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Review Article

Guidelines for the diagnosis, treatment, prevention and control of infections caused by carbapenem-resistant gram-negative bacilli

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Abstract The dissemination of carbapenem-resistant Gram-negative bacilli (CRGNB) is a global public health issue. CRGNB isolates are usually extensively drug-resistant or pandrug-resistant, resulting in limited antimicrobial treatment options and high mortality. A multidisciplinary guideline development group covering clinical infectious diseases, clinical microbiology, clinical pharmacology, infection control, and guideline methodology experts jointly developed the present clinical practice guidelines based on best available scientific evidence to address the clinical issues regarding laboratory testing, antimicrobial therapy, and prevention of CRGNB infections. This guideline focuses on carbapenem-resistant *Enterobacteriales* (CRE), carbapenem-resistant *Acinetobacter baumannii* (CRAB), and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA). Sixteen clinical questions were proposed from the perspective of current clinical practice and translated into research questions using PICO (population, intervention, comparator, and outcomes) format to collect and synthesize relevant evidence to inform corresponding recommendations. The grading of recommendations, assessment, development and evaluation (GRADE) approach was used to evaluate the quality of evidence, benefit and risk profile of corresponding interventions and formulate recommendations or suggestions. Evidence extracted from systematic reviews and randomized controlled trials (RCTs) was considered preferentially for treatment-related clinical questions. Observational studies, non-controlled studies, and expert opinions were considered as supplementary evidence in the

absence of RCTs. The strength of recommendations was classified as strong or conditional (weak). The evidence informing recommendations derives from studies worldwide, while the implementation suggestions combined the Chinese experience. The target audience of this guideline is clinician and related professionals involved in management of infectious diseases.

Introduction

The extensive spread of carbapenem-resistant Gram-negative bacilli (CRGNB) has become a global public health issue. The World Health Organization (WHO) identified carbapenem-resistant *Enterobacteriales* (CRE), carbapenem-resistant *Acinetobacter baumannii* (CRAB), and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) as the pathogens of critical threat in the global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics in 2017.[1] *Escherichia coli*, *Klebsiella pneumoniae*, *A. baumannii* and *P. aeruginosa* are listed among the six leading pathogens for resistance associated death, and CRAB and carbapenem-resistant *K. pneumoniae* (CRKP) are among the top seven multidrug resistant (MDR) pathogens each causing more than 50000 deaths attributed to antimicrobial resistance.[2] The China Antimicrobial Surveillance Network (CHINET) monitoring data shows, *E. coli*, *K. pneumoniae*, *A. baumannii* and *P. aeruginosa* are among the top five bacterial species in clinical isolates from hospitals across China, demonstrating a growing CRGNB prevalence over time,[3,4] from 3% in 2005 to 23.1% in 2021 for CRKP, and from 31.0% to 71.5% for CRAB. Although the prevalence of CRPA decreased from 36.8% to 23.0%, it remained at high level in general.[4]

CRGNB isolates are usually extensively drug-resistant (XDR) or pandrug-resistant (PDR), for which antimicrobial treatment options are limited. Such difficult-to-treat CRGNB infections result in heavy healthcare burden and high mortality.[5] Some novel antimicrobial agents have been approved for clinical use in the treatment of CRGNB infections in recent years, but there is a delay for their launch in some countries such as in China, further limiting choices of antimicrobial agents in these countries and increasing the challenge of providing effective treatment. In 2016, experts specialized in clinical infectious diseases, clinical microbiology, clinical pharmacology, and infection control, jointly developed the Chinese expert consensus statement on laboratory diagnosis, clinical management and infection control of infections caused by XDR-GNB to address the intractable clinical problems of XDR-GNB. The consensus statement published in Clinical Microbiology & Infection provided a practical guidance primarily to clinicians for the management and control of XDR-GNB infections.[6]

The current clinical practice guideline (CPG) is an update of the 2016 consensus with a more focused scope on CRGNB. While retaining the same structure as the 2016 consensus statement, the current CPG improves on methodological reliability and transparency. It is prepared in accordance with the standards and processes recommended by WHO, and adopting the internationally recognized grading of recommendations assessment, development and evaluation grade (GRADE) system. It integrates available evidence and new advances to formulate recommendations or suggestions for clinical practice to address a series of clinical priority questions concerning diagnosis, treatment and control of CRGNB infections. The Society of Bacterial Infection and Resistance of Chinese Medical Association, the Expert Committee on Clinical Use of Antimicrobial Agents and Evaluation of Antimicrobial Resistance of the National Health Commission, the Infectious Diseases Society of Chinese Medical Education Association, and the China Clinical Practice Guideline Alliance jointly developed this guideline.

In 2022, several international guidelines or guidance were published on the treatment of MDR GNB including CRGNB by the Infectious Diseases Society of America,[7,8] the European Society of Clinical Microbiology and Infectious Diseases,[9] and the Infectious Diseases Society of Taiwan.[10] While the current CPG focuses on CRGNB (CRE, CRAB and CRPA), it complements the aforementioned CPGs by including broader scope related to the management of CRGNB infections: in addition to antimicrobial therapy, recommendations relating to diagnosis (antimicrobial susceptibility testing and synergy testing, carbapenemase detection), therapeutic drug monitoring of common antimicrobials for CRGNB and infection control are also included in this CPG. Where possible, meta-analysis were carried out for comparison on efficacy and safety of various therapy regimens. This CPG aims to provide guidance on management of CRGNB infections mainly for clinicians, and related professionals involved in management of infectious diseases.

Methodology

Guideline development group (GDG) composition

GDG members are elected by the chair of guideline panel. They composed of 31 multidisciplinary clinical experts related to the diagnosis and treatment of CRGNB, such as infectious diseases, intensive care, respiratory, hematology, pediatrics, surgery, clinical microbiology, clinical pharmacology and infection control. Their conflict of interest (CoI) was collected and assessed using a standard form constructed under the guidance of principles listed on Guideline International Network (GIN). All GDG members

were free of financial and intellectual CoI and were permitted full participation. China Clinical Practice Guideline Alliance (GUIDANCE) provided methodological expertise and systematic review support. This CPG is registered on GIN website (https://guidelines.ebmportal.com/node/69996).

Guideline development

This CPG is developed following the WHO recommended process,[11] which adopts GRADE in assessing evidence quality, and utilizing Evidence to Decision (EtD) framework to formulate clinical recommendations. GRADE categorizes the quality of evidence into high, moderate, low and very low, through assessing risk of bias, inconsistency, indirectness, imprecision and publication bias of the body of evidence. Quality of evidence is taken into account informing the final recommendation, together with the balance of benefit and harm, stakeholders' values and preferences, cost effectiveness, acceptability and feasibility.[12] This CPG categorized strength of recommendation into strong, weak and conditional. Factors promote strong recommendation including high certainty of evidence, similarity in stakeholders' values and preferences, cost effectiveness, and sharp contrast between benefit and harm.[12]

The GDG identified 16 important clinical questions through discussion and converted these into research questions using PICO format to pave way for systematic reviews. The GDG held 5 online meetings between September and October 2021 to review evidence under each PICO question and reaching consensus on corresponding recommendations through open discussion and voting. Eighty percent votes are adopted as a threshold to pass a recommendation.

Upon completion, the full CPG report was sent to external guideline methodologists and clinicians without direct involvement to the current CPG for review. Their feedbacks were collected and incorporated as appropriate. We referenced AGREE II before and during the conduct of CPG to ensure conduct quality and scientific rigor of reporting.

Evidence synthesis

The systematic review team searched PubMed, Embase, Web of Science, Cochrane Library in March 2021 without date limit (Supplementary material S1). Additionally, reviewers hand searched references of all included articles for further relevant studies, and contacted clinicians for potentially relevant studies. The final update of hand search was conducted in December 2022. Two separate sets of searches were carried out to identify studies on efficacy and safety, and studies on other factors including cost-effectiveness, values and preferences, acceptability and feasibility.

