*Pseudomonas* spp. (n = 14)
Age (years) Mean± S.D.	69.9 ± 16.1	69.2 ± 17.5	71.6 ± 11.9
Male	34 (70.8)	22 (64.7)	12 (85.7)
Underlying diseases			
Malignancy	26 (54.2)	15 (57.7)	11 (42.3)
Diabetes mellitus	20 (41.7)	13 (65.0)	7 (35.0)
Other endocrine diseases[a]	7 (14.6)	5 (71.4)	2 (28.6)
COPD	9 (18.8)	9 (100)	0
CKD stage ≥ 3	15 (31.3)	13 (86.7)	3 (20.0)
Cardiovascular diseases	34 (70.8)	23 (67.6)	11 (32.4)
Previous CVA	8 (16.7)	7 (87.5)	1 (12.5)
Other neurological disorders[b]	10 (20.8)	8 (80.0)	2 (20.0)
Liver diseases	11 (22.9)	6 (54.5)	5 (45.5)
Diagnosis			
Pneumonia	29 (60.4)	19 (55.9)	10 (71.4)
Bacteremia	24 (50)	13 (38.2)	11 (78.6)
UTI	10 (20.8)	9 (26.5)	1 (7.1)
IAI	7 (14.6)	6 (17.6)	1 (7.1)
Wound infection	11 (22.9)	8 (23.5)	3 (21.4)
Shock	17 (35.4)	11 (32.4)	6 (42.9)
ICU admission after onset	24 (50.0)	18 (52.9)	6 (42.9)
120-day mortality	24 (50.0)	15 (44.1)	9 (64.3)
Discharge	24 (50.0)	18 (52.9)	6 (42.9)
Discharge to another institute	9 (18.8)	8 (23.5)	1 (7.1)
Discharge to home	15 (31.3)	11 (32.4)	4 (28.6)

April to August 2021, NTUH
CZA resistant: 41.6% (20/48)

*. Among the 48 isolates, 13 (27.1%) carried MBLs (one with two MBLs), 10 (20.8%) carried SBL, and two carried both MBL and SBL.
*. Sixteen out of the 20 isolates (80.0%) of the CZA-resistant isolates carried at least one MBLs
*. One K. pneumoniae isolate carrying bla OXA-48 and four isolates (two P. aeruginosa , one E. coli , and one K. pneumoniae) without carbapenemases were resistant to CZA.
*. among carbapenemase–encoding genes, the proportion of CRE carrying MBL was higher than previous data in Taiwan, 5 and might indicate a rapid emergence of MBL resulting in reduced CZA susceptibilities.

J Infect.2023 Jan;86(1):66-117.

Infection (2024) 52:19–28
https://doi.org/10.1007/s15010-023-02108-6

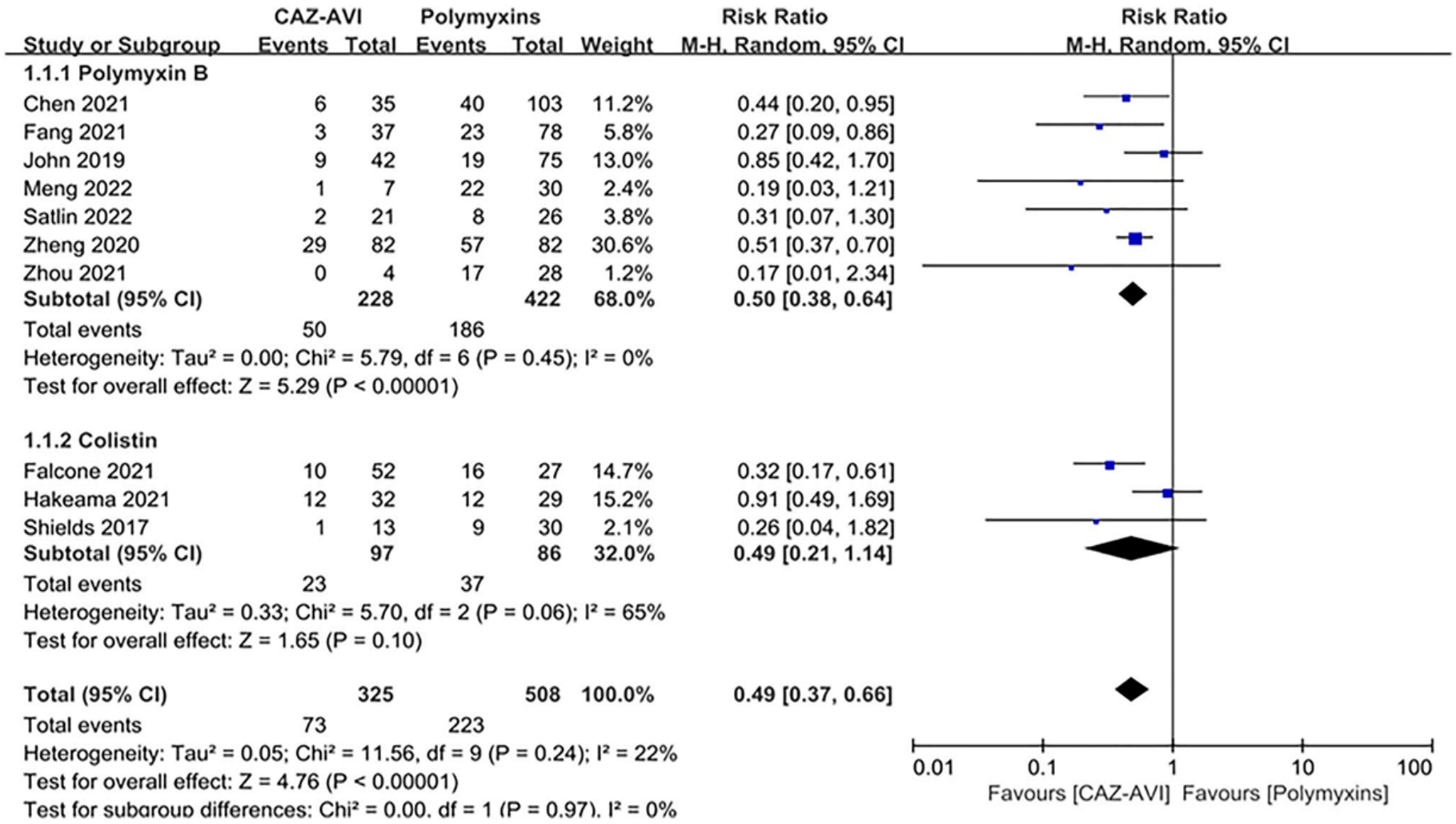
REVIEW

Ceftazidime–avibactam versus polymyxins in treating patients with carbapenem-resistant Enterobacteriaceae infections: a systematic review and meta-analysis

Jinglan Chen[1,2,3] · Qin Hu[1,3,6] · Pengxiang Zhou[4,5] · Sheng Deng[1,3]

Infection.2024 Feb;52(1):19-28.

Thirty-day mortality of the CAZ–AVI-based therapy compared with polymyxin-based therapy in CRE infections

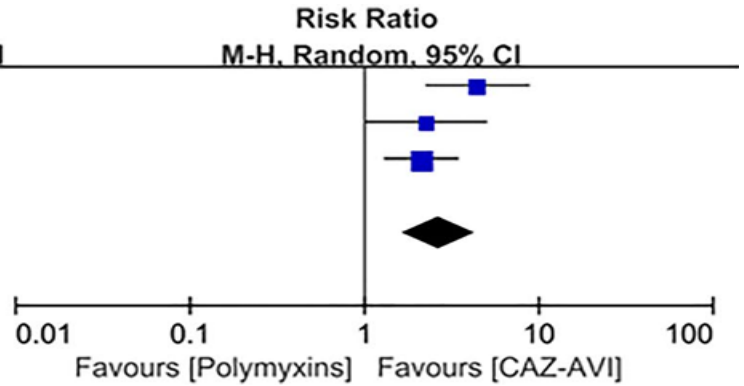


Infection.2024 Feb;52(1):19-28.

Clinical cure

Study or Subgroup	CAZ-AVI Events	CAZ-AVI Total	Polymyxins Events	Polymyxins Total	Weight	Risk Ratio M-H, Random, 95% CI
Fang 2021	19	37	9	78	30.7%	4.45 [2.23, 8.87]
Hakeama 2021	15	32	6	29	25.2%	2.27 [1.02, 5.05]
Shields 2017	11	13	12	30	44.1%	2.12 [1.29, 3.47]
Total (95% CI)		**82**		**137**	**100.0%**	**2.70 [1.67, 4.38]**
Total events	45		27			

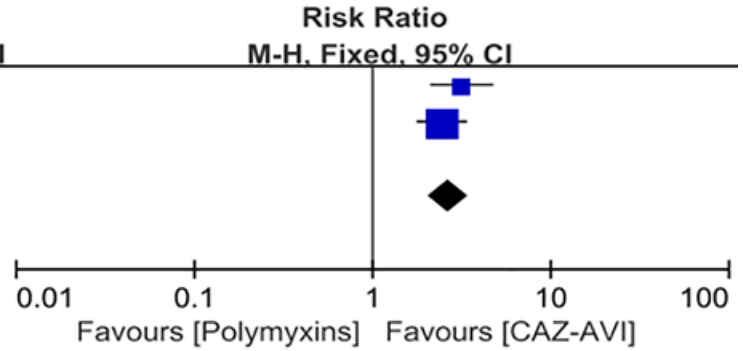
Heterogeneity: Tau² = 0.07; Chi² = 3.33, df = 2 (P = 0.19); I² = 40%
Test for overall effect: Z = 4.04 (P < 0.0001)



Microbial clearance

Study or Subgroup	CAZ-AVI Events	CAZ-AVI Total	Polymyxins Events	Polymyxins Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fang 2021	30	37	20	78	32.3%	3.16 [2.10, 4.76]
Zheng 2020	66	82	27	82	67.7%	2.44 [1.76, 3.39]
Total (95% CI)		**119**		**160**	**100.0%**	**2.68 [2.07, 3.46]**
Total events	96		47			

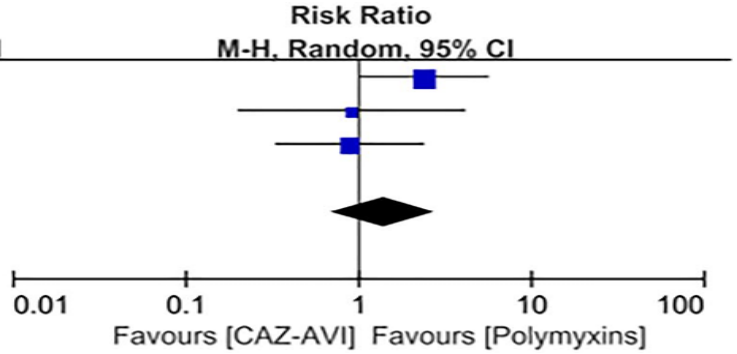
Heterogeneity: Chi² = 0.94, df = 1 (P = 0.33); I² = 0%
Test for overall effect: Z = 7.55 (P < 0.00001)



Acute kidney injury

Study or Subgroup	CAZ-AVI Events	CAZ-AVI Total	Polymyxins Events	Polymyxins Total	Weight	Risk Ratio M-H, Random, 95% CI
Fang 2021	9	37	8	78	44.8%	2.37 [1.00, 5.65]
Hakeama 2021	3	32	3	29	18.3%	0.91 [0.20, 4.14]
Satlin 2022	5	21	7	26	36.9%	0.88 [0.33, 2.39]
Total (95% CI)		**90**		**133**	**100.0%**	**1.38 [0.69, 2.77]**
Total events	17		18			

Heterogeneity: Tau² = 0.08; Chi² = 2.55, df = 2 (P = 0.28); I² = 22%
Test for overall effect: Z = 0.91 (P = 0.36)



Infection.2024 Feb;52(1):19-28.

