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Special Article

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Guidelines for Antibacterial Treatment of Carbapenem-Resistant Enterobacterales Infections

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ABSTRACT

This guideline aims to promote the prudent use of antibacterial agents for managing carbapenem-resistant Enterobacterales (CRE) infections in clinical practice in Korea. The general section encompasses recommendations for the management of common CRE infections and diagnostics, whereas each specific section is structured with key questions that are focused on antibacterial agents and disease-specific approaches. This guideline covers both currently available and upcoming antibacterial agents in Korea.

Keywords: Carbapenem-resistant Enterobacterales; Antibacterial agents; Practice guideline

INSTRUCTIONS FOR THE USE OF THE GUIDELINE

This guideline suggests customized fundamental principles for the antibacterial therapy of carbapenem-resistant Enterobacterales (CRE) infections tailored to the Korean context, considering the country's antibiotic resistance landscape and drug availability. These practice guidelines provide reference materials for physicians treating patients by considering individual circumstances, rather

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than generic application and thus should not be used as a standard reference for evaluating the appropriateness of clinician judgment. This guideline is intended for use in individual clinical settings and medical education and should not be utilized for the promotion of specific agents or for judging the appropriateness of treatment in medical litigation. For use besides treatment or education, a formal request for permission must be submitted to the Guideline Development Committee.

1. Background and Purpose

Since the advent of antibiotics, antibiotic-resistant bacteria have emerged relentlessly, with increasingly shorter timeframes for the development of resistance to newer antimicrobials. CRE are Enterobacterales resistant to one or more carbapenem antibiotics, such as imipenem, meropenem, doripenem, and ertapenem [1]. Since the first report in 1980, the incidence of resistance has surged, prompting the World Health Organization to classify CRE as a critical-priority pathogen and emphasize the need for effective CRE treatment [2]. According to the 2021 annual report on antibiotic resistance in Korea, 1% of *Klebsiella pneumoniae* isolated from urine in long-term care hospitals showed meropenem resistance, whereas, in secondary hospitals, the proportion of urinary *K. pneumoniae* carrying the *K. pneumoniae* carbapenemase (KPC) – a key enzyme that confers carbapenem resistance – increased sharply to 6.2% in 2021 [3]. CRE infections have been increasing annually since the implementation of the mandatory surveillance system in June 2017, with 30,548 cases reported in 2022, compared to 11,954 in 2018; of these 71.0% (21,695 cases) were identified as carbapenemase-producing Enterobacteriaceae (CPE) infections. Accordingly, the management and treatment of CRE and CPE infections have become significant public health challenges in Korea [4].

The United States (US) and Europe established CRE practice guidelines in 2021 and 2022, respectively, prioritizing novel antibiotics for moderate–severe infections based on their activity and efficacy against CRE [5, 6]. As of January 2024, novel CRE treatments, such as β-lactam-β-lactamase-inhibitor (BLBLI), cefiderocol, eravacycline, and plazomicin, have limited availability in Korea, with unresolved issues regarding insurance coverage and pricing. Despite monotherapy or combination therapy with the available drugs in clinical practice in Korea, there is currently no Korean practice guidelines for CRE infections. This guideline aims to provide a foundation for the effective use of both existing and novel agents and to establish practice guidelines accordingly.

2. Formulation of key questions and consensus development

A systematic review of the clinical studies and treatment guidelines of CRE infections was conducted, using primary databases, such as PubMed, Cochrane Library, and EMBASE, and the Korean databases, Korean Medical Database and the Research Information Sharing Service. The Guideline Development Committee, comprising ten infectious-disease specialists and one laboratory medicine specialist, finalized the key questions for this guideline after several meetings. Three experts in literature search conducted systematic searches using a combination of controlled vocabulary (MeSH terms for PubMed and Cochrane Library, Emtree terms for Embase) and natural language in a sensitive search strategy tailored to each key question. The selected references were reviewed, and a total of 151 references were cited in this clinical practice guideline.

3. Strength of recommendation and level of evidence

The level of evidence and strength of recommendation were determined using the Grading of Recommendations Assessment, Development and Evaluation approach. The level of evidence was classified into high, moderate, low, and very low, whereas the strength of recommendation was categorized as strong or weak [7].

4. External expert review

The draft recommendations prepared through internal meetings of the Guideline Development Committee were reviewed by an advisory committee comprising five infectious disease specialists. Feedback on the recommendations was gathered through academic conference presentations, roundtable discussions, and research review meetings. The discussed content was revised and supplemented through additional internal meetings of the Guideline Development Committee. The Korean Society of Infectious Diseases and the Korean Society for Antimicrobial Therapy reviewed and approved these guidelines before publication.

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RECOMMENDATIONS

Summary of key questions

General recommendations	
1	What are the general recommendations for the treatment of CRE infections?
2	What are the general recommendations for CRE genotype testing?
Part I. Antibiotic-specific recommendations	
3	What is the role of tetracycline in the treatment of CRE infections?
4	What is the role of polymyxin in the treatment of CRE infections?
5	What is the role of carbapenem in the treatment of CRE infections?
6	What are the roles of other antibiotics (*e.g.*, fluoroquinolones, aminoglycosides) in the treatment of CRE infections?
7	What is the role of combination therapy in the treatment of CRE infections?
Part II. Disease-specific recommendations	
8	What is the preferred antibiotic treatment for CRE urinary tract infections?
9	What are the recommendations for the treatment of complicated intra-abdominal infections caused by CRE?
10	What are the recommended antibiotics for the treatment of CRE infections (*e.g.*, bacteremia or pneumonia) other than urinary tract infections and complicated intra-abdominal infections?

1. Recommendations for each key question

Key question 1. What are the general recommendations for the treatment of CRE infections?

1. For hospitalized patients, obtain at least two sets of blood cultures and collect samples from the suspected infection site for culture [Strength of recommendation: strong, Level of evidence: low].
2. If the infection source is identifiable and controllable, actively manage the infection source [Strength of recommendation: strong, Level of evidence: moderate].
3. Determine CRE-infection treatment strategies according to the infection site (*e.g.*, uncomplicated/complicated urinary tract infection, intra-abdominal infection or pneumonia) and infection severity (*e.g.*, presence of bacteremia) [Strength of recommendation: strong, Level of evidence: moderate].