Reviewers worked in pairs to independently carry out reference screening, data extraction, and resolved any disagreements through discussion or consulting a third reviewer (Supplementary material S2). A data extraction form with standardized variable headings was used in this process. We employed Cochrane risk of bias table (RoB, version 1.0) to assess the risk of bias for RCTs, Newcastle—Ottawa Scale (NOS) for observational studies. We used RevMan 5.3 to analyze data from controlled clinical studies or RCT and R 4.0.2 for single arm studies. For binary outcome, we calculated Risk Ratio (RR) and its 95% confidence interval (CI); for continuous outcome, where possible, we calculated Mean Difference (MD) with its 95% CI. We employed $I^2 > 50\%$ as a general guide to identify heterogeneity in pooled analysis, and explored heterogeneity through subgroup analysis on clinical, methodological and statistical variations between studies. As stated in previous section, quality of evidence is appraised using GRADE and presented as Summary of Findings tables (SoF) (Online supplement tables).

Evidence extracted from systematic reviews and randomized controlled trials (RCTs) was considered preferentially for treatment-related clinical questions. Observational studies, non-controlled studies, and expert opinion were considered as supplementary evidence in absence of RCT, or if RCT evidence is indirect evidence, or if quality of evidence was very low. Evidence extracted from systematic reviews or cross-sectional studies was adopted preferentially for the clinical questions related to clinical microbiological diagnosis.

Recommendations

Sixteen key clinical questions were deemed to be of high priority in the management of CRGNB infections by the guideline development group (GDG), including three PICO questions for laboratory testing of CRGNB, ten for antimicrobial therapy and three for infection prevention and control.

Laboratory testing of CRGNB

CRGNB isolates are usually presented as XDR phenotypes, for which only limited number of antimicrobial agents remain effective. Some newly approved antimicrobial agents have not yet been included in routine antimicrobial susceptibility testing, which limits the choice of effective antimicrobials for the treatment of CRGNB infections. The precision treatment for CRGNB relies on clinical microbiology for determination of minimum inhibitory concentration (MIC) and rapid identification of the carbapenemase genotype of CRGNB isolates, as well as antimicrobial synergy testing to screen appropriate treatment options.

PICO question 1. should MIC testing be performed for determining antimicrobial susceptibility of CRGNB?

Recommendation: MICs should be determined where possible for commonly used antimicrobial agents which are available at local hospitals for treating CRGNB infections such as carbapenems, ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-cilastatin-relebactam, meropenem-vaborbactam, cefiderocol, tigecycline, eravacycline, polymyxin and fosfomycin (weak recommendation, low-quality evidence). Most automated antimicrobial

susceptibility testing systems can measure MIC value, but their clinical value is limited by the narrow concentration range of individual antibacterial agent. Broth microdilution (BMD), agar dilution method or E-test method are recommended as preferential methods in accordance with the requirements of the Clinical Laboratory Standards Institute (CLSI) or the European Committee for Antimicrobial Susceptibility Testing (EUCAST) documents regarding methodology.

Implementation suggestion: 1) Other methods can be used to determine MIC values of antimicrobial agents in the health care facilities where the above recommended method is unavailable; 2) It is suggested to initiate empirical antimicrobial therapy in parallel to MIC testing in the interest of providing earlier treatment. 3) For fosfomycin MIC testing, agar dilution method supplemented with glucose-6-phosphate is recommended by CLSI and EUCAST, but not broth dilution method.

Evidence summary: Five studies comparing the accuracy of other methods versus BMD in identifying CRE and testing the susceptibility of CRGNB to some key antimicrobial agents were included. A multicenter study[13] in Europe showed that EUCAST disc diffusion method has a good accuracy comparing with BMD to identify CRE, but it would likely miss the detection of CRE strains with meropenem MIC <1 mg/L. The semi-automated instruments VITEK 2 and Phoenix reported higher MIC values of meropenem compared to BMD MIC, resulting in higher proportion of major errors (MEs) (false resistant, 26% and 14%, respectively). The gradient MIC method such as E-test showed higher categorical agreement (73%) and lower ME rate (7%) in identifying CRE compared with BMD.[13] A study[14] conducted in the US indicated that for the 74 CRE isolates identified by carbapenemase genotype, E-test and disc diffusion method showed categorical agreement of 96% and 72% with BMD for ceftazidime-avibactam susceptibility, suggesting E-test was superior to disc diffusion method. Another US study showed that disc diffusion method had higher categorical agreement with VITEK 2 in testing the susceptibility of *P. aeruginosa* to meropenem.[15] A study in China demonstrated that agar dilution method, E-test, and Phoenix assay yielded higher categorical agreement (96%, 88%, and 93%, respectively) with BMD in determining the susceptibility of CRE strains to tigecycline.[16] Another study[17] in China reported that E-test and modified disc diffusion method (adding a re-sensitization buffer containing 175 μg EDTA to the disc) had high categorical agreement (96.7% and 96.5%) with BMD in determining susceptibility of CRKP isolates to tigecycline, while modified disc diffusion method yielded high categorical agreement (91.0%) with BMD in determining susceptibility of CRAB isolates to tigecycline.

Rationale for recommendation: 1) MIC values provides more accurate susceptibility information of CRGNB to antimicrobial agents, and thus directly influence clinicians' choice of antimicrobial therapy. 2) Although there is a lack of direct evidence demonstrating the impact of MIC results on clinical endpoints (e.g. mortality), the GDG believes MIC results can lead to improved clinical outcomes through improved precision on guiding antimicrobial choice. 3) BMD is the most widely recognized method for determining MIC, but has varied feasibility across different healthcare facilities due to its complexity in laboratory operation. In settings where BMD is unavailable, agar dilution and E-test method are suitable alternatives with relatively high accuracy. Automated antimicrobial susceptibility testing systems can also be used as alternative because they are convenient for use despite the relatively low accuracy.

PICO question 2. should carbapenemases detection (including phenotypic and genotypic tests) be recommended for CRE isolates?

Recommendation: It is suggested to detect carbapenemases of CRE isolates. This can be achieved by phenotypic or genotypic test in healthcare facilities, particularly in settings where the susceptibility results of novel β-lactamase inhibitor combinations such as ceftazidime-avibactam are unavailable (weak recommendation, low-quality evidence).

Implementation consideration: Genotypic test is preferred where possible, and phenotypic test could be used in settings where genotypic test is unavailable. Hospital laboratory could take into consideration of its own specific circumstances to select genotypic and/or phenotypic assay.

Evidence Summary: We included four studies reporting sensitivity and specificity of various phenotypic and genotypic tests in detecting carbapenemases of CRE isolates. For the CRE isolates confirmed by whole genome sequencing (WGS), both reverse transcription-polymerase chain reaction (RT-PCR) and Carba NP tests were highly sensitive (98.0% and 95.9%, respectively) and specific (both 100%) in detecting CRE with less than 3 h turnaround time.[18] Of the 60 carbapenem-resistant Gram-negative bacteria (CRGNB) isolates, 48 were identified to produce carbapenemase. Modified Hodge test and combined disc test (CDT) identified 47 and 48 isolates producing carbapenemases (NDM-1 and KPC), respectively. The loop-mediated isothermal amplification (LAMP) assay of carbapenemase genes showed consistent sensitivity and specificity to CDT in phenotypic test of carbapenemases, with a higher positive detection rate than PCR (44 isolates positive). LAMP assay had a turnaround time of 2–3 h.[19] CDT (meropenem disc plus 3-aminophenylboronic acid or meropenem disc plus EDTA) has a sensitivity of 100% in detecting the isolates producing KPC or metallo-beta-lactamases alone, 96.8% in detecting the isolates producing both KPC and metallo-beta-lactamases, and a specificity of 98.8% in detecting KPC producers.[20] In a recent study including the 247 CRE isolates, the compliance of phenotype results with genetic detection (by PCR amplification method) was 94%, 95%, 98%, and 99%, respectively for CDT, modified carbapenem inactivation method (mCIM)/EDTA-modified carbapenem inactivation method (eCIM), NG-Test CARBA 5 (CARBA), and color developing immunoassay (CDI).[21] However, CDT did not accurately detect IMP and showed a low specificity for carbapenemase detection, low negative predictive value (NPV), and low sensitivity for metallo-β-lactamase (79%, 55%, and 88%, respectively). The sensitivity and specificity of CARBA and CDI were higher than CDT and mCIM/eCIM, but CDI was unable to detect IMP-8.[21] These studies suggest that

phenotypic tests are highly sensitive and specific in detecting carbapenemases and are highly consistent with genotypic tests. Therefore, it is recommended to use CDT and mCIM to detect the phenotype of carbapenemase-producing CRE in the resource-constrained laboratories.