2024

IDSA Recommendations for treatment of DTR *Pseudomonas aeruginosa*

DTR: 抗 pip-tazo, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin, and levofloxacin.

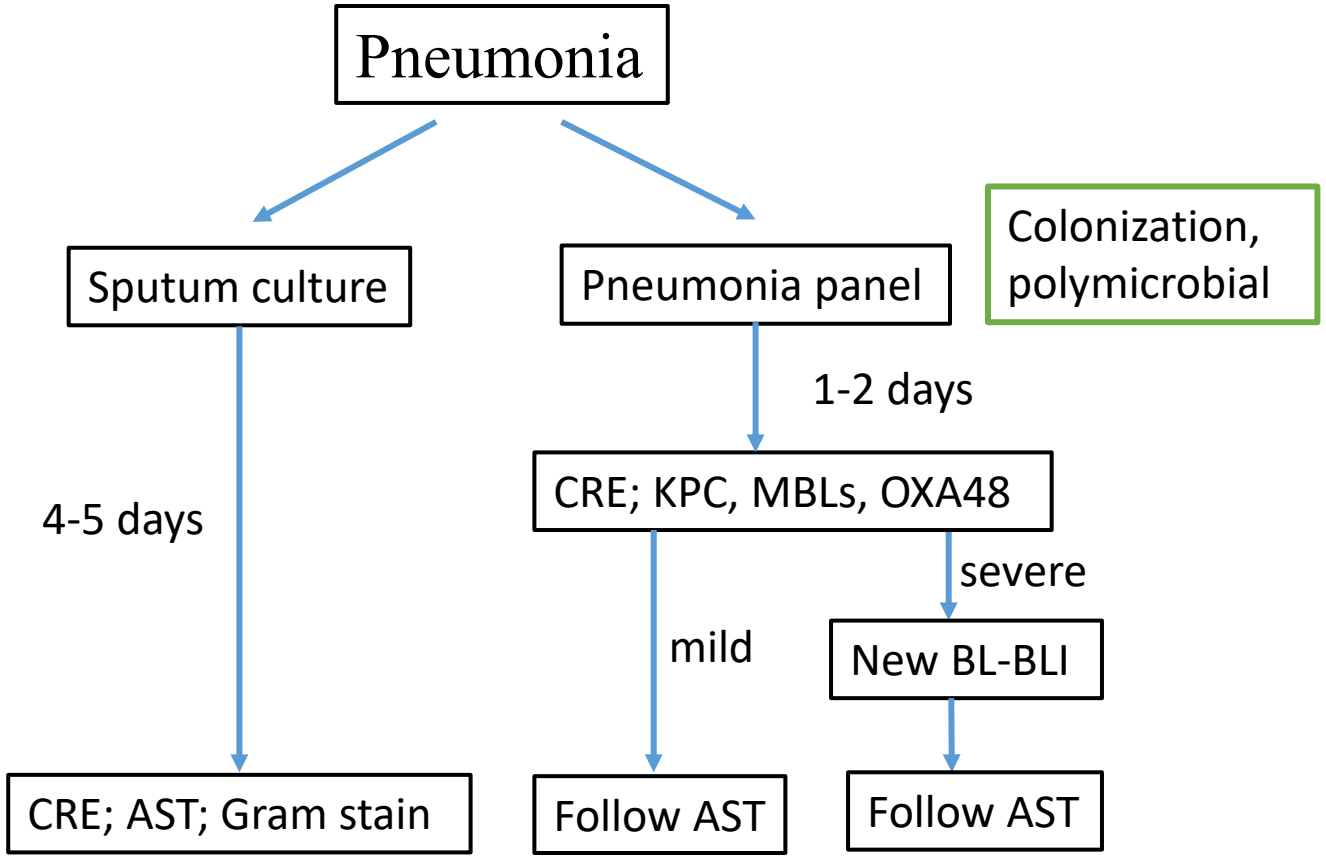
Uncomplicated cystitis	• **Ceftolozane-tazobactam** • Ceftazidime-avibactam • Imipenemcilastatin-relebactam • Cefiderocol	• A **single dose** of tobramycin or amikacin • Colistin (not polymyxin B)
Pyelonephritis & complicated UTI	• **Ceftolozane-tazobactam** • Ceftazidime-avibactam • Imipenemcilastatin-relebactam • Cefiderocol	• **Once-daily** tobramycin or amikacin
Infections outside of the urinary tract	• **Ceftolozane-tazobactam** • Ceftazidime-avibactam • Imipenemcilastatin-relebactam • Cefiderocol (Metallo-β-Lactamase)	• Cefiderocol

Combination antibiotic therapy **is not routinely recommended** for infections caused by DTR-*P. aeruginosa* if *in vitro* susceptibility to a first-line antibiotic

Not suggest the use of nebulized antibiotics

Courtesy of 鄭至宏醫師

CRE pneumonia in clinical practice



Ceftazidime-avibactam: KPC, OXA48
Meropenem-vaborbactam: KPC
Imipenem-cilastatin-relebactam: KPC
Cefiderocol: KPC, MBLs, OXA48

BL-BLI : β-lactam/β-lactamase inhibitor
AST: Antimicrobial Susceptibility Testing

2024

IDSA Recommendations for treatment of DTR *Pseudomonas aeruginosa*

DTR: 抗 pip-tazo, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin, and levofloxacin.

Uncomplicated cystitis	• **Ceftolozane-tazobactam** • Ceftazidime-avibactam • Imipenemcilastatin-relebactam • Cefiderocol	• A **single dose** of tobramycin or amikacin • Colistin (not polymyxin B)
Pyelonephritis & complicated UTI	• **Ceftolozane-tazobactam** • Ceftazidime-avibactam • Imipenemcilastatin-relebactam • Cefiderocol	• **Once-daily** tobramycin or amikacin
Infections outside of the urinary tract	• **Ceftolozane-tazobactam** • Ceftazidime-avibactam • Imipenemcilastatin-relebactam • Cefiderocol (Metallo-β-Lactamase)	• Cefiderocol

Combination antibiotic therapy **is not routinely recommended** for infections caused by DTR-*P. aeruginosa* if *in vitro* susceptibility to a first-line antibiotic

Not suggest the use of nebulized antibiotics

Courtesy of 鄭至宏醫師

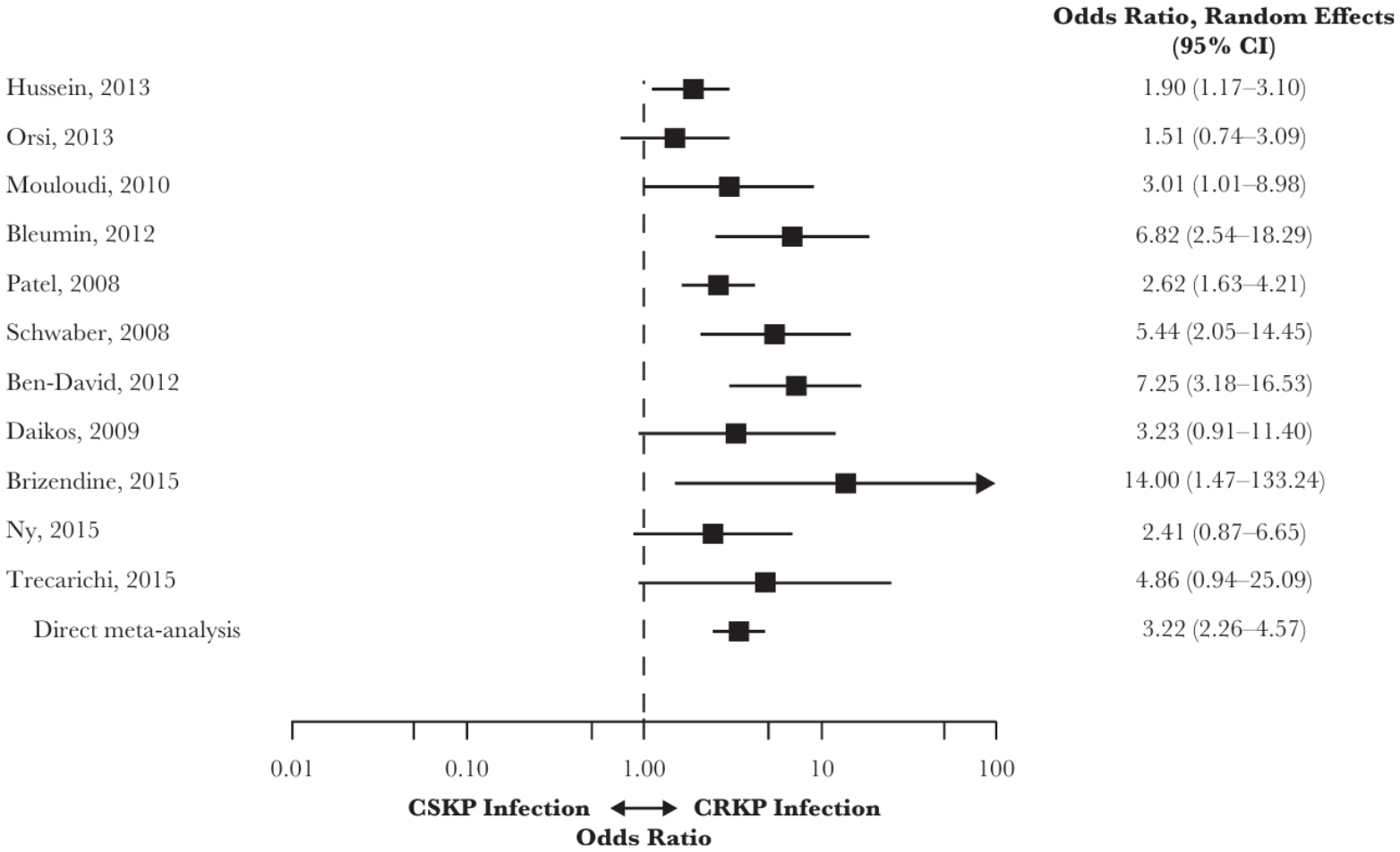
What Is the Likelihood of the Emergence of Resistance of DTR *P. aeruginosa* Isolates to the Newer β-Lactam Agents When Used to Treat DTR *P. aeruginosa* Infections?

- The frequency of resistance **may be** the highest for ceftolozane-tazobactam and ceftazidime-avibactam (prescribed more frequently in clinical practice); fewer data are available for imipenem-relebactam and cefiderocol.

