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Review Article

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

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

[a] *Division of Infectious Diseases, Department of Internal Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*
[b] *Division of Infectious Diseases, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan*
[c] *Division of Infectious Diseases, Department of Internal Medicine, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan*
[d] *Division of General Medicine, Infectious Diseases, Department of Internal Medicine, Taipei Veterans General Hospital, Taipei, Taiwan*
[e] *Division of Infectious Diseases and Tropical Medicine, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan*
[f] *Department of Pediatrics, Chi-Mei Medical Center, Tainan, Taiwan*
[g] *Division of Infectious Diseases, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan*
[h] *Department of Pediatrics, MacKay Children's Hospital and MacKay Memorial Hospital, Taipei, Taiwan*
[i] *Division of Infectious Diseases, Department of Internal Medicine, Changhua Christian Hospital, Changhua, Taiwan*

☆ Infectious Diseases Society of Taiwan, Medical Foundation in Memory of Dr. Deh-Lin Cheng, Foundation of Professor Wei-Chuan Hsieh for Infectious Diseases Research and Education, CY Lee's Research Foundation for Pediatric Infectious Diseases and Vaccines, The 6th Guidelines Recommendations for Evidence-based Antimicrobial agents use in Taiwan (GREAT) working group.

* Corresponding author. Kaohsiung Veterans General Hospital, School of Medicine, National Yang Ming Chiao Tung University Division of Infectious Diseases, Department of Internal Medicine 365, Ta-chung 1st Rd, Kaohsiung 813 Taipei Taiwan.Fax: +886 7 346 8296
E-mail address: ssjlee@gmail.com (S.S.-J. Lee).

[1] Co-first authors: Cheng Len Sy, Pao-Yu Chen, Chun-Wen Cheng, Ling-Ju Huang, and Ching-Hsun Wang contributed equally to the manuscript.

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[j] *Division of Pediatric Infectious Diseases, China Medical University Children's Hospital, China Medical University, Taichung, Taiwan*
[k] *Department of Pediatrics, Cathay General Hospital, Taipei, Taiwan*
[l] *Department of Pharmacy, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*
[m] *Department of Pediatrics, Chang Gung Children's Hospital, College of Medicine, Chang Gung University College of Medicine, Taoyuan, Taiwan*
[n] *Department of Medical Education and Research, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*
[o] *Department of Pharmacy, School of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan*
[p] *Department of Pediatrics, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*
[q] *Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[r] *Department of Internal Medicine, Kaohsiung Municipal Siaogang Hospital, Kaohsiung, Taiwan*
[s] *Division of Infectious Diseases, Department of Pediatrics, Taichung Veterans General Hospital, Taichung, Taiwan*
[t] *Division of Infectious Diseases, Department of Internal Medicine, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan*
[u] *Faculty of Medicine, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan*
[v] *Division of Infectious Diseases, Taipei Medical University Shuang Ho Hospital, Taipei, Taiwan*
[w] *Division of Infectious Diseases, Department of Internal Medicine, Taipei Veterans General Hospital, Taipei, Taiwan*
[x] *School of Medicine, National Yang Ming Chiao Tung University, Taiwan*

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Abstract Antimicrobial drug resistance is one of the major threats to global health. It has made common infections increasingly difficult or impossible to treat, and leads to higher medical costs, prolonged hospital stays and increased mortality. Infection rates due to multidrug-resistant organisms (MDRO) are increasing globally. Active agents against MDRO are limited despite an increased in the availability of novel antibiotics in recent years. This guideline aims to assist clinicians in the management of infections due to MDRO. The 2019 Guidelines Recommendations for Evidence-based Antimicrobial agents use in Taiwan (GREAT) working group, comprising of infectious disease specialists from 14 medical centers in Taiwan, reviewed current evidences and drafted recommendations for the treatment of infections due to MDRO. A nationwide expert panel reviewed the recommendations during a consensus meeting in Aug 2020, and the guideline was endorsed by the Infectious Diseases Society of Taiwan (IDST). This guideline includes recommendations for selecting antimicrobial therapy for infections caused by carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant Enterobacterales, and vancomycin-resistant *Enterococcus*. The guideline takes into consideration the local epidemiology, and includes antimicrobial agents that may not yet be available in Taiwan. It is intended to serve as a clinical guide and not to supersede the clinical judgment of physicians in the management of individual patients.

Introduction

Multidrug resistant organism (MDRO) infections cause prolonged hospitalization, excess morbidities and mortalities, and subsequently contribute to huge economic burdens.[1] Multidrug resistance is one of the top threats to global health. The "ESKAPE" pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) were first described in 2008 and remain to be leading causes of MDRO infections throughout the world. While infection rates due to MDRO are continuously increasing, antimicrobial agents which are active against MDRO, especially carbapenem-resistant Gram-negative bacteria (CR-GNB), remain limited. The Infectious Diseases Society of America proposed solutions to the stagnation of antimicrobial discovery in its 2004 policy report, "Bad Bugs, No Drugs: As Antibiotic R&D Stagnates, a Public Health Crisis Brews". In 2017, the World Health Organization (WHO) also urged prioritization of drug discovery and research for MDRO. The WHO listed *A. baumannii*, *P. aeruginosa*, and Enterobacterales as critical priority, and *E. faecium* as high priority in urgency for the need of new antimicrobial agents. This guideline aims to assist clinicians in selecting

antimicrobial therapy for infections caused by carbapenem-resistant pathogens including *A. baumannii* (CRAB), *P. aeruginosa* (CRPA), Enterobacterales (CRE), and vancomycin-resistant *Enterococcus* (VRE). Considering the limited number of active antimicrobial agents, the need for optimization of pharmacokinetics/pharmacodynamics (PK/PD) of antimicrobial agents and complete evaluation of disease extent and host immunity, the panel recommends infectious disease specialist consultation for the management of patients with MDRO infections..

Methodology

Panel composition

The "Guidelines Recommendations for Evidenced-based Antimicrobial use in Taiwan" (GREAT) working group is a special committee founded in 2014 by the Medical Foundation in the Memory of Deh-Lin Cheng and endorsed by the Infectious Diseases Society of Taiwan to develop treatment guidelines for infectious diseases.[2] The foundation adopted the "Grading of Recommendations Assessment, Development, and Evaluation" (GRADE) system in the development of its guidelines since 2014.[3] The GREAT working group has a steering committee and a guideline working committee. The steering committee is comprised of 2 infectious diseases doctors, an epidemiologist, and a GRADE system methodologist. The committee sets the purpose, scope, and target audience of the guideline to be developed. The guideline working committee includes 19 infectious diseases doctors and 3 pharmacists from 16 medical centers and hospitals in Taiwan. The working committee is further divided into 3 subcommittees, a CRAB and CRPA group, a CRE group, and a VRE group.

Process of guideline development

All members of the GREAT working group attended 5 in-person meetings with representatives of the expert review panel of the IDST from July 2019 to January 2020 to review the draft document addressing specific recommendations. Due to the COVID-19 pandemic, the joint consensus meeting of the GREAT working group with the nationwide expert review panel was deferred until August 22, 2020, where each recommendation was discussed based on an extensive review of the literature and clinical experience. The final version of the recommendations was approved and endorsed by the IDST on March 3, 2021. The scope of the literature review included high-quality studies including randomized controlled trials, observational studies and epidemiological reports. Studies on the treatment of MDROs including CRPA, CRAB, CRE and VRE were included in the review. Prevention and infection control for the spread of these pathogens are beyond the scope of this guideline.

Rating of the evidence and recommendation

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system[3] was used as a guide to assess the quality of the evidence and the strength of the recommendation. The system classifies quality of evidence as high (A), moderate (B), low (C), or very low (D) according to factors that include risk of bias, consistency of the results, directness of the evidence, precision, and publication bias. GRADE recommendations were classified as strong (1) or weak (2) after assessment of the balance between benefit and harm, cost and resources, values and preferences, and feasibility and acceptability of the intervention. A strong recommendation indicates that the desirable effects of a recommendation outweigh its possible undesirable effects and that majority would agree with the recommended actions. It implies that all or most individuals will be best served by the recommended course of action. A weak recommendation indicates that the undesirable effects of a recommendation may outweigh its desirable effects and not all individuals will be best served by the recommended course of action.[4] The strength of a recommendation however may not be directly correlated to its priority. A weak recommendation means that more consideration of the individual patient's circumstances, preferences, and values are needed when the recommended course of action is considered.

Literature search

We did a systematic literature search for relevant articles from January 1, 2000 to December 31, 2019 in PubMed and EMBASE and Cochrane Collaboration with the following terms: *A. baumannii,* pneumonia, bloodstream infections, antimicrobial treatment, *P. aeruginosa*, antibiotic resistance or carbapenem resistance, colistin/polymyxin, ceftazidime-avibactam, and ceftolozane-tazobactam, imipenem-cilastatin-relebactam, meropenem-vaborbactam, vancomycin resistant enterococc*, VRE, and bacteremia, bacteraemia, outcome, response and mortality. There was no language restriction in our search. Included studies were clinical trials or observational studies of the treatment of patients with VRE bacteremia, CRPA infections, *A. baumannii* pneumonia and bloodstream infections and CRE infections.

For CRAB infections, studies involving mixed infection sites, mixed GNB, single-arm studies, and pediatric subjects were excluded. The primary outcomes were clinical cure and microbiological cure, and the secondary outcome was all-cause mortality. Aminoglycosides have been used for combination in multiple drug-resistant pathogens, but monotherapy is hampered by PK/PD obstacles in the lungs, abscesses, and central nervous system. Our analysis excluded antimicrobial regimens including aminoglycoside monotherapy, rifampin, and vancomycin. Treatment recommendations for all MDRO infections assume that *in vitro* activity of preferred and alternative antibiotics has been demonstrated. (Tables 1—4) Pediatric dosing recommendations are shown in Table 5.

Definition

Carbapenem-resistant *A. baumannii* (CRAB) was defined as *A. baumannii* that was non-susceptible to any carbapenem. This

Table 1 Recommended treatment options for infections due to carbapenem-resistant *Acinetobacter baumannii*.

Clinical syndrome	Recommended Treatment	Alternative Treatment	Duration
Pneumonia	Colistin[a] 5 mg CBA/kg IV loading dose, then 2.5 mg CBA × (1.5 × CrCl + 30) IV q12 h +/-Imipenem/cilastatin[b] 500 mg IV q6h (2D) or Meropenem[b] 2 g IV q8h (2D) + Adjunctive colistin inhalation[a] 1.25–15 MIU/day IH in 2–3 divided doses (2D)	Sulbactam 6–9 g/day IV in 3 or 4 divided doses (2D)[c] Colistin[a] 5 mg CBA/kg IV loading dose, then 2.5 mg CBA × (1.5 × CrCl + 30) IV q12 h + Tigecycline[d,e] 100 mg IV loading dose, then 50 mg IV q12 h + Sulbactam 6–9 g/day IV in 3 or 4 divided doses (2D)[c]	at least 7 days
Bloodstream infections	Colistin[a] 5 mg CBA/kg IV loading dose, then 2.5 mg CBA × (1.5 × CrCl + 30) IV q12 h +/-Imipenem/cilastatin[b] 500 mg IV q6h (2D) or Meropenem[b] 2 g IV q8h (2D)	Colistin[a] 5 mg CBA/kg IV loading dose, then 2.5 mg CBA × (1.5 × CrCl + 30) IV q12 h + Tigecycline[d] 100 mg IV loading dose, then 50 mg IV q12 h (2D)[c] or Sulbactam 6–9 g/day IV in 3–4 divided doses (2D)[c]	10–14 days

[a] One MIU colistin methanesulfonate = 33 mg colistin base activity. For dosage of inhaled colistin please refer to "Recommendations and guidelines for the treatment of pneumonia in Taiwan". J Microbiol Immunol Infect 2019; 52: 172-99.
[b] Carbapenem: has *in vitro* synergistic benefit if carbapenem MIC ≤32 mg/L. Infusion time suggested to be > 3 h for each dose.
[c] No significant statistical difference on clinical outcomes between the alternative regimens.
[d] Tigecycline combination can be considered if tigecycline MIC ≤2 mg/L.
[e] Tigecycline monotherapy is not recommended for the treatment of pneumonia.
Abbreviations: CBA:colistin base activity, CrCl: creatinine clearance, g: grams, IV: intravenous, IH: inhalation, kg: kilograms, mg: milligrams, MIU: million international units, q6h: every 6 h, q8h: every 8 h, q12 h: every 12 h.
Grade of Recommendations: 1: strong recommendations; 2: weak recommendations.
Level of Evidence: A/High, B/Moderate, C/Low, D/Very low.

Table 2 Recommended treatment options for infections due to carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) and difficult-to-treat *P.aeruginosa* (DTR-PA).