Appropriate antibiotic selection is a crucial factor of patient outcomes in CRE infections [8-10]. A study with 92 patients with KPC-producing *K. pneumoniae* or *Escherichia coli* bacteremia in Korea found a 30-day mortality rate of 38% (35/92); the APACHE II score and appropriate antibiotic use significantly influenced mortality in multivariate analysis [8]. Data from the Global Antimicrobial Resistance Surveillance system on 579 cases of *K. pneumoniae* bacteremia revealed a higher frequency of inappropriate antibiotic use in cases with carbapenem resistance [10]. Therefore, it is recommended to obtain specimens from the suspected infection-site for culture, and a minimum of two sets of blood cultures should be performed in suspected bacteremia. When prescribing antibiotics empirically, recent antibiotic use, hospitalization history, and local resistance patterns should be considered [11]. A study in Korea that analyzed 133 cases of *E. coli* and *K. pneumoniae* CRE bacteremia showed that the presence of a non-eradicable focus was associated with higher mortality rates. Therefore, active control of the infective source is recommended [9]. Moreover, proper antibiotic use and source control were predictors of mortality in a study of 187 cases of CRE bacteremia in China [12]. Identifying and controlling the source of infection are crucial steps for improving CRE-infection treatment outcomes.

For lower urinary-tract infections (UTI), monotherapy with antibiotics that bacteria are susceptible to and that are available in Korea may be effective. In moderate-severe infections, combination therapy or higher-than-approved doses should be considered when treatment with available antibacterial agents is limited. The 2021 and 2022 CRE treatment guidelines from the US and Europe recommend newer BLBLIs (ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam) as the first-line therapy for moderate and severe CRE infections [5, 6]. However, due to limited data from Korea and restricted use of novel antibiotics, further evidence is needed to support these recommendations. When selecting antibiotics for CRE infections, the available antibiotics should be first identified, and the treatment strategy should be established by determining the infection site and severity.

Key question 2. What are the general recommendations for CRE genotype testing?

1. If CRE is isolated in the culture of a patient with suspected infection, perform carbapenemase testing [Strength of recommendation: strong, Level of evidence: moderate].
2. Perform carbapenemase testing in cases of recurrent CRE infections, relapse of treated infections, or changes in susceptibility patterns of the isolated strain [Strength of recommendation: weak, Level of evidence: low].

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Ceftazidime-avibactam, a novel agent for CRE, inhibits KPC and oxacillinase (OXA)-like carbapenemases (*e.g.*, OXA-48). Therefore, identifying the CPE genotype is crucial for determining the treatment [13]. If genotyping is unfeasible, antimicrobial susceptibility testing could determine susceptibility to ceftazidime-avibactam.

For accurate identification of carbapenemase genes, PCR-sequencing is used and, if in-house testing is unfeasible, it can be requested from the Provincial Research Institute of Public Health and Environment (Korea Disease Control and Prevention Agency) albeit with a longer turnaround time [14]. Automated real-time PCR (*e.g.*, Xpert Carba-R), available in some healthcare facilities, can provide faster results. The Xpert Carba-R test can detect common carbapenemases, such as KPC, imipenemase-1 (IMP-1), Verona integron-encoded metallo-β-lactamase (VIM), New Delhi metallo-β-lactamase (NDM), and OXA-48-like within 1 hour [15]. If genotyping is unfeasible, phenotypic testing methods, including immunochromatography (*e.g.*, NG-Test CARBA-5), can be used [16]. Using pure culture colonies, the NG-Test CARBA-5 can identify five types of carbapenemases (NDM, IMP, VIM, OXA-48, and KPC) in 15 minutes.

In cases of recurrent CRE infections in different sites or relapse of treated infections, it may be necessary to re-determine the presence and type of carbapenemase owing to a possible infection by a different genotype. Additionally, if the susceptibility pattern of the isolated strain changes during hospitalization, a retest is necessary to check for additional infection by a different genotype of carbapenemase-producing strain.

2. Part I. Antibiotic-specific recommendations

Key question 3. What is the role of tetracycline in the treatment of CRE infections?

1. If a newer β-lactam-β-lactamase-inhibitor is unavailable for a CRE infection, then tigecycline can serve as an alternative treatment [Strength of recommendation: weak, Level of evidence: low].
2. Tigecycline is not recommended for bloodstream infections or complicated UTI owing to its low blood and urine concentrations [Strength of recommendation: weak, Level of evidence: moderate].
3. For severe CRE infections or CRE pneumonia, high-dose therapy and combination therapy with tigecycline may be warranted [Strength of recommendation: weak, Level of evidence: moderate].
4. Doxycycline can be an option for uncomplicated CRE urinary tract infections [Strength of recommendation: weak, Level of evidence: low].

Tetracycline derivatives, such as minocycline, doxycycline, and tigecycline, are available, whereas eravacycline and omadacycline, approved in the US and Europe, have not yet been introduced in Korea. Most studies on the treatment of multidrug-resistant Gram-negative bacteria infections, such as CRE, have been primarily focused on tigecyclines; in vitro susceptibility studies of CRE suggest that resistance to tigecycline is not high. Studies on susceptibility to tetracycline derivatives in the US and Europe have shown that 89% to 99% of CRE strains are susceptible to these antibiotics [17, 18]. Although not many strains have been studied in Korea, only 2 out of 22 CRE strains exhibited tigecycline resistance [19]. In the US, tigecycline is used in 2–5% of CRE infections [20].

Owing to rapid distribution after administration and low blood and urinary concentrations, tigecycline is not recommended for UTIs or bloodstream infections and is not approved for the treatment of hospital-acquired and ventilator-associated pneumonia [21]. However, as many in vitro tests for CRE showed susceptibility to this antibiotic class, many studies have investigated the superiority of combination therapy with other antibiotics [22, 23] and high-dose therapy [24-26]. Based on these studies, major guidelines in the US and Europe suggest tigecycline combination therapy or high-dose therapy for severe CRE infections and cases where newer BLBLI combinations are unavailable [6, 27, 28]. In a meta-analysis of 21 studies on tigecycline treatment for CRE infections, Ni et al. showed decreased mortality rates and length of intensive care unit stay in the combination and high-dose therapy groups, respectively [29]. A meta-analysis has shown that minocycline combination therapy is effective for carbapenem-resistant *Acinetobacter baumannii* infections, although there is limited evidence for its use in CRE infections [30]. CRE has lower susceptibility to minocycline than to tigecycline [17]. The US guidelines recommend cautious use of minocycline for CRE infections [28]. There is limited evidence or doxycycline use in CRE infections; despite its lower rate of susceptibility than that to tigecycline, doxycycline, which achieves high urinary concentrations, can be considered for treatment in uncomplicated CRE UTIs [31, 32].

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Key question 4. What is the role of polymyxin in the treatment of CRE infections?

