EXPERT REVIEWS

Treatment of carbapenem-resistant *Klebsiella pneumoniae*: the state of the art

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The increasing incidence of carbapenem-resistant *Klebsiella pneumoniae* (CR-KP) fundamentally alters the management of patients at risk to be colonized or infected by such microorganisms. Owing to the limitation in efficacy and potential for toxicity of the alternative agents, many experts recommend using combination therapy instead of monotherapy in CR-KP-infected patients. However, in the absence of well-designed comparative studies, the best combination for each infection type, the continued role for carbapenems in combination therapy and when combination therapy should be started remain open questions. Herein, the authors revise current microbiological and clinical evidences supporting combination therapy for CR-KP infections to address some of these issues.

Keywords: carbapenem-resistant *Klebsiella pneumoniae* • carbapenemase-producing strains • combination antimicrobial therapy

Life-threatening infections caused by multidrug-resistant (MDR) and sometimes pan-resistant Gram-negative bacteria have increased dramatically in the last decade [1]. Empiric antibiotic therapy can improve the survival among patients with infections due to such microorganisms, as inadequate initial treatment is associated with higher mortality, even if adjustment is carried out when microbiological results are available [2]. Therefore, the rationale for optimizing the antimicrobial treatment in severe infections is to give a broad-spectrum empirical therapy and then to streamline it according to the results of antibiotic-susceptibility tests [3]. Indeed, most studies suggest that inappropriate antimicrobial treatment can be reduced by the administration of an empiric combination therapy [4,5].

Other appealing aspects of the combination therapy include the potential for a synergistic effects and suppression of emerging resistance [6,7]. However, synergy is a microbiological definition based on *in vitro* studies, which is often difficult to demonstrate *in vivo* for Gram-negative infections. As for the prevention of further resistance, some small *in vitro* studies suggest resistance emergence in *Pseudomonas aeruginosa* can be delayed with combinations of levofloxacin and imipenem (IMP) *in vitro* [8,9]. Yet, no clinical studies on combination therapy in Gram-negative infections to date have formally tested or proven this hypothesis [10].

On the other hand, the potential for adverse events is an important argument against combination therapy [5]. Combination regimens that include the use of aminoglycosides increase patient risk for nephrotoxicity and have been shown in several meta-analyses to have higher toxicity rates than monotherapay regimens. This is especially true in patients with Gram-negative sepsis who are often volume depleted, have metabolic acidosis and are exposed to other nephrotoxic agents [5]. Another possible severe adverse event is *Clostridium difficile*-associated colitis, but to date, there are no studies assessing the risk for *C. difficile*-associated colitis among patients receiving combination therapy versus monotherapy.

Nevertheless, combination therapy is largely used in the clinical practice, not only as empirical, but also as targeted therapy. This, in part, reflects the familiarity of infectious disease clinicians with combination antimicrobial therapy, as in case of HIV infection, tuberculosis, *Helicobacter pylori* infection, brucellosis and enterococcal endocarditis.

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Well-conducted studies addressing the question of whether a combination of antimicrobials is superior to a monotherapy for Gram-negative infections are lacking. *P. aeruginosa* is the most studied pathogen, yet clear evidence regarding the superiority of combination regimens versus monotherapy remains elusive [11,12]. In an old retrospective study of *P. aeruginosa* bacteremia, combination therapy, including β-lactam plus an aminoglycoside, had a significantly higher cure rate, but the comparator was an aminoglycoside alone [13]. When the comparator was an antipseudomonal β-lactam alone, combination regimens were not superior [13]. Other prospective studies and meta-analysis failed to evidence superiority of the combination therapy versus monotherapy against *P. aeruginosa* infections [14–16].

The impact of combination therapy on *Klebsiella pneumoniae* infection has rarely been evaluated. In an old study of 230 patients with *K. pneumoniae* bacteremia, no difference in mortality was found between patients receiving combination therapy (18%) versus monotherapy (20%) [17]. However, for the subgroup of patients who experienced hypotension within 72 h of taking blood cultures, mortality was significantly lower among patients treated with combination therapy (24%) than for those who received monotherapy (50%) [17]. The increasing interest on combination therapy for *K. pneumoniae* infections is due to its ability to acquire resistance against different classes of antibiotics, including carbapenems, with limited availability of effective agents [1]. Indeed, over the past few years, the increasing incidence and high mortality of infections due to carbapenem-resistant *K. pneumoniae* (CR-KP) have prompted physicians to use combination therapy even more frequently for the management of infections due to such microorganisms. The aim of this review is to summarize available *in vitro* and clinical data on the role of combination therapy in the treatment of infections due to CR-KP.

Epidemiology of CR-KP

K. pneumoniae is one of the most important causes of healthcare-associated infections, mainly among patients admitted to the intensive care units (ICUs). Initial studies of carbapenem resistance among *K. pneumoniae* identified overproduction of AmpC β-lactamases or extended-spectrum β-lactamases combined with porin defects as the principle mechanisms responsible for resistance [18,19]. More recently, carbapenemases, mainly *K. pneumoniae* carbapenemase (KPC) and metallo-β-lactamases (MBLs), have become the more prevalent mechanisms for CR-KP [20,21]. These enzymes are found on transferable plasmids and are able to hydrolyze nearly all β-lactam antibiotics. They are classified into different classes (A, B and D) on the basis of amino acid sequence homology, with class A and D carbapenemases having serine at their active site and class B using zinc [22].

KPC is a class A enzyme; it was first detected in *K. pneumoniae* from a clinical specimen in North Carolina (USA) and later spread to Europe in 2005–2006 [23–25]. Since that time, KPC-producing isolates have spread globally, causing outbreaks or becoming endemic in many countries [21]. KPC-producing strains spread in a clonal fashion, with the majority of US and European isolates belonging to the sequence-type-258 lineage [26–28]. To date, nine different variants (KPC-2–KPC-10) of the KPC enzyme have been described, with KPC-2 and KPC-3 reported most frequently [22].

MBLs belong to class B and include Verona integron-encoded MBL (VIM), IMP and New Delhi MBL (NDM). MBLs were first detected as IMP from Japan in *Serratia marcenscens* [29]. VIM-1 was then detected in 2001 in *Escherichia coli* from a hospitalized patient in Greece [30] but it rapidly spread among *K. pneumoniae*, becoming endemic in that country [31]. NDM was first identified in 2009 in a *K. pneumoniae* isolate from a Swedish patient who had received medical care in India [32], and was soon recognized as an emerging mechanism of resistance in multiple species of Enterobacteriaceae, mainly in India, Pakistan and UK [33].

The class D carbapenemase OXA-48 is remotely related (<46% amino acid identity) to oxacillinase, which hydrolyzes penicillins and carbapenems, but not expanded-spectrum cephalosporins, and has been reported in *K. pneumoniae* isolates from Turkey. It later spread to other Mediterranean countries and caused some outbreaks in northern Europe [31,34,35].

Over the past 10 years, the rate of carbapenem resistance among *K. pneumoniae* has increased dramatically worldwide [36]. In the USA, data from the CDC on healthcare-associated infections reported a significant increase in CR-KP from <1% in 2000 to 8% in 2007 [37]. In Europe, data from the EARS-Net database showed that during the year 2010, the rates of CR-KP ranged from 0.2% (Germany) to 59.5% (Greece), with higher rates generally observed in southern European countries [31]. Italy ranked third with a CR-KP rate of 15.8% [31].

Risk factors for CR-KP colonization & infection

A wide spectrum of clinical infections are caused by CR-KP, including primary or catheter-related bacteremia, nosocomial pneumonia, urinary tract infections, surgical site and wound infections, peritonitis, endocarditis and mediastinitis [38–43]. CR-KP infection is usually preceded by colonization, mainly at the level of gastrointestinal tract [44]; however, other sites such as respiratory and urinary tracts are also frequently colonized [45].

Acquisition of CR-KP among hospitalized patients has been associated to poor functional status, ICU stay, severity of underlying illness and prior antibiotic exposure to different classes of antibiotics including carbapenems, fluoroquinolones, cephalosporins and glycopeptides [44,46,47]. In one prospective surveillance study of 299 patients hospitalized in a medical–surgical ICU, 7% were colonized at admission and 27% acquired CR-KP during ICU stay. Recent surgery and severity of illness (SOFA score) were the independent risk factors for CR-KP acquisition. Among colonized patients, 47% developed infection [48].