Clinical Syndrome	Recommended treatment	Duration
Any clinical syndrome due to CRPA susceptible to other antimicrobial agents	Piperacillin[a] 3–4 g IV q6h (2D) Piperacillin/tazobactam[a] 3.375–4.5 g IV q6h (2D) Ceftazidime[a] 2 g IV q8h (2D) Cefepime[a] 2 g IV q8-12 h (2D) Cefpirome[a] 2 g IV q12 h (2D) Ciprofloxacin 400 mg IV q8h (2D) Levofloxacin 750 mg IV qd (2D) Amikacin[b] 15 mg/kg IV qd (2D)	5–14 days[c]
Any clinical syndrome due to DTR-PA	Colistin[d] monotherapy or combination therapy (2C) Ceftolozane/tazobactam[e,f] 1.5–3 g IV q8h (2C) Ceftazidime/avibactam[e] 2.5 g IV q8h (2C) Imipenem/cilastatin/relebactam[e,g]1.25 g IV q6h (2C)	5–14 days[c]

[a] Anti-pseudomonal penicillins or cephalosporins combined with aminoglycosides may be considered when the antimicrobial susceptibility testing results are interpreted as susceptible.
[b] Aminoglycoside monotherapy is only indicated for urinary tract infections.
[c] The suggested treatment duration is 5–10 days for complicated urinary tract infection and complicated intra-abdominal infection. A treatment course of 10–14 days is suggested for hospital-acquired or ventilator-associated pneumonia and bloodstream infection. Definitive treatment durations should be individualized according to infection sites, source control, the underlying comorbidities and the initial response to therapy.
[d] Colistin dose: 5 mg CBA/kg IV loading dose, then 2.5 mg CBA × (1.5 × CrCl + 30) IV q12 h. One MIU colistin methanesulfonate = 33 mg colistin base activity.
[e] β-Lactam/β-lactamase inhibitors may be considered when the antimicrobial susceptibility testing results are interpreted as susceptible.
[f] Ceftolozane/tazobactam 3 g (2 g ceftolozane/1 g tazobactam), infused intravenously for 1 h every 8 h, is indicated for hospital-acquired pneumonia or ventilator-associated pneumonia.
[g] Imipenem/cilastatin/relebactam has not been approved by the Taiwan Food and Drug Administration (Jan 2022).
Abbreviations: CBA:colistin base activity, CrCl: creatinine clearance, g: grams, IV: intravenous, kg: kilograms, mg: milligrams, MIU: million international units, q6h: every 6 h, q8h: every 8 h, q12 h: every 12 h, qd: every 24 h.
Recommendations: 1: strong recommendations; 2: weak recommendations.
Level of Evidence: A/High, B/Moderate, C/Low, D/Very low.

Table 3 Recommended treatment options for carbapenem-resistant Enterobacterales (CRE).

Clinical Syndrome	Recommended Treatment	Duration
Bloodstream infections	Ceftazidime/avibactam 2.5 g IV q8h (2D) Meropenem/vaborbactam[a] 4 g IV q8h (2C) Imipenem/cilastatin/relebactam[a] 1.25 g IV q6h (2C) Polymyxin based combinations[b]: Colistin[c] 5 mg CBA/kg IV loading dose, then 2.5 mg CBA × (1.5 × CrCl + 30) IV q12 h + Tigecycline 100 mg IV loading dose, then 50 mg IV q12 h (2D) or Meropenem[b] 1 g IV q8h by extended infusion (2D)	7–14 days[d]
Complicated urinary tract infections	Ceftazidime/avibactam 2.5 g IV q8h (2D) Meropenem/vaborbactam[a] 4 g IV q8h (2C) Imipenem/cilastatin/relebactam[a] 1.25 g IV q6h (2C) Aminoglycosides: Gentamicin 5–7 mg/kg/day IV QD (2D) or Amikacin dose 15 mg/kg/day IV QD (2D) or Plazomicin[a] 15 mg/kg IV q12hr (2D)	5–7 days[d]
Complicated intra-abdominal infections	Ceftazidime/avibactam 2.5 g q8h + metronidazole 500 mg q6h (2D) Imipenem/cilastatin/relebactam[a] 1.25 g IV q6h (2C) Tigecycline 100 mg IV loading dose, then 50 mg IV q12 h (2D)[e] Eravacycline[a] 1 mg/kg IV q12hr (2D) Polymyxin based combinations[b] Colistin[c] 5 mg CBA/kg IV loading dose, then 2.5 mg CBA × (1.5 × CrCl + 30) IV q12 h + Tigecycline 100 mg IV loading dose, then 50 mg IV q12 h (2D) or Meropenem[b] 1 g IV q8h by extended infusion (2D)	5–7 days[d]

[a] Imipenem/cilastatin/relebactam, meropenem/vaborbactam, plazomicin and eravacycline have not been approved by the Taiwan Food and Drug Administration (Jan 2022).
[b] Choice of combination antimicrobial therapy based on susceptibility test is recommended. Extended-infusion of meropenem for 3 h is suggested if meropenem MIC is ≤ 8 mg/L.
[c] One MIU colistin methanesulfonate = 33 mg colistin base activity.
[d] Definite treatment duration should be individualized according to infection sites, source control, the underlying comorbidities and the initial response to therapy.
[e] Combinations of tigecycline with polymyxin or meropenem is suggested in clinically unstable patients.
Abbreviations: CBA: colistin base activity, CrCl: creatinine clearance, g: grams, IV: intravenous, kg: kilograms, L:liters, mg: milligrams, MIU: million international units, q6h: every 6 h, q8h: every 8 h, q12 h: every 12 h, qd: every 24 h.
Recommendations: 1: strong recommendations; 2: weak recommendations.
Level of Evidence: A/High, B/Moderate, C/Low, D/Very low.

Table 4 Recommended treatment options for Vancomycin-resistant *Enterococci* (VRE).

Clinical syndrome	Recommended treatment	Duration
Pneumonia	Linezolid 600 mg IV q12 h (1C)	At least 7 days
Bloodstream infections[a]	Linezolid 600 mg IV q12 h (1C) Daptomycin 8–12 mg/kg IV qd ± IV beta-lactams[b] (2C)	10–14 days[c]
Complicated intra-abdominal infections	Linezolid 600 mg IV q12 h (1C) Tigecycline[c] 50 mg IV q12 h after loading dose IV 100 mg (2D)	5–7 days[c]
Complicated urinary tract infections	Linezolid 600 mg IV q12 h (1C) Daptomycin 6–12 mg/kg IV qd (2D)	5–7 days[c]
Uncomplicated urinary tract infections	Fosfomycin 3 g PO x 1 dose or 3 g PO qod (2D) Nitrofurantoin 100 mg PO qid (2D) Ampicillin 18–30 g/day IV in divided doses (2D) Amoxicillin 500 mg PO/IV q8h (2D)	3–7 days

[a] Cardiac surgery combined with antimicrobial therapy should be considered for the treatment of infective endocarditis.
[b] Combination with beta-lactams may be considered in VRE bloodstream infections with high daptomycin MIC (3–4 μg/mL). Beta-lactams include penicillins, carbapenems and cephalosporins other than cefotaxime and cefazolin.
[c] Definite treatment duration should be individualized according to infection sites, source control, the underlying comorbidities and the initial response to therapy. Currently available studies are inconclusive to make a recommendation on the optimal treatment duration. Individualized consideration and infectious diseases specialist consultation is suggested.
Abbreviations: g: gram, IV: intravenous, kg: kilograms, mg: milligrams, PO: per orem, q8h: every 8 h, q12 h: every 12 h, qd: every 24 h, qid: four times daily, qod: every other day.
Recommendations: 1: strong recommendations; 2: weak recommendations.
Level of Evidence: A/High, B/Moderate, C/Low, D/Very low.

Table 5 Recommended antimicrobial dosage for treatment of multidrug resistant infections (MDRO) in pediatrics.

Antimicrobial Agents	Dose and Frequency				Maximum Dose
	Neonates		Infants, Children, and Adolescents		
Amikacin	Gestational age <30 weeks:		Conventional dosing	5–7.5 mg/kg/dose IV q8h	
	Postnatal age ≤14 days	15 mg/kg/dose IV q48 h	Once daily dosing	15–22.5 mg/kg/dose IV q24 h	
	Postnatal age >14 days	15 mg/kg/dose IV q24 h			
	Gestational age 30–34 weeks:				
	Postnatal age ≤14 days	15 mg/kg/dose IV q36 h			
	Postnatal age >14 days	15 mg/kg/dose IV q24 h			
	Gestational age ≥35 weeks:				
	Postnatal age ≤7 days	15 mg/kg/dose IV q24 h			
	Postnatal age >7 days	18 mg/kg/dose IV q24 h			
Amoxicillin		15 mg/kg/dose PO q12 h		40–90 mg/kg/day PO in 2–3 divided doses	4000 mg/day
Ampicillin	Gestational age ≤34 weeks:			150–400 mg/kg/day IV in 4 divided doses	12,000 mg/day
	Postnatal age ≤7 days	50 mg/kg/dose IV q12 h			
	Postnatal age >7 days	75 mg/kg/dose IV q12 h			
	Gestational age >34 weeks:	50 mg/kg/dose IV q8h			
Cefepime	Gestational age <36 weeks:	30 mg/kg/dose IV q12 h		50 mg/kg/dose IV q8h for *Pseudomonas* infections	2000 mg/dose
	Gestational age ≥36 weeks:	50 mg/kg/dose IV 12 h			
Ceftazidime	Gestational age <32 weeks:			200–300 mg/kg/day IV in 3 divided doses for serious *Pseudomonas* infections	12,000 mg/day for serious *Pseudomonas* infections
	Postnatal age <14 days	50 mg/kg/dose IV q12 h			
	Postnatal age ≥14 days	50 mg/kg/dose IV q8h			
	Gestational age ≥32 weeks:				
	Postnatal age ≤7 days	50 mg/kg/dose IV q12 h			
	Postnatal age >7 days	50 mg/kg/dose IV q8h			
Ceftazidime/ avibactam[a]		No recommendations available	≥3 to <6 months	Ceftazidime dose: 40 mg/kg/dose IV q8h	2000 mg ceftazidime/ dose
			≥6 months and children	50 mg/kg/dose IV q8h	
Ciprofloxacin[b]		No recommendations available		10–20 mg/kg/dose PO q12 h	750 mg/dose PO
				10 mg/kg/dose IV q8h or q12 h	400mg/dose IV
Colistin (IH)		4 mg CBA/kg/dose IH q12 h		30–150 mg CBA/dose IH q12 h	150 mg CBA/dose
Colistin (IV)		2.5–5 mg CBA/kg/day IV in 2 or 4 divided doses		2.5–5 mg CBA/kg/day IV in 2 or 4 divided doses	100 mg CBA/dose
Daptomycin[c]		No recommendations available	1–6 years	12 mg/kg/dose IV q24 h	
			7 to ≤ 11 years	9 mg/kg/dose IV q24 h	
			12 to < 18years	7 mg/kg/dose IV q24 h	
Fosfomycin[d,e]		No recommendations available	<12 years[e]	2000 mg/dose PO as a single dose	2000–3000 mg/dose
			≥12 years	3000 mg/dose as a single dose	
Gentamicin	Gestational age <30 weeks:		Conventional dosing	2–2.5 mg/kg/dose IV q8h	
	Postnatal age ≤14 days	5 mg/kg/dose IV q48 h	Once daily dosing	5–7.5 mg/kg/dose IV q24 h	

	Postnatal age >14 days	5 mg/kg/dose IV q36 h			
	Gestational age 30–34 weeks:				
	Postnatal age ≤14 days	5 mg/kg/dose IV q36 h			
	Postnatal age >14 days	5 mg/kg/dose IV q24 h			
	Gestational age ≥35 weeks:				
	Postnatal age ≤7 days	4 mg/kg/dose IV q24 h			
	Postnatal age >7 days	5 mg/kg/dose IV q24 h			
Imipenem	Postnatal age ≤7 days	25 mg/kg/dose IV q12 h		15–25 mg/kg/dose IV q6h	4000 mg/day
	Postnatal age >7 days	25 mg/kg/dose IV q8h			
Linezolid	Gestational age <34 weeks:		<12 years	10 mg/kg/dose IV/PO q8h	600 mg/dose
	Postnatal age ≤7 days	10 mg/kg/dose IV/PO q12 h	≥12 years	600 mg/dose IV/PO q12 h	
	Postnatal age >7 days	10 mg/kg/dose IV/PO q8h			
	Gestational age ≥34 weeks:	10 mg/kg/dose IV/PO q8h			
Meropenem	Gestational age <32 weeks:			20–40 mg/kg/dose IV q8h	2000 mg/dose
	Postnatal age <14 days	20 mg/kg/dose IV q12 h			
	Postnatal age ≥14 day	20 mg/kg/dose IV q8h			
	Gestational age ≥32 weeks:				
	Postnatal age <14 days	20 mg/kg/dose IV q8h			
	Postnatal age ≥14 days	30 mg/kg/dose IV q8h			
Nitrofurantoin[d,f]		No recommendations available		5–7 mg/kg/day PO in 4 divided doses	100 mg/dose
Piperacillin		100–300 mg/kg/day IV in 3–4 divided doses		100–300 mg/kg/day IV in 3–4 divided doses	24,000 mg/day
Piperacillin/ tazobactam	Postmenstrual age ≤30 weeks:	Piperacillin dose: 100 mg/kg/dose IV q8h		Piperacillin dose: 240–300 mg/kg/day IV in 3–4 divided doses	16,000 mg/day
	Postmenstrual age >30 weeks:	Piperacillin dose: 80 mg/kg/dose IV q6h			
Sulbactam		50 mg/kg/day IV divided in 2–4 doses		50 mg/kg/day IV in 2–4 divided doses	4000 mg/day or 80 mg/kg/day
Tigecycline[b,g]		No recommendations available	8–11 years	1.2–2 mg/kg/dose IV q12 h	50 mg/dose
			≥12 years	50 mg/dose IV q12 h	

[a] Not approved for use in children ≤18 years by the Taiwan FDA.
[b] Pediatric infectious diseases specialists consultation is suggested prior to the use of ciprofloxacin in children.
[c] Daptomycin is not recommended for use in infants <1 year of age.
[d] Currently recommended for treatment of uncomplicated urinary tract infections. Oral formulation should not be used for pyelonephritis or perinephric abscess.
[e] Not approved for use in children <12 years by the Taiwan FDA.
[f] Recommended duration of treatment is 7 days or at least 3 days after obtaining a sterile urine.
[g] Use of tigecycline is not recommended in patients <18 years of age unless no alternative antimicrobial agents are available.

