三軍總醫院

Tri-Service General Hospital

Managing Carbapenem-resistant Gram-negative bacilli in ICU, from global guidelines to local experience

三軍總醫院胸腔內科

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Outline

- **Carbapenem-Resistant Gram-Negative Bacteria (CR-GNB) burden in clinical practice**

- **Carbapenem-Resistant *Enterobacterales* (CRE)**
  - Prevalence、resistant mechanism、treatment

- **Difficult-to-Treat Resistance *Pseudomonas aeruginosa* (DTR PA)**
  - Prevalence、resistant mechanism、treatment

- **Carbapenem-Resistant *Acinetobacter baumannii* (CRAB)**
  - Prevalence、resistant mechanism、treatment

2016至2025年醫學中心加護病房**肺炎**常見之醫療照護相關感染菌種排名

PNEU	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
菌種	排名	排名	排名	排名	排名	排名	排名	排名	排名	排名
Pseudomonas aeruginosa	1	1	1	1	1	1	2	2	1	1
Klebsiella pneumoniae	2	2	2	2	2	2	1	1	2	2
Stenotrophomonas maltophilia	5	5	4	3	3	3	3	3	4	3
Acinetobacter baumannii	3	3	3	4	4	4	4	4	3	4
Staphylococcus aureus	4	6	5	5	5	5	5	6	5	5
Serratia marcescens	7	8	8	11	9	10	6	10	8	6
Enterobacter species	6	4	6	6	8	7	8	8	6	7
Chryseobacterium indologenes	10	10	11	12	9	12	12	7	10	8
Escherichia coli	8	7	6	9	6	6	11	5	8	9
Enterobacter cloacae complex	-	22	12	7	23	10	10	10	7	10

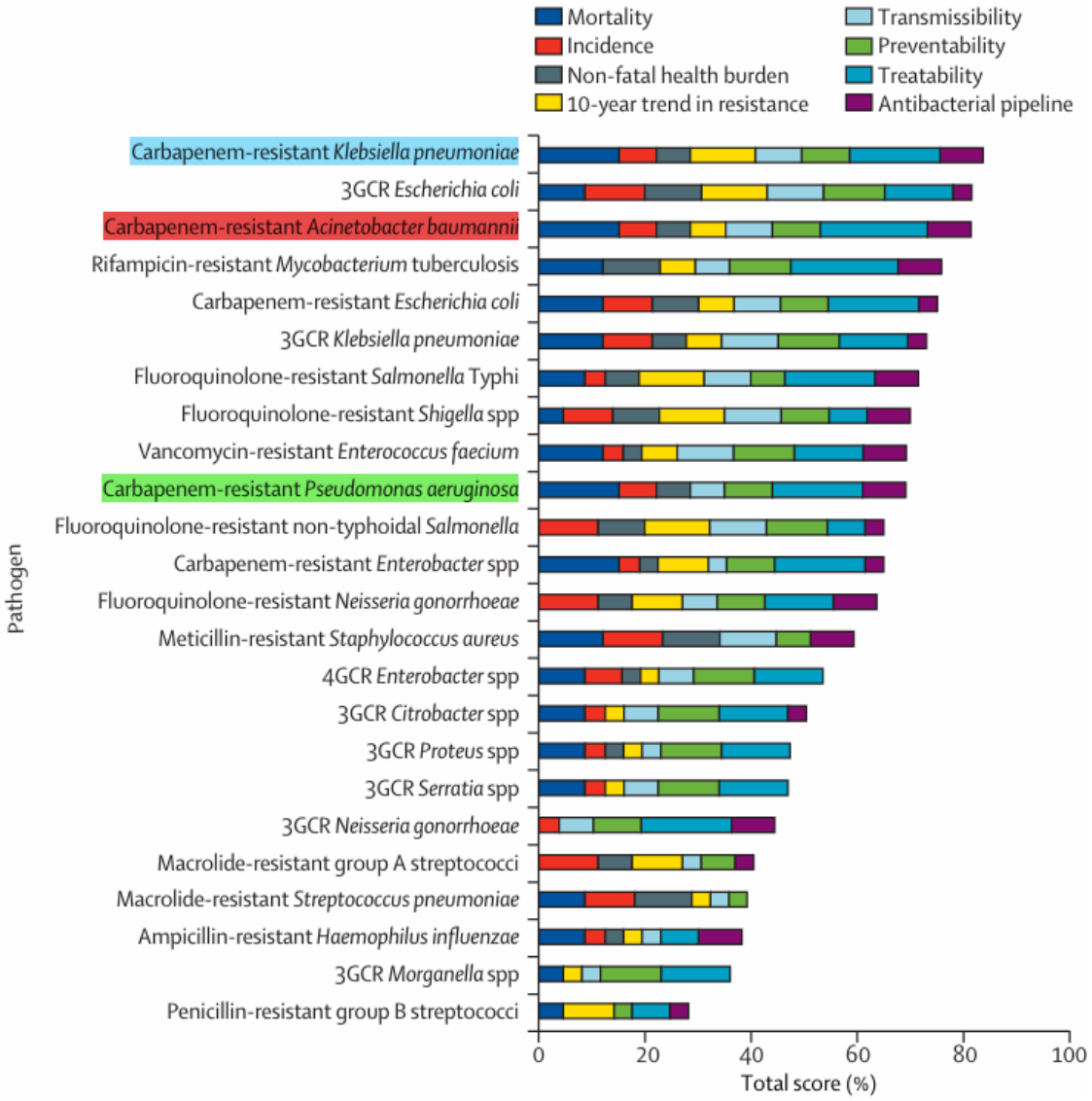
Bacterial pathogen priority tiers 2017 versus 2024

	2017	2024
Critical priority	*Acinetobacter baumannii*, carbapenem-resistant; *Pseudomonas aeruginosa*, carbapenem-resistant; Enterobacteriaceae, carbapenem-resistant, third-generation cephalosporin-resistant	*A baumannii*, carbapenem-resistant; Enterobacterales, third-generation cephalosporin-resistant; Enterobacterales, carbapenem-resistant; *Mycobacterium tuberculosis*, rifampicin-resistant*
High priority	*Enterococcus faecium*, vancomycin-resistant; *Staphylococcus aureus*, meticillin-resistant, vancomycin intermediate and-resistant; *Helicobacter pylori*, clarithromycin-resistant; *Campylobacter* spp, fluoroquinolone-resistant; salmonellae, fluoroquinolone-resistant; *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant	*Salmonella enterica* serotype Typhi, fluoroquinolone-resistant; *Shigella* spp, fluoroquinolone-resistant; *E faecium*, vancomycin-resistant; *P aeruginosa*, carbapenem-resistant; non-typhoidal *Salmonella*, fluoroquinolone-resistant; *N gonorrhoeae*, third-generation cephalosporin-resistant, fluoroquinolone-resistant; *S aureus*, meticillin-resistant
Medium priority	*Streptococcus pneumoniae*, penicillin non-susceptible; *Haemophilus influenzae*, ampicillin-resistant; *Shigella* spp, fluoroquinolone-resistant	Group A streptococci, macrolide-resistant; *S pneumoniae*, macrolide-resistant; *H influenzae*, ampicillin-resistant; group B streptococci, penicillin-resistant

Pathogens are streamlined by family or order and categorised into three priority tiers. *Rifampicin-resistant *M tuberculosis* was included after an independent analysis with parallel criteria and subsequent application of the multicriteria decision analysis matrix.

Table 2: **Comparative overview of bacterial pathogen priority tiers, 2017 versus 2024**

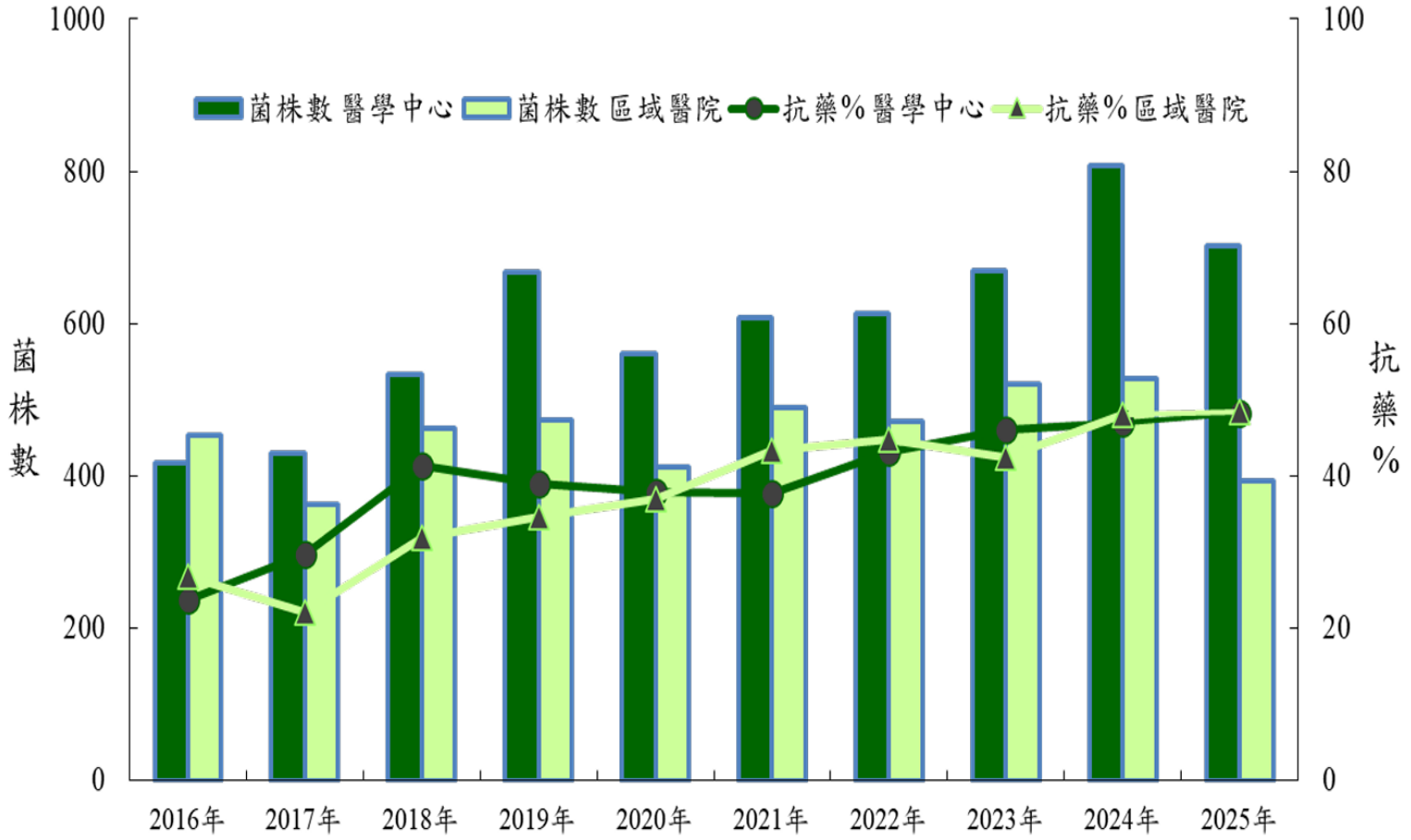
Ranking of antibiotic-resistant bacteria in the 2024 WHO BPPL

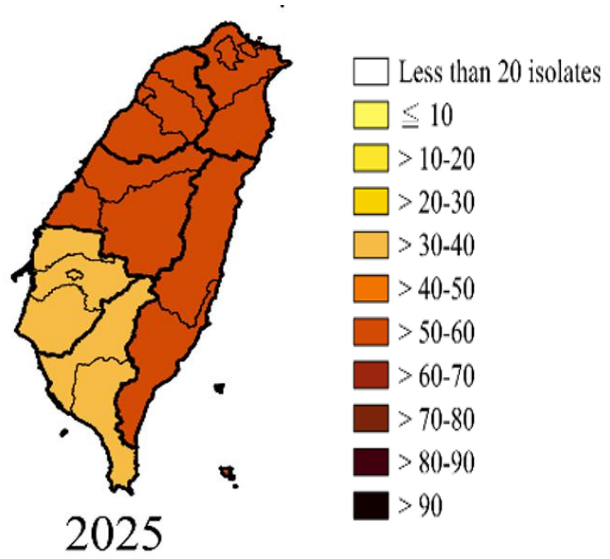


BPPL=Bacterial Priority Pathogens List

Lancet Infect Dis. 2025 Sep;25(9):1033-1043.

2016至2025年醫學中心及區域醫院加護病房醫療照護相關感染 *K. pneumoniae* 菌株總數與 CRKP百分比

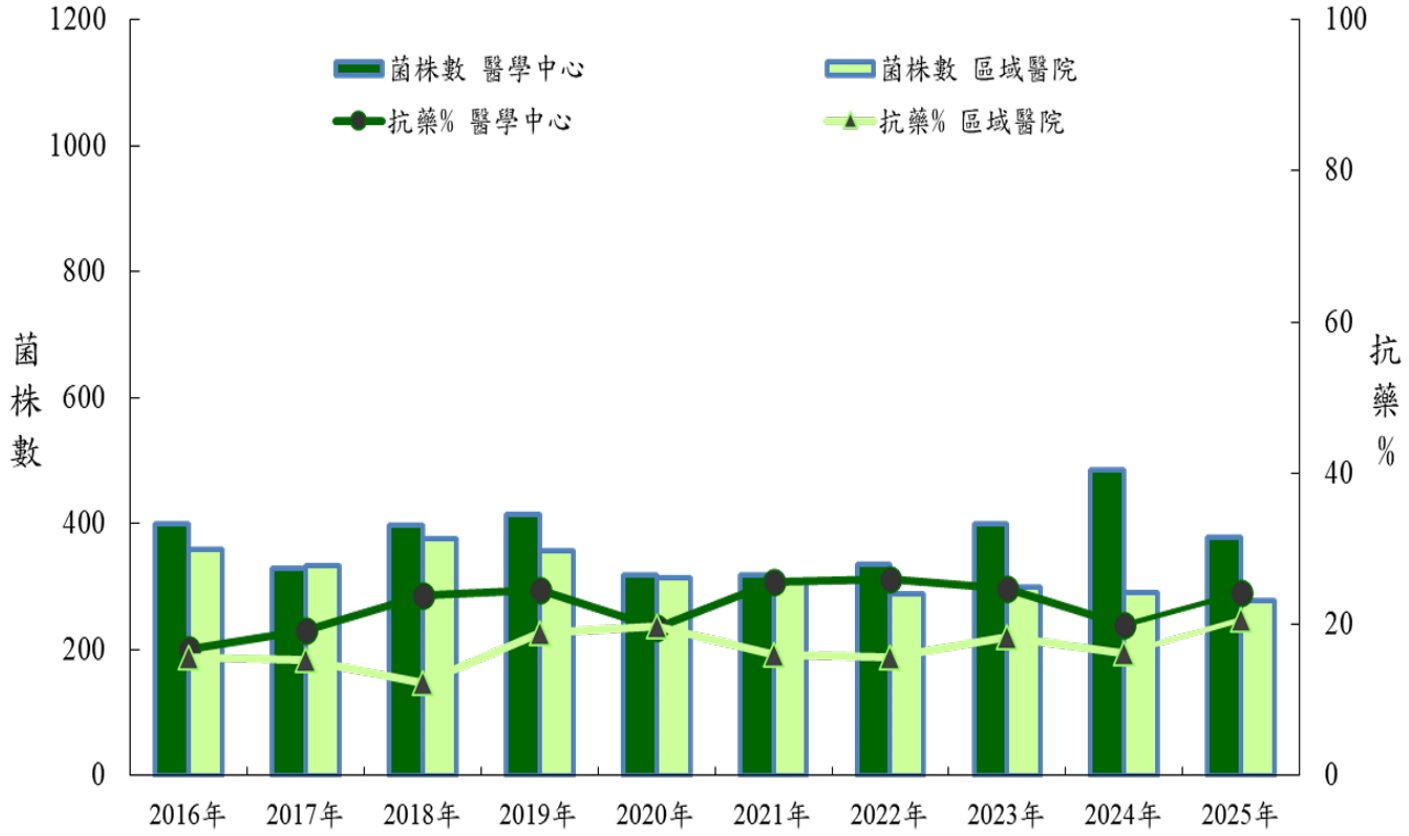


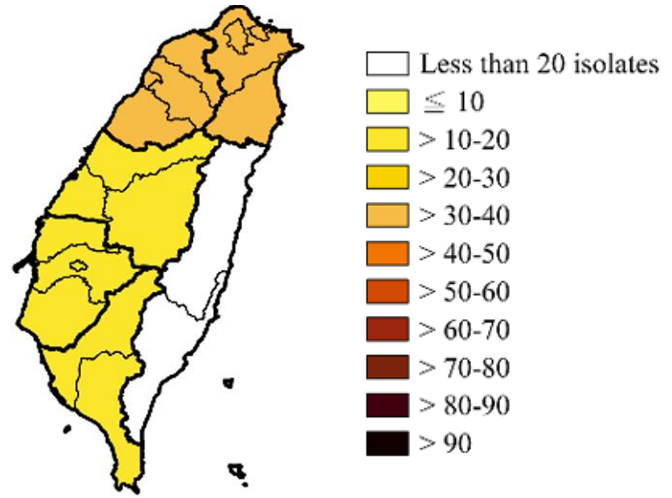


東區（59.1%），
北區（56.7%）

CRKP：對 carbapenem 類中的 imipenem、meropenem、ertapenem 或 doripenem 任一抗生素具抗藥性之KP。

2016至2025年醫學中心及區域醫院加護病房醫療照護相關感染 *P. aeruginosa* 菌株總數與 CRPA百分比



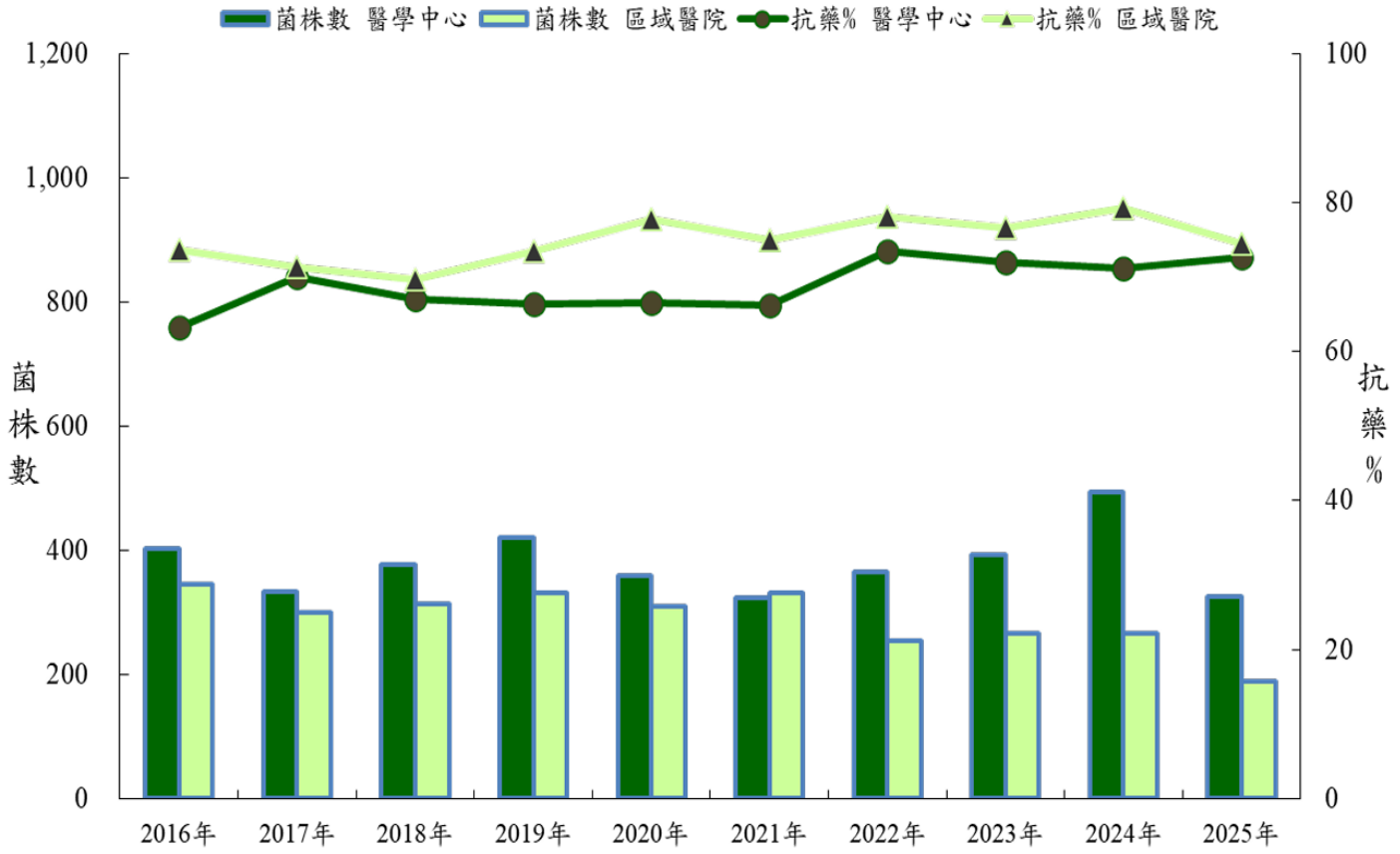


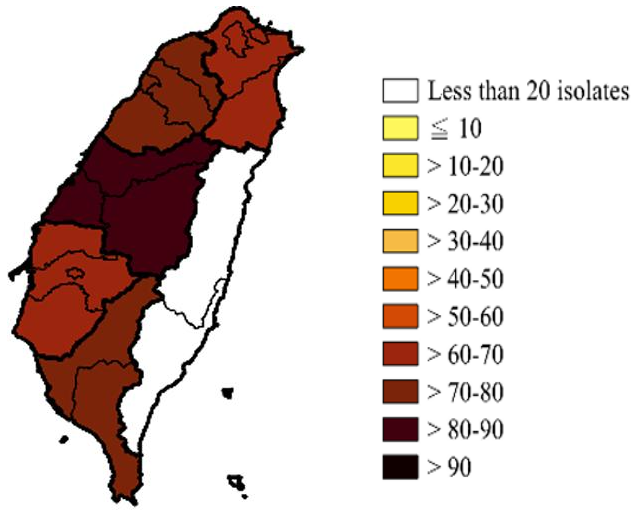
2025

北區（38.5%）
台北區（30.6%）

CRPA：對carbapenem 類中的imipenem 或meropenem 任一抗生素具抗藥性之*Pseudomonas aeruginosa*。

2016至2025年醫學中心及區域醫院加護病房醫療照護相關感染 *Acinetobacter baumannii-calcoaceticus* complex 菌株總數與 CRAB 百分比