Risk factors for CR-KP infection are similar to those for colonization [49–53]. Furthermore, some authors have shown patients with solid-organ and stem cell transplantation to be at higher risk for CR-KP infection [50].

To date, only one study investigated the risk factors for CR-KP infection among patients known to be colonized [38]. Among 464 patients who were identified by stool cultures to be rectal

carriers of CR-KP, 42 (9%) subsequently developed CR-KP infection, which was associated with the following risk factors: previous invasive procedure, diabetes mellitus, solid tumor, tracheostomy, urinary catheter insertion and prior exposure to an antipseudomonal penicillin [54].

Finally, residents in nursing homes, long-term care or postacute care facilities have been identified as an important reservoir for endemic CR-KP resistance [54–57]. In Israel, a cross-sectional prevalence survey of 1144 patients hospitalized in 12 postacute care facilities reported a prevalence of CR-KP rectal carriage of 12% [57]. Independent risk factors for CR-KP carriage were prolonged length of stay, sharing a room with a known carrier and increased prevalence of known carriers on the ward. A policy of screening for carriage on admission was protective for CR-KP infection, highlighting the importance of stringent infection control in preventing the spread of resistance [57].

Pharmacokinetic & pharmacodynamic principles of antibiotic therapy

The treatment of CR-KP is frequently limited to one of three strategies [58]. The first option is to administer a first-line antibiotic (i.e., meropenem, fluoroquinolone, aminoglycoside) at higher doses to overcome resistance. However, some CR-KP isolates exhibit such high minimal inhibitory concentrations to first-line agents that extreme doses with unacceptable toxicity would be required to achieve pharmacokinetic/pharmacodynamic (PK/PD) exposures required for efficacy. The second choice is to use a second-line antibiotic with Gram-negative activity for which resistance is not yet developed (e.g., colistin, tigecycline, gentamicin, fosfomycin). Unfortunately, many second-line agents are more toxic than first-line drugs or have significant PK deficiencies that limit their activity in anatomical sites where CR-KP are most likely to emerge, including the urine, bloodstream and lung [38–43]. Moreover, all of the second-line antimicrobials are prone to rapid emergence of resistance during treatment if used as monotherapy [22]. The final strategy for treating CR-KP infections is to combine first- and second-line antibiotics with the hope that synergistic interactions between antibiotics will lessen the need for extremely high antibiotic doses, suppress the emergence of resistance and overcome the PK weaknesses of individual agents [58].

Given these limited options, it is clear why many clinicians have embraced combination therapy as the preferred treatment strategy for CR-KP. Yet, the use of combination therapy does not preclude the need for adequate dosing of an individual drug [58]. In fact, a number of studies have suggested that higher-dose, PD-optimized dosing regimens are an essential component of effective combination regimens for CR-KP infection [59]. In the following section, the authors will review PK/PD principles and practical issues for dosing of core antibiotics (meropenem, colistin, tigecycline and gentamicin and fosfomycin) used in the treatment of CR-KP infections.

The importance of loading doses

In the past, the majority of PK/PD models examining the antibiotic dosing for severe Gram-negative infections focused on the drug exposures achieved at steady state in noncritically ill patients – that is, 2–3 days into therapy [60]. As such, recommendations surrounding the need for initially high antibiotic doses, or loading doses (LDs), were primarily considered only for antibiotics with long half-lives that require several days of therapy to achieve a PK steady state [60]. Yet, there is a growing consensus that patient drug exposures with the first antibiotic dose or within 24 h of starting therapy may be the most critical period for determining treatment outcome and risk for emergence of MDR pathogens [61]. This is because the first antibiotic dose is typically administered when inoculum of infection is high and likely to harbor moderately or severely resistant subpopulations. Variable, fluctuating or suboptimal antibiotic concentrations during the first few days of therapy, especially in a critically ill septic patient, greatly increases the risk of selecting resistant subpopulations that later breakthrough in the patient with untreatable levels of resistance. These risks are magnified in patients who do not receive timely (early) effective treatment for CR-KP, allowing progression to a higher inoculum. Consequently, contemporary dosing strategies directed to MDR-resistant organisms have begun to place greater emphasis on the administration of high antibiotic LDs in critically ill patients during the initial phases of treatment, even for agents with relatively short half-lives (i.e., β-lactams) [62].

LDs should be considered for many of the 'core' antibiotics used in a treatment regimen for CR-KP infections. The LD can be calculated using the formula $LD = V_d \times C_p$ (Table 1), where V_d is the calculated volume of distribution and C_p is the desired plasma concentration [62]. Importantly, patients who are critically ill with sepsis often have marked expansion of extracellular body water caused by capillary leakage and aggressive fluid repletion [62]. Higher LDs of hydrophilic agents, such as β-lactams, aminoglycosides and colistin, are often required in septic patients to overcome this increase in V_d and achieve desired plasma drug concentrations during the first 24 h of therapy [63,64]. Alternatively, lipophilic antibiotics (i.e., rifampin, tigecycline) have a greater affinity for adipose tissue, which may justify the use of higher LDs in obese patients [62].

A common misconception is that initial LDs need to be adjusted on the basis of the renal function of the patient. Although impaired drug clearance in a patient has relevance to prolonging the interval in between drug doses and adjustment of maintenance doses, renal function does not influence the LD required by the patient. Therefore, LDs are not adjusted or reduced in patients with impaired kidney function [62].

PK/PD optimization of maintenance doses

After administration of the LD, antibiotics are dosed according to their PK/PD characteristics, accounting for individual patient-specific factors such as kidney function and risk for toxicity. An accurate assessment of renal glomerular filtration rate (GFR) is important for devising appropriate maintenance dosing strategies for many antibiotics used to treat CR-KP infection (Table 1). However, methods for estimating GFR on the basis of measurement of plasma creatinine (i.e.,

Table 1. Core antibiotics and dosing regimens used for carbapenem-resistant *Klebsiella pneumoniae* infections.

Drug	PK:PD parameter	V_d (l) Typical loading dose†	Maintenance dose	Ref.
Doripenem	40% *f*Time > MIC	16.8 1000–2000 mg	1000–2000 mg every 8 h 4-h infusion CrCL >50 ml/min: standard dose CrCL 26–50: reduce dose by 50% CrCL 26 ml/min or HD/CVVHD: Use renally-adjusted dose with intermittent infusion	[111,112]
Meropenem	40% *f*Time > MIC	15–20 2000 mg	2000 mg every 8 h 4-h infusion CrCL 50 ml/min: standard dose CrCL 26–50: reduce dose by 50% CrCL 26 ml/min or HD/CVVHD: use renally-adjusted dose with intermittent infusion	[69]
Colistin‡	*f*AUC:MIC 25–50	45.1 Loading dose CBA (mg) = colistin C_p§ × 2 × weight (kg)¶	Daily dose of CBA (mg) colistin = C_p§ (1.50 × CrCL × 30) Recommended dosage intervals based on CrCL#: 10 ml/min/1.73 m^2: every 12 h, 10–70 ml/min/1.73 m^2 every 8–12 h and 70 ml/min/1.73 m^2: every 8–12 h Intermittent HD dosing: daily dose of CBA on a non-HD day to achieve each 1.0 mg/l colistin = C_p§ = 30 mg Supplemental dose of CBA on a HD day††: add 50% to the daily maintenance dose if the supplemental dose is administered during the last hour of the HD session, or add 30% to the daily maintenance dose if the supplemental dose. Twice-daily dosing is suggested Continuous renal replacement: daily dose of CBA to achieve each 1.0 mg/l colistin C_p§ target 192 mg. Doses may be given every 8–12 h	[79]
Tigecycline	*f*AUC:MIC 1	490–700 100–200 mg	50–100 mg every 12 h 'High-dose' therapy 200-mg loading dose, then 100 mg once daily	[87,90]
Gentamicin	*f*AUC:MIC 156	17.5 No loading dose recommendation	5 mg/kg/day for MIC <1; 7 mg/kg for MIC >2 Dose adjustment for renal dysfunction is guided by plasma concentration monitoring	[92]