Abbreviations: CBA: colistin base activity, IH: inhalation, IV: intravenous, kg: kilograms, mg: milligrams, PO: per orem, q6h: every 6 h, q8h: every 8 h, q12 h: every 12 h, q24 h: every 24 h, q36 h: every 36 h, q48 h: every 48 h.

included extensively drug-resistant *A. baumannii* (XDR-AB) and pan-drug-resistant *A. baumannii* (PDR-AB). Extensive-drug resistance (XDR) refers to non-susceptibility to carbapenem and at least one agent in all but $\leq$2 antimicrobial categories.[5] Pan-drug resistance was defined as non-susceptibility to all agents in all antimicrobial categories. Carbapenem-resistant *P. aeruginosa* (CRPA) are *P. aeruginosa* that are non-susceptible to any carbapenem. Difficult-to-treat resistance *P. aeruginosa* (DTR-PA) was defined as *P. aeruginosa* with non-susceptibility to all the following agents: piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin, and levofloxacin.[6] Carbapenem-resistant Enterobacterales (CRE) was defined as Enterobacterales that was resistant to doripenem, imipenem, or meropenem. This included carbapenemase-producing and non-producing Enterobacterales. Vancomycin-resistant enterococci (VRE) was defined as ampicillin and vancomycin-resistant enterococci with high-level resistance to aminoglycosides.

General management recommendations

1. Infectious disease consultation is highly recommended in the management of infections caused by MDRO *(Strong recommendation, low quality of evidence) (1C)*.
2. Prolonged infusion of β-lactams for pathogens with high minimum inhibitory concentration (MIC) is recommended *(Strong recommendation, low quality of evidence) (1C)*.
3. Treatment of pneumonia due to MDRO are discussed in "Recommendations and guidelines for the treatment of pneumonia in Taiwan"[2]
4. Antimicrobial susceptibility testing or genotypic characterization of resistance serves as a guide for clinicians in the selection of antimicrobial agents for the treatment of MDRO infections

Summary of Recommendations

Carbapenem-resistant *A. baumannii*

What is the recommended treatment for CRAB pneumonia?

Recommendations

1. We recommend colistin, with or without carbapenems, and adjunctive inhaled colistin therapy for CRAB pneumonia (*Weak recommendation, low quality of evidence*) *(2C)*.
2. We do not recommend tigecycline monotherapy for the treatment of CRAB pneumonia (*Strong recommendation, low quality of evidence*) *(1C)*.

What is the recommended treatment for CRAB bloodstream infection (BSI)?

Recommendation

1. We recommend colistin-carbapenem based combination therapy for the treatment of CRAB BSI (*Weak recommendation, low quality of evidence*) *(2C)*.

Carbapenem-resistant *P. aeruginosa*

What is the recommended treatment for carbapenem-resistant *P. aeruginosa* infections susceptible to other antimicrobial agents?

Recommendation

1. Anti-pseudomonal penicillins or cephalosporins or fluoroquinolones, with or without aminoglycoside, is recommended for treatment of infections due to CRPA susceptible to other antimicrobial agents *(Weak recommendation, very low-quality of evidence) (2D)*.

What is the recommended treatment for difficult-to-treat resistance *P. aeruginosa* infections (DTR-PA)?

Recommendations

1. Colistin based treatment is recommended in DTR-PA infections *(Weak recommendation, low-quality of evidence) (2C)*.
2. A loading dose of 9 MU (5 mg/kg) of colistin followed by a maintenance dose 4.5 MU [2.5 mg $\times$ (1.5 $\times$ CrCl+30)] twice daily is suggested in critically-ill patients *(Strong recommendation, low-quality of evidence) (1C)*.
3. Renal function should be monitored during colistin treatment *(Strong recommendation, low-quality of evidence) (1C)*.
4. The use of colistin-based combination therapy is controversial *(Weak recommendation, very low quality of evidence) (2D)*.

What is the role of new β-lactam/β-lactamase inhibitors in treating DTR- *P. aeruginosa* infections?

Recommendations

1. New β-lactam/β-lactamase inhibitors, including ceftazidime-avibactam, ceftolozane-tazobactam and imipenem-cilastatin-relebactam may be considered in the treatment of DTR-PA infections *(Weak recommendation, low quality of evidence) (2C)*.
2. Antimicrobial susceptibility testing of new β-lactam/β-lactamase inhibitors is recommended to guide treatment of CRPA infections (*Weak recommendation, very low quality of evidence) (2D)*.

Carbapenem-resistant Enterobacterales

What is the recommended treatment for BSI caused by CRE?

Recommendations

1. Polymyxin based combination therapy is recommended for BSI due to CRE *(Weak recommendation, very low quality of evidence) (2D)*.
2. Combination antimicrobial therapy should be based on the result of susceptibility testing *(Weak recommendation, very low quality of evidence) (2D)*.
3. Ceftazidime-avibactam 2.5 g IV q8h infused over 3 h is recommended for the treatment of CRE-BSI *(Weak*

recommendation, very low quality of evidence) (2D).
4. Meropenem-vaborbactam 4 g IV q8h infused over 3 h or imipenem-cilastatin-relebactam 1.25 g IV q6h is recommended in the treatment of CRE-BSI *(Weak recommendation, low quality of evidence) (2C).*

What is the recommended treatment for complicated urinary tract infection (cUTI) caused by CRE?

Recommendations

1. Ceftazidime-avibactam 2.5 g IV q8h is recommended for cUTI caused by CRE *(Weak recommendation, very low quality of evidence) (2D).*
2. Meropenem-vaborbactam 4 g IV q8h or imipenem-cilastatin-relebactam 1.25 g IV q6h is recommended for cUTI caused by CRE *(Weak recommendation, low quality of evidence) (2C).*
3. Plazomicin 15 mg/kg IV q12 h is recommended for cUTI due to CRE *(Weak recommendation, very low quality of evidence) (2D).*
4. Single-dose aminoglycoside is recommended for patients with simple cystitis due to CRE *(Weak recommendation, very low quality of evidence) (2D).*
5. Single-dose aminoglycoside is recommended as an alternative regimen for patients with cUTI due to CRE *(Weak recommendation, very low quality of evidence) (2D).*

What is the recommended treatment for complicated intraabdominal infections (cIAI) caused by CRE?

Recommendations

1. Ceftazidime-avibactam 2.5 g IV q8h in combination with metronidazole is recommended for cIAI caused by CRE *(Weak recommendation, very low quality of evidence) (2D).*
2. Tigecycline 100 mg IV loading dose then 50 mg IV q12 h or eravacycline 1 mg/kg infused over 60 min IV q12 h is recommended for cIAI caused by CRE *(Weak recommendation, very low quality of evidence) (2D).*
3. Polymyxin based combination therapy is recommended for cIAI caused by CRE *(Weak recommendation, very low quality of evidence) (2D).* The selection of combination antimicrobial agent should be based on susceptibility testing results *(Weak recommendation, very low quality of evidence) (2D).*

Vancomycin-resistant *Enterococcus*

What is the recommended treatment for vancomycin resistant enterococcal infections?

Recommendations

1. Linezolid 600 mg IV or PO every 12 h is recommended for enterococcal infection. The treatment duration is dependent on the site of infection and clinical response *(Strong recommendation, low quality of evidence) (1C).*
2. High dose daptomycin 8—12 mg/kg IV daily or in combination with β-lactams including penicillins, or cephalosporins, or carbapenems is recommended for VRE bacteremia *(Weak recommendation, low quality of evidence) (2C).*
3. Tigecycline 100 mg IV loading dose then 50 mg IV q12 h is recommended for intraabdominal infections due to VRE. The duration of treatment is based on the clinical response (*Weak recommendation, very low quality of evidence) (2D).*
4. A single dose of fosfomycin 3 g PO is recommended for uncomplicated urinary tract infections due to VRE (*Weak recommendation, very low quality of evidence) (2D).*
5. Nitrofurantoin 100 mg PO every 6 h is recommended for the treatment of uncomplicated urinary tract infections due to VRE *(Weak recommendation, very low quality of evidence) (2D).*
6. High dose ampicillin (18—30 g IV daily in divided doses) or amoxicillin 500 mg IV or PO every 8 h daily is recommended for uncomplicated urinary tract infections due to VRE *(Weak recommendation, very low quality of evidence) (2D).*

Carbapenem-resistant *A. baumannii*

Carbapenem-resistant *A. baumannii* (CRAB) is one of the most common pathogens associated with healthcare-acquired infections in intensive care units in Taiwan since 2009. The Taiwan Healthcare associated infections and Antimicrobial resistance Surveillance (THAS), previously known as Taiwan Nosocomial Infections Surveillance System (TNIS), reported that the rate of carbapenem resistance of *A. baumannii* increased from 59.7% in 2009 to 75.3% in 2020.[7,8] The United States Centers for Disease Control and Prevention's (U.S. CDC) National Healthcare Safety Network reported non-susceptibility rates of *A. baumannii* to carbapenem between 12 and 47.2%.[9] As *A. baumannii* can form biofilms and colonize innate surfaces, isolation of this pathogen may represent either invasive infection or mere colonization. Pneumonia and bloodstream infection are the two most common manifestations of *A. baumannii* infections. Clinical manifestations of *A. baumannii* bloodstream infections range from transient bacteremia to severe septic shock. *A. baumannii* causes 63% of bloodstream infections among *Acinetobacter* spp.[10] Resistance of *A. baumannii* to carbapenems may arise through various mechanisms such as efflux pumps, porin expression, antibiotic target mutations, and drug-inactivating enzymes. None of the novel β-lactam/β-lactamase inhibitor combinations recommended for the treatment of CRE are clinically active against CRAB.[11,12] Mortality rates of up to 86.1% have been reported in CRAB-infected patients who received inappropriate empirical antimicrobial therapy.[13] Carbapenem remains the preferred drug during empirical therapy for these infections even with the emergence of resistance.

What is the recommended treatment for CRAB pneumonia?

Recommendations

1. We recommend colistin, with or without carbapenems, and adjunctive inhaled colistin therapy for CRAB

pneumonia (*Weak recommendation, low quality of evidence*) *(2C)*.
2. We do not recommend tigecycline monotherapy for the treatment of CRAB pneumonia (*Strong recommendation, low quality of evidence*) *(1C)*.

Summary of the evidence

We performed a network meta-analysis which included 12 studies[14–25] evaluating 8 antimicrobial treatments, tigecycline, triple therapy with colistin, sulbactam and tigecycline, colistin and tigecycline, colistin, colistin and sulbactam, sulbactam, sulbactam and tigecycline, and colistin and carbapenem (Fig. 1 and Fig. 2). Ampicillin-sulbactam and cefoperazone-sulbactam were categorized as sulbactam. A random-effects pairwise and network meta-analysis was done to obtain estimates for primary and secondary outcomes of CRAB infections and these estimates are presented as odds ratios with 95% confidence intervals (CI). The inconsistency between direct and indirect evidence within the network was evaluated by testing the design-by-treatment interaction. We ranked the antimicrobial treatments with surface under the cumulative ranking (SUCRA) probabilities. A larger SUCRA value indicated a more effective antimicrobial treatment. All statistical analyses were conducted using Stata 15.1 mvmeta, network, and network graph commands. Pairwise meta-analysis of monotherapy and combination therapy showed that tigecycline monotherapy had a lower clinical cure rate than combination therapy for the treatment of pneumonia. A randomized study of extensively drug resistant *A. baumannii* (XDR-AB) ventilator-associated pneumonia demonstrated that combination of tigecycline and cefoperazone-sulbactam showed an *in vitro* synergistic activity and had a higher clinical response rate than tigecycline monotherapy.[16] Tigecycline monotherapy had a higher rate of treatment failure compared to colistin monotherapy, colistin combination therapy, and sulbactam-based therapy.[22] A matched cohort study comparing colistin versus tigecycline also favors colistin-based therapy for multi-drug-resistant (MDR) *A. baumannii* pneumonia.[26] The excess mortality may be related to a higher MIC of tigecycline (>2 μg/mL). Therefore, we do not recommend tigecycline monotherapy for the treatment of CRAB pneumonia (Table 1).

Several studies have demonstrated an increased mortality for polymyxins compared with alternative agent even when the MIC for colistin is in the "susceptible" category.[27,28] The Clinical and Laboratory Standards Institute has eliminated this interpretative category for colistin while the European Committee on Antimicrobial Susceptibility Testing (EUCAST) has maintained the "susceptible" category. Colistin-based combination therapy, such as polymyxin-carbapenem, showed *in vitro* synergism against clinical isolates of *A. baumannii*.[29,30] An *in vitro* study observed synergistic killing of colistin-meropenem in CRAB even when the MIC of meropenem is $\geq$ 32 mg/L, when the MIC of colistin $\leq$1 mg/L.[31] However, a murine model demonstrated lack of synergistic effects of colistin-meropenem combination against CRAB strains having higher meropenem MICs ($\geq$64 μg/mL).[32] The use of polymyxin–carbapenem combination therapy is common in clinical practice. This raises a concern since a study from Taiwan showed that both the meropenem MIC_{50} and MIC_{90} of CRAB isolates from nosocomial bloodstream infection were $>$32 μg/mL.[33] Our direct comparison meta-analysis shows that there was no significant differences in clinical cure, microbiological cure, and mortality between colistin monotherapy and other combination therapy (Fig. 1). Colistin plus meropenem combination therapy was not superior to colistin monotherapy in a randomized controlled trial for severe carbapenem-resistant Gram-negative bacteria infections, in which 77% were due to *A. baumannii*. However, colistin-carbapenem combinations ranked first in improving clinical cure (SUCRA, 91.7%) and second in microbiological cure (SUCRA, 68.7%) in our network meta-analysis of various treatment regimens (Fig. 2).

