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Colistin in the 21st Century

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Abstract

Purpose of review—Colistin is a 50 year-old antibiotic that is being used increasingly as a 'last-line' therapy to treat infections caused by MDR Gram-negative bacteria, when essentially no other options are available. Despite its age, or because of its age, there has been a dearth of knowledge on its pharmacological and microbiological properties. This review focuses on recent studies aimed at optimizing the clinical use of this old antibiotic.

Recent findings—A number of factors, including the diversity in the pharmaceutical products available, have hindered the optimal use of colistin. Recent advances in understanding of the pharmacokinetics and pharmacodynamics of colistin, and the emerging knowledge on the relationship between the pharmacokinetics and pharmacodynamics, providing a solid base for optimization of dosage regimens. The potential for nephrotoxicity has been a lingering concern, but recent studies provide useful new information on the incidence, severity and reversibility of this adverse effect. Recent approaches to the use of other antibiotics in combination with colistin hold promise for increased antibacterial efficacy with less potential for emergence of resistance.

Summary—Because few, if any, new antibiotics with activity against MDR Gram-negative bacteria will be available within the next several years, it is essential that colistin is used in ways that maximize its antibacterial efficacy and minimize toxicity and development of resistance. Recent developments have improved use of colistin in the 21st century.

Keywords

colistin; approaches to optimizing therapy; Gram-negative infections

Introduction

Colistin (also known as polymyxin E) has been marketed as its inactive prodrug colistin methanesulfonate (CMS) [1] for fifty years. Colistin was one of the first antibiotics with significant activity against Gram-negative bacteria, notably *Pseudomonas aeruginosa*. It exhibits rapid, concentration-dependent bactericidal activity [2–4]. CMS was largely replaced by aminoglycosides in the 1970s because of concern about nephrotoxicity and

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Disclosures

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neurotoxicity [5–8]. In the last 10 – 15 years, however, CMS/colistin has been a limited option and used as ‘salvage’ therapy for infections caused by multidrug-resistant (MDR) Gram-negative bacteria, in particular *P. aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae* [5–8]. The lack of alternative antibiotics has been exacerbated by the dry antimicrobial-drug development pipeline [9]. Having entered clinical use in 1959, CMS/colistin was never subjected to drug development procedures that are now mandated by international drug regulatory agencies such as the Food and Drug Administration. As a result, there is a dearth of pharmacological information informing rational use, which aims to maximize antibacterial activity while minimizing toxicity and development of resistance [5, 8]. There are no scientifically-based dosage regimens for various categories of patients, in particular people with cystic fibrosis (CF) and subsets of critically-ill patients (e.g. with differing levels of renal function including those on renal replacement therapy). Even though rates of colistin resistance have been relatively low, probably because of its infrequent use, there have recently been several outbreaks of infections caused by colistin-resistant bacteria [10–13]. Since no novel antibiotics with activity against Gram-negative bacteria will be available within the next 9 – 11 years [14], there is an urgent need to optimize use of CMS/colistin. Background information on colistin is summarized in recent extensive reviews [5–8]. The present review will focus on recent advances in colistin pharmacology, clinical use and ongoing dilemmas.

Do we know how to optimize dosing of colistin?