2025

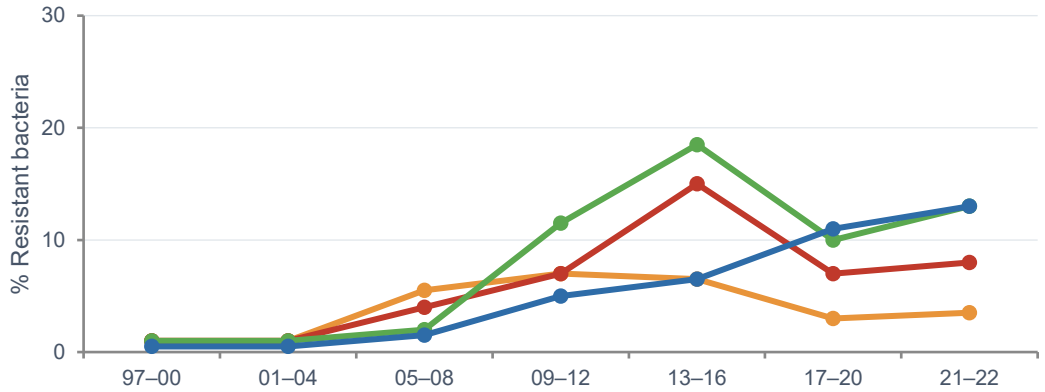
中區（82.2%）
北區（76.5%）

CRAB：對carbapenem 類中的imipenem 或meropenem 任一抗生素具抗藥性之AB。

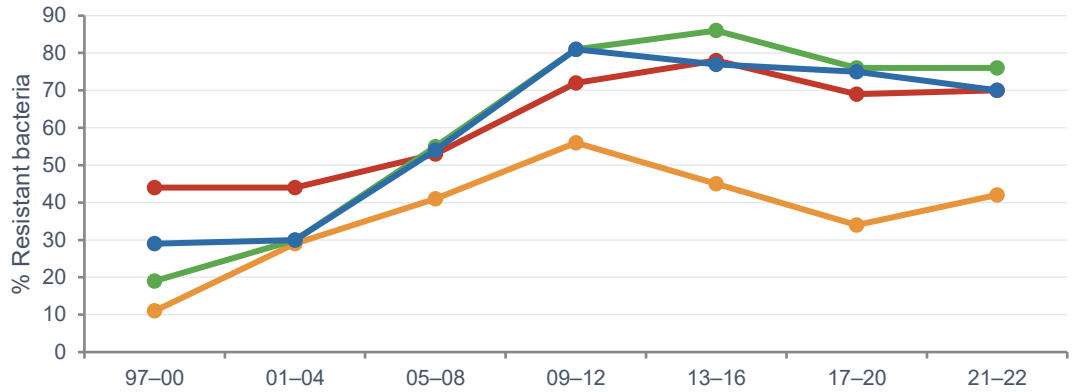
Carbapenem resistance keeps rising; CRAB exceeds 70% in most regions

Regional trends in % resistant isolates, 1997–2022, and attributable deaths in 2019

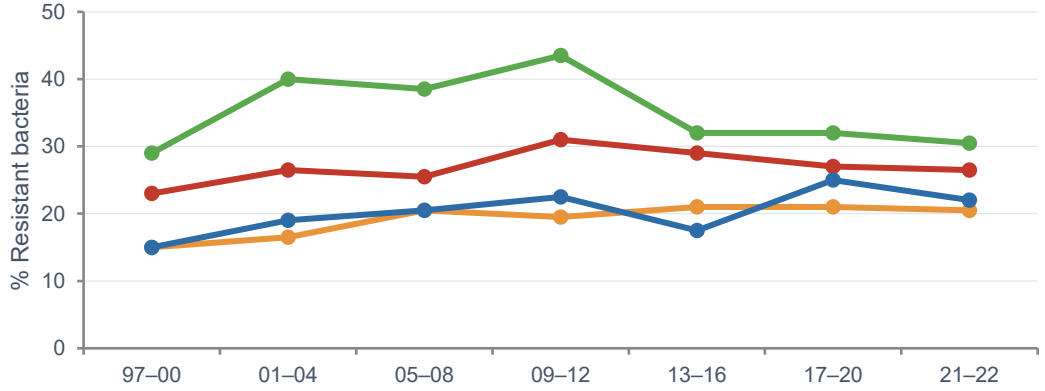
CRE



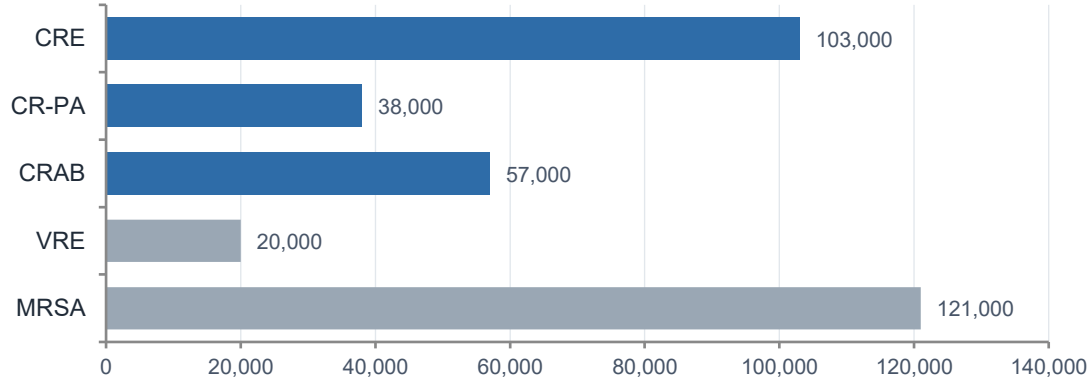
CRAB



CR-PA



Worldwide deaths due to AMR bacteria, 2019



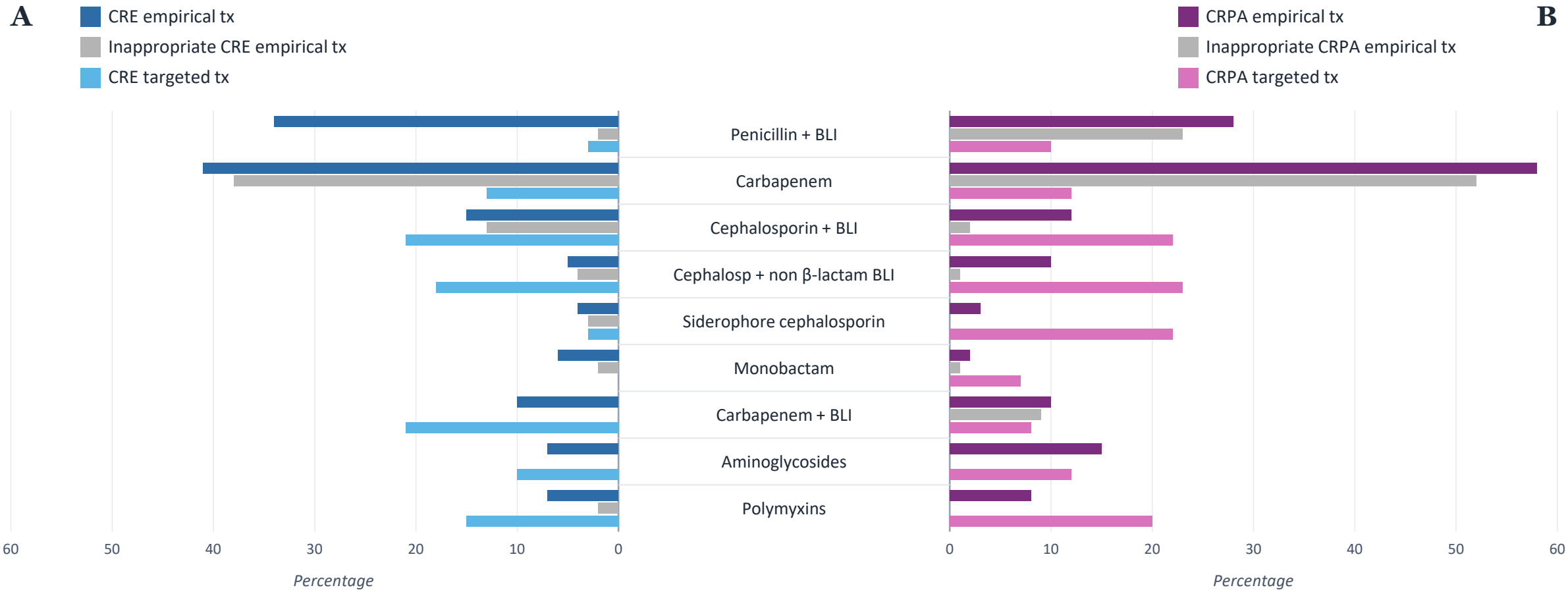
North America Europe Latin America Asia–Pacific

Nat Rev Microbiol. 2024 Oct;22(10):598-616.

High rates of inappropriate empirical therapy in CRE & CRPA

A multicenter prospective cohort study in Italy • **CRE** (n = 98) • **CRPA** (n = 60)

Antibiotic classes against gram-negative bacteria — used as empirical, inappropriate empirical, and targeted therapy



Overall, empiric therapy was inappropriate in **59.2% (77/130)** of analysed patients.
Inappropriateness was higher for **CRE (74%)** — 73.1% for KPC-producing and 80% for MBL-CRE — than for **CRPA (37.7%)**.

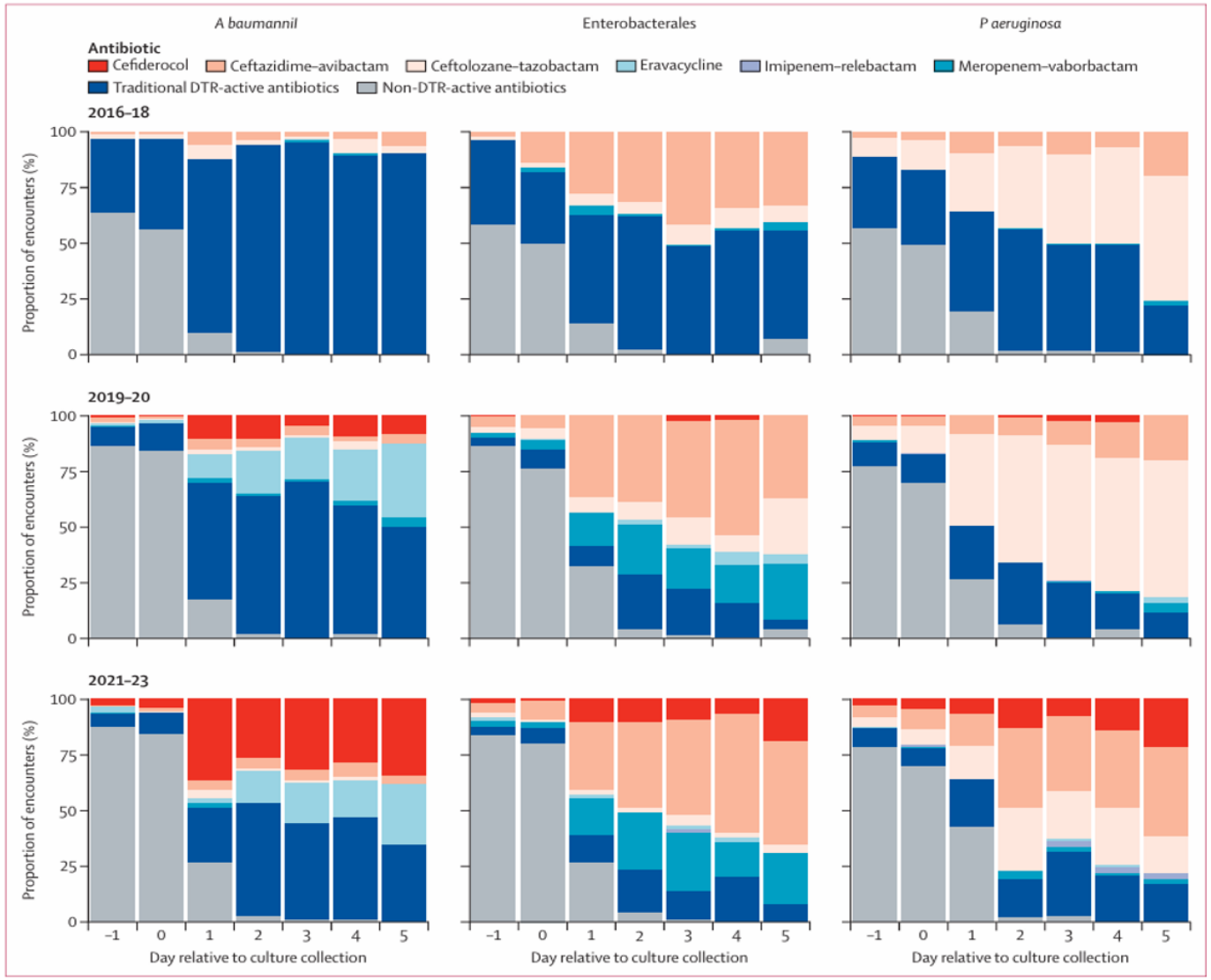
Survival trends in patients with difficult-to-treat, antibiotic-resistant, Gram-negative infections in the era of next-generation antibiotics in the USA: a retrospective cohort study

Morgan K Walker, Christina Yek, Sadia Sarzynski, Sarah Warner, Anthony D Harris, Jonathan D Baghdadi, Katherine E Goodman, John H Powers III, Michael Klompas, Chanu Rhee, Bruce Swihart, Sameer S Kadri, for the NIH Antimicrobial Resistance Outcomes Research Initiative (NIH-ARORI)

Lancet Infect Dis.2026 Mar 25:S1473-3099(26)00020-4.

Newer DTR-active agents increasingly replace traditional therapy after culture collection

Antibiotic type by day relative to culture collection (day 0), across three eras and three DTR pathogen groups



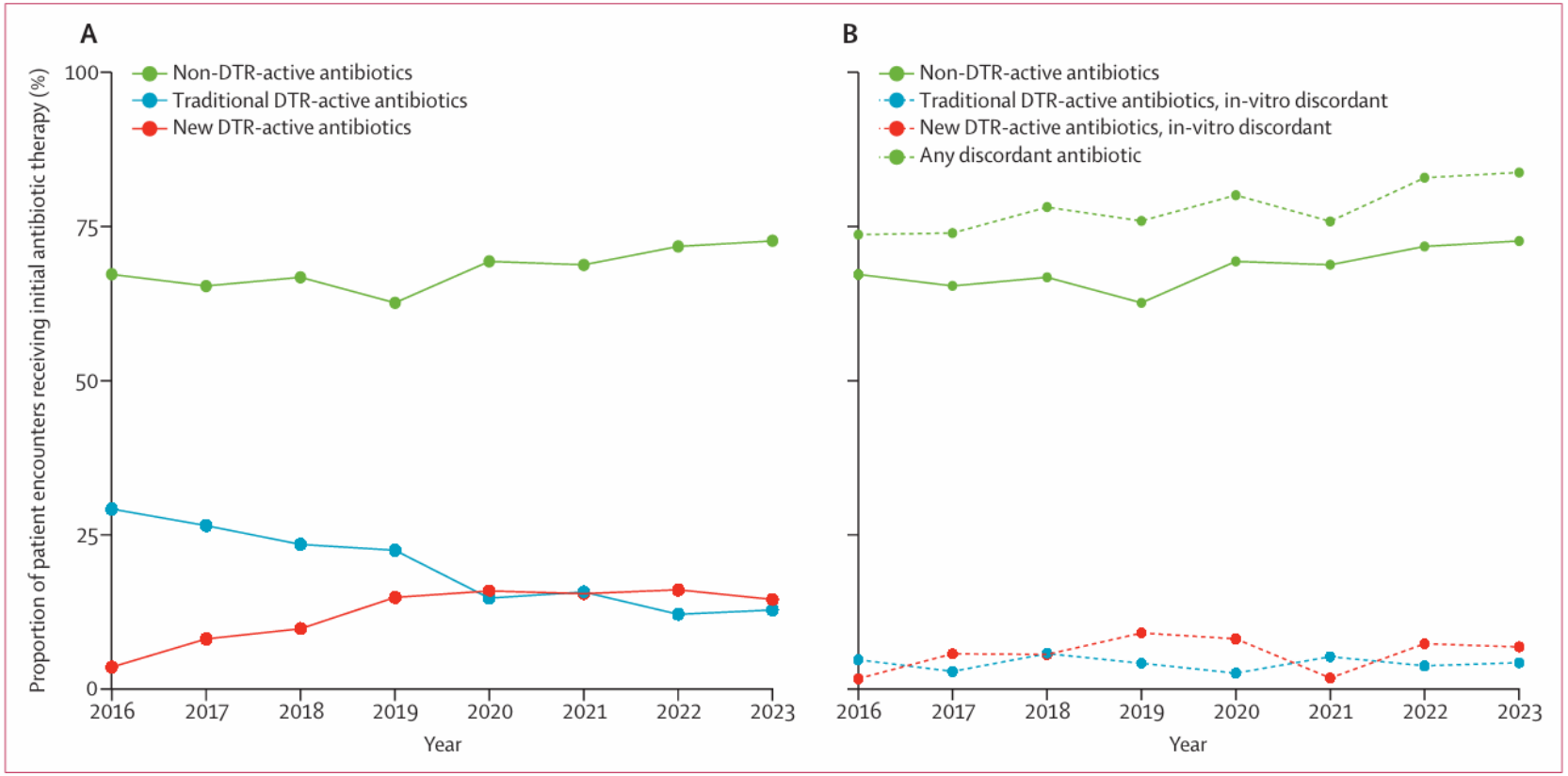
- Retrospective cohort study in the USA
- Between Jan 1, 2016, and Aug 31, 2023, 9384 patients with DTR organisms
- Across eras (2016–18 → 2021–23), newer agents expand sharply: **cefiderocol** becomes prominent for *A. baumannii*; **ceftazidime–avibactam / ceftolozane–tazobactam** dominate later therapy for *P. aeruginosa* and *Enterobacterales*.
- Net effect: **traditional DTR drugs** recede as **newer DTR-active agents** take over directed treatment.

DTR: difficult-to-treat resistant (resistance to all fluoroquinolones, carbapenems and other β-lactams, excluding new drugs)

Lancet Infect Dis.2026 Mar 25:S1473-3099(26)00020-4.

Initial therapy stays empiric and often microbiologically discordant.

(A) class of initial antibiotic therapy, 2016–2023; (B) in-vitro discordance of initial therapy



Initial class (A)

Traditional DTR-active: ~29% (2016) → ~12% (2023)
New DTR-active: ~3% → ~15%
Non-DTR-active: steady ~63–73%

Discordance (B)

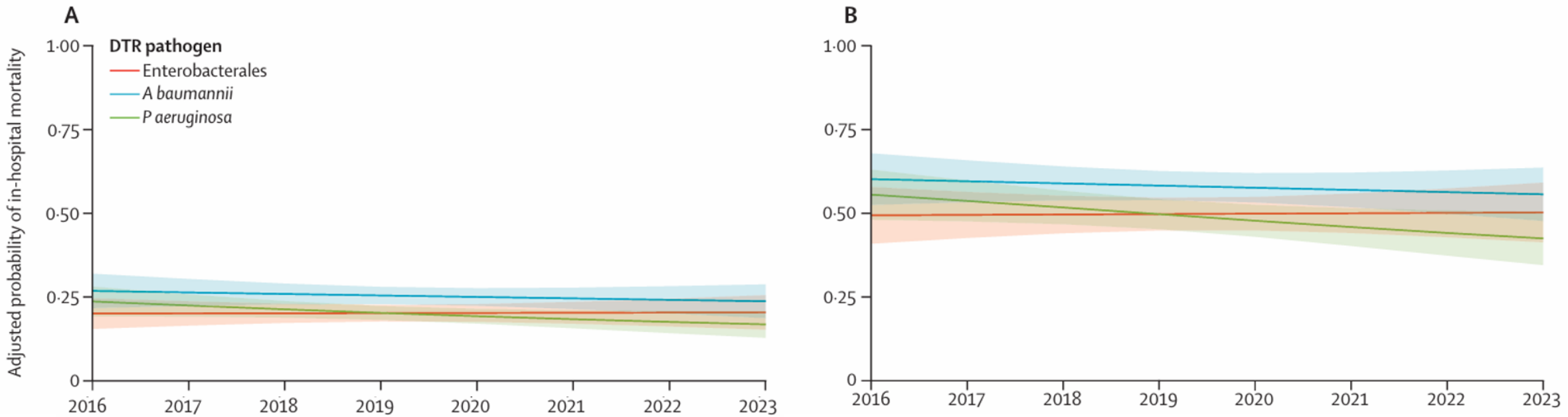
Most initial therapy is empiric and frequently **in-vitro discordant**.
Any discordant antibiotic rose to ~83% by 2023.

New DTR-active antibiotics : ceftolozane–tazobactam, ceftazidime avibactam, meropenem–vaborbactam, imipenem– relebactam, omadacycline, and cefiderocol)
DTR: difficult-to-treat resistant (resistance to all fluoroquinolones, carbapenems and other β-lactams, excluding new drugs)

Lancet Infect Dis.2026 Mar 25:S1473-3099(26)00020-4.

Adjusted in-hospital mortality changed little from 2016 to 2023

Adjusted predicted probability of in-hospital mortality, by DTR pathogen



Overall patients

Overall (A): mortality is broadly flat (~0.20–0.27)
A. baumannii highest (~0.27 → 0.24).

High-risk patients (SOFA score >1, Elixhauser Comorbidity Index >5, and sepsis)

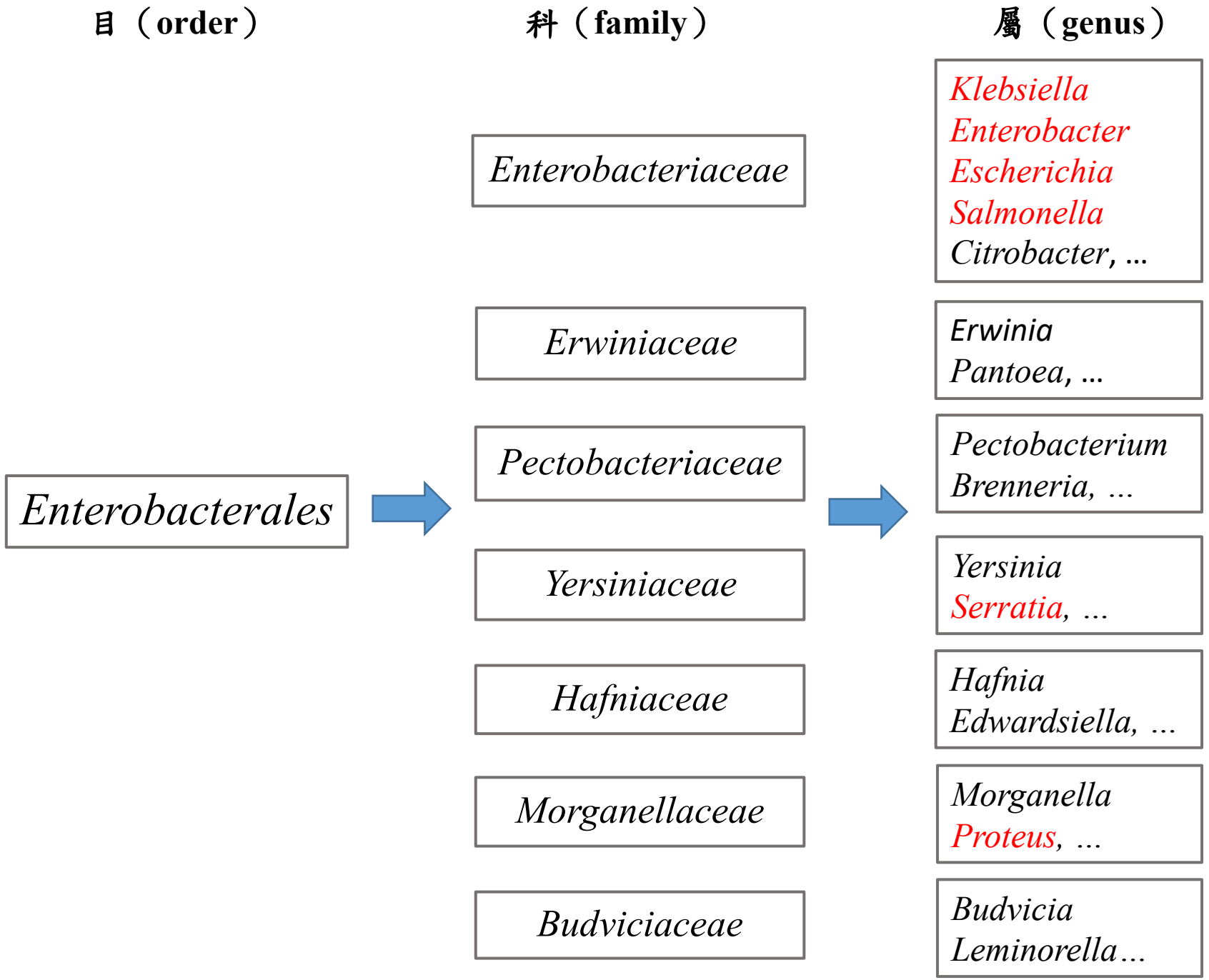
High-risk (B): mortality is far higher (~0.5–0.6).
A. baumannii stays ~0.6
P. aeruginosa declines (~0.5 → 0.43)
Enterobacterales flat ~0.5

- Despite rising use of newer DTR-active agents, adjusted mortality did not meaningfully improve.
- Prompt recognition of both the pathogen and resistance phenotype could be a crucial component in reducing mortality.