- Recent DTR PA infection => repeat AST for the 4 newer β-lactams, consider imipenem-relebactam or cefiderocol if recently treated with ceftolozane-tazobactam or ceftazidime-avibactam

Tamma et al. Clin Infect Dis.2024 Aug 7:ciae403

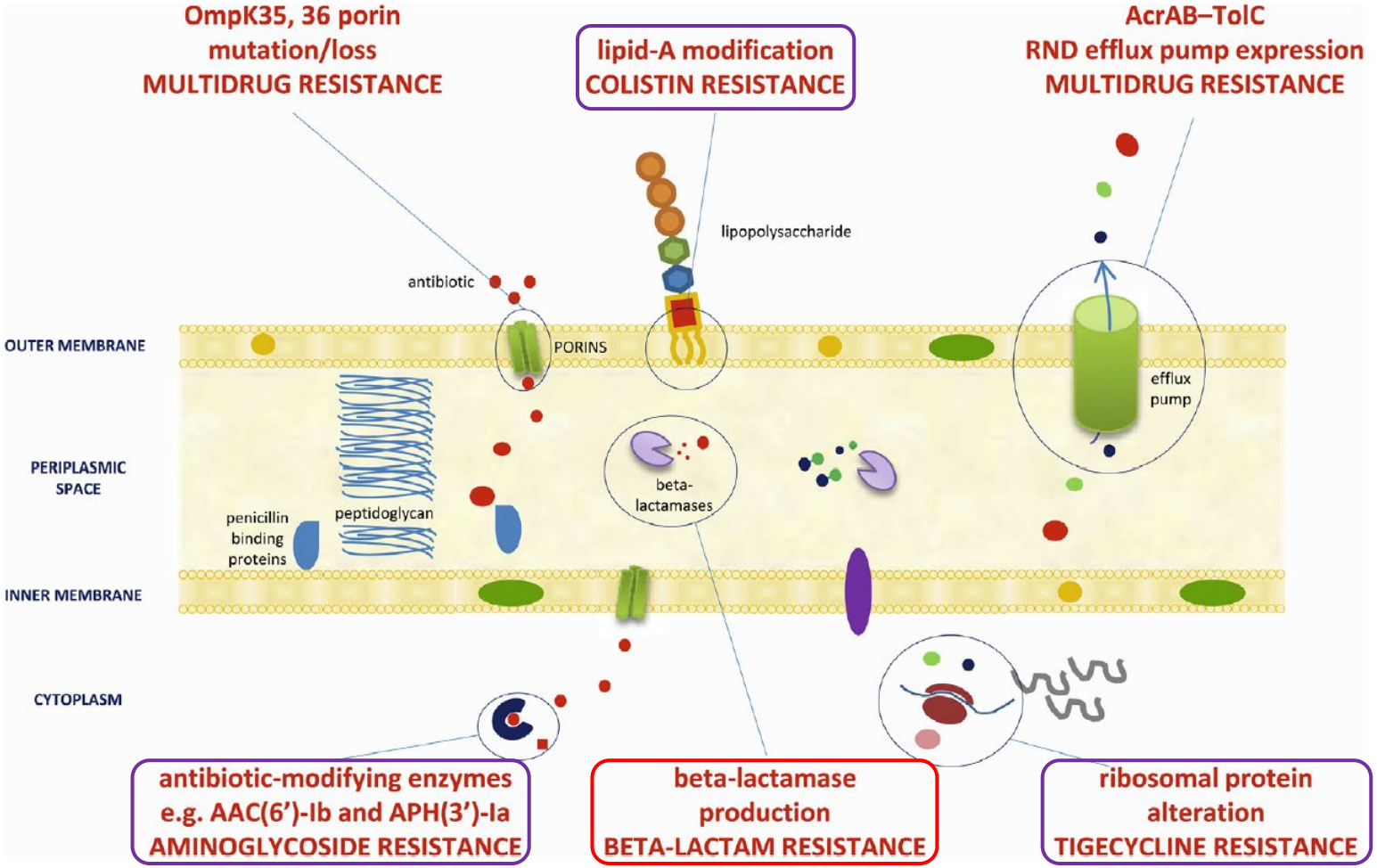
Mortality in patients with CRKP vs CSKP infections



CSKP, carbapenem-susceptible *K. pneumoniae*

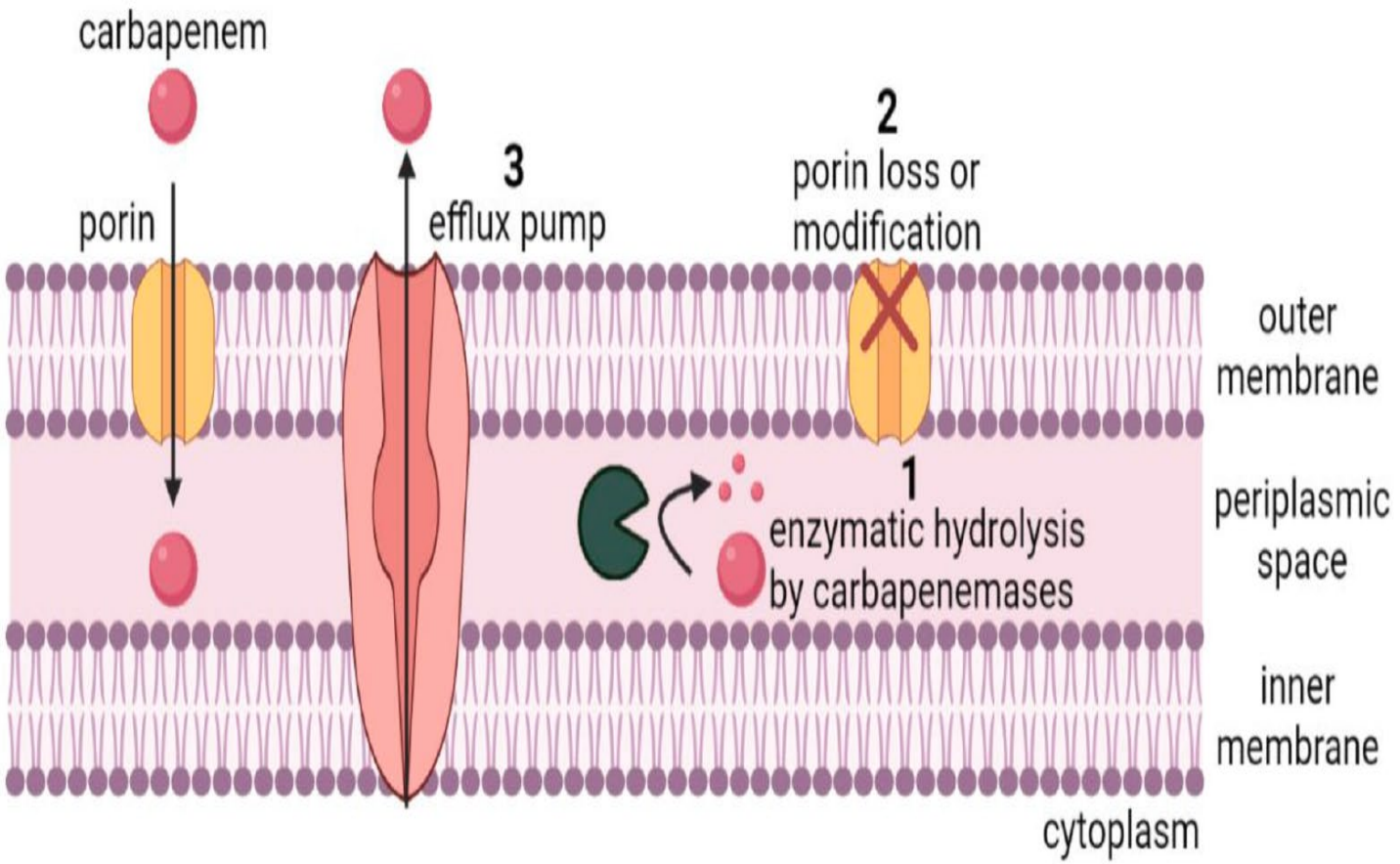
Open Forum Infect Dis.2018 Jun 28;5(7):ofy150.

Major mechanisms of antimicrobial resistance in *Enterobacterales*



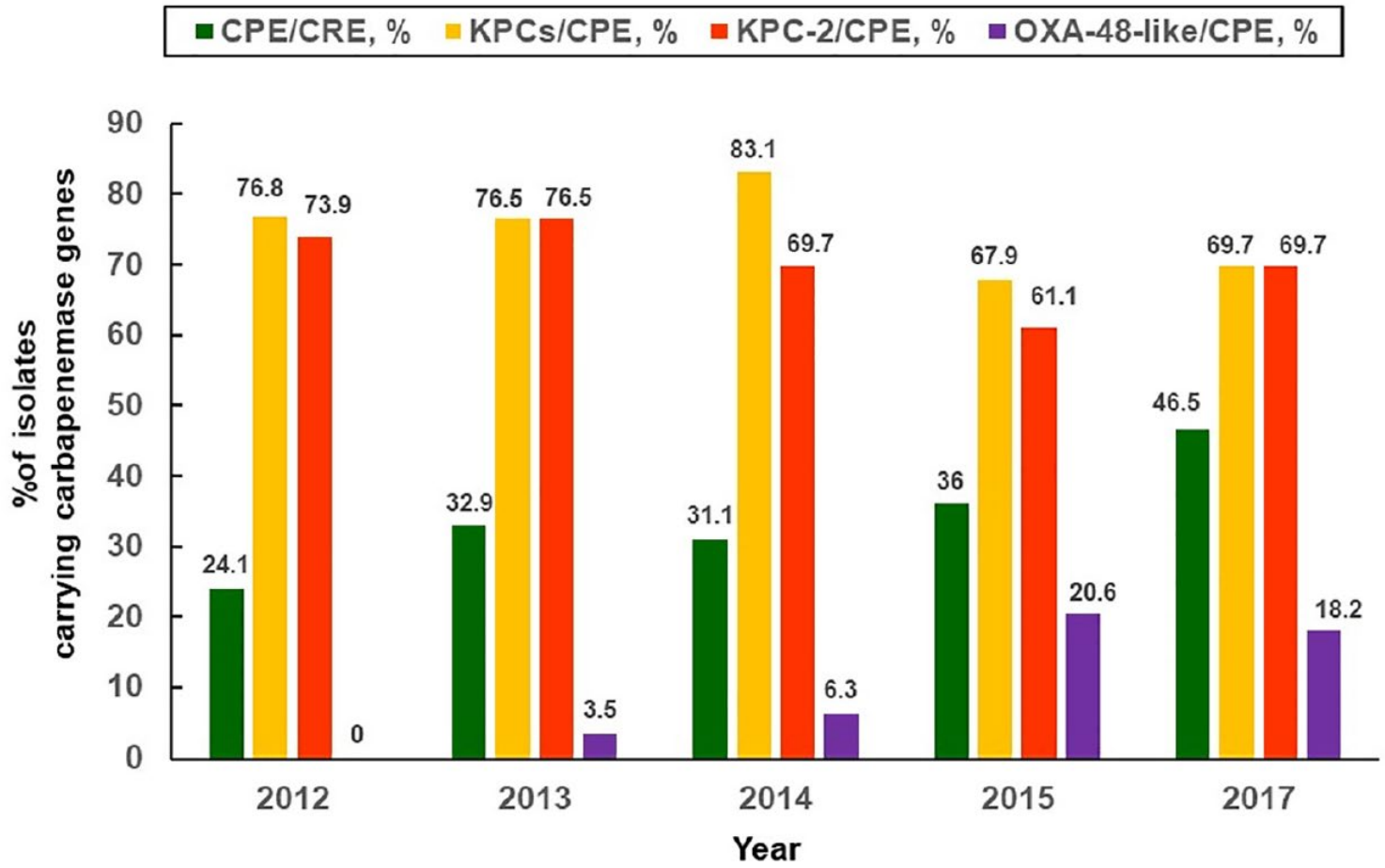
Clin Microbiol Infect. 2019 Aug;25(8):943-950

The mechanisms of carbapenem resistance in CRE



J Mass Spectrom Adv Clin Lab. 2022 Nov; 26: 9–19

Carbapenemase in CRKP between 2012 and 2017 in Taiwan



CPE: Carbapenemase-producing *Enterobacteriaceae*

Front Microbiol. 2018 Nov 27:9:2888.