1. Colistin can be considered for CRE infections when newer BLBLI (ceftazidime-avibactam, meropenem-vaborbactam, or imipenem-cilastatin-relebactam) are unavailable [Strength of recommendation: weak, Level of evidence: low].
2. Combination therapy with colistin is recommended for severe CRE infections, such as hospital-acquired pneumonia and bloodstream infections [Strength of recommendation: weak, Level of evidence: moderate].
3. Inhaled colistin for CRE pneumonia has limited efficacy and is generally not recommended [Strength of recommendation: weak, Level of evidence: very low].
4. Dose adjustment based on creatinine clearance is necessary, and adverse effects like nephrotoxicity should be monitored [Strength of recommendation: strong, Level of evidence: low].

Polymyxin B and polymyxin E (colistin) are used clinically, although only colistin is available in Korea. Colistin methane sulfonate is administered intravenously, and because it is hydrolyzed metabolically to the active molecule colistin, it is challenging to achieve and maintain therapeutic concentrations in critically ill or patients with renal impairment, which confers higher nephrotoxicity risks [27]. Additionally, increased resistance to colistin and lack of routine drug susceptibility testing further hampers colistin use [33, 34]. Most studies on the clinical efficacy of colistin against Gram-negative bacteria were published prior to 2010, before widespread CRE dissemination [35-38]. Recent studies comparing colistin-based combination therapy with novel agents, such as ceftazidime-avibactam [39-45], meropenem-vaborbactam [46], and imipenem-relebactam [47], showed comparable or inferior treatment outcomes of colistin for CRE. Therefore, new BLBLIs are recommended as the first-line treatment for CRE infections, with colistin considered only when these agents are unavailable. Given the superiority of new BLBLIs, the 2022 Infectious Diseases Society of America (IDSA) guidelines for CRE treatment no longer recommend colistin [28]. Similarly, the European Society of Clinical Microbiology and Infectious Diseases guidelines recommend considering colistin only when no other effective agents are available for severe CRE or aerobic Gram-negative bacterial infections [6].

Previous guidelines and meta-analyses primarily recommend colistin combination therapy for CRE, with several studies demonstrating its superiority. In a meta-analysis of 22 studies, Zusman et al. showed lower mortality with polymyxin combination therapy, compared to monotherapy, for infections caused by carbapenem-resistant Gram-negative bacteria, although most studies were of low quality [48]. Sy et al., in a meta-analysis of 10 studies on CRE bloodstream infections, found an association of colistin combination therapy with lower 30-day mortality compared to monotherapy [49]. Other research studies and meta-analyses support the superiority of colistin combination therapy [50-55].

There is very limited evidence for inhaled colistin in CRE pneumonia. Most studies on the efficacy of inhaled colistin focused on patients with cystic fibrosis or non-CRE Gram-negative infections, such as *Pseudomonas aeruginosa* and *A. baumannii*; few studies have specifically investigated CRE pneumonia. A recent meta-analysis of 13 studies found no significant difference in efficacy between intravenous colistin monotherapy and combination therapy with intravenous and inhaled colistin [56].

Key question 5. What is the role of carbapenem in the treatment of CRE infections?

1. For carbapenemase-negative organisms with resistance to ertapenem (minimum inhibitory concentration [MIC] ≥2 μg/mL) but susceptible to meropenem (MIC ≤1 μg/mL), consider extended infusion of meropenem 2 g over 3 hours every 8 hours [Strength of recommendation: weak, Level of evidence: low].
2. If BLBLIs (ceftazidime-avibactam, meropenem-vaborbactam, or imipenem-cilastatin-relebactam) are unavailable for CRE infections, and the meropenem MIC is ≤8 mg/L, combination therapy with meropenem and another antibiotic can be used for CRE infections, with the consideration of extended meropenem infusion in such cases [Strength of recommendation: weak, Level of evidence: low].

Before the development of new antibiotic treatments for CRE infections, the usefulness of combining older carbapenems, such as meropenem and imipenem-cilastatin, with other antibiotics needs investigation. Similar to other β-lactam antibiotics, carbapenems are time-dependent antibiotics, and the time above the MIC (T >MIC) is associated with clinical efficacy [57]. Administration of 1 g meropenem every 8 hours versus continuous infusion of 3 g meropenem over 24 hours in

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patients with sepsis and normal renal function resulted in higher meropenem concentrations in subcutaneous tissue and plasma with continuous infusion, suggesting superior pharmacokinetic parameters with this method [58].

The AIDA trial, a prospective clinical trial conducted in six hospitals in Israel, Greece, and Italy, evaluated whether colistin and meropenem combination therapy compared to colistin monotherapy improve clinical outcomes in bloodstream infections, ventilator-associated pneumonia, hospital-acquired pneumonia, and UTI caused by carbapenem-resistant Gram-negative bacteria [59], wherein an extended infusion of 2 g meropenem was administered over 3 hours every 8 hours. The most common carbapenem-resistant Gram-negative bacterium was *A. baumannii*, followed by *Enterobacteriaceae* and *Pseudomonas*. There was no intergroup difference in rates of treatment failure, 28-day mortality, or 14-day mortality, or in outcomes in a subgroup analysis of CRE patients.

A retrospective Italian study of prognostic factors in 661 patients with KPC-producing *K. pneumoniae* infections found that meropenem-containing combination therapy reduced the 14-day mortality rate at a meropenem MIC ≤8 mg/L [60]. A post-hoc analysis of 595 patients with bacteremia included in this study showed that meropenem-containing combination therapy was associated with lower 14-day mortality rates even at meropenem MIC ≥16 mg/L, with meropenem administered as an extended infusion of 2 g over 3 hours every 8 hours [61].

Key question 6. What are the roles of other antibiotics (*e.g.*, fluoroquinolones, aminoglycosides) in the treatment of CRE infections?

1. For uncomplicated urinary tract infections, consider using antibiotics like ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, nitrofurantoin, aminoglycosides, or colistin, which have proven bacterial susceptibility, before resorting to the use of newer drugs such as new BLBLIs. This helps to preserve the effectiveness of novel antibiotics and promotes antibiotic stewardship [Strength of recommendation: weak, Level of evidence: low].
2. For simple urinary tract infections caused by CRE, choose antibiotics like ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, nitrofurantoin, aminoglycosides (*e.g.*, amikacin, gentamicin, tobramycin), or colistin based on susceptibility [Strength of recommendation: weak, Level of evidence: low].
3. For complicated urinary tract infections caused by CRE, aminoglycoside monotherapy can be used for susceptible organisms [Strength of recommendation: weak, Level of evidence: low].