Lancet Infect Dis.2026 Mar 25:S1473-3099(26)00020-4.

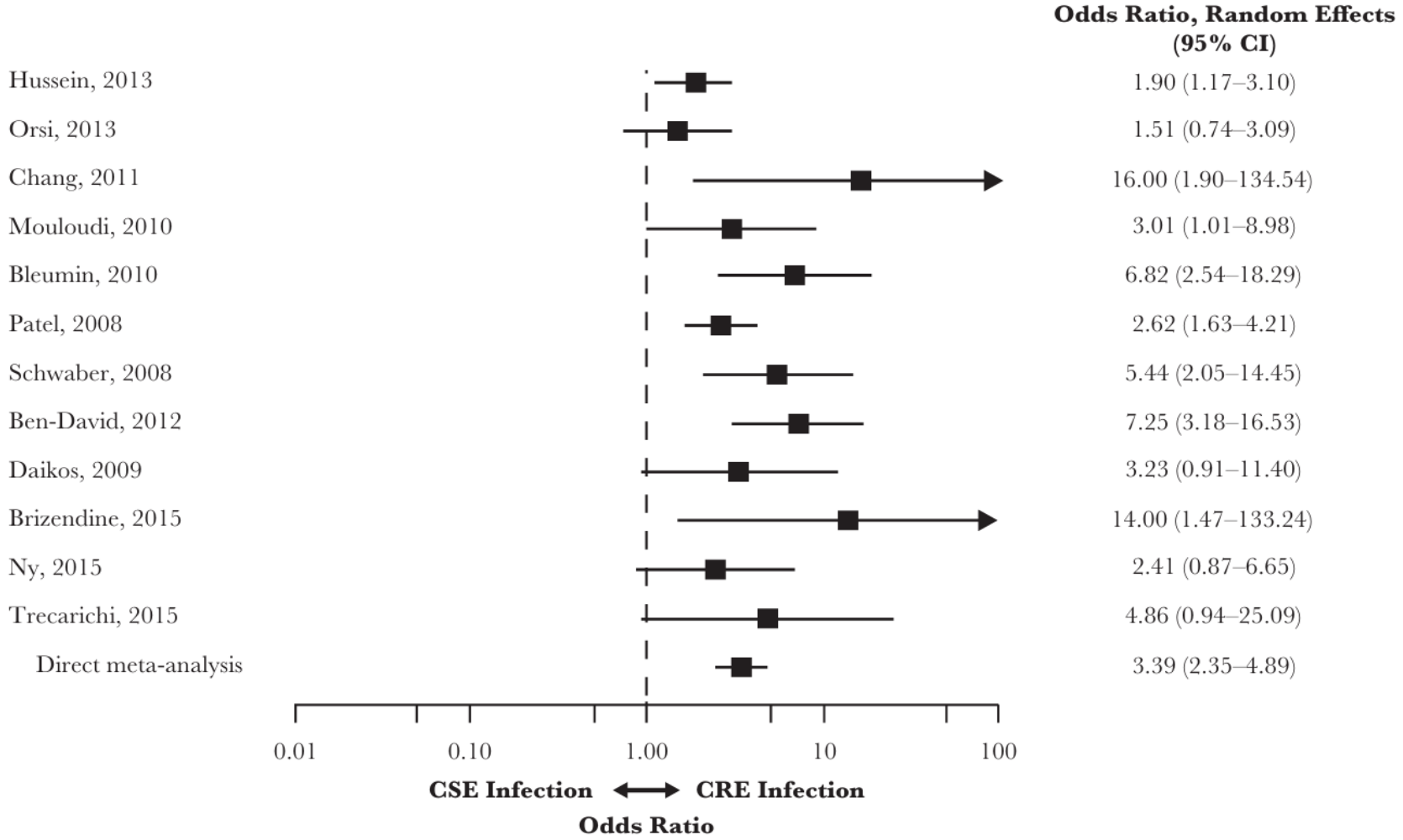
Carbapenem-Resistant *Enterobacterales* (CRE)

CRE are defined as members of the *Enterobacterales* order resistant to at least 1 carbapenem antibiotic (ie, ertapenem, meropenem, imipenem, doripenem) or producing a carbapenemase enzyme.



Int J Syst Evol Microbiol . 2016 Dec;66(12):5575-5599

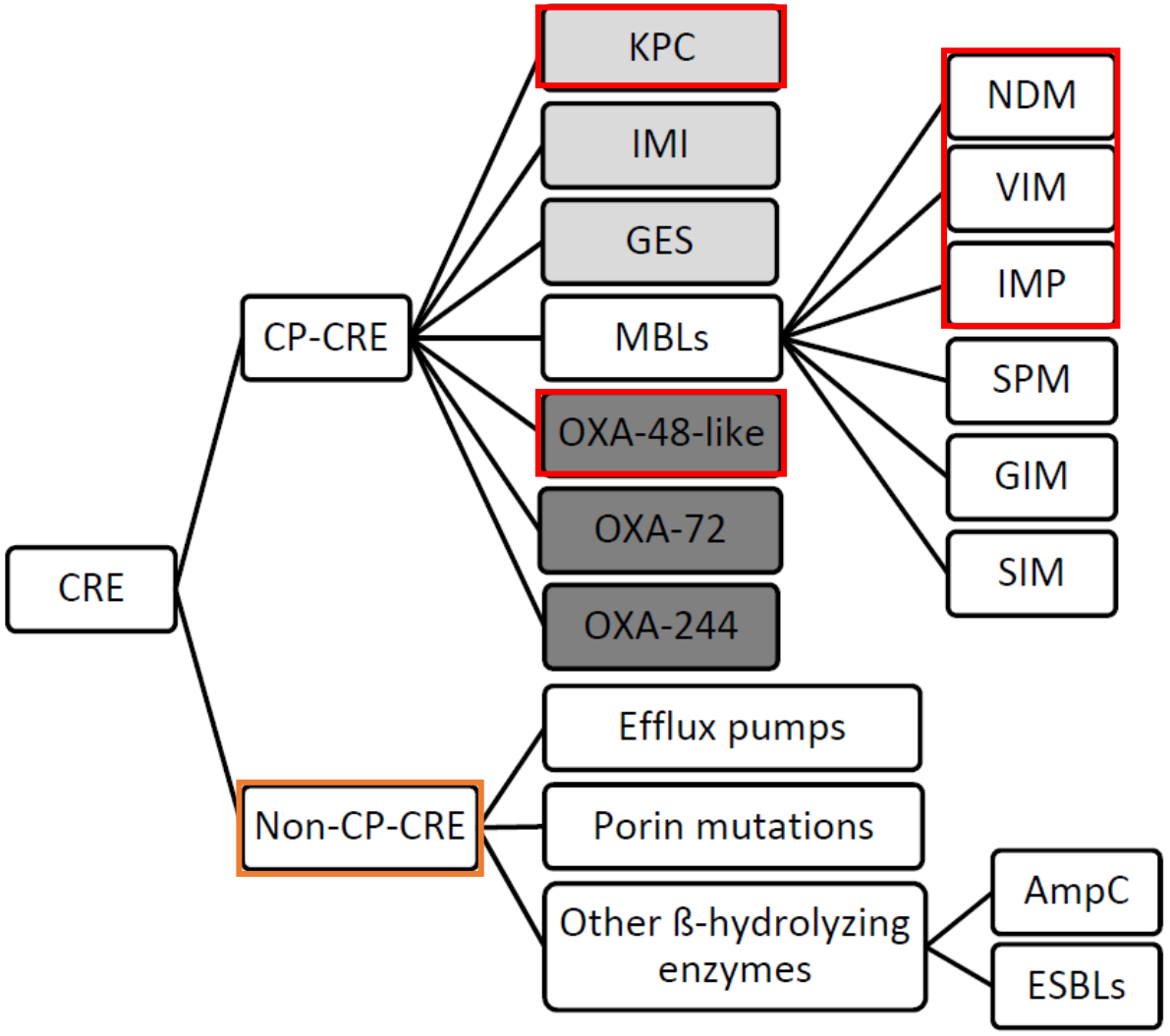
Mortality in patients with CRE vs CSE infections



CSE: carbapenem- susceptible *Enterobacteriaceae*.
Data for overall mortality were analyzed using 30-day or in-hospital mortality.

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

Classification of the different mechanisms of drug resistance in CRE



Ambler class:

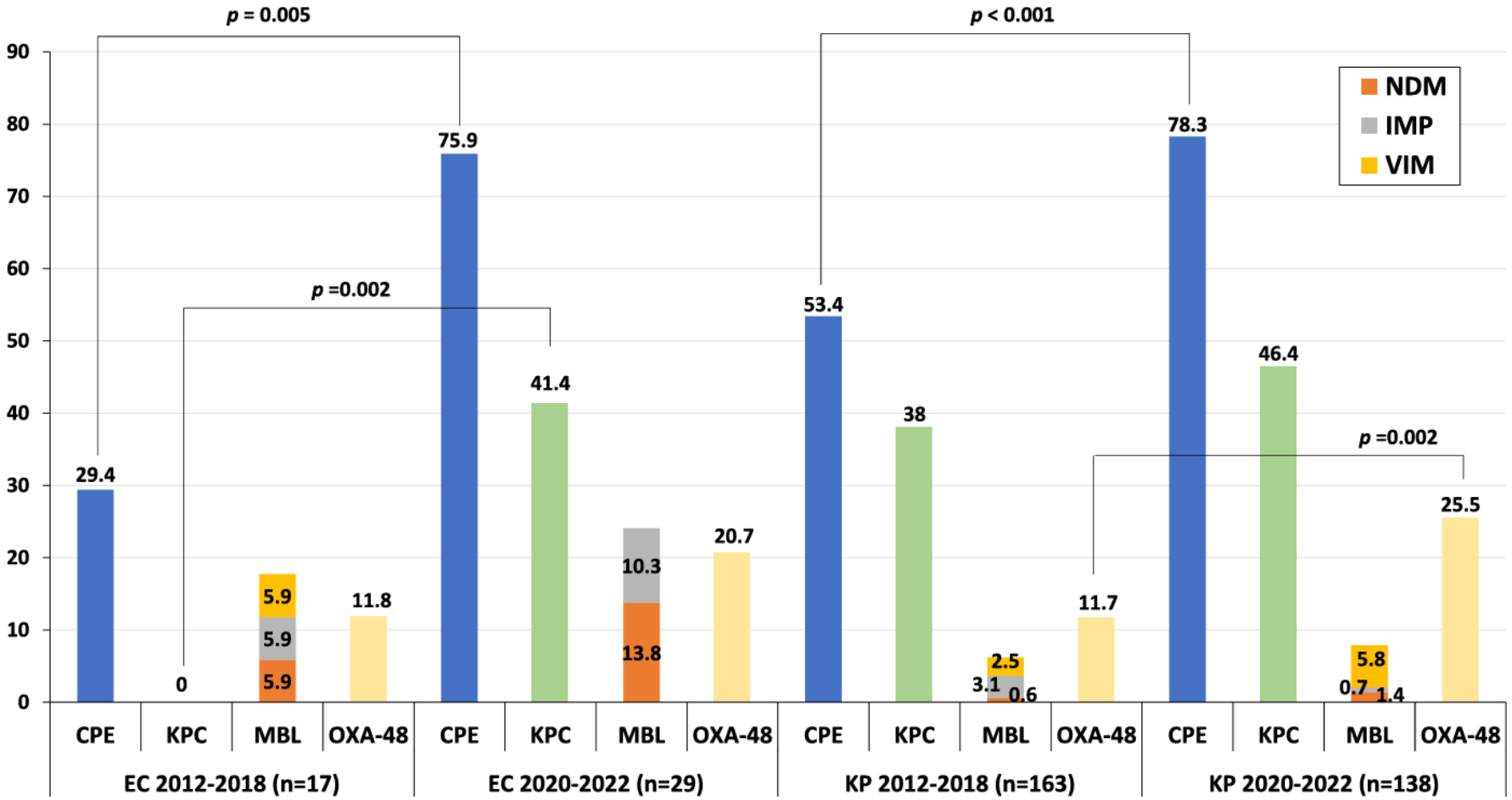
A B D

CP: carbapenemase producing

Antibiotics (Basel). 2019 Aug 19;8(3):122.

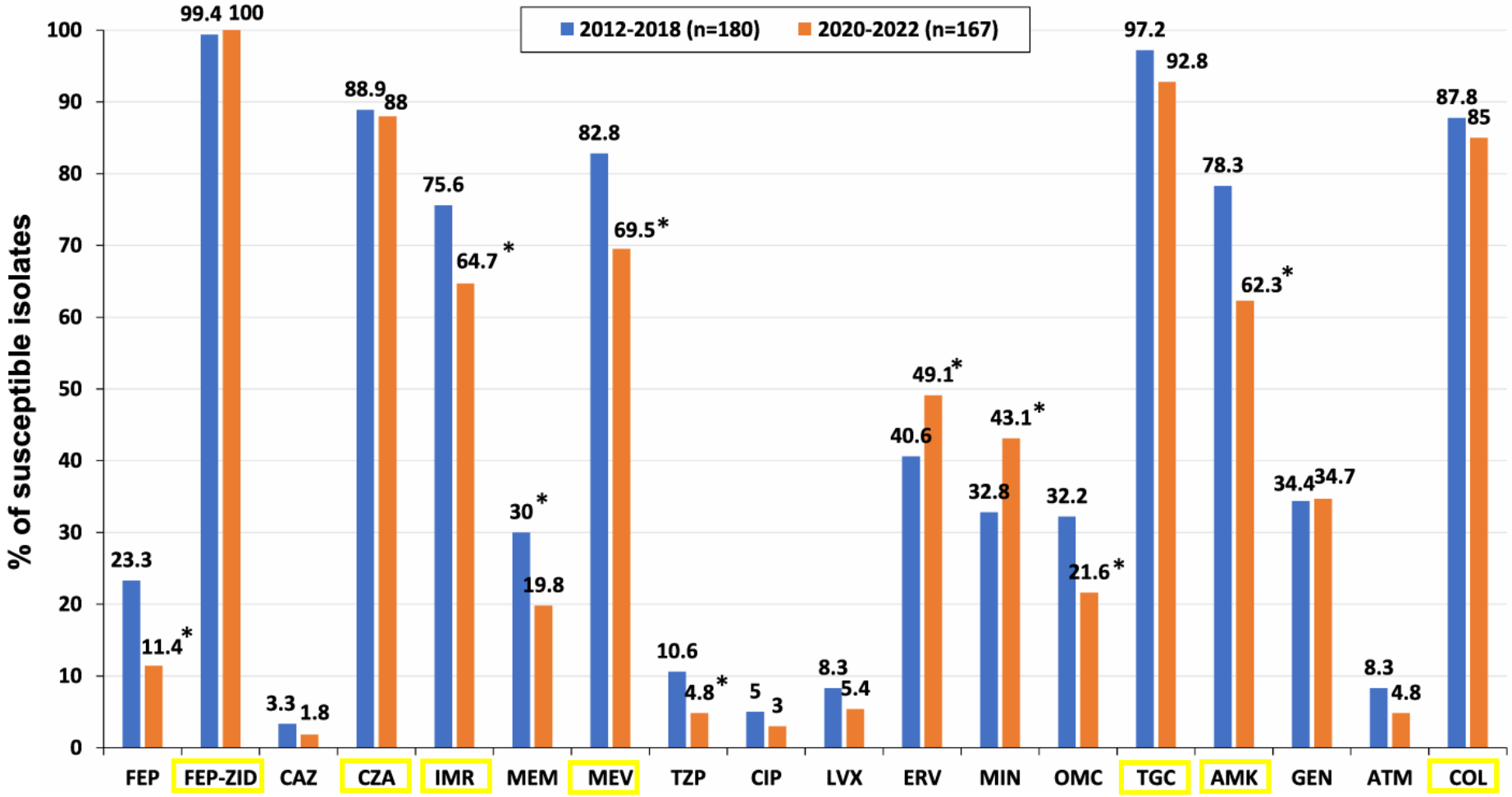
Proportion of β-Lactamase genes for imipenem-non-susceptible *Escherichia coli* and *Klebsiella pneumoniae* between 2012–2018 and 2020–2022

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



CPE: Carbapenemase-producing *Enterobacteriaceae*

In vitro susceptibility to antibiotics among imipenem-non-susceptible *Escherichia coli* and *Klebsiella pneumoniae* between 2012–2018 (n = 180) and 2020–2022 (n = 167)



FEP: cefepime; FEP-ZID: cefepime-zidebactam; CAZ: ceftazidime; CZA: ceftazidime-avibactam; IMR: imipenem-relebactam; MEM: meropenem; MEV: meropenem-vaborbactam; TZP: piperacillin-tazobactam; CIP: ciprofloxacin; DLX: delafloxacin; LSFX: lascufloxacin; LVX: levofloxacin; ERV: eravacycline; MIN: minocycline; OMC: omadacycline; TGC: tigecycline; AMK: amikacin; GEN: gentamicin; ATM: aztreonam; COL: colistin.

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

Susceptibility of imipenem-non-susceptible bacteria with different genotypes and phenotypes

Species with different genotypes and phenotypes	No.	% susceptible								
		FEP[a]	FPZ	CAZ	CZA	IPM	IMR	MEM	MEV	CZT
E. coli and *K. pneumoniae*	167	11.4	100	1.8	88	0	64.7	19.8	69.5	5.4
with carbapenemase genes	130	2.3	100	2.3	84.6	0	57.7	6.2	61.5	2.3
with class B carbapenemase genes	18	0	100	0	0	0	0	5.6	27.8	0
with $bla_{\text{KPC-like}}$ only	73	0	100	0	97.3	0	90.4	0	79.5	0
with $bla_{\text{OXA-48-like}}$ only	36	8.3	100	8.3	100	0	22.2	19.4	41.7	8.3
without carbapenemase genes	37	43.2	100	0	100	0	89.2	67.6	97.3	16.2
with ESBL genes[b] only	2	0	100	0	100	0	100	50	100	0
with AmpC genes only	16	93.8	100	0	100	0	93.8	68.8	93.8	31.3
with ESBL and AmpC genes[b]	17	0	100	0	100	0	88.2	70.6	100	0

FEP, cefepime; FPZ, cefepime/zidebactam; CAZ, ceftazidime; CZA, ceftazidime/avibactam; IPM; imipenem; IMR, imipenem/relebactam; MEM, meropenem; MEV, meropenem/vaborbactam. CZT, ceftolozane/tazobactam.

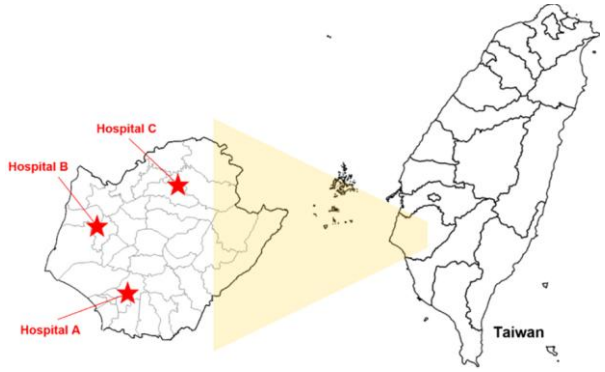
Contents lists available at ScienceDirect

Journal of Infection and Public Health

journal homepage: www.elsevier.com/locate/jiph

A longitudinal seven-year multicenter study on the molecular epidemiology of carbapenemase-producing *Enterobacterales* in Taiwan: The burden of metallo-β-lactamases

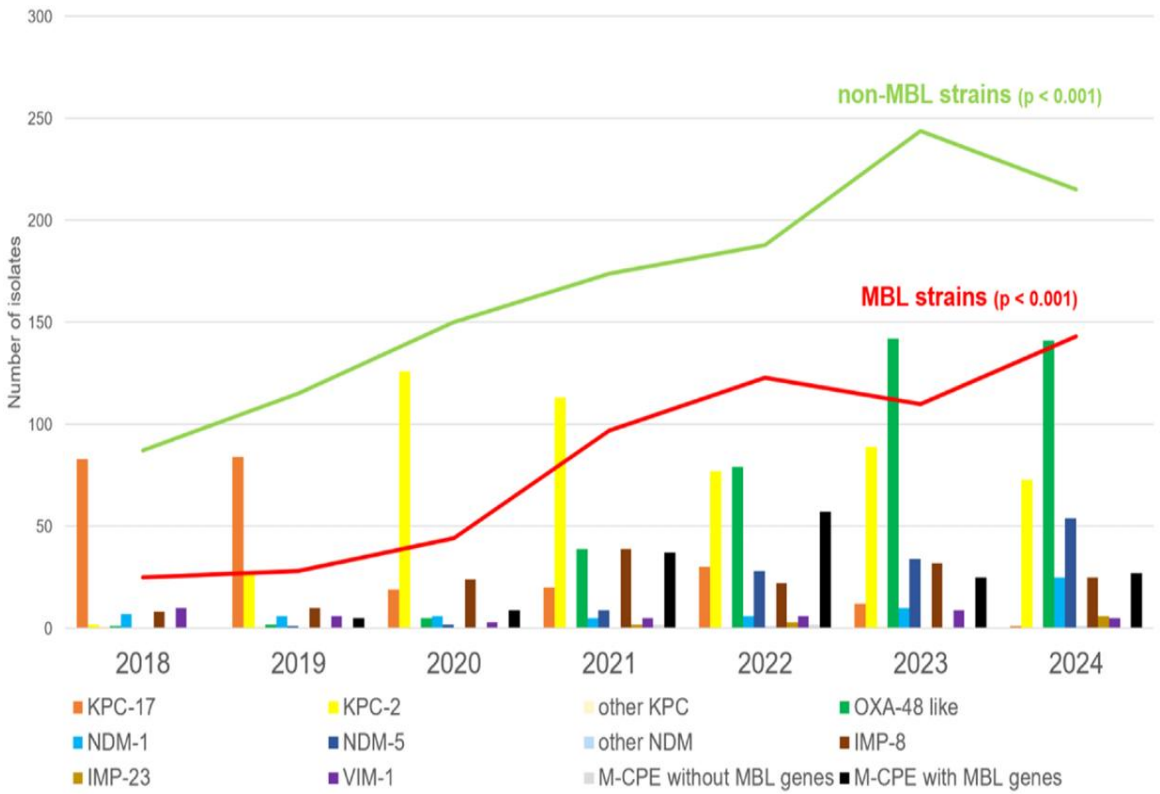
Jin-Wei Liu [a], Chih-Cheng Lai [b], Chi-Chung Chen [c,d], Hsiu-Yin Chou [e], Cheng-Han Li [a], Chia-Hung Tsai [a], Po-An Su [a], Hung-Jen Tang [a], Hung-Jui Chen [a,f,*]