Rationale for recommendation: 1) Vast majority of CREs are carbapenemase-producing isolates. The detection of carbapenemase phenotype or genotype is of great value in predicting the susceptibility of bacteria to carbapenems. Such test results enable clinicians to optimize treatment plan by adjusting antibiotics accordingly. Therefore, the GDG is highly confident that phenotypic/genotypic tests will improve clinical outcomes, despite the lack of direct evidence linking the tests to improvement in clinical outcomes (e.g., mortality). 2) The genotypic and some phenotypic tests are rapid and accurate in detecting carbapenemases, which can inform the clinicians in selection of antimicrobial agents at early stage.

PICO question 3. should antimicrobial synergy testing be performed to support treatment of CRGNB infections?

Recommendation: Antimicrobial synergy testing may be useful for prescribing precise anti-infective drugs for managing CRGNB infections, especially in situations where drug choices are limited (e.g., poor response to monotherapy, conventional susceptibility testing prompts no effective treatment option, or limited treatment option). In such cases, it is suggested to perform antimicrobial synergy test to screen for appropriate combination treatment regimens if possible (conditional recommendation, low-quality evidence).

Implementation consideration: Antimicrobial synergy testing is not routinely performed in clinical microbiology laboratory, therefore, clinicians should ensure adequate communication with laboratory when requesting the test. Appropriate testing method should take into account of local laboratory conditions. If possible, the checkerboard method is preferred, followed by disc elution method, MIC strip crossing or stacking method.

Evidence summary: A systematic review with 136 included studies (using time—kill and pharmacokinetic/pharmacodynamic (PK/PD) methods for testing antimicrobial synergic activities) found significantly enhanced bactericidal activity and lowered emergence of resistant strains with polymyxin- and/or carbapenem-based combinations (with tigecycline, fosfomycin, amikacin),indicating considerable synergistic effect on CRAB, CRKP, and CRPA. This evidence suggests that antimicrobial synergy testing can inform clinicians to prescribe antimicrobial agents for the treatment of CRGNB infections.[22] One study compared methods in testing the activity of ceftazidime-avibactam combined with aztreonam against CRE and CRPA. Taking modified broth microdilution (mBMD) method as reference, the most accurate and reproducible methods were broth disc elution and strip stacking or crossing methods using MIC test strips (MTS), all with 100% sensitivity and specificity, followed by E-test strip crossing (95.8% sensitivity, 100% specificity) or stacking (87.5% sensitivity, 100% specificity). Despite of an 100% specificity value, the sensitivity value of the conventional disc stacking method is only 42.7%. MTS methods yielded higher categorical agreements and lower MEs relative to E-test. This study indicates that broth disc elution method is particularly valuable in resource-constrained laboratories.[23] In the other four studies, different methods of antimicrobial synergy testing (e.g., checkerboard microdilution method, time-killing curve, disc approximation assay) were used to determine the *in vitro* antimicrobial activity of antimicrobial combinations against CRE, CRPA and CRAB. Results showed that some antimicrobial agents were inactive against CRGNB when used alone, but demonstrated good *in vitro* synergistic effect on CRGNB when combined with other antimicrobial agents.[24—27] A study, however, showed that *in vitro* synergism between colistin and meropenem did not translate into clinical benefit in the treatment of severe CRGNB infections.[28]

Rationale for recommendation: 1) Antimicrobial synergy testing can be used to determine *in vitro* activity and synergistic effect of antimicrobial combinations on CRGNB, thus may be informative to clinicians on selection of appropriate antimicrobial combination therapy. 2) Categorical agreement varies across the methods used in antimicrobial synergy testing. Checkerboard assay uses fractional inhibitory concentration (FIC), a quantitative index, to evaluate the level of synergy. It is the most frequently applied standard method but the procedure is complex and inconvenient. Time-killing curve assay is highly accurate but also complex and time-consuming, which hinders its clinical application. Broth disc elution and MTS crossing or stacking methods provide high sensitivity and specificity, and low complexity of operation. Disc stacking method performs poorly in sensitivity. The GDG has moderate level of confidence in the accuracy of antimicrobial synergy test. 3) The GDG believes that test result may be informative to clinicians on optimizing antimicrobial regimen.

Antimicrobial therapy of CRGNB infections

It is highly challenging to treat CRGNB infections. Accurate selection of effective antimicrobial agents and prescription of appropriate dosing regimen play a key role in improving clinical efficacy and reducing adverse reactions. This section focuses on the antimicrobial agents used to treat CRGNB infections, including polymyxins (intravenous and aerosolized preparations), ceftazidime-avibactam, tigecycline and other new tetracycline derivatives, sulbactam and sulbactam-containing combinations, aminoglycosides, and fosfomycin, especially those combination therapies containing these antimicrobial agents. Research evidence on efficacy and safety was collected and analyzed to inform recommendations on treatment.

PICO question 4. should polymyxin combination therapy be preferred over polymyxin monotherapy for treatment of CRGNB infections?

Recommendation: Polymyxin combination therapy is recommended as a preferential choice over monotherapy for treating CRGNB infections in patients who requires polymyxin treatment (strong recommendation, moderate-quality evidence).

Implementation consideration: 1) Patients' renal function should be monitored during polymyxin treatment. The GDG encourages therapeutic drug monitoring (TDM) to be performed for polymyxin where possible. 2) The ototoxic and nephrotoxic drugs (including antimicrobial agents) should be avoided in combination with polymyxin. 3) Polymyxin carbapenem combination may be suggested for treatment of CRGNB infections if meropenem MIC is $\leq$ 8 mg/L for CRE or $\leq$32 mg/L for CRAB, and with an extended-infusion of meropenem for 3h.[9,10] 4) The dose unit of polymyxin is expressed in different ways, so attention should be paid to the correct conversion of dosage. There are two ways to express the dosage of colistin methanesulfonate (CMS): international unit (U) and colistin base activity (CBA) in mg (an active unit, not a mass unit). Dose conversion: 1 million U $\approx$ 80 mg mass CMS $\approx$33 mg CBA; polymyxin B sulfate: 1 mg $\approx$ 10000 U; colistin sulfate: 1 mg $\approx$ 22700 U.

Evidence summary: Six RCTs (N = 876) compared CMS combination therapy versus CMS monotherapy in the treatment of CRGNB infections, two of which investigated ventilator-associated pneumonia (VAP) caused by CRAB (CMS combined with rifampicin, ampicillin-sulbactam),[29,30] one on hospital-acquired pneumonia (HAP)/VAP caused by CRKP (combined with meropenem),[31] one on CRAB infections (78.7% pneumonia, followed by primary bacteremia, urinary tract infection, combined with fosfomycin),[32] one on XDR *A. baumannii* infections (77.5% HAP/VAP, 20.1% bloodstream infection, combined with rifampicin),[33] and one trial on CRAB, CRPA or CRE infections (51.0% HAP/VAP, 42.6% bloodstream infection, combined with meropenem).[34]

Compared to CMS monotherapy, in every 1000 patients receiving CMS combination therapy there might be on average 14 fewer deaths (N = 779, RR = 0.97, 95% CI 0.84–1.13, moderate-quality evidence) (Online supplement Fig. S4.1), probably on average 119 fewer treatment failure (N = 578, RR = 0.82, 95% CI 0.72–0.93, moderate-quality evidence) (Online supplement Fig. S4.2),[29–32,34] might be on average 74 fewer cases of pathogen eradication failure (N = 779, RR = 0.81, 95% CI 0.67–0.98, low-quality evidence) (Online supplement Fig. S4.3),[29,30,32–34] and probably shorter time to microbiological clearance.[29] There were no apparent differences in renal toxicity and hepatotoxicity between groups.[29, 31-33]The AIDA study reported CMS-meropenem combination reduced incidence of mild renal failure (30% vs 20%), but increased incidence of diarrhea (27% *vs* 16%).[34] One RCT on XDR *A. baumannii* infections reported no difference in length of hospital stay between polymyxin monotherapy and combination therapy.[33] SoF available in Online Supplement Table.