Regarding antibiotic stewardship, drugs with proven susceptibility (*e.g.*, ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, nitrofurantoin, aminoglycosides, and colistin) can be considered before newer agents, such as new BLBLI for uncomplicated UTIs caused by CRE. The choice of drugs may be limited, as the effectiveness of available drugs for mild CRE infections is not clearly established, and the susceptibility rates of CRE strains to these drugs vary: colistin (80%), amikacin (50%), fosfomycin (50%), gentamicin (40%), ciprofloxacin (<5%), and trimethoprim-sulfamethoxazole (<5%) [62]. However, uncomplicated UTIs, such as cystitis, can be successfully treated with agents to which susceptibility has been established. The IDSA guidelines recommend ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, nitrofurantoin, and single-dose aminoglycosides as the first-line therapy for CRE-induced cystitis, and the European guidelines recommend using one of the available drugs with established susceptibility based on the infective source for mild CRE infections [6, 63]. Fosfomycin is not preferred for simple CRE-induced UTIs, as Gram-negative bacteria, excluding *E. coli*, have fosfomycin hydrolase genes [64], and a randomized controlled trial showed that, for simple UTIs, single-dose fosfomycin treatment had a higher treatment failure rate than a 5-day nitrofurantoin regimen [65].

Aminoglycosides can be used as monotherapy for complicated CRE-induced UTIs because of the pharmacokinetic property of aminoglycosides, which achieve high concentrations in renal tissues and urine. A retrospective study showed markedly higher microbiological eradication rate in carbapenem-resistant *K. pneumoniae* bacteriuria with aminoglycosides compared to polymyxin B or tigecycline [66]. In Korea, the most commonly used aminoglycosides are amikacin, gentamicin, and tobramycin, and although the bacterial susceptibility to these drugs may vary, these drugs are equally effective in susceptible strains [67].

In contrast to simple cystitis, treatable with single-dose aminoglycosides, complicated UTIs require treatment lasting several days, and monitoring for adverse reactions, such as nephrotoxicity and ototoxicity (hearing

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impairment or balance disorders), is required. Drug toxicity can be reduced and efficacy maximized through drug-concentration monitoring or once-daily infusion methods [68].

Key question 7. What is the role of combination therapy in the treatment of CRE infections?

1. For severe infections caused by CRE, it is recommended to use monotherapy with a susceptible newer BLBLIs (ceftazidime-avibactam, meropenem-vaborbactam, or imipenem-cilastatin-relebactam), and combination therapy is not advised [Strength of recommendation: strong, Level of evidence: low].
2. For infections caused by metallo-β-lactamase-producing strains (*e.g.*, NDM, VIM, or IMP), consider combination therapy with ceftazidime-avibactam plus aztreonam [Strength of recommendation: weak, Level of evidence: moderate].
3. If a newer BLBLI is not available for severe CRE infections, consider combination therapy with existing drugs that have established susceptibility [Strength of recommendation: weak, Level of evidence: low].

Newer BLBLI monotherapy is recommended for the treatment of severe CRE infections [5, 67]. A retrospective observational study of 577 patients with KPC-producing *K. pneumonia* infection (including 391 patients with bloodstream infections) showed no significant difference (26.1% *vs.* 25.0%, *P*=0.79) in mortality rates between ceftazidime-avibactam monotherapy (n=165) and combination therapy with other effective agents (n=412) [43]. Combination therapy may be necessary for infections by metallo-β-lactamase-producing CRE (*e.g.*, NDM, VIM, or IMP). Among the new β-lactamase inhibitors, avibactam inhibits carbapenemases, such as KPC and OXA, but not metallo-β-lactamases. Therefore, newer BLBLI monotherapy can fail against metallo-β-lactamase-producing strains [5, 6, 67, 69]; however, aztreonam is resistant to metallo-β-lactamases and can be used in such strains. An in vitro model showed that aztreonam has bactericidal activity against VIM-1-producing *K. pneumoniae* [70], and several animal studies have confirmed its efficacy against NDM and VIM-producing susceptible isolates [71, 72]. However, a significant portion of metallo-β-lactamase-producing strains also produce extended-spectrum β-lactamases (ESBL), conferring resistance to aztreonam [73]. Therefore, ceftazidime-avibactam + aztreonam combination therapy is recommended for infections caused by metallo-β-lactamase-producing CRE strains [5, 6].

If newer BLBLIs are not a treatment option for severe CRE infections, combination therapy with existing susceptible agents can be considered. Although no randomized controlled trial has specifically addressed the efficacy of combination therapy with available agents exclusively in patients with CRE infections, several well-designed retrospective observational studies have shown that combination therapy with two or more susceptible agents is associated with a lower mortality than monotherapy in severe CRE infections, including bacteremia [54, 60], although it is unclear which agents which combination is most effective. However, a retrospective cohort study of 661 patients with KPC-producing *K. pneumoniae* infections (including 447 with bacteremia) found that meropenem (MIC ≤8 mg/L)-containing combination therapy was associated with improved survival [60]. Thus, combination therapy including meropenem can be considered as first-line for severe infections caused by CRE with a low meropenem MIC. For other cases, effective agents should be combined considering the source of infection and renal function. In strains resistant to all drugs with limited number of available drugs, double carbapenem therapy, including ertapenem, can be considered [6].

2. Part II. Disease-specific recommendations

Key question 8. What is the preferred antibiotic treatment for CRE urinary tract infections?

1. Antibiotic selection for CRE relies primarily on susceptibility test results. If ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, nitrofurantoin, or aminoglycosides show susceptibility, they can be used. Nitrofurantoin is suitable for uncomplicated cystitis but not for pyelonephritis or complicated cystitis [Strength of recommendation: strong, Level of evidence: low].
2. If CRE is susceptible to meropenem and no carbapenemase is detected, meropenem can be used. Extended-infusion meropenem therapy is preferred for pyelonephritis or complicated cystitis [Strength of recommendation: weak, Level of evidence: low].
3. If CRE is not susceptible to ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, nitrofurantoin, aminoglycosides, or meropenem, consider ceftazidime-avibactam, colistin, meropenem-vaborbactam, imipenem-cilastatin-relebactam, or cefiderocol [Strength of recommendation: weak, Level of evidence: high].

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Not many studies have investigated effective agents for CRE UTIs. However, many antibiotics, including cephalosporins and fluoroquinolones, undergo renal metabolism and attain higher urinary, rather than blood, concentrations, which suggest that effective antibiotics can be used in UTIs, as they often show favorable clinical outcomes compared to the susceptibility results [74-76]. Considering this, non-beta-lactams, such as ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, and nitrofurantoin, recommended in existing Korean guidelines, may be an option [77]. Aminoglycosides are not primarily recommended in the IDSA guidelines due to concerns about nephrotoxicity; however, given the limited options for antibiotics for CRE in Korea, effective aminoglycosides can be used [78]. As nephrotoxicity is a major adverse effect of aminoglycosides, once-daily dosing regimen is recommended [79]. Furthermore, given the limited antibiotic options for CRE, single-dose aminoglycosides can be used in uncomplicated cystitis, although not orally [80]. Regarding fosfomycin, it is difficult to determine the accurate MIC values for *E. coli* and *K. pnuemoniae* through antibiotic susceptibility testing methods widely used in hospitals (*e.g.*, Sensititre, VITEK-2, Phoenix, manual tests performed by *E*-test) [81, 82]. A single-center study in the US reported a FosA gene detection rate close to 80% in KPC-producing Enterobacterales, and a recent multicenter randomized controlled trial in patients with uncomplicated cystitis showed that single-dose fosfomycin is inferior to a 5-day regimen of nitrofurantoin; thus, fosfomycin cannot be recommended, which contradicts current Korean guidelines [65, 83]. Nitrofurantoin is not recommended for pyelonephritis as it is difficult to maintain adequate concentrations in the renal parenchyma [84].