The simple answer to this question is: No. In part this is due to inconsistent labeling and different dosing regimens recommended for different pharmaceutical products [8, 15]. [16, 17]). Some product labels express the content of CMS as international units (IU; there are ~12,500 IU/mg of CMS). Other products are labeled with ‘colistin base activity’ (based upon microbiological standardization), even though the material contained in the vials is CMS. For products labeled in international units, the manufacturer-recommended dose for a patient with normal renal function who is over 60 kg is 1 – 2 million IU three times daily (to a maximum of 6 million IU per day), equivalent to 240 – 480 mg of actual CMS per day. In contrast, for products labeled with ‘colistin base activity’, the manufacturer-recommended dose range 2.5 – 5 mg/kg of ‘colistin base activity’ per day, in 2 to 4 divided doses; this is equivalent to ~6.67 – 13.3 mg/kg of actual CMS per day. Hence, for a person with normal renal function and body weight of 60 kg, the recommended daily dose of this type of product is 400 – 800 mg of CMS. While this disparity in labeling and manufacturer-recommended daily doses was identified 2 – 3 years ago and an urgent call made for international harmonization [8, 15, 18], the problem is unresolved and is arguably worse because of the proliferation of generic brands of parenteral CMS formulations. There are two important implications of the differences. First, for those clinicians referring to published reports of studies involving CMS/colistin to guide their practice, insufficient detail is often provided in published papers to ascertain the doses of CMS actually used. Confusion regarding this is illustrated in a recent review [19] of intraventricular CMS for treatment of *A. baumannii* ventriculitis, where doses of CMS were tabulated in mg but for a product labeled with ‘colistin base activity’ [20] it was not clear whether the mg of ‘colistin base activity’ had been converted to mg of CMS). The second unresolved issue is the most appropriate daily dose. However, in an era where CMS/colistin is being used increasingly as ‘salvage’ therapy for infections that are resistant to most other antibiotics, it is clearly important to administer doses that maximize antibacterial effect and minimize the potential for development of resistance. Since acceptable and similar safety appears to exist for both types of products [21–27], at this time it would be prudent to regard the daily dose of the products labeled with ‘colistin base activity’ as a ‘reasonable’ choice (i.e. 2.5 – 5 mg/kg of ‘colistin base activity’ per day (corresponding to ~400 – 800 mg CMS per day) in a 60 kg patient with normal renal function). In fact, despite manufacturer recommendations not to exceed 6

million units per day, some clinicians [28, 29] are now routinely using an upper daily dose of 9 million IU per day (corresponding to ~720 mg CMS per day). Clearly studies must be done to resolve the dosage issue. Furthermore the number of doses per day suggested for patients with normal kidney function is 2 – 4, although twice- or thrice-daily dosing appears to be the most commonly used [6–8]. In the absence of supporting pharmacokinetic/ pharmacodynamic (PK/PD) data, some have used once-daily dosing, even in patients with normal kidney function [26]. We recommend against this practice. In an *in vitro* PK/PD model that simulated human dosing regimens incorporating higher doses of colistin administered once daily there was greater emergence of resistance in *P. aeruginosa* than occurred with a thrice-daily regimen involving administration of essentially the same total daily dose [30]. Moreover, intravenous administration of CMS to rats in week-long multiple-dose regimens mimicking twice- and once-daily administration of a clinically relevant human daily dose, resulted in a greater range and severity of renal lesions with the once-daily dosing equivalent. This suggests that the potential for nephrotoxicity may be greater with extended-interval dosing [31]. In support of this, *in vitro* studies have shown that the toxicity of colistin on mammalian cells is concentration- and time-dependent [32].

Until the last few years, little has been known of the PK and PD and, importantly, the relationship between the PK and PD for CMS/colistin. A recent study conducted in a standard mouse thigh infection model [33], revealed that the ratio of the area under the plasma concentration - time curve to MIC (AUC/MIC) is the most predictive index of activity against *P. aeruginosa* [34]; a study conducted in the same model against the same micro-organism, but without measurement of PK behavior, suggested that activity may be correlated with the ratio of the maximum plasma concentration to MIC (C_{max}/MIC) [35]. There is evidence that the protein binding of polymyxins may be different in the plasma of infected patients (and animals), possibly related to infection-induced changes in the plasma concentration of α_1 -acid glycoprotein, an acute-phase reactant that is important for the binding of many basic drugs [36, 37], and whose concentration is higher in critically-ill patients [38]. The ability to translate PK/PD targets, based upon total plasma concentration, determined in animal models or in humans, to assist in optimizing dosing strategies for patients requires a more complete understanding of the plasma protein binding of colistin.