Contents lists available at ScienceDirect

Journal of Microbiology, Immunology and Infection

journal homepage: www.e-jmii.com

Antimicrobial resistance among imipenem-non-susceptible *Escherichia coli* and *Klebsiella pneumoniae* isolates, with an emphasis on novel β-lactam/β-lactamase inhibitor combinations and tetracycline derivatives: The Taiwan surveillance of antimicrobial resistance program, 2020–2022

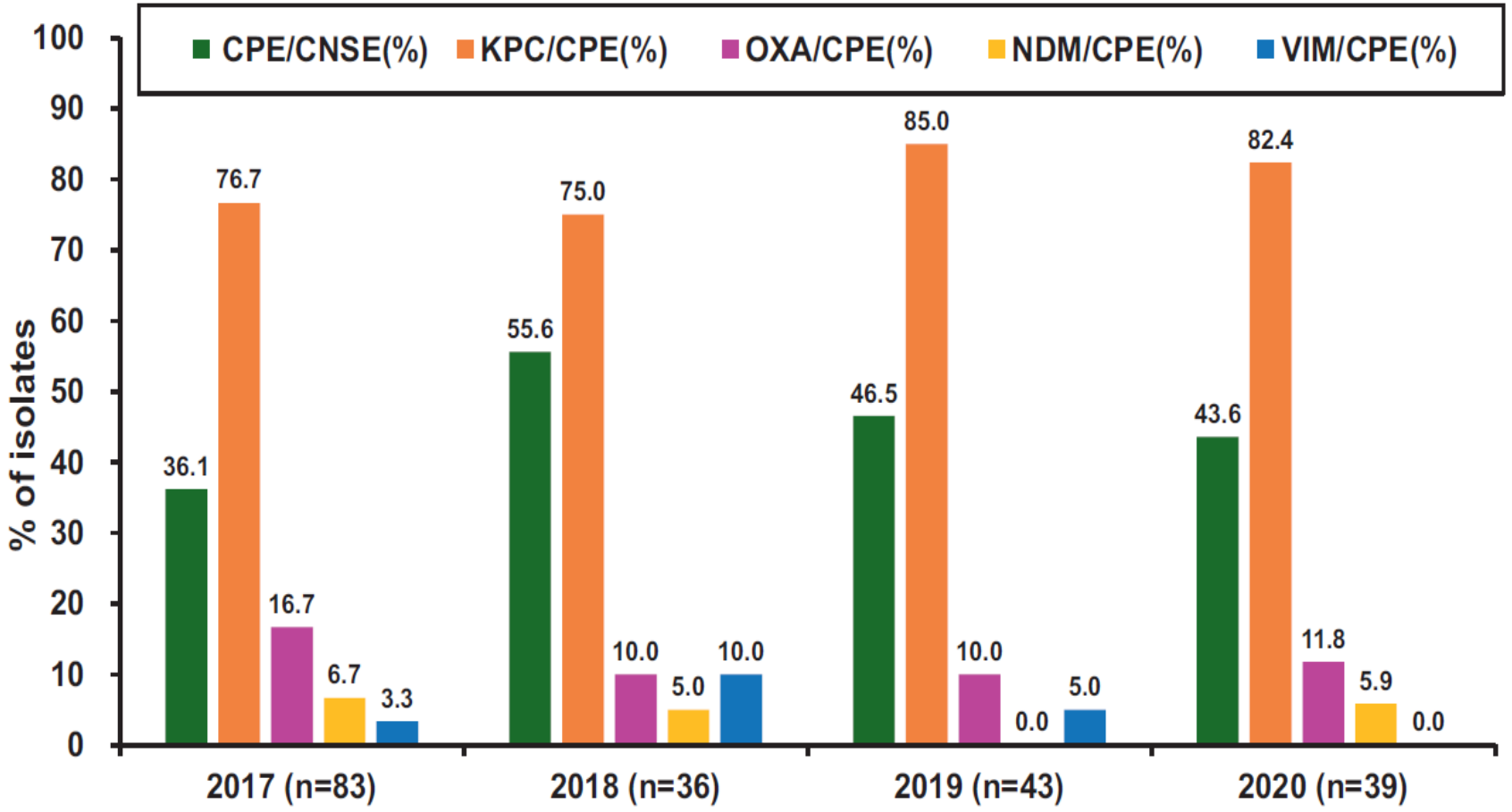
Yu-Lin Lee [a,b,c,1], Chun-Eng Liu [d,1], Wei-Yao Wang [a,c], Mei-Chen Tan [e], Pei-Jing Chen [e], Yih-Ru Shiau [e], Hui-Ying Wang [e], Jui-Fen Lai [e], I-Wen Huang [e], Ya-Sung Yang [f,g,**], Shu-Chen Kuo [e,*]

Taiwan Surveillance of Antimicrobial Resistance (TSAR) Program
28 hospitals in Taiwan

J Microbiol Immunol Infect.2025 Apr;58(2):219-225

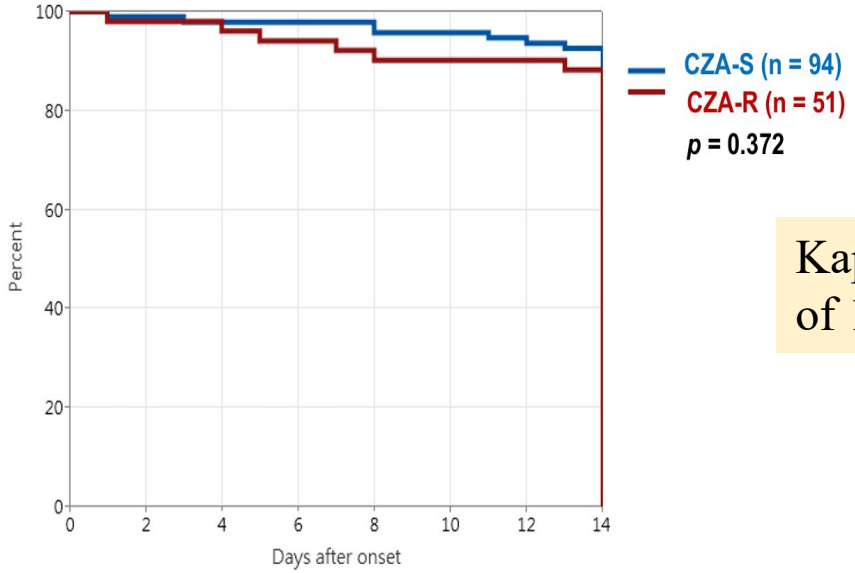
Carbapenemase in CRE between 2017 and 2020 in Taiwan

16 Taiwanese hospitals, 201 CRE (26 CR Ecoli, 175 CRKP)



CPE: Carbapenemase-producing *Enterobacteriaceae*
CNSE: Carbapenem-nonsusceptible *Enterobacteriaceae*

Int J Antimicrob Agents. 2021 Sep;58(3):106377



Kaplan–Meier plot of 14-day survival

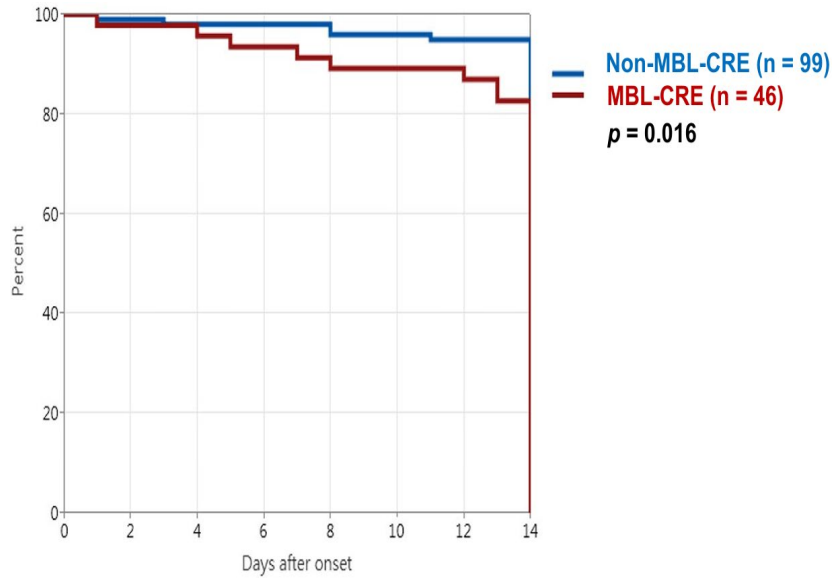


Table 5 Risk factors associated with 14-day and 30-day mortality

	14-day mortality univariate analysis		multivariate analysis		30-day mortality univariate analysis		multivariate analysis	
Variables	Odds ratio	P value	Odds ratio	P value	Odds ratio	P value	Odds ratio	P value
Intensive care unit when onset	3.9	0.029	2.4	0.200	4.4	<0.001	4.0	0.001
Cardiovascular diseases other than hypertension	3.4	0.053	2.5	0.179	2.2	0.053	1.7	0.218
Bacteremia	3.0	0.061	2.9	0.101	1.8	0.164		
Hypertension	2.8	0.092	1.7	0.422	1.8	0.139		
MBL	2.8	0.082	2.6	0.127	1.6	0.283		
Chronic kidney disease ≥ stage 3	2.5	0.126			0.8	0.611		
Prior symptomatic COVID-19	1.9	0.316			0.9	0.767		
CZA resistant	1.2	0.795			1.3	0.564		
Type 2 DM	1.1	0.838			1	0.946		

- MBL-CRE: poorer crude 14-day survival, but not independently associated with 14-day mortality.

Eur J Clin Microbiol Infect Dis.2025 Feb;44(2):251-262.

