The Smart Choice of Novel Antibiotics in the Era of CRE in ICU

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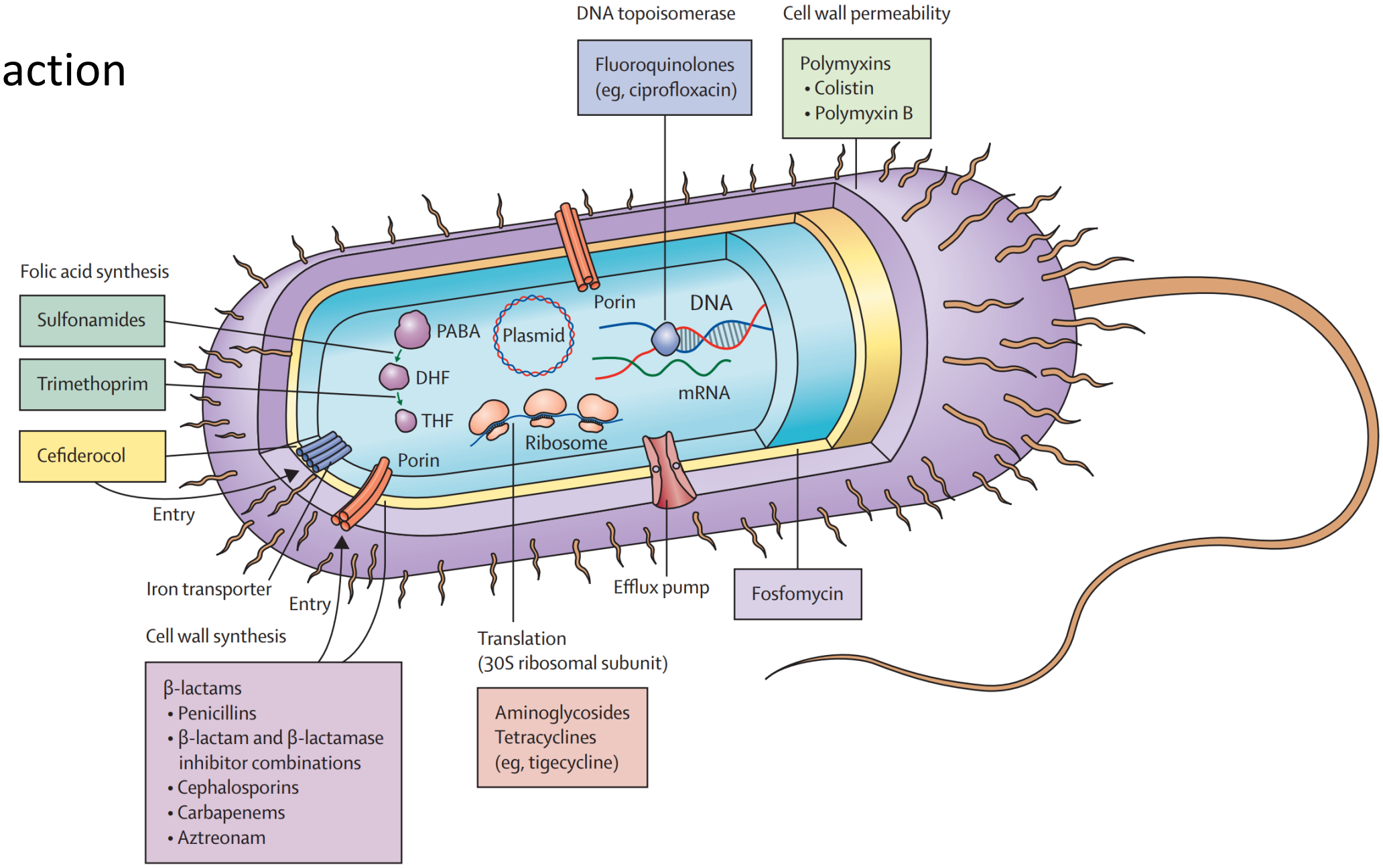
Mechanism of action for antibiotics



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

WHO priority pathogens

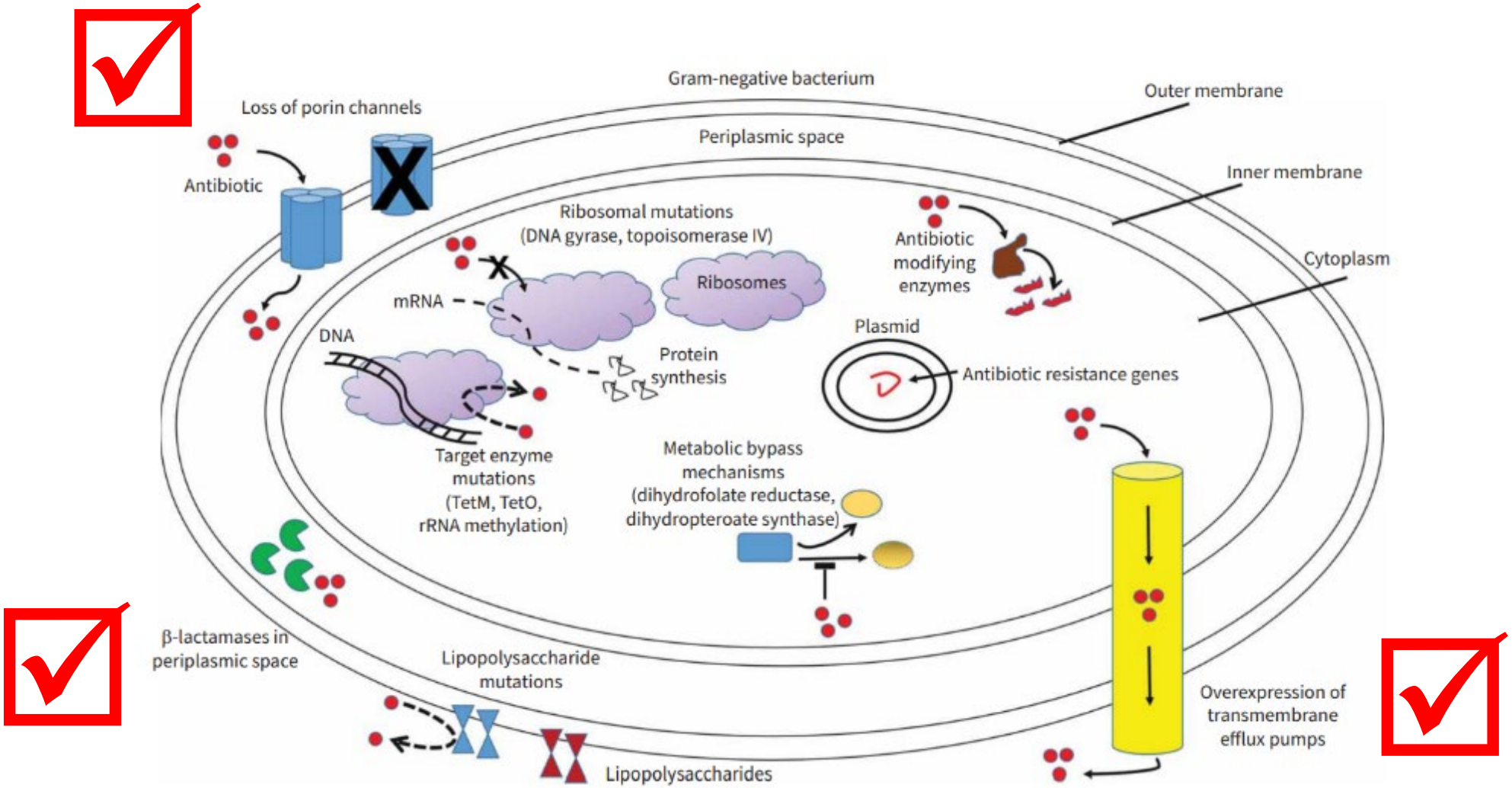
Priority	Pathogen	Resistance
Critical	*Acinetobacter baumannii*	Carbapenem
	Pseudomonas aeruginosa	Carbapenem
	Enterobacteriaceae	Carbapenem Third generation cephalosporin
High	*Enterococcus faecium*	Vancomycin
	Staphylococcus aureus	Methicillin Vancomycin
	Helicobacter pylori	Clarithromycin
	Campylobacter	Fluoroquinolone
	Salmonella spp.	Fluoroquinolone
	Neisseria gonorrhoeae	Fluoroquinolone Third generation cephalosporin
Medium	*Streptococcus pneumoniae*	Penicillin
	Haemophilus influenzae	Ampicillin
	Shigella spp.	Fluoroquinolone

Carbapenem resistance rates by region

	Asia-Pacific	Europe	North America
Acinetobacter baumannii	25-90.5	2.5-100	11.4-50.4
Pseudomonas aeruginosa	10.3-50	0-56.4	10.3-58.5
Klebsiella pneumoniae	1.6-25	0.2-58.6	3.1-12.9
Escherichia coli	0-7.1	0-7	0.2-4.3

CID 2019:69 (Suppl 7)

Mechanisms of antibiotics resistance in GNB

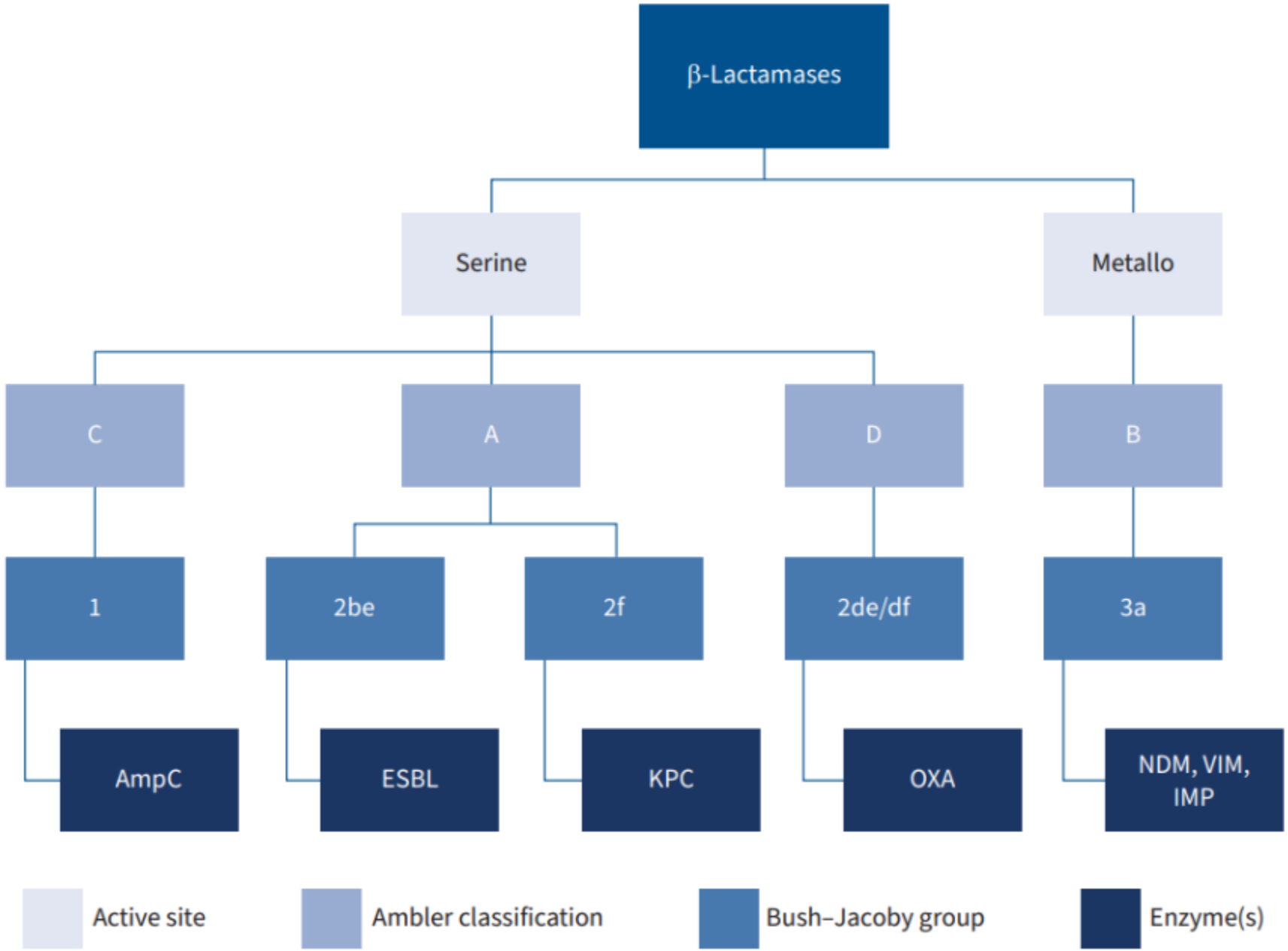


Eur Respir Rev. 2022 Oct 19;31(166):220068.

Mechanisms of GNB resistance

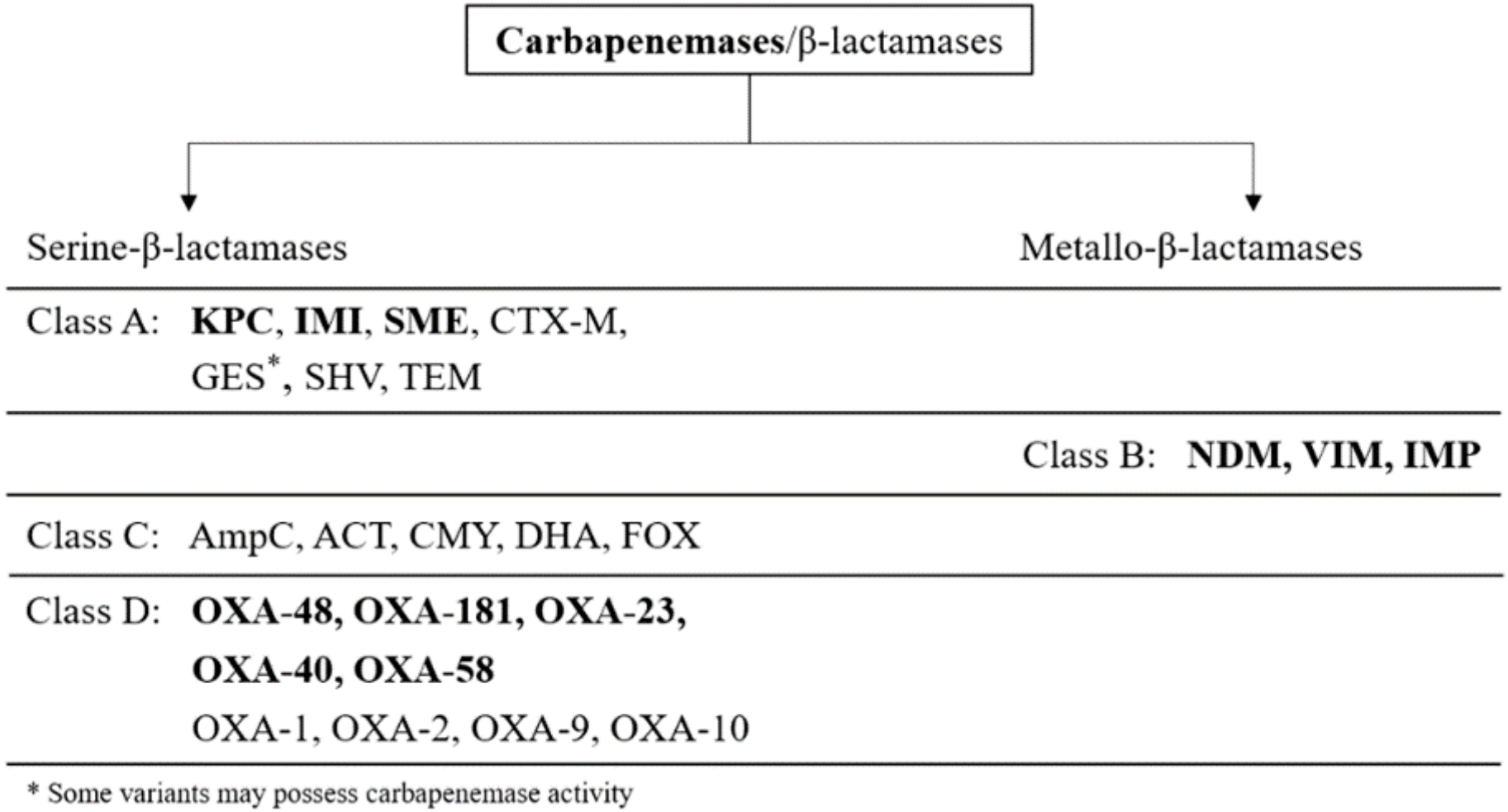
	Categories	Examples
β-lactams[19,20] (eg, piperacillin–tazobactam, cefepime, meropenem, and ceftazidime–avibactam)		
Antibiotic modification	β-lactamase enzymes	Extended-spectrum β-lactamases (SHV, TEM, and CTX-M); carbapenemases (KPC, OXA-48, NDM, IMP, and VIM)
Decreased entry	Porin mutations	*Escherichia coli* (OmpC and OmpF); *Klebsiella pneumoniae* (OmpK35 and OmpK36); *Pseudomonas aeruginosa* (OprD); *Acinetobacter baumannii* (CarO)
Increased efflux	Efflux pumps	*E coli* (AcrAB-TolC); *P aeruginosa* (MexAB-OprM); *A baumannii* (AdeABC and AdeIJK)
Aminoglycosides[21–24] (eg, gentamicin, tobramycin, and amikacin)		
Antibiotic modification	Aminoglycoside-modifying enzymes (AMEs)	N-acetyltransferases (AAC); O-adenyltransferases (ANT); O-phosphotransferases (APH)
Decreased entry	Alterations in bacterial cell outer membrane	PhoPQ; PmrAB; ParRS; CprRS
Target alteration	16S-ribosomal RNA methyltransferases (RMTs)	ArmA; RmtA; RmtB; RmtC; RmtD; RmtE; RmtF; RmtG; NpmA; NpmB; NpmC
Target alteration	30S ribosome subunit binding site mutations	*rrs* and *rpsL* gene mutations
Tetracycline derivatives[25–28] (eg, minocycline, tigecycline, and eravacycine)		
Antibiotic modification	Increased breakdown	Tet(X); Tet(X2); Tet(X3); Tet(X4)
Increased efflux	Major facilitator superfamily (MFS) of transporters	Tet(A); Tet(B); Tet(C); Tet(D)
Increased efflux	Resistance nodulation division (RND)-type multidrug efflux pumps	AdeABC; TmexCD1-ToprJ1
Target alteration	Ribosomal protein alteration	RpsJ
Fluoroquinolones[29,30] (eg, ciprofloxacin)		
Antibiotic modification	Increased breakdown	AME: AAC(6′)-Ib-cr
Increased efflux	Efflux pumps	QepA; OqxAB
Target alteration	Topoisomerase substitution	GyrA; GyrB; ParC; ParE
Target alteration	DNA gyrase protection	QnrA
Polymyxins[31] (eg, colistin and polymyxin B)		
Target alteration	Two component systems	*K pneumoniae* (PhoPQ, PmrAB, MgrB, and CrrAB); *P aeruginosa* (PhoPQ, PmrAB, ParRS, ColRS, and CprRS); *A baumannii* (PmrAB)
Target alteration	Mobile (plasmid-mediated) colistin resistance enzymes	Encoded by *mcr* genes
Fosfomycin[32]		
Antibiotic modification	Fosfomycin modifying enzymes	Encoded by *fos* genes
Decreased entry	Alterations in fosfomycin transporters	GlpT; UhpT; CyaA; PtsI

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



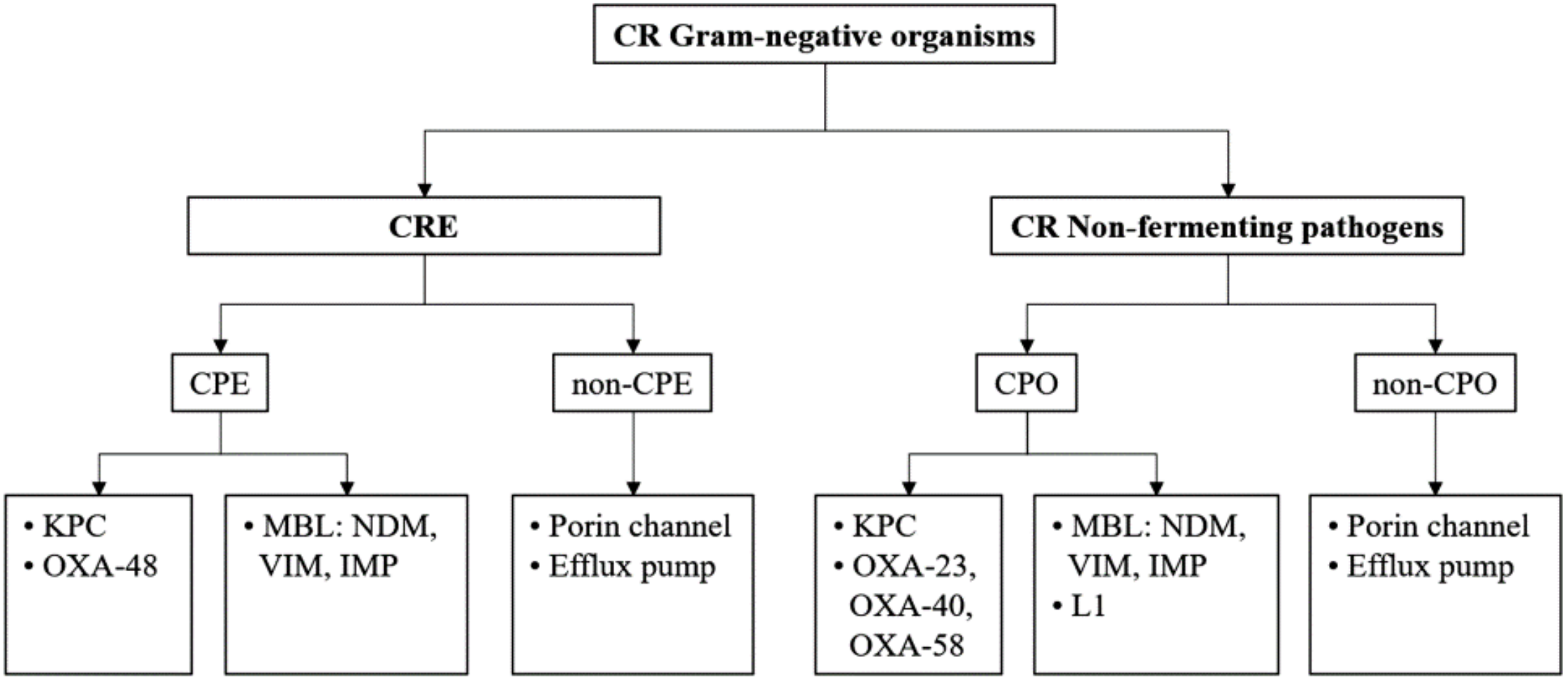
Eur Respir Rev. 2022 Oct 19;31(166):220068.