A network meta-analysis showed that there was no difference in clinical cure, microbiological cure, and mortality between colistin monotherapy and other combination therapy (including colistin-based combination therapy) for treatment of CRAB pneumonia. Nonetheless, colistin-carbapenem combinations ranked first in improving clinical cure (SUCRA, 91.7%) and second in microbiological cure (SUCRA, 68.7%) among various treatment regimens.[10]

The application of polymyxin and carbapenem combination therapy in the treatment of CRGNB is somewhat controversial. Two recent guidelines[9,10] and a guidance[8] attached specific conditions to the recommendation of this combination. Both guidelines recommend polymyxin-carbapenem combinations for CRE infections when meropenem MIC is $\leq$ 8 mg/L, and high-dose extended-infusion meropenem is used. Polymyxin-meropenem combination is recommended for the treatment of CRAB infections,[8] for CRAB pneumonia and bloodstream infections if carbapenem has *in vitro* synergistic benefit even if carbapenem MIC $\leq$32 mg/L,[10] and for the treatment of moderate to severe CRAB infections with the combination of CMS and high-dose, extended-infusion meropenem with a third agent.[8]

Rationale for recommendation: 1) The benefit of polymyxin combination therapy may outweigh any potential harm, compared to polymyxin monotherapy in the treatment of CRGNB infections, evidenced by lower rates of mortality, treatment failure, and eradication failure. 2) *In vitro* antimicrobial synergy tests demonstrated synergistic effect of polymyxin combinations on CRGNB.[22] 3) Several colistin-based combinations have been shown *in vitro* to prevent the emergence of the resistant subpopulations,but its clinical impact needs further investigation.[35]

PICO question 5. should aerosolized polymyxin be used for treatment of CRGNB respiratory tract infections?

Recommendation: It is suggested using aerosolized polymyxin in addition to intravenous polymyxin in patients with CRGNB respiratory tract infections (weak recommendation, low quality evidence).

Implementation consideration: 1) Aerosolized polymyxin can be considered in addition to intravenous polymyxin when the clinical efficacy is less than desirable. In general, aerosolized polymyxin is not used alone. 2) Currently, no polymyxin preparation is available specifically for inhalation in some countries. CMS is preferred for inhalation therapy, even though all of the three intravenous polymyxin preparations are appropriate (in addition to CMS and polymyxin B sulfate, polymyxin E sulfate is also available in China). Relevant adverse events (especially bronchospasm) caused by inhalation should be monitored closely.

Evidence summary: Seven observational studies (N = 1177)[36–42] compared the efficacy of aerosolized CMS plus intravenous CMS versus intravenous CMS alone (or combined with other intravenous antimicrobial agents) in the treatment of VAP/HAP caused by resistant pathogens such as CRAB/MDR *A. baumannii*, CRPA/MDR *P. aeruginosa*, and CRE (mainly CRKP)/MDR *K. pneumoniae*.[36–40] Six observational studies described the administration of inhaled colistin.[36–40,42] For spontaneously breathing patients or extubated patients, inhaled colistin was delivered by a jet nebulizer,.[36,37,39] vibrating-mesh nebulizer,[40] ultrasonic nebulizer,[39] or with oxygen flow.[38] For patients receiving ventilator support, inhaled colistin was delivered by ventilator,[38,40] vibrating plate nebulizer,[42] or ultrasonic nebulizer.[39] Compared to intravenous CMS alone, intravenous CMS plus aerosolized CMS therapy may be associated with an average of 50 fewer deaths (RR = 0.86, 95% CI 0.72–1.03) (Online supplement Fig. S5.1), 77 fewer clinical

treatment failure (RR = 0.82, 95% CI 0.70—0.96) (Online supplement Fig. S5.2),[36—42] and an average of 62 fewer pathogen eradication failure (N = 607, RR = 0.84; 95% CI 0.69—1.03) (Online supplement Fig. S5.3)[37, 39-42] in every 1000 patients treated, but the certainty of these evidcence are either low or very low, which indicates these effect might be altered by future study. SoF available in Online Supplement Table.

One study showed that aerosolized plus intravenous CMS therapy was associated with significantly fewer days of mechanical ventilation than intravenous CMS alone (8 *vs* 12 days, $P = 0.001$). Aerosolized plus intravenous CMS therapy was an independent predictor of clinical cure.[39] There appears no obvious difference in 28-day ventilator weaning rate between aerosolized plus intravenous CMS therapy and intravenous CMS alone in HAP patients (50.6% vs 44.0%).[36]

Rationale for recommendation: 1) Intravenous polymyxin combined with aerosolized polymyxin may reduce mortality rate, clinical treatment failure, and increase clearance of pathogens. 2) Polymyxin inhalation is relatively simple to operate in clinical practice.

PICO question 6. should ceftazidime-avibactam be preferred over other antibacterial therapies for the treatment of serine carbapenemase-producing CRE infections?

Recommendation: Ceftazidime-avibactam is suggested to treat infections caused by CRE producing serine carbapenemase, including KPC and OXA-48, which may be more effective than other antibacterial therapies (weak recommendation, very low-quality evidence).

Implementation consideration: It is suggested to determine the carbapenemase type and/or ceftazidime-avibactam susceptibility of CRE isolate before initiation of treatment. The application should be a joint decision by doctor and patient in healthcare settings where ceftazidime-avibactam is outside of medical insurance coverage.

Evidence summary: Five observational studies (N = 592) compared the efficacy of ceftazidime-avibactam versus other antimicrobial agents in the treatment of infections caused by CRE,[43—45] CRKP (97% KPC-producing strains),[46] and KPC-producing CRKP.[47] One study characterized the genotypes of CRE isolates (OXA-48 positive in 62%, KPC-positive in 12%, and NDM-positive in 26% of the 61 strains).[45] Infections included bloodstream infection[45,46] and multiple site infections (bloodstream, pulmonary, urinary tract, and intraabdominal infections).[43,44,47] Compared to other antimicrobial therapies, ceftazidime-avibactam may be associated with, on average, 182 fewer deaths (N = 592, RR = 0.55, 95% CI 0.42—0.72) (Online supplement Fig. S6.1),[43—47] 307 fewer treatment failures (N = 247, RR = 0.49, 95% CI 0.34—0.70) (Online supplement Fig. S6.2),[43,45,46] 52 fewer relapse (N = 455, RR = 0.67, 95% CI 0.39—1.14) (Online supplement Fig. S6.3),[43,45—47] 179 fewer pathogen eradication failure (N = 127, RR = 0.37, 95% CI 0.16—0.83) (Online supplement Fig. S6.4),[43,45] and 95 fewer acute renal injury (N = 242, RR = 0.55, 95% CI 0.23—1.33) (Online supplement Fig. S6.4) [44—46] per 1000 patients treated, but due to the low certainty of evidence, these observed effect may change by future studies. Ceftazidime-avibactam had a shorter mean length of ICU stay compared to the control group (44.9 ± 7.6 and 55.9 ± 7.8 days, respectively), but the difference was not significant.[43] Clinical harm associated with ceftazidime-avibactam treatment was not observed in these studies. Quality of the body of evidence derived from observational studies is very low. SoF available in Online Supplement Table.

Rationale for recommendation: 1) In China, the majority of CRE strains, especially CRKP, produce KPC enzymes. Nearly 100% of KPC-producing and OXA48-producing CRE strains are susceptible to ceftazidime-avibactam.[48] 2) Our meta-analysis shows that in patients with CRE infection, ceftazidime-avibactam treatment may reduce the risk of mortality and treatment failure. Incidence of adverse events is low during ceftazidime-avibactam treatment. 3) Although the cost of ceftazidime-avibactam is relatively high, a study demonstrated ceftazidime-avibactam is a cost-effective treatment for CRE bacteremia and pneumonia.[49]

PICO question 7. should ceftazidime-avibactam combined with aztreonam be preferred over other antimicrobial therapies for the treatment of infections caused by metallo-β-lactamases-producing CRE?

Recommendation: Ceftazidime-avibactam combined with aztreonam is suggested as a preferential choice over other antimicrobial therapies for the treatment of infections caused by metallo-β-lactamases-producing CRE (weak recommendation, very low-quality evidence).

Implementation consideration: In practice, the carbapenemase type produced by CRE strain should be ascertained before initiation of ceftazidime-avibactam treatment, whenever possible.