Although colistin-sulbactam or colistin-tigecycline showed *in vitro* synergy, there is no strong evidence that combination therapy is superior to monotherapy for the treatment of CRAB pneumonia. One network meta-analysis suggest that there is no significant difference in clinical cure among currently available treatment options. However, colistin-based combination therapy, especially with sulbactam, demonstrates a microbiological benefit in treating MDR and XDR-AB infected patients.[34] Our network meta-analysis shows that the colistin-carbapenem combination was superior to other treatment regimens in providing clinical cure for pneumonia. Colistin-carbapenem, sulbactam and colistin-sulbactam-tigecycline triple therapy were superior to the other regimens when using a composite outcome of clinical cure, microbiological cure, and mortality (Fig. 2 and online supplement Fig. S1).

Inhaled colistin has been used as a monotherapy or as an adjuvant to intravenous antimicrobial agents in the treatment of CRAB pneumonia and airway eradication of Gram-negative bacteria.[24,35] Aerosolized colistin monotherapy was not inferior to aerosolized colistin-tigecycline in attaining a favorable clinical outcome and decreasing mortality in XDR-AB pneumonia.[24] Observational studies suggested that the combination of aerosolized colistin plus intravenous colistin was associated with a higher clinical response than intravenous colistin alone, but most studies did not observe significant differences in mortality.[11,36–38]

Minocycline has *in vitro* activity against CRAB, with reported susceptibility rates of 60–80%, and there is accumulating literature reporting successful use of intravenous minocycline for treatment of serious CRAB/XDR-AB infections, but most were small case series. Therefore, minocycline was not included in our meta-analysis, but remains a potential option for treatment.[39]

High dose sulbactam of 6–9 g of sulbactam per day was recommended as an alternative choice for treatment of CRAB infections based on 2 randomized controlled trials.[14,16] In these studies, sulbactam was prescribed in fixed-dose combinations of cefoperazone 1.5 g/sulbactam 1.5 g every 6 h and ampicillin 18 g/sulbactam 9 g per day.

We suggest clinicians to consider all clinically relevant factors, including local antimicrobial susceptibility and MIC, patients' renal and hepatic functions, and comorbidities, in deciding which regimen should be considered for use in combination with colistin to treat CRAB pneumonia.

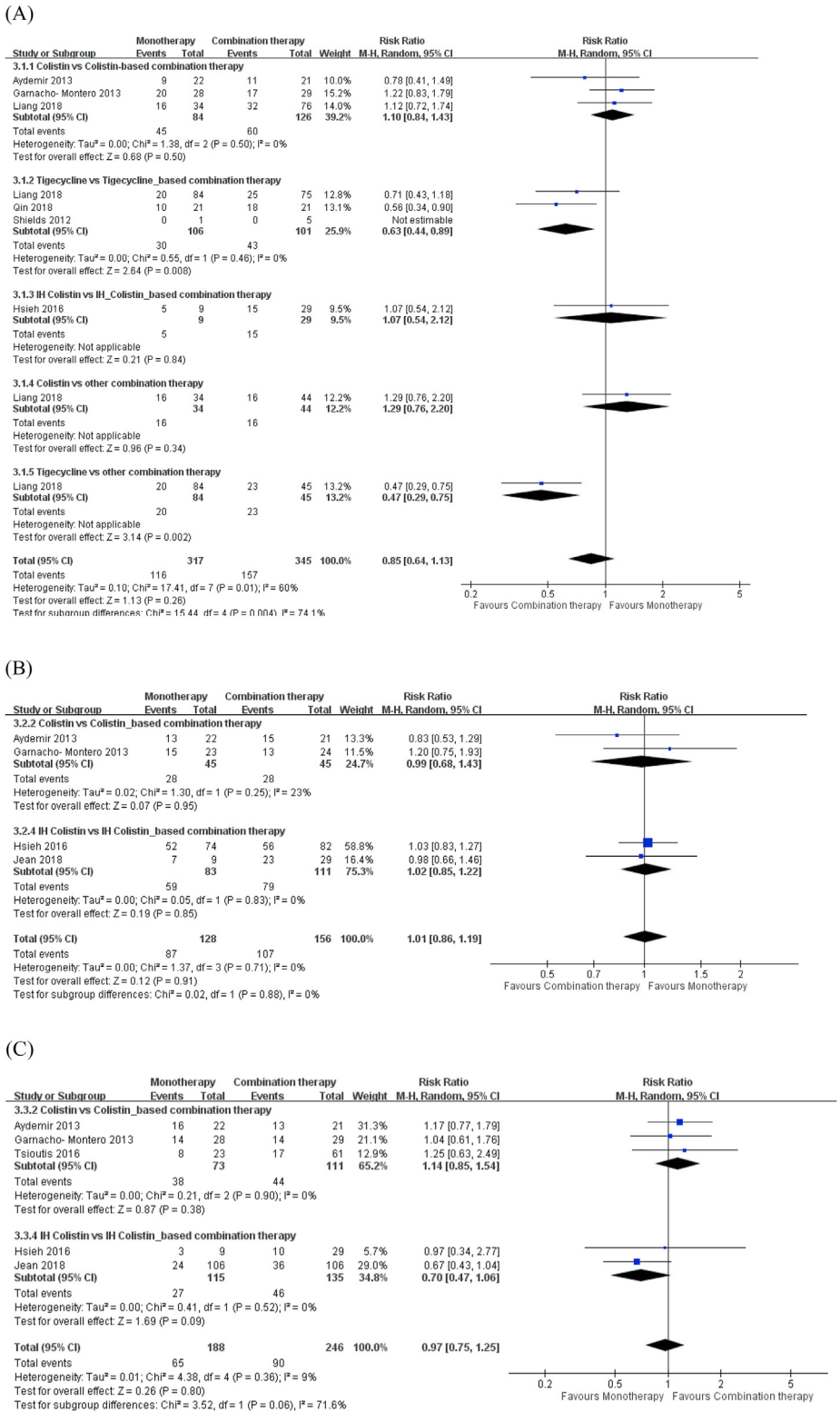
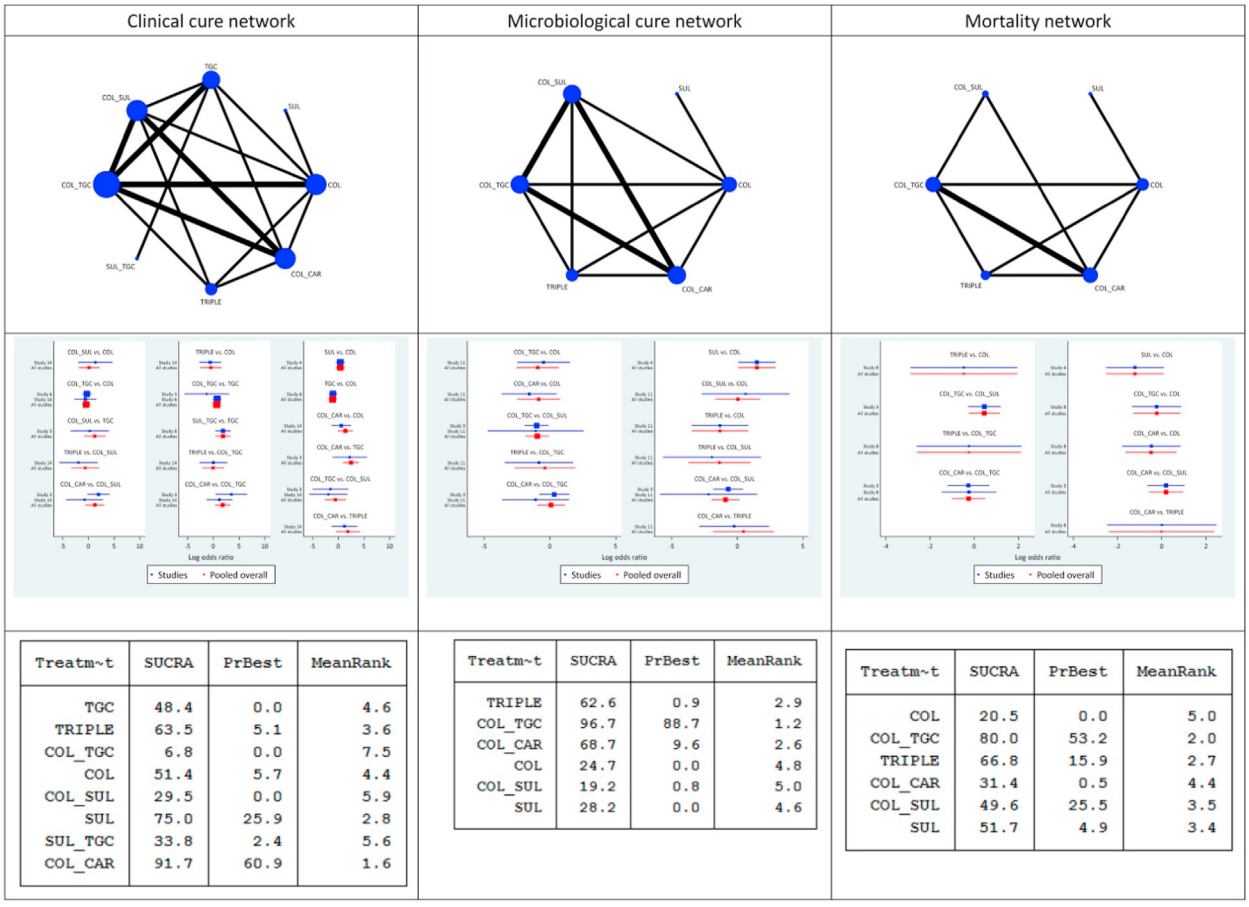


Figure 1. Meta-analysis comparing (A) clinical cure (B) microbiological cure and (C) mortality of patients treated with monotherapy versus combination therapy for carbapenem-resistant *Acinetobacter baumannii* pneumonia.



Treatment	SUCRA	PrBest	MeanRank
TGC	48.4	0.0	4.6
TRIPLE	63.5	5.1	3.6
COL_TGC	6.8	0.0	7.5
COL	51.4	5.7	4.4
COL_SUL	29.5	0.0	5.9
SUL	75.0	25.9	2.8
SUL_TGC	33.8	2.4	5.6
COL_CAR	91.7	60.9	1.6

Treatment	SUCRA	PrBest	MeanRank
TRIPLE	62.6	0.9	2.9
COL_TGC	96.7	88.7	1.2
COL_CAR	68.7	9.6	2.6
COL	24.7	0.0	4.8
COL_SUL	19.2	0.8	5.0
SUL	28.2	0.0	4.6

Treatment	SUCRA	PrBest	MeanRank
COL	20.5	0.0	5.0
COL_TGC	80.0	53.2	2.0
TRIPLE	66.8	15.9	2.7
COL_CAR	31.4	0.5	4.4
COL_SUL	49.6	25.5	3.5
SUL	51.7	4.9	3.4

Figure 2. Network comparisons of treatment of carbapenem-resistant *Acinetobacter baumannii* pneumonia. The size of the nodes and the thickness of the lines are weighted according to the number of studies assessing each treatment and direct comparison.

What is the recommended treatment for CRAB bloodstream infection?

Recommendations

1. We recommend colistin-carbapenem based combination therapy for the treatment of CRAB BSI (*Weak recommendation, low quality of evidence*) *(2C)*.

Summary of the evidence

There are limited therapeutic options for the treatment of CRAB bloodstream infections. Eravacycline and cefiderocol are novel agents which have shown potent *in vitro* activity against CRAB,[12] however, clinical studies are lacking at the time of this review. Combination therapy using current and old antimicrobial agents targeting different resistance mechanisms are often used clinically based on the rationale of potential synergistic effect. Several *in vitro* study demonstrated synergistic activity using combination therapy with colistin, or carbapenems, even when the isolates are resistant to carbapenems.[40,41] However, *in vitro* synergy may not translate into clinical benefit. In a study evaluating the correlation of *in vitro* synergy of colistin-meropenem and clinical outcome, the clinical failure rate in the synergistic, indifferent, and antagonistic group were 74%, 75.6%, and 55%, respectively.[42] This may be due to insufficient dosing, insufficient fraction of time exposed to synergistic concentrations, host immune—pathogen interactions and presence of colistin resistant subpopulations.

Several retrospective studies showed that colistin-based combination therapy, such as colistin-meropenem, resulted in higher microbiological eradication rates and reduced mortality compared to colistin monotherapy in patients with XDR-AB[43] and CRAB bloodstream infections.[44,45] In contrast, some reports show that combination therapy was not superior to monotherapy. Addition of meropenem to colistin monotherapy did not improve outcome in patients with severe infections with CRAB that were also resistant to colistin.[46,47] In our network meta-analysis, the combination of colistin-carbapenem had the highest SUCRA ranking for effective clinical care (SUCRA, 83.6%) followed by colistin-tigecycline and colistin-sulbactam (SUCRA, 70.1%, 27.5% respectively). Colistin-carbapenem (SUCRA, 87.1%) also had the highest ranking for microbiological cure followed by colistin-sulbactam (SUCRA, 57.9%). The colistin-tigecycline combination showed the lowest mortality rate (SUCRA, 93.4%). Based on the above evidence, we suggest that

combination therapy with colistin-meropenem is preferred for the treatment of CRAB bacteremia (Table 1, Fig. 3 and online supplement Fig. S2).