†Estimated volume of distribution in 70 kg patient.
‡Expressed as milligrams of CBA, 33.3 mg base = 10^6 units = 50 mg colistin sulfate = 80 mg of CMS. The suggested maintenance dose daily dose would commence 24 hours after the administration of a CMS loading dose. However, some studies suggest maintenance dosing should be started 12 hours after the loading dose, especially in critically-ill patients [76].
§Colistin concentration-steady state, average target is expressed in milligrams per liter. The dosing target is based on the MIC, site and severity of infection.
¶Use the lower of ideal or actual body weight, expressed in kilograms. Caution is suggested using CBA loading doses >300 mg (see the text for more details).
#C_p target expressed in milligrams per liter. CrCL expressed in ml/min/1.73 m^2. Although the Jelliffe equation was used to estimate CrCL in this study, other means (e.g., Cockcroft–Gault equation) may be used to estimate CrCL, which should then normalized to a body surface area of 1.73 m^2. See original publication [23] regarding the possibility of dosing recommendations in patients with CrCL >70 ml/min/1.73 m^2 or when targeting a 'high' colistin C_p, both being circumstances where the algorithm may predict daily doses of CBA substantially greater than the current upper limit in the product label.
††Supplemental dose of CMS to achieve a similar colistin C_p on a HD day as occurs on a non-HD day. The dosing recommendation assumes that the HD session occurs toward the end of a CMS dosage interval.
AUC: Area under the curve; CBA: Colistin base activity; CMS: Colistin methanesulfonate; C_p: Plasma concentration; CrCL: Creatinine clearance; CVVHD: Continuous venovenous hemodialysis; HD: Hemodialysis; PD: Pharmacodynamic; PK: Pharmacokinetic.

Table 1. Core antibiotics and dosing regimens used for carbapenem-resistant *Klebsiella pneumoniae* infections (cont.).

Drug	PK:PD parameter	V_d (l) Typical loading dose†	Maintenance dose	Ref.
Fosfomycin	60% *f*Time > MIC	17–25 No loading dose recommendation	8000 mg every 12 h	[95]
Rifampin	*f*AUC:MIC (not elucidated as monotherapy for Gram negatives)	80–90 No loading dose recommendation	10 mg/kg every 12 h	[100]

†Estimated volume of distribution in 70 kg patient.
‡Expressed as milligrams of CBA, 33.3 mg base = 10^6 units = 50 mg colistin sulfate = 80 mg of CMS. The suggested maintenance dose daily dose would commence 24 hours after the administration of a CMS loading dose. However, some studies suggest maintenance dosing should be started 12 hours after the loading dose, especially in critically-ill patients [76].
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AUC: Area under the curve; CBA: Colistin base activity; CMS: Colistin methanesulfonate; C_p: Plasma concentration; CrCL: Creatinine clearance; CVVHD: Continuous venovenous hemodialysis; HD: Hemodialysis; PD: Pharmacodynamic; PK: Pharmacokinetic.

Cockcroft–Gault and modification of diet in renal disease) can produce inaccurate estimates of GFR in critically ill patients with changing renal function [65]. Moreover, these methods frequently overestimate renal function in elderly patients with low muscle mass, while underestimating renal clearance in other populations. Specifically some ICU patients display patterns of augmented renal clearance (i.e., creatinine clearance: CL_{CR} 130 ml/min/1.73 m^2), which may lead to subtherapeutic antibiotic bloodstream concentrations at currently recommended doses [66]. The physiological basis for augmented renal clearance is multifactorial, but probably arises from the hyperdynamic state associated with Gram-negative sepsis [62,66], application of vasoactive medications and the use of large-volume fluid resuscitation [62]. Younger trauma and postoperative patients with lower illness severity scores, burn victims and pregnant patients are more likely to manifest augmented renal clearance despite apparently 'normal' renal function estimated by conventional calculations [62,66]. The risks of antibiotic underdosing are even present in septic patients with severe renal dysfunction [67]. Consequently, therapeutic drug monitoring is increasingly being explored, even for β-lactams, as an approach to reduce the risk of antibiotic underdosing in critically ill patients with augmented renal clearance [68]. However, the clinical benefits of such monitoring for patients remain unproven.

Carbapenems

Despite increasing resistance, antipseudomonal carbapenems (doripenem, IMP, meropenem) continue to be essential antibiotics for the treatment of healthcare-associated infections in critically ill and immunocompromised patients. Following intravenous infusion, carbapenems distribute widely into various body fluids (i.e., epithelial lining fluid of the lung, blood, urine, central nervous system), which contributes to their efficacy for a wide range of infections [60]. In terms of their PD profile, carbapenems display time-dependent bactericidal activity against Gram-negative bacteria when free drug concentrations remain, at minimum, above the MIC of the infecting pathogen for 40–50% of the dosing interval (40–50% *f*Time > MIC) [60]. As carbapenems are rapidly cleared (unchanged) through the kidney with plasma half-lives ranging from 1 to 2 h, the most efficient strategy for prolonging carbapenem *f*Time > MIC in plasma and tissue when treating pathogens with elevated MICs is to administer the drug at higher doses by prolonged or continuous infusion (Figure 1A & B) [69]. Indeed, extended-infusion strategies have been associated with improved clinical response compared with bolus infusions of the same dose at higher MICs in patients with ventilator-associated pneumonia [70].

Depending on the circulating strains and prior antibiotic treatment, some patients may be infected with CR-KP isolates that exhibit relatively low (<4 mg/l) or moderately elevated carabapenem MICs (8–16 mg/l). Although these strains are reported as resistant to carbapenems by the microbiology laboratory, they are often treatable with higher-dose regimens in combination with other agents. Qureshi *et al.* reported that in a cohort of 41 patients with CR-KP bacteremia, the highest clinical response rates were observed in patients who received a carbapenem-containing combination regimen, even though nearly a third of the isolates were classified as carabapenem–resistant by current breakpoints [71]. Daikos *et al.* also found that patients with CR-KP infections who received carbapenem-containing combination regimens (usually administered with an aminoglycoside or tigecycline) had significantly lower mortality rates compared with patients who received noncarbapenem-containing regimens (12 vs 41%; p = 0.006), especially in cases where the MIC of the infecting isolate was <4 mg/l [72]. These clinical observations are supported by PK:PD simulations that predicted a meropenem regimen of

2000 mg every 8 h administered as a 4-h infusion could achieve adequate exposures (40% *f*Time > MIC) in 100, 75 and 40% of septic patients infected with CR-KP isolates with MICs of 4, 8 and 16 mg/l, respectively (Figure 1C) [72]. Tumbarello *et al*. recently reported that clinical response to tigecycline–colistin combination regimens for CR-KP infection was substantially higher if meropenem was included in the combination [73]. Survival rates for combination regimens that included meropenem were 87% at meropenem MICs < 4, 75% at MICs of 8 mg/l and 65% at MICs > 16 mg/l, which was better than the overall survival rate (58%) reported in the study.

Several practical issues must be considered when using higher-dose, prolonged infusion carbapenem regimens. First, these antibiotics are relatively unstable at room temperature after reconstitution; therefore, bags must typically be changed every 4–6 h. However, some investigators have reported that meropenem will remain stable up to 8 h if infusion bags are maintained <23°C, allowing for the administration of a continuous-infusion-like regimen (i.e., 2000 mg every 8 h administered over 8 h) [69].

IMP is generally not used for high-dose, prolonged-infusion therapy because of its poor stability at room temperature and higher risk for seizures at high doses compared with meropenem or doripenem. Finally, the administration of extended or continuous infusion can complicate the administration schedules of other drugs that are noncompatible with carbapenems. However, the benefits of prolonged-infusion regimens often outweigh these logistical concerns for the patient in the setting of CR-KP treatment.