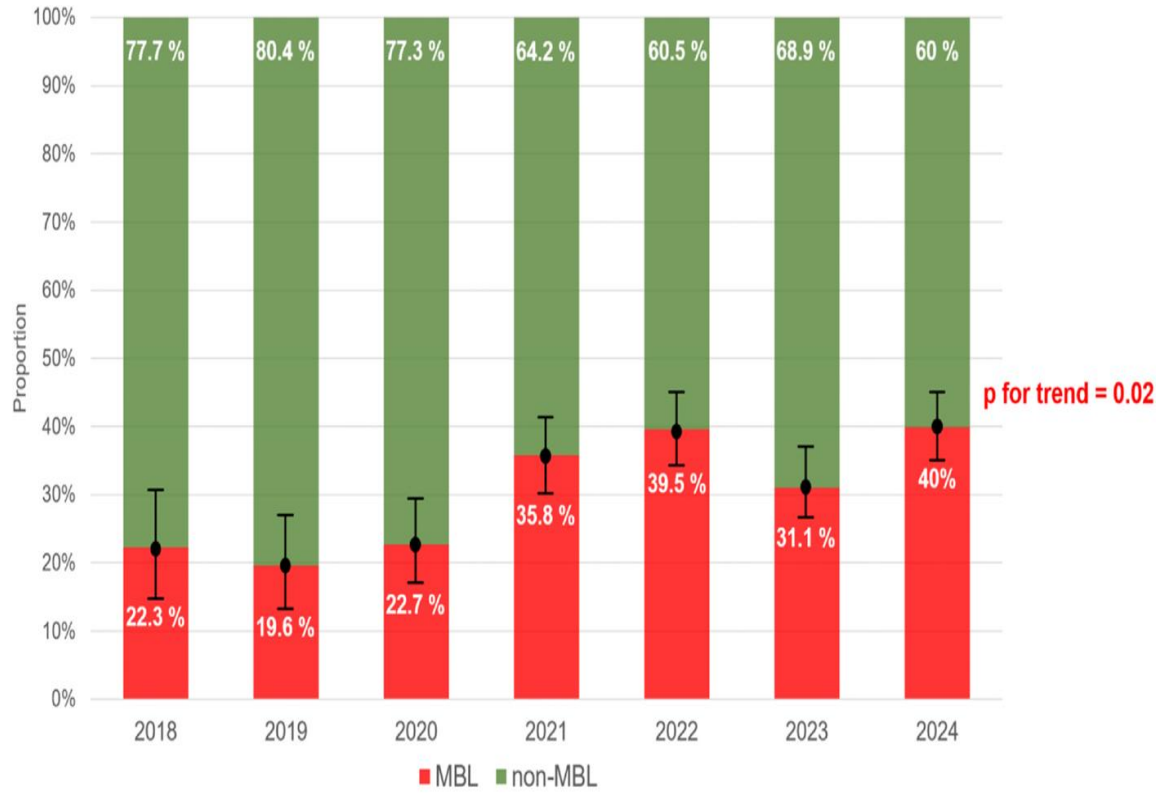
- Chi Mei Medical Center, 2018-2024
- Prospective 7-year surveillance of clinical CRE isolates
- CRE non-susceptible to ≥2 carbapenems were screened for carbapenemase genes by PCR/sequencing

MBL-Producing CPE Increased in Both Isolate Counts and Proportion in Chi Mei Medical Center, 2018–2024

Absolute numbers — count trend (p < 0.001)



MBL share within CPE — p for trend = 0.02



- The absolute number of MBL-CPE increased over time, and the proportion of MBL producers among CPE rose from 22.3% in 2018 to 40.0% in 2024.

J Infect Public Health.2026 Feb;19(2):103052.

Clinically available serine β-lactamase inhibitors and metallo-β-lactamase inhibitors

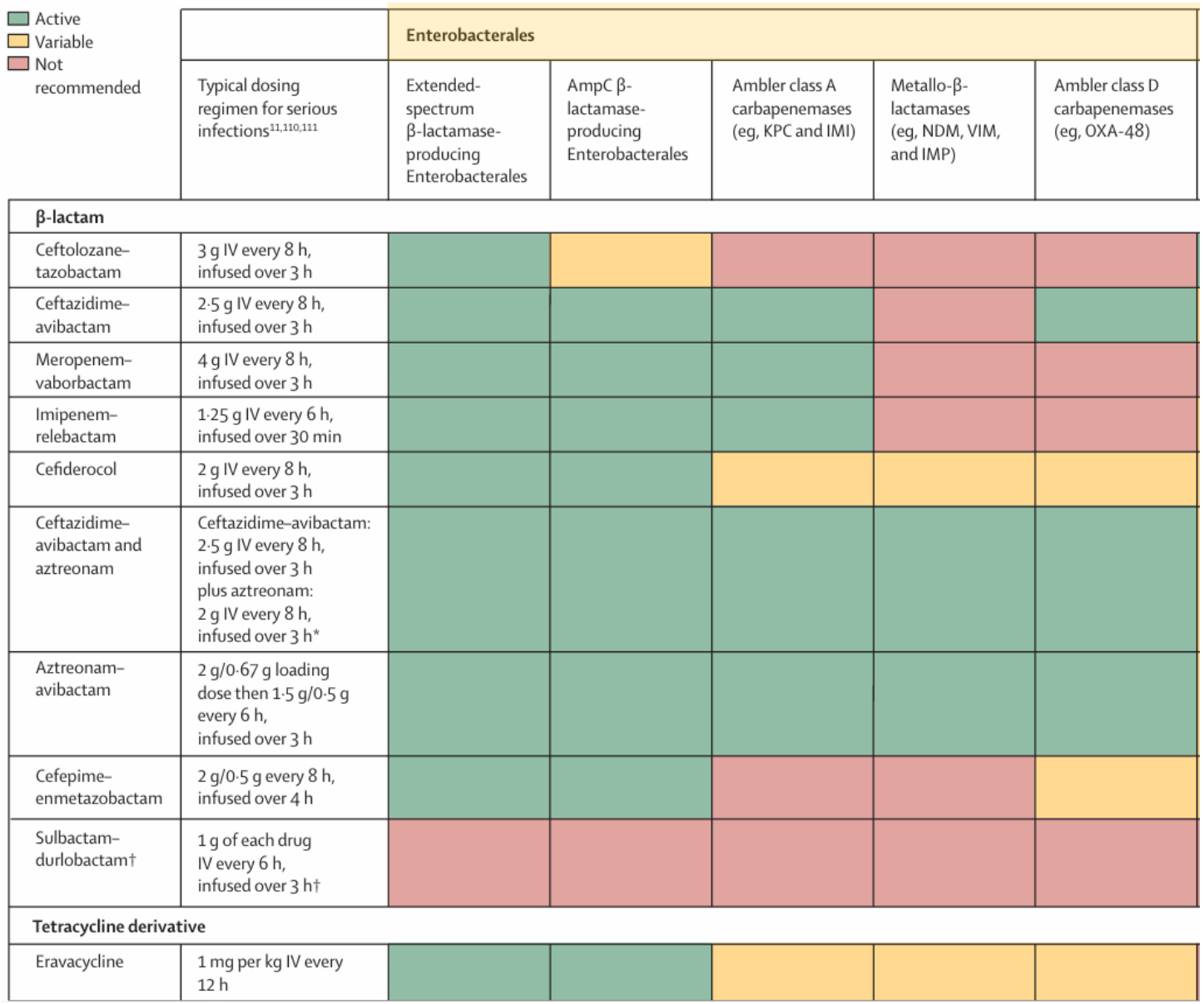
	Year of FDA approval	Clinical trial phase	β-lactam partner	Formulation	Usage	Inhibitor type	Inhibition mechanism	Inhibition profile of the inhibitor					
								Serine β-lactamases				Metallo-β-lactamases	
								Class A (extended-spectrum β-lactamase)	Class A (KPC)	Class C	Class D (OXA 48)	Subclass B1	Subclass B3
Clavulanic acid	1984	..	Amoxicillin	Augmentin	Wide*	First generation	Suicide inhibitor, β-lactam analogue	Yes	No	No	No	No	No
Sulbactam	1987	..	Ampicillin	Unasyn	Wide†	First generation	Suicide inhibitor, β-lactam analogue	Yes	No	No	No	No	No
Tazobactam	1993	..	Piperacillin	Zosyn	Wide‡	First generation	Suicide inhibitor, β-lactam analogue	Yes	No	No	No	No	No
Tazobactam	2014	..	Ceftolozane	Zerbaxa	cIAIs and cUTIs	First generation	Suicide inhibitor, β-lactam analogue	Yes	No	No	No	No	No
Avibactam	2015	..	Ceftazidime	Avycaz (Zavicefta)	cIAIs and cUTIs	Second generation	Reversible inhibitor, DBO type	Yes	Yes	Yes	Yes	No	No
Avibactam	..	Phase 3 (NCT03580044)	Aztreonam	(Emblaveo)	To be determined§	Second generation	Reversible inhibitor, DBO type	Yes	Yes	Yes	Yes	Yes	Yes
Vaborbactam	2017	..	Meropenem	Vabomere	cUTIs	Third generation	β-lactam transition state analogue, boronate type	Yes	Yes	Yes	Yes OXA 48 x	No	No
Relebactam	2019	..	Imipenem and cilastatin¶	Recarbrio	cUTIs and cIAIs	Second generation	Reversible inhibitor, DBO type	Yes	Yes	Yes	No	No	No
Taniborbactam	..	Phase 3 (NCT03840148)	Cefepime	..	cUTIs	Third generation	β-lactam transition state analogue, boronate type	Yes	Yes	Yes	Yes	Yes‖	No
QPX7728	..	Phase 1 (NCT04380207)	..	..	..	Third generation	β-lactam transition state analogue, boronate type	Yes	Yes	Yes	Yes	Yes‖	No

FDA=US Food and Drug Administration. cIAI=complicated intra-abdominal infection. cUTI=complicated urinary tract infection. DBO=diazabicyclooctanone. *Clavulanic acid is used to treat a wide variety of bacterial infections, among them: lower respiratory tract infections, acute bacterial otitis media, sinusitis, skin and skin structure infections, and cUTIs. †Sulbactam is used to treat a wide variety of bacterial infections, among them: gynaecological infections, bone and joint infections, cIAIs, and skin and skin structure infections. ‡Tazobactam with piperacillin is used to treat a wide variety of bacterial infections, among them: cIAIs, skin and skin structure infections, gynaecological infections, community-acquired pneumonia, and nosocomial pneumonia. §The phase 3 study will determine the efficacy against cIAIs, nosocomial pneumonia (including hospital-acquired pneumonia and ventilator associated pneumonia), cUTIs, or bloodstream infections due to metallo-β-lactamase-producing Gram-negative bacteria. ¶Relebactam is in combination with imipenem and cilastatin. ‖IMP-type metallo-β-lactamases are weakly inhibited.

Table: Clinically available serine β-lactamase inhibitors and metallo-β-lactamase inhibitors in clinical trials

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

New antibiotic agents for the treatment of multidrug-resistant GNB infections



Active
Variable
Not recommended

		Enterobacterales				
	Typical dosing regimen for serious infections[11,110,111]	Extended-spectrum β-lactamase-producing Enterobacterales	AmpC β-lactamase-producing Enterobacterales	Ambler class A carbapenemases (eg, KPC and IMI)	Metallo-β-lactamases (eg, NDM, VIM, and IMP)	Ambler class D carbapenemases (eg, OXA-48)
β-lactam						
(Zerbaxa) Ceftolozane–tazobactam	3 g IV every 8 h, infused over 3 h					
(Zavicefta) Ceftazidime–avibactam	2·5 g IV every 8 h, infused over 3 h					
(Vabomere) Meropenem–vaborbactam	4 g IV every 8 h, infused over 3 h					
(Recarbrio) Imipenem–relebactam	1·25 g IV every 6 h, infused over 30 min					
(Fetroja) Cefiderocol	2 g IV every 8 h, infused over 3 h					
Ceftazidime–avibactam and aztreonam	Ceftazidime–avibactam: 2·5 g IV every 8 h, infused over 3 h plus aztreonam: 2 g IV every 8 h, infused over 3 h*					
(Emblaveo) Aztreonam–avibactam	2 g/0·67 g loading dose then 1·5 g/0·5 g every 6 h, infused over 3 h					
Cefepime–enmetazobactam	2 g/0·5 g every 8 h, infused over 4 h					
Sulbactam–durlobactam†	1 g of each drug IV every 6 h, infused over 3 h†					
Tetracycline derivative						
Eravacycline	1 mg per kg IV every 12 h					

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

> Clin Infect Dis. IF: 8.3 Q1 2026 Aug 8:ciag481. doi: 10.1093/cid/ciag481. Online ahead of print.

Infectious Diseases Society of America 2026 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections

Pranita D Tamma [1], Robert A Bonomo [2], Emily L Heil [3], Julie Ann Justo [4], Michael J Satlin [5], Amy J Mathers [6]

CRE: Urinary Tract Infections

2026 IDSA Update — changes from 2024 marked ★ 2026

Uncomplicated Cystitis

PREFERRED

- **Aminoglycoside (single dose) — upgraded from alternative ★ 2026**
- Nitrofurantoin
- TMP-SMX
- Ciprofloxacin or levofloxacin

ALTERNATIVE

- Colistin (NOT polymyxin B)
- Oral fosfomycin (E. coli only)
- **Gepotidacin — new oral agent (2025 approval) ★ 2026**
- **Pivmecillinam — avoid if KPC likely (0% active) ★ 2026**
- IV reserve: aztreonam-avibactam, CAZ-AVI, MEV, IMI-REL, cefiderocol, fosfomycin

Pyelonephritis / cUTI

PREFERRED

- Ciprofloxacin, levofloxacin, or TMP-SMX (if susceptible — likelihood LOW)
- **Aztreonam-avibactam ★ 2026**
- Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, or cefiderocol

ALTERNATIVE

- Once-daily aminoglycosides
- **IV fosfomycin (preferentially E. coli) — now available in the US ★ 2026**

What changed in 2026

Aminoglycoside single-dose moved to preferred for uUTI. Gepotidacin & pivmecillinam are new 2025-approved oral agents.

Aztreonam-avibactam is added across uUTI/cUTI. IV fosfomycin is now available in the US and suggested for cUTI — distinct from oral fosfomycin, still not used for pyelonephritis.

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

CRE Non-UTI Infections — Non-Carbapenemase & KPC

2026 IDSA Update

Non-Carbapenemase-Producing CRE

PREFERRED

- a. Resistant to ertapenem; susceptible to meropenem/imipenem
  - Extended-infusion meropenem or imipenem-cilastatin
- b. Resistant to all carbapenems
  - **Aztreonam-avibactam ★ 2026**
  - Ceftazidime-avibactam
  - Imipenem-relebactam
  - Meropenem-vaborbactam
- ***Modest preference for CAZ-AVI / IMI-REL over MEV in this group (in vitro study) ★2026***

KPC-Producing CRE

PREFERRED (ranked)

- Meropenem-vaborbactam > Ceftazidime-avibactam > Imipenem-relebactam (observational data + risk of resistance)
- *Resistance emergence on therapy: ~10% CAZ-AVI vs <3% MEV / IMI-REL*

ALTERNATIVE

- **Aztreonam-avibactam ★ 2026**
- Cefiderocol
- Tigecycline / eravacycline (non-BSI, non-UTI only)

⚠ Unchanged from 2024

Polymyxins NOT recommended for CRE.

Combination therapy NOT routinely needed once β-lactam susceptibility is confirmed.

KPC ranking (MEV > CAZ-AVI > IMI-REL) and ~10% vs <3% resistance-emergence figures carry over from 2024 — only aztreonam-avibactam and the non-carbapenemase preference note are new in 2026.

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

CRE Non-UTI Infections — NDM/MBL & OXA-48-like

2026 IDSA Update — largest change in the CRE section

NDM / Other MBL-Producing CRE

PREFERRED

- **Aztreonam-avibactam (fixed combination) ★ 2026**
- Cefiderocol (monotherapy)

ALTERNATIVE

- **Ceftazidime-avibactam + Aztreonam — only if ATM-AVI unavailable (was preferred in 2024) ★ 2026**
- Tigecycline/eravacycline (non-BSI, non-UTI only)

⚠ New resistance signal (2026)

NDM-producing E. coli with PBP3 insertions (YRIN/YRIK) + co-produced CMY can be resistant to BOTH aztreonam-avibactam AND cefiderocol.

2024: called “rare in the US.” 2026: found in ~30% of NDM-E E. coli in the US mid-Atlantic region.

If both agents fail: individualized combination (**IV fosfomycin + tigecycline and/or polymyxin B**).

OXA-48-like-Producing CRE

PREFERRED

- Ceftazidime-avibactam

ALTERNATIVE

- **Aztreonam-avibactam ★ 2026**
- Cefiderocol
- Tigecycline/eravacycline (non-BSI, non-UTI only)

Still true (unchanged since 2024)

MEV and IMI-REL are NOT suggested for OXA-48-E even if the isolate tests susceptible in vitro — vaborbactam and relebactam poorly inhibit OXA-48-like enzymes. This exclusion was already in the 2024 guidance, not a 2026 addition.

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

CRE: Tetracyclines & Polymyxins — Role & Restrictions

2026 IDSA Update

Tigecycline / Eravacycline	**Use for:** Alternative for IAI, SSTI, osteomyelitis, respiratory infections (activity independent of carbapenemase type) **NOT for:** BSI | UTI	***High-dose tigecycline: 200 mg load → 100 mg q12h*** ***Nausea: tigecycline ~20–25% vs eravacycline ~5%; tigecycline has far more clinical experience ★2026*** *Tigecycline MIC ≥ 0.5 µg/mL → poor outcomes despite FDA-susceptible ≤ 2 µg/mL*
Minocycline / Omadacycline	**Use for:** Consider with caution as part of combination therapy **NOT for:** Routine first-line use	***2026: panel groups both together — "use with caution," limited outcomes data for either agent ★2026*** *Omadacycline more active in vitro than minocycline, but neither has robust CRE clinical outcome data*
Colistin	**Use for:** Alternative for uncomplicated cystitis ONLY **NOT for:** BSI | Pyelonephritis | Other systemic infections	*Converts to active form in the urinary tract*
Polymyxin B	**Use for:** NOT recommended for any CRE infection **NOT for:** All CRE (predominantly non-renal clearance)	

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

CRE: Combination Therapy & Rescue Scenarios

New slide summarizing Question 3.8 (2026)

Combination Therapy — Not Routine

GENERAL PRINCIPLE

- Adding an aminoglycoside, fluoroquinolone, tetracycline, or polymyxin to an active β-lactam is NOT routinely suggested once in vitro susceptibility is confirmed
- Largest study: 577 KPC-E patients — 30-day survival ~74% (CAZ-AVI alone) vs ~75% (CAZ-AVI + 2nd agent) — no added benefit
- Continued 2nd agent increases toxicity risk without proven reduction in resistance emergence

IV Fosfomycin — Niche Rescue Role

RESCUE OPTION

- **Only for select carbapenem-resistant *E. coli* when NO active β-lactam remains ★ 2026**
- Typical scenario: NDM-E with PBP3 insertion + CMY, resistant to BOTH aztreonam-avibactam and cefiderocol
- Must be combined with another active agent — tigecycline and/or polymyxin B — never alone
- Supporting clinical data are limited; routine combination use is still not suggested

Why this is new in 2026

2024 guidance: “IV fosfomycin is not clinically available in the United States” — it had no defined treatment role.

2026 guidance: IV fosfomycin is now available in the US. It has been given two specific, narrow roles —

1) alternative agent for cUTI, and

2) last-resort combination-therapy partner for pan-β-lactam-resistant NDM-producing *E. coli*.

Outside these two scenarios, the 2026 stance on combination therapy for CRE is unchanged from 2024.

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

European Journal of Clinical Microbiology & Infectious Diseases (2025) 44:251–262
https://doi.org/10.1007/s10096-024-04993-7

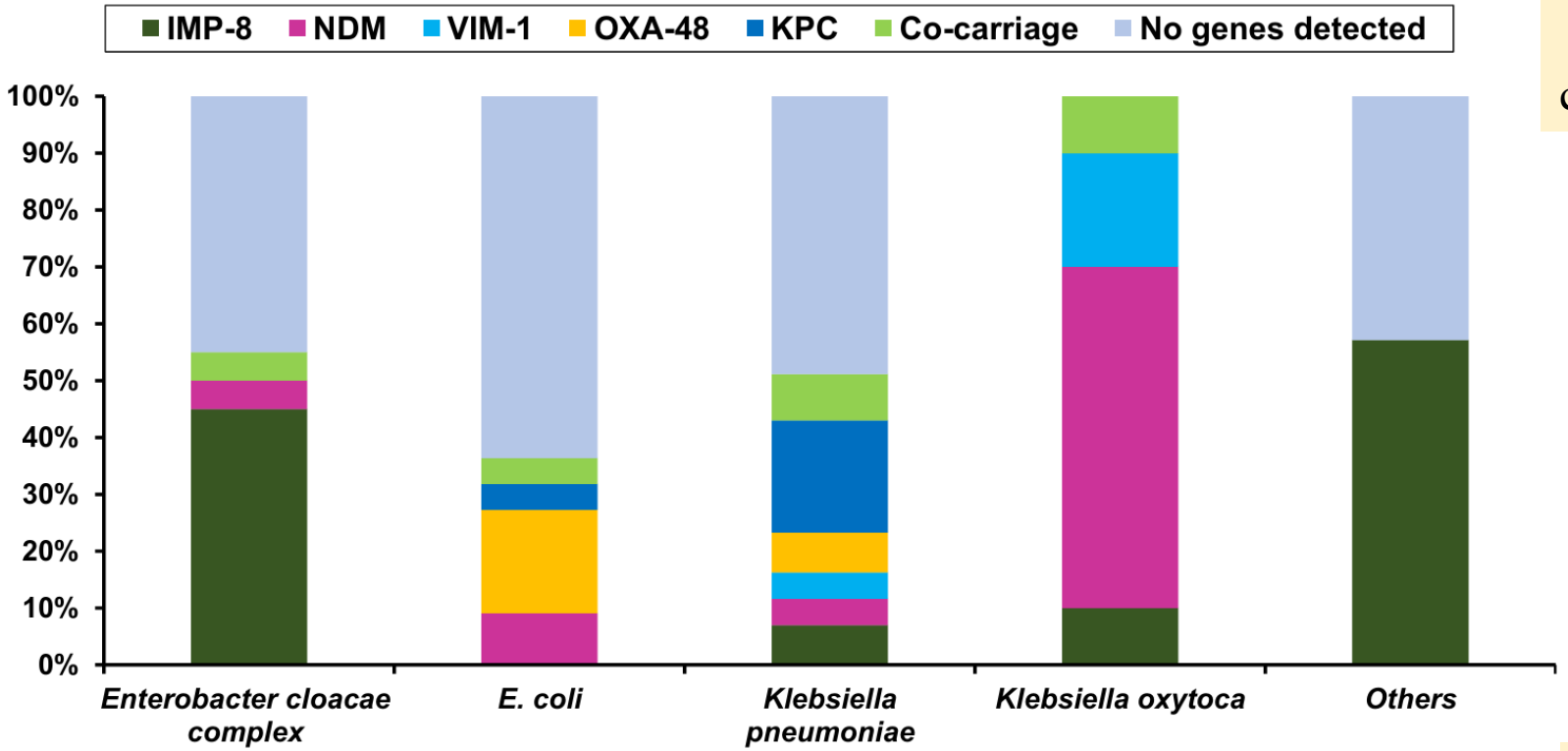
RESEARCH

High diversity of strain clonality and metallo-β-lactamases genes among carbapenem-resistant Enterobacterales in Taiwan