Carbapenem-resistant *P. aeruginosa*

Carbapenem-resistance in *P. aeruginosa* (CRPA) infections are associated with increased mortality, and most frequently cause pneumonia and bloodstream infections.[48—50] In a recent global antimicrobial surveillance report, rates of non-susceptibility to meropenem were highest in isolates from patients with pneumonia, around 27.1%, and were lower in isolates from other sites, ranging from 19.2% to 22.3%. The trend in rates of meropenem non-susceptibility to *P. aeruginosa* isolates in the Asia—Pacific region initially increased from 15.3% in 1997—2000 to 22.9% in 2009—2012, and then decreased to 17.2% during the period 2013—2016.[50] Another multinational study focusing on healthcare-associated infections in intensive care units (ICU) showed a significant decrease in the number of CRPA isolates in Asia, with a reduction of 50.4% in Korea and 38.4% in Taiwan between 2008 and 2015.[51] In contrast, THAS reports showed that the rate of CRPA from clinical isolates of healthcare associated infections in the ICU increased from 14.9% in 2009 to 22.6% in 2020 in medical centers, and from 16.7% to 20.3% in regional hospitals.[7,8]

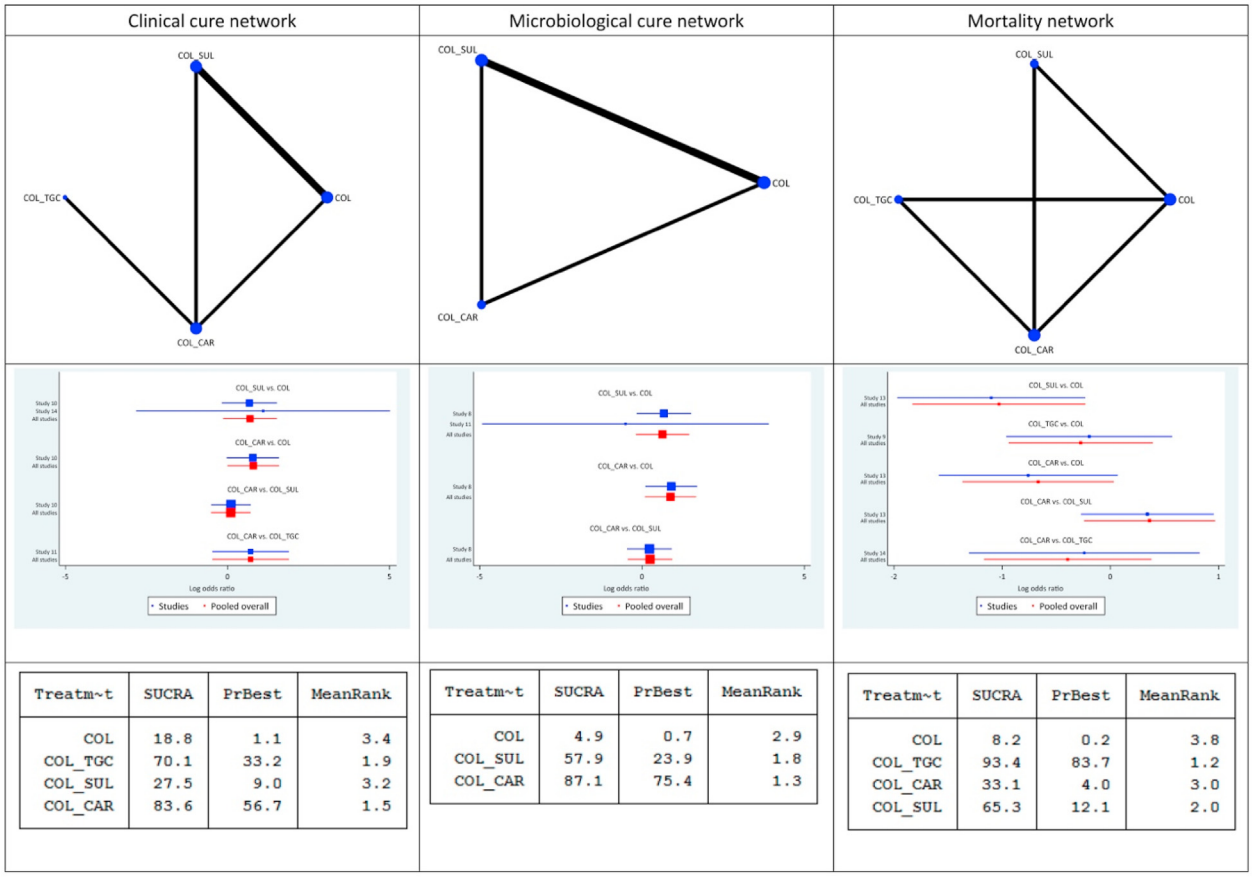
What is the recommended treatment for CRPA infections susceptible to other antimicrobial agents?

Recommendations

1. Anti-pseudomonal penicillins or cephalosporins or fluoroquinolones, with or without an aminoglycoside is recommended for treatment of infections due to CRPA susceptible to other antimicrobial agents (*Weak recommendation, very low-quality of evidence*) *(2D)*.

Summary of the evidence

The mechanism of antimicrobial resistance in carbapenem-resistant-cephalosporin-susceptible (CR/Ceph-S) *P. aeruginosa* is unique in comparison to difficult-to-treat resistance *P. aeruginosa* (DTR-PA). Overexpression of efflux systems and decreased expression of OprD were mainly found in *P. aeruginosa* with this susceptibility pattern.[52] Coexistence of β-lactamase and/or other drug-resistant genes often confers the resistance of *P. aeruginosa* to multiple classes of antimicrobial agents.[52—54] Monotherapy with susceptible antipseudomonal agents have been used extensively clinically without differences in mortality compared to other antimicrobial regimens.[55] Although no specific comparative



Treatm~t	SUCRA	PrBest	MeanRank
COL	18.8	1.1	3.4
COL_TGC	70.1	33.2	1.9
COL_SUL	27.5	9.0	3.2
COL_CAR	83.6	56.7	1.5

Treatm~t	SUCRA	PrBest	MeanRank
COL	4.9	0.7	2.9
COL_SUL	57.9	23.9	1.8
COL_CAR	87.1	75.4	1.3

Treatm~t	SUCRA	PrBest	MeanRank
COL	8.2	0.2	3.8
COL_TGC	93.4	83.7	1.2
COL_CAR	33.1	4.0	3.0
COL_SUL	65.3	12.1	2.0

Figure 3. Network comparisons of carbapenem-resistant *Acinetobacter baumannii* bacteremia studies included in the analyses. The size of the nodes and the thickness of the lines are weighted according to the number of studies assessing each treatment and direct comparison.

studies have been conducted to confirm superiority among different classes of active antimicrobial agents, one retrospective study demonstrated that aminoglycoside monotherapy was associated with an increased risk of mortality among patients with *P. aeruginosa* sepsis.[55] Therefore, the panel recommends that aminoglycosides should not be used as monotherapy to treat clinical syndromes caused by *P. aeruginosa* other than urinary tract infections.[55] The panel also suggests a colistin-sparing strategy, and use of anti-pseudomonal β-lactams or fluoroquinolones in the treatment of various clinical syndromes caused by CR/Ceph-S *P. aeruginosa* (Table 2). The adjunctive role of aminoglycoside with anti-pseudomonal β-lactams against *P. aeruginosa* has been widely evaluated and a survival benefit was found only in resistant GNB infections or patients with neutropenia or in shock at presentation.[56] Therefore, the panel suggests that anti-pseudomonal β-lactams and aminoglycoside combinations against *P. aeruginosa* is only considered when benefits outweighing risks due to possible adverse effects of aminoglycosides.

Other combinations, including β-lactams plus fluoroquinolones, may be considered in selected patient populations with *P. aeruginosa* infections such as patients with unstable hemodynamics due to hospital-acquired pneumonia or ventilator-associated pneumonia.[2]

In patients with sepsis due to *P. aeruginosa*, a recent meta-analysis demonstrated that prolonged (extended or continuous) infusion of β-lactams (≥3 h) lowered mortality compared to those who received short-term infusion (≤1 h).[57] This is attributable to the time-dependent nature of β-lactams. Real world evidence support the use of novel β-lactam/β-lactamase inhibitors delivery by prolonged infusion to achieve PK/PD targets for either maximizing efficacy and clinical outcome or suppressing the emergence or development of resistance.[58] Therefore, the panel suggests prolonged infusion of β-lactams as a strategy to optimize PK/PD of β-lactams for treatment of CR-GNB infections. Infectious diseases consultation is recommended for individualized evaluation of infections caused by antimicrobial-resistant pathogens.

What is the recommended treatment for DTR-PA infections?

Recommendations

1. Colistin-based treatment is recommended in DTR-PA infections *(Weak recommendation, low quality of evidence) (2C)*.
2. A loading dose of 9 MU (5 mg/kg) of colistin followed by a maintenance dose 4.5 MU [2.5 mg × (1.5 × CrCl+30)] twice daily is suggested in critically-ill patients *(Strong recommendation, low quality of evidence) (1C)*.
3. Renal function should be monitored during colistin treatment *(Strong recommendation, low-quality of evidence) (1C)*.
4. The use of colistin-based combination therapy is controversial *(Weak recommendation, very low quality of evidence) (2D)*.

Summary of the evidence

Colistin has *in vitro* activity against carbapenem-resistant, non-fermenting GNB, including *P. aeruginosa*. There are no randomized controlled trials comparing treatment outcomes of CRPA infections treated with colistin or other agents. Several retrospective studies showed that patients with CRPA or DTR-PA infections who were treated with colistin have a survival rate of 39%–83%.[59–66] The heterogeneity between studies and variability in disease entities and bacterial strains makes interpretation of results difficult.

There is controversy on whether colistin-based combination therapy is superior to monotherapy for treatment of infections due to CR-GNB. A randomized controlled trial concluded that the combination of colistin and meropenem was not superior to colistin monotherapy, with a 14-day mortality for *Pseudomonas* or other CR-GNBs of 25% (2/8) vs 31% (4/13), $p = 1.0$. This result was inconsistent with another study which demonstrated that polymyxin B combination therapy for treatment of DTR-PA had a lower mortality rate compared to monotherapy even when the combined antimicrobial agent lacked *in vitro* activity.[67] Based on the low quality of evidence and expert opinion, the panel suggests that colistin may be considered in combination with one or more additional agents to which the pathogen displays *in vitro* susceptibility. If a susceptible second agent is not available, colistin may be used in combination with a second and/or a third nonsusceptible agent (e.g., a carbapenem) with the lowest MIC.[68,69]

Pharmacodynamic studies in critically ill patients have shown that the optimal dose of colistin is 9 MU of colistin methanesulfonate (CMS) initially followed by 4.5 MU CMS twice a day as the maintenance dose.[70] This regimen is also supported by international consensus guidelines and expert panel discussions.[68] The optimal dosage of colistin in pediatric patients remains uncertain. The U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) recommends a loading dose of 0.15 MU/kg of colistin in children followed by a maintenance dose of 0.075 MU/kg every 12 h (equivalent to 2.5–5 mg colistin base activity (CBA) per kg per day). A recent population pharmacokinetic study, and previous case reports, indicate that the colistin dose range recommended by the U.S. FDA and EMA for pediatric patients may be inadequate in cases where the MIC of the infecting pathogen is ≥ 1 mg/L or when the patient has augmented renal clearance or good renal function for their age.[71,72] The range of treatment duration for different clinical syndromes varied among studies. Definitive treatment duration for CRPA infections should be individualized according to the site of infection, source control, the underlying comorbidities and the initial response to therapy.

Acute kidney injury during and after colistin treatment is one of the most important factor related to clinical failure and mortality.[73] There is no current consensus regarding frequency of dose adjustment and timing of withdrawal of therapy in the presence of acute kidney injury. The panel recommends that renal function be closely monitored during colistin therapy. Clinicians should weigh the benefits

and harms of treatment in patients with a higher risk of developing kidney injury, such as in the elderly or patients with chronic kidney disease.

What is the role of new β-lactam/β-lactamase inhibitors in treating DTR-PA infections?

Recommendations

1 New β-lactam/β-lactamase inhibitors, including ceftazidime-avibactam, ceftolozane-tazobactam and imipenem-cilastatin-relebactam may be considered in the treatment of DTR-PA infections. *(Weak recommendation, low quality of evidence) (2C).*
2 Antimicrobial susceptibility testing of new β-lactam/β-lactamase inhibitors is recommended to guide treatment of CRPA infections. (*Weak recommendation, very low quality of evidence) (2D).*

Summary of the evidence

The molecular mechanisms of antimicrobial resistance in DTR-PA are complex. The prevalence of metallo-β-lactamase in these pathogens remains low in Taiwan.[74—76] Data from the Study for Monitoring Antimicrobial Resistance Trends for 2018 to 2020 shows that 80% of imipenem-resistant *P. aeruginosa* bloodstream isolates in Taiwan are susceptible to amikacin and novel agents including cefiderocol, ceftazidime-avibactam, and ceftolozane-tazobactam.[77] Current evidence regarding the effectiveness of β-lactam/β-lactamase inhibitors for the treatment of CR-GNB infections are limited. Most studies enrolled relatively small number of patients and included GNBs other than *P. aeruginosa*. One study reported a better cure rate with less risk of acute kidney injury in the ceftolozane-tazobactam treatment group compared to polymyxin- or aminoglycoside-combination group when treating infections due to DTR-PA. Novel β-lactam/β-lactamase inhibitors, including ceftolozane-tazobactam and ceftazidime-avibactam, may be considered for treatment of CRPA and DTR-PA infections when antibiotic susceptibility testing results of new β-lactam/β-lactamase inhibitors are available.