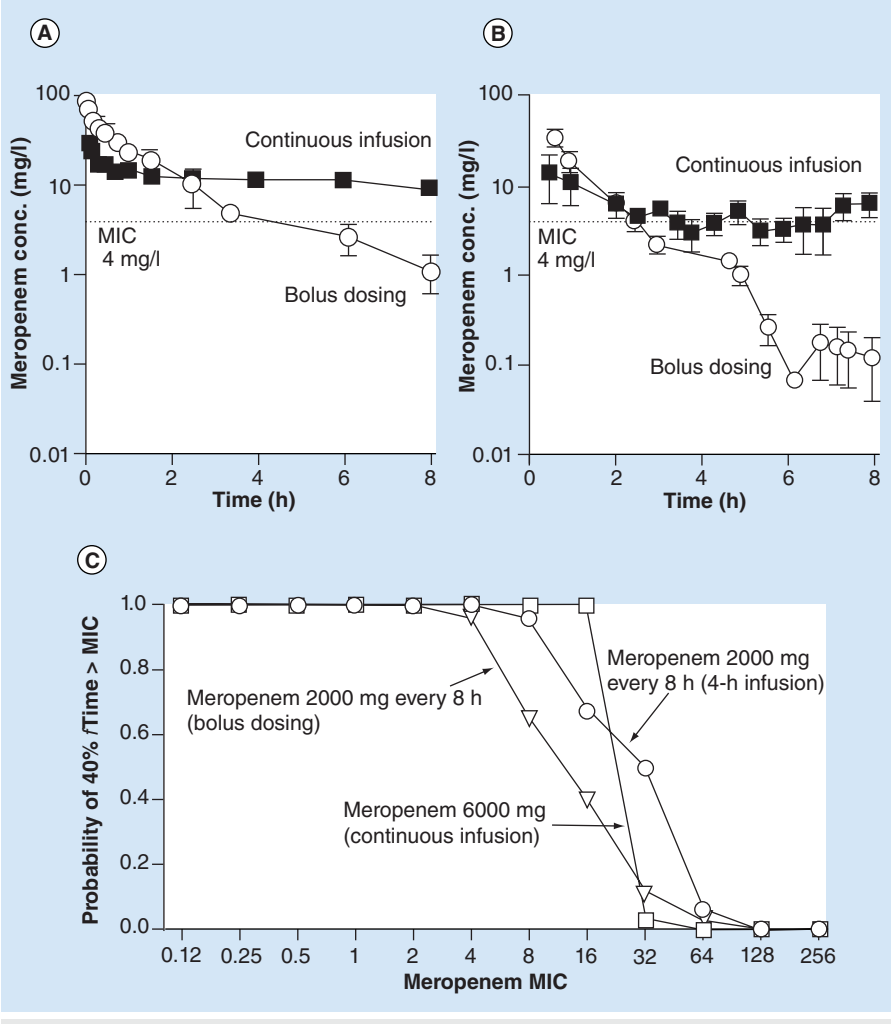

Figure 1. Meropenem concentrations in critically ill patients with sepsis without renal dysfunction administered as intermittent or continuous-infusion regimens of meropenem. (A) Plasma and **(B)** subcutaneous tissue concentrations observed in ten critically ill patients administered 500-mg loading dose, then 1000 mg every 8 h continuous infusion (filled squares); or 1500-mg loading dose followed by 1000 mg every 8 h bolus dose (open circles). **(C)** Monte Carlo dosing simulations, meropenem 6000 mg/day. Pharmacokinetic data from the critically ill patients were used to develop a population pharmacokinetic model to analyze the pharmacokinetic/pharmacodynamic performance of simulated high-dose (6000 mg/day) meropenem regimens over a range of hypothetical pathogen MICs. High-dose extended or continuous-infusion meropenem regimens had high probability pharmacokinetic:pharmacodynamic target attainment up to an MIC of 8–16 mg/l.
Reproduced with permission from [69].

Colistin

Colistin is a cationic antimicrobial peptide with activity against Gram-negative pathogens originally introduced for clinical use in the late 1950s, however its use fell out of favor until recently due to nephrotoxicity and neurotoxicity concerns. Increasing resistance rates among Gram-negative pathogens have resurrected use of this old drug, particularly for the treatment of carbapenem-resistant organisms. Because colistin was never subjected to intensive regulatory review prior to clinical use, its chemical, PK and PD properties of the parent drug (colistin sulfate) or the sulfomethyl derivative prodrug administered to patients (colistin methanesulfonate [CMS]) were incompletely characterized. However, recent investigations have clarified key aspects of colistin PK:PD properties, prompting revised dosing recommendations especially in critically ill patients infected with MDR organisms [74,75].

Older colistin PK studies did not reliably differentiate between the inactive CMS prodrug and formed colistin *in vivo*, which is the microbiologically active component responsible for drug activity [74,75]. As such, much of the PK information underlying prescribing recommendations over the past 50 years was inaccurate and contributed to the use of ineffective doses, especially in patients with good renal function [75]. More recent studies have utilized

analytical methods that differentiate inactive CMS from formed colistin and have revealed important differences in the pathways of elimination and clearance half-life between the two drug forms. Specifically, colistin formed *in vivo* following a CMS dose is present in much lower bloodstream concentrations that previously reported, displays a longer elimination half-life than the CMS prodrug and does not undergo extensive renal elimination [76].

Colistin is a concentration-dependent killing antibiotic against *K. pneumoniae*, including MDR CR-KP strains [77]. Colistin concentrations at or above the MIC result in rapid initial bacterial killing, which is attenuated at higher inocula and with continued dosing, often resulting in regrowth when the drug is used as monotherapy. The diminishing activity of colistin with each subsequent dose may reflect high basal rates of heteroresistance at high inocula, which allow resistant subpopulations to dominate after several doses of colistin monotherapy [78]. In animal thigh and lung infection models, the activity of colistin most closely correlates with the ratio of time-averaged, nonprotein-bound (free) drug exposure relative to the MIC (*f*AUC/MIC). Specifically, dosing regimens that produce formed colistin *f*AUC/MIC exposures of 50–65 or higher are associated with bactericidal activity *in vivo* against *P. aeruginosa* [75]. In practical terms, CMS dosing regimens that are likely to be effective *in vivo* result in twofold higher colistin concentrations on average than the pathogen MIC.

Recent population PK studies evaluating the PK of formed colistin in critically ill patients have confirmed that previously recommended doses often result in inadequate or delayed drug exposure insufficient for treating CR-KP isolates. Plachouras *et al.* reported that significant delay in the attainment of steady-state plasma concentrations of formed colistin when CMS was started without a LD resulted in drug exposures that were below the MIC susceptibility breakpoint of 2 mg/l for several days, with many patients never forming sufficient active drug until several days into therapy [76]. In the largest population PK study to date, Garonzik *et al*. examined the impact of renal function on the rate and disposition of formed colistin in critically ill patients [79]. Of note, as renal function declined, so too did the renal clearance of CMS, resulting in a greater fraction of the dose being converted to active colistin, thus giving the false appearance that the clearance of formed colistin was decreased in patients with poor renal function. Importantly, the authors found that the administration of colistin at the highest current product-recommended dose range (300 mg colistin base or 9 million units [MU]) in patients with moderate to good renal function resulted in low and potentially suboptimal plasma concentrations, especially if the infecting organism had a MIC >1 mg/l, confirming the suboptimal PK/PD of colistin monotherapy in this population. On the basis of this large population PK study, the authors provided specific dosing recommendations for colistin as described in Table 1.

One concern with the use of higher-dose regimens is that patients at greater risk for developing nephrotoxicity and neurotoxic adverse effects. Dalfino *et al*. recently described their clinical experience with higher-dose colistin regimens in 28 critically ill septic patients [80]. Patients received CMS administered as a 9 MU LD (300 mg base) followed by 9 MU maintenance dose administered as twice daily (b.i.d.) doses adjusted for renal function based on the recommendations of Plachouras *et al.* [76] and Garonzik *et al.* [79]. Colistin monotherapy was used in 50% of the cases or administered in combination with carbapenems (16%) or aminoglycosides (35%). The rates of clinical (82%) and microbiological success (74%) were relatively high in this study compared with previous case series, with no reports of breakthrough infections. Although 17% of patients developed evidence of acute kidney injury, the majority of patients recovered to baseline renal function once colistin was stopped, and no neurotoxic events were reported [80]. Although more data are needed in diverse patient populations, these data suggest that the higher-dose colistin regimens were relatively effective with acceptable and reversible nephrotoxicity in the treatment of life-threatening infection, provided doses are adjusted in accordance with renal function.