A US single-center study reported that approximately 76% of non-carbapenemase-producing CRE strains is susceptible to meropenem, whereas only about 36% of carbapenemase-producing CRE strains is susceptible to meropenem [85]. Additionally, the treatment failure rates of carbapenems were significantly lower for non-carbapenemase CRE infections than those with carbapenemase-producing CRE [85]. Accordingly, despite inadequate study findings on the efficacy and effects of meropenem monotherapy, the IDSA recommends considering meropenem monotherapy for uncomplicated UTIs caused by CRE without carbapenemase or unknown carbapenemase status [28]. Owing to uncertainties regarding the MIC, meropenem is not recommended when carbapenemase is present [86]. Given the limited data in Korea on CRE susceptibility to meropenem, the present guidelines limit the recommendation for meropenem specifically for non-carbapenemase-producing CRE infections. Based on evidence suggesting better treatment outcomes, extended-infusion meropenem in severe infections is recommended when treating pyelonephritis or complicated CRE UTIs [87].

Ceftazidime-avibactam was introduced in Korea in July 2023 and is covered by reimbursement from February 1, 2024. As it is relatively expensive and lacks confirmed effectiveness against NDM-producing strains, it can be considered for uncomplicated cystitis and pyelonephritis/complicated cystitis caused by non-NDM type CRE without susceptibility to all other antibiotics [88, 89].

Colistin has been used previously for the treatment of CRE infections and is widely used in Korea [90, 91]. However, due to the global trend of increased resistance, difficulty in accurately measuring the MIC, and high risk of nephrotoxicity, colistin is no longer recommended as a first-line treatment for CRE infections in North America and Europe [30, 92, 93]. Nonetheless, in Korea, colistin is the only option for uncomplicated cystitis caused by CRE that is unsusceptible to all other antibiotics, as there are insufficient antibiotic options for CRE infections.

In developed countries, including North America and Europe, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are widely used [28, 90]. As these drugs are known to be more effective than previously used agents, such as colistin or carbapenems, for treating CRE infections, including UTIs, they would be feasible treatment options for uncomplicated CRE-induced cystitis in Korea [94-97].

Key question 9. What are the recommendations for the treatment of complicated intra-abdominal infections (cIAIs) caused by CRE?

1. For cIAIs caused by CRE, polymyxin-based combination therapy may be an option [Strength of recommendation: weak, Level of evidence: low].
2. Polymyxin-based combination therapy can involve combining colistin with either tigecycline or meropenem, with the choice of additional antibiotics determined on the basis of susceptibility testing results [Strength of recommendation: weak, Level of evidence: low].
3. For non-severe cIAIs caused by CRE, consider tigecycline or eravacycline monotherapy [Strength of

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recommendation: weak, Level of evidence: very low].
4. For cIAIs caused by CRE excluding metallo-β-lactamase-producing Enterobacterales, consider combination therapy with ceftazidime–avibactam and metronidazole [Strength of recommendation: weak, Level of evidence: low].
5. For cIAIs caused by CRE except those involving metallo-β-lactamase-producing Enterobacterales, consider imipenem–cilastatin–relebactam monotherapy [Strength of recommendation: weak, Level of evidence: low].

IAI broadly includes cases of inflammation caused by intraperitoneal microbial exposure, and can be categorized as complicated and uncomplicated, depending on the anatomical location. Infections that extend beyond the gastrointestinal tract to the peritoneal cavity and result in abscesses or peritonitis are cIAIs, whereas those confined to a single organ with maintained anatomical boundaries are considered uncomplicated IAIs [98, 99].

Currently in Korea, the standard treatment for cIAIs caused by CRE is polymyxin-based combination therapy. Recently, new antibiotics, namely ceftazidime-avibactam and imipenem-cilastatin-relebactam, have received Food and Drug Administration (FDA) approval for treating cIAIs and thus are available for use in patients with high risk for severe CRE cIAIs. Ceftazidime-avibactam is currently available in Korea. However, these new drugs are ineffective against NDM and other metallo-β-lactamases [13, 100], limiting their suitability in regions where these enzymes are prevalent, such as Korea and other parts of Asia [20]. Therefore, polymyxin-based combination therapy remains essential for managing CRE infections with little or high risk for progression to a severe infection, particularly in areas with a high prevalence of metallo-β-lactamase-producing CRE.

Although no study has specifically focused on the treatment of cIAIs caused by CRE, six studies on secondary CRE bloodstream infections following IAIs have indicated lower mortality rates with polymyxin-based combination therapy than monotherapy [53, 54, 101-104]. This trend was supported by the results of a meta-analysis of the six studies (39.3% *vs.* 56.4%; odds ratio [OR], 0.52; 95% CI, 0.33–0.83; *P*=0.006) [49]. Additionally, a systematic review and meta-analysis of carbapenem-resistant *K. pneumoniae* infections showed polymyxin-based combination therapy conferred lower overall mortality rates than monotherapy (OR, 1.45; 95% CI, 1.18–1.78; *P*<0.001) [105].

Despite limited evidence, polymyxin-tigecycline or polymyxin-meropenem combination therapy may be used to treat CRE-induced cIAIs, and antibiotic selection must be based on CRE antibiotic-susceptibility test results [49].

Tigecycline is an effective antibiotic against most pathogens causing cIAIs, and clinical CRE isolates showed a high 98% susceptibility in a 2016 study [106]. If the CRE strain is susceptible to tigecycline, it can be used to treat stable cIAIs [18, 29, 62]. Tigecycline can be used alone or in combination to treat cIAIs. However, as patients with severe cIAIs may have a lower response to tigecycline treatment (SOFA score <7 *vs.* ≥7: 78.6% [33/42] *vs.* 54.2% [33/59]) [107], tigecycline is recommended in combination with meropenem or polymyxin in sepsis or septic shock [49].