Carbapenem-resistant Enterobacterales

The Clinical Laboratory Standards Institute defines Enterobacterales as carbapenem-resistant if they have minimum inhibitory concentrations (MIC) of $\geq$2 μg/mL against ertapenem or $\geq$ 4 μg/mL against doripenem, meropenem, or imipenem.[78] However an infection caused by ertapenem-resistant and imipenem- and meropenem-susceptible Enterobacterales may be treated by doripenem, meropenem, or imipenem.[79] We define carbapenem-resistant Enterobacterales (CRE) as Enterobacterales that are resistant to doripenem, imipenem, or meropenem.

Carbapenem-resistant Enterobacterales have spread rapidly globally in the recent years.[80] Between 2011 and 2020, the prevalence rate of CRE among nosocomial infections in ICUs have gradually risen from 8.6% to 26.1% in medical centers in Taiwan and from 5.4% to 20.3% in major regional teaching hospitals. The mechanisms of carbapenem resistance among Enterobacterales include production of extended-spectrum β-lactamase (ESBL) and/or AmpC enzymes in combination with loss of outer membrane protein or up-regulation of efflux pump, and presence of carbapenemases. In Taiwan, a significant proportion (29—47%) of carbapenem-resistant-*K. pneumoniae* (CR-KP) isolates harbor a plasmid allele encoding *K. pneumoniae* carbapenemases (KPC), most frequently KPC-2.[81—83] A significant increase in the number of oxacillinase (OXA)-48-like carbapenemases among CR-KP isolates was observed between 2012 and 2015.[83,84] The main mechanism for non-susceptibility of carbapenem-resistant-*Escherichia coli* (CR-EC) to carbapenems in Taiwan is the co-existence of a plasmid AmpC β-lactamase (DHA-1, CMY-2) combined with loss of an outer membrane porin (OmpC/F).[85,86]

What is the recommended treatment for BSI caused by CRE?

Recommendations

1. Polymyxin based combination therapy is recommended for BSI due to CRE *(Weak recommendation, very low quality of evidence) (2D).*
2. Combination antimicrobial therapy should be based on the result of susceptibility testing *(Weak recommendation, very low quality of evidence) (2D).*
3. Ceftazidime-avibactam 2.5 g IV q8h infused over 3 h is recommended for the treatment of CRE-BSI *(Weak recommendation, very low quality of evidence) (2D).*
4. Meropenem-vaborbactam 4 g IV q8h infused over 3 h or imipenem-cilastatin-relebactam 1.25 g IV Q6h is recommended in the treatment of CRE-BSI *(Weak recommendation, low quality of evidence) (2C).*

Summary of the evidence

Polymyxin based combination therapy

At the time of this writing, there were no prospective randomized controlled trials available that compared the treatment efficacy of polymyxin monotherapy and combination treatment in CRE infection. We performed a meta-analysis of ten retrospective studies regarding polymyxin mono-versus combination therapy of CRE infections.[87—96] Most studies defined CRE by the presence of carbapenemase. Two studies defined CRE as non-susceptibility to meropenem or imipenem. The majority of the studies included CR-KP and the most frequently found carbapenemase was KPC. The pooled results showed that the 28-day or 30-day mortality was lower in patients receiving colistin-based combination therapy, compared to those who received colistin monotherapy (35.7% vs 55.5%; Odds ratio [OR]: 0.46, 95% CI, 0.30—0.69; $p = 0.0003$) (Fig. 4). The INCREMENT cohort study, which included 437 patients with BSI due to carbapenemase producing Enterobacterales, showed no difference in the 30-day mortality between combination therapy and monotherapy. A subgroup analysis showed that combination therapy lowered mortality in patients with high INCREMENT-CPE mortality score.[91] The most frequently prescribed polymyxin was colistin. The standard

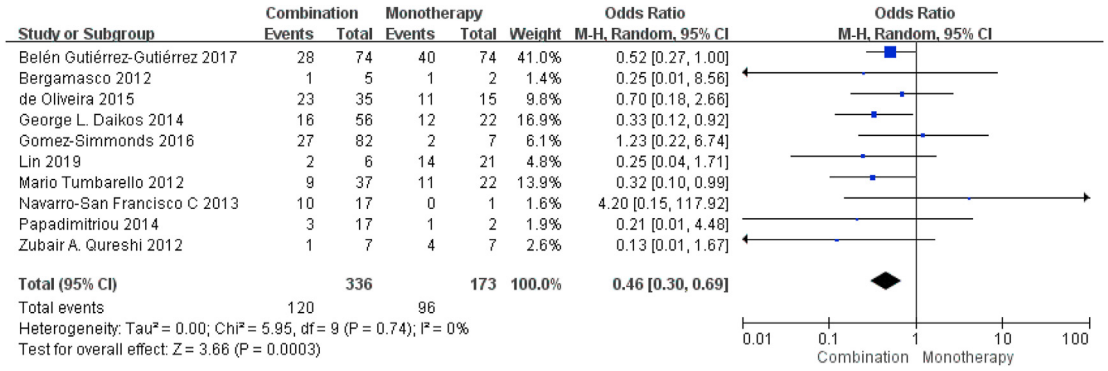


Figure 4. One-month mortality rate in carbapenem-resistant Enterobacterales (CRE) bloodstream infections treated with colistin-based combination therapy compared with colistin monotherapy in a meta-analysis of 10 studies.

colistin dose in patients with normal renal function was a loading dose of 300 mg CMS (9 MU) infused for 0.5∼1 h, and a maintenance dose of 300∼360 mg CMS (9 MU∼10.9 MU) divided in two doses.[68]

Combinational antimicrobial agents used for the treatment of CRE infections include tigecycline, carbapenem, and aminoglycosides. Tigecycline was the most commonly used combinational agent for the treatment of CRE-BSI.[87–96] Currently, there are no study that compares the treatment efficacy between different combination regimens.

Tigecycline

The role of tigecycline in the treatment of bacteremia and urinary tract infection due to CRE is limited due to its low serum and urinary concentration.[97,98] Although tigecycline is not approved for bacteremia, it may have a role in combination therapy for CRE-BSI. A meta-analysis including 24 studies demonstrated that there was no difference in the all-cause mortality between tigecycline compared to other antimicrobial agents in the treatment of CRE-BSI. Subgroup analysis showed that tigecycline monotherapy was associated a higher mortality (OR 2.73, 95% CI 1.53–4.87) compared with tigecycline-based combination therapy. However, tigecycline significantly reduced mortality when used to treat BSI due to KPC-producing CR-KP (OR 0.64, 95% CI 0.42–0.97).[99] Tigecycline was defined as appropriate when treating infections caused by isolates that had a minimum inhibitory concentration (MIC) $\leq$ 0.5 mg/L and was not associated with increased mortality when treating patients with CR-KP or CR-EC bacteremia.[92]

High dose tigecycline (HDT) regimen, with a loading dose of 200 mg and maintenance dose of 100 mg every 12 h, has been shown to significantly lower mortality among CR-KP infected patients treated with HDT-based combination therapy compared to standard dose tigecycline-based combination therapy.[100,101] No clinical benefit was seen in critically ill patients infected with CR-KP.[102] However, the sample sizes of these studies were too small to draw a conclusion. A recent meta-analysis including 10 studies with 593 patients showed that HDT group had a statistically lower mortality rate compared to the control group (OR 0.44, 95% CI 0.30–0.66, $I^2 = 49\%$, $p < 0.0001$). In subgroup analysis, HDT-containing regimen also reduced mortality in carbapenem-resistant bacterial infections (OR 0.20, 95% CI 0.09–0.45, $I^2 = 0\%$, $p = 0.0001$).[103] No difference in the incidence of adverse events were seen in the two groups. However, most of the enrolled studies were observational studies with small sample sizes and high risks of bias. Current evidence shows that combination regimens containing HDT may have a role in critically ill patients infected with CRE, but further large-scale investigations are needed to support this recommendation.

Ceftazidime-avibactam

Ceftazidime-avibactam is a novel β-lactam/β-lactamase inhibitor combination that restores the antibacterial activity of ceftazidime against Ambler class A (e.g. ESBL, KPC), class C (AmpC), and some class D enzymes (e.g. OXA-48) due to the addition of avibactam.[104] Avibactam does not inhibit class B metallo-β-lactamase enzymes (MBLs) such as NDM, VIM or IMP. Studies on the efficacy of ceftazidime-avibactam on treatment of CRE-BSI are limited, mostly retrospective, often with small number of patients or mixed with other sites of infection. Patients with BSI who received ceftazidime-avibactam had significantly higher rates of microbiological eradication and clinical cure than the comparator group, even in critically ill, mechanical ventilated patients.[105,106] Several studies reported that patients who received ceftazidime-avibactam had a significantly overall lower rates of 30-day mortality compared to other antimicrobial regimens (including 137 patients with BSI),[106–108] while other studies showed no difference (including 60 with BSI).[105,109,110] There were no differences in the frequency and profile of side effects including liver and renal function and coagulation tests between the two groups.[106,107] Based on the limited evidence, the panel recommends ceftazidime-avibactam as a treatment option for CRE-BSI (Table 3).

The use of ceftazidime-avibactam combination therapy with aminoglycosides, colistin, carbapenem, fosfomycin and tigecycline demonstrated no significant difference in mortality and microbiological cure rates compared to ceftazidime-avibactam monotherapy in observational studies and 2 meta-analysis for CRE infection.[105,111–113] An indication bias towards more severely ill patients could explain for the lack of effectiveness of combination

therapies.[110,114] However, combination therapy was associated with a lower mortality compared to monotherapy in patients with severe illnesses.[111] Studies with larger samples are needed to address this issue. The panel supports the general view that combination therapy is not routinely recommended for the treatment of CRE infections.[28,112,113]

Carbapenems

Meropenem—vaborbactam is the combination of a carbapenem with the first boron-based β-lactamase inhibitor vaborbactam. Vaborbactam has no anti-bacterial activity, but it inhibits Ambler class A (KPC) and class C β-lactamases, and not class B or D β-lactamases. The TANGO-II trial showed that monotherapy with meropenem-vaborbactam for CRE infection (in which 22 patients had CRE-BSI) was associated with overall increased clinical cure, decreased 28-day-all-cause mortality rate (5/32, 15.6% vs 5/15, 33.3%, 95% CI of difference, −44.7%—9.3%), and reduced nephrotoxicity compared with best available therapy.[115] A retrospective study comparing meropenem-vaborbactam (n = 26) with ceftazidime-avibactam (n = 105) for treatment of CRE infection, of whom 40% had bacteremia, found no difference in treatment success and 30-day mortality.[110] Based on the limited evidence, the panel recommends meropenem-vaborbactam as a treatment option for CRE-BSI (Table 3).

Imipenem-cilastatin-relebactam is a β-lactam/β-lactamase inhibitor approved by the U.S FDA in July 2019. Relebactam is a novel β-lactamase inhibitor that is active against class A carbapenemase and class C cephalosporinase, but inactive against class B and class D carbapenemase. The RESTORE-IMI-1 trial is a randomized controlled trial comparing efficacy and safety of imipenem-relebactam in patients with imipenem-nonsusceptible bacterial infections.[116] Only 2 patients had BSI in that trial. The susceptibility rate of CRE to imipenem-cilastatin-relebactam was 83.8% (553/660 isolates) in a national surveillance study done in Taiwan (2012—2015).[117] Based on the limited evidence, the panel recommends imipenem-cilastatin-relebactam as a treatment option for CRE-BSI.

What is the recommended treatment for complicated urinary tract infection (cUTI) caused by CRE?

Recommendations

1. Ceftazidime-avibactam 2.5 g IV q8h is recommended for cUTIs caused by CRE *(Weak recommendation, very low quality of evidence) (2D)*.
2. Meropenem-vaborbactam 4 g IV q8h or imipenem-cilastatin-relebactam 1.25 g IV q6h is recommended for cUTIs caused by CRE *(Weak recommendation, low quality of evidence) (2C)*.
3. Plazomicin 15 mg/kg IV q12 h is recommended for cUTI due to CRE *(Weak recommendation, very low quality of evidence) (2D)*.
4. Single-dose aminoglycoside is recommended for patients with simple cystitis due to CRE *(weak recommendation, very low quality of evidence) (2D)*.
5. Single-dose aminoglycoside is recommended as an alternative regimen for patients with cUTI due to CRE *(Weak recommendation, very low quality of evidence) (2D)*.

Summary of the evidence

Ceftazidime-avibactam

Ceftazidime-avibactam was first approved by the U.S. FDA in April 2015 for the treatment of cUTI including pyelonephritis, and cIAI in combination with metronidazole, in adults and patients ≥3 months of age.[104,118,119] The EMA also granted approval for the same indications and for hospital-acquired pneumonia including ventilator-associated infections and infections due to aerobic Gram-negative organisms in adults and pediatric patients aged 3 months and older with limited treatment options.[120] Several retrospective studies reported treatment of CRE infections with ceftazidime-avibactam was associated with either overall lowering of mortality or non-difference compared to other antibacterial regimens.[105—110] Based on limited evidence, the panel recommends ceftazidime-avibactam as a treatment option for CRE-UTI.