Colistin displays relatively poor pulmonary distribution, especially at lower doses (6 MU/day) in patients with ventilator-associated pneumonia [81,82]. Consequently, the efficacy of aerosolized colistin as an adjunctive therapy has been investigated in patients with ventilator-associated pneumonia with mixed results [83]. The bulk of the evidence to date, however, suggests that inhaled colistin as an adjunct to intravenous therapy is safe and may have some benefit in patients with CR-KP colonization of the respiratory tract [84].

Tigecycline

Tigecycline is broad-spectrum, bacteriostatic minocycline derivative (glycylcyline) that was chemically designed to be a poor substrate for tetracycline-specific efflux pumps. As such, tigecycline retains activity against many tetracycline-resistant Gram-positive, Gram-negative, anaerobic and atypical pathogens, including many CR-KP strains [85]. Unfortunately, resistance to tigecycline is becoming more prevalent in endemic regions for CR-KP infection, and acquired resistance in CR-KP strains develops quickly if tigecycline is administered as monotherapy [85,86].

Tigecycline demonstrates concentration-dependent PD characteristics with higher treatment responses in nosocomial pneumonia (excluding *P. aeruginosa*) observed as the plasma *f*AUC:MIC approaches 1 [87,88]. The low plasma *f*AUC:MIC ratio associated with tigecycline treatment response reflects the extremely large volume of distribution (7–10 kg/l) of the drug, which rapidly accumulates in intracellular and tissue compartments, resulting in low residual drug concentrations in the bloodstream, epithelial lining fluid of the lung or urinary tract, where only 22% of the drug is excreted in active form (Table 1) [87]. As such, tigecycline is not generally considered adequate monotherapy for CR-KP infections, especially in those body sites where concentrations are low. This concern is supported by pooled analysis of outcomes in nosocomial pneumonia and bloodstream infection trials, which demonstrated higher overall mortality rates in tigecycline-treated patients versus comparator drugs that achieve higher concentrations in the lung and bloodstream [89]. The peak plasma concentrations achieved with standard parenteral tigecycline dosing (100 mg LD, 50 mg b.i.d.) typically range from 0.6 to 0.9 mg/l [87,88], while the EUCAST susceptibility breakpoint is defined at 1 mg/l. Not surprisingly, persistent or

Table 2. Preclinical investigations of combination therapy with core antibiotics used for carbapenem-resistant *Klebsiella pneumoniae* infections.

Combination	Test method	Summary of results	Ref.
Carbapenem† with:			
– Aminoglycoside	TK (n = 4 isolates)	Synergy (2 $\log_{10}$) improved kill reported in all carbapenem and amikacin-R isolates versus either drug alone	[113]
– Polymyxin B/E	TK (n = 8 colistin and imipenem-S; n = 16 imipenem-R and colistin-S; n = 15 imipenem and colistin-R; n = 4 imipenem-S and colistin-R	Synergy observed in 50%; indifference in 50% of colistin-S strains, irrespective of imipenem MIC. Less benefit and occasional antagonism (55%) observed in colistin-R strains	[114]
	Etest and TK studies (n = 14 isolates)	Etest synergy (43%); TK (64%)	[115]
	TK (n = 12 isolates with carbapenem MICs ≥16, 14/16 colistin-R)	Synergy (50%); indifference (50%); antagonism (0%)	[116]
– Doxycycline	TK (n = 12 isolates with carbapenem MICs ≥16, 14/16 colistin-R)	Synergy (25%); indifference (58%); antagonism (17%)	[116]
– Tigecycline	IVPM (simulated pulmonary exposures) against carbapenem-S and -R strains	Improvement in area under bactericidal curves up to a meropenem MIC of 64 mg/l	[117]
	TK studies (n = 4 isolates)	No evidence of synergy	[118]
	CK (n = 10 isolates)	Synergy (30%)	[119]
	TK studies (n = 15 carbapenem-R isolates; n = 6 colistin-R)	Synergy (65%), indifference (25%), antagonism (0%)	[120]
– Fosfomycin	Etest n = 65 isolates	Synergy (66–75%)	[121]
– Ertapenem	IVPM, murine thigh infection model	Improved activity of doripenem (prolonged bactericidal activity *in vitro*) and significantly greater reduction in tissue bacterial burden	[122]
Polymyxin B/E with:			
– Aminoglycoside	TK (n = 12 isolates with carbapenem MICs ≥16, 14/16 colistin-R)	Synergy (50%), indifference (50%), antagonism (8%)	[116]
– Tigecycline	CK (n = 12 isolates, carbapenem and colistin-R)	Synergy described in representative strains (% not reported)	[123]
	TK studies (n = 4 isolates)	Bactericidal synergy observed with most strains	[118]
	CK (n = 12 isolates, carbapenem and colistin-R)	Synergy described in representative strains (% not reported)	[123]
	Etest and TK studies (n = 14 isolates)	Etest synergy (43%); TK synergy (100%)	[115]
– Doxycycline	CK (n = 12 isolates, carbapenem and colistin-R)	Synergy described (% not reported)	[124]
– Rifampin	TK assay (16 isolates)	Synergistic bactericidal activity observed in 15/16 isolates	[124]
– Fosfomcyin	Etest (n = 65 isolates)	Synergy (29%)	[121]
Tigecycline with:			
– Aminoglycoside	CK (n = 10 isolates)	Indifference	[119]
– Rifampin	CK (n = 10 isolates)	Synergy (67%)	[119]
– Fosfomycin	Etest (n = 65 isolates)	Synergy (27%)	[121]

EUCAST susceptibility breakpoints: meropenem, imipenem, doripenem, colistin.
†Doripenem, imipenem or meropenem.
CK: Checkerboard dilution; IVPM: *In vitro* pharmacodynamic model; R: Resistant; S: Susceptible; TK: Time-kill study.

breakthrough bacteremia has been reported even in patients infected with tigecycline-'susceptible' *K. pneumoniae* strains [86]. Although higher daily doses of tigecycline (i.e., 200 mg LD, then 100 mg daily) can transiently elevate plasma concentrations [90], these higher doses have been reported to be associated with an even greater V_d and longer elimination half-life, suggesting

Table 3. Outline of clinical studies with sufficient data about antimicrobial treatment and response of carbapenem-resistant *Klebsiella pneumoniae* infection.

Study (year)	Study design	Patients (n)	Infections site	CR-KP mechanism	Treatment	Outcome	Ref.
Daikos *et al.* (2009)	Prospective observational study	67	All BSI	All VIM	Monotherapy: 37 (colistin: 15; carbapenem: 14; aminoglycoside: 8) Combination therapy: 12 (carbapenem + colistin: 8; carbapenem + aminoglycoside: 4)	Mortality among patients who received one active drug 27% Mortality among patients who received combination therapy with two active drugs 8.3%	[102]
Weisenberg *et al.* (2009)	Case series	21	LRTI 9 (5 HAP, 4 TAS) UTI 5 (4 complete) BSI 4 Other 3 (1 shunt-associated meningitis)	All KPC	Monotherapy: 19 (carbapenem: 11; tigecycline: 5; gentamicin: 3) Combination therapy: 2 (tigecycline + gentamicin: 1, tigecycline + imipenem: 1)	Patients who received combination therapy had each: shunt-associated meningitis cured with tigecycline plus gentamicin (intrathecally and intravenous); primary bacteremia, patient died during therapy with tigecycline plus imipenem	[40]
Michalopoulos *et al.* (2010)	Case series	11 (critically ill)	BSI 2 VAP and BSI 3 VAP and UTI 2 UTI 2 BSI and SSI 1 SSI 1	ND	Combination therapy with fosfomycin IV plus colistin: 7; gentamicin: 3 and piperacillin/tazobactam: 1	Microbiological and clinical cure for all cases Overall mortality 18.2%	[41]
Nguyen *et al.* (2010)	Retrospective study	48	All BSIs	ND	Monotherapy: 28 (tigecycline: 10; colistin: 9; other: 9) Combination therapy with colistin + tigecycline: 13 No potentially active therapy: 7	Mortality at 7 days and at discharge: 23 and 60%, respectively Favourable response rate at 7 days for combination therapy, colistin and tigecycline monotherapy: 46, 33 and 30%, respectively	[86]
Mouloudi *et al.* (2010)	Case–control study	37	All BSIs	VIM 18 (17 VIM-1, 1 VIM-12)	Colistin monotherapy: 35	Overall in-hospital mortality 57%	[52]
				KPC 19 (all KPC-2)	Colistin + gentamicin: 18	No impact of treatment on outcome	

†Most common combination therapy includes colistin and tigecycline (n = 9).
‡Following regimens were employed: colistin-based regimens with meropenem (n = 4), tigecycline (n = 2), rifampicin (n = 1); meropenem + amikacin (n = 2); tigecycline + amikacin + cefepime (n = 1); and tobramycin + cefepime (n = 1).
§Most common combination regimens were carbapenem with either colistin (5) or tigecycline (3).
BSI: Bloodstream infection; CR-KP: Carbapenem-resistant *Klebsiella pneumoniae*; HAP: Hospital-acquired pneumonia; IAI: Intra-abdominal infection; KPC: *K. pneumoniae* carbapenemase; LRTI: Lower respiratory tract infection; ND: Not defined; SBT: Serum bactericidal titers; SSI: Surgical site infection; UTI: Urinary tract infection; VAP: Ventilator associated pneumonia; VIM: Verona integron-encoded metallo-β-lactamase.