Classification of carbapenemases/β-lactamases



CID 2019:69 (Suppl 7)

Mechanism of carbapenem resistance



CID 2019:69 (Suppl 7)

台灣醫院感染管制與抗藥性監測管理系統(THAS系統)

2016~2025Q1 加護病房常見之醫療照護相關感染菌種
部位別: PNEUMONIA

衛生福利部疾病管制署 TAIWAN CDC

醫學中心

PNEU	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025Q1
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
Acinetobacter baumannii	3	3	3	4	4	4	4	4	3	3
Stenotrophomonas maltophilia	5	5	4	3	3	3	3	3	4	3
Staphylococcus aureus	4	6	5	5	5	5	5	6	5	5
Enterobacter species	6	4	6	6	8	7	8	8	6	8
Enterobacter cloacae complex	-					10	10	10	7	10
Escherichia coli	8					6	11	5	8	7
Serratia marcescens	7	8	8	11	9	10	6	10	8	6
Chryseobacterium indologenes	10	10	11	12	9	12	13	7	10	8

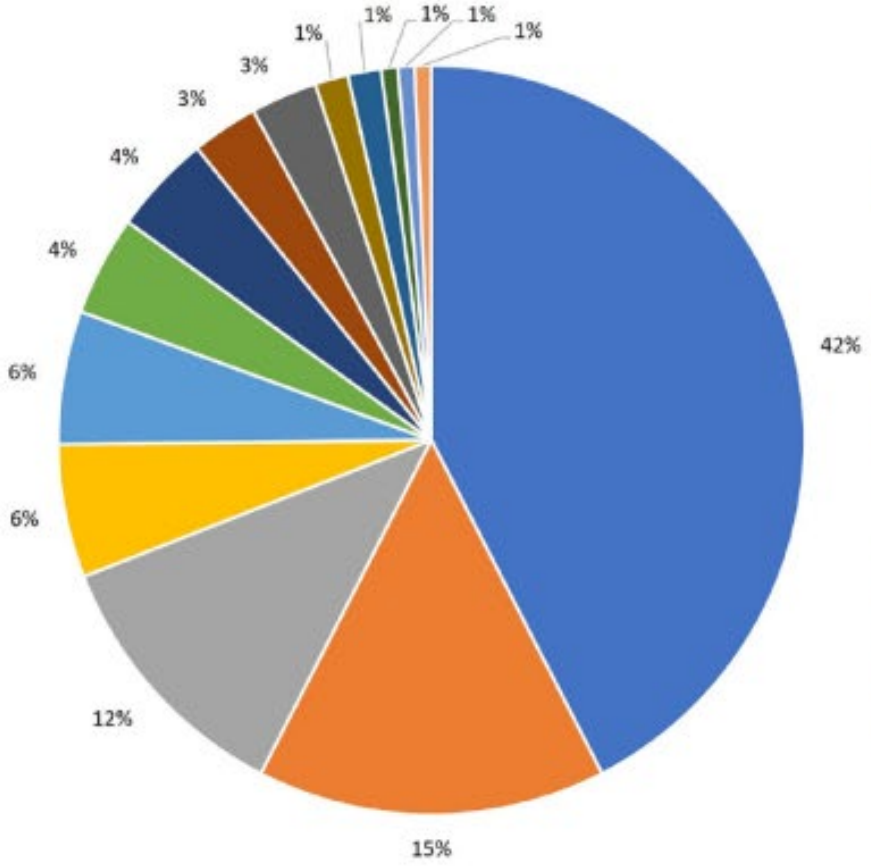
PA > KP > AB

區域醫院

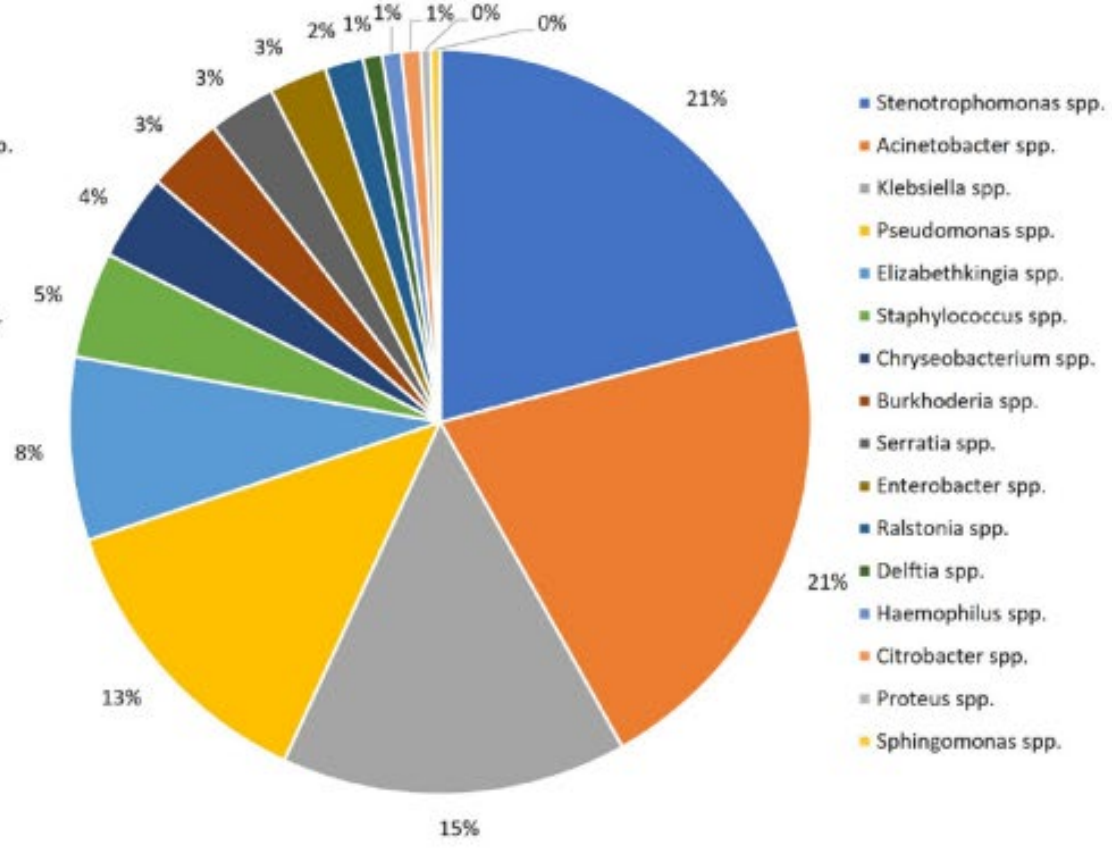
PNEU	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025Q1
菌種	排名	排名	排名	排名	排名	排名	排名	排名	排名	排名
Klebsiella pneumoniae	3	3	3	3	3	1	1	2	1	1
Pseudomonas aeruginosa	1	2	2	1	2	2	2	1	2	2
Acinetobacter baumannii	2	1	1	2	1	3	3	3	3	3
Stenotrophomonas maltophilia	5	5	4	5	4	5	4	4	4	4
Escherichia coli	8	7	6	7	7	7	7	7	5	8
Staphylococcus aureus	4					4	5	5	6	5
Enterobacter species	6					6	6	6	7	6
Serratia marcescens	9	9	9	9	10	9	10	9	8	6
Candida albicans	7	8	8	8	8	8	8	8	9	13
Acinetobacter nosocomialis	-	-	22	22	-	22	16	17	10	13

KP > PA > AB

COVID-19 MV with nosocomial pneumonia



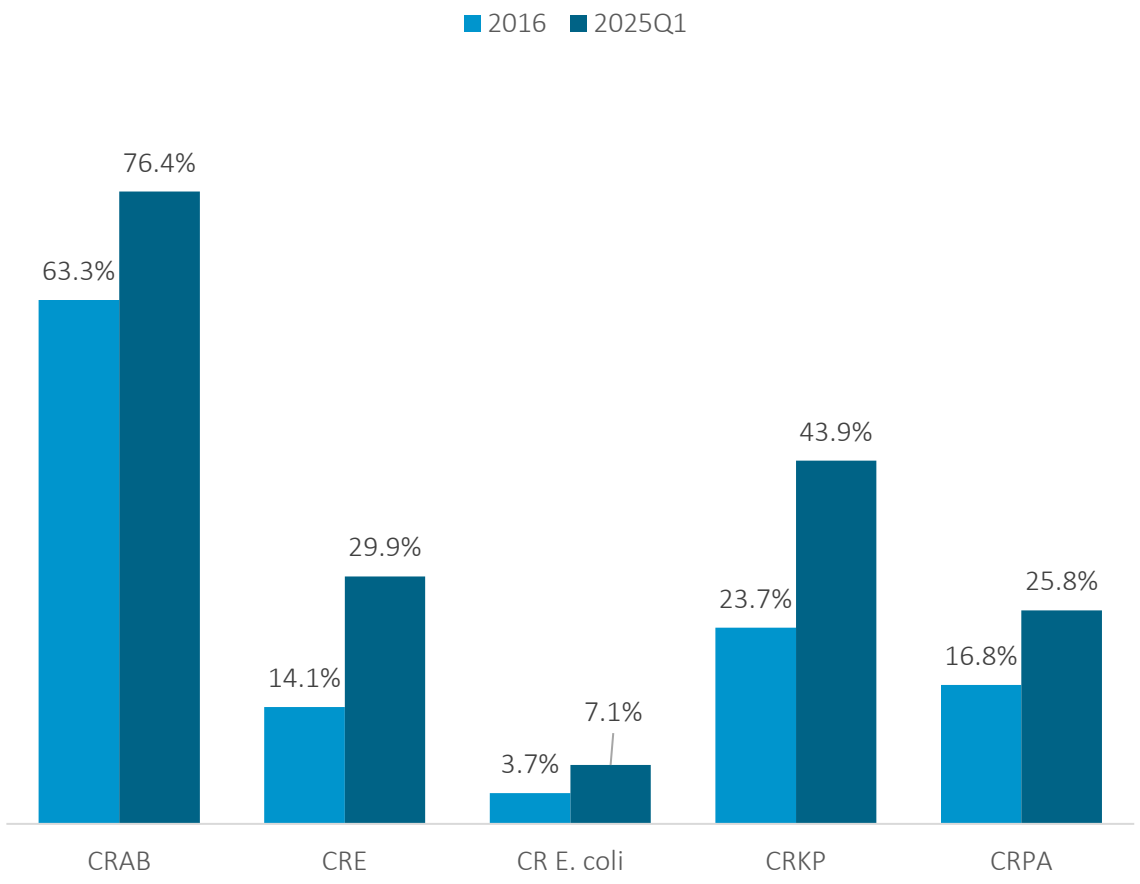
Alpha variant with secondary pneumonia



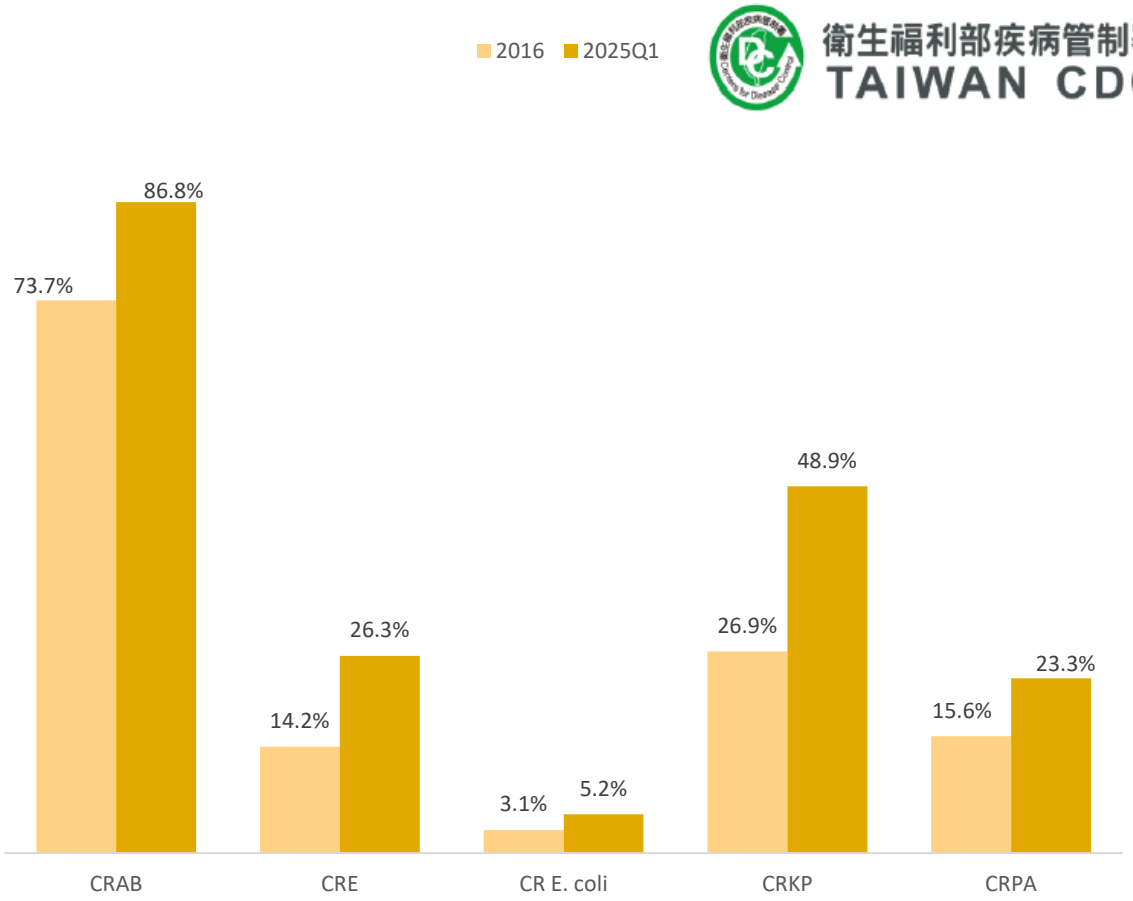
Omicron variant with secondary pneumonia

Ther Adv Respir Dis. 2023 Jan-Dec:17:17534666231213642.

Carbapenem resistant GNB 比例居高不下

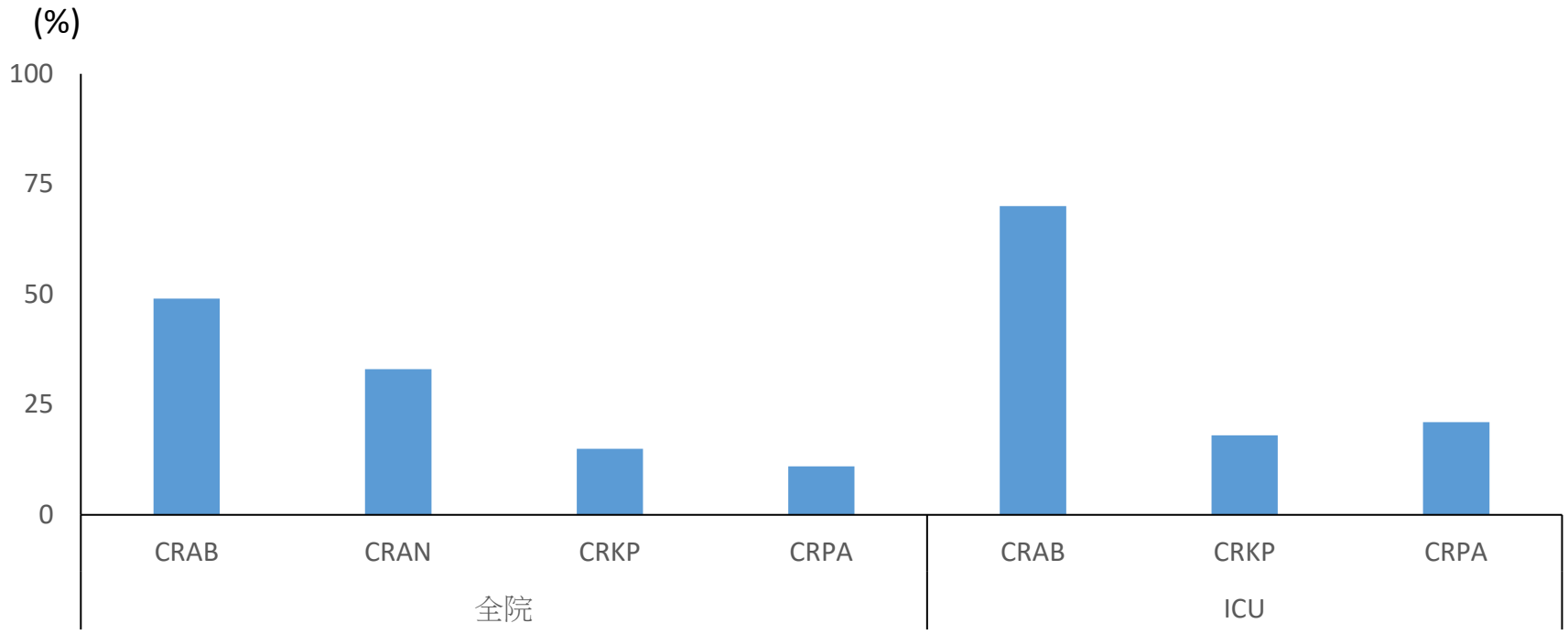


醫學中心



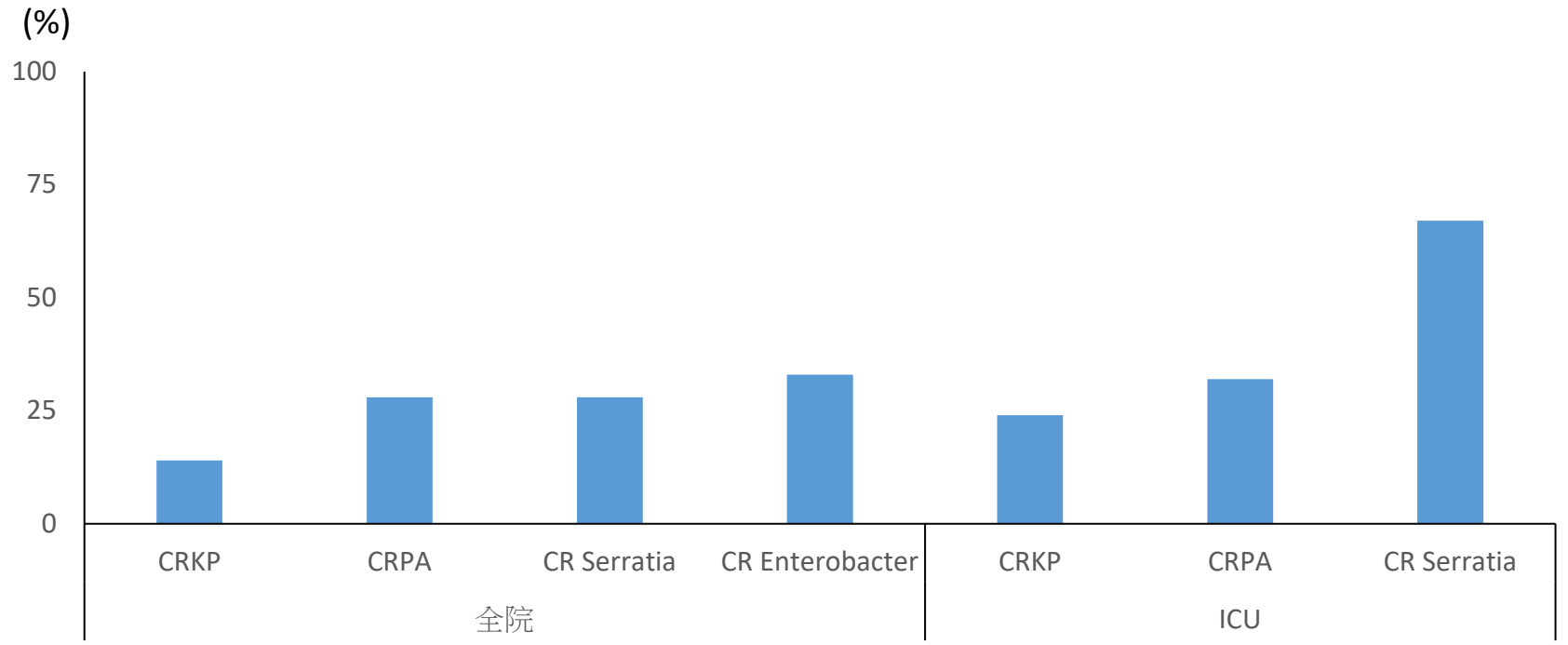
區域醫院

CRGNB in ordinary culture
VGHTPE 2025/7-2025/12



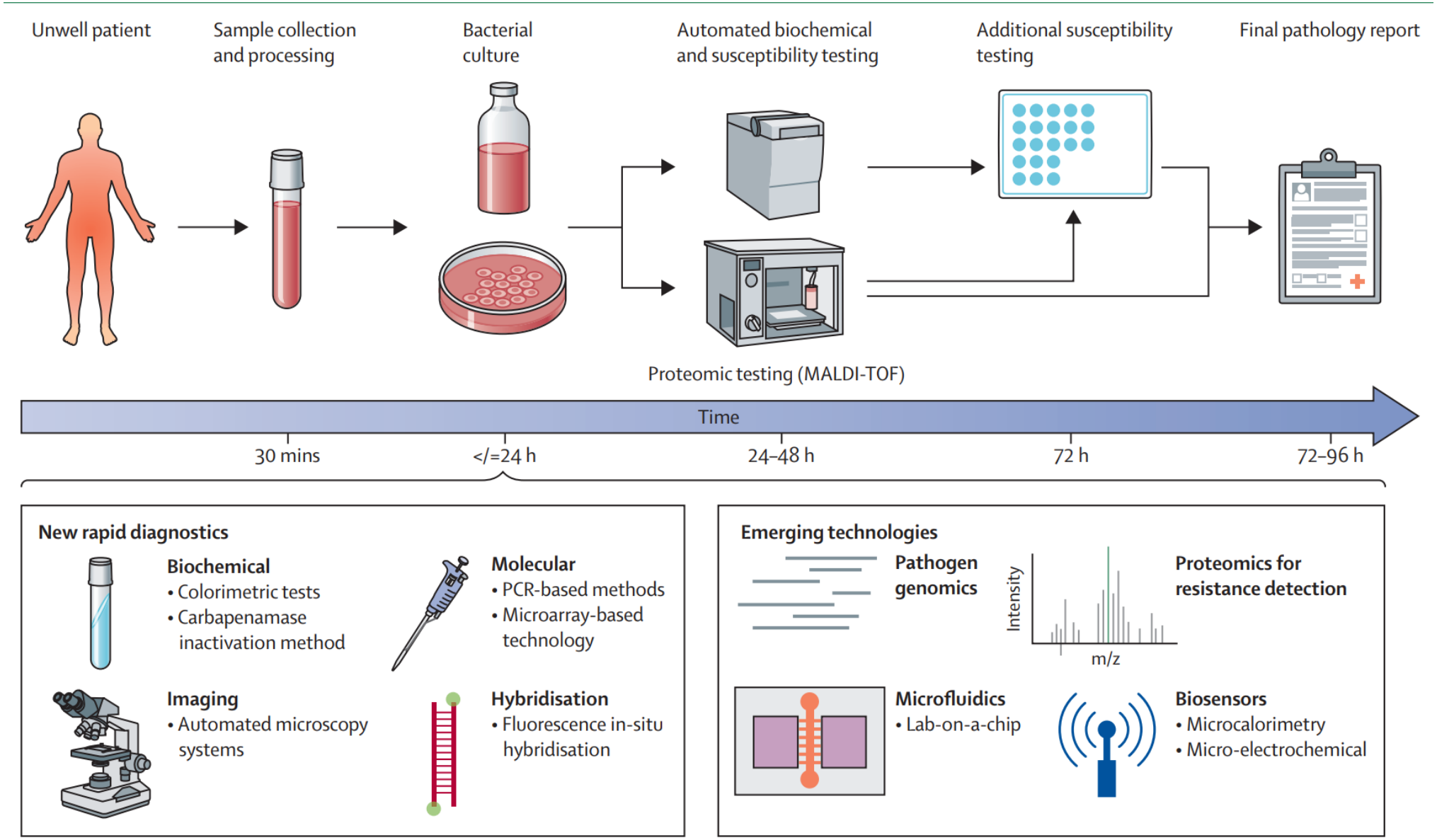
Ref: From VGHTPE Lab

CRGNB in blood culture
VGHTPE 2025/7-2025/12



Ref: From VGHTPE Lab

Diagnostic testing In MDR infection



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

The BioFire FilmArray Pneumonia Panel

BACTERIA:
(Semi-Quantitative)