The emergence of ceftazidime-avibactam resistance in carbapenemase-producing *K. pneumoniae* (CP-KP) has been reported. Risk factors include prior administration of ceftazidime-avibactam, which may result in replacement of MBLs as the predominant carbapenemase in CP-KP isolates or emergence of mutation in the bla_{KPC-3} gene.[121,122] A "see-saw effect"-like phenomenon was observed in these variant KPC3 enzymes, with a ≥ 4-fold reduction in meropenem MICs to the susceptible range, in parallel with the rise in ceftazidime-avibactam MICs. Therefore, the British Society for Antimicrobial Chemotherapy recommends that when treating infections due to KPC-3 producers, the combination of ceftazidime-avibactam with a carbapenem or colistin may be considered.[123] The panel is unable to make recommendations on combination treatment of ceftazidime-avibactam for treatment of UTI due to CRE due to insufficient evidence.

Carbapenems

Meropenem-vaborbactam was approved by the U.S. FDA in Aug 2017 for the treatment of cUTI.[124] In the TANGO-II trial, meropenem-vaborbactam monotherapy was noninferior to best available treatment in CRE infections, including bacteremia, hospital-acquired/ventilator-associated bacterial pneumonia, cIAI, cUTI/acute pyelonephritis.[115] Based on limited evidence, the panel recommends meropenem-vaborbactam as a treatment option for CRE-UTI.

Imipenem-cilastatin-relebactam was approved by the U.S FDA in July 2019 for the treatment of cUTI and cIAI. It is active against most KPC-producing CRE strains and CRPA, but not CRAB or carbapenem-resistant-*Stenotrophomonas maltophilia*.[125,126] The RESTORE-IMI-1 trial showed that imipenem-cilastatin-relebactam was a well-tolerated treatment option for carbapenem-nonsusceptible infections compared to colistin-imipenem combination.[116] However, only 7 patients in the RESTORE-IMI-1 trial had

infections due to CRE (1 cIAI and 6 cUTI). Based on limited evidence, the panel recommends imipenem-cilastatin-relebactam as a treatment option for CRE-UTI.

Aminoglycosides

Aminoglycosides are ideal agents for single dose treatment of UTI since urinary concentrations remains above the therapeutic level for days after a single dose. Aminoglycosides are excreted in the active form primarily by the renal route with a concentration exceeding peak plasma levels by 25- to 100-fold. A meta-analysis of 13 studies including 13,804 patients, found that a single-dose of aminoglycoside was effective in the treatment of lower urinary tract infections, with high microbiologic cure rates of 87–100%.[127] Aminoglycosides have maintained excellent activity against the majority of uropathogens, including CRE. Clinical isolates of CRE in Taiwan from the Surveillance of Multicenter Antimicrobial Resistance in Taiwan[128] study in 2016 reported amikacin as the most susceptible agent (82.4%), with lower susceptibility to gentamicin (38.2%).[129] There is currently insufficient evidence to support the use of single-dose aminoglycoside for patients with cUTI due to CRE. The panel gives single dose aminoglycoside a weak recommendation when treating patients with CRE associated cystitis.

Plazomicin is a novel, semisynthetic aminoglycoside approved by the U.S. FDA in June 2018 for the treatment of cUTI in adults. Plazomicin is stable against aminoglycoside-modifying enzymes that compromise the activity of traditional aminoglycosides. It is active against KPC and OXA-48 producing CRE, and have variable activity against MBL-producing strains.[130] In the CARE trial enrolling 39 patients, treatment of serious CRE infections with plazomicin-based combination regimens resulted in numerically fewer deaths (24% vs 50%) and lower acute renal injury (16.7% vs 50%) compared with colistin-based combination regimen. This trial was stopped prematurely due to slow enrollment.[131] The EPIC trial also showed that plazomicin was noninferior to meropenem for the treatment of cUTIs caused by Enterobacterales, and included isolates with ESBL phenotype (107 strains) and carbapenem non-susceptible strains (15 strains).[132] Based on limited evidence, the panel recommends plazomicin as a treatment option for CRE-UTI.

Fosfomycin

Fosfomycin displayed good *in vitro* activity against CRE, and is recommended by guidelines of the European Society of Clinical Microbiology and Infectious diseases (ESCMID) for treatment of complicated UTI without septic shock,[133] based on the ZEUS trial[134] which included patients with cUTI or acute pyelonephritis, and showed no significant differences in clinical or microbiological cure between IV fosfomycin and comparators in a very small subgroup of patients with cephalosporin-resistant or ESBL-producing Enterobacterales. Larger studies are required to confirm these findings.

What is the recommended treatment for complicated intraabdominal infections caused by CRE?

Recommendations

1. Ceftazidime-avibactam 2.5 g IV q8h in combination with metronidazole is recommended for cIAI caused by CRE *(Weak recommendation, very low quality of evidence) (2D)*.
2. Tigecycline 100 mg IV loading dose then 50 mg IV q12 h or eravacycline 1 mg/kg infused over 60 min IV q12 h is recommended for cIAI caused by CRE *(Weak recommendation, very low quality of evidence) (2D)*.
3. Polymyxin based combination therapy is recommended for cIAI caused by CRE *(Weak recommendation, very low quality of evidence) (2D)*. The selection of combination antimicrobial agent should be based on susceptibility testing results *(Weak recommendation, very low quality of evidence) (2D)*.

Summary of the evidence

Polymyxin

There are no studies that focused solely on the treatment of intraabdominal infections caused by CRE. Six prior studies on BSI secondary to intraabdominal infections showed a lower mortality in patients receiving polymyxin-based combination therapy (39.3% vs 56.4%; OR: 0.52, 95% CI, 0.33–0.83; $p = 0.006$) (Fig. 5).[88–93] A systematic review and meta-analysis of treatment outcomes of CR-KP infections showed that combination therapy had lower overall mortality compared to monotherapy (OR: 1.45; 95% CI, 1.18–1.78; $p < 0.001$). There was no significant difference in the overall mortality, clinical and microbiological responses in different 2-drug or 3 drug combination regimens.[135] Based on limited evidence, the panel gives a weak recommendation to colistin in combination with either tigecycline or meropenem as a treatment option for CRE-IAI, and the selection of the combination agent should be based on susceptibility testing results (Table 3).

Tigecycline

Tigecycline has a broad spectrum of antibacterial activity including difficult-to-treat pathogens, and retained a 98% susceptibility against CRE in a global surveillance of clinical isolates in 2016.[136] It is effective against the most common causative pathogens in cIAI and is approved by the U.S. FDA in 2005 for this indication. A meta-analysis of 15 randomized controlled trials on the treatment of cIAI showed that there was no difference in the clinical and microbiological outcomes of patients treated with carbapenems or tigecycline.[137] Real world evidence from pooling of 5 observational studies in patients with cIAI suggests that overall clinical response rate to tigecycline may be lower in those with high disease severity (33/42, 78.6% vs 33/59, 54.2% in those with SOFA scores <7 and ≥ 7, respectively).[138] The clinical response rate was

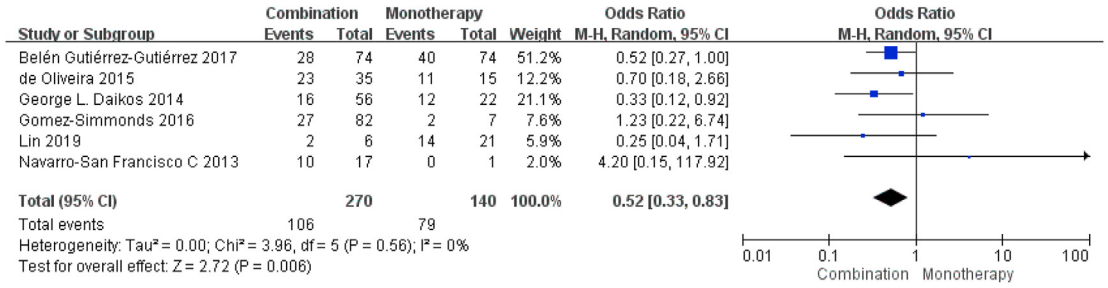


Figure 5. The treatment effect of polymyxin-based combinations on carbapenem-resistant Enterobacterales (CRE) bloodstream infections secondary to intra-abdominal infections in a meta-analysis of 6 studies.

comparable for patients with cIAI who received tigecycline monotherapy versus combination therapy (329/408, 80.6% vs 283/325, 73.2%), but this may be subject to indication bias. The INCREMENT cohort demonstrated that combination therapy significantly lowered mortality by 44% in patients with CRE-BSI with high-mortality scores, but not in those with low-mortality scores. However, only 37 patients had cIAI in that study.[91] Combinational agents most commonly used included tigecycline, colistin, carbapenems, fosfomycin and aminoglycosides. The panel suggests that tigecycline-based combination therapy with polymyxin or meropenem may be considered for CRE IAI when patients are complicated with severe sepsis or septic shock.

Eravacycline

Eravacycline is a novel, synthetic fluorocycline, structurally similar to tigecycline with unique modifications to the tetracycline D-ring, approved for use in cIAI by the U.S.FDA in Aug 2018.[139] Eravacycline is active against a broad-spectrum of Gram-positive and Gram-negative aerobic, and anaerobic microorganisms associated with cIAI.[140] The clinical efficacy of eravacycline in cIAI was evaluated in two randomized, multicenter trials, meeting the non-inferiority criteria for rates of clinical cure to ertapenem in IGNITE1 and to meropenem in IGNITE4.[141,142] A small observational cohort including 50 patients, of which 17 had cIAI, showed a clinical cure rate of 94% with treatment with eravacycline.[143] Another real-world experience including 35 severely ill patients, with a median APACHE II score of 16 (IQR: 11—21), reported a 30-day survival of 74%. Eight patients were infected with CRE and 7 (87.5%) achieved 30-day survival.[144] Based on the evidence, the panel recommends the use of eravacycline in patients with cIAI due to CRE.

Vancomycin-resistant Enterococcus

Vancomycin resistance in Enterococcus has been increasing in prevalence around the world since it was first encountered in 1988. The U.S. CDC's National Healthcare Safety Network reported in 2019 non-susceptibility rates of *Enterococcus* spp. to vancomycin in device-associated health-care associated infection (HAIs) to vary between 7.2% for *Enterococcus faecalis* to 82.1% for *Enterococcus faecium*.[9] The European Antimicrobial Resistance Surveillance Network (EARS-Net) by 30 European Union and European Economic Area countries reported an increase in vancomycin-resistant *E. faecium* from 8.1% in 2012 to 19% in 2018.[145]

The THAS reports an increase in the prevalence of VRE in ICU of medical centers from 22.7% in 2011 to 45% in 2020, a slight reduction of 6.6% compared to 2019.[8] The predominant species of VRE is *E. faecium* with a prevalence of 5.8—8% at admission to an ICU setting, and an incidence 5.7—10% during their ICU stay.[146,147] A retrospective study at a university hospital in Taiwan found that the prevalence of VRE bacteremia increased significantly from 3.9% in 2003 to 18.9% in 2010.[148]

What is the recommended treatment for vancomycin resistant enterococcal infections?

Recommendations

1. Linezolid 600 mg IV or PO every 12 h is recommended for enterococcal infections. The treatment duration is dependent on the site of infection and clinical response *(Strong recommendation, low quality of evidence) (1C)*.
2. High dose daptomycin 8—12 mg/kg/day or in combination with β-lactams including penicillins, cephalosporins, or carbapenems is recommended for VRE bacteremia *(Weak recommendation, low quality of evidence) (2C)*.
3. Tigecycline 100 mg IV loading dose then 50 mg IV q12 h for intraabdominal infection due to VRE. The duration of treatment is based on the clinical response (*Weak recommendation, very low quality of evidence) (2D)*.
4. A single dose of fosfomycin 3 g PO is recommended for uncomplicated urinary tract infections due to VRE (*Weak recommendation, very low quality of evidence) (2D)*.
5. Nitrofurantoin 100 mg PO every 6 h is recommended for uncomplicated urinary tract infections due to VRE *(Weak recommendation, very low quality of evidence) (2D)*.
6. High dose ampicillin (18—30 g IV daily in divided doses) or amoxicillin 500 mg PO/IV every 8 h daily is recommended for uncomplicated urinary tract infections due to VRE *(Weak recommendation, very low quality of evidence) (2D)*.

Summary of the evidence

VRE infections are most commonly treated with either linezolid or daptomycin, with no randomized clinical trials existing to support one treatment option over the other.[149] Linezolid was approved by the U.S. FDA in 2000 for the

treatment of VRE infections, based on a randomized trial of 2 linezolid dosing regimens and a compassionate use program. The open-label, compassionate-use program with 796 patients, of whom 66.3% were due to VRE infection showed that the overall microbiological and clinical cure rates using linezolid were 86.4% and 81.4%, respectively.[150] Clinical cure rates of VR-*E. faecium* varied with site of infection, higher in UTI (92%) and IAI (91.4%), and lower in lower respiratory tract and bone and joint infections (75%), endocarditis (76.9%), bacteremia (78%) and skin and soft tissue infections (79.3%). The treatment duration of VRE infection is dependent on the site of infection and on the clinical response.