Table 3. Outline of clinical studies with sufficient data about antimicrobial treatment and response of carbapenem-resistant *Klebsiella pneumoniae* infection (cont.).

Study (year)	Study design	Patients (n)	Infections site	CR-KP mechanism	Treatment	Outcome	Ref.
Falagas *et al.* (2010)	Retrospective study	18	LRTI BSI IAI CR-BSI other	ND	Colistin monotherapy: 0 Colistin + meropenem: 15 Colistin + other agents: 3	Cure 83.3% Deterioration 27.8%	[125]
Souli *et al.* (2010)	Observational (retrospective and prospective) study	18	BSI 14 SSI 2 LRTI 1 UTI 1	All KPC-2	Colistin monotherapy: 7 Colistin + other agents: 11	Cure 66.7% Failure 33.3% Cure rate was the same for monotherapy and combination therapy	[45]
Neuner *et al.* (2011)	Retrospective study	51	All BSI	ND	Monotherapy (tigecycline, colistin) Combination therapy with tigecycline + colistin	Microbiological cure for 74.5% of cases 14-day mortality 31% No differences of outcome for monotherapy and combination therapy	[103]
Zarkotou *et al.* (2011)	Prospective observational study	53 (35 treated at least 48 h)	All BSI	KPC-2	Combination therapy: 20[†] Monotherapy: 15 (colistin: 7; tigecycline: 5; gentamicin: 2; carbapenem: 1)	Infection mortality 34% Overall mortality 52.8% Combination therapy was strongly correlated with survival (p = 0.001)	[104]
Rihani *et al.* (2012)	Retrospective study	42	Colonization 18 Infection 24	ND	Combination therapy: 11[‡]	Microbiological and clinical cure were higher for patients treated with combination therapy than for those receiving monotherapy (83% vs 60%, p = 0.35)	[105]
Qureshi *et al.* (2012)	Prospective observational study	41 (34 received definitive treatment)	All BSI	21 KPC-2 20 KPC-3	Monotherapy: 19 (colistin: 7; tigecycline: 5; carbapenem: 4) Combination therapy: 15[§]	Mortality for monotherapy 66.7% Mortality for combination therapy 12.5% Combination therapy was independently associated with survival	[71]

[†]Most common combination therapy includes colistin and tigecycline (n = 9).
[‡]Following regimens were employed: colistin-based regimens with meropenem (n = 4), tigecycline (n = 2), rifampicin (n = 1); meropenem + amikacin (n = 2); tigecycline + amikacin + cefepime (n = 1); and tobramycin + cefepime (n = 1).
[§]Most common combination regimens were carbapenem with either colistin (5) or tigecycline (3).
BSI: Bloodstream infection; CR-KP: Carbapenem-resistant *Klebsiella pneumoniae*; HAP: Hospital-acquired pneumonia; IAI: Intra-abdominal infection; KPC: *K. pneumoniae* carbapenemase; LRTI: Lower respiratory tract infection; ND: Not defined; SBT: Serum bactericidal titers; SSI: Surgical site infection; UTI: Urinary tract infection; VAP: Ventilator associated pneumonia; VIM: Verona integron-encoded metallo-β-lactamase.

Table 3. Outline of clinical studies with sufficient data about antimicrobial treatment and response of carbapenem-resistant *Klebsiella pneumoniae* infection (cont.).

Study (year)	Study design	Number of patients	Infections site	CR-KP mechanism	Treatment	Outcome	Ref.
Tumbarello *et al.* (2012)	Retrospective study	125	All BSI	98 KPC-3	Monotherapy: 46 (colistin: 22; tigecycline: 19)	Overall 30-day mortality 41.6%, varied from 34.1% to 54.3% for combination therapy and monotherapy (p = 0.02)	[73]
				27 KPC-2	Combination therapy: 79 (colistine + tigecycline: 23; colistin + tigecycline + meropenem: 16)	Combination therapy with colistin + tigecycline + meropenem was independently associated to survival	

†Most common combination therapy includes colistin and tigecycline (n = 9).
‡Following regimens were employed: colistin-based regimens with meropenem (n = 4), tigecycline (n = 2), rifampicin (n = 1); meropenem + amikacin (n = 2); tigecycline + amikacin + cefepime (n = 1); and tobramycin + cefepime (n = 1).
§Most common combination regimens were carbapenem with either colistin (5) or tigecycline (3).
BSI: Bloodstream infection; CR-KP: Carbapenem-resistant *Klebsiella pneumoniae*; HAP: Hospital-acquired pneumonia; IAI: Intra-abdominal infection; KPC: *K. pneumoniae* carbapenemase; LRTI: Lower respiratory tract infection; ND: Not defined; SBT: Serum bactericidal titers; SSI: Surgical site infection; UTI: Urinary tract infection; VAP: Ventilator associated pneumonia; VIM: Verona integron-encoded metallo-β-lactamase.

increased intracellular accumulation or tissue distribution at higher doses [87,91]. Moreover, higher doses of tigecycline may be associated with increased nausea, although this can frequently be managed with slower infusion rates [90]. Therefore, it is still unknown whether higher daily tigecycline doses truly result in higher concentrations of microbiologically active drug in the bloodstream, urine or epithelial lining fluid needed to treat CR-KP pathogens.

Aminoglycosides

Although many CR-KP strains harbor modifying enzymes or 16S RNA methylases that confer cross-resistance to all aminoglycosides, some strains retain susceptibility to gentamicin, which can be an important component of combination regimens directed toward the treatment of bloodstream and/or urinary tract infections. In a reanalysis of aminoglycoside dosing recommendations based on updated PK/PD and toxicodynamic data, Drusano *et al.* recommended an empirical dose of gentamicin of 5 mg/kg for isolates with MICs < 1 mg/l administered once daily (or less frequently in patients with renal dysfunction), with consideration of discontinuing therapy after 1 week of therapy [92]. Larger gentamicin doses (e.g., 7 mg/kg/day) were recommended for isolates with MICs as high as 2 mg/l, but shorter treatment courses should be considered (i.e., to 5 days) to reduce the risk of nephrotoxicity. Therapy is then individualized through serum drug level monitoring when microbiological data become available, especially in critically ill patients who are more likely to have suboptimal exposures and are at greater risk for nephrotoxicity [93,94].

Fosfomycin

Fosfomycin is a broad-spectrum, time-dependent bactericidal antibiotic that inhibits an early enzymatic step in bacterial cell wall synthesis with activity against many CR-KP isolates, including tigecycline and colistin-resistant strains [95]. Although primarily used as oral formulation for the treatment of urinary tract infections, a disodium salt formulation for intravenous administration is available in Japan and some European countries. Fosfomycin has several favorable PK characteristics that make it an appealing agent for treating CR-KP infections in critically ill patients, including an ability to achieve high concentrations in the urine, plasma, lung, cerebrospinal fluid and muscle, and relatively low risk for nephrotoxicity [95]. In a recent analysis of adverse effects associated with 72 fosfomycin treatment courses, hypokalemia was possibly associated with rapid infusions over 30 min was the most common reported adverse effect (26% of patients), followed by injection-site pain (4%) and heart failure (3%) that was likely a consequence of the high salt concentration of the intravenous formulation [96].