- *Acinetobacter calcoaceticus-baumannii* complex
- *Enterobacter cloacae* complex
- *Escherichia coli*
- *Haemophilus influenzae*
- *Klebsiella aerogenes*
- *Klebsiella oxytoca*
- *Klebsiella pneumoniae* group
- *Moraxella catarrhalis*
- *Proteus* spp.
- *Pseudomonas aeruginosa*
- *Serratia marcescens*
- *Staphylococcus aureus*
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*

ATYPICAL BACTERIA:
(Qualitative)

- *Chlamydia pneumoniae*
- *Legionella pneumophila*
- *Mycoplasma pneumoniae*

VIRUSES:

- Adenovirus
- Coronavirus
- Human metapneumovirus
- Human rhinovirus/enterovirus
- Influenza A virus
- Influenza B virus
- Parainfluenza virus
- Respiratory syncytial virus

ANTIMICROBIAL RESISTANCE GENES:

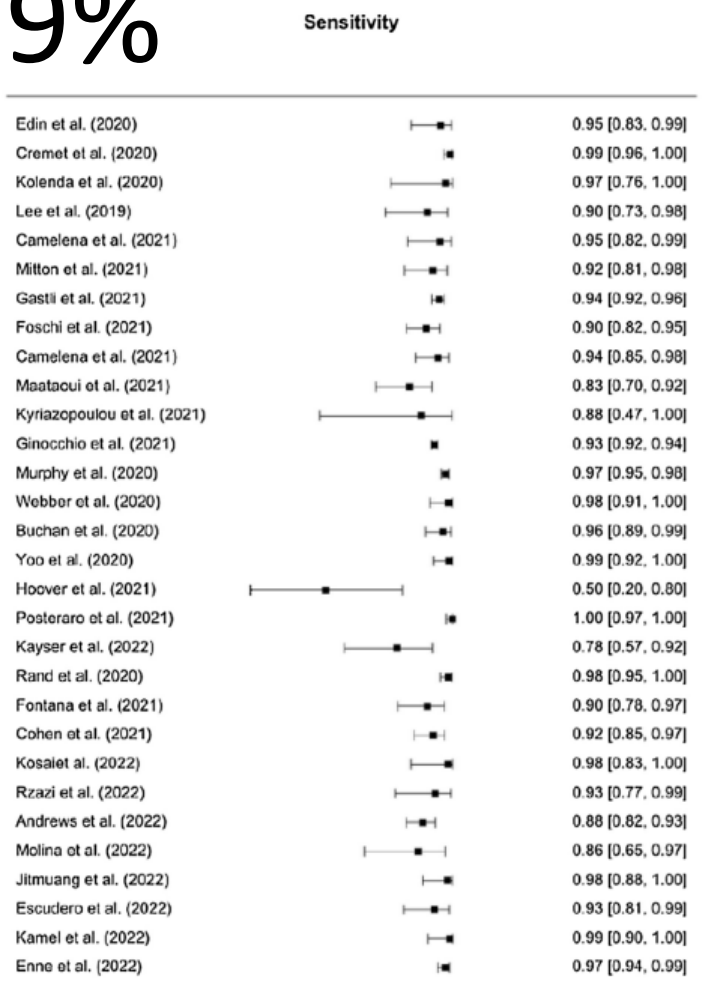
Carbapenemases:
- IMP
- KPC
- NDM
- OXA-48-like
- VIM

ESBL:
- CTX-M

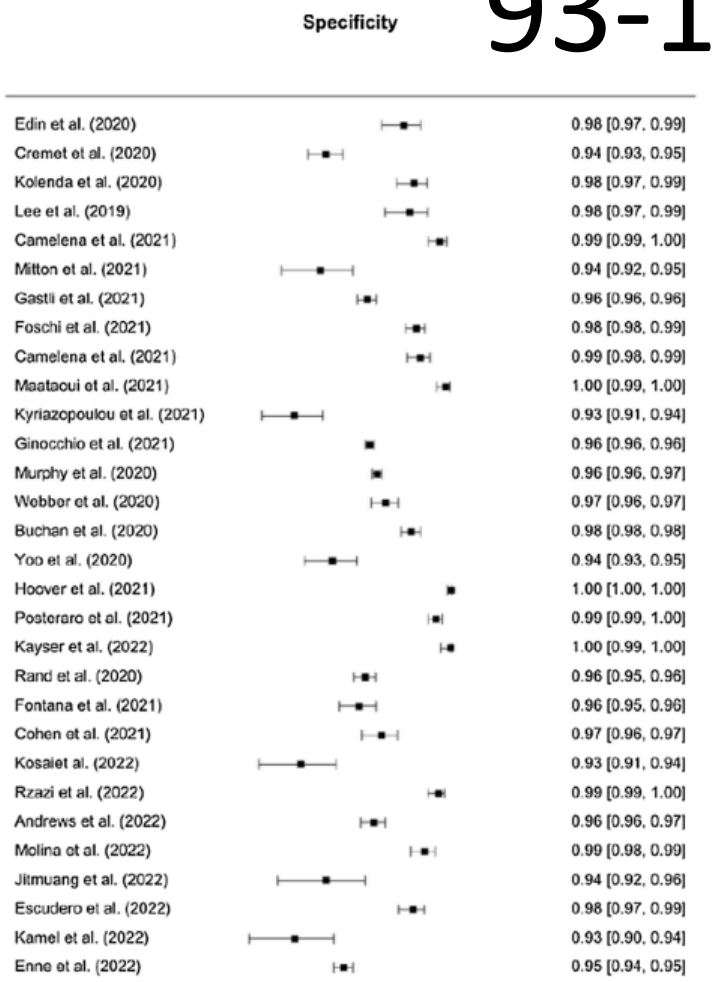
Methicillin resistance:
- *mecA/C* and MREJ (MRSA)

Diagnostic utility by multiplex PCR exam

50-99%



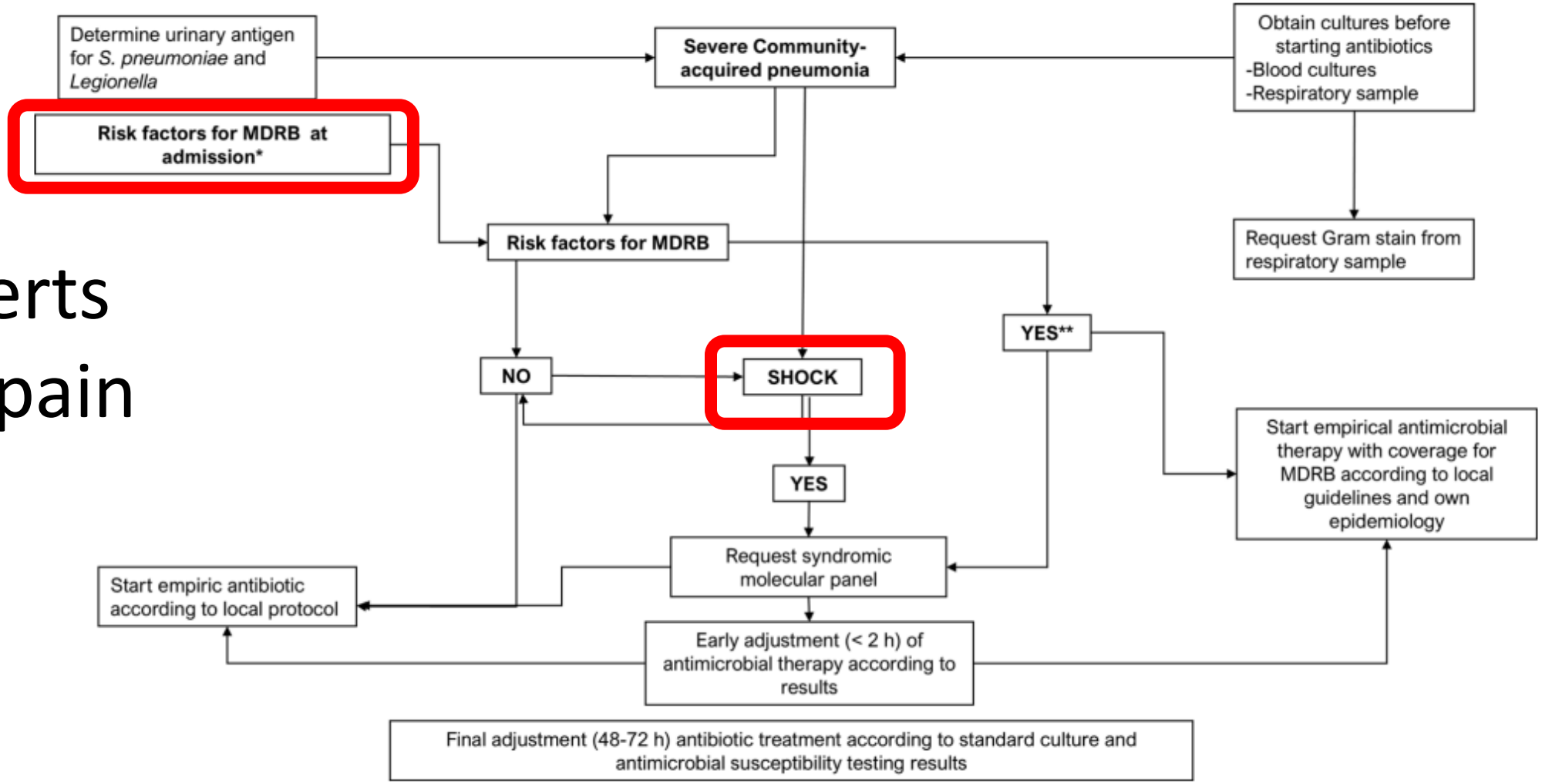
93-100%



Anaesth Crit Care Pain Med. 2023 Dec;42(6):101300.

If HAP/VAP, testing with syndromic panels is recommended regardless of the risk for MDR bacteria involvement or shock risk factors

11 experts
From Spain



Crit Care. 2024 Dec 30;28(1):440.

Antibiotics activity Against MDRGNB

Active
Variable
Not recommended

		Enterobacterales					Lactose non-fermenting organisms	
	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)	Difficult-to-treat resistant *Pseudomonas aeruginosa*	Carbapenem-resistant *Acinetobacter baumannii*
β-lactam								
Ceftolozane–tazobactam	3 g IV every 8 h, infused over 3 h						✓	
Ceftazidime–avibactam	2·5 g IV every 8 h, infused over 3 h					✓		
Meropenem–vaborbactam	4 g IV every 8 h, infused over 3 h							
Imipenem–relebactam	1·25 g IV every 6 h, infused over 30 min			✓				
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*							
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.

Risk factors for carbapenem-resistant Gram-negative bacterial infections

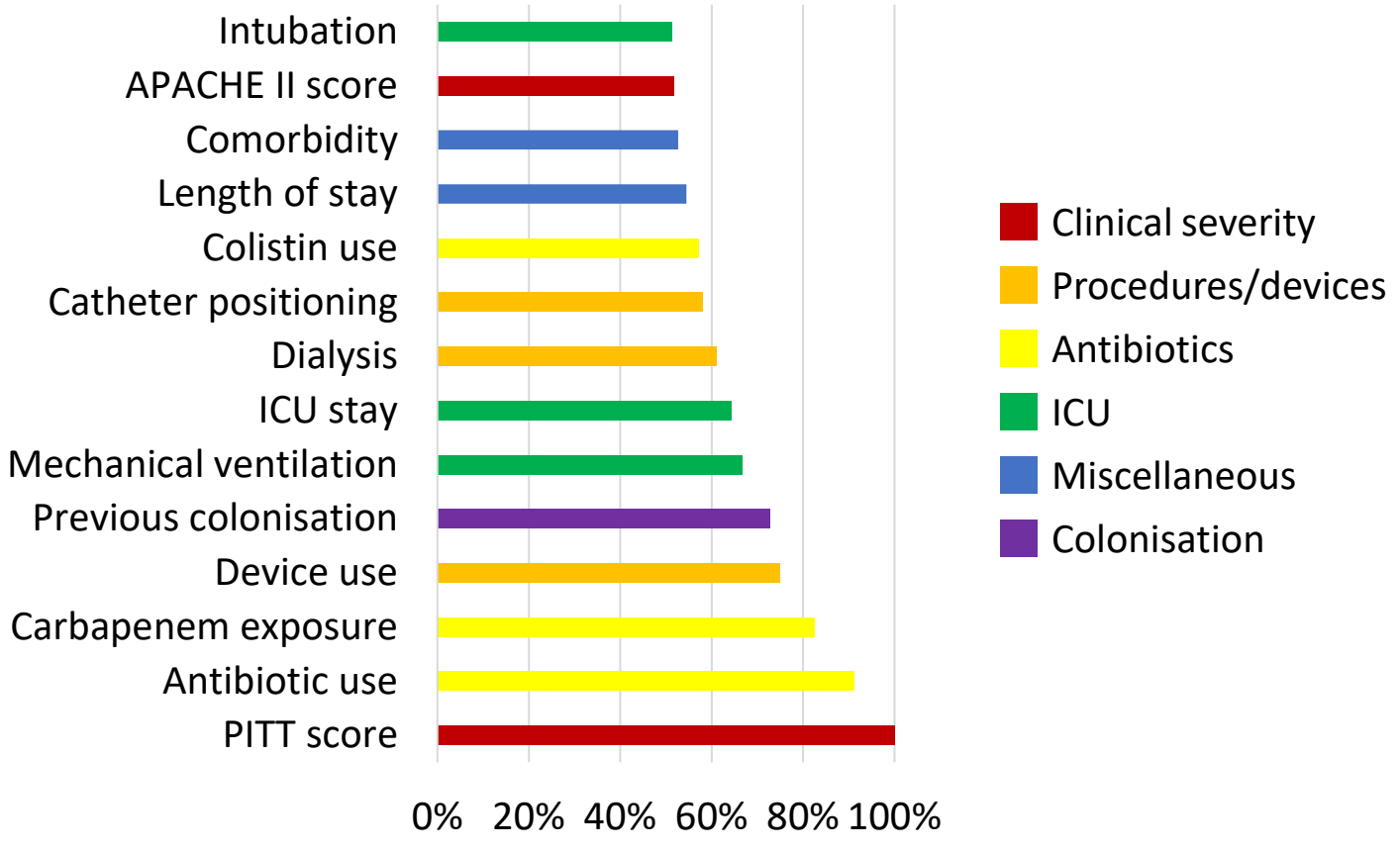
Design

Systematic review of studies reporting risk factors associated with infections due to carbapenem-resistant Gram-negative pathogens in hospitalized patients

- 92 studies identified

Outcomes

Figure 2 from Palacios-Baena Z 2021



HUMANITAS UNIVERSITY

Palacios-Baena Z, et al. *Clin Microbiol Infect* 2021;27:228–235.

Who is in danger?

Previous antibiotic use[1]

Admission to ICU[1]

Comorbidities[1] (e.g., COPD, malignancy, organ transplantation)

Presence of indwelling catheters / drains[1]

Prior healthcare and long-term care exposure[1]

Mechanical ventilation[1]

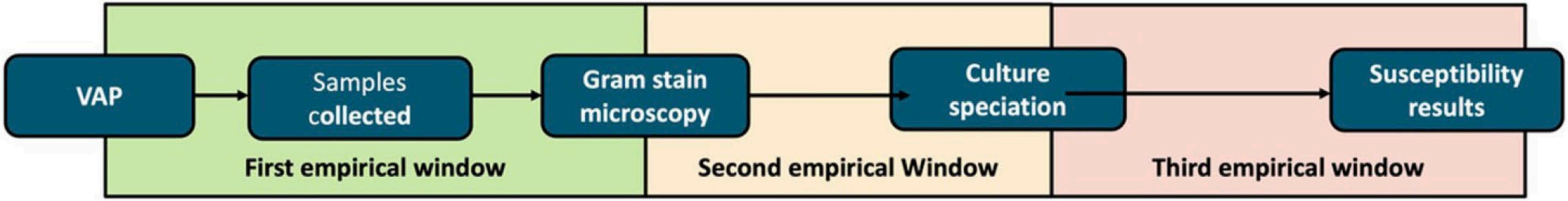
COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.

1. Bassetti M, *et al*. Patient specific risk stratification for antimicrobial resistance and possible treatment strategies in Gram-negative bacterial infections. Expert Rev Anti Infect Ther. 2017;15(1):55–65.

Icons from The Noun Project.

Empiric Therapeutic Window in VAP

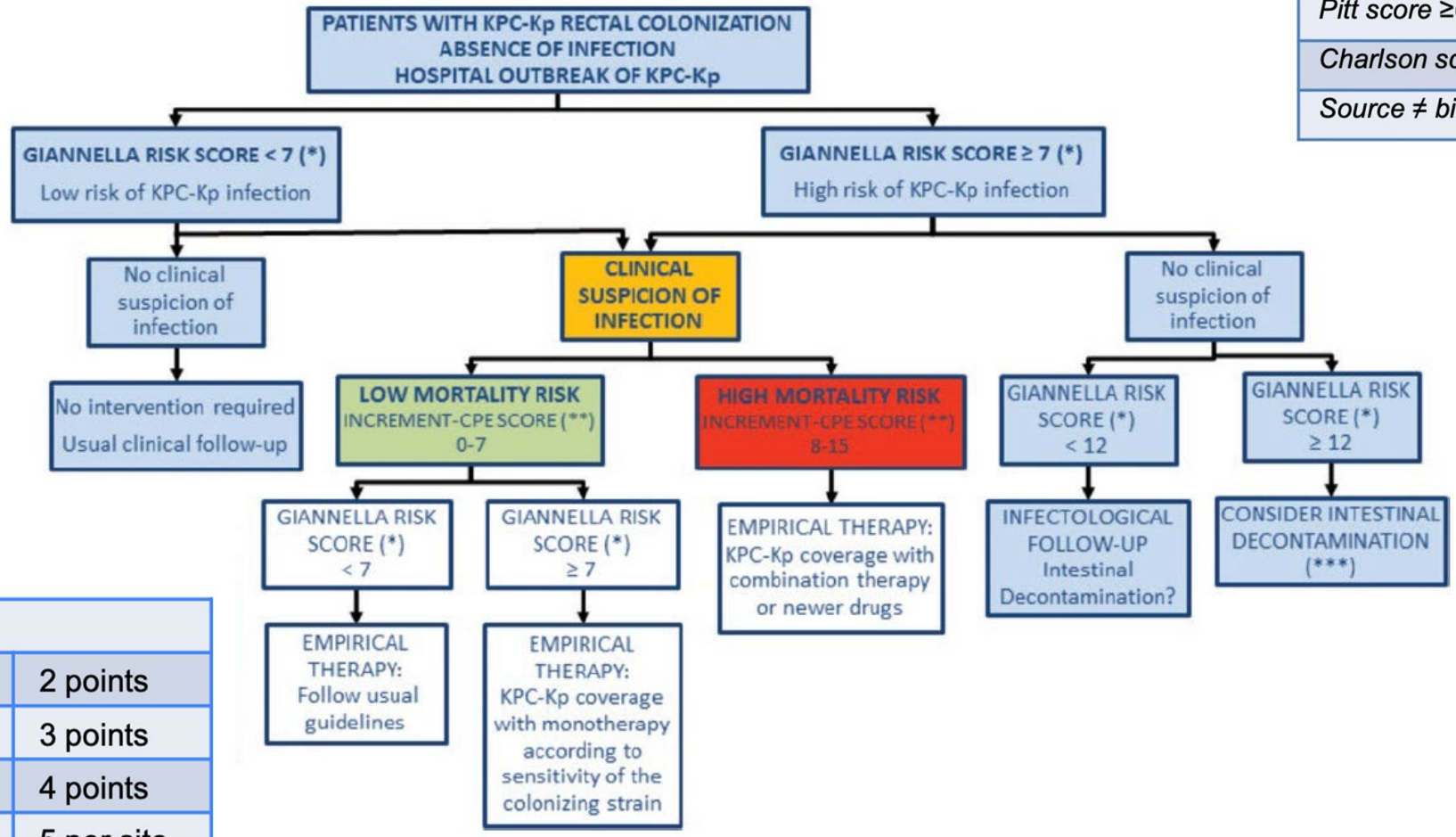
Amani Alnimir Infect Dis Ther 2023



Risks of Infection & Mortality among Patients Colonized with KPC-Kp: Validation of Scores & Proposal for Management

Cano A et al, Clin Infect Dis 2017 Nov 8.

INCREMENT Score	
Severe sepsis or septic shock	*5*
Pitt score ≥6	*4*
Charlson score ≥2	*3*
Source ≠ biliary or urinary	*3*



Giannella Risk Score	
ICU	2 points
Abdominal surgery	3 points
Chemo/Radiotherapy	4 points
Colonization (no rectal)	5 per site

MDR colonization and immunocompromised patients

Article

Development of a Clinical Score to Stratify the Risk for Carbapenem-Resistant Enterobacterales Bacteremia in Patients with Cancer and Hematopoietic Stem Cell Transplantation

Variables	Univariate Analysis		Multivariate Analysis		Points
	OR (95%CI)	*p*-Value	OR (95%CI)	*p*-Value	
Recent carbapenems use	4.1 (2.3–7.7)	0.001			
>7 days of antibiotic use prior to bacteremia	4.6 (2.6–4.1)	0.001	4.65 (2.29–9.46)	<0.001	2
Neutropenia	3.6 (1.6–8.2)	0.002			
≥10-days of hospitalization prior to bacteremia	4.4 (2.3–8.6)	0.001	4.03 (1.88–8.66)	<0.001	2
Recent intensive care unit admission	3 (1.4–6.8)	0.006			
Central venous catheter in place	3.4 (1.7–6.7)	0.002			
Previous colonization with KPC-CPE	10.6 (4.4–25.5)	0.001			
Recent colonization with KPC-CPE	24.9 (1.3–55)	0.001	33.08 (11.7–93.25)	<001	5

Score	Sensitivity	Specificity	PPV	NPV
7	35%	98%	77%	91%

Tables adapted from Herrera F, Torres D, Laborde A et al. Development of a Clinical Score to Stra$fy the Risk for Carbapenem-Resistant Enterobacterales Bacteremia in Pa$ents with Cancer and Hematopoie$c Stem Cell Transplanta$on. Anbiocs 2023, 12, 226

Impact of Inappropriate Initial Antibiotics (IIAT)

In critically ill patients with GN sepsis/septic shock (N=1076, St.Louis, U.S.A.)