Evidence summary: Aztreonam shows good *in-vitro* synergy activities with ceftazidime-avibactam against NDM-producing and KPC-producing CRKP isolates, as, aztreonam is not hydrolyzed by metallo-β-lactamases.[50,51] One prospective study evaluated treatment outcome of patients with bloodstream infection caused by metallo-β-lactamases-producing CRE.[52] The 30-day mortality rate was 19.2% in 52 patients received ceftazidime-avibactam plus aztreonam and 44% in 50 patients treated with other active antimicrobial agents ($P = 0.007$). Ceftazidime-avibactam combined with aztreonam was associated with lower 30-day mortality rate (HR: 0.37, 95% CI 0.13—0.74), lower clinical treatment failure rate (HR: 0.30, 95% CI 0.14—0.65), and shorter length of hospital stay (HR: 0.49, 95% CI 0.30—0.82).[52] In another study including 57 cases of CRE infection (71.9% critical cases, 57.9% intraabdominal infection and HAP), the curative rate was 77.5% in 40 patients who received ceftazidime-avibactam combined with aztreonam (plus polymyxin or fosfomycin if indicated) for treatment of NDM- or NDM + OXA-48-positive CRE infection, and 82.3% in 17 patients who received ceftazidime-avibactam alone (plus polymyxin or fosfomycin if indicated) for treatment of OXA-48-positive CRE infection, The

overall mortality rate was 21%.[53] Quality of evidence on critical outcomes from these two studies is very low.

Rationale for recommendation: 1) Studies indicate that ceftazidime-avibactam combined with aztreonam is associated with lower mortality rate and clinical treatment failure rate compared to other antimicrobial therapies in treatment of CRE infections. However, the GDG has low confidence in the observed efficacy due to very low certainty of evidence. 2) Aztreonam combines with ceftazidime-avibactam shows good *in-vitro* synergy activities against CRE produces metallo-β-lactamases. 3) Overall, the GDG believes the benefit of ceftazidime-avibactam combined with aztreonam probably outweighs potential harm (very low quality evidence).

PICO question 8. should tigecycline-based combination therapy or polymyxin-based combination therapy be preferred in treatment of CRAB pulmonary infections?

Recommendation: Both tigecycline-based combination therapy and polymyxin-based combination therapy are equally preferable in the treatment of pulmonary infection caused by CRAB. Choice of therapy regimen should be made according to patient's condition (weak recommendation, very low-quality evidence).

Implementation consideration: 1) In practice, the GDG suggests choice of antimicrobial regimen should balance strength and weaknesses of tigecycline-based and polymyxin-based combination therapy based on the clinical conditions. 2) It is suggested to determine the MIC value of tigecycline against CRAB before treatment initiation. Studies indicated that tigecycline treatment achieved higher success rate when MIC is $\leq$ 2 mg/L[54] 3) Polymyxin should be used judiciously in patients with renal insufficiency and tigecycline should be used cautiously in patients with liver insufficiency.

Evidence summary: Seven retrospective observational studies (N = 745) evaluated the efficacy of tigecycline-based versus CMS-based antimicrobial therapies in treatment of infections caused by CRAB, MDR, or XDR *A. baumannii*, five of which were pulmonary infection,[54–58] and two studies on multiple site infections with pulmonary infection accounting for 74.5%[59] and 50.5%[60] of patients. The antimicrobial regimens were primarily antimicrobial combinations (e.g., in combination with carbapenems, sulbactam, aminoglycosides, rifampicin, minocycline, doxycycline, or fosfomycin).

Compared to CMS-based combination therapies, tigecycline-based therapy was associated with an average of 58 more deaths (N = 658, RR = 1.12, 95% CI 0.95–1.33) (Online supplement Fig. S8.1), an average of 90 more clinical treatment failure (N = 190, RR = 1.17, 95% CI 0.91–1.51) (Online supplement Fig. S8.2)[57–59] and an average of 225 fewer nephrotoxicity (N = 383, RR = 0.23, 95% CI 0.11–0.46) (Online supplement Fig. S8.3)[54, 55, 58, 59] in every 1000 patients treated, but due to the low and very low certainty of evidence, the observed differences between groups may be changed by future studies. A retrospective observational study showed that pathogen eradication rate did not show significant difference between tigecycline-based and CMS-based treatment groups (23% vs 30%, *P* = 0.54).[58] Another study reported that the clinical efficacy of tigecycline was associated with its MIC value against MDR *A. baumannii*. Its efficacy was comparable to polymyxin when tigecycline MIC $\leq$2 mg/L, and inferior to polymyxin when tigecycline MIC >2 mg/L.[54] One study reported that tigecycline-based therapy was associated with significantly lower incidence of nausea and vomiting (6.3% vs. 35.9%, P = 0.025; N = 55), but significantly higher incidence of abdominal pain (18.8% vs. 2.6%, P = 0.036; N = 55), and possibly higher but statistically insignificant incidence of other adverse events, such as thrombocytopenia and aspartate aminotransferase elevated.[59] These retrospective studies were of very low-quality evidence. SoF available in Online Supplement Table.

Tigecycline is a broad-spectrum antibiotic which can potentially reach high tissue concentration, for example, the concentration of tigecycline in lung was 2 times higher than the simultaneously concentration in serum.[61] Tigecycline is recommended for treatment of pulmonary and intra-abdominal infections caused by CRAB and CRE.[7,8,9,10] The *in vitro* antibacterial activity of eravacycline was 2–8 times higher than that of tigecycline against CRAB and CRE. Eravacycline showed higher concentration in lung tissue and lower incidence of adverse events than tigecycline. Therefore, eravacycline appears to have advantages over tigecycline,[62,63] the clinical efficacy of which requires further studies to confirm.

Rationale for recommendation: 1) Both tigecycline-based and polymyxin-based combination therapies have their unique strengths and weaknesses. Tigecycline-based combination therapy may reduce the incidence of adverse events such as nephrotoxicity, but its efficacy is numerically lower than polymyxin-based combination therapy. 2) Current evidence is derived from observational studies and deemed to be very low quality, therefore the GDG is uncertain about the observed magnitude of effect.. 3) Combination therapy including two *in vitro* active antibiotics such as polymyxin, tigecycline, eravacycline is recommended for the treatment of CRAB infection in the ESCIMD and IDSA guidelines.[8,9,10] Overall, the GDG believes either tigecycline-based or polymyxin-based combination therapy can be used for treatment of CRAB pulmonary infections as clinically indicated.

PICO question 9. should sulbactam-containing combination or non-sulbactam-containing combination be recommended for the treatment of CRAB infections?

Recommendation: Sulbactam or sulbactam-containing β-lactamase inhibitor combination therapy regimens are suggested for the treatment of CRAB infections (weak recommendation, low-quality evidence).

Implementation consideration: 1) In clinical practice, sulbactam or sulbactam-containing β-lactamase inhibitor combination is usually augmented with tigecycline, polymyxin, doxycycline, or minocycline according to the results of antimicrobial susceptibility testing. 2) The sulbactam-containing combination therapy is not indicated for

patients who are hypersensitive to penicillin. 3) The dose of sulbactam can be increased to 6.0—9.0 g/d for severe CRAB infections.

Evidence summary: Of the four RCTs investigating VAP caused by CRAB or MDR *A. baumannii* (N = 142),[30,64—66] three used ampicillin-sulbactam-based combination therapy (combined with intravenous or aerosolized polymyxin, meropenem), and one used ampicillin-sulbactam alone. Intravenous polymyxin alone or in combination with aerosolized polymyxin or meropenem was used as control groups. Compared to the control groups, ampicillin-sulbactam-based therapies had an average of 103 fewer 28-day mortality (RR = 0.77, 95% CI 0.51—1.15) (Online supplement Fig. S9.1), 140 fewer treatment failure (RR = 0.72, 95% CI 0.49—1.04) (Online supplement Fig. S9.2), 255 fewer pathogen eradication failure (RR = 0.49, 95% CI 0.31—0.77) (Online supplement Fig. S9.3), and 134 fewer acute renal injury (N = 103, RR = 0.54, 95% CI 0.25—1.14) (Online supplement Fig. S9.4)[64-66] per 1000 patients. All of the above were of low quality of evidence, indicating the observed effect could be altered by future studies. SoF available in Online Supplement Table.