Different PKs in various patient groups clearly has potential to impact the dosage regimens required to treat infections. There is emerging evidence that the PK of CMS/colistin differs in the key groups, namely people with CF [25, 39, 40] and critically-ill patients ([41–44], unpublished data). For example, the half-life of the active antibacterial, colistin, formed *in vivo* from its prodrug, CMS, is about 4 h in cystic fibrosis patients [25, 39, 40] but is longer in critically-ill patients ([41–44], unpublished data). A recently reported population PK study, albeit with a small number of patients ($n = 18$), provided useful new insights into the disposition of CMS and formed colistin in critically-ill patients [42]. Patients received CMS intravenously (as a 15-min infusion) at a dose of 3 million IU (equivalent to ~240 mg CMS) every 8 h; the dose was reduced empirically to 2 million IU (~160 mg CMS) every 8 h in two patients with a creatinine clearance <50 mL/min. Mean creatinine clearance was 82.3 mL/min (range 41 – 126 mL/min) and none of the patients required renal replacement therapy. CMS and colistin plasma levels were measured after the first and fourth doses. The predicted maximum plasma concentration of formed colistin (0.60 mg/L) after the first dose was substantially lower than that at steady state (2.3 mg/L after the fourth dose) because of a slow rate of formation of colistin from CMS and accumulation of formed colistin over the first several doses, in keeping with its estimated half-life of 14.4 h. The plasma binding of colistin was not considered in this study. Even so, the plasma concentrations of colistin, which was administered at a daily dose 50% higher than that recommended by the manufacturer, were well below (1st dose) or modestly above (4th dose) the CLSI and EUCAST MIC breakpoint (2 mg/L) for *P. aeruginosa* and *A. baumannii*. This prompted the

authors to question the appropriateness of the current dosage regimens. In view of the delay in attainment of plasma colistin concentrations in this study [42] and the known importance of initiating appropriate antimicrobial therapy as quickly as possible [45], the authors also suggested that it may be advantageous to administer a loading dose of CMS (e.g. 9 million IU, equivalent to ~720 mg CMS) with a maintenance dose of 4.5 million IU (equivalent to ~360 mg CMS) every 12 hours [42], though such regimens remain to be tested clinically. This study [42] highlights the for a large population pharmacokinetic study, incorporating pharmacodynamic endpoints (e.g. bacterial eradication, clinical cure, development of resistance) together with toxicodynamic endpoints (e.g. nephrotoxicity) and involving patients with a wider range of renal function (including those requiring renal replacement therapy) and other co-morbidities. An NIH-funded project (grant number 5R01AI070896-02) that addresses these requirements is currently underway in various categories of critically-ill patients.

Current clinical uses of colistin

The resurgence in the use of CMS/colistin began in the late 1980s and early 1990s, when it was administered intravenously and/or by inhalation to manage infections or colonization with *P. aeruginosa* in pediatric and adult CF. In the last decade it has been used to treat of a range of infections (e.g. ventilator-associated pneumonia (VAP), bacteremia) caused by MDR Gram-negative bacteria, in particular *P. aeruginosa*, *A. baumannii* and *K. pneumoniae*, in critically-ill adult patients; most typically it is administered intravenously. Although generally considered to be efficacious and safe in this setting [6, 8] there is a paucity of randomized controlled trials, many studies are retrospective in nature and other antibiotics are often used in combination (e.g. [6, 8, 46]). In addition, small sample sizes and resultant lack of power substantially compromise the usefulness of many studies; for example, a recent prospective cohort study in adult critically-ill patients intended to compare high-dose ampicillin/sulbactam versus CMS intravenous monotherapy for treatment of MDR *A. baumannii* VAP had a power of 6% [47].

Inhalation of CMS has been used in CF over the last two decades and in Greece, is now being used in critically-ill and ICU patients for treatment of VAP [48, 49]. The rationale is appealing: delivery of antibiotic directly to the infection site with the intention of achieving selective targeting (i.e. effective concentrations in lung fluid, while minimizing systemic exposure and potential adverse effects such as nephrotoxicity) [50]. Aerosolized CMS (2.2 ± 0.7 million IU per day (equivalent to 176 ± 56 mg CMS per day), for a mean duration of 16.4 days) was examined prospectively in 60 critically-ill patients requiring treatment for VAP caused by MDR *P. aeruginosa*, *A. baumannii* or *K. pneumoniae*. Bacteriological and clinical response of VAP was observed in 83.3% of patients, no adverse effects were recorded and all-cause hospital mortality was 25% [49]. It should be noted that all but three of the 60 patients received concomitant intravenous treatment with CMS or other antibiotics. In a retrospective case series (five patients), the same group examined inhaled CMS as 'monotherapy' (meaning no concurrent intravenous CMS) for treatment of nosocomial pneumonia caused by *P. aeruginosa*, *A. baumannii* and/or *K. pneumoniae* [48]. While no intravenous CMS was administered, patients did receive other intravenous antibiotics (to which the isolated pathogens were resistant). While it was concluded from these studies that inhaled CMS may be safe and effective for treatment of VAP [48, 49], the confounding influences (e.g. concomitant administration of intravenous CMS or other antibiotics), small sample sizes and lack of control groups complicate interpretation of the data. Other factors that require consideration are the appropriateness of the inhaled dose (i.e. dose-ranging studies are required) and pharmaceutical formulation (e.g. does the current inhalational formulation, which is largely based upon the parenteral formulation, maximize delivery of appropriately sized droplets to the airways?). In addition, the conversion of CMS to colistin