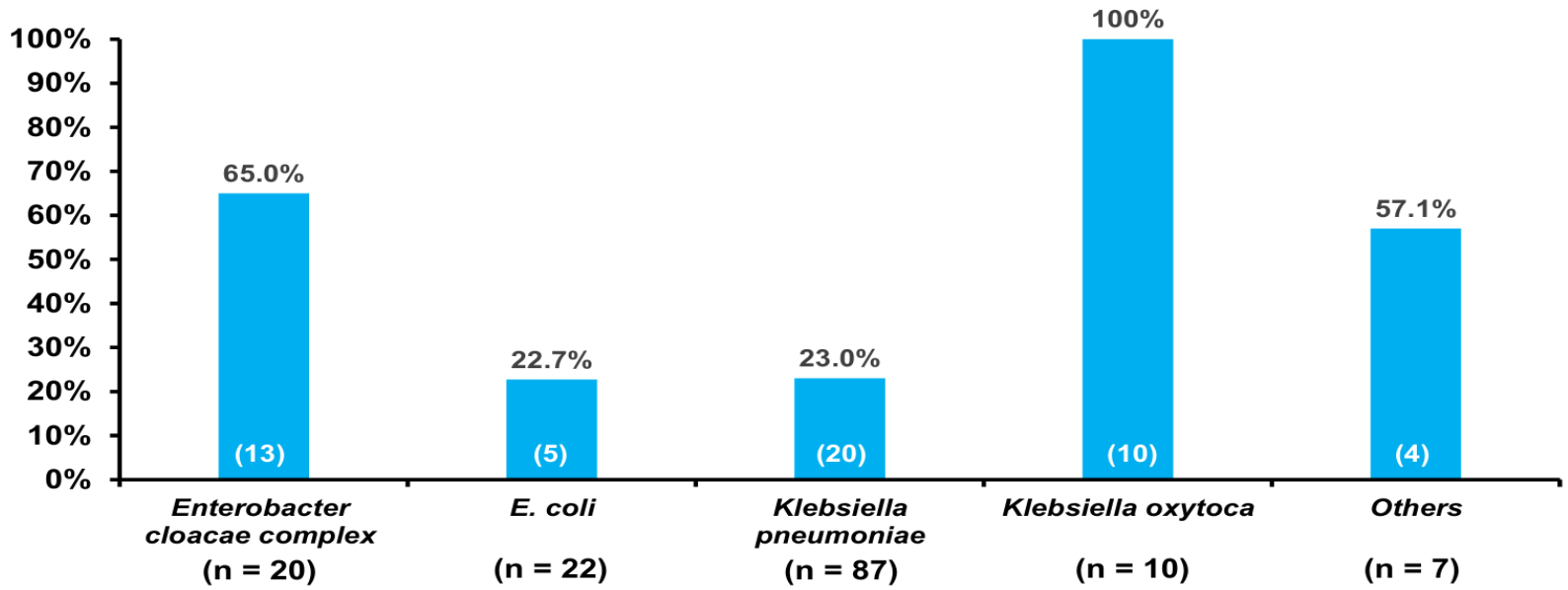
Jia-Arng Lee[1,2] · Yao-Wen Kuo[3] · Shin-Hei Du[1] · Tai-fen Lee[1] · Chun-Hsing Liao[4,5] · Yu-Tsung Huang[1,2] · Po-Ren Hsueh[1,6,7,8]

- A total of **146 CRE** were collected **in NTUH in 2022**.(retrospective study)
- Carbapenemase inactivation method (+) => carbapenemase-producing *Enterobacterales* (CPE)
- Multiplex PCR detection of the five common carbapenemases (*bla*KPC, *bla*NDM, *bla*VIM, *bla*IMP, and *bla*OXA-48)
- PCR amplicons => Sanger sequencing to determine the variants of carbapenemases
- Multilocus sequence types (MLST) for CPE

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



Proportion of different carbapenemase genes in CRE



Ceftazidime/avibactam resistant rate by species

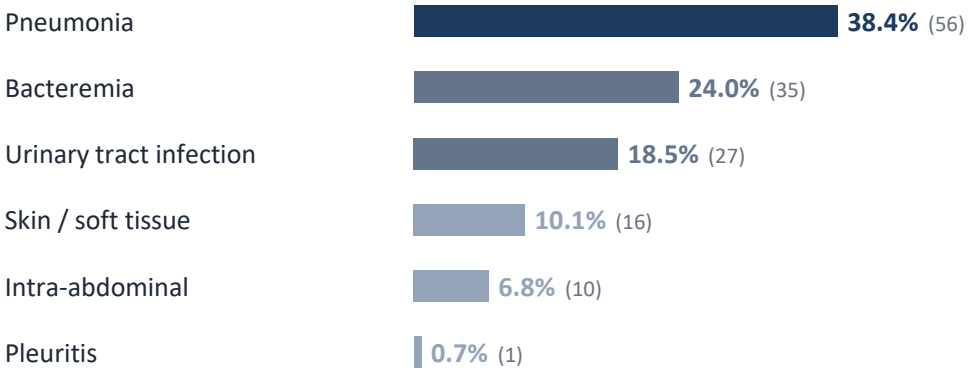
MBL-encoding genes were detected in 31.5% of all tested CRE isolates (n=146), with 82.6% of them exhibiting resistance to CZA.

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

Empirical therapy often missed the pathogen

After susceptibility testing, definite therapy shifted to CZA — yet CRE mortality stayed high

Diagnosis (site of infection)



Outcomes

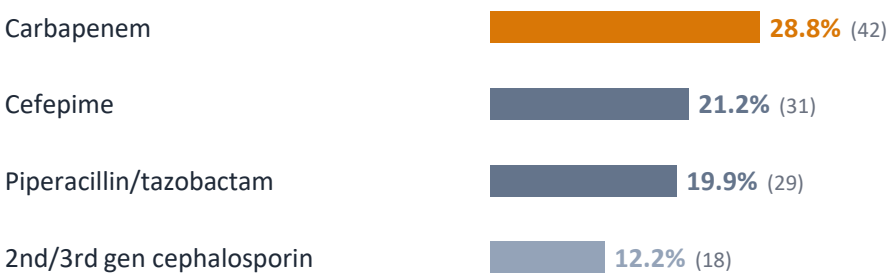
9.0%
14-day mortality
n = 13 / 146

22.8%
30-day mortality
n = 33 / 146

39.0%
In-hospital mortality CRE-related
n = 57 / 146

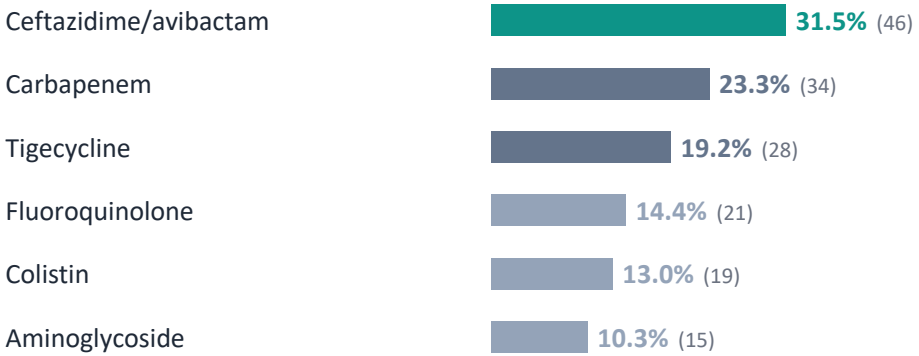
Empirical antibiotics

Before susceptibility known — mostly broad-spectrum β-lactams



Definite antibiotics (after susceptibility)

Regimen modified in 80.1% after susceptibility & CZA E-test



Source: Lee J-A, et al. Eur J Clin Microbiol Infect Dis 2025;44:251–262 (NTUH, 2022; 146 patients with CRE infection, Table 1)

DTR *Pseudomonas aeruginosa* (Difficult-to-Treat Resistance)

Definitions

- **Multidrug-resistant (MDR) *P. aeruginosa***: resistant to at least 1 antibiotic in at least 3 antibiotic classes for which *P. aeruginosa* susceptibility is generally expected: penicillins, cephalosporins, fluoroquinolones, aminoglycosides, and carbapenems

- **Carbapenem-resistant (CR) *P. aeruginosa***: resistant to at least one carbapenem, e.g., imipenem, meropenem, and doripenem

- **Difficult-to-treat resistant (DTR) *P. aeruginosa***: resistant to all of the following: piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin, and levofloxacin. (all classical agents, not include aminoglycosides and polymyxin, fosfomycin)

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

Major mechanisms of antibiotic resistance in *P. aeruginosa*

➢ Intrinsic antibiotic resistance

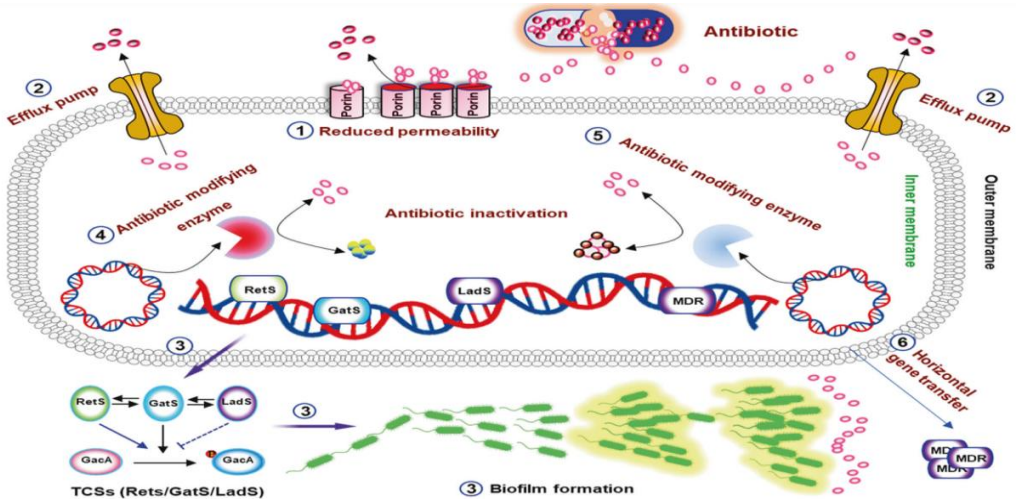
- Outer membrane permeability (porin channels)
- Efflux systems (efflux pumps)
- Antibiotic-inactivating enzymes, ex: AmpC, aminoglycoside modifying enzymes

➢ Acquired antibiotic resistance

- Resistance by mutations, ex: PBP3 variants, altered LPS synthesis, altered metabolism
- Acquisition of resistance genes: horizontal gene transfer (carbapenemase)

➢ Adaptive antibiotic resistance

- Biofilm-mediated resistance
- Persister cells in antibiotic resistance



Signal Transduct Target Ther.2022 Jun 25;7(1):199; Biotechnol Adv.2019 Jan-Feb;37(1):177-192

Antibiotic-inactivating enzymes, ex: AmpC

- **Chromosomally encoded class C** β-lactamase in PA, **intrinsic** resistance to many penicillins and cephalosporins

- AmpC overexpression => reducing susceptibility to ceftazidime, cefepime, aztreonam, and piperacillin, but little/no effect on susceptibility to carbapenems
  - overexpression by the presence of β-lactams or by mutations that alter the pathway

- Over 500 variants (*Pseudomonas*-derived cephalosporinases, PDC), **ex: Ω-loop remodeling**
  - AmpC point mutations may increase the **catalytic activity**; reduce the **affinity of inhibitors** such as avibactam (ceftazidime) and tazobactam (ceftolozane)

Glen et al. Pathogens.2021 Dec 18;10(12):1638

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Ceftazidime, Carbapenems, or Piperacillin-tazobactam as Single Definitive Therapy for *Pseudomonas aeruginosa* Bloodstream Infection: A Multisite Retrospective Study

Europe
Australia
Israel

- No significant difference between antibiotics for mortality, clinical failure and adverse events
- Definition of new resistance: isolation of *P. aeruginosa* (colonization or infection) of any site with new resistance to any of the following within 30 days.
- New resistance: carbapenems: 17.5% (36/206), ceftazidime: 12.4% (25/201), piperacillin-tazobactam: 8.4% (28/332)
- Repeat AST of subsequent clinical MDR *P. aeruginosa* isolates obtained from the same patient to monitor for the development of resistance

AST: Antimicrobial Susceptibility Testing

Babich et al. Clin Infect Dis.2020 May 23;70(11):2270-2280.

Global epidemiology and clinical outcomes of carbapenem-resistant *Pseudomonas aeruginosa* and associated carbapenemases (POP): a prospective cohort study

Jinnethe Reyes, Lauren Komarow, Liang Chen, Lizhao Ge, Blake M Hanson, Eric Cober, Erica Herc, Thamer Alenazi, Keith S Kaye, Julia Garcia-Diaz, Lanjuan Li, Souha S Kanj, Zhengyin Liu, Jose M Oñate, Robert A Salata, Kalisvar Marimuthu, Hainv Gao, Zhiyong Zong, Sandra L Valderrama-Beltrán, Yunsong Yu, Paul Tambyah, Gregory Weston, Soraya Salcedo, Lillian M Abbo, Qing Xie, Karen Ordoñez, Minggui Wang, Martin E Stryjewski, Jose M Munita, David L Paterson, Scott Evans, Carol Hill, Keri Baum, Robert A Bonomo, Barry N Kreiswirth, Maria Virginia Villegas, Robin Patel, Cesar A Arias, Henry F Chambers, Vance G Fowler Jr, Yohei Doi, David van Duin, Michael J Satlin, on behalf of the Antibacterial Resistance Leadership Group and Multi-Drug Resistant Organism Network Investigators

- Prospective cohort study, multi-country study, between Dec 1, 2018, and Nov 30, 2019.
- Source: bloodstream (69), respiratory (358), wound (66), urine (88)

Lancet Microbe.2023 Mar;4(3):e159-e170.

Outcomes of CRPA infection

	Total (n=581)	USA (n=308)	China (n=120)	South and central America (n=73)	Middle East (n=52)	Australia and Singapore (n=28)	p value*
Mortality†							
30-day (primary outcome)	105 (18%)	60 (19%)	7 (6%)	20 (27%)	15 (29%)	3 (11%)	0·0002
90-day	148 (25%)	87 (28%)	10 (8%)	23 (32%)	21 (40%)	7 (25%)	<0·0001
Length of hospital stay from infection onset, days	13 (6–30)	10 (5–20)	15 (7–30)	18 (7–41)	28 (11–59)	39 (19–72)	<0·0001
Desirability of outcomes ranking outcome at 30 days‡							
Alive without events	211 (36%)	120 (39%)	51 (43%)	22 (30%)	12 (23%)	6 (21%)	..
Alive with 1 event	123 (21%)	73 (24%)	36 (30%)	9 (12%)	2 (4%)	3 (11%)	..
Alive with 2 or 3 events	142 (24%)	55 (18%)	26 (22%)	22 (30%)	23 (44%)	16 (57%)	..
Death	105 (18%)	60 (19%)	7 (6%)	20 (27%)	15 (29%)	3 (11%)	..
Disposition after discharge							<0·0001
Home	223 (38%)	94 (31%)	47 (39%)	42 (58%)	27 (52%)	13 (46%)	..
Long-term care facility	145 (25%)	129 (42%)	4 (3%)	5 (7%)	1 (2%)	6 (18%)	..
Transfer to another hospital or to a foreign country	57 (10%)	5 (2%)	48 (40%)	2 (3%)	1 (2%)	1 (4%)	..
Hospice	27 (5%)	15 (5%)	11 (9%)	1 (1%)	0	0	..
Death	121 (21%)	63 (20%)	10 (8%)	22 (30%)	20 (38%)	6 (21%)	..
Remained in the hospital	8 (1%)	2 (1%)	0	1 (1%)	3 (6%)	2 (7%)	..
Clinical response	283 (49%)	175 (57%)	56 (47%)	29 (40%)	14 (27%)	9 (32%)	<0·0001

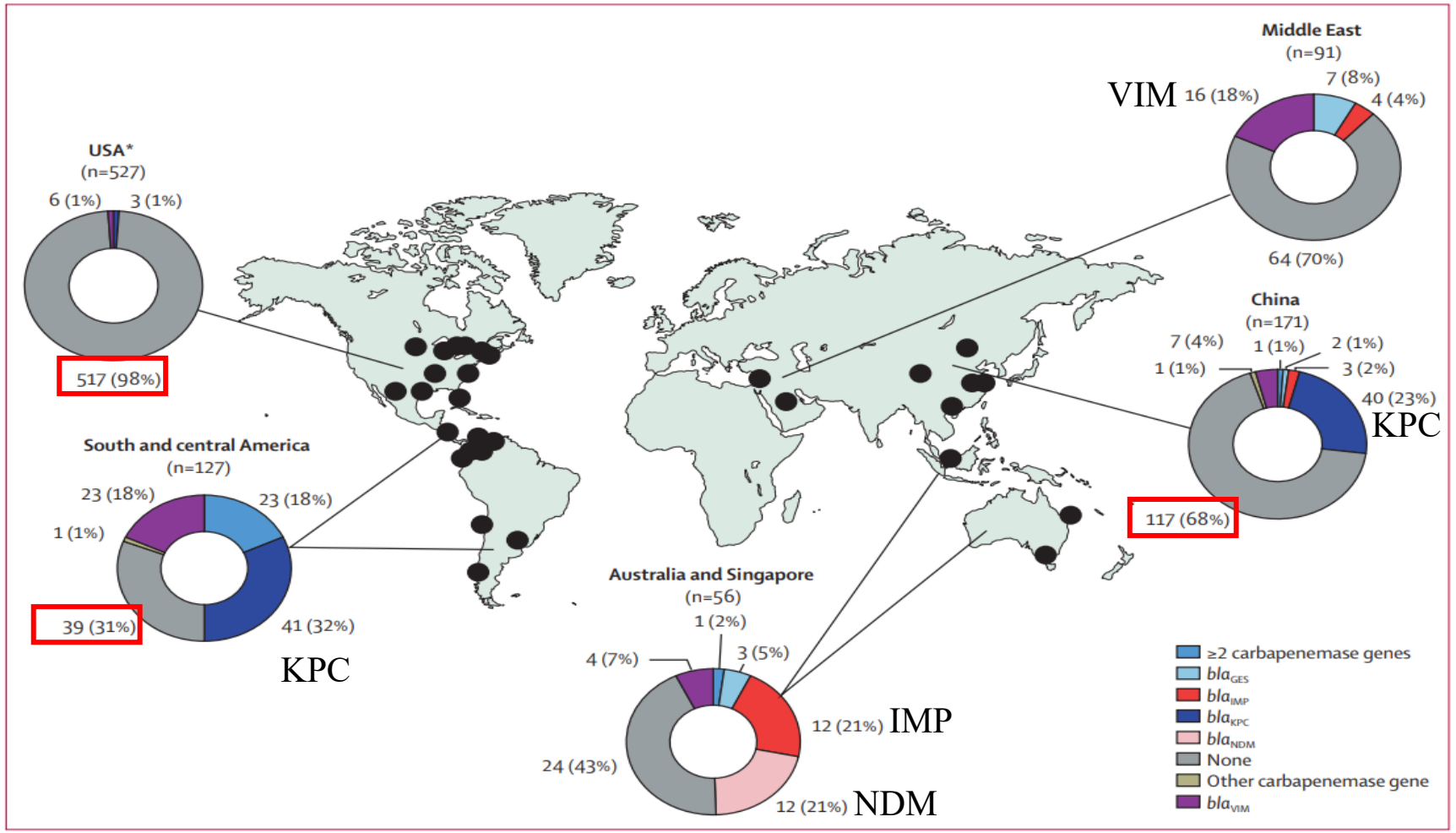
Data are n (%) or median (IQR). *χ^2 test was used for categorical variables, and Kruskal-Wallis test was used for continuous variables. †Patients who were discharged to hospice were not considered to have died. ‡The three adverse events assessed by desirability of outcomes ranking were lack of clinical response, lack of discharge within 30 days or readmission within 30 days, and incident renal failure or *Clostridioides difficile* infection. The unadjusted probability estimates for a favourable outcome (ie, clinical response, discharge or hospital readmission, and absence of renal failure or *Clostridioides difficile* infection) using China as the reference region were 44% (95% CI 39–50) for the USA, 35% (27–43) for south and central America, 28% (20–37) for the Middle East, and 31% (21–42) for Australia and Singapore (appendix p 5).

- 30-day mortality: BSI 30%、respiratory 19%、wound 14%、urine 7%。

Lancet Microbe.2023 Mar;4(3):e159-e170.

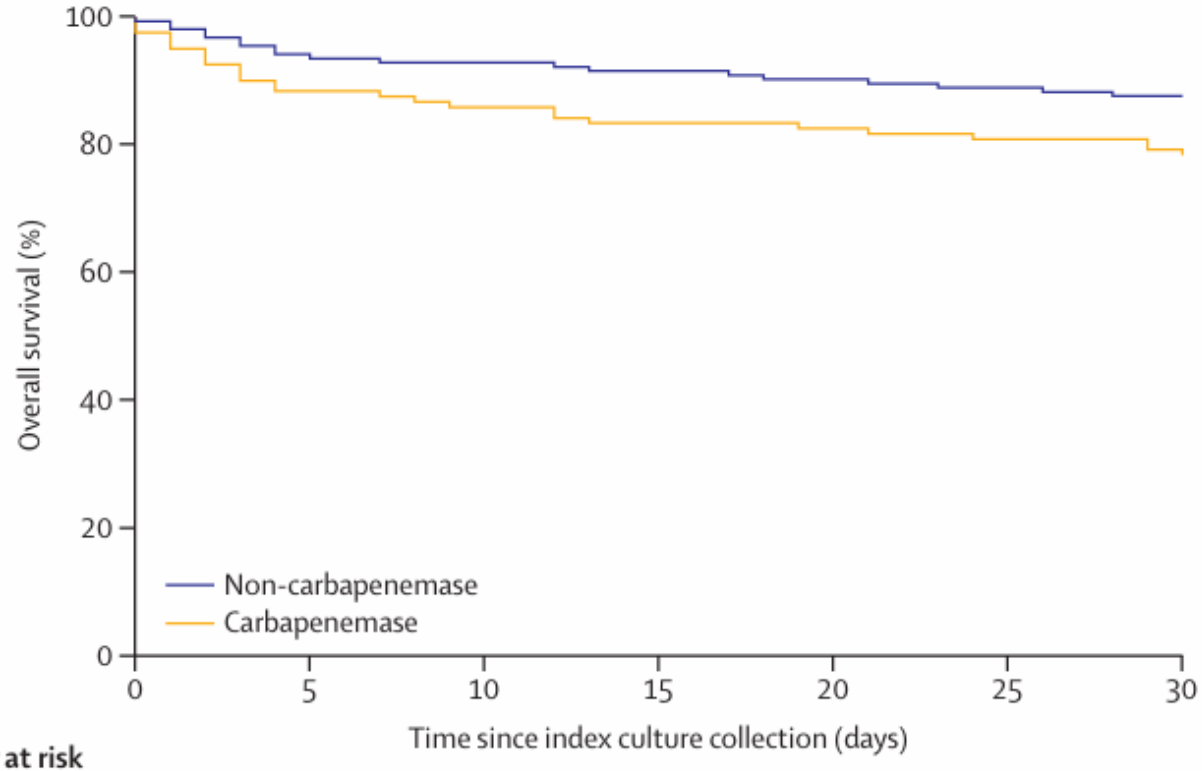
Carbapenemase genes identified in CRPA infection and colonization isolates

- KPC-2 and VIM-2 were the most common carbapenemases



Lancet Microbe.2023 Mar;4(3):e159-e170.