Eravacycline, a new synthetic fluorocycline that is structurally similar to tigecycline, has been approved in the US and Europe but has not yet been introduced in Korea, and exhibits broad-spectrum antimicrobial activity against both Gram-negative and Gram-positive bacteria that cause cIAIs, including CRE [108, 109]. In the investigating Gram-negative infections treated with eravacycline (IGNITE) trial, a multicenter randomized controlled trial (RCT) for the clinical development of eravacycline, the clinical cure rate of eravacycline for cIAIs was non-inferior to ertapenem (IGNITE1) or meropenem (IGNITE4) [110, 111]. A small study of the clinical cure rate of eravacycline in 17 patients with cIAIs reported a cure rate of 94% [112]. In a study of 35 critically ill patients treated with eravacycline, the 30-day survival rate was 74%, of whom 8 had a CRE infection, and 7 survived on day 30 [113]. Although eravacycline may be considered for the treatment of cIAIs caused by CRE based on these results, the strength of recommendation is weak [49].

The ceftazidime-avibactam and metronidazole combination therapy showed promising results in a phase 2 clinical trial for treating abdominal infections [114] and was effective for cIAIs in the phase 3 clinical trials RECLAIM and REPRISE [89, 115], and received FDA approval in 2015 for the treatment of cIAIs and was introduced in Korea in 2023. According to several retrospective studies, treating CRE infections with ceftazidime-avibactam reduced overall mortality or non-inferiority compared to other antimicrobial therapies [39, 40, 42, 44, 116, 117]. Although the evidence is limited, the combination of ceftazidime-avibactam and metronidazole can be considered for treating cIAIs caused by CRE.

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In an RCT involving patients with cIAIs, imipenem-cilastatin-relebactam showed similar efficacy and safety to imipenem-cilastatin [118]. In July 2019, the FDA approved imipenem-cilastatin-relebactam for treating cIAIs. The RESTORE-IMI-1 study, a multinational, double-blind, randomized trial conducted in various countries including the US, Europe, and Asia, was a small clinical trial involving 31 patients with carbapenem-resistant infections, which demonstrated the efficacy and safety of imipenem-cilastatin-relebactam compared to the combination of colistin and imipenem [47]. However, this study included only 7 patients with CRE infections and only 1 patient with cIAI, the specific therapeutic effects of imipenem-relebactam on CRE-induced cIAI cannot be determined and warrants further research. Additionally, imipenem-cilastatin-relebactam is effective against most KPC-producing CRE strains and carbapenem-resistant *P. aeruginosa*, but not against carbapenem-resistant *A. baumannii* or carbapenem-resistant *Stenotrophomonas maltophilia* [119, 120].

Key question 10. What are the recommended antibiotics for the treatment of CRE infections outside UTIs and cIAI (*e.g.*, bacteremia or pneumonia)?

1. For CPE infections beyond urinary tract infections and complicated intra-abdominal infections, newer BLBLIs (ceftazidime–avibactam, meropenem–vaborbactam, or imipenem–cilastatin–relebactam) are the preferred first-line treatment and are chosen based on the carbapenemase Ambler class [Strength of recommendation: strong, Level of evidence: high].
2. For KPC-producing strains infections, meropenem–vaborbactam, ceftazidime–avibactam, or imipenem–cilastatin–relebactam treatments are recommended [Strength of recommendation: strong, Level of evidence: moderate].
3. For CPE infections caused by NDM or other metallo-β-lactamase-producing organisms, ceftazidime–avibactam and aztreonam combination therapy, or cefiderocol monotherapy, is recommended. If aztreonam is not feasible, avoid ceftazidime–avibactam monotherapy; instead, determine susceptibility to colistin, tigecycline, or aminoglycosides and consider a combination of susceptible agents [Strength of recommendation: strong, Level of evidence: moderate].
4. For infections caused by OXA-48-like carbapenemase-producing CPE, use ceftazidime–avibactam [Strength of recommendation: strong, Level of evidence: moderate].
5. If newer BLBLIs are not available, treat CPE infections by selecting antibiotics that the organism is susceptible to, opting for monotherapy or combination therapy based on various factors like pharmacokinetics, infection site, side effects, and contraindications [Strength of recommendation: strong, Level of evidence: moderate].
6. If newer BLBLIs are not available, consider combination therapy for severe infections like bacteremia. Determine susceptibility to colistin, tigecycline, or aminoglycosides and opt for a combination of susceptible agents [Strength of recommendation: weak, Level of evidence: moderate].
7. If newer BLBLIs are not available, consider using combination therapy with meropenem and other antibiotics for CRE infections with a meropenem MIC ≤8 mg/L. Administer an extended-infusion of 2 g meropenem for 3 hours every 8 hours [Strength of recommendation: weak, Level of evidence: low].
8. For carbapenemase-negative, ertapenem-resistant, or meropenem-susceptible CRE infections, consider an extended-infusion of 2 g meropenem for 3 hours every 8 hours. Alternatively, explore other susceptible antibiotics [Strength of recommendation: weak, Level of evidence: low].
9. For ertapenem-resistant or meropenem-susceptible CRE infections with unknown carbapenemase status, consider meropenem-extended infusion, ceftazidime-avibactam, or meropenem-varbobactam [Strength of recommendation: weak, Level of evidence: low].
10. For CRE strains with phenotypic resistance to ertapenem and meropenem and unknown or negative carbapenemase status, opt for ceftazidime-avibactam, meropenem-varbobactam, and imipenem-cilastatin-relebactam, with cefiderocol as a potential alternative [Strength of recommendation: weak, Level of evidence: low].
11. If carbapenemase status is unknown or negative and infection is caused by CRE with phenotypic resistance to ertapenem and meropenem, and newer BLBLIs are unavailable, consultation with an infectious disease specialist is recommended. Based on antibiotic susceptibility results, consider combination therapy with colistin- or meropenem-extended infusion for severe infections, particularly bloodstream infections [Strength of recommendation: weak, Level of evidence: low].

Compared to traditional antibiotics, such as colistin, newer BLBLI antibiotics have demonstrated superior efficacy and fewer adverse effects in CPE infections [42, 45, 47]. Thus, if available, newer BLBLIs are recommended as the first-line treatment for CPE infections. This

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guideline suggests recommended treatment options with the available and upcoming antibiotics, depending on the carbapenemase-producing strain, and suggests alternative options when the antibiotics are unavailable.