One retrospective study in China included 210 cases of CRAB bloodstream infection showed that cefoperazone-sulbactam group had significantly lower 28-day mortality rate (29.3%, 22/75) than tigecycline group (51.9%, 70/135) (P = 0.001), and cefoperazone-sulbactam combined with imipenem-cilastatin had significantly lower mortality than cefoperazone-sulbactam alone (P = 0.048).[67] One systematic review with 29 included studies (N = 2529 patients) reported no clear difference among various antimicrobial regimens in the treatment of infections caused by MDR/XDR *A. baumannii*. However, polymyxin plus sulbactam-containing combination resulted in higher pathogen eradication rate than polymyxin combined with tigecycline, and safety was comparable to polymyxin monotherapy.[68] Another systematic review with 18 included studies demonstrated that high-dose sulbactam (≥6 g/d) in combination with tigecycline or levofloxacin achieved higher clinical cure rate and efficacy rate than other antimicrobial regimens, while polymyxin-based combination therapy group had higher risk of nephrotoxicity than other antimicrobial treatments.[69]

Rationale for recommendation: 1) Sulbactam-containing combination therapies demonstrated clinical benefits. 2) Ampicillin-sulbactam and cefoperazone-sulbactam are the two sulbactam combination available, while the former is used worldwide, the latter is mainly used in some Asian countries. The most frequently prescribed β-lactamase inhibitor in China is cefoperazone-sulbactam, because the *in vitro* antimicrobial susceptibility testing demonstrated that *A. baumannii* isolates in China were more susceptible to cefoperazone-sulbactam than to ampicillin-sulbactam (resistance rates 48.8% *vs* 59.1% in 2021).[3,4] 3) With consideration to the above, the GDG believes the aforementioned interventions is likely to produce clinical benefit despite of the low quality of evidence.

PICO question 10. Should aminoglycosides-containing combination therapy be recommended for improving clinical efficacy of CRE infections?

Recommendation: Combination therapies containing amikacin or other aminoglycosides are suggested for treatment of CRE infection in patients without contraindication for aminoglycoside use. (conditional recommendation, very low quality evidence).

Implementation consideration: The use of aminoglycoside can lead to ototoxicity and nephrotoxicity, so patient should be monitored closely for any potential adverse effects during treatment. Other nephrotoxic drugs should be avoided in the combination regimen. It is suggested that TDM should be performed during aminoglycoside treatment if available, especially when high dose is administered. CRE strains may show highly variable susceptibility to different aminoglycoside drugs. For example, CRE isolates in China showed significantly higher susceptibility to amikacin than to gentamicin.[4] Aminoglycosides should be prescribed appropriately according to the results of local antimicrobial susceptibility testing.

Evidence summary: We included nine observational studies on CRE infection (N = 608 patients) with aminoglycoside-containing regimens for the treatment of bloodstream infection,[70—74] urinary tract infection,[75] multiple infections (bloodstream, pulmonary, urinary tract, surgical site, intraabdominal, and skin and soft tissue infection).[76—78] The therapy regimens includes gentamicin (N = 174),[70,77] amikacin (N = 160),[71,72,76,78] both gentamicin and amikacin (N = 274),[73—75] as well as combination therapies (e.g., in combination with tigecycline, polymyxin, carbapenem, or fosfomycin). The antimicrobial regimens used in control groups include tigecycline-, polymyxin-, or fosfomycin-containing combination therapies.

Compared with combination therapies without aminoglycosides, aminoglycoside-containing combination therapy had an average 59 fewer deaths (N = 525, RR = 0.86, 95% CI 0.69—1.07) (Online supplement Fig. S10.1),[70—74,76—78] and had 417 fewer clinical treatment failure (N = 84, RR = 0.41, 95% CI 0.25—0.69) (Online supplement Fig. S10.2)[75, 76] per 1000 patients in the treatment of CRE infection, but the certainty of evidence are very low indicating future studies may well change the current observed effect. There were no adverse events reported in these studies relating to aminoglycoside-containing combination therapy. However, the quality of evidence derived from these studies is very low, which limits our confidence in the estimates of effects. SoF available in Online Supplement Table.

Rationale for recommendation: 1) Aminoglycoside-containing combination therapy may improve curative rate and reduce mortality rate in the treatment of CRE infections. 2) Aminoglycosides are easily accessible and inexpensive. 3) With consideration to the above, the GDG concludes that the clinical benefits probably outweigh any potential harms in patients without contraindications to aminoglycoside use, despite of low quality of evidence.

PICO question 11. Should intravenous fosfomycin-containing combination therapy be recommended for patients with CRE infections?

Recommendation: It is suggested to use intravenous fosfomycin-containing combination therapies for patients with CRE infection when CRE isolate is susceptible to fosfomycin or fosfomycin combination has synergistic effect on the CRE isolate (conditional recommendation, very low-quality evidence).

Implementation consideration: 1) Before treatment initiation, pathogens should be confirmed to be susceptible to fosfomycin through antimicrobial susceptibility testing or fosfomycin-containing combination has synergistic effect confirmed by antimicrobial synergy testing. 2) Patients with hypernatremia, cardiac or renal insufficiency should avoid use of fosfomycin.

Evidence summary: Fosfomycin susceptibility rates in CRKP are variable, from 39% to 99%.[79] *fosA*-like genes may be prevalent in CRKP causing fosfomycin resistance.[50,80] Fosfomycin presents synergistic *in-vitro* activity against CRKP even if against CRKP strains carrying *fosA*-like genes.[50] Four observational comparative studies (N = 213, including one study of neonatal infection)[70,81–83] compared the efficacy of fosfomycin-containing combination therapies versus other antimicrobial combinations in the treatment of CRKP infection, including sepsis, bacteremia, urinary tract infection, or multiple infections. The antimicrobial agents used to combine with fosfomycin included tigecycline, polymyxin, and carbapenems. Compared to the control groups, fosfomycin-containing combination therapy had an average of 114 fewer deaths (RR = 0.55, 95% CI 0.28–1.10) (Online supplement Fig. S11.1) per 1000 patients in the treatment of CRKP infections (very low-quality evidence).[70,81–83] Due to the very low certainty in evidence, the current observed effect may be changed by future studies. SoF available in Online Supplement Table.

One Italian study compared the outcomes of ceftazidime-avibactam plus fosfomycin combination with ceftazidime-avibactam plus other antimicrobials in the treatment of bloodstream infections caused by KPC-producing *K. pneumoniae* (KPC-Kp). It found no difference in overall mortality between these two groups, while the control group had more new non-bloodstream KPC-Kp infections and a higher number of deaths attributable to secondary infections.[84] One single-arm observational study in Greece reported 48 ICU patients with CRKP and CRPA infection (including bloodstream infection and VAP) who received fosfomycin-containing combination therapy, primarily in combination with polymyxin or tigecycline.[85] In this study, all the bacterial isolates were susceptible to fosfomycin, the treatment efficacy was 54.2%, the bacterial eradication rate was 56.3%, the 28-day mortality rate was 37.5%, and the main adverse reaction was reversible severe hypokalemia (15.2%). Antimicrobial resistance emerged during treatment in 3 patients.[85] A systematic review suggests that intravenous fosfomycin is generally safe and the adverse reactions are mild in general.[86]

Rationale for recommendation: 1) Fosfomycin has synergistic *in vitro* activity against CRKP. 2) Evidence derived from observational studies suggests that fosfomycin-containing combination therapy may reduce mortality rate in treatment of CRE infections. However, the quality of evidence is very low indicating low certainty in the treatment efficacy and clinical benefit. 3) The adverse reactions of fosfomycin are mostly reversible. Fosfomycin treatment is generally safe. After comprehensive assessment of the balance between benefit and harm, the GDG believes that fosfomycin-containing combination therapy probably yields more benefits than harm.

PICO question 12. Should antimicrobial TDM be performed during the treatment of CRGNB infections?

Recommendation: It is suggested to perform TDM where possible in patients receiving polymyxins, aminoglycosides, or carbapenems for treatment of CRGNB infections (weak recommendation, very low quality evidence).