30-day overall survival after CRPA infection
by presence of carbapenemase outside the USA



Number at risk (number censored)							
Non-carbapenemase	153 (0)	144 (0)	142 (0)	140 (0)	138 (0)	136 (0)	134 (0)
Carbapenemase	120 (0)	106 (0)	103 (0)	100 (0)	99 (0)	97 (0)	95 (0)

No-carbapenemase

Carbapenemase

30-day mortality
Carbapenemase: 22% (26/120)
No-carbapenemase: 12% (19/153)
adjusted difference 7%, 95% CI 1–14

Lancet Microbe.2023 Mar;4(3):e159-e170.

Carbapenemase carriage among *P. aeruginosa* in Taiwan from 2015–2021, SMART study

- Carbapenemase genes were carried by **2.2%** (**13**/600) of the *P. aeruginosa* isolates. (C/T non-susceptible or imipenem MIC ≥4 (not CRPA); BSI + IAI + LRTI + UTI)

- Overall, **10** harbored MBL (6 VIM, 1 IMP, 3 cocarrying VIM/KPC), the other 3 isolates were KPC.

- Only **2.1%** (9/433) of CRPA isolates carried a carbapenemase.

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

Susceptibility of antimicrobial agents for CRPA and DTR PA from 2012 to 2021 in Taiwan, SMART study

Group/year (no. of isolates)	Percent susceptible[a]								
	C/T (Zerbaxa)	CZA (Zavicefta)	IMP	MEM	CAZ	FEP	TZP	LVX	AMK
All *P. aeruginosa*									
2012 (114)	NA	NA	84.2	NA	88.6	90.4	90.4	79.8	94.7
2013 (139)	NA	NA	84.9	NA	87.1	87.1	86.3	77.7	98.6
2014 (112)	NA	NA	84.8	NA	88.4	88.4	88.4	80.4	94.6
2015 (336)	NA	NA	83.3	NA	81.5	83.0	76.8	74.4	99.4
2016 (366)	96.7	NA	81.6	84.4	80.3	82.8	73.2	69.9	98.9
2017 (428)	94.2	NA	79.9	83.6	80.1	82.5	74.3	68.0	98.8
2018 (357)	98.0	96.6	77.0	77.9	80.4	82.9	74.8	75.6	99.4
2019 (386)	96.9	96.4	71.2	82.9	79.0	82.6	73.8	73.8	98.4
2020 (399)	99.2	96.7	67.9	79.2	77.9	81.7	74.4	72.9	97.7
2021 (376)	97.3	96.0	73.9	84.3	76.9	77.1	66.8	73.9	98.7
All years (3013)[a,b]	97.0	96.4	77.3	82.1	80.5	82.6	75.2	73.3	98.4
Carbapenem-resistant *P. aeruginosa*[b,c]									
2012 (14)	NA	NA	0	NA	50.0	57.1	50.0	50.0	85.7
2013 (16)	NA	NA	0	NA	68.8	56.3	56.3	43.8	93.8
2014 (13)	NA	NA	0	NA	61.5	61.5	61.5	38.5	84.6
2015 (41)	NA	NA	0	NA	61.0	63.4	53.7	63.4	97.6
2016 (56)	91.1	NA	5.4	12.5	50.0	50.0	30.4	39.3	94.6
2017 (68)	79.4	NA	1.5	5.9	52.9	48.5	35.3	29.4	97.1
2018 (73)	93.2	87.7	4.1	9.6	56.2	54.8	39.7	41.1	97.3
2019 (75)	90.7	84.0	1.3	16.0	50.7	42.7	41.3	32.0	94.7
2020 (91)	98.9	92.3	1.1	16.5	53.8	57.1	47.3	47.3	95.6
2021 (73)	91.8	84.9	1.4	27.4	53.4	49.3	37.0	30.1	93.2
All years (520)[c]	91.3	87.5	1.9	14.9	54.2	52.3	41.7	39.6	95.0
DTR *P. aeruginosa*									
All years (156)[d]	78.4	60.7	0	0	0	0	0	0	86.5

C/T, ceftolozane/tazobactam; IMP, imipenem; MEM, meropenem; CZA, ceftazidime/avibactam; CAZ, ceftazidime; FEP, cefepime; TZP, piperacillin/tazobactam; LVX, levofloxacin; AMK, amikacin

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

Susceptibility of CRPA According to Acquired β-Lactamase Gene Status

14 countries in Asia-Pacific region from 2015 to 2019 (ATLAS program)

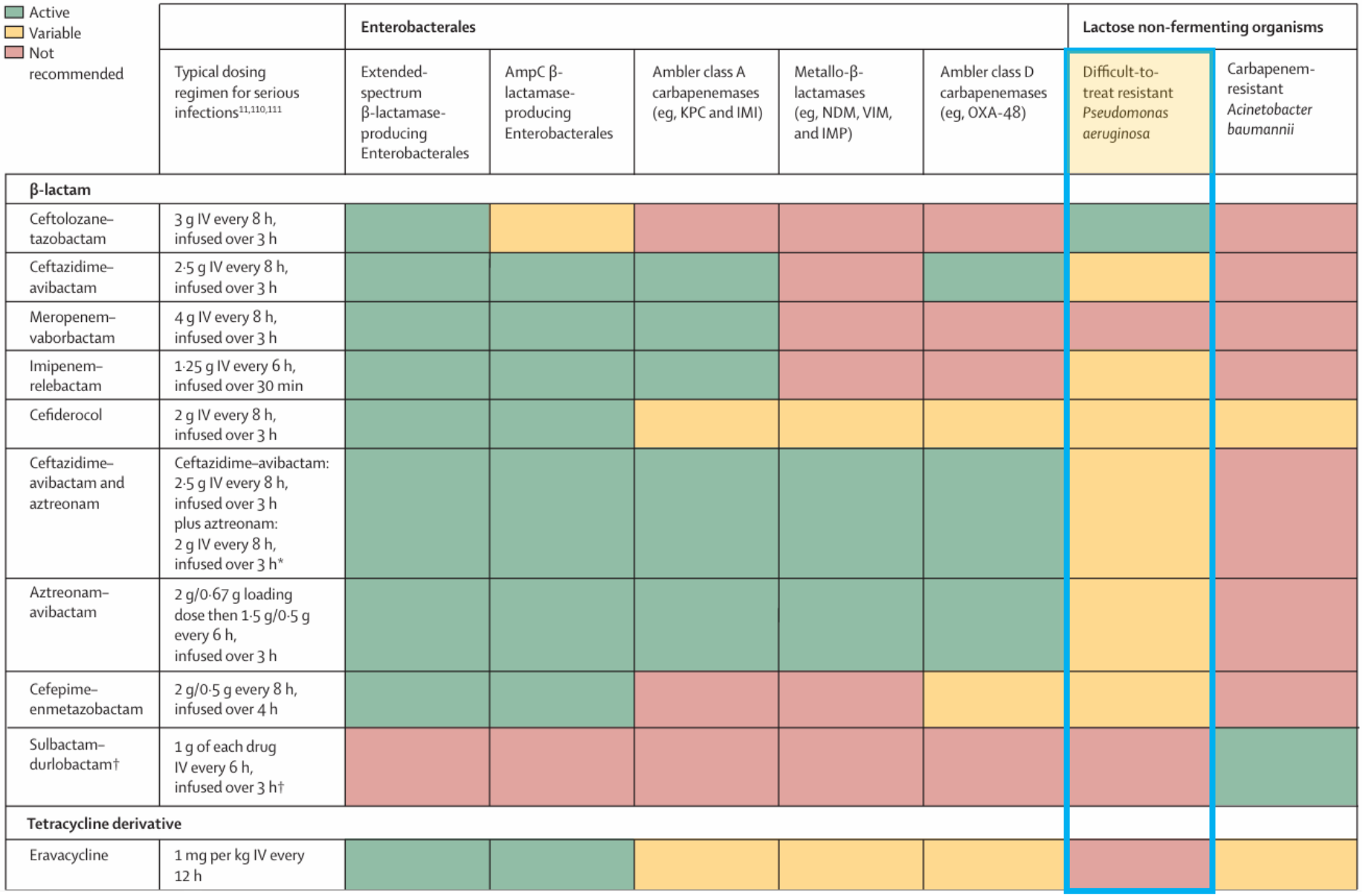
Antimicrobial agent	Carbapenem-resistant *Pseudomonas aeruginosa*[g]								
	Without detected β-lactamase gene (n = 502)			With class a β-lactamase gene (n = 74)[a]			With class B β-lactamase gene (n = 171)[b]		
	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	S (no. [%])[c]	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	S (no. [%])[c]	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	S (no. [%])[c]
Amikacin	4	32	430 (85.7)	64	128	13 (17.6)[d]	64	128	29 (17.0)[e]
Aztreonam	32	128	64/377 (17.0)	256	256	4 (5.4)[d]	32	256	34 (19.9)
Cefepime	16	64	215 (42.8)	64	64	2 (2.7)[d]	32	64	3 (1.8)[e]
Ceftazidime	8	64	238 (47.4)	256	256	0 (0)[d]	256	256	2 (1.2)[e]
(Zavicefta) Ceftazidime-avibactam	4	16	313/377 (83.0)	128	256	17 (23.0)[d]	256	256	6 (3.5)[e]
(Zerbaxa) Ceftolozane-tazobactam	2	8	47/49 (95.9)	16	64	1/7 (14.3)[d]	64	64	0/33 (0)[e]
Ciprofloxacin	4	16	83/275 (30.2)	8	8	0/41 (0)[d]	8	8	0/95 (0)[e]
Colistin[e]	1	2	375/377 (99.5)[f]	1	2	74 (100)[f]	1	2	171 (100)[f]
Imipenem	16	16	14/377 (37.1)	16	16	0 (0)	16	16	0 (0)
Levofloxacin	8	16	131 (26.1))	16	16	1 (0)[d]	16	16	3 (1.8)[e]
Meropenem	16	32	0 (0)	16	32	0 (0)	32	32	0 (0)
Piperacillin-tazobactam	64	256	166 (33.1)	128	256	4 (5.4)[d]	128	256	9 (5.3)[e]

[a]The class A β-lactamase genes included bla_{VEB} (n = 51), bla_{GES} (n = 14), bla_{TEM} (n = 8), and bla_{KPC} (n = 4); 3 isolates harbored bla_{VEB} + bla_{KPC}.
[b]The class B β-lactamase genes included bla_{IMP} (n = 44), bla_{NDM} (n = 61), bla_{VIM} (n = 71); 2 isolates harbored bla_{VIM} + bla_{IMP}, and 3 isolates harbored bla_{VIM} + bla_{NDM}.
[c]Breakpoints were adopted from Clinical and Laboratory Standards Institute (CLSI) M100-S31.

- Intrinsic antibiotic resistance dominates in CRPA (porin channel、efflux pump、AmpC)
- Zerbaxa better than Zavicefta in CRPA: 1. more stable to AmpC. 2. poor efflux substate (Ceftolozane)

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

New antibiotic agents for the treatment of multidrug-resistant GNB infections



Active
Variable
Not recommended

	Typical dosing regimen for serious infections[11,110,111]	Enterobacterales					Lactose non-fermenting organisms	
		Extended-spectrum β-lactamase-producing Enterobacterales	AmpC β-lactamase-producing Enterobacterales	Ambler class A carbapenemases (eg, KPC and IMI)	Metallo-β-lactamases (eg, NDM, VIM, and IMP)	Ambler class D carbapenemases (eg, OXA-48)	Difficult-to-treat resistant *Pseudomonas aeruginosa*	Carbapenem-resistant *Acinetobacter baumannii*
β-lactam								
(Zerbaxa) Ceftolozane–tazobactam	3 g IV every 8 h, infused over 3 h							
(Zavicefta) Ceftazidime–avibactam	2·5 g IV every 8 h, infused over 3 h							
(Vabomere) Meropenem–vaborbactam	4 g IV every 8 h, infused over 3 h							
(Recarbrio) Imipenem–relebactam	1·25 g IV every 6 h, infused over 30 min							
(Fetroja) Cefiderocol	2 g IV every 8 h, infused over 3 h							
Ceftazidime–avibactam and aztreonam	Ceftazidime–avibactam: 2·5 g IV every 8 h, infused over 3 h plus aztreonam: 2 g IV every 8 h, infused over 3 h*							
(Emblaveo) Aztreonam–avibactam	2 g/0·67 g loading dose then 1·5 g/0·5 g every 6 h, infused over 3 h							
Cefepime–enmetazobactam	2 g/0·5 g every 8 h, infused over 4 h							
Sulbactam–durlobactam†	1 g of each drug IV every 6 h, infused over 3 h†							
Tetracycline derivative								
Eravacycline	1 mg per kg IV every 12 h							

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

Antimicrobial spectrum expected for classical and novel BLBLIs against *P. aeruginosa* resistance mechanisms

		Intrinsic resistance			Acquired resistance						
	Antibiotic	**AmpC ↑**	**MexAB↑ (efflux)**	**OprD- (porin)**	**AmpC Ω-loop***	**OXA ESBL**	**ESBL**	**CarbA**	**CarbA Mut****	**CarbB**	**Iron transp.**
	Piperacillin/tazobactam	R	r	S	S/r	R	R	R	R	R	S
	Ceftazidime	R	r	S	R	R	R	R	R	R	S
	Cefepime	r/R	r/R	S	R	R	R	R	R	R	S
	Aztreonam	r/R	R	S	R	r/R	R	R	R	S	S
	Imipenem	S	S	r/R	S	S	S	R	S	R	S
	Meropenem	S	r	r	S	S	S	R	S	R	S
(Zerbaxa)	**Ceftolozane/tazobactam**	S	S	S	R	R	r/R	R	R	R	S
(Zavicefta)	**Ceftazidime/avibactam**	S/r	r	S	r/R	r/R	S/r	S	R	R	S
(Vabomere)	**Meropenem/vaborbactam**	S	r	r	S	S	S	r/R	S	R	S
(Recarbrio)	**Imipenem/relebactam**	S	r	r	S	S	S	r/R	S	R	S
(Fetroja)	**Cefiderocol**	S	S	S	S/r	S/r	S/r	S/r	S/r	S/r	r
(Emblaveo)	**Aztreonam/avibactam**	S	R	S	r/R	r/R	S/r	S/r	r/R	S	S
	Cefepime/zidebactam	S	r/R	S	S/r	S/r	S/r	S/r	S/r	r/R	S
	Cefepime/taniborbactam	S	r/R	S	S/r	S/r	S/r	S/r	S/r	r/R	S

S (green), fully susceptible; r (orange), reduced susceptibility; R (red) clinical resistance.
*AmpC (PDC) variants associated with ceftolozane/tazobactam and/or ceftazidime/avibactam resistance.
**KPC or GES mutations associated with ceftazidime/avibactam resistance and collateral carbapenem susceptibility.

Clin Microbiol Infect.2024 Apr;30(4):469-480

Main resistance mechanisms to classical and novel antibiotics in *P. aeruginosa*

Anti-pseudomonal categories	Anti-pseudomonal agents	Main mutational resistance mechanisms	Alternative mutational resistance mechanisms	Mutational resistance on horizontally acquired determinants	Horizontally acquired resistance mechanisms
Penicillins + β-lactamase inhibitors	Piperacillin/tazobactam	AmpC↑	PBP3, GalU		ESBLs, class A and B carbapenemases
Cephalosporins	Ceftazidime	AmpC↑	PBP3, GalU	OXA-2/10	ESBLs, class A and B carbapenemases
	Cefepime	MexXY↑, AmpC↑	PBP3, GalU	OXA-2/10	ESBLs, class A and B carbapenemases
Monobactams	Aztreonam	MexAB↑, AmpC↑	PBP3, GalU	OXA-2/10	ESBLs and class A carbapenemases
Carbapenems	Imipenem	OprD-	MexST, PBP2, PBP1a		Class A and B carbapenemases
	Meropenem	OprD-, MexAB↑	PBP3, GalU		Class A and B carbapenemases
Fifth-generation cephalosporins + classical β-lactamase inhibitors	Ceftolozane/tazobactam	AmpC Ω-loop	PBP3, GalU Efflux pumps	OXA-2/10	ESBLs, class A and B carbapenemases
Cephalosporins + diazabicyclooctanes β-lactamase inhibitors	Ceftazidime/avibactam	AmpC Ω-loop, MexAB↑	PBP3, GalU	OXA-2/10, GES, KPC	Class B carbapenemases
Carbapenems + diazabicyclooctanes β-lactamase inhibitors	Imipenem/relebactam	OprD-, MexAB↑[b]	MexST, ParRS PBP2, PBP1a		Class A and B carbapenemases
Carbapenems + boronic acid β-lactamase inhibitors	Meropenem/vaborbactam	OprD-, MexAB↑	PBP3, GalU		Class A and B carbapenemases
Siderophore cephalosporins	Cefiderocol	Iron transporters AmpC Ω-loop	PBP3, GalU	OXA-2/10[b]	ESBLs, class A and B carbapenemases[b]
Monobactams + diazabicyclooctanes β-lactamase inhibitors	Aztreonam/avibactam[a]	MexAB↑	PBP3, GalU		ESBLs and class A carbapenemases[b]
Cephalosporins + diazabicyclooctanes β-lactamase and PBP2 inhibitors	Cefepime/zidebactam[a]	MexXY↑, MexAB↑	PBP3, GalU PBP2		ESBLs, class A and B carbapenemases[b]
Cephalosporins + boronic acid β-lactamase inhibitors including MBLs	Cefepime/taniborbactam[a]	MexXY↑, MexAB↑	PBP3, GalU		IMPs
Fluoroquinolones	Ciprofloxacin, levofloxacin	QRDR	MexAB/XY/CD/EF↑		Qnr
Aminoglycosides	Tobramycin, amikacin	MexXY↑[b]	FusA1		Aminoglycoside modifying enzymes, 16S rRNA methylases
Polymyxins	Colistin, polymyxin B	PmrAB/PhoPQ/ParRS			MCR (Very uncommon)
Fosfonic acids	Fosfomycin	GlpT			FosA

➢ Mutations in the Ω-loop region of AmpC that modify the enzyme active site and expand or alter β-lactam hydrolysis.

Oliver et al. Clin Microbiol Infect.2024 Apr;30(4):469-480

DTR *P. aeruginosa*: Urinary Tract Infections

2026 UPDATE

2026: uncomplicated cystitis + pyelonephritis/cUTI questions merged into a single "cUTI" recommendation

PREFERRED — cUTI (listed alphabetically; no order of preference)

- Cefiderocol
- Ceftazidime-avibactam
- Ceftolozane-tazobactam
- Imipenem-relebactam

ALTERNATIVE — cUTI

- Once-daily amikacin or tobramycin
- Duration-dependent nephrotoxicity risk; useful for completing a course

uUTI (uncomplicated cystitis) — now a brief note, not its own question

DTR-PA uUTI is "exceedingly uncommon." Options: single-dose amikacin/tobramycin, cefiderocol, CAZ-AVI, C/T, IMI-REL, or colistin (converted to active form in urine — polymyxin B is NOT an option here).

Clinical reasoning note

Cefiderocol has unique activity beyond *P. aeruginosa* (NDM-producing Enterobacterales, other non-fermenters) — consider **reserving it** for those indications when the other 3 agents are active for a straightforward cUTI.

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

DTR *P. aeruginosa*: Non-UTI Infections

2026 NEW

2026: ceftolozane-tazobactam now specifically preferred for DTR-PA pneumonia

PREFERRED — Non-UTI (all sites)

- Ceftazidime-avibactam
- Ceftolozane-tazobactam
- Imipenem-relebactam
- → **For PNEUMONIA specifically: ceftolozane-tazobactam is the preferred agent among the three (NEW 2026)**

ALTERNATIVE

- Cefiderocol
- Not superior to alternative regimens in RCT subgroups (survival 75–82% both arms)
- Reserve for when preferred β-lactams are inactive/not tolerated

WHY C/T FOR PNEUMONIA? (NEW mechanistic rationale, 2026)

Epithelial lining fluid (ELF) penetration: Ceftolozane reaches ≥50% of plasma levels, exceeding its 4 µg/mL breakpoint for 100% of the dosing interval in pneumonia. CAZ-AVI reaches only ~30% of plasma levels for both components — potentially inadequate given CAZ-AVI's dual-component activity requirement.
Observational outcomes: Largest cohort (n=210/pneumonia): **clinical success** 63% (C/T) vs. 51% (CAZ-AVI); 30-day **recurrent infection** 15% (C/T) vs. 21% (CAZ-AVI). A second cohort: recurrent pneumonia 8% (C/T) vs. 18% (CAZ-AVI).

Imipenem-relebactam: fewer clinical outcomes data and lower susceptibility rates than C/T or CAZ-AVI among DTR-PA — still preferred, but trial-vs-observational emergence-of-resistance data diverge.

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

DTR *P. aeruginosa*: Carbapenemase-Guided Therapy

2026 NEW

Entirely new question in 2026 — carbapenemase identification now directs agent selection

KPC-Producing DTR-PA (NEW)

- **Preferred: cefiderocol, ceftazidime-avibactam, imipenem-relebactam**
- **Ceftolozane-tazobactam NOT suggested — tazobactam does not inhibit KPC**
- **Real-world activity lower than expected**: in one series of 44 KPC-PA isolates, 48% resistant to CAZ-AVI and 75% resistant to IMI-REL despite in vitro KPC inhibition by avibactam/relebactam
- **Final agent choice must be AST-guided**, not assumed from carbapenemase gene alone

MBL-Producing DTR-PA (NDM / VIM / IMP)

- **Preferred: cefiderocol monotherapy**
- CAZ-AVI, C/T, and IMI-REL all NOT suggested — none of their inhibitors act on MBLs
- VIM is the most common *P. aeruginosa* carbapenemase in the US — suspect MBL when an isolate resists all 3 other newer β-lactams
- **Aztreonam-avibactam / CAZ-AVI+ATM: limited activity vs. MBL-PA** (unlike Enterobacterales) — no CLSI/FDA breakpoints; use only when cefiderocol resistance precludes its use
- **Cefiderocol-resistant MBL-PA now being reported — leaves no active β-lactam option**

⚠ Real-world case highlighted in the 2026 guidance: US artificial-tears outbreak

2022–2023 outbreak of *P. aeruginosa* co-producing **VIM** (MBL) and **GES** (some alleles also carbapenemases) carbapenemases, traced to contaminated artificial-tear eyedrops — 81 confirmed infections across the US, with permanent vision loss in 17% and death in 5% of cases. Underscores why carbapenemase identification (**multiplex PCR** now covers KPC/NDM/VIM/IMP/OXA-48, often resulted before phenotypic AST) is increasingly critical to real-time DTR-PA management.