KPC-PRODUCING INFECTIONS

Antibiotics recommended for KPC-producing infections include meropenem-vaborbactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam, which have demonstrated superior clinical outcomes and lower toxicity, compared to the available polymyxin-based combination therapy [42, 45, 47]. Few studies have compared the efficacy of preferred drugs, and no clinical trial has compared the new drugs. An observational study compared the clinical outcomes after ≥72-hour meropenem-vaborbactam or ceftazidime-avibactam treatment of CRE infection and found no significant intergroup difference in clinical remission and 30-day mortality rates (69% *vs.* 62%, *P*=0.49 and 12% *vs.* 19%, *P*=0.48, respectively) [117], although the carbapenemase type was unspecified in most cases. Among those with recurrent CRE infection, 0 out of 3 *vs.* 3 out of 15 patients who received meropenem-vaborbactam and ceftazidime-avibactam, respectively, demonstrated resistance to the initial treatment in subsequently collected CRE isolates. However, these results require special considerations for interpretation, including the risk of selection bias owing to an observational design, relatively small sample size, heterogeneity in CRE infection sites, and polymicrobial infection and additional antibiotic therapy in the majority of patients. Despite these limitations, the study suggests that meropenem-vaborbactam and ceftazidime-avibactam have comparable efficacies, albeit with a higher risk for resistance with ceftazidime-avibactam. Thus, if all new drugs were approved in Korea, then both ceftazidime-avibactam and meropenem-vaborbactam would be recommended for the treatment of KPC-producing infections; moreover, considering the risk of resistance, meropenem-vaborbactam may be the preferred choice over ceftazidime-avibactam (further research is required).

Compared to other newer BLBLIs, there is limited clinical data for imipenem-cilastatin-relebactam. An RCT among patients with imipenem-resistant Gram-negative (Enterobacterales) infection [47] showed good clinical response in 40% (2 out of 5) and 100% (2 out of 2) of participants randomized to the imipenem-cilastatin-relebactam and imipenem-cilastatin-colistin groups, respectively, although the small sample size detracted from the significance. Nevertheless, imipenem-cilastatin-relebactam is predicted to be effective for treating CRE infections [121-123], considering its in vitro activity, clinical experiences with imipenem-cilastatin, and the safety of the β-lactamase inhibitor, relebactam [124]. In CRE infections, there is no comparative data of clinical outcomes with imipenem-cilastatin-relebactam, ceftazidime-avibactam, and meropenem-vaborbactam; thus, ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam are all drugs of choice for KPC-producing infections.

Cefiderocol is another treatment for KPC-producing Enterobacterales [125]. In a clinical trial of patients with CRE infection, 65.5% (19/29) and 45.5% (5/11) of patients treated with cefiderocol and an alternative drug (mostly polymyxin-based therapies), respectively, improved clinically [97]. Cefiderocol treatment of carbapenem-resistant *K. pneumoniae* or *E. coli* infections resulted in all-cause mortality rates of 22.5% (9/40) and 21.1% (4/19), respectively. Although no clinical trial has compared the treatment effects of cefiderocol and newer BLBLIs in KPC-producing infections, the available data shows the non-inferiority of cefiderocol. However, as cefiderocol can be used in infection by metallo-β-lactamase-producing Enterobacterales (*e.g.*, NDM, VIM, or IMP) and non-fermenting Gram-negative bacteria [126], BLBLIs are preferred to cefiderocol for KPC-producing infections.

NDM- OR OTHER METALLO-Β-LACTAMASE-PRODUCING INFECTIONS

For NDM (or other metallo-β-lactamase)-producing infections, the preferred antibiotics include ceftazidime-avibactam/aztreonam combination therapy or cefiderocol monotherapy [127-129] because ceftazidime-avibactam monotherapy, meropenem-vaborbactam, and imipenem-cilastatin-relebactam are ineffective in metallo-β-lactamase-producing infections.

NDM hydrolyzes penicillin, cephalosporin, and carbapenem but not aztreonam, which is active against NDM, but can be hydrolyzed by other carbapenemases, such as ESBL, AmpC β-lactamases, or OXA-48, that are frequently co-produced by NDM-producing isolates. An observational study of 102 adults with metallo-β-lactamase-producing Enterobacterales bloodstream infections compared the outcomes of 52 patients treated with ceftazidime-

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avibactam and aztreonam against 50 patients treated with alternative regimens, primarily polymyxins or tigecycline [130]. The 30-day mortality rate was 19% and 44% in the ceftazidime-avibactam/aztreonam and alternative regimen groups, respectively, which demonstrated the clinical efficacy of the ceftazidime-avibactam/aztreonam regimen. Simultaneous administration is recommended over sequential administration for metallo-β-lactamase-producing infections [131]. If aztreonam is unavailable, ceftazidime-avibactam monotherapy is not recommended; thus, susceptibility to colistin, tigecycline, or aminoglycosides, should be tested, and combination therapy with effective agents should be considered [132].

Cefiderocol is an alternative treatment for NDM- and other metallo-β-lactamase-producing Enterobacterales. Cefiderocol effectively acted against 98% of 151 CRE isolates, with 100% activity against 75 KPC-producing Enterobacterales and 32 OXA-48-producing Enterobacterales, but only 58% activity against 12 NDM-producing isolates (susceptibility defined as cefiderocol MIC ≤4 μg/mL) [133]. In a clinical trial of patients with metallo-β-lactamase-producing bacterial infections (not limited to Enterobacterales), clinical remission was observed in 75% (12/16) of patients treated with cefiderocol, compared to 29% (2/7) in patients who received alternative therapies (primarily polymyxin-based regimens) [97]. However, the clinical responses to the ceftazidime-avibactam/aztreonam combination therapy and cefiderocol have not been compared directly. Both treatment options are recommended for infections caused by metallo-β-lactamase-producing Enterobacterales.

OXA-48-PRODUCING INFECTION

Ceftazidime-avibactam is recommended, and cefiderocol is an alternative antibiotic, for OXA-48-like enzyme-producing infections (CRE) [134], against which meropenem-vaborbactam and imipenem-cilastatin-relebactam are inactive [134-136]. These infections are predicted to be susceptible to cefiderocol, but there is limited clinical data on cefiderocol regimens.