Daptomycin is the first intravenous cyclic lipopeptide class discovered in the early 1980s from the fermentation of *Streptomyces roseosporus*. It was approved by the U.S. FDA in 2003 for the treatment of complicated skin and skin structure infections, and *S. aureus* bloodstream infections. Despite lacking U.S. FDA approval for the treatment of VRE infections, daptomycin had been documented to have better *in vitro* bactericidal activity for VRE than the other antimicrobial agents including vancomycin, linezolid, and quinupristin-dalfopristin.[151]

Studies comparing daptomycin and linezolid have conflicting results.[152–154] Earlier meta-analyses comparing treatment of VRE bacteremia with daptomycin versus linezolid found a higher mortality and lower microbiological cure rates associated with daptomycin use.[154] However, there were significant limitations including study heterogeneity, definitions of mortality, small and retrospective observational assessments, confounders between treatment groups, inclusion of low-quality conference abstracts and a large number of patients treated with low-dose daptomycin (<6 mg/kg).[155] Thereafter, a large, retrospective cohort study of 644 patients found linezolid to be associated with significantly higher treatment failure, microbiological failure and 30 day mortality compared with daptomycin.[156] However, a meta-analysis including 11 studies and 1339 patients, including only studies where daptomycin dosing was adequate (>6 mg/kg), found no difference in mortality, clinical and microbiological cure rate, compared with linezolid.[157] We conducted a meta-analysis of 3067 patients from thirteen cohort studies for the effect of daptomycin (>6 mg/kg) and linezolid in patients with VRE BSI.[158–169] The major pathogen of VRE BSI was *E. faecium*, ranging from 62% to 100%. The crude mortality rate was 35.7% for daptomycin and 32.8% for linezolid (RR, 1.24; 95% CI, 1.02–1.50; $p = 0.03$) (Fig. 6 and online supplement Table S1). Mortality rate was lower with the linezolid group but significant heterogeneity existed between the studies. In contrast, no significant difference in the 1-month mortality rate between daptomycin and linezolid (33.1% vs 34.1%, RR, 1.11, 95% CI, 0.88–1.41, p = 0.36) was found in a second analysis pooling 6 studies (Online supplement Fig. S3).[148,158,160,164,166,169] The microbiologic cure rate of daptomycin and linezolid (93% vs. 91%, RR, 0.95; 95% CI, 0.73–1.25; p = 0.71) was comparable (Online supplement Fig. S4).[159,163–165,168,169]

Growing evidences suggest that higher daptomycin dose contributed to better treatment outcomes for treatment of VRE bacteremia.[162,170–172] The CLSI revised the daptomycin MIC breakpoints for *Enterococcus* species and introduced a new susceptible-dose dependent (SDD) category which was based on dosing regimen of 8–12 mg/kg/day in 2019.[173] The CLSI designated the SDD category specifically for *E. faecium* in 2020.[174] Several studies evaluated standard-dose (6 mg/kg) versus high-dose (>6 mg/kg) daptomycin for the treatment of VRE bacteremia. One study including 62 patients found no difference between high dose daptomycin (≥8 mg/kg) versus lower dosing, however 31 patients had a high daptomycin MIC of 3–4 μg/mL.[175] A prospective cohort study conducted in Taiwan concluded that high daptomycin doses (≥9 mg/kg/day) led to a lower mortality in patients with VRE-BSI, with a 74–91% reduction in 14-day mortality.[172] A clear dose-dependent effect was observed between dosing of daptomycin and mortality, each 1 mg/kg increase in daptomycin dose was associated with a 24–40% decrease in 14-day mortality.[160,172] Another large, retrospective study including 911 patients, where 27/34 (62.8%) patients had a high daptomycin MIC of 3 or 4 mg/L, found that patients receiving lower doses of daptomycin were 2.5 times more likely to die than those receiving high daptomycin dose (OR 2.58 for dose ≥8 mg/kg and OR 2.52 for dose ≥10 mg/kg).[170] This study also demonstrated a significant dose-dependent decrease in time to microbiologic clearance. We conducted a meta-analysis of two cohort studies and also found that using high dose daptomycin (≥10 mg/kg/day) contributed to a lower 30-day mortality in patients with VRE-BSI (RR 0.56, 95% CI 0.36–0.90) (Fig. 7 and online supplement Table S2). The most notable side effect of daptomycin was elevation of serum creatinine kinase (CK) level. Some observational

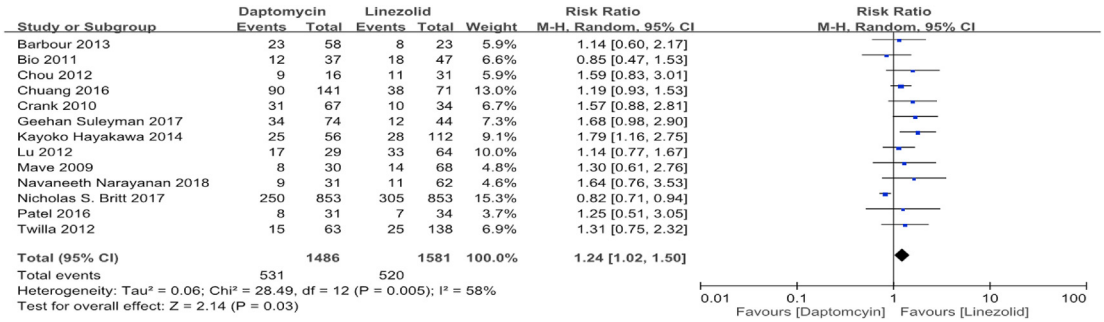


Figure 6. Crude in-hospital mortality of vancomycin resistant enterococci (VRE) bloodstream infections in a meta-analysis of 13 cohort studies.

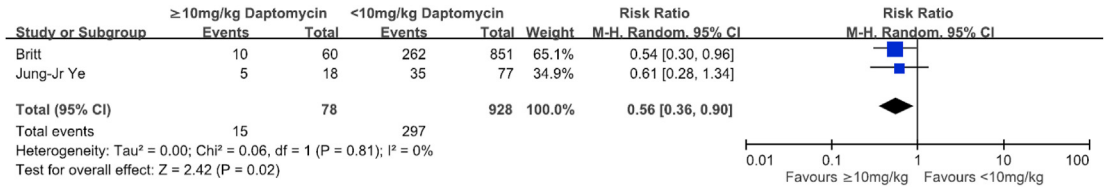


Figure 7. 30-day mortality rate of vancomycin resistant enterococci (VRE) bloodstream infections in patients treated with high dose (≥10 mg/kg/day) versus standard dose in a meta-analysis of 2 cohort studies.

studies showed that there was no significantly increased risk of CK elevation in high dose daptomycin group.[170,172,176] The safety of high dose daptomycin was evaluated in 2 studies, and did not observe an increased risk of serum CK elevations among those with high dose versus standard dose of daptomycin.[154,170] There was no significant difference between daptomycin and linezolid in the occurrence of thrombocytopenia (10.6% vs 12.1%, RR, 0.85; 95% CI, 0.68–1.05; p = 0.13) or CK elevation (2.8% vs 2.6%, RR, 0.61; 95% CI, 0.26–1.42; p = 0.25) (Online supplement Fig. S5 and Fig. S6).[159,160,162,164,168] Based upon current evidence, the panel recommends that high dose daptomycin at 8–12 mg/kg daily may be used to treat VRE-BSI (Table 4). Although there was no significant risk of CK elevation, we still recommend monitoring of CK levels when using higher dose of daptomycin. The panel recommends VRE-BSI to be treated for at least 14 days and duration of treatment should be based on individual clinical conditions. Infection disease specialist consultation is suggested in patients with poor treatment response or when longer duration of treatment is considered.

Combination antimicrobial therapy may be considered in severely ill patients or those who fail treatment with traditional options.[177] Most studies evaluated the effect of daptomycin combined with β-lactams antibiotics.[178,179] An *in vitro* study found that combining daptomycin with ampicillin or ceftaroline had synergistic activity in daptomycin-susceptible VRE strains. Combining ceftaroline with daptomycin restored the clinical efficacy of daptomycin in a daptomycin-nonsusceptible clinical isolate.[180] A prospective, observational cohort study in Taiwan enrolled 114 patients who received either daptomycin monotherapy or daptomycin-β-lactams combinations, and found no significant differences in overall mortality. Combinational agents included penicillins, cephalosporins and carbapenems. Subgroup analysis of VRE with a lower daptomycin MIC (≤2 mg/L) found a significantly reduction in mortality by 77% in the daptomycin-β-lactams combination group. Better survival was also observed in the high-dose (≥9 mg/kg) daptomycin-β-lactams group compared to daptomycin monotherapy (adjusted hazard ratio (aHR) 5.16, $p = 0.02$ for low dose; aHR 19.01, $p = 0.002$ for high dose) or low-dose (6–9 mg/kg) daptomycin-β-lactams combination group (aHR 5.39, $p = 0.006$).[178] In another retrospective study of 262 patients, a higher daptomycin MIC (3–4 μg/mL) was associated with treatment failure (OR = 3.23, $p = 0.013$), but not in those who received daptomycin-β-lactams combination.[179] Successful treatment has also been reported when daptomycin is combined with non-β-lactams antimicrobial agents such as gentamicin, linezolid, rifampin, tigecycline, and tobramycin.[177,179] The combination of daptomycin and cefotaxime or cefazolin was not shown to be synergistic against VRE.[181] Linezolid has also been combined with other agents, such as gentamicin, rifampin, and doxycycline, for the salvage treatment of VRE infections.[177] Due to the limited number of studies, the clinical efficacy of these combinations warrants further study.

Tigecycline is a glycylcycline that is active against VRE. It has a broad-spectrum of activity and achieves high penetration into the peritoneal space making it an ideal option for the treatment of IAI involving VRE. However, tigecycline should not be used for the treatment of VRE bacteremia due to a large volume of distribution and low serum levels.[149] There is limited evidence on the clinical efficacy of tigecycline for the treatment of VRE infections. A retrospective study evaluating 132 patients with a variety of infections also involving VRE in 42 patients, found an overall success rates of 97.6% (including 27 IAI, 3 SSTI, 1 CAP, 4 BSI and 4 multiple sites).[182] The panel recommends tigecycline as drug of choice for intra-abdominal infections caused by VREs. The duration of treatment is dependent on the site of infection and on the clinical response.

Fosfomycin is FDA approved for the treatment of UTI caused by *E. faecalis*. It has *in vitro* activity against VRE infections. *In vitro* studies show that the combination of fosfomycin with linezolid, tigecycline or gentamicin showed synergistic or additive effect against VRE.[183,184] Limited subset data from several retrospective, observational studies showed promising results in treating uncomplicated urinary tract infections due to VRE.[185–187]

Nitrofurantoin was approved by the U.S. FDA in the 1950s for treatment of lower urinary tract infection. It has good *in vitro* activity against VREs.[188,189] Clinical data regarding its efficacy on treating VRE infections is rarely reported.[190,191]

Some VRE isolates remains susceptible to ampicillin and can be successfully treated by the combination of ampicillin and gentamicin.[192] High urinary concentrations of ampicillin may overcome the high ampicillin MIC of ampicillin–resistant VRE and achieve the necessary drug concentration for optimal bactericidal activity in urinary tract infections.[193] One retrospective study reported that patients with UTI due to ampicillin–resistant VRE treated with ampicillin had promising clinical outcomes. Clinical and microbiological eradication were 88.1% and 86%, respectively.[194] Ampicillin is the drug of choice for enterococcal infections. This may still be true in regardless of the ampicillin susceptibility in urinary tract infections due to VRE. High dose of ampicillin (18–30 g IV daily) or amoxicillin (500 mg PO/IV every 8 h) is suggested to achieve sufficient

urinary concentrations to treat VRE-UTI.[149] It is important to differentiate colonization from true infection prior to empiric prescription of anti-VRE antimicrobial agents.

A retrospective cohort study of 50 patients with VRE infective endocarditis (IE), showed that *E. faecalis* is associated with mitral valve infection, presence of central venous lines, and liver transplantation, while *E. faecium* was associated with tricuspid valve infection. Hemodialysis and liver transplantation were risk factors for VRE IE. Vancomycin-resistant *E. faecium* IE was associated with a higher mortality and longer duration of bacteremia compared to vancomycin-resistant *E. faecalis* IE. Cardiac surgery and combination antibiotic therapy tended to improve survival outcomes.[192] Due to its bactericidal activity, daptomycin is preferred for the treatment of serious VRE infections at a dosing of at least 8 mg/kg and up to 10—12 mg/kg.[195] In the absence of more clinical evidence, reducing central catheters, effective antibiotic treatment, and infection control policies should be encouraged for in all patients.

Novel agents including eravacycline and ceftaroline has been shown to exhibit *in vitro* activity against Gram-positive organisms. Eravacycline, which is structurally similar to tigecycline, has *in vitro* activity against a broad-spectrum of Gram-positive and Gram-negative aerobic including VRE.[196] There are currently no complete evidence available to provide guidance on its role for VRE infections. Ceftaroline is a novel fifth-generation cephalosporin which exhibits broad-spectrum activity against Gram-positive bacteria but has poor activity against enterococcus and should not be empirically used for the treatment of VRE infections.[197]

Conclusion

The emergence of multidrug resistance is multifactorial and dynamic. Emergence of antimicrobial resistance is highly correlated with selective pressure from inappropriate use of these antimicrobial agents. Unnecessary prolonged use of empiric broad-spectrum antibiotics should be avoided, whenever possible. Choices of antimicrobial agents should be made based on local microbiologic data. Continuous development of new antimicrobial agents should be matched with programs that facilitates understanding of the importance of its prudent and appropriate use.

Declaration of competing interest

The authors declare no potential conflicts of interest with regards to the research, authorship, or publication of this article.

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