Mechanisms of antimicrobial resistance in *P. aeruginosa*

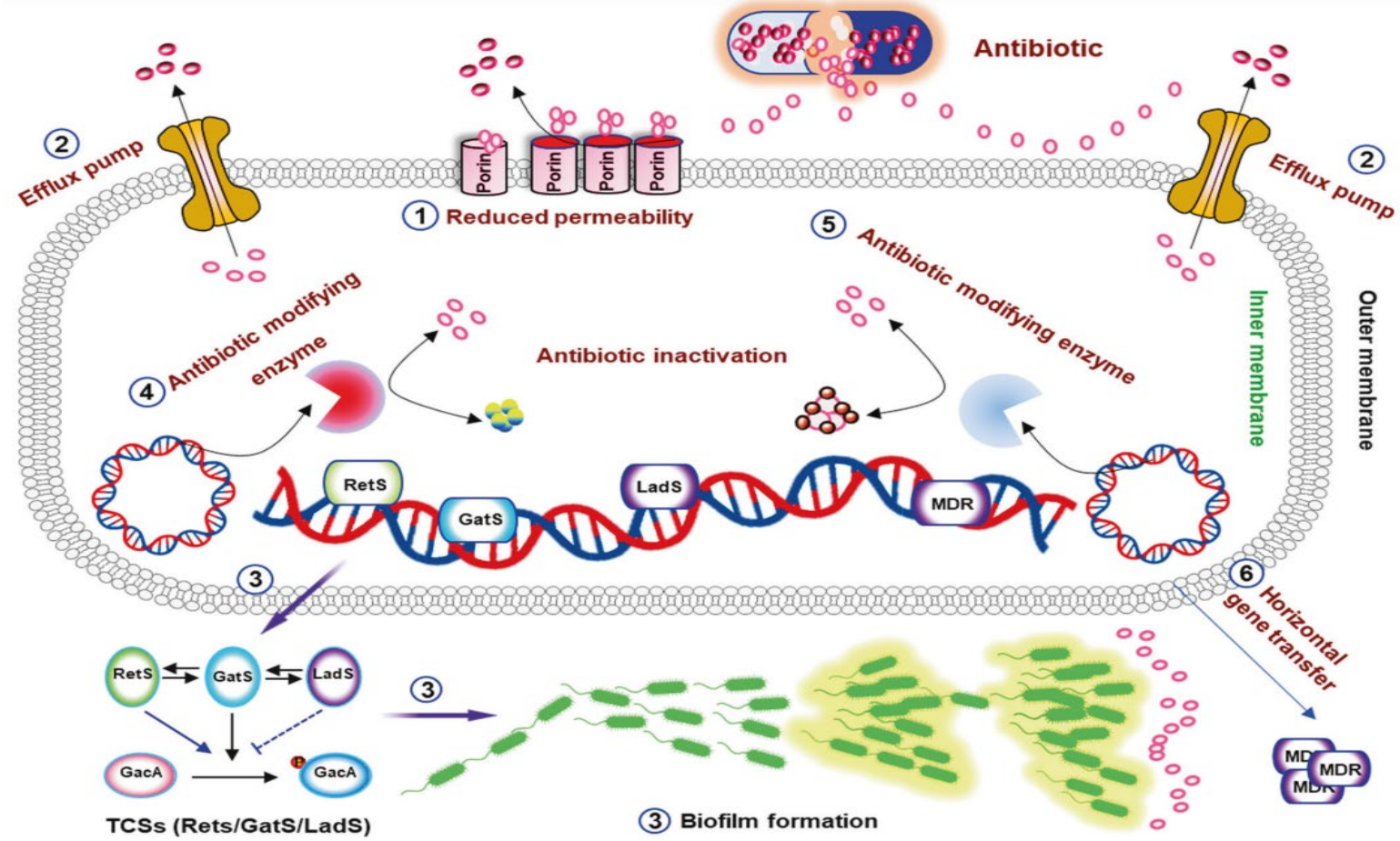
① outer membrane permeability

② efflux systems

③ biofilm-mediated resistance

④ antibiotic-modifying enzymes

⑤ antibiotic inactivating enzymes



Signal Transduct Target Ther.2022 Jun 25;7(1):199.

Cefiderocol versus standard therapy for hospital-acquired and health-care-associated Gram-negative bacterial bloodstream infection (the GAME CHANGER trial): an open-label, parallel-group, randomised trial

*David L Paterson, Helmi Sulaiman, Po-Yu Liu, Mark D Chatfield, Mesut Yilmaz, Zeti Norfidiyati Salmuna, Mohd Zulfakar Mazlan, Siriluck Anunnatsiri, Rujipas Sirijatuphat, Darunee Chotiprasitsakul, David C Lye, Jyoti Somani, Shirin Kalimuddin, Abdullah T Aslan, Visanu Thamlikitkul, Yi-Tzu Lee, Ya-Sung Yang, Yi-Tsung Lin, Wan Nurliyana Wan Ramli, Chien-Hao Tseng, Sophia Archuleta, Yvonne Fu Zi Chan, Brian M Forde, Hugh Wright, Adam G Stewart, Kay A Ramsay, Weiping Ling, Vicki Rossi, Tiffany M Harris-Brown, Patrick N A Harris, on behalf of the GAME CHANGER Trial Investigators**

Lancet Infect Dis.2026 Feb;26(2):148-159.

Cefiderocol Non-Inferior but Not Superior to Standard of Care (GAME CHANGER)

Cefiderocol vs standard of care for hospital-acquired / health-care–associated Gram-negative bloodstream infection

Open-label, parallel-group RCT · 17 tertiary hospitals / 6 countries · Nov 2019–Oct 2023 · cefiderocol 2 g IV q8h (3-h infusion) vs clinician-chosen SOC

POPULATION

504 main analysis (250 cefiderocol / 254 SOC) · 127 (25%) carbapenem-resistant

DESIGN

Open-label RCT · non-inferiority (10% margin) then superiority test

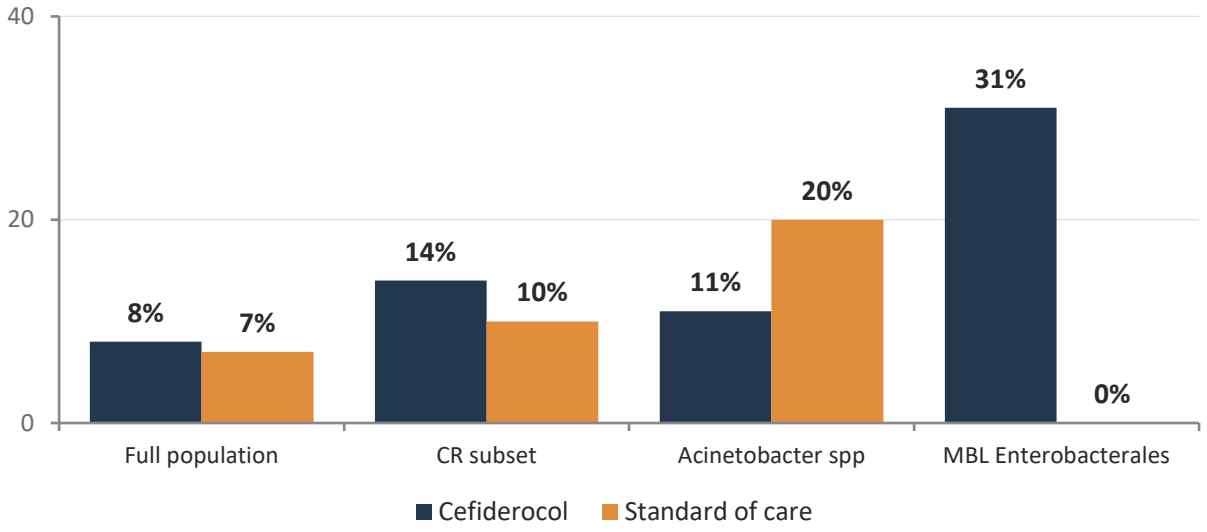
COMPARISON

Cefiderocol 2 g q8h vs standard of care (up to 3 active agents)

PRIMARY ENDPOINT

14-day all-cause mortality (main analysis population)

14-day all-cause mortality: cefiderocol vs standard of care (%)



Key results — non-inferior, not superior

8% vs 7%

14-day mortality (primary)

Full population · ARD 1% (95% CI −3 to 6) · non-inferior

14% vs 10%

Carbapenem-resistant subset

14-day mortality · ARD 5% (−7 to 16) · superiority not shown

31% vs 0%

MBL-producing Enterobacterales

14-day 5/16 vs 0/11 · 30-day 50% vs 18% · cefiderocol signal

- **Cefiderocol was non-inferior but NOT superior to standard of care — including the carbapenem-resistant subset.**
- **A higher mortality signal with MBL-producing *Enterobacterales* urges caution and combination strategies; *Acinetobacter* outcomes were reassuring.**

Lancet Infect Dis.2026 Feb;26(2):148-159.

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Review Article

Recommendations and guidelines for the treatment of infections due to multidrug resistant organisms☆ IDST, 2022

Cheng Len Sy [a,1], Pao-Yu Chen [b,1], Chun-Wen Cheng [c,1], Ling-Ju Huang [d,x,1], Ching-Hsun Wang [e,1], Tu-Hsuan Chang [f], Yi-Chin Chang [g], Chia-Jung Chang [h], Ing-Moi Hii [i], Yu-Lung Hsu [j], Ya-Li Hu [k], Pi-Lien Hung [l], Chen-Yen Kuo [m], Pei-Chin Lin [n,o], Po-Yen Liu [p], Ching-Lung Lo [q], Shih-Hao Lo [r], Pei-Ju Ting [s], Chien-Fang Tseng [h], Hsiao-Wei Wang [t], Ching-Hsiang Yang [l], Susan Shin-Jung Lee [a,u,*], Yao-Shen Chen [a,u], Yung-Ching Liu [v], Fu-Der Wang [w]

J Microbiol Immunol Infect.2022 Jun;55(3):359-386.

Carbapenem-Resistant Enterobacterales (CRE): Treatment at a Glance

CRE · IDST / GREAT Guideline, J Microbiol Immunol Infect 2022 (Taiwan)

GRADE 1 strong / **2** weak · **A–D** high→very-low quality

Bloodstream infection *7–14 days*	▪ CAZ-AVI 2.5 g IV q8h (infuse 3 h) **(2D)** ▪ MEV 4 g IV q8h · IMI-REL 1.25 g IV q6h **(2C)** ▪ Polymyxin combo: colistin + tigecycline OR extended-infusion meropenem 1 g q8h **(2D)**
Complicated UTI *5–7 days*	▪ CAZ-AVI 2.5 g q8h **(2D)** ▪ MEV 4 g q8h · IMI-REL 1.25 g q6h **(2C)** ▪ Aminoglycoside: gentamicin / amikacin / plazomicin **(2D)** ▪ Single-dose aminoglycoside for simple cystitis **(2D)**
Complicated intra-abdominal *5–7 days*	▪ CAZ-AVI 2.5 g q8h + metronidazole 500 mg q6h **(2D)** ▪ IMI-REL 1.25 g q6h **(2C)** ▪ Tigecycline OR eravacycline 1 mg/kg q12h **(2D)** ▪ Polymyxin-based combination (susceptibility-guided) **(2D)**

Combination therapy is not routinely recommended; choose the partner agent by susceptibility testing. Avibactam / vaborbactam / relebactam do NOT inhibit MBLs (NDM, VIM, IMP). MEV, IMI-REL, plazomicin and eravacycline were not TFDA-approved as of Jan 2022. Use extended-infusion meropenem (3 h) when meropenem MIC ≤ 8 mg/L.