Implementation consideration: Antimicrobial TDM has important clinical value in treatment of CRGNB infections, especially in critical cases of CRGNB infections. Antimicrobial TDM should be carried out whenever possible in the following cases: 1) Narrow therapeutic index drugs including polymyxins and aminoglycosides, for which, small differences in dose or blood concentration may lead to serious therapeutic failures and/or adverse drug reactions that are life-threatening or result in persistent or significant disability or incapacity[87] 2) Antimicrobial agents, the dosage of which is difficult to adjust in case of organ dysfunction or hyperfunction, such as renal insufficiency or hyperfunction; 3) The sites of infection that are difficult to reach effective therapeutic concentration, such as central nervous system, and severe infections, such as bloodstream infection and sepsis.

Evidence summary: One systematic review with two RCTs and three retrospective comparative cohort studies evaluated the effect of carbapenems TDM on the treatment outcome in adults with severe infection, sepsis, or septic shock. The results indicated that TDM may be associated with therapeutic target attainment and clinical cure rate (clinical cure was defined as 80% of reduction in procalcitonin level or favorable outcome and resolution of infection), but may not be associated with reduction of mortality rate (low quality evidence).[88] In a report involving 30 cases of infection caused by KPC-producing CRKP, meropenem MIC was $\geq$16 mg/L for the CRKP strains isolated from 16 (53.3%) patients who received continuous intravenous infusion of high dose meropenem combined with polymyxin or tigecycline. The dosage was adjusted according to real-time TDM, leading to treatment success rate of 73.3% after a median treatment of 14 days. The clinical efficacy was significantly correlated to Css/MIC ratio $\geq$1. This study suggests that real-time TDM can improve the outcome of patients who receive continuous IV infusion of high dose meropenem combination therapy for treatment of CRKP infection.[89]

In 2020, several international societies jointly issued a position paper on the antimicrobial TDM for critically ill patients, recommending TDM for aminoglycosides and β-lactams including carbapenems, and neither supporting nor

opposing polymyxin TDM. Aminoglycoside TDM can optimize dosing regimen, improve treatment efficacy, and reduce incidence of nephrotoxicity during the treatment of gram-negative bacterial infections in critically ill patients.[90] One study reported that TDM-guided gentamicin treatment (n = 105) was associated with shorter hospital stay (20.0 ± 13.7 vs 26.3 ± 31.5 days), lower mortality rate (8.6% vs 14.2%), and lower incidence of nephrotoxicity (2.8% vs 13.4%) compared with non-TDM-guided gentamicin (n = 127) in the treatment of Gram-negative bacterial infections.[91]

In 2019, the international consensus on optimal application of polymyxins recommended that TDM should be carried out for clinical use of polymyxins, which can optimize dosage, improve clinical efficacy, and reduce adverse reactions.[92] An international multicenter study showed that 162 critically ill patients with various levels of renal function received polymyxin E treatment at the dose recommended by the U.S. Food and Drug Administration (FDA) or European Medicines Agency (EMA), resulting in highly variable rates of reaching average plasma steady-state concentration ($C_{ss,avg}$). The dose recommended by the EMA achieved higher rate of attaining therapeutic target than the dose recommended by the FDA. For patients with creatinine clearance rate ≥80 ml/min, both recommended doses yielded $C_{ss,avg} \geq 1$ mg/L in only 65%–75% of the patients.[93] This study suggests that TDM is necessary in critically ill patients to adjust the individualized doses of polymyxins to reach effective target therapeutic concentration.

Rationale for recommendation: As demonstrated by the above evidence, TDM can inform clinicians to prescribe timely and precise dosing regimen, the GDG concludes that TDM probably results in more benefits than harms. TDM should be performed as far as possible for the main categories of antibiotics used to treat CRGNB infections.

Prevention and control of nosocomial infections caused by CRGNB

CRGNB infections are mostly hospital-acquired. Effective implementation of infection control measures is paramount in the prevention and control of CRGNB infections. This section investigates the effect of measures such as active CRE screening and contact isolation, decolonizing intestinal CRE, and sink design and placement in hospital units on the prevention and control of CRGNB.

PICO question 13. Should active CRE screening be performed in hospital settings, particularly for patients with hematologic malignancy, be recommended to receive CRE screening before chemotherapy or transplantation?

Recommendation: It is recommended to actively screen for CRE carriage in the following populations in hospital setting (conditional recommendation, very low quality evidence): 1) patients with a history of CRE colonization/infection; 2) patients sharing hospital wards with other patients who have CRE colonization/infection; 3) patients who are expected for ICU admission (including neonatal ICU) for greater than 2 days; 4) patients with hematologic malignancy before chemotherapy, solid organ, bone marrow or hematopoietic stem cell transplantation, and febrile neutropenic patients.

Implementation consideration: The decision to perform active CRE screening and in which populations to perform screening is determined by individual healthcare facilities, with reference to the actual local situations, specific needs and feasibility in the individual facilities (e.g., prevalence of CRE in specific population, distribution pattern in each ward/department, screening tests and methods available locally). It is suggested to collect feces for CRE screening from patients with low platelet count or rectal/perianal lesions (such as abscess or ulcer). Selective culture media can be used for bacterial culture. Genetic testing for carbapenem resistance can also be used in health care facilities if possible.

Evidence summary: A systematic review re-analyzed 17 studies meeting the effective practice and organization of care (EPOC) criteria and interrupted time series (ITS) design. The results of which indicates that bundle interventions including active screening for infection prevention and control could reduce incidence of CRE, CRAB and CRPA infection or colonization.[94] Nine CRE-related studies demonstrated that series of interventions including active screening significantly reduced the incidence of CRE infection or colonization (slope change: −0.01 to −3.55, level change or immediate change: −1.19 to −31.80). Four studies showed that the incidence of CRE infection per 10000 patient-days reduced significantly after interventions (slope change: −0.32 to −3.55, level change: −1.19 to −31.80). A study in Israel demonstrated that weekly active screening of intestinal CRKP in addition to contact precautions for hospitalized patients in ICU and in step-down units during an outbreak of CRKP infection decreased the rate of CRKP infection in high-risk units by 4.7-fold at 17 months after implementation of active screening intervention.[95] The evidence currently available is derived from observational studies with relatively high risk of bias. Moreover, it is difficult to accurately judge what proportion of the observed clinical benefits is directly related to screening. Due to the lack of direct evidence, the body of evidence for critical outcomes is of very low quality.

Three before-and-after intervention studies (N = 2971) in China[96–98] evaluated the effect of CRE screening (continuous or one-off) versus no screening in patients undergoing hematopoietic stem cell transplantation, receiving chemotherapy or immunotherapy. Active CRE screening on average reduced 13 cases of CRE infection (RR = 0.47, 95% CI 0.29–0.77) (Online supplement Fig. S13.1) and 12 deaths (RR = 0.32, 95% CI 0.16–0.64) (Online supplement Fig. S13.2) in every 1000 patients compared to no active screening. The quality of the body of evidence is very low. SoF available in Online Supplement Table.

Rationale for recommendation: 1) Studies on active CRE screening consistently show that the incidence of CRE infection decreases significantly with implementation of screening, suggesting such an intervention may bring some clinical benefits. 2) Active CRE screening using conventional methods (such as collecting feces or rectal swabs) is

feasible and acceptable in most healthcare facilities. 3) Active screening may incur additional health resource consumption and potential harms (such as mucosal damage caused by rectal swab sampling). The space for isolation of CRE carriers is very limited in many medical institutions. Overall, the GDG agrees that active screening is favorable because its benefits outweigh costs and harms.

PICO question 14. Should bundle interventions including contact isolation of CRGNB infected patients/carriers be implemented to prevent CRGNB infections?

Recommendation: It is recommended to adopt bundle intervention scheme including single room or cohorting isolation for patients with CRGNB infections or colonization in hospital settings (strong recommendation, low quality evidence).

Implementation consideration: 1) Single room isolation is preferred, and separate toilet should be provided for those infected/colonized with CRGNB. 2) When resource is limited (e.g. too many patients requiring isolation while too few rooms available), priority of single room isolation should be given to those with fecal or urinary incontinence, using invasive device/equipment, or having continuous wound secretion; cohorting isolation for those infected or colonized with the same CRGNB species. 3) Nursing staffs designated to care for patients with CRGNB infections or colonization should not participate in caring for other patients (Nursing staff cohorting). 4) It is recommended that no caregivers be permitted to stay in the ward to care for the isolated patients.