- Retrospective, single-center study, adult ICU at Barnes-Jewish Hospital (2008-2012)
- **In-hospital mortality**: 351, **29.2%**

- **Risk factors for mortality:**
  - Older (66.5 vs 63 ys)
  - Vasopressors (OR 2.79)
  - Ventilated (OR 3.06)
  - MDR infections (10.% vs 4%, p < 0.001)
  - IIAT (43.4% vs 14.6%, p < 0.001)

Inappropriate Initial Antimicrobial Therapy ↑ Mortality 3.8-fold

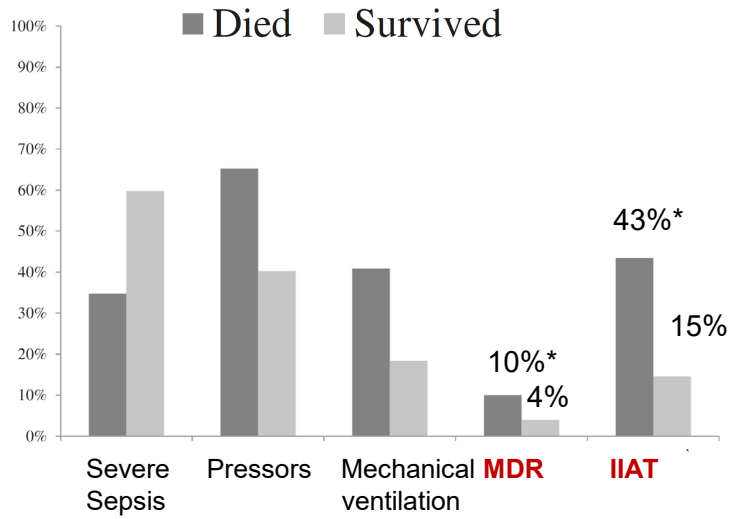


Figure 1 Sepsis severity, resistance and initial treatment. IAAT, initially appropriate antibiotic therapy; MDR, multidrug resistant.
*P <0.001 for each comparison.

Multidrug Resistant ↑ IIAT 13-fold

Zilberberg et al. Critical Care 2014, 18:596

Table 3 Predictors of hospital mortality[a]

	Odds ratio	95% confidence interval	*P* value
Non-IAAT	3.872	2.770 to 5.413	<0.001
Chronic liver disease	1.942	1.319 to 2.860	0.001
Septic shock	1.846	1.335 to 2.553	<0.001
Pneumonia	1.766	1.237 to 2.522	0.002
Mechanical ventilation	1.669	1.172 to 2.376	0.005
APACHE II score (per 1 point)	1.076	1.047 to 1.105	<0.001
Surgery	0.701	0.560 to 0.879	0.002
Admitted from home	0.677	0.489 to 0.936	0.018
Urosepsis	0.675	0.469 to 0.972	0.034

IAAT: Initially appropriate antibiotic therapy

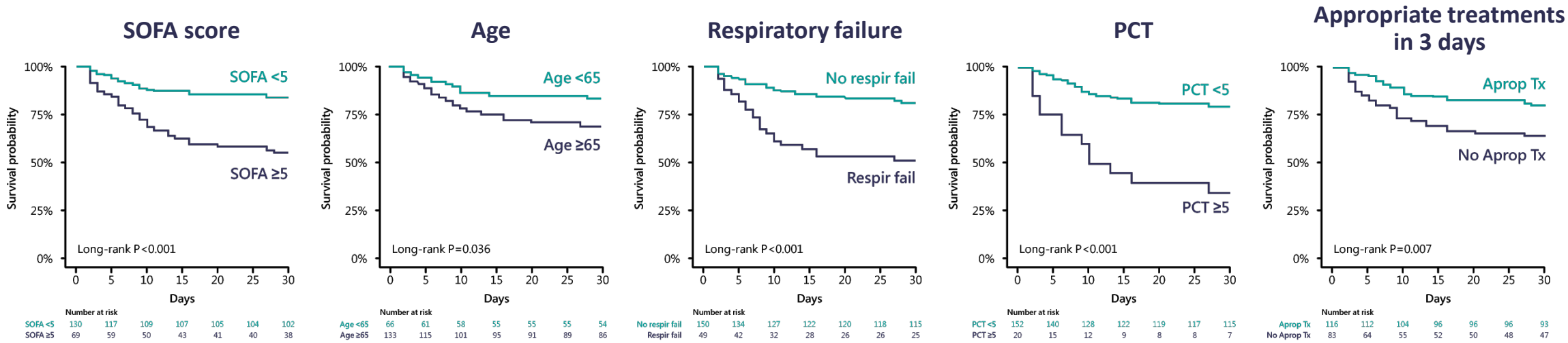
Table 4 Predictors of receiving initially inappropriate antibiotic therapy[a]

	Odds ratio	95% confidence interval	*P* value
Multidrug resistant	13.05	7.00-24.31	<0.001
HIV	3.64	1.02-12.95	0.046
Transferred from another hospital	2.86	2.00-4.08	<0.001
Nursing home resident	2.28	1.35-3.84	0.002
Prior antibiotics	2.06	1.47-2.87	<0.001
Polymicrobial	1.90	1.30-2.77	0.001
Congestive heart failure	1.61	1.11-2.35	0.013
APACHE II score (per 1 point)	1.05	1.02-1.07	<0.001

Inadequate treatment within 3 days may increase the risk of 30-day mortality in patients with CRKP infection

- Primary outcome: the 7-, 15-, and 30-day mortality rates were 13.6% (26/191), 22.0% (42/191), and 26.7% (51/191).
- The risk factors for 30-day mortality among adult patients with CRKP infection were established to be the presence of **respiratory failure**, **high SOFA score**, **PCT >5 ng/mL**, **age >65 years**, and **non-appropriate treatments in 3 days**.

Kaplan–Meier survival plots of risk factor



Adapted from Chen J, et al. 2022

A total 199 adult patients diagnosed with CRKP infection in a tertiary hospital in Shanghai between September 2019 and March 2021 were included. The primary outcome was the time to all-cause death up to 30 days from CRKP detection. The secondary outcome was the effect of treatment on CRKP infection, which was defined as effective (cure or improvement in the infection status) or noneffective (stable or deterioration of infection) within 7 and 15 days, based on the clinical, radiological, and laboratory findings.

CRKP = carbapenem-resistant *Klebsiella pneumoniae*; SOFA = Sequential Organ Failure Assessment; PCT = procalcitonin.

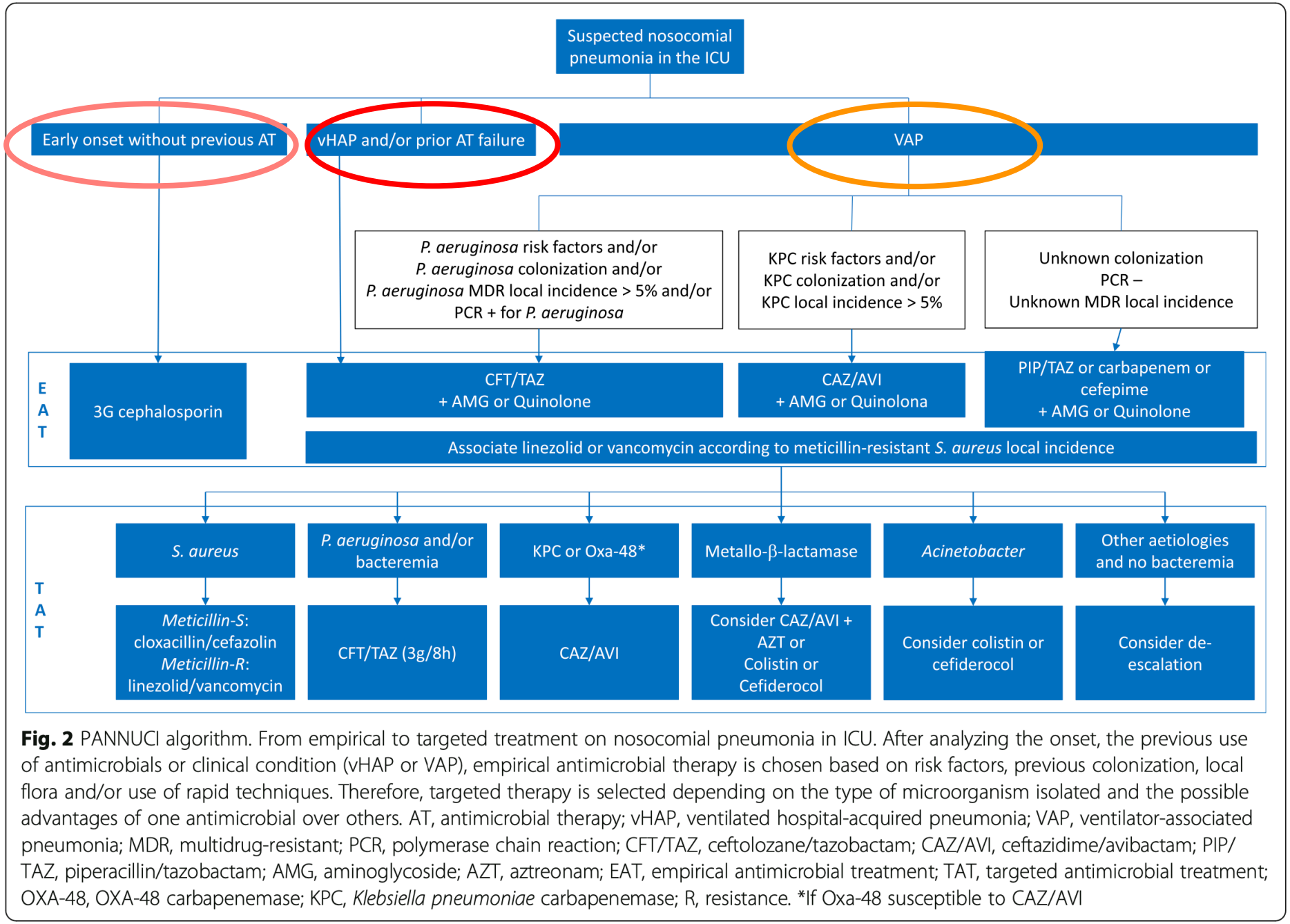
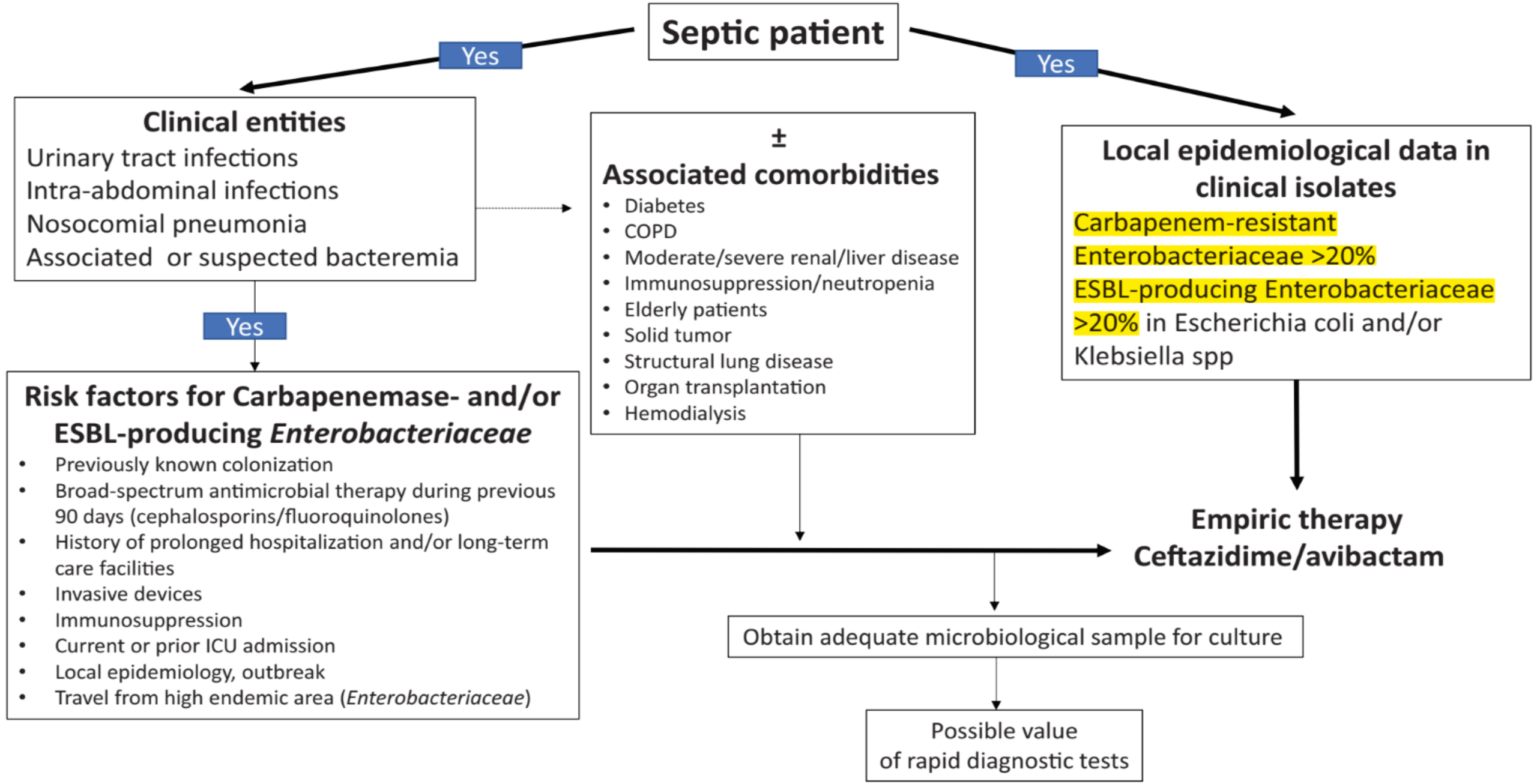


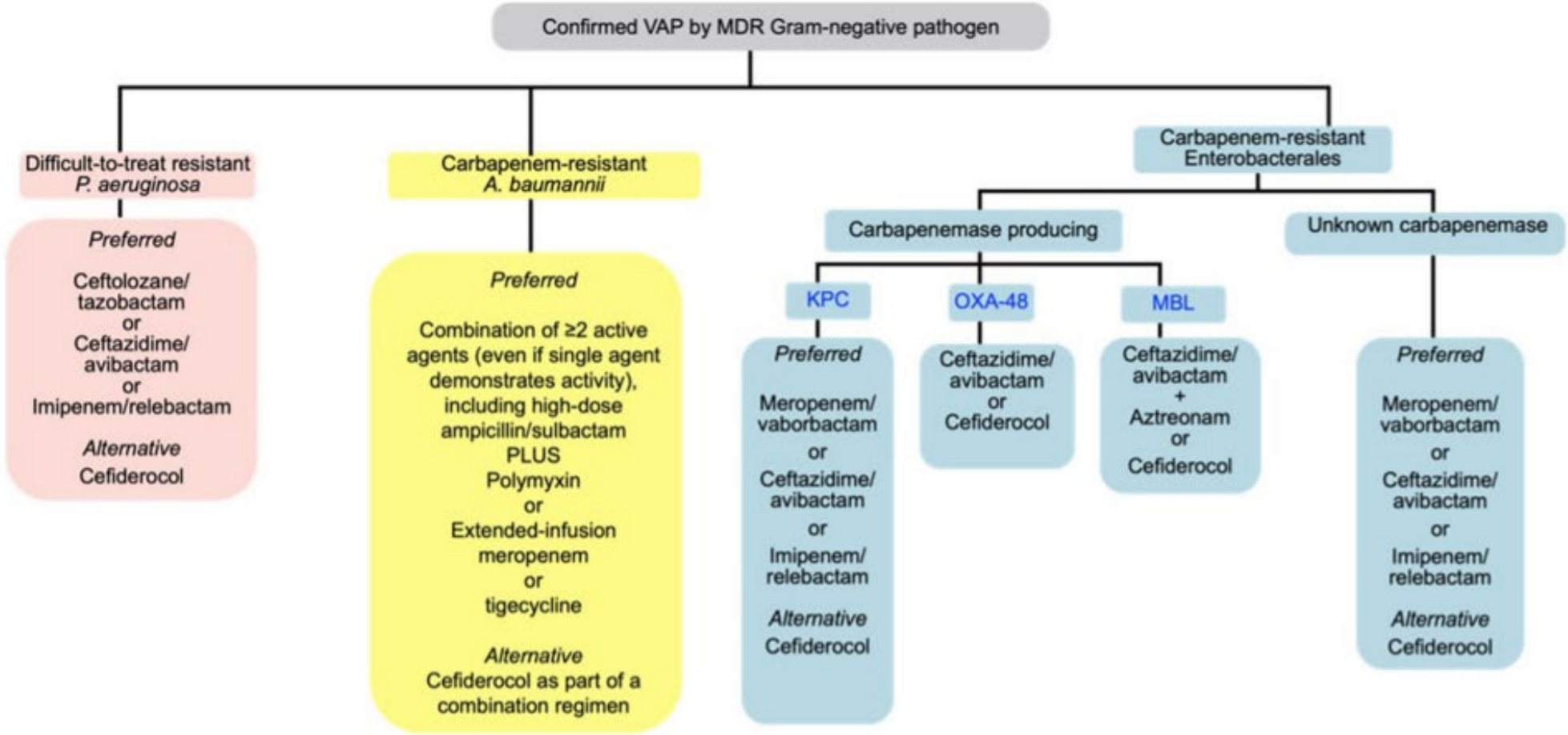
Fig. 2 PANNUCI algorithm. From empirical to targeted treatment on nosocomial pneumonia in ICU. After analyzing the onset, the previous use of antimicrobials or clinical condition (vHAP or VAP), empirical antimicrobial therapy is chosen based on risk factors, previous colonization, local flora and/or use of rapid techniques. Therefore, targeted therapy is selected depending on the type of microorganism isolated and the possible advantages of one antimicrobial over others. AT, antimicrobial therapy; vHAP, ventilated hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; MDR, multidrug-resistant; PCR, polymerase chain reaction; CFT/TAZ, ceftolozane/tazobactam; CAZ/AVI, ceftazidime/avibactam; PIP/TAZ, piperacillin/tazobactam; AMG, aminoglycoside; AZT, aztreonam; EAT, empirical antimicrobial treatment; TAT, targeted antimicrobial treatment; OXA-48, OXA-48 carbapenemase; KPC, *Klebsiella pneumoniae* carbapenemase; R, resistance. *If Oxa-48 susceptible to CAZ/AVI

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



Curr Opin Infect Dis. 2018 Dec;31(6):587-593.

Treatment of MDRO in VAP by IDSA



Infect Dis Ther. 2023 Jun;12(6):1527-1552.

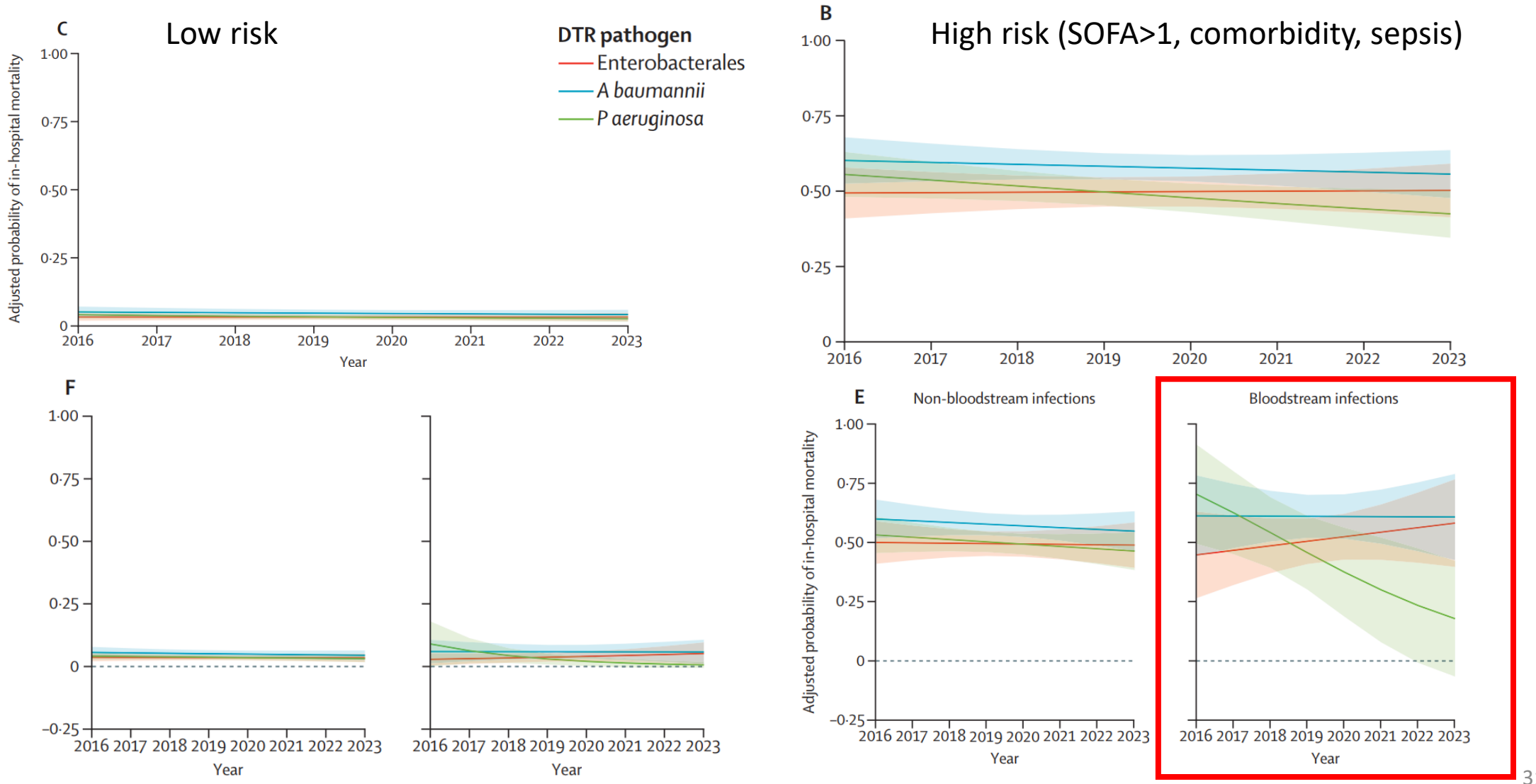
ESCMID 2022 & IDSA 2023 Guidance for the Treatment of Serious GNB infections

Agent	ESBL/AmpC producers	CRE - class A carbapenemases (e.g.; KPC)	CRE - class D carbapenemases (e.g.; OXA-48)	CRE - MBL-producers (e.g.; NDM)	DTR *P. aeruginosa*[#]
Carbapenems	preferred*	–	–	–	–
Ceftolozane-tazobactam	against (unless polymicrobial)	–	–	–	preferred*
Ceftazidime-avibactam†	optional* (stewardship)	preferred*	preferred*	–	preferred*
Meropenem-vaborbactam	optional* (stewardship)	preferred*	–	–	–
Imipenem-relebactam	optional* (stewardship)	preferred*	–	–	preferred*
Cefiderocol	optional* (stewardship)	optional (while waiting for AST)	optional (while waiting for AST)	preferred*	optional*
Polymyxins	–	–	–	–	–

1. Paul M, et al. Clin Microbiol Infect. 2022;28:521-547; 2. Tamma PD, et al. Clin Infect Dis. 2023; ciad428.

Mortality from DTR-GNB in US (2016-2023)