Resistance to fosfomycin will often develop rapidly if the drug is used as monotherapy, especially when treating *K. pneumoniae*. Although fosfomycin PK/PD has not been studied in humans as extensively as other agents recommended for CR-KP infection, intravenous doses of 8 g b.i.d. have been reported to achieve *f*Time > MIC of 60–70% against pathogens with MICs up to 35 mg/L [97,98]. Daily doses of up to 20 g per day, possibly

administered by prolonged or continuous infusion, may allow for the treatment of isolates with marginally higher MICs. However, few data are available to support the safety of such regimens. Renal impairment decreases the excretion of fosfomycin; therefore, doses are reduced in patients with estimated clearance <50 ml/min (Table 1).

Rifampin

Although best known for its antimycobacterial and Gram-positive activity, rifampin has been reported to have synergistic activity with colistin against MDR organisms such as CR-KP [99,100]. Rifampin is also occasionally considered for inclusion in combination regimens because of its unique capacity to penetrate intracellular sites and biofilms, which could be important in the treatment of CR-KP infections involving prosthetic material [100]. Nevertheless, there are few data to support the routine use of rifampin for the treatment of CR-KP infections beyond *in vitro* synergy studies and a few case series that lack adequate controls [58,100]. Use of rifampin increases the risk for a number of clinically significant PK drug interactions, particularly with immunosuppressive agents, warfarin, chemotherapy and antifungal agents. Therefore, concomitant medications should be carefully screened before considering the addition of rifampin to any treatment regimen for CR-KP infection.

Outcome

Mortality attributable to CR-KP infection varies between 18 and 60% [1], with the highest mortality rates reported in patients with bacteremia, especially in patients with underlying immunosuppression, such as recipients of solid-organ transplantation [38,44,101]. When patients with CR-KP were compared with those with carbapenem-susceptible *K. pneumoniae* infection, carbapenem resistance was associated with higher crude patient mortality [44,50,52,53,102]. Age, higher Charlson comorbidity score, malignancy, heart disease, receipt of solid-organ transplant, ICU stay, severity of underlying conditions (SOFA, APACHE II), mechanical ventilation, higher Pitt bacteremia score and inappropriate antibiotic therapy have been associated with higher mortality among patients with CR-KP bacteremia [50,52,57,86,103,104], whereas removal of the infectious focus (e.g., catheter removal, debridement or drainage) were factors independently associated with survival [50,53].

Some recent studies have examined the impact of specific antimicrobial regimen outcomes in patients with CR-KP infections. These studies have demonstrated a consistent favorable trend of improved patient survival when CR-KP infections are treated with combination regimens [71,73,104,105].

Methods

Literature research was performed by MEDLINE (PubMed), using the keywords '*Klebsiella pneumoniae* AND combination therapy', and as limits 'English language'. Case series and research articles with information on antimicrobial treatment, microbiological and/or clinical outcome were reviewed. The studies cited in these manuscripts were also reviewed.

Results

In vitro *analysis of combinations for CR-KP isolates*

Several *in vitro* methods have been used to assess combination therapy for CR-KP infections including the checkerboard test, time-kill studies, plasma bactericidal activity, disc diffusion, Etest or agar dilution and *in vitro* PD models. Most of these studies are rarely performed in the clinical laboratory and have little or no evidence supporting their correlation with clinical outcomes of CR-KP treatment [5]. Other factors that make interpretation of *in vitro* combination studies difficult include the inconsistency of reported synergy among clinical isolates with identical antimicrobial susceptibility patterns (i.e., 50–60% of isolates tested) and the static nature of most testing that does not reflect the dynamically changing ratios of drug that occur *in vivo.* Furthermore, *in vitro* combination studies do not evaluate the potential PK benefits of administering combination regimens for CR-KP, and rarely examine the activity of the combination beyond 24 h when regrowth of resistant isolates is frequently observed. Therefore, it is difficult to compare the relative activity of various combinations for CR-KP based on *in vitro* data alone. A summary of representative *in vitro* study results with various drug combinations is presented in Table 2.

Clinical evaluation of combination therapy

Combination treatment regimens for CR-KP infections have not been compared in prospective randomized trials. Therefore, the bulk of evidence regarding the efficacy of specific combination regimens comes from retrospective and observational case series. As such, it is difficult to definitively state which regimens are more effective given the heterogeneity in underlying disease severity, infection diagnosis and definitions used for clinical response.

Reviewing the published studies, in which at least ten patients treated for an infection due to a CR-KP were described, we found 507 patients treated ≥48 h (Table 3). Information on the type of therapeutic regimen was available for 416 of them: 206 were treated with monotherapy and 210 received combination therapy. Sixty-five out of the 210 patients in combination therapy received a carbapenem-based treatment. The mean mortality rates were 49.1 and 18.3% among patients with monotherapy and combination therapy, respectively. Furthermore, lower rates of mortality were observed among those patients receiving a carbapenem-based combination therapy [71,73,102].

In the largest retrospective cohort study to date, Tumbarello *et al*. examined the outcome of CR-KP bacterememia in 125 patients treated at three large Italian teaching hospitals [73]. The overall 30-day mortality rate was 42%, but was significantly higher among patients who received monotherapy versus combination regimens (54 vs 34%; p = 0.02). In logistic regression analysis, post-antibiogram therapy with a combination of tigecycline, colistin and meropenem was associated with the lowest mortality risk for CR-KP bloodstream infection. Of note, mortality rates increased in patients receiving these combinations as the meropenem MIC increased above 4 mg/l. Yet, meropenem combinations were still associated with lower patient mortality rates, even in patients infected with CR-KP