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

DTR *P. aeruginosa*: Resistance & Adjunctive Therapy

2026 UPDATE

2026: updated resistance-emergence data; refined combination & nebulized-therapy nuance

SUSCEPTIBILITY & TREATMENT-EMERGENT RESISTANCE (2019–2023 US DATA)

Agent	In vitro susceptibility*	Emergence of resistance on therapy
Cefiderocol	~99% (highest of the 4 agents)	< 10% (limited data)
Ceftolozane-tazobactam	61–74%	~20–24%; crosses > 50% with CAZ-AVI
Ceftazidime-avibactam	50–61%	~20–24%; crosses > 50% with C/T
Imipenem-relebactam	37–71%	0% in RCTs vs. ~24% in observational cohorts

**Ranges reflect two separate US surveillance cohorts (2019–2021 and 2020–2023); MEV (meropenem-vaborbactam) testing/discussion removed entirely from the 2026 DTR-PA chapter.*

COMBINATION THERAPY — unchanged principle

- Still **NOT routinely suggested** once susceptibility to a β-lactam is confirmed
- Last resort **only if NO β-lactam is active**: tobramycin (if susceptible) + β-lactam with MIC closest to breakpoint; **polymyxin B** preferred over colistin outside the urinary tract

NEBULIZED ANTIBIOTICS — refined in 2026

- Still **no routine use** when an active systemic β-lactam is confirmed (no RCT survival benefit)
- **NEW nuance: selective adjunctive use is reasonable if NO β-lactam is active AND clinical response to systemic therapy is suboptimal**

Clinical implication

Because emergence of resistance approaches 20–24% on CAZ-AVI/C/T therapy with substantial cross-resistance, **repeat AST** on any new/relapsed DTR-PA isolate from a patient recently exposed to one of the 4 agents — do not assume continued activity.

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

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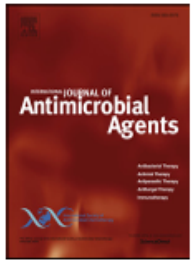


Short Communication

In vitro activity of cefepime-zidebactam, ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-relebactam, and other comparators against imipenem-non-susceptible *Pseudomonas aeruginosa* in Taiwan, 2022

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

- Taiwan Surveillance of Antimicrobial Resistance (TSAR) program
- Biennial program that collects bacterial isolates from 25 hospitals across Taiwan

Susceptibility of imipenem non-susceptible *Pseudomonas aeruginosa* from the TSAR program, 2022.

Antibiotics	R	I	S	MIC_{50}	MIC_{90}	MIC range
Cefepime	56.5	16.5	27.1	32	>32	1 - >32
Cefepime/zidebactam	1.2	9.4	89.4	4	16	0.5 - 32
Ceftazidime	60	7.1	32.9	64	>64	1 - >64
(Zavicefta) Ceftazidime/avibactam	35.3	0	64.7	8	32	1 - >64
(Zerbaxa) Ceftolozane/tazobactam	18.8	10.6	70.6	2	32	≤0.25 - >32
Imipenem	88.2	11.8	0	16	>16	4 - >16
(Recarbrio) Imipenem/relebactam	16.5	20	63.5	2	8	0.25 - >16
Meropenem	83.5	4.7	11.8	16	32	0.5 - >32
Piperacillin/tazobactam	63.5	11.8	24.7	64	>64	≤8 - >64
Ciprofloxacin	58.8	5.9	35.3	>2	>2	≤0.06 - >2
Levofloxacin	68.2	8.2	23.5	16	>32	≤0.25 - >32
Gentamicin	38.8	3.5	57.6	4	>8	≤1 - >8
Tobramycin	42.4	4.7	52.9	≤1	>8	≤1 - >8
Aztreonam	57.6	18.8	23.5	32	>64	2 - >64
Colistin	10.6	89.4	-	2	4	≤0.25 - >4

Int J Antimicrob Agents.2025 Sep;66(3):107550.

In vitro **cross-susceptibilities** of *P. aeruginosa* isolates between novel BLBLIs

	Susceptible to			
	FEP-ZID	CZA	C/T	I/R
Non-susceptible to CZA (n = 30)	73.3% (22/30)	-	40% (12/30)	33.3% (10/30)
Non-susceptible to C/T (n = 25)	80.0% (20/25)	28% (7/25)	-	32.0% (8/25)
Non-susceptible to I/R (n = 31)	71.0% (22/31)	35.5% (11/31)	45.2% (14/31)	-

Shown as % (n/N); n: number of susceptible isolates; N: number of non-susceptible isolates.

FEP-ZID: cefepime-zidebactam, CZA : ceftazidime-avibactam, C/T: ceftolozane-tazobactam, I/R: imipenem-relebactam

There was substantial cross-resistance among CZA, C/T, and I/R.

Int J Antimicrob Agents.2025 Sep;66(3):107550.

Susceptibility of imipenem-non-susceptible *Pseudomonas aeruginosa* with different **genotypes** and phenotypes, 2018 vs 2022

P. aeruginosa isolates	No.	% susceptible										
		FEP	FEP-ZID	CAZ	CZA	IPM	I/R	MEM	C/T	CIP	LVX	COL[a]
TSAR 2022	85	27.1	89.4	32.9	64.7	0	63.5	11.8	70.6	35.3	23.5	89.4
with $bla_{KPC\text{-}like}$	1	0	100	0	0	0	0	0	0	100	0	100
with class B carbapenemase gene	8	12.5	87.5	0	25	0	0	0	0	12.5	0	75
without carbapenemase gene	76	28.9	89.5	36.8	69.7	0	71.1	13.2	78.9	36.8	26.3	90.8
TSAR 2018	81	45.7	91.4	43.2	81.5	0	85.2	28.4	-	35.8	28.4	96.3
with class B carbapenemase gene	4	0	75	0	0	0	0	0	-	0	0	75
without carbapenemase gene	77	48.1	92.2	45.5	85.7	0	89.6	29.9	-	37.7	29.9	97.4

Abbreviations: FEP, cefepime; FEP-ZID, cefepime-zidebactam; CAZ, ceftazidime; CZA, ceftazidime-avibactam; C/T, ceftolozane-tazobactam; IPM; imipenem; I/R, imipenem-relebactam; MEM, meropenem; CIP, ciprofloxacin; LVX, levofloxacin; COL, colistin.

[a] Isolates with colistin MIC $\leq$ 2 mg/L (classified as intermediate by the CLSI criteria).

- Carbapenemase gene in CRPA: 4.9% (4/81) in 2018 => 10.6% (9/85) in 2022
- Class B carbapenemase genes (VIM and IMP) predominated among carbapenemase-positive CRPA

Int J Antimicrob Agents.2025 Sep;66(3):107550.

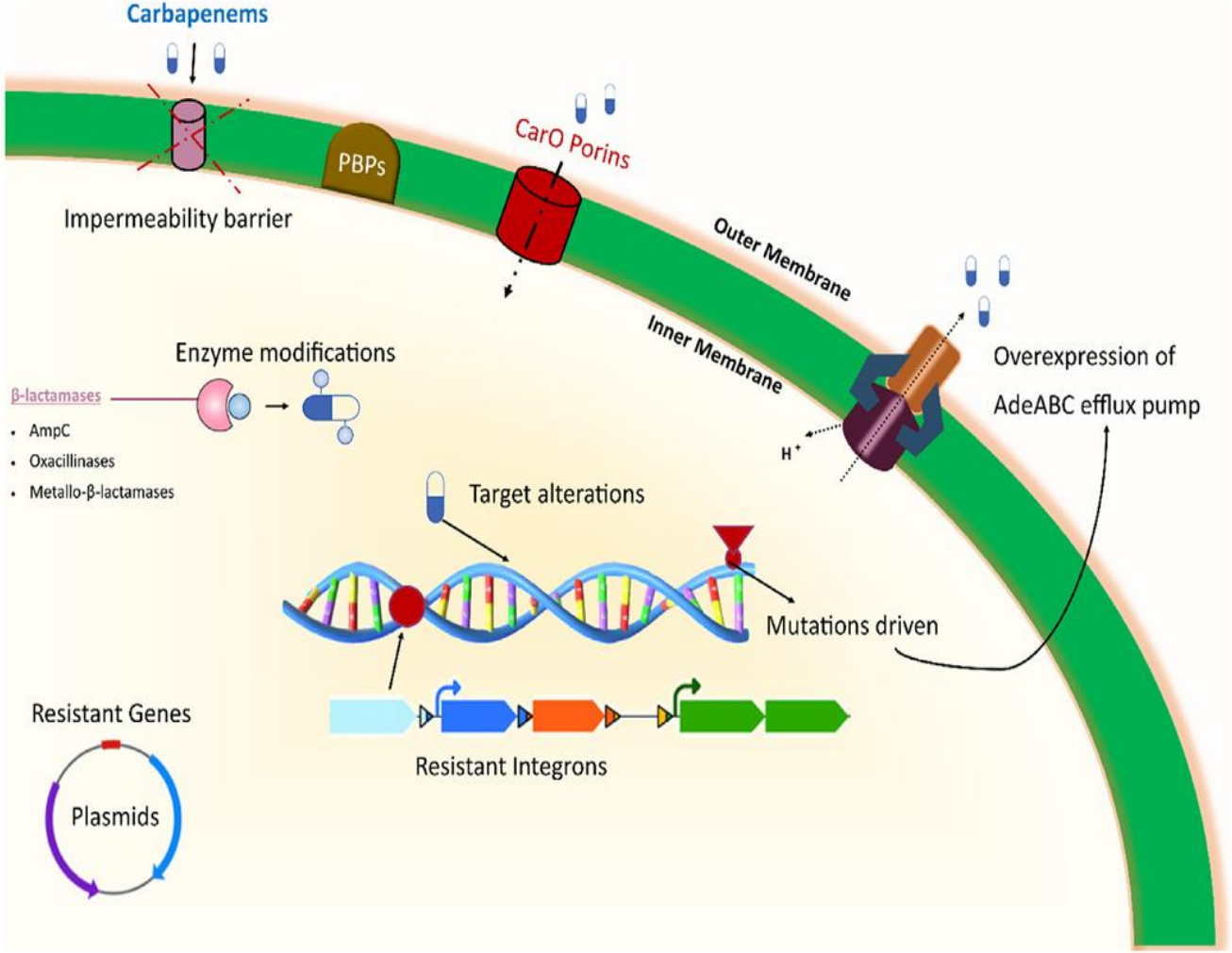
Carbapenem-Resistant *Acinetobacter baumannii* (CRAB)

Common resistance mechanisms of CRAB infections

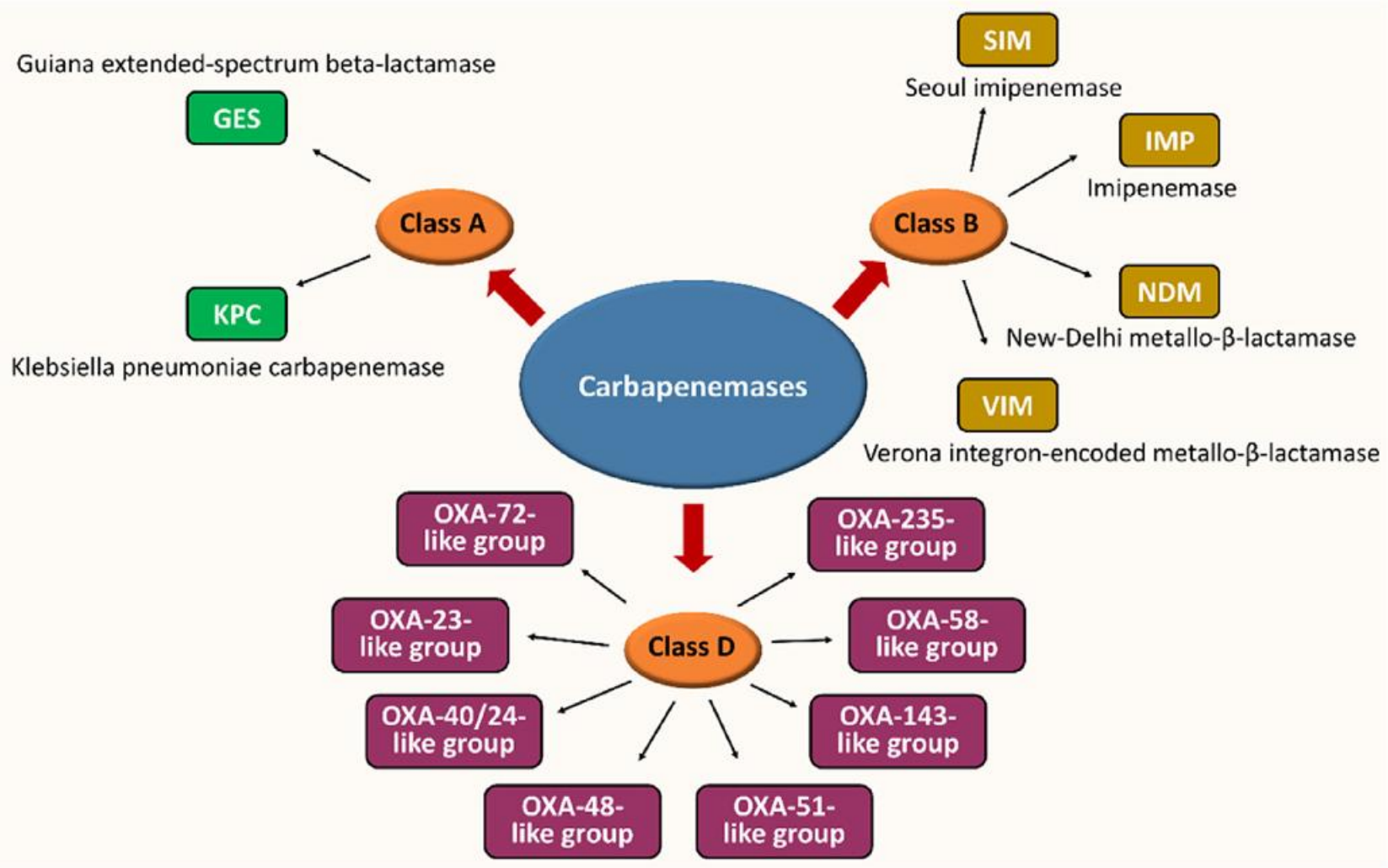
- **Reduced outer-membrane permeability (porin loss)**
- **Efflux-pump overexpression**
- **Enzymatic inactivation of antibiotics**
  - OXA-type carbapenemases
  - Metallo-β-lactamases
  - AmpC β-lactamases

***. Acquisition and mobilization of resistance genes**

- Insertion sequences
- Transposons
- Integrons
- Resistance islands
- Conjugative plasmids



Acquired resistance mechanisms in *A. baumannii*



Carbapenemases in CRAB: OXA-type enzymes dominate

Global WGS cohort: 313 phenotypically confirmed CRAB isolates from 114 centers in **47 countries** between 2012 and 2016

Acquired carbapenemase gene detected

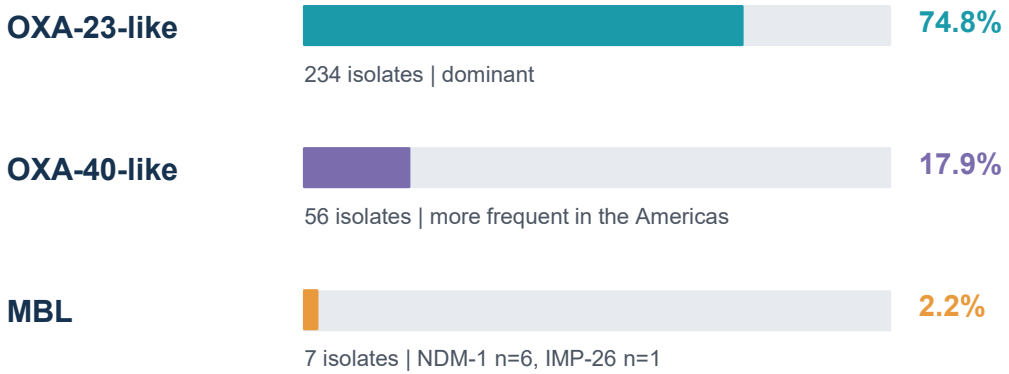
96%

300 / 313 isolates

Remaining ~4%: carbapenem resistance attributed to **ISAba1** upstream of intrinsic *bla*OXA-51-like

Major carbapenemase families

Percentages below are among all 313 CRAB isolates



- **Carbapenem resistance in CRAB was overwhelmingly linked to acquired class D OXA-type carbapenemases, with OXA-23-like as the main determinant. (not primarily KPC/NDM-driven)**
- Local epidemiology matters: OXA-40-like enzymes were enriched in Latin/North America; MBL-positive CRAB remained uncommon.

Carbapenem resistance is OXA-driven and dominated by OXA-23-like in Taiwan

Study cohort: 269 CRAB blood isolates from 4 tertiary medical centers in Taiwan, 2009–2013

92.2% **had an acquired carbapenemase gene**

(248/269; OXA-23-like or OXA-24-like)

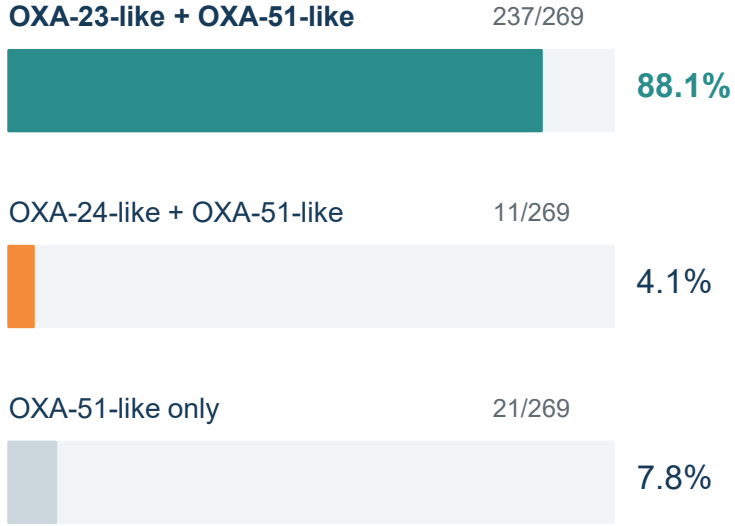
Key findings

- **Intrinsic *bla*OXA-51-like:** 269/269 (100%)
- **Dominant acquired gene:** *bla*OXA-23-like
- ***bla*OXA-24-like was uncommon** but associated with higher carbapenem MICs
- **No *bla*OXA-58-like or MBL genes** detected

Taiwanese CRAB bloodstream isolates were predominantly OXA-23-like producers.

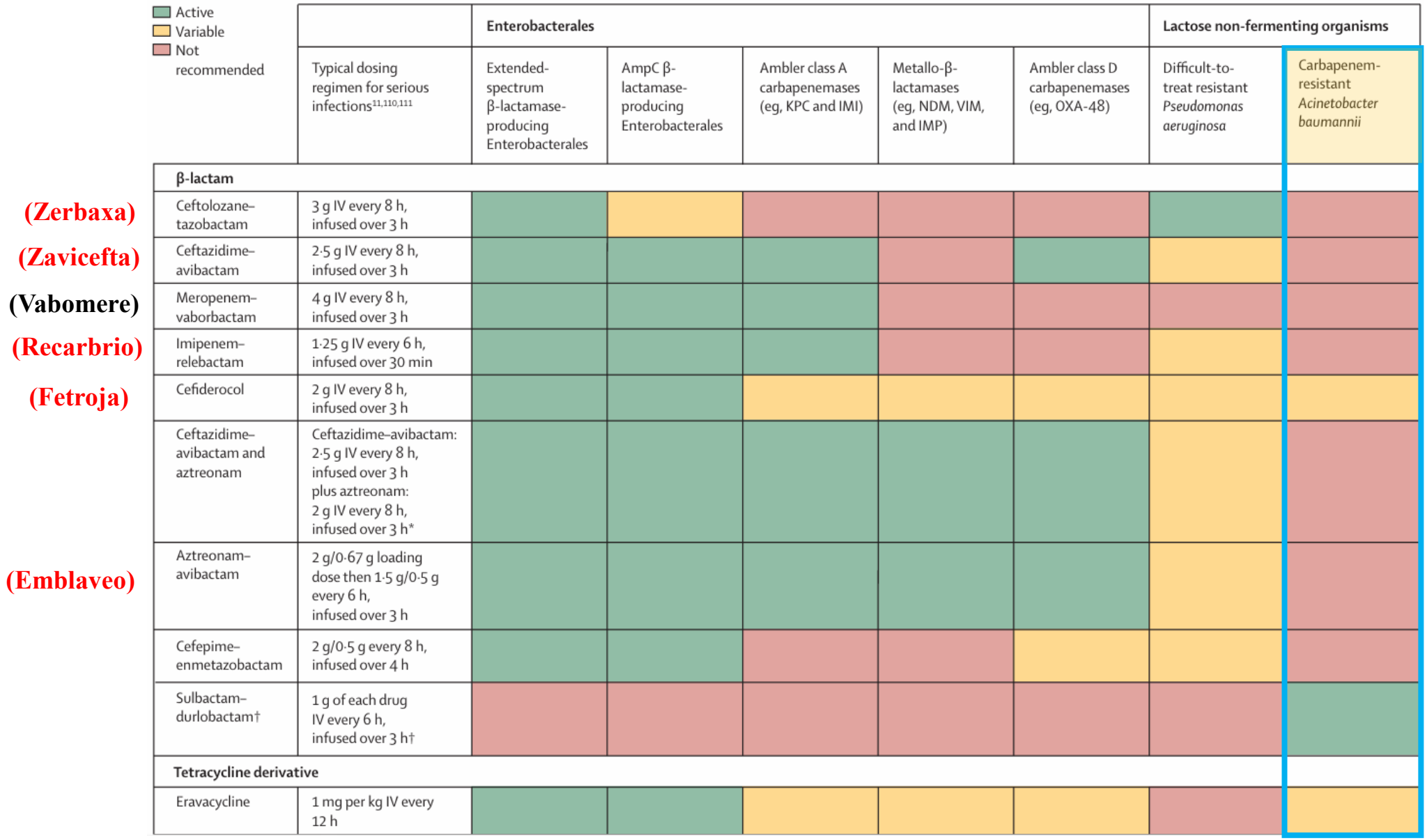
Carbapenemase gene patterns

Percentage of 269 CRAB blood isolates



Class D OXA-type predominated; MBL-encoding genes were not detected in this cohort.