Annual 4.5% mortality reduction in PA bacteremia



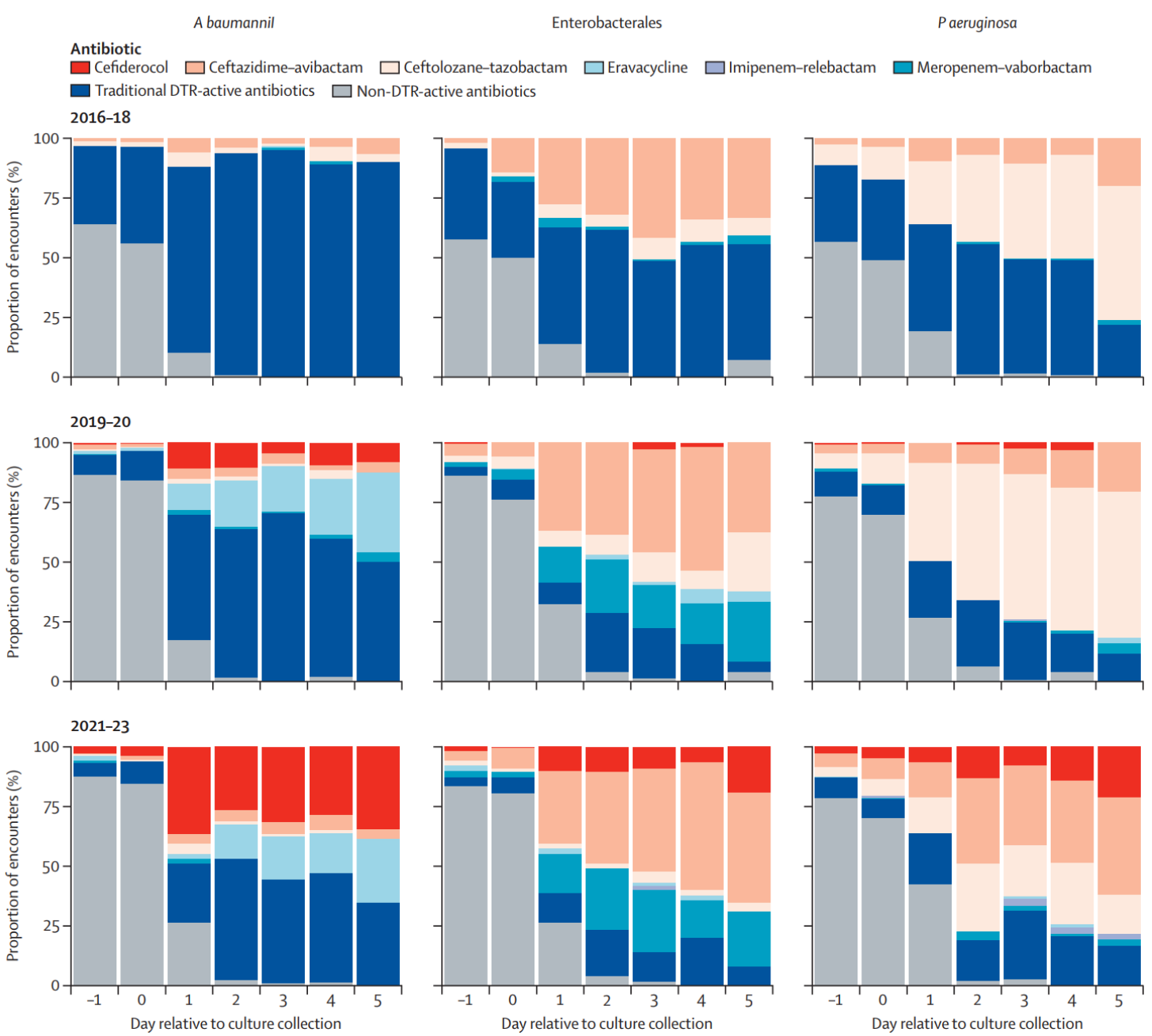
Walker MK et al, Lancet Infect Dis. 2026 Jul;26(7):659-670.

Abx prescription

AB
Cefiderocol
Old
Eravacycline

Enterobacterales
CAZ-AVI
Mer-Vab
Cefiderocol

PA
CAZ-AVI
Old
Cefiderocol
CT



Walker MK et al, Lancet Infect Dis. 2026 Jul;26(7):659-670.

Comparison of official recommendations - CRE

Similarities	ESCMID	IDSA
Non-severe	Old antibiotics with in vitro S	Quinolones, TMP-SMX, single dose aminoglycoside
Metallo-beta-Lactamase (MBL)	Cefiderocol (conditional); ceftazidime-avibactam + aztreonam	Cefiderocol or ceftazidime-avibactam + aztreonam
Tigecycline	Not in BSI, HAP/VAP	Avoided in non-IAI
Combination therapy	Not routinely recommended	Not routinely recommended

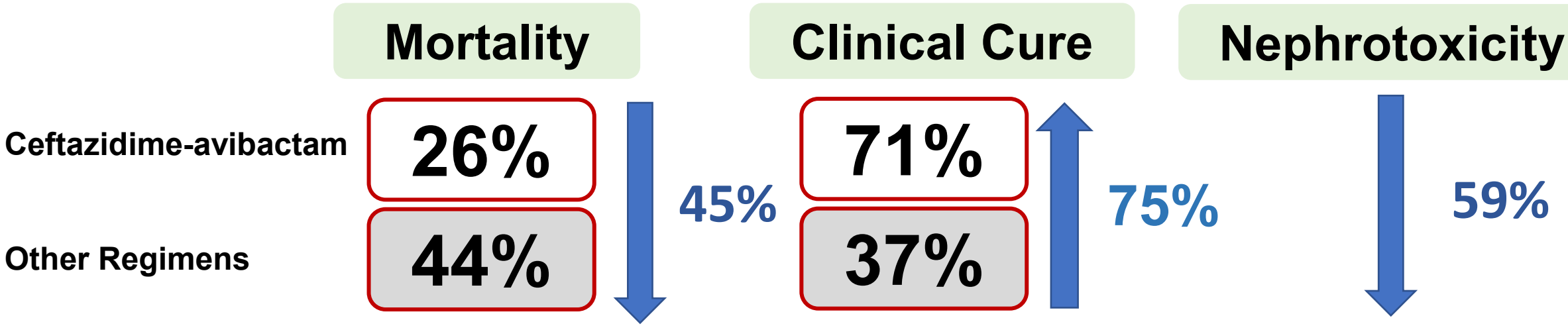
Clin Microbiol Infect. 2022 Feb 9;S1198-743X(22)00054-4.
Clin Infect Dis. 2024 Aug 7:ciae403.

Comparison of official recommendations - CRE

Differences	ESCMID	IDSA
Severe	Ceftazidime-avibactam or meropenem-vaborbactam (conditional); no recommendation on imipenem-relebactam, cefiderocol	Ceftazidime-avibactam, Meropenem-vaborbactam, Imipenem-relebactam, or cefiderocol for severe UTI
Complicated UTI	Aminoglycosides over tigecycline	Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, or cefiderocol
Eravacycline	No evidence	In IAI only
Combination therapy with carbapenem	Use when MIC ≤ 8 mg/L and with extended infusion	-

Clin Microbiol Infect. 2022 Feb 9;S1198-743X(22)00054-4.
Clin Infect Dis. 2024 Aug 7:ciae403.

Ceftazidime-avibactam for Treatment of CRE BSI (Meta-analysis, 11 studies, 1205 patients)



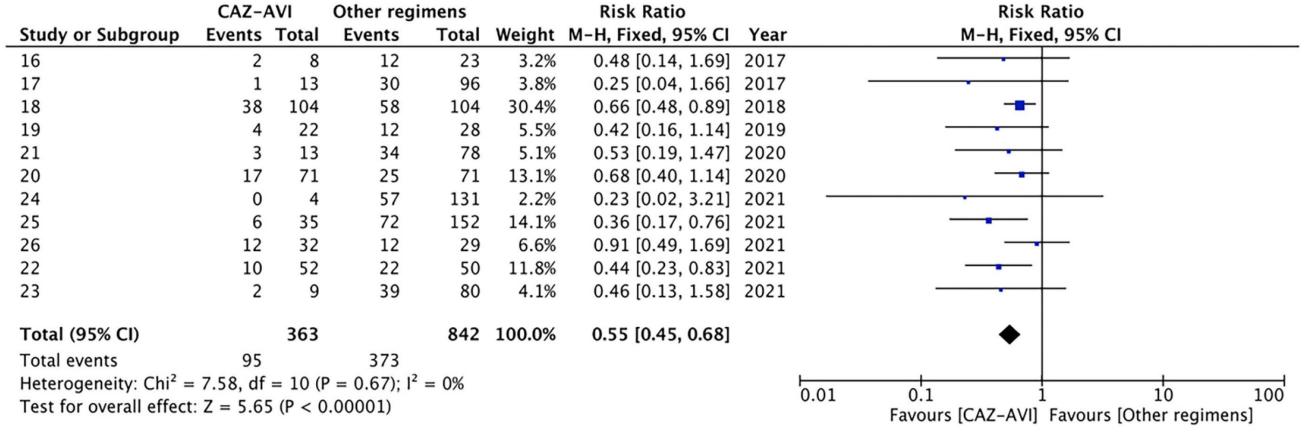


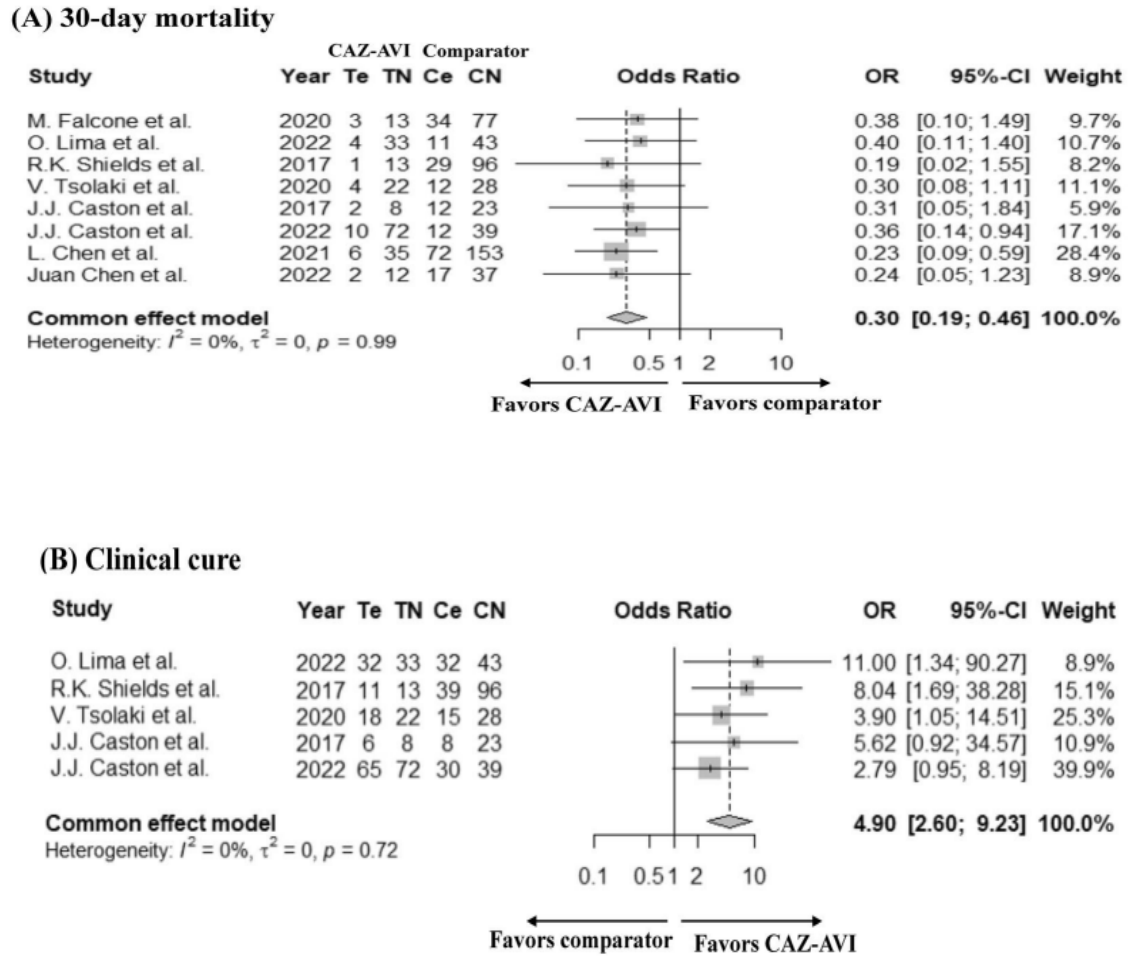
FIG 2 Thirty-day mortality of the CAZ-AVI regimens compared with controls in CRE BSI.

- **Lower 30-day mortality rate**: Overall: **45% reduction** (RR = 0.55, 95% CI:0.45-0.68, P < 0.00001)**vs Colistin-based regimen: 52% reduction** (RR = 0.48, 95% CI 0.33-0.69, P<0.0001).
- **Higher clinical cure rate** (RR = 1.75, 95% CI of 1.57-2.18, P < 0.00001)
- **Lower nephrotoxicity rate: 59% reduction** (RR = 0.41, 95% CI of 0.20-0.84, P = 0.02)

Chen Y et al. Microbiol Spectrum 2022 Apr;10(2):e0260321

Ceftazidime-Avibactam in the Treatment of Patients with Bacteremia or Nosocomial Pneumonia: A Systematic Review and Meta-analysis

- The databases included in the search, until November 7, 2022, were Embase and PubMed. A total of 24 studies (retrospective: 22, prospective: 2) with separate outcomes for patients with bacteremia or pneumonia were included.
- This SLR and meta-analysis synthesized clinical outcome data and presents quantitative and qualitative evidence that may be considered while using CAZ-AVI for the treatment of patients with bacteremia and nosocomial pneumonia caused by non-MBL producing CRE Infect Dis and/or MDR P. aeruginosa



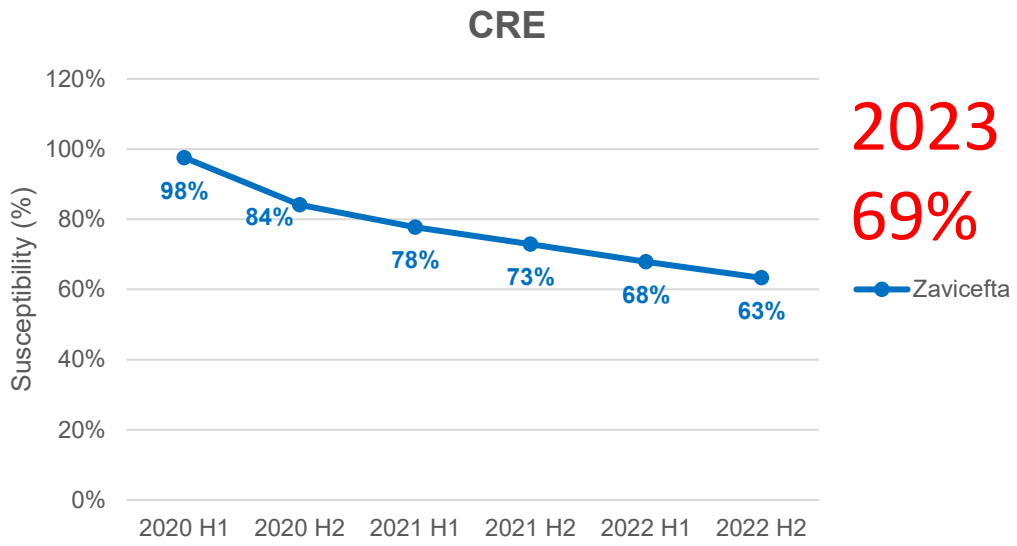
Infect Dis Ther (2024) 13:1639–1664
https://doi.org/10.1007/s40121-024-00999-y

Question 3.7: What is the likelihood of the emergence of resistance of CRE isolates to the newer β-lactam agents when used to treat CRE infections?

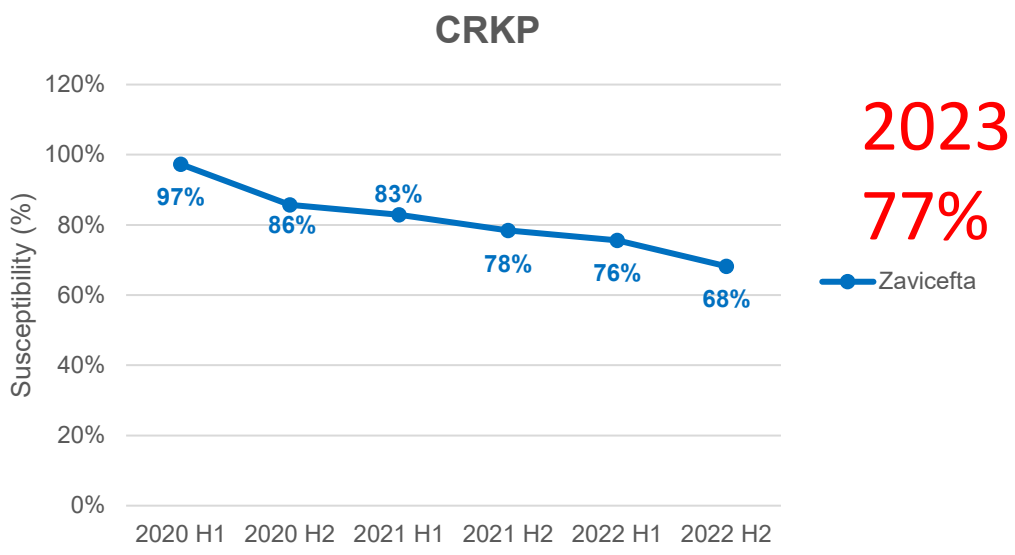
- Suggested approach: The emergence of resistance is a concern with all β-lactams used to treat CRE infections. Available data suggest the frequency may be highest for ceftazidime-avibactam.

Clin Infect Dis. 2024 Aug 7:ciae403.

2020~2023年度台北榮總藥物敏感性報告趨勢圖



2023
69%



2023
77%

7. 全院MDRO (% Susceptible): 2025

菌名	株數	CT	CZA	MEM	MXF	TGC
Klebsiella pneumoniae (CRE)	446	9	73	38	18	75
Escherichia coli (CRE)	120	14	74	52	16	99
Serratia marcescens (CRE)	80	-	19	30	14	37
Enterobacter hormaechei (CRE)	52	6	46	44	31	52
Klebsiella oxytoca (CRE)	48	0	8	6	0	72
Enterobacter cloacae (CRE)	28	7	43	39	43	71

(CRE)：對 carbapenem 類中的 imipenem 或 ertapenem 任一抗生素具抗藥性。

菌名	株數	CT	CZA	MI	SFP
Pseudomonas aeruginosa (CR)	347	83	84	-	44
Acinetobacter baumannii (CR)	148	-	-	61	41
Acinetobacter nosocomialis (CR)	25	-	-	90	92

(CR)：對 carbapenem 類中的 imipenem 或 meropenem 任一抗生素具抗藥性。

菌名	株數	DAP^	LNZ	TGC
Enterococcus faecium (VRE)	255	99	98	99

^: %SDD

菌名	株數	LEV	MI	MXF
Staphylococcus aureus (MRSA)	25	14	76	14

抗生素名稱

CT: Ceftolozane/Tazobactam
CZA: Ceftazidime/Avibactam
DAP: Daptomycin
LEV: Levofloxacin
LNZ: Linezolid
MEM: Meropenem
MI: Minocycline
MXF: Moxifloxacln
SFP: Cefoperazone/Sulbactam
TGC: Tigecycline
- : Not available, or Method limitation

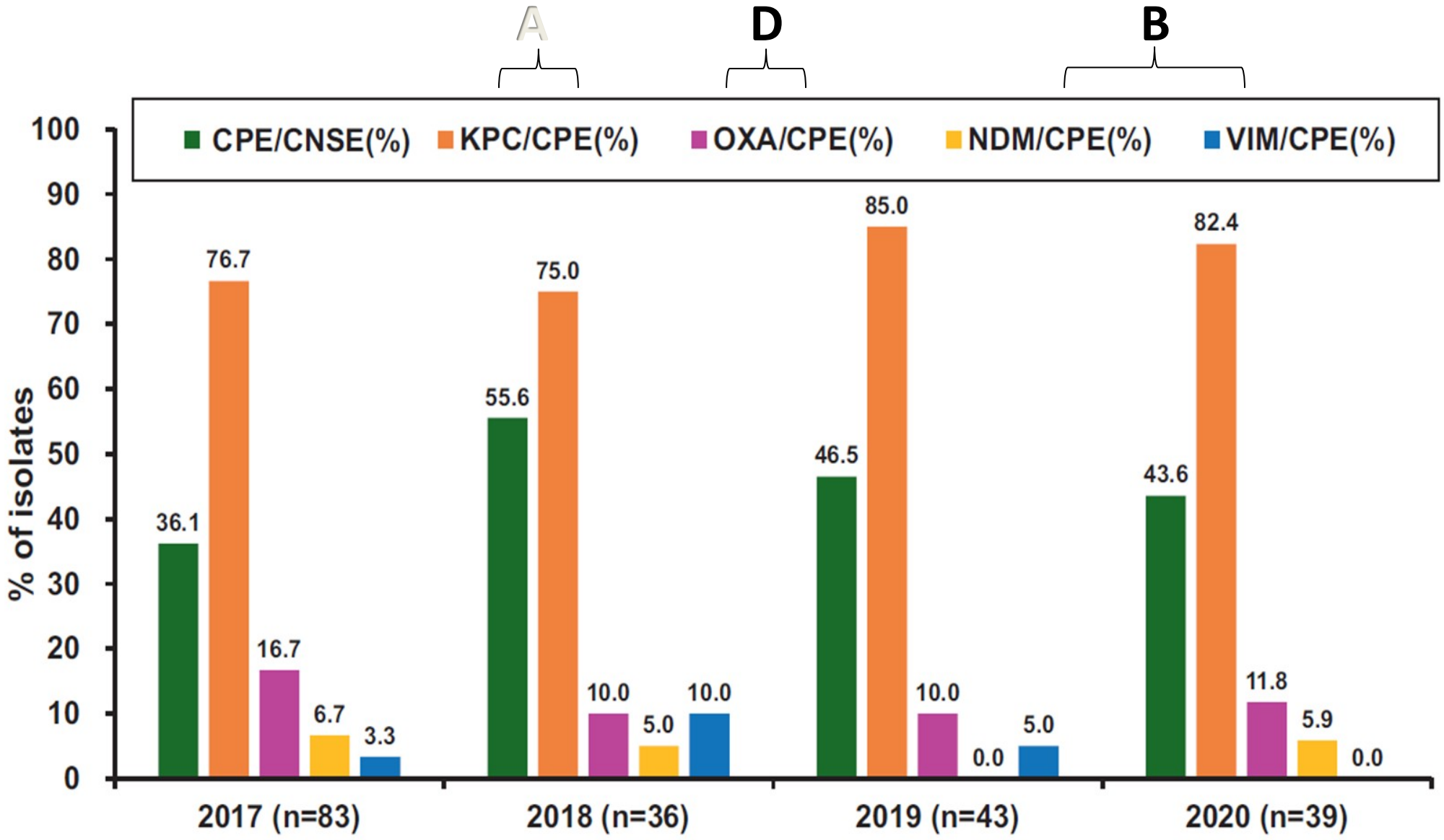
8. 全院Candida from BLOOD CULTURE (% Susceptible): 2025