CASES WHEREIN A NOVEL ANTIBIOTIC IS UNAVAILABLE

1. Combination therapy

The effectiveness of monotherapy versus combination therapy for CPE infections has been explored in studies with varied designs and combinations, but without consistent conclusions. Studies on combination therapy have not described the antibiotic types, dosages, or durations. A few studies with adequate sample sizes and controlled confounders suggested better outcomes with combination therapy compared to monotherapy [48, 53, 137-139], primarily in severe cases with regimens combining one or more antibiotics with confirmed susceptibility. A large retrospective cohort study in Italy of patients with *K. pneumoniae* bloodstream infections (N=447) and non-bloodstream infections (N=214) showed that treatment with two or more susceptible antibiotics conferred lower 14-day mortality rates (OR, 0.52; 95% CI, 0.35–0.77) [60]. In another retrospective study, combination therapy was associated with a lower 30-day mortality rate in severe (adjusted hazard ratio [HR], 0.56; 95% CI, 0.34–0.91), but not in non-severe, CRE bloodstream infections [54]. Concurrent use of two or more in vitro active antibiotics (including colistin, tigecycline, gentamicin, carbapenems, and rifampin) was independently associated with 30-day survival in a retrospective study of 111 critically ill patients with KPC-producing *K. pneumoniae* infections and septic shock [137]. The efficacy of combination therapy is potentially attributed to the often suboptimal dosages and inappropriate pharmacokinetics of monotherapy for certain infection sites [23, 140, 141]. As no study has focused on specific antibiotic combinations, it is unclear as to which antimicrobials should be included in the regimen. Smaller studies analyzing specific drugs suggest that colistin-tigecycline can be considered [102, 142-145]. With the high heterogeneity in the included treatments, even small studies cannot derive concrete conclusions about which drugs should be added with colistin or tigecycline, although treatment with at least one susceptibility-confirmed antibiotic may be beneficial.

2. Colistin

When newer BLBLIs are unfeasible, colistin is the base drug for treating CPE infections. Colistin (polymyxin E) is a lipopeptide antibiotic against which CPE shows the highest susceptibility in vitro. An RCT of the clinical outcomes of colistin monotherapy versus colistin/meropenem combination therapy for severe carbapenem-resistant Gram-negative infections showed the non-superior clinical efficacy of combination therapy versus colistin monotherapy [59]; however, *A. baumannii* was the most common pathogen, and only 18% of all cases (n=73) had Enterobacteriaceae infections, and 28-day mortality

non-significantly differed between colistin monotherapy and colistin+meropenem combination therapy (35% *vs.* 21%, respectively). Thus, limited evidence exists for colistin monotherapy in CPE infections.

A meta-analysis of ten retrospective studies showed that colistin-based combination therapy conferred lower 28-day or 30-day mortality rates compared to colistin monotherapy (35.7% *vs.* 55.5%; OR, 0.46; 95% CI, 0.30–0.69; *P*<0.001) [49]. In the INCREMENT study among 437 patients with CPE bloodstream infections, there was no difference in the 30-day mortality rates of combination therapy and monotherapy [54], although subgroup analysis showed combination therapy reduced mortality in patients with high INCREMENT-CPE mortality risk scores, whereby combination therapy could be considered for severe infections [54]. Colistin was the main component of combination therapy, with other drugs including tigecycline, aminoglycosides, and carbapenems [101, 103, 146]. Thus far, no study has compared the effectiveness of different combination therapies.

3. Tigecycline

Due to its low serum concentration, tigecycline has limited relevance and is not approved for treating CRE bloodstream infections [21, 147], but may be used in combination therapy for CRE pneumonia and bacteremia. A meta-analysis of 15 randomized trials showed that, compared to alternative therapies, tigecycline monotherapy induced higher mortality rates for pneumonia [148]. Subsequent studies showed the non-significance of differences in mortality rates between high-dose tigecycline (200 mg initially, followed by 100 mg intravenously every 12 hours) and control drugs [24-26]. Therefore, tigecycline could be prescribed in high doses for the treatment of CRE infections, such as pneumonia.

CASES WITH NEGATIVE OR UNKNOWN CARBAPENEMASE STATUS

In cases with ertapenem-resistant (*i.e.*, MIC ≥2 μg/mL) and meropenem-susceptible (*i.e.*, MIC ≤1 μg/mL) bacteria, extended-infusion meropenem can be considered [149]. Compared to carbapenemase-producing strains, non-carbapenemase-producing Enterobacterales have lower meropenem MICs [85]. In carbapenamase-negative cases, extended-infusion meropenem without new drugs is recommended to preserve the activity of new antibiotics. Alternative susceptibility-confirmed antibiotics can be considered, although tigecycline and aminoglycoside monotherapy is not recommended in bloodstream infections.

If the carbapenemase status is unknown, the local epidemiology, antimicrobial spectrum, and efficacy of antibiotics should be considered. In cases with phenotypic ertapenem resistance or meropenem susceptibility, extended-infusion meropenem, ceftazidime-avibactam, and meropenem-vaborbactam are recommended. Compared to carbapenems, ceftazidime-avibactam has similar microbiological responses as the control group in various CRE infections (response rate 78.4% [399/509] and 71.6% [388/542]), respectively, in clinical trials [150]. Meropenem-vaborbactam is more effective than optimal therapy (treatment rate 65.6% [21/32] *vs.* 33.3% [5/15]; 95% CI, 3.3-1.3; *P*=0.03) [46], and had similar efficacy as ceftazidime-avibactam [117]. Due to the limited samples with multidrug resistant Enterobacterales in clinical trials [47], there is insufficient evidence for the use of imipenem-cilastatin-relebactam in Enterobacterales infections with unknown carbapenemase results and meropenem susceptibility. When novel antibiotics are unavailable, combination therapy can be considered based on in vitro susceptibility results.

For non-urinary tract CPE infections with unknown or negative carbapenemase results and phenotypic resistance to ertapenem and meropenem, ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam are recommended, given their demonstrated activity against CRE infections. Cefiderocol can be administered as an alternative antibiotic. If newer BLBLI antibiotics are unavailable, the carbapenemase result is unknown or negative, and there is resistance to ertapenem and meropenem, consultation with an infectious disease specialist is recommended. Based on antibiotic susceptibility results, polymyxin-based combination therapy can be considered for severe infections (especially bloodstream infections). A meta-analysis showed that compared to other drugs, polymyxin-based combination therapy conferred a lower mortality rate on day 28 in bloodstream infections [49]. Additionally, extended infusion meropenem-based combination therapy can be considered. In KPC-producing *K. pneumoniae* bloodstream infections, extended meropenem infusion (2 g for 3 hours every 8 hours) independently influenced survival on day 14 (HR, 0.64; 95% CI, 0.43–0.95; *P*=0.03), even at MIC ≥16 μg/mL [61]. Considering the epidemiology of CPE distribution in Korea, empirical antibiotics can

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be selected for KPC-producing infections in confirmed CRE infection when carbapenemase testing cannot be performed, or only carbapenemase production is confirmed without data on the specific subtype. If the patient has come from regions with a high prevalence or recent outbreak of metallo-β-lactamase, such as South Asia, Central Asia, and the Mediterranean [151]; the infection was acquired in a region affected by a metallo-β-lactamase outbreak in the past 12 months or with high prevalence of metallo-β-lactamase; or carbapenem-resistant *E. coli* or *Enterobacter cloacae* has previously been confirmed to produce metallo-β-lactamase in Korea, treatment recommendations given accordingly [97, 130].

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