New antibiotic agents for the treatment of multidrug-resistant GNB infections



Active
Variable
Not recommended

	Typical dosing regimen for serious infections[11,110,111]	Enterobacterales					Lactose non-fermenting organisms	
		Extended-spectrum β-lactamase-producing Enterobacterales	AmpC β-lactamase-producing Enterobacterales	Ambler class A carbapenemases (eg, KPC and IMI)	Metallo-β-lactamases (eg, NDM, VIM, and IMP)	Ambler class D carbapenemases (eg, OXA-48)	Difficult-to-treat resistant *Pseudomonas aeruginosa*	Carbapenem-resistant *Acinetobacter baumannii*
β-lactam								
(Zerbaxa) Ceftolozane–tazobactam	3 g IV every 8 h, infused over 3 h							
(Zavicefta) Ceftazidime–avibactam	2·5 g IV every 8 h, infused over 3 h							
(Vabomere) Meropenem–vaborbactam	4 g IV every 8 h, infused over 3 h							
(Recarbrio) Imipenem–relebactam	1·25 g IV every 6 h, infused over 30 min							
(Fetroja) Cefiderocol	2 g IV every 8 h, infused over 3 h							
Ceftazidime–avibactam and aztreonam	Ceftazidime–avibactam: 2·5 g IV every 8 h, infused over 3 h plus aztreonam: 2 g IV every 8 h, infused over 3 h*							
(Emblaveo) Aztreonam–avibactam	2 g/0·67 g loading dose then 1·5 g/0·5 g every 6 h, infused over 3 h							
Cefepime–enmetazobactam	2 g/0·5 g every 8 h, infused over 4 h							
Sulbactam–durlobactam†	1 g of each drug IV every 6 h, infused over 3 h†							
Tetracycline derivative								
Eravacycline	1 mg per kg IV every 12 h							

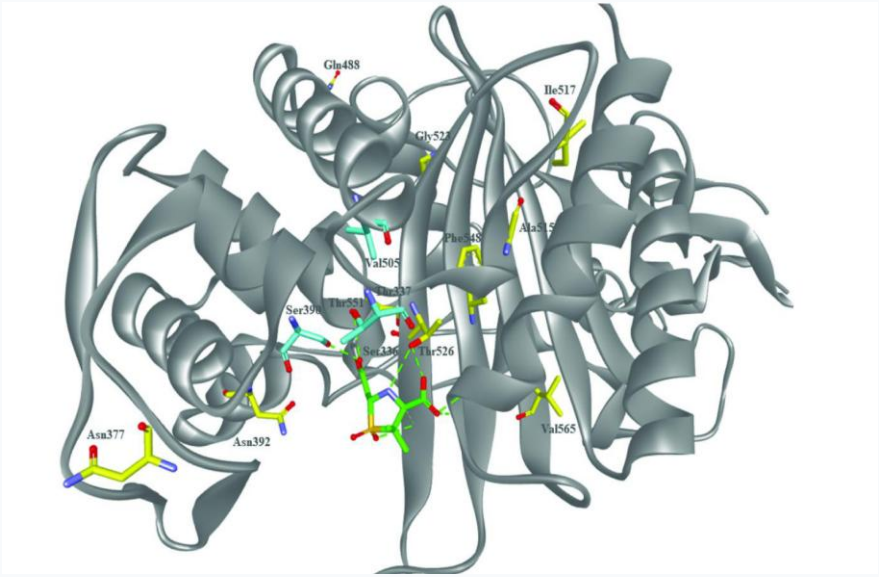
Lancet.2025 Jan 18;405(10474):257-272

Why Sulbactam–Durlobactam Works Against CRAB

Mechanistic rationale: sulbactam kills; durlobactam protects sulbactam from OXA-mediated hydrolysis

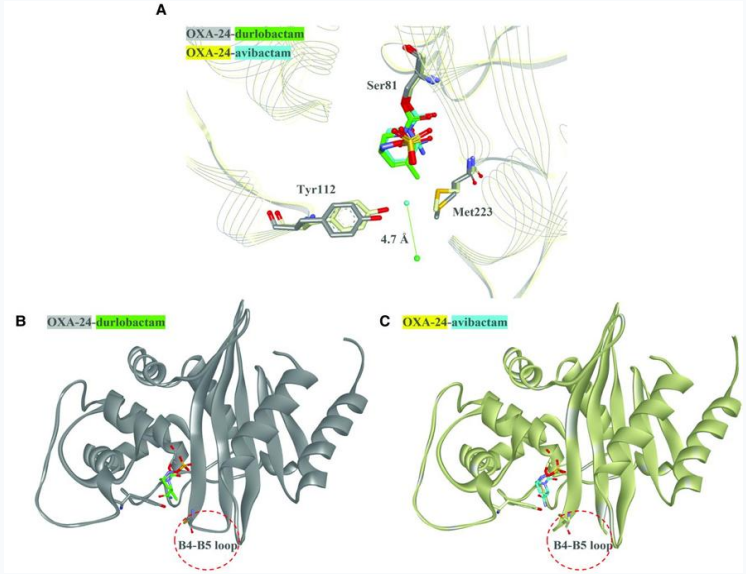
1. Sulbactam: direct antibacterial activity

Binds *A. baumannii* PBP3 → inhibits cell-wall synthesis



2. Durlobactam: β-lactamase inhibition

Inhibits class A/C/D serine β-lactamases, including OXA-23, OXA-24, OXA-58



Sulbactam
active PBP-targeting agent

→

Durlobactam
blocks OXA/ADC enzymes

→

Restored activity
against CRAB

- Sulbactam–durlobactam is rational for OXA-dominant CRAB because sulbactam targets PBP3, while durlobactam inhibits class D OXA β-lactamases and protects sulbactam from hydrolysis.
- Durlobactam does not inhibit metallo-β-lactamases such as NDM.

Clin Infect Dis.2023 May 1;76(Suppl 2):S194-S201.

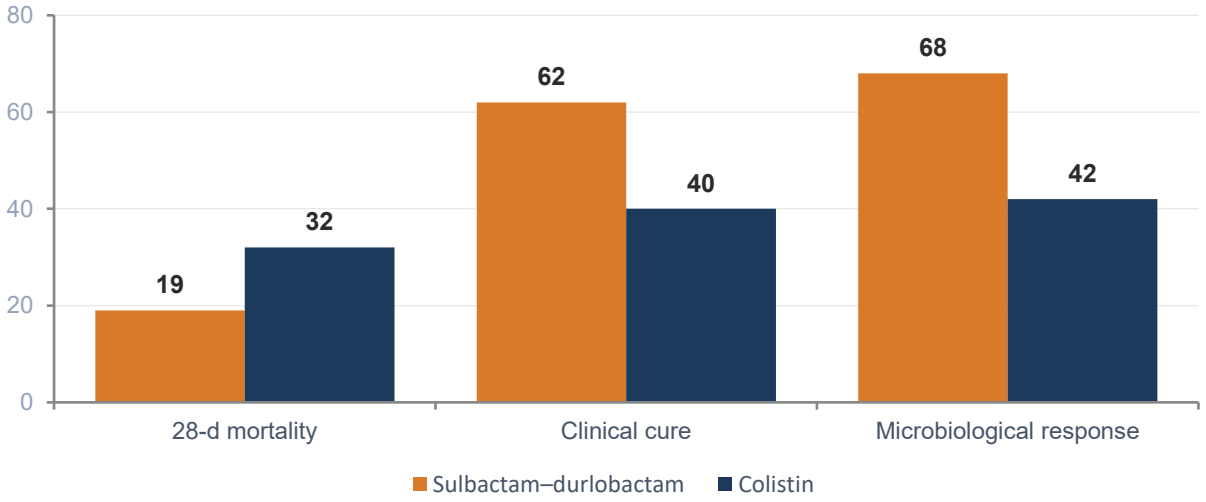
Sulbactam–Durlobactam vs Colistin (ATTACK)

Sulbactam–durlobactam vs colistin for serious carbapenem-resistant ABC infections

*Multicentre phase 3 RCT, 59 sites / 16 countries, **Non-inferiority design** (margin +20%), both arms received imipenem-cilastatin background*

POPULATION	DESIGN	COMPARISON	PRIMARY ENDPOINT
125 CRAB (efficacy) · 181 rand.	Phase 3 non-inferiority RCT	SUL-DUR vs colistin (+imipenem)	28-day all-cause mortality

Efficacy: SUL-DUR vs Colistin (%)



Key results — SUL-DUR vs colistin

–13.2%
28-day mortality difference (primary)
95% CI –30.0 to 3.5 · 19% vs 32%

13% vs 38%
Nephrotoxicity (modified RIFLE)
P < 0.001 · favours SUL-DUR

62% vs 40%
Clinical cure rate
microbiological response 68% vs 42%

➢ SUL-DUR was non-inferior to colistin for 28-day mortality with markedly less nephrotoxicity and higher clinical cure — the basis for preferring SUL-DUR, with high-dose amp-sulbactam as the alternative.

. SUL-DUR = sulbactam-durlobactam; ABC = A. baumannii-calcoaceticus complex; RIFLE = kidney-injury score.

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

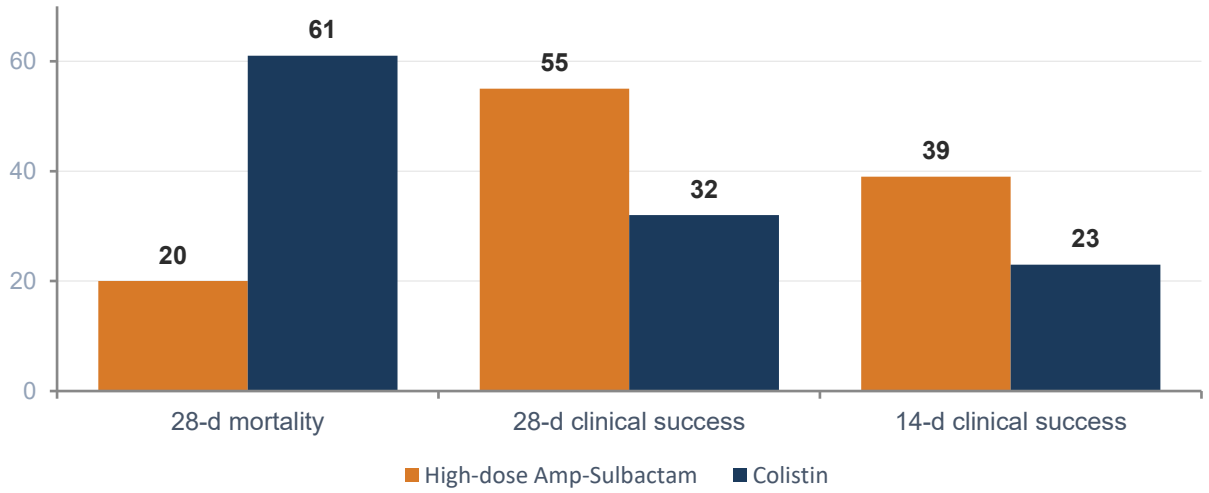
High-Dose Ampicillin-Sulbactam vs Colistin

Colistin-based vs high-dose ampicillin/sulbactam-based combination therapy for CRAB nosocomial pneumonia

Single-center retrospective cohort, university-affiliated hospital, South Korea

POPULATION	AMP-SULBACTAM ARM	COLISTIN ARM	PRIMARY ENDPOINT
N = 179 CRAB pneumonia	n = 95 · sulbactam 9 g/day	n = 84 · loading + maintenance	28-day all-cause mortality

Outcomes: AMP-SUL vs Colistin (%)



Adjusted relative risk (aRR) — favours amp-sulbactam

aRR 0.16 — **28-day mortality**
95% CI 0.08 – 0.32 (20% vs 61%)

aRR 2.71 — **28-day clinical success**
95% CI 1.14 – 5.20 (55% vs 32%)

aRR 0.56 — **28-day kidney injury (RIFLE)**
95% CI 0.40 – 0.79 (0.63 vs 1.06)

- High-dose amp-sulbactam–based combination therapy was associated with lower 28-day mortality, higher clinical success, and less nephrotoxicity than colistin-based therapy.

CRAB = carbapenem-resistant Acinetobacter baumannii; aRR = adjusted relative risk; RIFLE = kidney-injury score.

CRAB Treatment: What Changed — 2024 → 2026 IDSA Guidance

Section 5 restructured from 10 questions (Q5.1–5.10) to 6 questions (Q5.1–5.6)

UPDATED

Q5.1–5.5

Alternative agents reframed as “bridging therapy” only

High-dose ampicillin-sulbactam, cefiderocol, minocycline, and polymyxin B are no longer parallel alternatives — they are now positioned strictly as a bridge until SUL-DUR (+ carbapenem) is available, or for use when SUL-DUR resistance is confirmed.

UPDATED

Q5.4

Minocycline CLSI breakpoint lowered

Susceptible breakpoint tightened from ≤4 to ≤1 μg/mL (2025 CLSI). CRAB susceptibility to minocycline falls from a previously reported 60–80% to now <50%.

UPDATED

Q5.3

Cefiderocol evidence base expanded — but still inconsistent

2024 cited only CREDIBLE-CR. 2026 adds 2 more RCTs and 2 meta-analyses; results conflict (RCT data favor comparators, meta-analyses favor cefiderocol). Remains an alternative agent only.

UPDATED

Q5.6

Nebulized antibiotics: narrow exception added

Still not routine, but “selective use may be reasonable” when SUL-DUR resistance is documented or systemic response is suboptimal — a caveat absent from the 2024 text.

UPDATED

removed

Rifamycins and routine extended-infusion carbapenem dropped

The standalone 2024 questions on rifamycin combinations (Q5.9) and extended-infusion carbapenem ± colistin (Q5.8) have been removed — consistent lack of survival benefit across trials.

CRAB: Preferred Regimen (2026 IDSA)

Question 5.1 — Sulbactam-Durlobactam

PREFERRED

Sulbactam-Durlobactam (SUL-DUR) + Imipenem or Meropenem

SUL-DUR: 1 g sulbactam / 1 g durlobactam IV q6h over 3h (CrCl ≥130 mL/min: q4h)

Add imipenem or meropenem for the full treatment course — may stop the carbapenem after sustained clinical improvement in prolonged-therapy infections (e.g., osteomyelitis)

ATTACK TRIAL: SUL-DUR + Imipenem vs Colistin + Imipenem (n=125 CRAB pneumonia / bloodstream infection)

28-Day Survival	Clinical Cure	Microbiologic Response*	Nephrotoxicity*
81% vs 68%	62% vs 40%	68% vs 42%	13% vs 38%

**Microbiologic response and nephrotoxicity retained from the original ATTACK dataset; the 2026 text re-reports survival (formerly framed as mortality: 19% vs 32%) and clinical cure specifically.*

2026 NEW

Why add a carbapenem to SUL-DUR? Complementary PBP binding — sulbactam engages PBP1a/1b & PBP3, imipenem/meropenem preferentially binds PBP2, and durlobactam protects both from β-lactamase hydrolysis. In vitro, adding a carbapenem lowers sulbactam MICs 1–2-fold and produces >2-log CFU/mL reductions in time-kill assays not seen with SUL-DUR alone (clinical confirmation still pending).

2026 NEW

If SUL-DUR resistant (MIC ≥16/4 µg/mL) or an MBL gene (e.g., blaNDM) is identified → switch to a non-sulbactam combination (cefiderocol, minocycline, polymyxin B, or tigecycline). Limited in vitro data suggest SUL-DUR may still enhance cefiderocol activity in this setting.

CRAB: Bridging Therapy (SUL-DUR Unavailable)

Question 5.2–5.5 — reframed in 2026: no longer a parallel "alternative," only a bridge or resistance workaround

BRIDGE / SUL-DUR-RESISTANCE OPTION ONLY

High-Dose Ampicillin-Sulbactam (9 g sulbactam/day) + ONE Partner Agent

9 g amp-sulbactam (3 g sulbactam) IV q8h over **4h** OR 27 g as continuous 24h infusion — use only until SUL-DUR + carbapenem can be started

2026 NEW

Only ~10% of CRAB isolates are truly sulbactam-susceptible, and non-reference AST methods may misclassify resistant isolates as "susceptible." High-dose, prolonged-infusion dosing is favored even for isolates reported as susceptible.

Minocycline

preferred tetracycline

UPDATED

- 2025 CLSI breakpoint tightened: ≤1 µg/mL (was ≤4)
- CRAB susceptibility now <50% (was 60–80%)
- 200 mg IV/PO q12h — no RCT data, observational only

Cefiderocol

alternative, combination only

UPDATED

- >90% in vitro susceptibility (~60% if NDM-producing)
- 3 RCTs + 2 meta-analyses — conflicting results
- Reserve for SUL-DUR resistance or as bridge

Polymyxin B

alternative, combination only

- ~85% of isolates: MIC ≤2 µg/mL (intermediate category)
- 6 RCTs of colistin monotherapy: survival only 27–57%
- Preferred over colistin (more reliable PK, non-renal clearance)

Tigecycline (high-dose 200 mg→100 mg q12h) remains a reasonable alternative to minocycline but lacks CLSI/FDA breakpoints for A. baumannii.

CRAB: Treatment at a Glance (2026 IDSA)

Bridging framework replaces the 2024 "parallel alternative" model

STEP 1 Confirm infection (not colonization)	STEP 2 SUL-DUR available?	STEP 3 Partner agent for bridging / resistance	STEP 4 SUL-DUR resistant (MIC ≥16/4) or MBL+?
CRAB frequently colonizes respiratory/wound sites. Treat only confirmed invasive infection.	YES → SUL-DUR + imipenem or meropenem (PREFERRED) NO → Bridge with high-dose ampicillin-sulbactam (9 g sulbactam/day) + ONE partner agent until SUL-DUR can be started	Minocycline (preferred tetracycline, CLSI ≤1 µg/mL) or Cefiderocol (>90% susceptible, alternative) or Polymyxin B (~85% MIC ≤2, alternative)	Switch to non-sulbactam combination (cefiderocol + minocycline or polymyxin B) → consult ID specialist

• Combination therapy (≥2 agents) still recommended until clinical improvement. • Carbapenem may stop after sustained improvement in prolonged infections (e.g., osteomyelitis). **• Nebulized antibiotics: not routine, but selective use reasonable if SUL-DUR-resistant or response suboptimal (2026 update).**

CRAB: Cefiderocol — Expanded 2026 Evidence

Question 5.3 — 2 new RCTs + 2 meta-analyses added since 2024 (CREDIBLE-CR only); results remain inconsistent

3 RANDOMIZED TRIALS

CREDIBLE-CR subgroup (n=54)

28-day survival: 51% (cefiderocol) vs 82% (mostly polymyxin-based)

CRAB pneumonia RCT (n=47)

14-day survival: 78% (cefiderocol) vs 83% (high-dose extended-infusion meropenem)

CRAB bacteremia RCT (n=25)

30-day survival: 55% vs 50% (mostly amp-sulbactam + polymyxin)

2 META-ANALYSES

1 RCT + 7 observational studies

Pooled 30-day survival: 58% (cefiderocol) vs 40% (alternative)

4 observational studies

30-day survival: 62% (cefiderocol) vs 37% (alternative)

Note: no observational-study comparator arm included sulbactam-durlobactam; no head-to-head cefiderocol vs SUL-DUR data exist.

Panel conclusion: Cefiderocol remains an ALTERNATIVE agent only, always in combination, reserved for SUL-DUR resistance or as a bridge until SUL-DUR is available.

UPDATED

Nebulized antibiotics (Q5.6)

Still not routine — no RCT (3 trials) shows survival benefit. New in 2026: selective use "may be reasonable" if **SUL-DUR-resistant** or **systemic response is suboptimal**.

REMOVED

Dropped from 2026 guidance

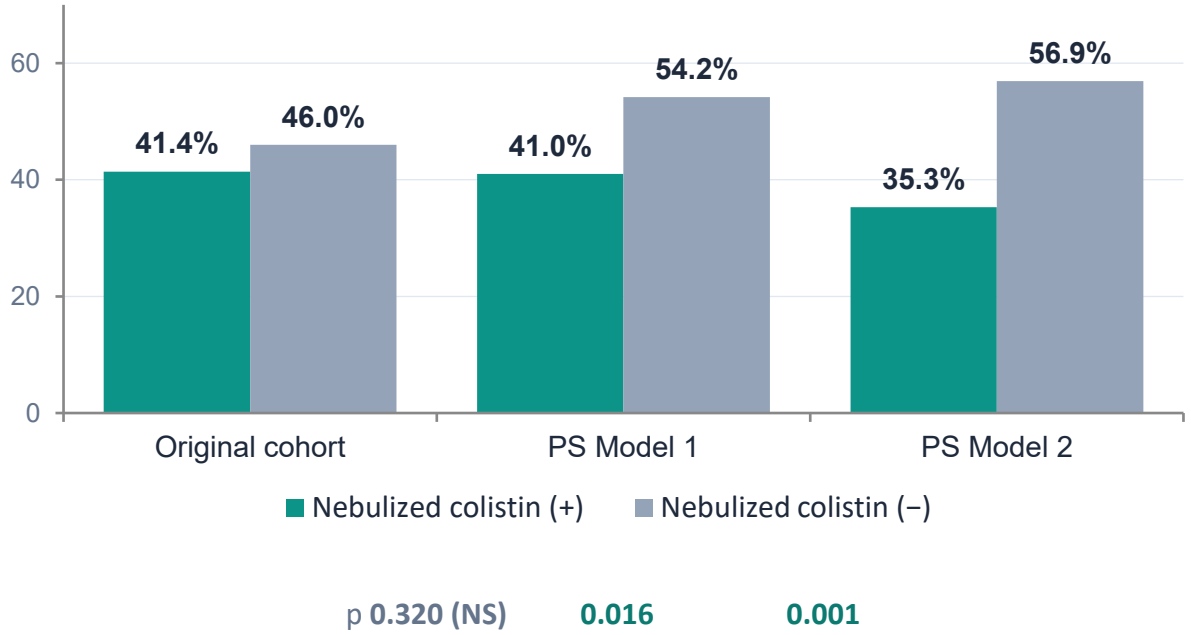
Rifamycin combinations (3 RCTs, no benefit) and routine **extended-infusion carbapenem ± colistin** (2 large RCTs, no benefit) are no longer discussed as standalone questions.

Adjunctive Nebulized Colistin Reduces Day-14 Clinical Failure — Not Mortality — in CRAB-Predominant CR-GNB Pneumonia (T-CARE)

Feng J-Y et al., T-CARE Group · Retrospective multicentre, 5 Taiwan ICUs · n=507 colistin-susceptible CR-GNB nosocomial pneumonia · ***CRAB 76.5%***

Concurrent antibiotics: colistin (42%), sulbactam (33%), tigecycline (37%)

Day-14 clinical failure rate (%)



✓ **Independent reduction in day-14 clinical failure**

Multivariate aOR **0.59 (0.37–0.92)** in Model 1; **0.37 (0.21–0.65)** in Model 2 (time-window adjusted).

≠ **No independent mortality benefit**

14-day mortality not reduced in time-dependent analysis (both models). Original **14.9% vs 21.8%**, p 0.061 — trend only.

\+ **Secondary signals**

Fewer new dialysis events: **5.0% vs 9.2%**.

- CRAB made up 76.5% of the cohort (85–88% after matching), but no CRAB-specific outcome analysis performed.
- Jet (not vibrating-mesh) nebulizer may underestimate efficacy.

Different resistance mechanism in CR-GNB

- **CRKP**: 50% CR in KP; 50-80% carbapenemase producer; KPC predominant, MLB increasing

- **CRPA**: 20% CR in PA; intrinsic antibiotic resistance (porin, efflux pump, AmpC) predominant, <10% carbapenemase

- **CRAB**: >70% CR in AB; > 90% carbapenemase producer, OXA-23 predominant

Take-Home Messages: CRGNB in the ICU

Do not use one algorithm for all carbapenem-resistant GNB: CRE = enzyme logic, DTR-PA = AST logic, CRAB = sulbactam logic

CRE

Carbapenemase-directed therapy

- Define the mechanism: non-CPE, KPC, MBL/NDM, or OXA-48-like
- KPC/OXA-48-like: use an active novel BL/BLI when susceptible
- MBL/NDM: aztreonam-avibactam or cefiderocol
- Once an active β-lactam is confirmed, avoid routine polymyxin or combination therapy

DTR-PA

Phenotype-driven therapy

- If a traditional β-lactam remains susceptible, use high-dose extended infusion
- If DTR: C/T (PN), CAZ-AVI, or IMI-REL; cefiderocol for MBL-producing isolates
- Repeat AST after recent novel β-lactam exposure or recurrent infection
- Expect cross-resistance among C/T, CAZ-AVI, and imipenem-relebactam

CRAB

Sulbactam-first combination

- Confirm true infection; respiratory and wound colonization are common
- Preferred: SUL-DUR + imipenem-cilastatin or meropenem
- If SUL-DUR unavailable: high-dose amp-sulbactam + one active partner
- Avoid routine colistin-carbapenem, rifampin, standard-dose tigecycline, and routine nebulized antibiotics

Taiwan / local lens: CRAB burden is very high; MBL-CRE is rising; CRPA carbapenemase remains uncommon but MBL predominate when present.

ICU execution: prior cultures + local antibiogram → rapid AST/MIC/carbapenemase testing → source control + PK/PD optimization → fast de-escalation.

Abbreviations: BL/BLI = β-lactam/β-lactamase inhibitor; CAZ-AVI = ceftazidime-avibactam; C/T = ceftolozane-tazobactam; IMI-REL = imipenem-relebactam; SUL-DUR = sulbactam-durlobactam.


thank
you