菌名	株數	AMB	CAS	5FC	FCA	MF	VRC
Candida albicans	65	100	100	100	98	100	97
Candida glabrata	44	100	-	100	-	100	-
Candida tropicalis	40	100	100	95	85	100	83
Candida parapsilosis	37	97	100	100	70	100	70

抗真菌藥物名稱

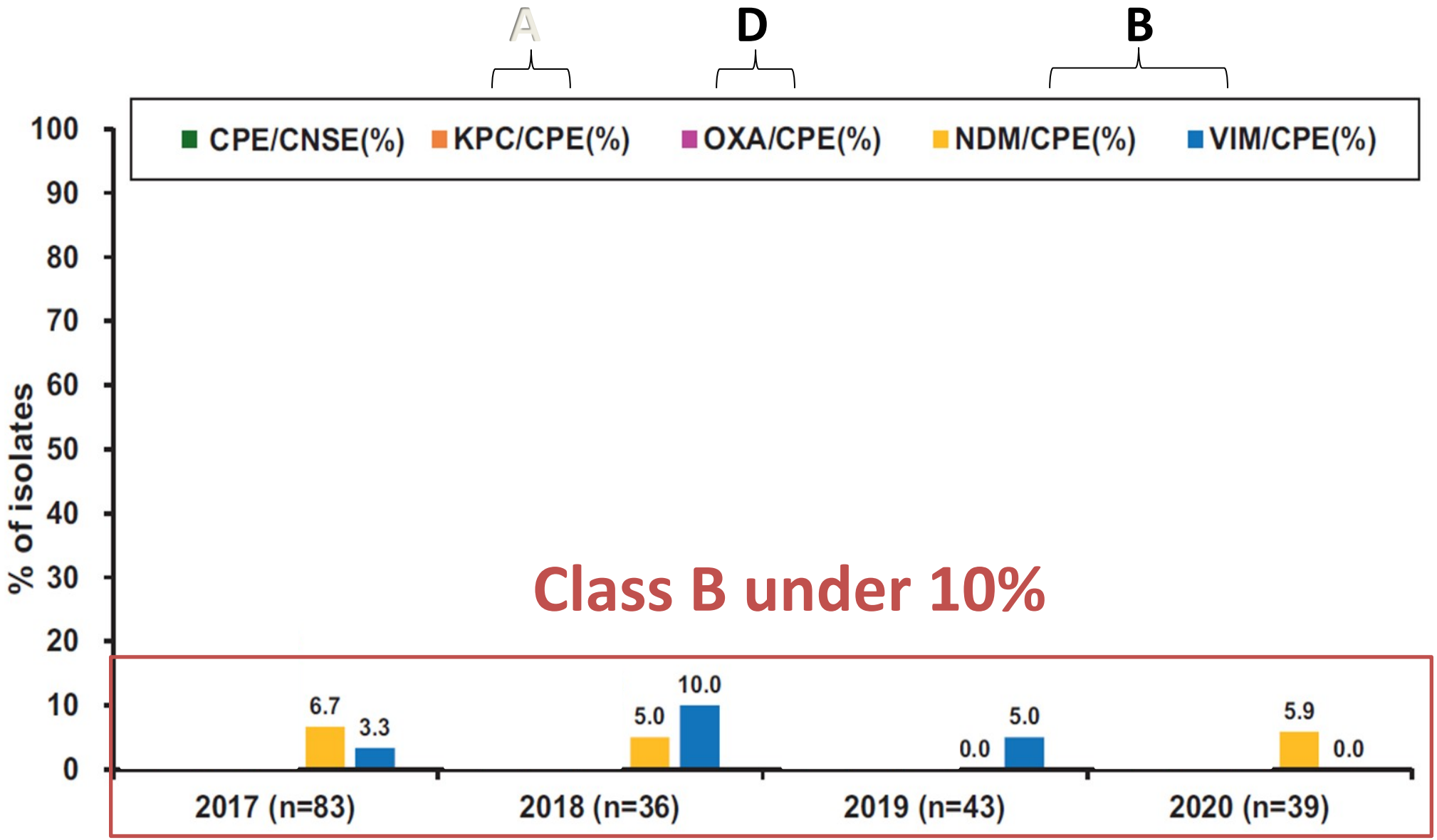
AMB: Amphotericin B
CAS: Caspofungin
5FC: Flucytosine
FCA: Fluconazole
MF: Micafungin
VRC: Voriconazole

Epidemiological situation of CRE in Taiwan (SMART study)



Lee YL et al. IJAA 2021: 106377.

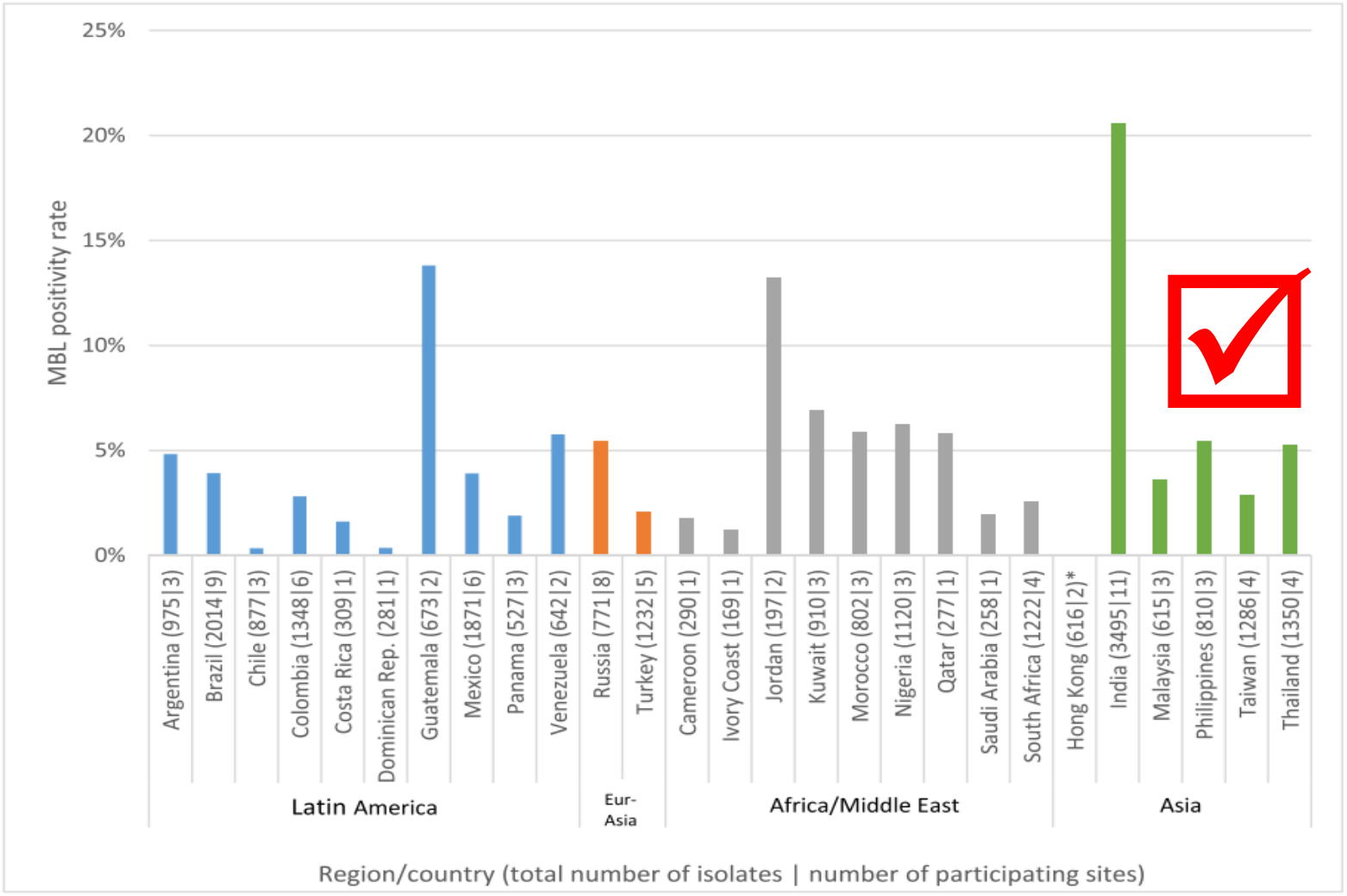
Epidemiological situation of CRE in Taiwan (SMART study)



Lee YL et al. IJAA 2021: 106377.

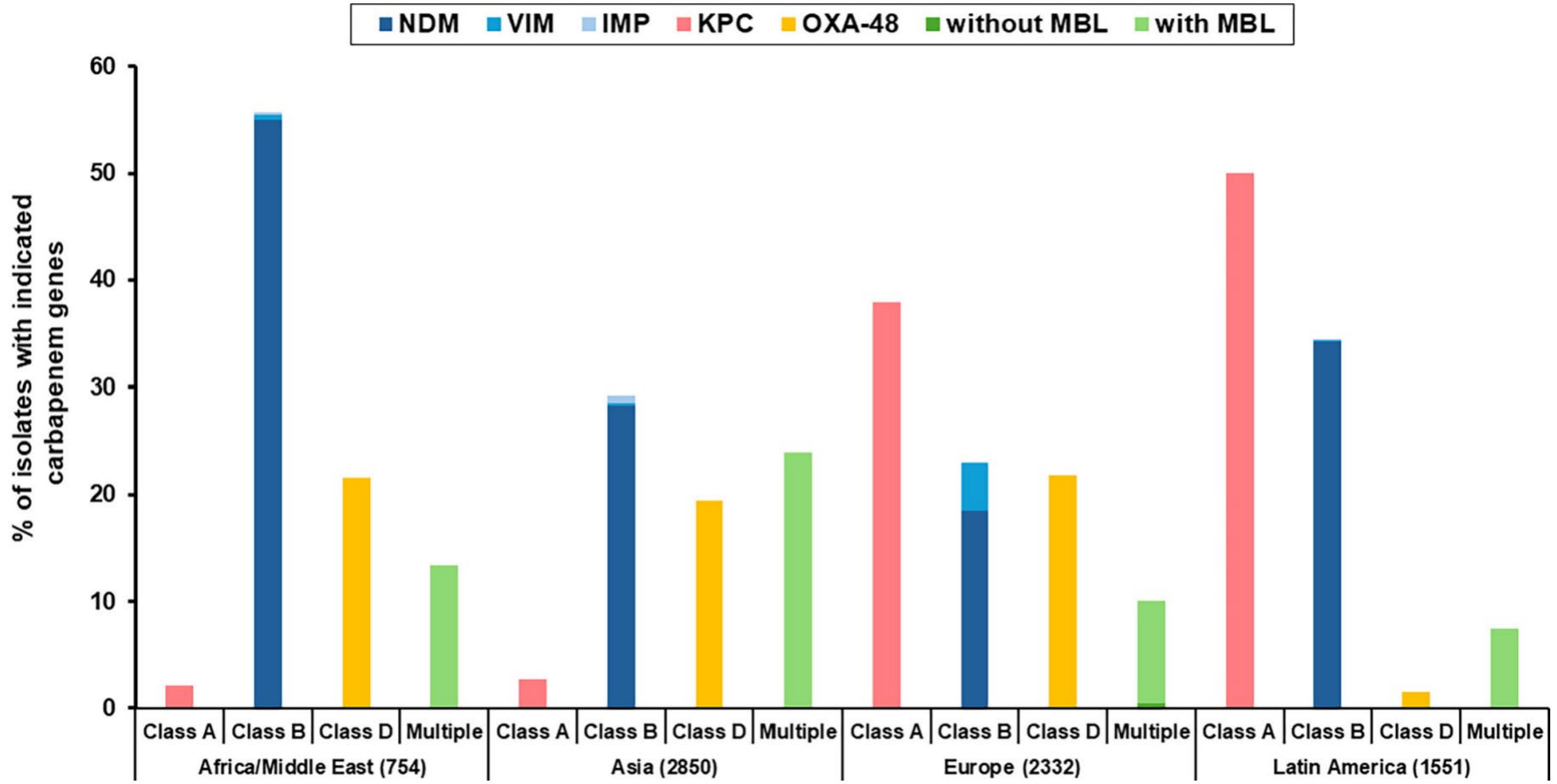
MBL prevalence: TW: around 2.5% (ATLAS study)

Fig. 2 Incidence of MBL positivity among isolates collected for the ATLAS surveillance project in 2019–2021 by country. Asterisk indicates no MBL producers collected in Hong Kong



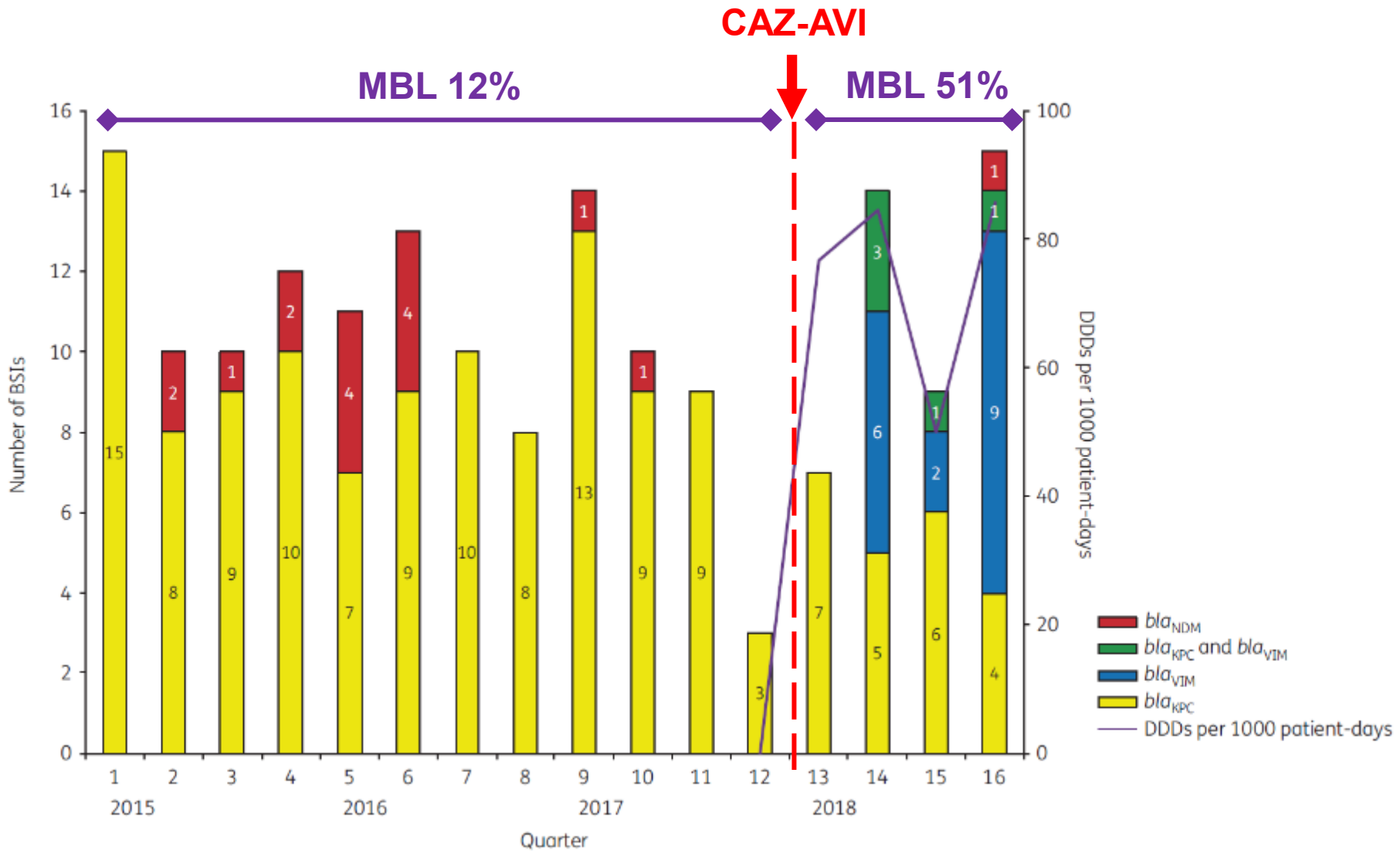
European Journal of Clinical Microbiology & Infectious Diseases (2023) 42:1135–1143

Global CRE genes by ATLAS (2019-2023)



Lee YL et al, Antimicrob Agents Chemother. 2026 Apr;70(4):e0154925.

Ceftazidime-avibactam use and types of carbapenemase production



J Antimicrob Chemother. 2019 Jul 1;74(7):2051-2054. [44]

Risk factors for ceftazidime-avibactam clinical failure in CRE infections

Retrospective in US, clinical failure rate 45%

Risk factor[a]	Value[b] for patients with: Success (n = 42)	Failure (n = 35)	P value	Multivariate P value (OR, 95% CI)[c]
Demographics and underlying conditions				
Male gender	29 (69)	18 (51)	0.16	
Age (yr)	64 (19–91)	59 (26–79)	0.22	
Solid-organ transplant recipient	9 (21)	9 (26)	0.79	
Charlson Comorbidity Index	4 (0–10)	5 (0–10)	0.86	
Severity of illness				
ICU at disease onset	17 (40)	27 (77)	0.001	Excluded
Renal replacement therapy	**3 (7)**	**13 (37)**	**0.002**	**0.046 (4.78, 1.03–22.2)**
SOFA score	5 (0–18)	8 (0–20)	0.0007	0.13
SAPS II score	37 (8–62)	43 (17–81)	0.04	0.98
Infection characteristics				
Infection type				
Pneumonia	**12 (29)**	**21 (60)**	**0.01**	**0.045 (3.09, 1.03–9.34)**
Primary bacteremia	15 (36)	5 (14)	0.04	
Urinary tract infection	7 (17)	1 (3)	0.07	
Intra-abdominal infection	3 (7)	4 (11)	0.70	
Skin/soft tissue infection	4 (10)	2 (6)	0.68	
Other	1 (2)	2 (6)	0.59	

- CRE: KP 78% (60/77), E coli 12% (9/77), Enterobacter cloacae 6% (5/77), and others.

Antimicrob Agents Chemother. 2018 Apr 26;62(5):e02497-17.

The presence of KPC-3 variant was associated with ceftazidime/avibactam resistance (P < 0.0001)

- One KPC-3 variant-carrying isolate was resistant to both ceftazidime/avibactam and imipenem (MICs = 16 and 8 µg/ml, respectively).

Associations between imipenem, Imipenem/relebactam , ceftazidime, and ceftazidime/avibactam MICs against *KPC-K. pneumoniae* isolates

	Median MIC (µg/mL) (range)											
	Imipenem			**Imipenem/relebactam**			Ceftazidime			**Ceftazidime/avibactam**		
Factor	Factor absent	Factor present	P value	Factor absent	Factor present	P value	Factor absent	Factor present	P value	Factor absent	Factor present	P value
ESBL	8 (0.125-256)	16 (2-128)	0.03	0.25 (0.125-2)	0.5 (0.125-4)	0.39	128 (8-1,024)	256 (8-1,024)	0.002	2 (0.25-512)	1 (0.25-4)	0.03
KPC-3 variant	16 (0.125-256)	0.5 (0.25-8)	0.0007	**0.5 (0.125-4)**	**0.25 (0.125-0.5)**	**0.31**	256 (8-1,024)	256 (128-1,024)	0.26	**2 (0.25-16)**	**128 (16-512)**	**0.0001**
Major OmpK36 mutations	8 (0.125-64)	64 (2-256)	0.0001	0.25 (0.125-1)	1 (0.125-4)	0.0002	128 (8-1,024)	384 (8-1,024)	0.007	1.5 (0.25-256)	2 (0.25-512)	0.09

[α]Isolates that carried MBL and OXA-carapenemases were excluded from analysis.

Adapted from Haidar G, et al. 2017

One hundred clinical CRE isolates were selected from previous studies or sequenced in this study, sourced from UPMC and Rutgers-New Jersey Medical School. Geographically, isolates were mostly from the US (88), with a few from India, China, and other countries. MICs for imipenem ± relebactam and ceftazidime ± avibactam were determined using broth microdilution. Antibiotic susceptibility was assessed per CLSI breakpoints, and CRE was defined using revised CDC criteria.

CRE = carbapenem-resistant Enterobacteriaceae; KPC = *Klebsiella pneumoniae* carbapenemase; KPC-K = KPC-producing *Klebsiella pneumoniae*; MIC = minimum inhibitory concentration; ESBL = extended-spectrum β-lactamases; CLSI = Clinical and Laboratory Standards Institute; UPMC = University of Pittsburgh Medical Center; CDC = Centers for

Ceftazidime/avibactam resistant clinical strains expressing KPC-2 variants with substitutions in the Ω-loop are emerging

- The **KPC-2 D179N (Ω-Loop hydrogen bond networking changes)**[1] variant when expressed confers resistance to imipenem (MIC 4 µg/mL).
- Addition of avibactam overcomes the ceftazidime resistance mediated by KPC-2 but **not that mediated by the Asp179 variants**.

MICs of various BL, BLI and combinations against strains containing KPC-2 Asp179 variants

Strain	MIC		
	Ceftazidime	Ceftazidime/avibactam	Imipenem
K. pneumoniae KPC-2	64 µg/mL	1 µg/mL	16 µg/mL
*E. Coli bla*KPC-2 179 Asp (WT)	128 µg/mL	1 µg/mL	8 µg/mL
***E. Coli bla*179 Asn (D179N)**	**512 µg/mL**	**16 µg/mL**	**4 µg/mL**

Imipenem/relebactam
KPC-2 D179N variant
MIC = 0.5 µg/mL

Adapted from Barnes MD,et al. 2017

Reference1: Whole-cell viability assays. Mueller-Hinton (MH) agar-dilution MIC measurements were performed according to Clinical and Laboratory Standards Institute (CLSI) guidelines. The MICs are reported as the concentrations at which bacterial growth was no longer observed. Avibactam was tested at a constant 4 µg/ml in combination with its respective antibiotic partners. All MIC measurements were performed at least three times.

BL/BLI = β-lactam/β-lactamaseinhibitor combinations; D = Aspartic acid; KPC = *Klebsiella pneumoniae* carbapenemases; MIC = minimum inhibitory concentration; N = Asparagine; *E. coli* = *Escherichia coli*; *K. pneumoniae* = *Klebsiella pneumoniae.*

Question 3.8: What is the role of tetracycline derivatives for the treatment of infections caused by CRE?

- Suggested approach: Although β-lactam agents remain preferred treatment options for CRE infections, tigecycline and eravacycline are alternative options when β-lactam agents are either not active or unable to be tolerated. The tetracycline derivatives are not suggested for the treatment of CRE urinary tract infections or bloodstream infections.
- Limited clinical data are also available investigating the effectiveness of minocycline against CRE infections, but data suggest a lower proportion of CRE isolates are likely to be susceptible to minocycline compared to tigecycline or eravacycline. The panel suggests using minocycline with caution for the treatment of CRE infections.

Clin Infect Dis. 2024 Aug 7:ciae403.