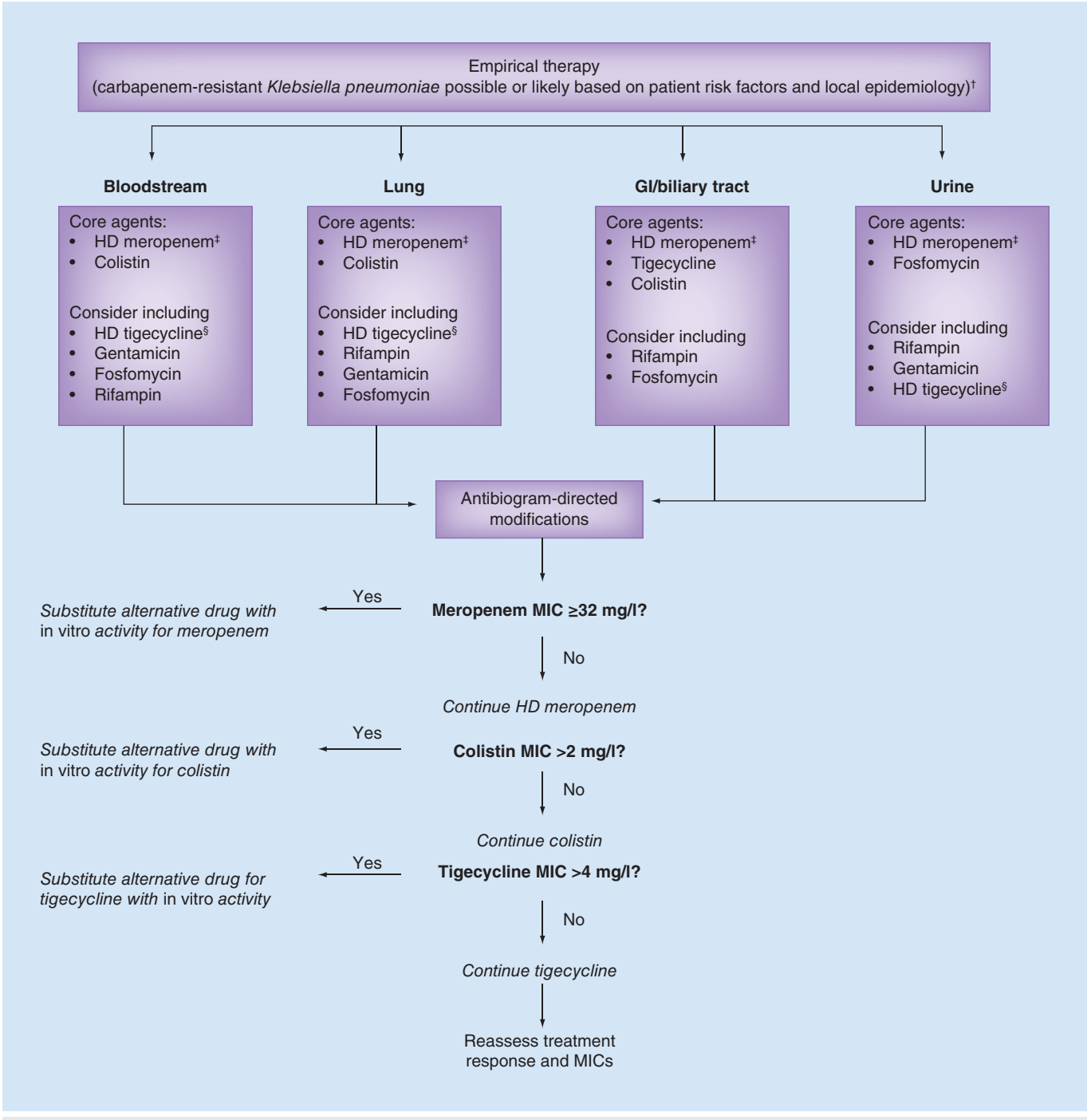

Figure 2. Potential antibiotic combination therapy algorithm for the treatment of carbapenem-resistant *Klebsiella pneumoniae* infections stratified to site of infection and antibiogram results.

†Algorithm would be appropriate for institution where >50% of isolates exhibit carbapenem MICs in the treatable range with HD therapy (MIC <32 mg/ml). Specific drugs used for empirical therapy should be tailored the epidemiology of endemic carbapenem-resistant *Klebsiella pneumoniae* strains.

‡HD meropenem (6 g daily, administered as prolonged infusion).

§HD tigecycline (200 mg loading dose, 100 mg once a day), see text regarding the limitations and evidence supporting the use of HD regimens.

HD: High-dose.

strains exhibiting meropenem MICs 16 mg/l (35 vs 42%), suggesting some residual benefit with carbapenem therapy, even for isolates with MICs up to 32 mg/l [73]. The authors concluded that combined treatment with two or more drugs with *in vitro* activity, especially those including a carbapenem, was more effective than monotherapy regimens for CR-KP bloodstream infection.

Expert commentary

The emergence of CR-KP in a healthcare institution fundamentally alters treatment approaches for many common infections in hospitalized patients. Patients with a medical history of hospitalization requiring broad-spectrum antibiotics, mechanical ventilation, ICU care or recipients of solid-organ or stem cell transplantation are most likely to harbor CR-KP strains [51]. Although there is a growing consensus that combination therapy with two or more adequately dosed antimicrobials is needed for CR-KP infections, when these combinations should be started (i.e., empirically, preemptively based on the identification of Gram-negative organisms prior to availability of the antibiogram, and so on) and what combination of antibiotics should be used are still unknown. Clearly, the answers to these questions will depend on the resistance profile of the circulating CR-KP strains and the type of patients treated in that institution.

What does not change, however, are the fundamental concepts of effective antimicrobial therapy in critically ill patients; timely initiation of a therapy, selection of agents with a high probability of susceptibility and adequate penetration to the likely site(s) of infection, adequate doses to ensure bactericidal activity in the first 24 h, minimization of unacceptable toxicity and expeditious removal or drainage of infected sources [106]. With these factors in mind, a provisional strategy for empiric treatment of CR-KP can be considered that tailors therapy to the likely site(s) of infection and is modified once antibiogram results are available (Figure 2).

Five-year view

The pandemic of CR-KP resistance is already having a broad impact on the management of healthcare-associated infections, which is unlikely to change in the near future. Paterson and Rogers [59] predicted six trends in Gram-negative resistance that are driven, in part, by the spread and treatment of CR-KP infections, including a continued widespread increase in carabapenem resistance necessitating routine use of polymyxins and tigecycline in the hospital, increasingly high rates of tigecycline and polymyxin resistance in some hospitals rendering some strains potentially untreatable, worsening ICU survival rates due to the impact of Gram-negative resistance, need for universal screening of MDR Gram-negative bacteria at the time of hospitalization, increased spread and acquisition of carbapenem-resistant organisms outside hospitals and an increased need for hospitalization for community-acquired urinary tract infections due to the lack of reliable oral antibiotic treatment options.

Some optimism may be justified, however, as several new antimicrobials with activity against CR-KP have advanced into Phase III clinical trials. Ceftolozone is a potent new cephalosporin that is not degraded by current AmpC cephalosporinases or affected by known porin mutations and efflux pumps circulating in CR-KP strains. When tested in combination with tazobactam, the drug has demonstrated promising activity *in vitro* against MDR Gram-negative isolates, including CR-KP [107,108].

Additionally, the development of novel β-lactamase inhibitors, such as avibactam, whose spectrum includes not only

Key issues

- In recent years, carbapenem resistance among *Klebsiella pneumoniae* has dramatically increased. It is mostly due to horizontally acquired genes encoding for carbapenemase enzymes, and a spread of few carbapenemase-producing clones has occurred in healthcare facilities worldwide.
- Intensive care unit admission, prolonged broad-spectrum antibiotic therapy, surgery or invasive procedures and immunosuppression are the risk factors for colonization and subsequent infection with carbapenem-resistant *Klebsiella pneumoniae* (CR-KP). Fatality rates are highest among patients with bloodstream infection. Inadequate empirical therapy increased the probability of poor outcome, whereas combination therapy and removal of the infection source are associated with improved patient survival.
- The current components of an effective combination regimen recommended for treatment of CR-KP include high-dose carbapenem therapy administered by extended infusion (e.g., meropenem), which is combined with colistin and/or tigecycline, gentamicin or fosfomycin if susceptibility can be demonstrated. The selection of a specific second-line agent should be individualized to the local resistance patterns, site of infection and specific toxicity risks of the patient.
- Antibiotic loading doses should be considered for any patient with suspected CR-KP infection, especially if the patient is critically ill and has evidence of impending or florid sepsis. Contemporary pharmacokinetic studies of carbapenems, colistin and tigecycline have utilized loading doses to optimize drug activity and exposures early in the course of treatment.
- The value of *in vitro* studies to asses which combinations are more likely to be effective in patients is limited, as they do not take into account the potential for *in vivo* pharmacokinetic benefits and other clinical conditions.
- Clinically available data on treatment of CR-KP infections have demonstrated that monotherapy is associated with lower success rates than combination therapy and increased risk of resistance to 'second-line' antibiotics – that is, colistin, tigecycline, fosfomycin. These data have also demostrated that carbapenem-containing combinations are more effective than noncarbapenbem-containing regimens, especially for isolates with MICs of 4 mg/l. Currently, the MIC 'ceiling' precluding the beneficial use of carbapenems is unknown, but a benefit has been observed in case series against isolates with MICs up to 16 mg/l.

cephalosporinases but also most carbapenemases with the exception of rare (but emerging) NDM-1 metallo β-lactamases, would restore activity of older agents such as ceftazidime against CR-KP isolates [109]. Other novel β-lactamase inhibitors and new-generation aminoglycosides (neoglycosides) could further expand the treatment options in the not too distant future [107]. However, resistance, even to these newer agents, is inevitable and should not overshadow the critical need for improvements in infection control, screening and early detection of these increasingly extremely drug-resistant pathogens.

Finally, a multidisciplinary approach that involves not only clinicians, pharmacologists and microbiologists, but also infection control professionals, is critical. Institutions need to develop preemptive strategies for limiting and controlling CR-KP outbreaks, including guidelines for cohorting, cleaning and screening, patient and staff education and training, and CR-KP alerts similar to those proposed by Ciobotaro *et al.* [110]. These strategies should also be incorporated into comprehensive programs of antimicrobial stewardship, designed to optimize antimicrobial therapy for critically ill patients, to improve patients' outcomes, ensure cost-effective therapy and reduce adverse effects associated with antimicrobial use, including antimicrobial resistance.

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No writing assistance was utilized in the production of this manuscript.

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