CAZ-AVI = Ceftazidime-avibactam | MEV = Meropenem-vaborbactam | IMI-REL = Imipenem-cilastatin-relebactam | C/T = Ceftolozane-tazobactam | CBA = Colistin base activity | MIU = Million IU | MBL = Metallo-β-lactamase | DTR-PA = Difficult-to-treat-resistant P. aeruginosa | BSI = Bloodstream infection | cUTI / cIAI = Complicated UTI / intra-abdominal infection

Carbapenem-Resistant Pathogens in Pneumonia (HAP/VAP)

CR-GNB · Pathogen-Specific Therapy for HAP/VAP, J Microbiol Immunol Infect **2019**;52:172–199 (Taiwan)

No item-level GRADE ratings in source table

Scope note: This guideline does not stratify pneumonia treatment by CRE vs. CRAB vs. other GNB — the table below applies to carbapenem-resistant pathogens broadly, not CRE specifically.

Stable hemodynamics	• Colistin 5 mg/kg IV × 1 loading dose, then 2.5 mg × (1.5 × CrCl + 30) IV q12h • ± one of: Imipenem 500 mg IV q6h | Meropenem 1 g IV q8h | Ampicillin/sulbactam 3 g IV q6h • + Adjunctive inhaled colistin: 1.25–15 MIU/day, divided q8–q12h, each dose in 5 mL saline
Unstable hemodynamics	• Colistin 5 mg/kg IV × 1 loading dose, then 2.5 mg × (1.5 × CrCl + 30) IV q12h • + (recommended, not ±) Imipenem 500 mg IV q6h or Meropenem 1 g IV q8h — combination favored in critical illness • + Adjunctive inhaled colistin: 1.25–15 MIU/day, divided q8–q12h, each dose in 5 mL saline

Extended infusion of carbapenems may be appropriate for high-MIC isolates. A randomized trial (Paul et al., Lancet Infect Dis 2018) found no outcome difference from adding a carbapenem to colistin, but 77% of isolates were Acinetobacter and only ~half of patients had pneumonia — not CRE-specific evidence. General HAP/VAP duration guidance: 7 days if adequate initial therapy and clinical improvement.

CrCl = creatinine clearance | MIU = million international units | HAP = hospital-acquired pneumonia | VAP = ventilator-associated pneumonia | GNB = gram-negative bacteria | CRE = carbapenem-resistant Enterobacterales | CRAB = carbapenem-resistant A. baumannii

Difficult-to-Treat-Resistant P. aeruginosa (DTR-PA): Treatment at a Glance

CRPA / DTR-PA · IDST / GREAT Guideline, J Microbiol Immunol Infect 2022 (Taiwan) **GRADE 1** strong / **2** weak · **A–D** high→very-low quality

CRPA still susceptible to other agents (CR / Ceph-S) *5–14 days*	▪ Anti-pseudomonal β-lactam: piperacillin ± tazobactam, ceftazidime, cefepime, cefpirome ± aminoglycoside **(2D)** ▪ Fluoroquinolone: ciprofloxacin or levofloxacin ± aminoglycoside **(2D)** ▪ Prefer a colistin-sparing strategy; aminoglycoside monotherapy only for UTI **(2D)**
DTR-PA (non-susceptible to all first-line β-lactams + FQ) *5–14 days*	▪ Colistin-based therapy — mono or combination **(2C)** ▪ Critically ill: colistin load 9 MU then 4.5 MU q12h; monitor renal function **(1C)** ▪ New BL/BLI may be considered: C/T, CAZ-AVI, IMI-REL (susceptibility-guided) **(2C)** ▪ Colistin-based combination therapy remains controversial **(2D)**

MBL prevalence in P. aeruginosa remains low in Taiwan. JMII 2022 leads with colistin-based therapy; new β-lactam/β-lactamase inhibitors are positioned as "may be considered" with confirmed susceptibility (note: this ordering differs from IDSA 2024, which favors novel BL/BLI first). Susceptibility testing of new BL/BLI is recommended to guide therapy. IMI-REL was not TFDA-approved as of Jan 2022.

CAZ-AVI = Ceftazidime-avibactam | MEV = Meropenem-vaborbactam | IMI-REL = Imipenem-cilastatin-relebactam | C/T = Ceftolozane-tazobactam | CBA = Colistin base activity | MIU = Million IU | MBL = Metallo-β-lactamase | DTR-PA = Difficult-to-treat-resistant P. aeruginosa | BSI = Bloodstream infection | cUTI / cIAI = Complicated UTI / intra-abdominal infection

DTR P. aeruginosa: 2026 IDSA Update Overview

Difficult-to-Treat Resistance (DTR) — non-susceptible to aztreonam, cefepime, ceftazidime, ciprofloxacin, imipenem, levofloxacin, meropenem & piperacillin-tazobactam

UNCHANGED FROM 2024

CORE FRAMEWORK

- MDR / DTR definitions unchanged
- 4 β-lactams remain the only agents with reliable DTR-PA activity: cefiderocol, ceftazidime-avibactam (CAZ-AVI), ceftolozane-tazobactam (C/T), imipenem-relebactam (IMI-REL)
- AST for all 4 agents still recommended for every DTR-PA isolate — activity is highly variable between agents
- Carbapenemase production still uncommon in US P. aeruginosa, but rising globally (Latin America ~69%, Asia ~57%, S. Europe ~50%)
- Combination therapy still NOT routinely suggested once an active β-lactam is confirmed

WHAT'S NEW IN 2026

2026 GUIDANCE CHANGES

- Question count: 9 → 7 — uncomplicated cystitis & pyelonephritis/cUTI questions MERGED into one “cUTI” question
- NEW: Ceftolozane-tazobactam is now the preferred agent specifically for DTR-PA PNEUMONIA (previously all 3 were equal)
- NEW independent question: carbapenemase identification (KPC vs. MBL) now drives agent selection — KPC-producing DTR-PA addressed for the first time
- NEW real-world case example: 2022–2023 US artificial-tears VIM+GES P. aeruginosa outbreak
- Updated 2019–2023 US resistance-emergence & susceptibility surveillance data
- Meropenem-vaborbactam discussion removed entirely from the DTR-PA chapter

CAZ-AVI = Ceftazidime-avibactam | C/T = Ceftolozane-tazobactam | IMI-REL = Imipenem-relebactam | ATM = Aztreonam | MBL = Metallo-β-lactamase | KPC = Klebsiella pneumoniae carbapenemase | GES = Guiana extended-spectrum β-lactamase | ELF = Epithelial lining fluid | cUTI = Complicated UTI | uUTI = Uncomplicated UTI

Carbapenem-Resistant A. baumannii (CRAB): Treatment at a Glance

CRAB · IDST / GREAT Guideline, J Microbiol Immunol Infect 2022 (Taiwan)

GRADE 1 strong / **2** weak · **A–D** high→very-low quality

PNEUMONIA · ≥ 7 days

RECOMMENDED

- Colistin (5 mg CBA/kg load → maintenance) **(2D)**
- ± imipenem/cilastatin 500 mg q6h OR meropenem 2 g q8h **(2D)**
- + adjunctive inhaled colistin 1.25–15 MIU/day **(2D)**

ALTERNATIVE

- Sulbactam 6–9 g/day in 3–4 divided doses **(2D)**
- OR colistin + tigecycline + sulbactam (triple) **(2D)**

BLOODSTREAM INFECTION · 10–14 days

RECOMMENDED

- Colistin-carbapenem combination:
- Colistin + imipenem/cilastatin OR meropenem **(2C)**

ALTERNATIVE

- Colistin + tigecycline **(2D)**
- OR colistin + sulbactam **(2D)**

✗ **Tigecycline monotherapy is NOT recommended for CRAB pneumonia** *(GRADE 1C — strong)*

Carbapenem gives in-vitro synergy when carbapenem MIC ≤ 32 mg/L; infuse each dose > 3 h. Add tigecycline only if tigecycline MIC ≤ 2 mg/L. Novel BL/BLIs (CAZ-AVI, MEV, IMI-REL) are NOT clinically active against CRAB. Note: 2022 JMII predates routine availability of sulbactam-durlobactam and mature cefiderocol clinical data.

CAZ-AVI = Ceftazidime-avibactam | MEV = Meropenem-vaborbactam | IMI-REL = Imipenem-cilastatin-relebactam | C/T = Ceftolozane-tazobactam | CBA = Colistin base activity | MIU = Million IU | MBL = Metallo-β-lactamase | DTR-PA = Difficult-to-treat-resistant P. aeruginosa | BSI = Bloodstream infection | cUTI / cIAI = Complicated UTI / intra-abdominal infection

Understanding β-lactamases classifications for clinicians in choosing the appropriate antimicrobial agent

Table 1 | **Comparison of two β-lactamase classification schemes**

Ambler class[8]: catalytic site (spectrum)	Bush–Jacoby–Medeiros group[9]: catalytic site (spectrum)	Substrates	Inhibited by	Examples
A: serine (variable)	2a: serine (penicillinases)	Penicillins	Clavulanate, avibactam and other newer inhibitors[a]	Penicillinases from Gram-positive bacteria
	2b: serine (penicillinases)	Penicillins and narrow-spectrum cephalosporins	Clavulanate, avibactam and other newer inhibitors	TEM-1, TEM-2 and SHV-1
	2be: serine (ESBLs)	Penicillins and cephalosporins, including extended-spectrum	Clavulanate, avibactam and other newer inhibitors	SHV-2, TEM-10, CTX-M and GES-1
	2br: serine (inhibitor-resistant)	Penicillins	Avibactam and other newer inhibitors	TEM-30 and SHV-72
	2c: serine (penicillinases)	Penicillins and carbenicillin	Clavulanate, avibactam and other newer inhibitors	PSE (CARB)
	2f: serine (carbapenemases)	Penicillins, cephalosporins and carbapenems	Avibactam and other newer inhibitors	KPC, SME, NMC-A and GES-2
B: metallo (carbapenemase)	3: metallo (carbapenemases)	Most β-lactams, including carbapenems, but not monobactams (Aztreonam)	Chelating agents (EDTA) and ANT431	IMP, VIM and NDM
C[b]: serine (cephalosporinases)	1: serine (cephalosporinases)	Penicillins and cephalosporins	Cloxacillin, avibactam and other newer inhibitors	Chromosomal AmpC, CMY, ACT-1 and DHA
D[c]: serine (oxacillinases)	2d: serine (oxacillinases)	Penicillins and cloxacillin; some include cephalosporins and/or carbapenems	Sodium chloride; some by clavulanate, avibactam and other newer inhibitors	OXA-1/30, OXA-10, OXA-23 and OXA-48

ESBL, extended-spectrum β-lactamase. [a]The term 'newer inhibitors' refers to the diazabicyclooctanone and boronic acid inhibitors. [b]See REF.[139] for original reference to class C cephalosporinases. [c]See REF.[140] for original reference to class D β-lactamases.