Mechanisms of CZA-resistant KP in Taiwan (VGHTPE)

- 456 CRKP isolates were collected in VGHTPE in 2020
  - 31 (6.8%) are non-CP strains (CPE/CRE = 93.2%)
  - 301 (66%) KPC, 83 (18.2%) OXA-48, 41 (9.0%) MBL
- 35(7.6%) CZA-resistant CRKP strains with exposure to CZA were analyzed
  - 20 (57.1%) MBL producers
  - 10 (28.6%) KPC variants, exhibiting MIC for CZA ranging from 64 to ≥256 mg/L.
    - KPC-33 (n = 3), KPC-31 (n = 1), KPC-39 (n = 1), KPC-44 (n = 1), KPC-58 (n = 1), KPC-90 (n = 1), and 2 novel KPC variants.
  - 5 wild type KPC with reduced susceptibility

SH Chou, YT Lin et al. Int J Antimicrob Agents. 2024;64:107244

Question 3.9: What is the role of polymyxins for the treatment of infections caused by CRE?

- Suggested approach: Polymyxin B and colistin are not suggested for the treatment of infections caused by CRE. Colistin is an alternative agent for uncomplicated CRE cystitis.
- Polymyxin B should not be used as treatment for CRE cystitis, due to its predominantly nonrenal clearance.

Clin Infect Dis. 2021 Apr 8;72(7):e169-e183.
Clin Infect Dis. 2023 Jul 18:ciad428.
Clin Infect Dis. 2024 Aug 7:ciae403.

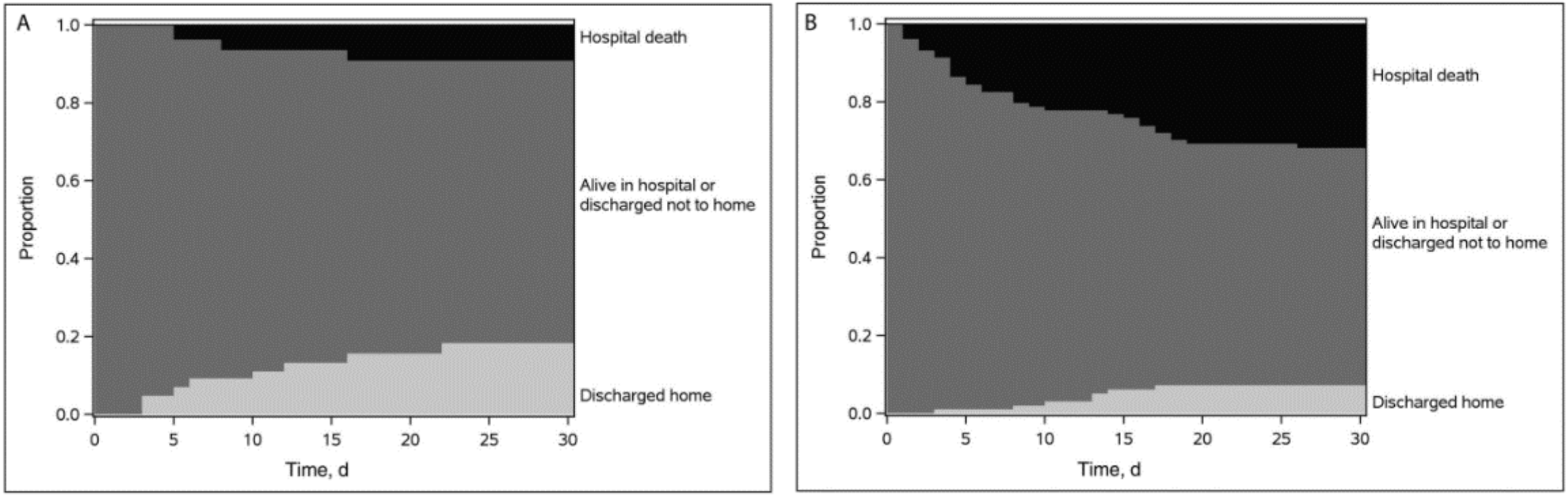
Question 3.10: What is the role of combination antibiotic therapy for the treatment of infections caused by CRE?

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

Clin Infect Dis. 2021 Apr 8;72(7):e169-e183.
Clin Infect Dis. 2023 Jul 18:ciad428.
Clin Infect Dis. 2024 Aug 7:ciae403.

Ceftazidime-Avibactam(A) VS Colistin(B) in CRE: inverse probability of treatment weighting

137 Patient characteristics: 61 yrs, 47% male, 50% White, 34% critical
46% bacteremia, 21% pneumonia, 97% CRKP



IPTW P=0.001

CAZ-AVI reduced 30-day mortality (9% vs. 32%) with lower incident renal failure (4% vs. 13%) *vs.* Colistin

Clin Infect Dis. 2018 Jan 6;66(2):163-171.

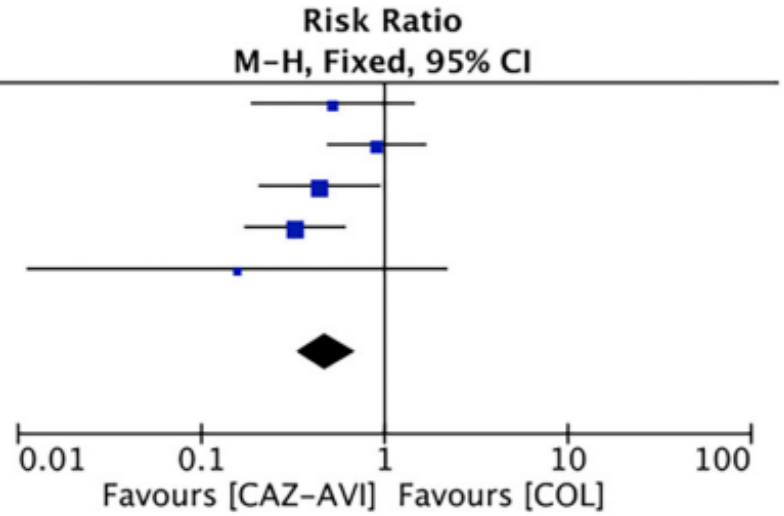
Observational retrospective analyses are designed to evaluate associations among variables and cannot establish causality; they are not intended for direct comparison with clinical trials

CAZ-AVI VS Colistin in CRE BSI in 30-D mortality

Study or Subgroup	CAZ-AVI Events	CAZ-AVI Total	COL Events	COL Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
21	3	13	27	61	13.8%	0.52 [0.19, 1.46]	2020
26	12	32	12	29	18.3%	0.91 [0.49, 1.69]	2021
25	6	35	40	103	29.5%	0.44 [0.20, 0.95]	2021
22	10	52	16	27	30.6%	0.32 [0.17, 0.61]	2021
24	0	4	18	28	7.9%	0.16 [0.01, 2.21]	2021
Total (95% CI)		**136**		**248**	**100.0%**	**0.48 [0.33, 0.69]**	
Total events	31		113				

Heterogeneity: $Chi^2 = 6.21$, $df = 4$ ($P = 0.18$); $I^2 = 36\%$

Test for overall effect: $Z = 3.94$ ($P < 0.0001$)



Observational retrospective analyses are designed to evaluate associations among variables and cannot establish causality; they are not intended for direct comparison with clinical trials

Chen Y et al. Microbiol Spectrum 2022 Apr;10(2):e0260321

CAV/AVI group *vs.* polymyxin B group had 75% lower 30-day mortality risk

A single-center retrospective observational study included patients with CRPA infection treated with CAZ/AVI or polymyxin B between January 2018 and December 2020.

- 51 patients were treated with ceftazidime/avibactam monotherapy while 85 patients received the therapy of **polymyxin B mostly combined with other antibiotics** (carbapenems and amikacin etc.)
- After adjustment by propensity score matching, the CAV/AVI group *vs.* polymyxin B group had
  - Lower 30-day mortality (14.3% vs 42.9%, p=0.018)
  - Higher bacterial clearance rate (42.9% vs 14.3%, p=0.018)

Table 5 Univariate and Multivariate COX Regression Analysis Associated with 30-Day Mortality After Adjustment

	Univariate Analysis		Multivariate Analysis	
	P value	HR (95% CI)	P value	HR (95% CI)
Age (1-year increments)	0.033	1.047 (1.004–1.093)	0.022	1.050 (1.007–1.094)
Central venous catheter	0.021	0.262 (0.084–0.816)	0.027	0.268 (0.084–0.859)
Duration of therapy (1-day increments)	0.027	0.871 (0.771–0.984)		
CAZ/AVI use	0.031	0.287 (0.092–0.890)	0.016	0.244 (0.078–0.765)

Abbreviations: HR, Hazard ratios; CI, Confidence interval; CAZ/AVI, Ceftazidime/avibactam.

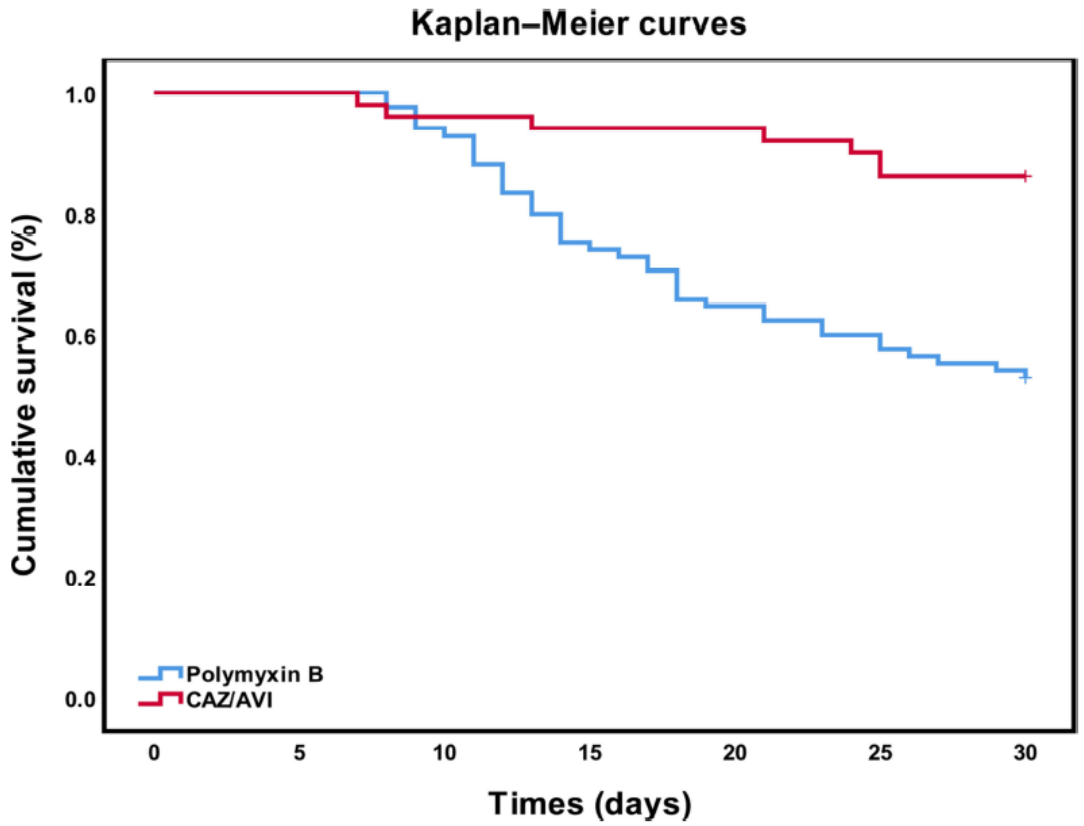


Figure 2 Kaplan–Meier curves of patients with CRPA infection treated with CAZ/AVI or polymyxin B.
Abbreviations: CRPA, Carbapenem-resistant *Pseudomonas aeruginosa*; CAZ/AVI, ceftazidime/avibactam.

Infect Drug Resist. 2022;15:655-667.

Observational retrospective analyses are designed to evaluate associations among variables and cannot establish causality; they are not intended for direct comparison with clinical trials

Cefiderocol in HAP/VAP treatment

	HAP/VAP		Overall	
	Cefiderocol (n=45)	Best available therapy (n=22)	Cefiderocol (n=101)	Best available therapy (n=49)
Day 14	11 (24%; 12·9–39·5)	3 (14%; 2·9–34·9)	19 (19%; 11·7–27·8)	6 (12%; 4·6–24·8)
Day 28	14 (31%; 18·2–46·6)	4 (18%; 5·2–40·3)	25 (25%; 16·7–34·3)	9 (18%; 8·8–32·0)
End of study	19 (42%; 27·7–57·8)	4 (18%; 5·2–40·3)	34 (34%; 24·6–43·8)	9 (18%; 8·8–32·0)

Table 5: All-cause mortality in the safety populati

	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

In the **cefiderocol** group, 83% (66/80) of patients received **monotherapy**; in the best available therapy group, 71% (27/38) received combination therapy. 25 patients **(66%)** of 38 in the **best available therapy** group received **colistin-based treatment**.

Despite the similarities in clinical and microbiological outcomes, the **all-cause mortality rate in the cefiderocol group was higher** than in the best available therapy group.

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

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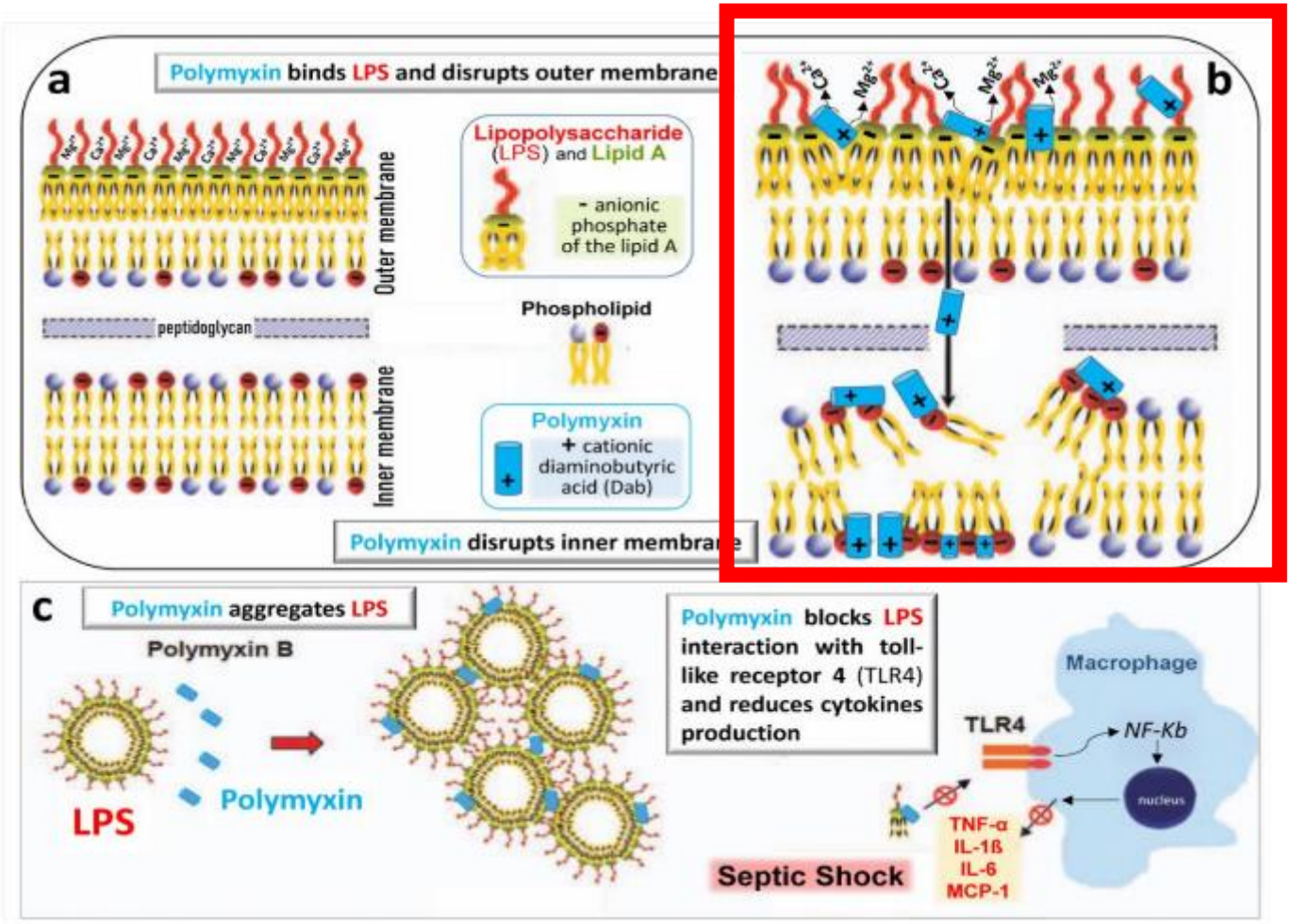
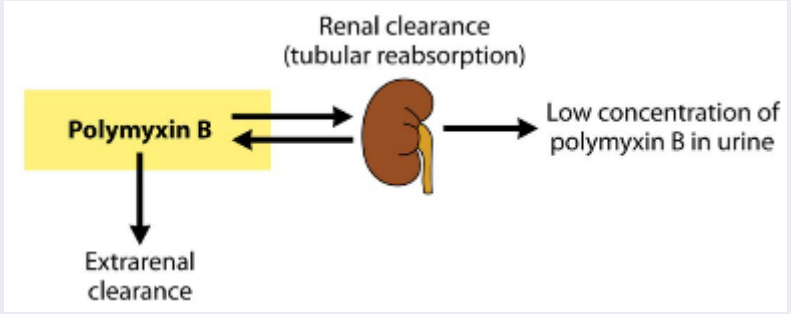
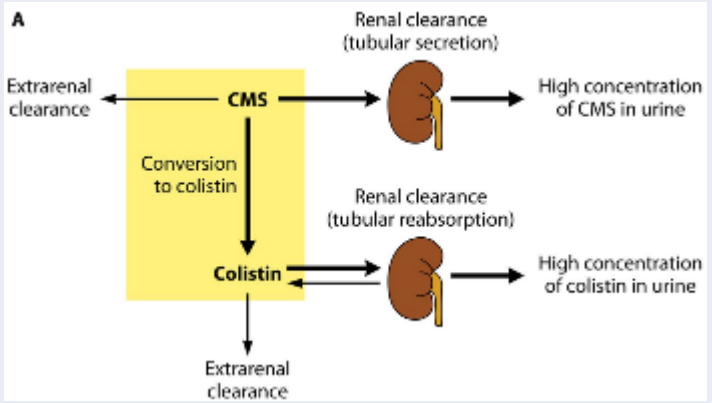
Schematic Representation of the Bactericidal Action of Polymyxins

- Cationic, cyclic decapeptide
- Binds anionic lipopolysaccharide (LPS) in outer membrane of GNB
- Displacing Ca^{2+} & Mg^{2+} from outer cell membrane
- Permeability change, leakage of cell content, cell death
- Polymyxin reduce the sepsis severity by blocking LPS interaction with macrophage receptor, TLR4.



Zhu Y et al., Microorganisms. 2021 May 27;9(6):1154.

The difference between Polymyxin B and Colistin

	Polymyxin B [1]	Colistimethate Sodium (Colistin, Polymyxin E) [1]
Brand Name	Bobimixyn 寶比黴素	Colimycin 克痢黴素
Commercial Formulations	50 mg/vial; 500,000(500K) units/vial	66.8 mg Colistin base/vial; 2,000,000 units/vials
Prodrug Form	No	Yes (Colistimethate sodium)
Pharmacokinetic Pathways	No renal metabolism, excreted unchanged 	Prodrug is metabolized in kidneys to active form; excreted by kidneys 
Dosing Regimen	Loading dose: 2.5mg/kg Maintain dose: 1.5mg/kg, q12h[2]	Loading dose: 5mg/kg Maintain dose: 2.5 mg x (1.5 x CrCl + 30) IV divided for q12h [3]

1. Poirel L et al., Clin Microbiol Rev. 2017 Apr;30(2):557-596.; 2.2014 Sanford Guide; 3. 2018 肺炎診治指引

Bobimixyn Potential Adverse Effects

- **Nephrotoxicity**: Acute Tubular Necrosis (ATN)
  - Clinical Signs:
    - Rise in **serum creatinine (sCr)** and **blood urea nitrogen (BUN).**
    - Decreased **urine output**.
    - Electrolyte imbalances (e.g., potassium, magnesium).

- **Neurotoxicity**: Interfere with ion channels on neurons and disrupt the release of the neurotransmitter acetylcholine at the neuromuscular junction.
  - Clinical Signs:
    - **Paresthesias**: A tingling or numbness, most commonly around the mouth, face, and extremities.
    - **Dizziness and Ataxia**: Feeling dizzy, unsteady, or having poor coordination.
    - **Neuromuscular Blockade**: It can cause generalized muscle weakness, which can progress to affect the respiratory muscles, leading to respiratory distress or failure. This risk is much higher in patients also **receiving anesthetics** or other **neuromuscular blockers.**

- **Skin Hyperpigmentation**: Subsequent melanocyte activation
  - Clinical Signs:
    - Predominantly of the head and neck in shades of brown

RESEARCH Open Access

Clinical outcomes and safety of polymyxin B in the treatment of carbapenem-resistant Gram-negative bacterial infections: a real-world multicenter study

Xiaojuan Zhang[1], Shaoyan Qi[2], Xiaoguang Duan[1], Bing Han[1], Shuguang Zhang[1], Shaohua Liu[1], Haixu Wang[1], Haibo Zhang[3*] and Tongwen Sun[1*]

- The real-world study included 100 patients treated with intravenous PMB for at least 7 days during the period of October 2018 through June 2019.
- Temperature (38 °C vs 37.1 °C), white blood cells (14.13 × 109/l vs 9.28 × 109/l), C-reactive protein (103.55 ug/l vs 47.60 ug/l), procalcitonin (3.89 ng/ml vs 1.70 ng/ml) and APACHE II levels (17.75 ± 7.69 vs 15.98 ± 7.95) were significantly decreased after PMB treatment.
- Bacteria eradication rate was **77.65%**. Overall mortality at discharge was **15%**, and 28-day mortality was **40%**. Major adverse reactions occurred in 16 patients. Nephrotoxicity was observed in 7 patients (**7%**).

J Transl Med. 2021 Oct 16;19(1):431.