Evidence summary: Bundle management measures such as contact isolation and active screening are closely linked to the prevention and control of nosocomial infection. Usually, the first step is screening, followed by isolation. Therefore, the evidence and conclusions of several studies are the same as those in PICO 13.[94] Three CRAB-related studies showed that multiple interventions including isolation of infected/colonized individuals reduced the rate of CRAB infection/colonization significantly (slope change from −0.01 to −4.81).[94] Multiple interventions including isolation reduced the rate of CRPA infection/colonization significantly (slope change: −1.36).[94] A study in a Korean hospital demonstrated that active contact precautions and isolation combined with intensive hand hygiene education and active monitoring significantly decreased the rate of CRE infection or colonization.[99] A Chinese study reported that active screening of CRE colonization was implemented for the hospitalized children across CRE high-risk departments (pediatric ICU, neonatal ICU, and hematology), and more than 80% of the CRE-positive neonates were isolated in single room or cohorting isolation. These interventions reduced the incidence of nosocomial CRE infection from 1.96% to 0.63% in neonatal ICU, from 0.57% to 0.30% in general neonatal wards ($P < 0.05$). However, in the same period, the rate of nosocomial CRE infection showed no significant change in other non-neonatal wards where isolation was not implemented.[100] The evidence currently available is derived from observational studies. The evidence is somewhat indirect, and the quality of the evidence for critical outcomes is low or very low.

Rationale for recommendation: 1) Although no high-quality RCT has been conducted to explore this clinical question, observational studies consistently show that bundle management scheme including contact isolation may reduce the rate of CRGNB infection or colonization in hospitalized patients. 2) Expert experience derived from clinical practice shows that bundle management including isolation is generally well accepted during clinical management, and it is feasible in most medical institutions. However, the feasibility of single room isolation is poor in some countries, and no sufficient single rooms are available for CRGNB-infected/colonized patients in most medical institutions. 3) Isolation may cause psychological discomfort in some patients and increase consumption of health resources, particularly single room isolation. The GDG agrees that clinical adoption of bundle management scheme including isolation results in more benefits than harm.

PICO question 15. Should patients with CRE colonization, particularly those with hematologic malignancy be recommended for intestinal CRE decolonization?

Recommendation: The GDG does not support or refute intestinal CRE decolonization in clinical practice (no recommendation, low quality evidence).

Implementation consideration: The evidence currently available is insufficient to either support or refute intestinal CRE decolonization. Intestinal decolonization should be considered on individual case basis, and fully evaluate its potential benefit (the possibility of progression to infection, e.g., whether the patient is in a state of serious immunodeficiency or poor immunity) and harm (impairing the intestinal flora and causing collateral damage). At present, no definitely effective protocol is available for decolonization.

Evidence summary: Two RCTs (N = 192)[101,102] and one observational before-and-after controlled study (N = 221)[103] from Israel evaluated the effect of intestinal CRE decolonization. The regimen for decolonization included oral gentamicin or polymyxin E alone or in combination for 7 or 60 days,[101,102] oral gentamicin or amikacin combined with neomycin for 10 days or until discharge.[103] These RCTs demonstrated that intestinal CRE decolonization is effective and on average reduced 238 all-cause deaths (RR = 0.50, 95% CI 0.31–0.82) (Online supplement Fig. S15.1) and increased 296 cases of successful eradication (RR = 3.58, 95% CI 2.16–5.94) (Online supplement Fig. S15.2) per 1000 patients compared to the control groups.[101,102] The quality of overall evidence is low. Another before-and-after controlled study indicated that CRE decolonization was ineffective. The rate of intestinal CRE eradication was comparable between the intervention group receiving decolonization and the control group. The median days to intestinal CRE eradication was 72 days in the decolonization group and 65 days in the control group, respectively.[103] SoF available in Online Supplement Table.

Rationale for recommendation: 1) Current evidence indicates that intestinal CRE decolonization may reduce all-cause mortality, but the quality of evidence is low, and the GDG has low certainty on the observed effect. 2) Intestinal CRE decolonization is likely to be cost-effective without prominent negative impact on the consumption of health resources. 3) Based on their clinical experience, the GDG suggests that intestinal CRE decolonization is relatively well acceptable and feasible in clinical settings. The potential obstacle to feasibility is the lack of clinical research evidence on the best decolonization protocol, thus no consensus is available for the time being.

PICO question 16. Should handwashing sink be removed from areas directly related to patient's treatment for the purpose of CRGNB prevention and control?

Recommendation: It is suggested to remove sink from areas directly related to patient's treatment (e.g., ward, treatment room where invasive procedures are performed) under the following conditions (conditional recommendation, low quality evidence): 1) healthcare facilities under construction or reconstruction, where the above recommendation can be incorporated; 2) In existing healthcare facilities, if resources permit, handwashing sinks should be removed from areas directly related to patient's treatment in wards at high risk of CRGNB infection, such as ICUs, neonatal, hematology, burns and other wards where handwashing sink has been installed.

Implementation consideration: 1) Sink/basin dedicated to handwashing can be placed outside the area for patient management, for example, corridor outside the ward, medical staff working areas. 2) For wards at high risk of CRGNB infections and already equipped with a sink, the sink should be removed or relocated as far away from the patient's bedside as possible; If it is not feasible to adjust the location, consider installing a baffle made of smooth, disinfectant resistant and moisture-proof materials on the side of the sink, and the height should be sufficient to prevent water from splashing out of the baffle. 3) The handwashing sink/basin should be used only for hand hygiene, and should not be used for disposing body fluid and excreta, cleaning equipment and other purposes.

Evidence summary: A 6-year longitudinal observational study[104] in Spain showed that in an ICU, implementation of interventions such as removal of all sinks, implementation of water-safe policy, medical staff hand hygiene, and environmental cleaning reduced annual incidence rate of MDR GNB (*K. pneumoniae* and *P. aeruginosa*) infection from 9.15 per 1000 patient-days before removal of sinks to 2.20 per 1000 patient-days after removal of sinks. The spread of resistant bacteria was successfully contained.[104] A before-and-after controlled study demonstrated that removal of sinks in ICU and introduction of "water-free patient care" significantly reduced rate of GNB colonization in ICU patients, from 26.3 to 21.6 per 1000 ICU patient-days (RR = 0.82, 95% CI 0.67—0.95). The reduction in GNB colonization rate became more pronounced in patients with a longer ICU-Length of Stay (LOS): from a 1.22-fold reduction (≥2 days), to a 1.6-fold (≥5 days; P = 0.002), 2.5-fold (for ≥10 days; P < 0.001) to a 3.6-fold (≥14 days; P < 0.001) reduction.[105] A quasi-experimental study in Spain investigated the prevalence of non-fermenting gram-negative bacilli in bronchoaspirate samples in ICU before and after sink removal and found that the incidence density ratio decreased significantly from 11.28/1000 to 1.91 isolates/1000 ventilated days (deceased 5.90 times, 95% CI: 1.49—51.05, P=.003).[106]

Rationale for recommendation: Contaminated sink promotes spread of drug-resistant bacteria and outbreak of infection in hospital.[107] Current evidence shows that removal of handwashing sinks may reduce the risk of transmission and infection of drug-resistant bacteria in ICU, although the quality of evidence is low, indicating uncertainty on the observed effect. However, the GDG believes that benefit of removing handwashing sink may outweigh any potential harm. Feasibility of removing sink varies across hospitals, and likely to incur additional costs, which must be considered when implementing the recommendation.

Conclusions

Antimicrobial resistance (AMR) is a major threat to human health. Healthcare professionals have to address the increasing challenge of CRGNB in clinical practice. This CPG used a rigorous approach to produce 16 recommendations relevant to the diagnosis, treatment, and prevention of CRGNB infection. Its strength includes adherence to the requirement for trustworthy guideline, and the application of the WHO endorsed GRADE EtD framework which reinforces transparency in this process. The transparency in production and reporting promotes scientific discourse and improves usability of this guideline for clinicians in various settings. The GDG recognizes the lack of high-quality evidence for some recommendations is a limitation of this CPG, but tried to take this in to consideration in forming recommendations. Further studies orientated by clinical problems will be needed to address knowledge gaps and help inform the choice of optimal antimicrobial therapy for CRGNB infections, assess the utility of *in vitro* testing and infection prevention control measures to predict clinical outcomes.

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Declaration of competing interest

All authors have no conflict interest to declare.

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Appendix A. Supplementary data

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