Nat Rev Microbiol. 2019 May;17(5):295-306.

CRE: Treatment at a Glance

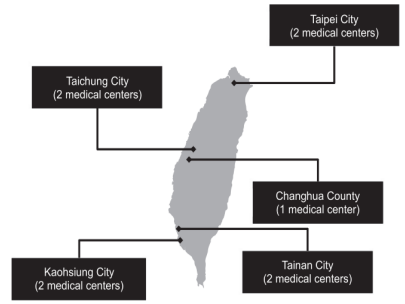
2026 IDSA Update summary table — ★ = changed since 2024

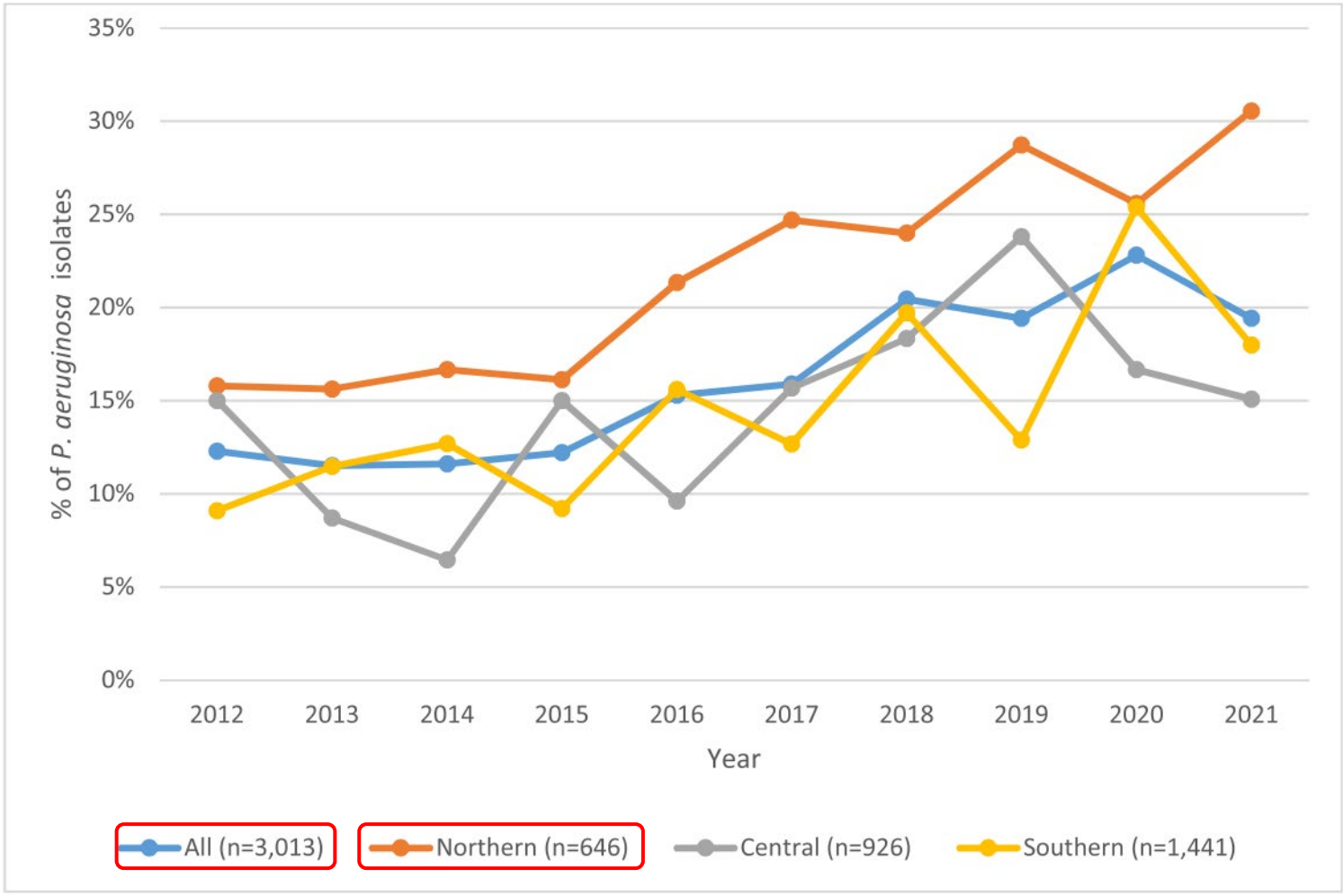
Carbapenemase Type	Preferred	Alternative
Non-carbapenemase producing	a. R to erta; S to mero/imi → extended-infusion mero or imi-cilastatin **b. R to all carbapenems → Aztreonam-avibactam / CAZ-AVI / IMI-REL / MEV ★ 2026** ***(modest preference: CAZ-AVI, IMI-REL over MEV) ★2026***	Cefiderocol *Tigecycline/eravacycline**
KPC	Meropenem-vaborbactam > Ceftazidime-avibactam > Imipenem-relebactam	**Aztreonam-avibactam ★ 2026** Cefiderocol *Tigecycline/eravacycline**
NDM / MBL	**Aztreonam-avibactam ★ 2026** Cefiderocol	**CAZ-AVI + Aztreonam (only if ATM-AVI unavailable) ★ 2026** *Tigecycline/eravacycline**
OXA-48-like	Ceftazidime-avibactam	**Aztreonam-avibactam ★ 2026** Cefiderocol *Tigecycline/eravacycline**

** Non-BSI and non-UTI only. Always use high-dose tigecycline (200 mg load → 100 mg q12h). Red bold text = changed/added in the 2026 IDSA guidance.*

CAZ-AVI = Ceftazidime-avibactam | ATM-AVI = Aztreonam-avibactam | MEV = Meropenem-vaborbactam | IMI-REL = Imipenem-cilastatin-relebactam | ATM = Aztreonam | MBL = Metallo-β-lactamase | BSI = Bloodstream infection | UTI = Urinary tract infection | TMP-SMX = Trimethoprim-sulfamethoxazole

Percentage of CRPA in PA isolates stratified by region of Taiwan, 2012-2021, SMART study





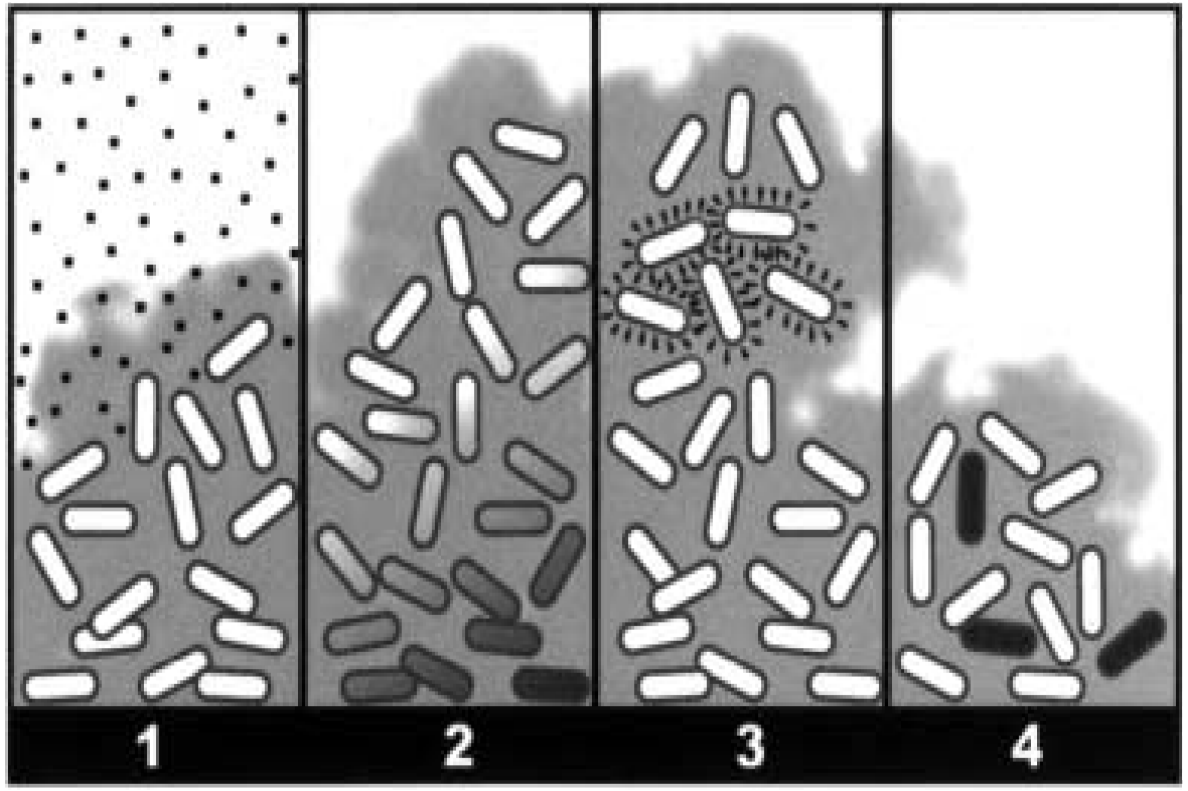
All *P. aeruginosa*
- Bloodstream (131)
- Intra-abdominal (670)
- Lower respiratory tract (1725)
- Urinary Tract (481)

J Glob Antimicrob Resist.2023 Sep:34:106-112.

Four hypothesized biofilm resistance mechanisms

- A **biofilm** is an aggregate of **microorganisms** that adhere to each other on a living or non-living surface, and are embedded within a self produced **matrix** of extracellular polymeric substances, including **exopolysaccharides**, **proteins**, **metabolites** and **extracellular DNA**.