Polymyxin B 可參考Colistin 藥敏作為處方依據
MIC<=2可考慮使用

台灣感染症醫學會
The Infectious Diseases Society of Taiwan

26th Annual Meeting of Antimicrobial Resistance in Taiwan

The Burden of Multidrug-resistant Organisms and the Potential Application of Information and Bio-molecular Technologies

Polymyxin B 在常見的MDR-GNB MIC ≤ 2 比例高(9成以上)，
根據CLSI 及其他文獻論述：

- Polymyxin B **藥敏可參考Colistin**；
- Polymyxin B MIC 可參考Colistin，**MIC ≤ 2 即可考慮使用**

2024/10/05第二十六屆台灣抗微生物製劑抗藥性現況研討會
http://idsroc.org.tw/news/news_info.asp?news_type=4&id=922

In vitro MDR Enterobacterales sensitivity from ATLAS (2021-2022) with HAP/VAP and IAI

All 14564 isolates: CRE prevalence 10.4%, MBL 4% by EUCAST method

Phenotype	Antimicrobials	%S (EUCAST)	% R (EUCAST)	MIC_{50}	MIC_{90}	MIC range
All Enterobacterales ($n=14\,564$)						
MDR	Amikacin	82.7	17.3	2	128	0.25–128
($n=6217$)	Aztreonam	30.5	69.5	32	128	0.03–128
	Aztreonam/avibactam	98.9	1.0	0.12	0.5	0.015–128
	Cefepime	43.9	56.0	8	64	0.12–64
	Colistin	83.0	17.0	0.25	16	0.12–16
	Meropenem	82.5	17.5	0.06	32	0.06–32
	Tigecycline*	93.9	6.1	0.5	2	0.03–16
ESBL	Amikacin	66.3	33.6	4	128	0.25–128
($n=1688$)	Aztreonam	2.3	97.7	128	128	0.12–128
	Aztreonam/avibactam	99.0	1.0	0.12	0.5	0.015–128
	Cefepime	6.5	93.5	64	64	0.12–64
	Colistin	86.5	13.5	0.25	8	0.12–16
	Meropenem	62.0	38.0	0.5	32	0.06–32
	Tigecycline*	97.2	2.8	0.5	2	0.06–16
CRE	Amikacin	33.3	66.6	64	128	0.5–128
($n=1088$)	Aztreonam	7.0	93.0	128	128	0.03–128
	Aztreonam/avibactam	96.4	3.6	0.25	1	0.015–128
	Cefepime	1.0	99.0	64	64	1–64
	Colistin	75.9	24.1	0.25	16	0.12–16
	Meropenem	0	100	32	32	16–32
	Tigecycline*	90.2	9.8	1	2	0.12–16

CRE S
Aztreonam/avibactam: 96.4%
Colistin 75.9%
Tigecycline 90.2%

		MIC_{90} (mg/L)/% susceptible (%S), EUCAST											
		Aztreonam/ avibactam		Aztreonam		Colistin		Cefiderocol		Cefepime		Tigecycline[a]	
Genotypes	*n*	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}
Overall ($n=577$)													
NDM	508	94.5	2	13.8	>64	74.8	>8	47.4	8	0.0	>32	98.0	2
VIM	48	100.0	2	14.6	>64	72.9	>8	72.9	4	0.0	>32	81.0	4
IMP	25	100.0	2	24.0	>64	60.0	>8	68.0	4	8.0	>32	68.0	>8
Co-carriage													
OXA-48-like	145	98.6	0.5	6.2	>64	73.8	>8	61.4	4	0.0	>32	99.3	2
KPC	30	100.0	1	0.0	>64	60	>8	40.0	16	0.0	>32	86.7	4
ESBL[b] ($n=450$)	353	98.9	1	0.6	>64	74.8	>8	50.1	8	0.0	>32	98.6	2
pAmpC[b] ($n=450$)	72	66.7	16	2.8	>64	84.7	8	37.5	>32	0.0	>32	94.4	1
YRIK[c] ($n=81$)	21	57.1	32	0	>64	100.0	0.5	19.1	4	0.0	>32	100.0	0.5
YRIN[c] ($n=81$)	40	52.5	16	2.5	>64	100.0	0.25	20.0	>32	0.0	>32	100.0	0.5
YRIK/YRIN+pAmpC	35	31.4	32	0	>64	100.0	0.25	17.1	>32	0.0	>32	100.0	0.5

MBL NDM S
Aztreonam/avibactam: 94.5% but poor activity
With PBP
Colistin 74.8%; Cefiderocol 47.4%; Tigecycline 98%

Yang Q et al, J Antimicrob Chemother. 2026 Jun 3;81(7):dkag198.

In vitro MDR Enterobacterales bacteremia sensitivity from ATLAS (2021-2022)

All 10376 isolates (46% KP, 24% E coli, 11% Enterobacter)

: CRE prevalence 6.8% (74.3% KP, 11.1% E coli), MBL 3.3% by EUCAST method

Antimicrobial agent	Susceptibility (EUCAST)		MIC (mg/L)		No. of isolates inhibited at respective MIC (mg/L) (% cumulative inhibition)										
	%S	%R	MIC_{50}	MIC_{90}	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
CRE isolates (N = 710)[a]															
Aztreonam/ avibactam	98.9	1.1	0.25	1	62 (8.7)	140 (28.5)	266 (65.9)	158 (88.2)	44 (94.4)	14 (96.3)	18 (98.9)	5 (99.6)	0 (99.6)	0 (99.6)	3 (100)
Aztreonam	5.6	93.4	128	128	7 (1)	5 (1.7)	10 (3.1)	14 (5.1)	4 (5.6)	1 (5.8)	6 (6.6)	4 (7.2)	9 (8.5)	23 (11.7)	627 (100)
Cefepime	0.1	99.3	64	64	0	0	0	0	1 (0.1)	1 (0.3)	3 (0.7)	9 (2.0)	12 (3.7)	47 (10.28)	637 (100)
Colistin	80.1[c]	19.9	0.25	16	0	183 (25.8)	315 (70.1)	36 (75.2)	21 (78.2)	14 (80.1)	19 (82.8)	33 (87.5)	89 (100)		
Meropenem	0	100	32	32	0	0	0	0	0	0	0	0	128 (18.0)	582 (100)	
Tigecycline[b]	93[c]	1.3	1	2	0	15 (2.1)	58 (10.3)	193 (37.5)	257 (73.7)	137 (93.0)	41 (98.7)	7 (99.7)	2 (100)		
Amikacin	43.1	56.9	16	128	0	0	0	4 (0.6)	60 (9.0)	63 (17.9)	100 (32)	79 (43.1)	58 (51.3)	45 (57.6)	301 (100)

Antimicrobial agent	Susceptibility (EUCAST)		No. of isolates inhibited at respective MIC (mg/L) (% cumulative inhibition)									
	%S	%R	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
NDM (N = 407)[a]													
Aztreonam/ avibactam	96.8	3.2	74 (18.2)	66 (34.4)	103 (59.7)	99 (84.0)	32 (91.9)	8 (93.9)	12 (96.8)	7 (98.5)	4 (99.5)	0 (99.5)	2 (100)
Aztreonam	10.1	87.5	12 (2.9)	3 (3.7)	12 (6.6)	6 (8.1)	8 (10.1)	5 (11.3)	5 (12.5)	6 (14.0)	5 (15.2)	27 (21.9)	318 (100)
Cefepime	0.2	99.5	0	1 (0.2)	0 (0.2)	0 (0.2)	0 (0.2)	1 (0.5)	0 (0.5)	2 (1.0)	6 (2.5)	15 (6.1)	382 (100)
Cefiderocol	51.1	48.9	0	3 (0.7)	2 (1.2)	7 (3.0)	49 (15.0)	147 (51.1)	146 (87.0)	26 (93.4)	7 (95.1)	3 (95.8)	17 (100)
Colistin	81.3[d]	18.7	0	5 (1.2)	225 (56.5)	83 (76.9)	12 (79.9)	6 (81.3)	3 (82.1)	20 (87.0)	53 (>8) (100)		
Ertapenem	0.7	99.3	2 (0.5)	0 (0.5)	1 (0.7)	0 (0.7)	1 (1.0)	0 (1.0)	1 (1.2)	7 (3.0)	395 (>8) (100)		
Minocycline[b]	34.9	39.8	0	0	2 (0.5)	6 (2.0)	33 (10.1)	53 (23.1)	48 (34.9)	103 (60.2)	74 (78.4)	88 (>16) (100)	
Tigecycline[c]	97.5[d]	0	2 (0.5)	25 (6.6)	86 (27.8)	103 (53.1)	132 (85.5)	49 (97.5)	10 (100)				
Tobramycin	10.1	89.9	0	1 (0.3)	12 (3.2)	18 (7.6)	7 (9.3)	3 (10.1)	11 (12.8)	50 (25.1)	305 (>8) (100)		

CRE S

Aztreonam/avibactam: 98.9%

Colistin 80.1%

Tigecycline 93%

MBL NDM S

Aztreonam/avibactam: 96.8%

Colistin 81.3%; Cefiderocol 51.1%; Tigecycline 97.5%

Rossolini GM et al, Microbiol Spectr. 2026 Jun 30:e0024126.

In vitro activity of aztreonam/avibactam in CRE from US 62 centers (2017-2022)

Agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Range (mg/L)	%S	%I	%R
CREs with only class A carbapenemases (360 isolates)						
Aztreonam-avibactam	0.25	0.5	≤0.03–8	99.4	N/A	0.6
Ceftazidime-avibactam	1	2	<0.03–32	98.9	N/A	1.1
Meropenem-vaborbactam	0.03	0.5	<0.03–>32	98.3	0.6	1.1
Imipenem-relebactam	0.125	1	0.03–>8	92.8	2.2	5.0
Cefiderocol	0.5	2	<0.03–64	98.9	0.3	0.8
Tigecycline	0.5	2	≤0.06–8	96.7	1.9	1.4
Colistin	0.25	>8	≤0.06–>8	N/A	82.7	17.3
CREs with class B carbapenemases[c] (50 isolates)						
Aztreonam-avibactam	0.25	0.5	≤0.03–8	98.0	N/A	2.0
Ceftazidime-avibactam	>32	>32	0.125–>32	4.0	N/A	96.0
Meropenem-vaborbactam	16	>32	0.5–>32	16.0	6.0	78.0
Imipenem-relebactam	8	>8	1–>8	2.0	4.0	94.0
Cefiderocol	2	16	<0.03–32	74.0	14.0	12.0
Tigecycline	0.5	2	0.25–4	92.0	8.0	0.0
Colistin	0.25	16	0.06–>8	N/A	86.0	14.0
CREs with only class D carbapenemases (12 isolates)						
Aztreonam-avibactam	0.25	0.5	≤0.03–0.5	100.0	N/A	0.0
Ceftazidime-avibactam	1	2	0.125–2	100.0	N/A	0.0
Meropenem-vaborbactam	32	>32	1–>32	16.7	8.3	75.0
Imipenem-relebactam	4	8	1–>8	16.7	0.0	83.3
Cefiderocol	0.5	2	<0.03–4	100.0	0.0	0.0
Tigecycline	1	4	0.25–4	83.3	16.7	0.0
Colistin	0.125	0.25	≤0.06–>8	N/A	91.7	8.3
CREs without carbapenemases (89 isolates)						
Aztreonam-avibactam	0.5	4	0.03–>16	94.4	N/A	5.6
Ceftazidime-avibactam	1	8	<0.03–>32	96.6	N/A	3.4
Meropenem-vaborbactam	1	8	0.03–16	88.8	9.0	2.2
Imipenem-relebactam	0.25	2	0.06–4	89.9	5.6	4.5
Cefiderocol	1	8	0.03–64	88.8	5.6	5.6
Tigecycline	0.5	4	≤0.06–4	89.9	10.1	0.0
Colistin	0.25	2	≤0.06–>8	N/A	91.0	9.0

- All 54576 isolates: CRE prevalence 0.9%, MBL 3.7% in CRE
- Class A: S% 92.8-99.4%, colistin I% 82.7%
- Class B: ATM-AVI 98%S, Tige 92%S, Coli 86%I
- Class D: ATM-AVI 100%S, Cef-Avi 100%S, Cefiderocol 100%S, Coli 91.7%I

Papp-Wallace KM et al, Open Forum Infect Dis . 2025 Apr 25;12(5):ofaf250.

ATM-AVI R CRE by ATLAS (2019-2023)

FIG 1 Geographic distribution of ATM–AVI-R carbapenem-resistant isolates belonging to *Escherichia coli* (CR-*Escherichia*) and *Proteus mirabilis* (CR-*Proteus*) collected worldwide in the ATLAS program, 2019–2023. Countries with CR-*Escherichia* and CR-*Proteus* but without ATM–AVI-R isolates are not shown, including Argentina, Australia, Belgium, Brazil, Canada, Colombia, Costa Rica, Croatia, Czech Republic, Denmark, France, Greece, Guatemala, Israel, Italy, Ivory Coast, Japan, Jordan, Latvia, Lithuania, Malawi, Malaysia, Panama, Philippines, South Africa, South Korea, Spain, Ukraine, United States, and Venezuela. Image source: World Map Blank (https://worldmapblank.com/).

Lee YL et al, Antimicrob Agents Chemother. 2026 Apr;70(4):e0154925.

Aztreonam-avibactam resistance mechanisms.

Primary resistance mechanisms	Species	MIC (μg/mL)	Geographical source	Predominant MLST (ST)	Key references
Enterobacterales					
1. PBP3 Insertions + AmpC/ESBL Production					
PBP3 insertion (YRIN/YRIK) + CMY-42 AmpC	*E. coli*	8-32	Global	ST167, ST361, ST405, ST410, ST617, ST38	Sadek et al. [78]; Le Terrier et al. [79]; Mushtaq et al. [80]; Mendes et al. [81]; Tellapragada et al. [82]
PBP3 insertion (YRING) + CMY-145 AmpC	*E. coli*	8	Singapore	ST167, ST361	Chew et al. [83]
PBP3 insertion (YRIN/YRIK) + PER-2/PER-6/PER-7 ESBL	Engineered *E. coli*	8-256	NA	NA	Le et al. [84]
PBP3 insertion (YRIN) + KPC-21 mutation (W105R) + CMY-42 AmpC	*E. coli*	512	China	ST410	Ma et al. [85]
PBP3 insertion (YRIN/YRIK) + NDM5/NDM1/OXA+CMY-42 AmpC + porins loss	*E. coli*	8-32	Sweden	ST361, ST405, ST167, ST448, ST410, ST4450, ST617, ST1284	Tellapragada et al. [82]
PBP3 insertion (YRIN) and mutation (A417V) + CMY-145 AmpC mutation (L139R/N366Y)	*E. coli*	128		ST361	Haidar at al. [86]
2. PER-type β-Lactamases					
PER-2 + AmpC + ompF-like truncation	*E. cloacae*	8-16	Latin America	ST200, ST1324, ST88	Estabrook et al. [87]
PER-4 + OXA-1	*K. oxytoca*	16	Latin America	ST40	
PER-14 + SHV + TEM-1	*R. ornithinolytica*	16	Latin America	NA	
3. KPC Variants + Porin Defects					
KPC-2 S109P + OmpK36 truncation + Efflux pump upregulation	*K. pneumoniae*	128	USA	ST258	Xian et al. [88]
KPC overexpression + OmpK35/36/37 defects	*K. pneumoniae*	32-128	China	ST11	Yu et al. [89]
4. Novel PBP3 + Porin Mutations					
PBP3 Gly420dup + OmpC G151D	*P. hangzhouensis*	>64	Singapore	ST44	Chew et al. [90]
5. Efflux/Porins Alterations					
acrA efflux overexpression + OmpK35/36 truncation + DHA-1 AmpC	*K. pneumoniae*	8-16	Argentina, Taiwan, Thailand	ST872, ST15, ST273	Mendes et al. [81]
OmpC/OmpK36 variants (P177A, D188E) + PBP3 variant (S259insE) + AmpC hyperproduction	*E. cloacae complex*	16	Poland	ST78	Mendes et al. [81]
6. Altered β-Lactamase-Avibactam Interaction					
SHV-12 R244G substitution	*Enterobacter mori*	16	China	NA	Wu et al. [91]
CMY-16 T150S/N346H mutation + OmpK porin defects	*K. pneumoniae*	8-256	USA	ST101, ST147, ST377	Niu et al. [92]
Non-fermenting Gram-negative bacteria					
1. Efflux/Porins Alterations					
MexAB-OprM overexpression + OprD porin loss	*P. aeruginosa*	8	Sapin, Italy	ST175, ST235	Sastre et al. [93]; Gonzalez et al. [94]
2. Pyocyanin Overproduction					
PA4292 mutation or deletion-induced Pyocyanin overproduction	*P. aeruginosa*	128-256	China	NA	Zhao et al. [95]

Abbreviations: MIC, minimal inhibitory concentration; MLST, multilocus sequence typing; YRIN, an amino-acid insertion (Tyr-Arg-Ile-Asn) in the PBP3 sequence; YRIK, an amino-acid insertion (Tyr-Arg-Ile-Lys) in the PBP3 sequence; YRING, an amino-acid insertion (Tyr-Arg-Ile-Asn-Gly); *E. coli, Escherichia coli; E. cloacae, Enterobacter cloacae; K. oxytoca, Klebsiella oxytoca; R. ornithinolytica, Raoultella ornithinolytica; K. pneumoniae, Klebsiella pneumoniae; P. hangzhouensis, Providencia hangzhouensis; P. aeruginosa, Pseudomonas aeruginosa*; NA, data not available.

Antimicrobial stewardship programme

	Description	Outcomes
Pre-authorisation	Prescribers are required to gain approval prior to use of certain antimicrobials	Ensures appropriate antibiotic selection and dosing Prevents unnecessary initiation of antibiotics
Prospective audit and feedback	External review of antibiotics after initiation, with suggestions from experts on optimal use	Reduction in unnecessary use of broad-spectrum antibiotics
Facility-specific treatment guidelines	Specific treatment guidelines for common conditions, such as community-acquired pneumonia, UTI and surgical prophylaxis, taking into account national guidelines and local susceptibilities and formulary options	Simplifies antibiotic prescribing for common conditions Allows for consensus between stewardship team and prescribers
Antibiotic time-outs	Provider-led reassessment of the continuing need for antibiotics after additional clinical information has returned	Improves the appropriateness of antibiotic use Encourages antibiotic de-escalation when appropriate
Pharmacy-based interventions	Prescribing interventions by pharmacy to optimise antibiotic use May be incorporated into electronic health record	Dose optimisation, dose adjustments based on renal function, changing intravenous antibiotics to oral formulation
Rapid diagnostics	Early pathogen identification using technology such as PCR to identify bacterial infection prior to awaiting culture results	Earlier identification of causative organism can lead to antibiotic de-escalation and optimisation of antibiotics
Clinical decision support system	Incorporation of clinical and patient-specific data into electronic health record to provide providers with relevant information prior to prescribing antibiotics	Decreased overall antibiotic use and improved use of antibiotics in patients with sepsis

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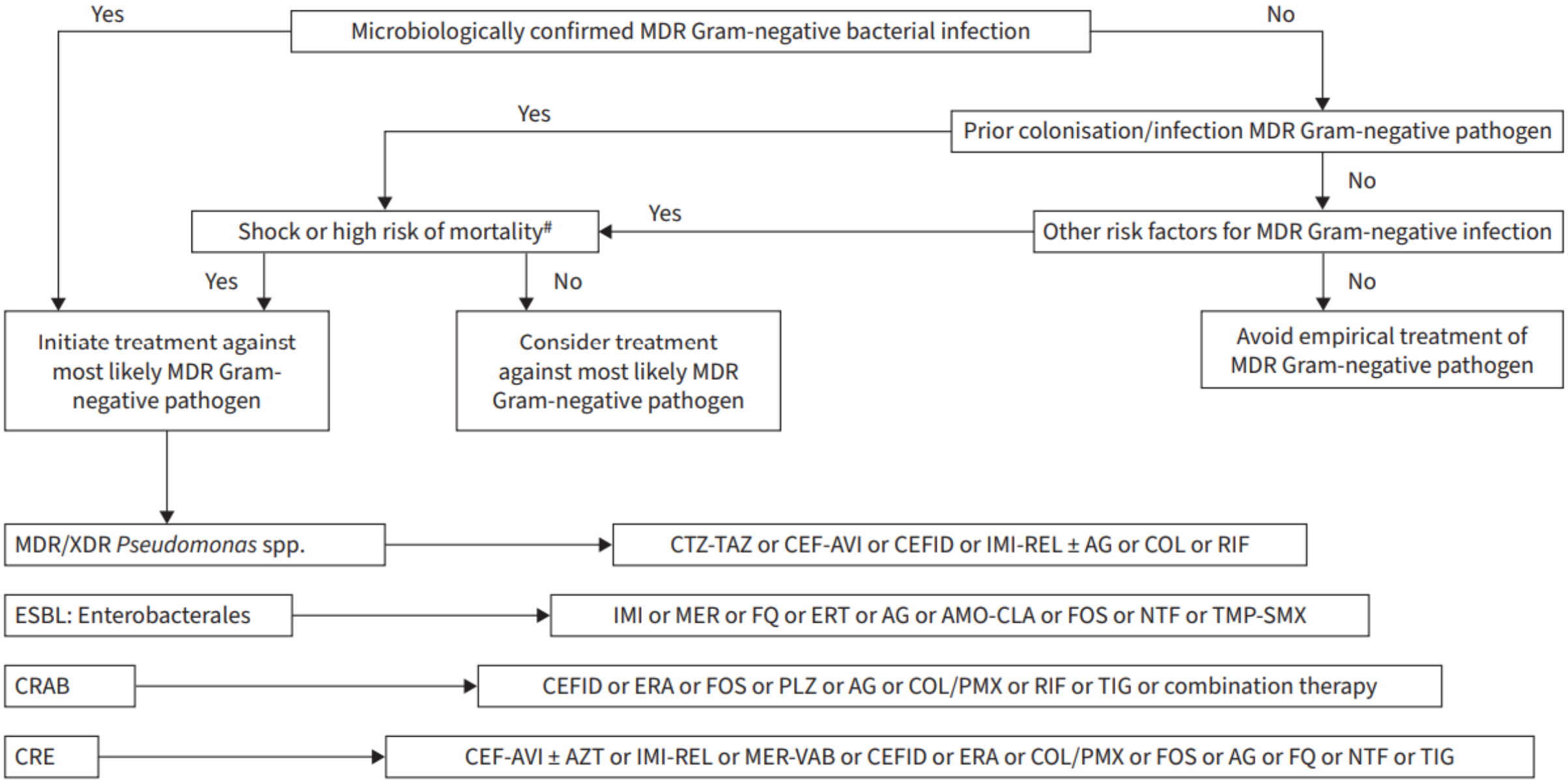
Recommendations from Taiwan IDST 2024

	CRAB		CRE		DTR-PA
	Pneumonia	**BSI**	**BSI**	**Pneumonia**	• Ceftolozane-tazobactam • Ceftazidime-avibactam • Imipenem-relebactam • Cefiderocol • Polymyxin based therapy: Colistin or Polymyxin B
Recommended treatment	• Tigecycline + β-lactams or Imipenem • Cefiderocol +/- Tigecycline or Fosfomycin or Carbapenem • Sulbactam-durlobactam + Imipenem • Sulbactam+Tigecycline • Polymyxins(Colistin or Polymyxin B) + Fosfomycin Any one of the above IV regimens + Adjunctive Colistin inhalation	• Polymyxins(Colistin or Polymyxin B) + Tigecycline or Sulbactam • Cefiderocol +/- Tigecycline or Fosfomycin	• Ceftazidime-avibactam • Meropenem-vaborbactam • Imipenem-relebactam • Polymyxin based combination: Colistin or Polymyxin B + Tigecycline or Amikacin	• Ceftazidime-avibactam • Polymyxin based combinations: Colistin or Polymyxin B • Imipenem-relebactam Any one of the above IV regimens + Adjunctive Colistin inhalation	
			cUTI	**cIAI**	
			• Ceftazidime-avibactam • Meropenem-vaborbactam • Imipenem-relebactam • Aminoglycosides • Colistin	• Ceftazidime-avibactam • Imipenem-relebactam • Tigecycline or Eravacycline • Polymyxin based combination: Colistin or Polymyxin B + Tigecycline • Cefiderocol	

IDST 2024.7 Prefinal Version



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Take home messages

- *Carbapenem-resistant GNBs are* important nosocomial pathogens with high mortality.
- Choice of antibiotics against CR-GNB should consider resistance mechanisms.
- For CRE severe infection, monotherapy with newer antibiotics, such as Ceftazidime-avibactam, Meropenem-vaborbactam, Imipenem-relebactam, or cefiderocol was recommended.
- KPC variant is important in Ceftazidime-avibactam resistance and imipenem-relebactam preserves sensitivity in them.
- Polymyxins might be considered in CRE in local guidance with caution in adverse event and treatment efficacy.
- Aztronam-Avibactam has excellent in vitro activity against MBL pathogens.

Thank you for your attention.