- The microbial cells grown in biofilms are **less sensitive to antimicrobial agents** and **host immune response.**



Hypothesis:

1. the antibiotic (squares) **penetrates slowly or incompletely**

2. **concentration gradient of a metabolic substrate** leads to zones of **slow or non-growing bacteria** (shaded cells)

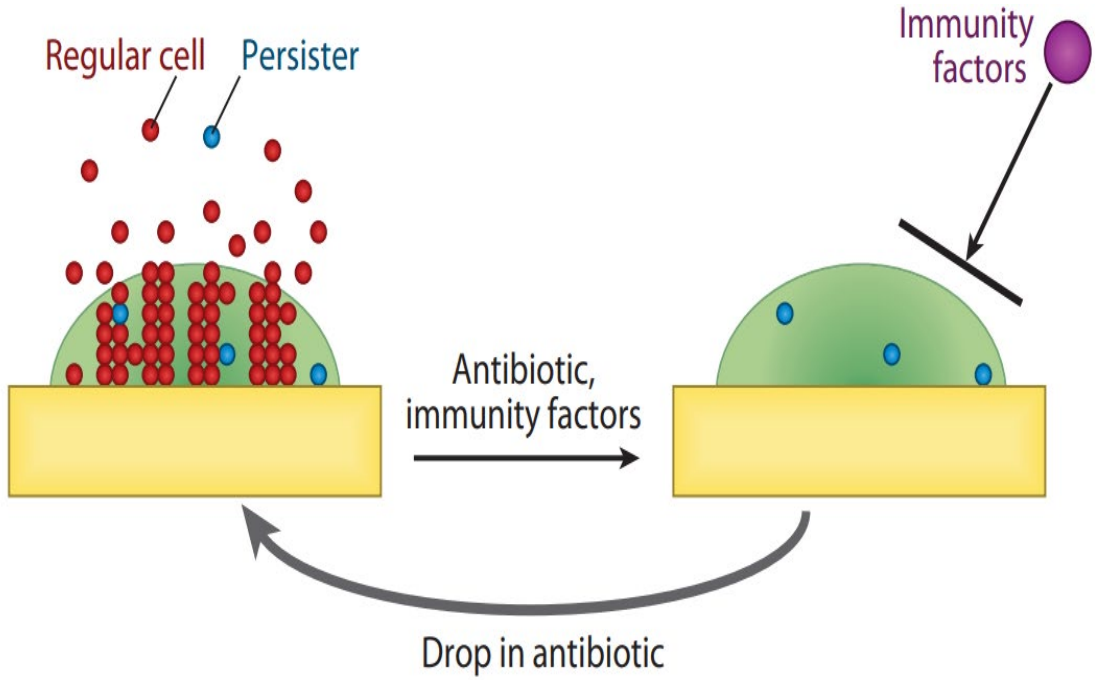
3. **adaptive stress response** (marked cells) to cope with environmental fluctuations

4. a small fraction of the cells differentiate into a highly protected **persister** state (dark cells).

Stewart. Int J Med Microbiol.2002 Jul;292(2):107-13

Persister cells in antibiotic resistance

- Transient phenotype developed as a consequence of heterogeneous responses to the environment within a genetically identical bacterial population.
- Persister cells comprise about 1% of biofilm cells, and are slow-growing, metabolically inactive and highly tolerant to antibiotic.
- the existence of a dormant state that shuts down the synthesis of the antibiotic targets
- not proliferate in the presence of antibiotics, resume growth once the antibiotics are removed



The matrix protects persister cells from the immune system

Pang et al. Biotechnol Adv.2019 Jan-Feb;37(1):177-192; Lewis et al . Annu Rev Microbiol.2010:64:357-72

DTR P. aeruginosa: Treatment at a Glance (2026)

Updated summary — 2026 changes marked ★

Infection Type	Preferred	Alternative
cUTI ★ (merged from 2 questions)	Cefiderocol | CAZ-AVI | C/T | IMI-REL (alphabetical, equal)	Once-daily amikacin/tobramycin
uUTI (now a brief sub-note)	Single-dose amikacin/tobramycin, or any cUTI agent, or colistin	—
Non-UTI — general	CAZ-AVI | C/T | IMI-REL	Cefiderocol
Non-UTI — Pneumonia ★ NEW	**Ceftolozane-tazobactam preferred among the three**	Cefiderocol
KPC-producing ★ NEW question	Cefiderocol | CAZ-AVI | IMI-REL (AST-guided)	— (C/T not suggested)
MBL-producing (NDM/VIM/IMP)	Cefiderocol (monotherapy)	CAZ-AVI + aztreonam only if cefiderocol-R
CR-PA, other β-lactam susceptible	High-dose extended-infusion traditional β-lactam	Novel β-lactam for critically ill / poor source control

★ = new or materially changed in the 2026 IDSA guidance vs. 2024. Combination therapy not routinely recommended with a confirmed active β-lactam; nebulized antibiotics not routine but reasonable salvage adjunct when no β-lactam is active and response is suboptimal; MEV (meropenem-vaborbactam) discussion removed from the DTR-PA chapter in 2026.

CAZ-AVI = Ceftazidime-avibactam | C/T = Ceftolozane-tazobactam | IMI-REL = Imipenem-relebactam | ATM = Aztreonam | MBL = Metallo-β-lactamase | KPC = Klebsiella pneumoniae carbapenemase | GES = Guiana extended-spectrum β-lactamase | ELF = Epithelial lining fluid | cUTI = Complicated UTI | uUTI = Uncomplicated UTI

Frequency of resistance emergence to newer β-lactam agents for *P. aeruginosa* treatment

- Ceftolozane-tazobactam: 38% (14/37), 50%(14/28) , 79% (11/14), median duration of 15 days of therapy, but likely overestimation (exclude patients w/o recurrent PA infections)
- Ceftazidime-avibactam: 25% (8/32)
- Imipenem-cilastatin-relebactam: 0% (0/31) - 26%(5/19)
- Cefiderocol: 6% (1/17)

✓ Recent DTR PA infection => repeat AST for the 4 newer β-lactams, consider imipenem-relebactam or cefiderocol if recently treated with ceftolozane-tazobactam or ceftazidime-avibactam

Tamma et al. Clin Infect Dis.2021 Dec 6;73(11):e4599-e4606; Tamma et al. Clin Infect Dis.2024 Aug 7:ciae403; Hareza et al. Antimicrob Agents Chemother.2024 Oct 8;68(10):e0090724

Methods to decrease resistance to newer β-lactam agents

Variable	Increase in TOL-TAZ MIC (mcg/mL) (n = 14, 50%)	No Increase in TOL-TAZ MIC (mcg/mL) (n = 14, 50%)	*P*-value
Demographics			
Age in years (median, IQR)	56 (40–65)	56 (48–60)	.95
Female	5 (36%)	3 (21%)	.40
Weight in kilograms (median, IQR)	62 (56–79)	63 (56–76)	.87
Renal replacement therapy	4 (29%)	1 (7%)	.14
Underlying medical condition			
Cystic fibrosis	2 (14%)	1 (7%)	.54
Chronic ventilator dependence	3 (21%)	4 (29%)	.66
Burn	1 (7%)	1 (7%)	.99
Active immunosuppressive therapy	8 (57%)	5 (36%)	.26
Complex cardiovascular disease with foreign material[a]	3 (21%)	1 (7%)	.28
Site of infection			
Pneumonia	9 (64%)	10 (71%)	.69
Bacteremia	4 (29%)	1 (7%)	.14
Intra-abdominal infection	1 (7%)	3 (21%)	.28
Treatment data			
3 grams IV every 8 hours of TOL-TAZ	12 (86%)	14 (100%)	.14
1.5 grams IV every 8 hours of TOL-TAZ	2 (14%)	0	.14
1-hour TOL-TAZ infusion	14 (100%)	10 (71%)	.04
3-hour TOL-TAZ infusion	0	4 (29%)	.04
Duration of TOL-TAZ therapy	15 (8–22)	8.5 (6–14)	.32
Combination therapy for > 48 hours	6 (43%)	4 (29%)	.43
No source control[a]	4 (29%)	0	.04

Variable	≥4-fold increase in MIC (22, 32%)	<4-fold increase in MIC (47, 68%)	*P* value
Intensive care unit on day 1 of infection	13 (59%)	39 (64%)	0.79
Charlson Comorbidity Index ≥5	6 (27%)	22 (47%)	0.19
Severe immunocompromise	9 (41%)	10 (21%)	0.15
Continuous renal replacement therapy	9 (41%)	8 (17%)	0.04
Cystic fibrosis	2 (9%)	3 (6%)	0.65
Bacteremia	4 (18%)	7 (15%)	0.73
Pneumonia	14 (64%)	26 (55%)	.61
Uncontrolled source of infection	4 (18%)	5 (10%)	0.45
Combination antibiotic therapy	4 (18%)	7 (15%)	0.73
Number of days ceftolozane-tazobactam or ceftazidime-avibactam administered (median) [IQR]	15 [11–18]	10 [8–15]	0.04

1. Optimize drug exposures with extending infusion time and robust dosages (especial CCRT dosage)
2. Decrease the days of administration

Tamma et al. Clin Infect Dis.2021 Dec 6;73(11):e4599-e4606; Hareza et al. Antimicrob Agents Chemother.2024 Oct 8;68(10):e0090724

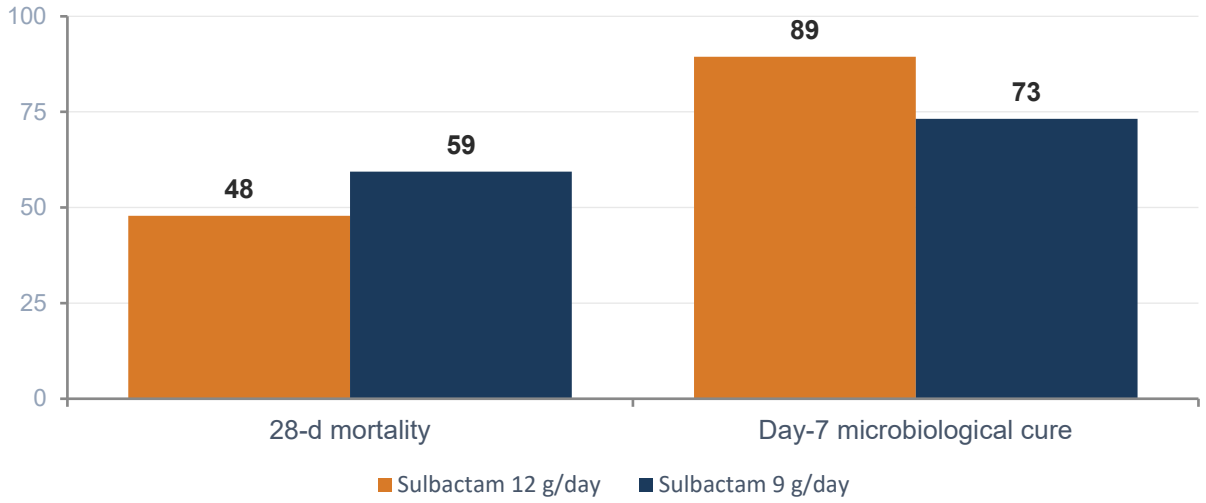
Sulbactam 12 g/day vs 9 g/day

Colistin + sulbactam 9 g vs 12 g/day on mortality in CRAB pneumonia: a randomized controlled trial

*Open-label, single-center **superiority** RCT, Thailand (2019–2023)*

POPULATION	INTERVENTION	COMPARISON	PRIMARY ENDPOINT
N = 138 CRAB pneumonia	Colistin + sulbactam, both arms	12 g/day vs 9 g/day sulbactam	28-day all-cause mortality

Outcomes: 12 g/day vs 9 g/day (%)



Key results — sulbactam 12 g/day vs 9 g/day

aHR 0.54
28-day mortality (adjusted)
95% CI 0.33 – 0.87 · P = 0.011

89.4%
Day-7 microbiological cure
vs 73.2% (9 g/day) · P = 0.02

P 0.158
Unadjusted 28-d mortality
47.8% vs 59.4% · not significant

- Sulbactam 12 g/day was not superior to 9 g/day (unadjusted 28-d mortality).
- After **adjustment**, sulbactam 12 g/day was associated with lower 28-day mortality and higher day-7 microbiological cure.
- Sulbactam MICs in this cohort were unusually high (MIC_{50} 96 µg/mL; ~47.5% ≥256 µg/mL, vs 64–192 µg/mL in prior reports).

Int J Infect Dis.2024 Dec:149:107267.