within the lung fluid would be a prerequisite for antibacterial activity, but there is no information regarding this or indeed other aspects of the disposition of CMS and colistin following pulmonary administration (e.g. effective half-life in lung fluid, absolute systemic bioavailability).

Inhalational administration of CMS is not approved by the FDA [51] but, as discussed above, is common in cystic fibrosis clinics throughout the world and increasingly so in some ICUs [52–54]. Recently, the purported formation of colistin in a solution of CMS (reconstituted from the CMS parenteral formulation, Coly-Mycin® M) was implicated in the death of a patient with CF following inhalation [55] and this led to the issuing of an FDA Alert (<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm118080.htm>). Unfortunately, virtually no information relating to the death has been made publicly available (e.g. the concentration of CMS in the solution and the transportation and storage conditions for the solution). However, a stability study conducted on a CMS Solution for Inhalation (77.5 mg CMS per mL) specially prepared by a hospital pharmacy department found that the conversion of CMS to colistin was highly concentration dependent; less than 0.1% colistin was formed over a 1-year period when the CMS Solution for Inhalation was stored at either 4°C or 25°C [17]. Despite the low level of colistin observed in that study, it is prudent to reconstitute lyophilized CMS as close as possible prior to administration by inhalation (or parenteral injection) to minimize the potential for *in vitro* formation of colistin in these CMS dosing solutions [17]. As noted above, colistin is formed *in vivo* after inhalational [56] or intravenous [39, 41, 42, 44] administration of CMS.

The intrathecal or intraventricular administration of CMS to treat CNS infections has been reviewed previously [6, 8, 57] and reports continue to accumulate [19, 58]. Administration via these routes is usually instituted when there is concern that intravenous CMS will adequately penetrate into site of infection or when intravenous administration has actually been shown to be ineffective. Recently, it has been suggested that intraventricular administration of CMS is effective for the treatment of ventriculitis caused by MDR *A. baumannii* [19, 58]. It is interesting that this treatment appears to be remarkably well tolerated although chemical ventriculitis, chemical meningitis and seizures have been reported in some patients [19]. Clearly, the potential for publication bias needs to be kept in mind when considering the apparent efficacy and safety of this form of treatment.

Although CMS/colistin has been used in pediatric patients with CF for decades, only recently has it been used outside this group, as an important last-line antibiotic for treatment of MDR Gram-negative infections [59, 60].

Potential for nephrotoxicity and neurotoxicity

Nephrotoxicity and neurotoxicity are the most common adverse effects of intravenous administration of CMS. Neurotoxicity is rare [6, 8, 22, 61, 62]. Nephrotoxicity is more common and is of most concern to prescribing clinicians. A recent retrospective cohort study [22] comparing the safety and efficacy of CMS/colistin and tobramycin for treatment of MDR *A. baumannii* infections in ICU patients found that the risks of nephrotoxicity were similar. The authors acknowledged a number of limitations of this small study [22].

A retrospective study conducted at the Walter Reed Army Medical Center involving personnel injured in Iraq and Afghanistan assessed the incidence of nephrotoxicity associated with intravenous administration of CMS [63]. In that study, the majority of patients were young and previously healthy, without underlying risk factors for kidney dysfunction. CMS was administered intravenously in a mean ($\pm$ SD) dose of 4.3 ± 1.2 mg/kg/day of ‘colistin base activity’ (equivalent to $\sim 11.5 \pm 3.2$ mg CMS /kg/day) for 15.8 ± 9.2

days. The authors used the well-validated RIFLE system of criteria (risk, injury, failure, loss and end-stage kidney disease [64]) to categorize acute kidney injury (AKI, as opposed to acute renal failure) from mild renal dysfunction to the need for renal replacement therapy. The incidence of AKI (categorized at the R, I or F level as defined by RIFLE) while receiving CMS at the time of the peak serum creatinine was 45% in the 66 patients who met inclusion criteria (18 years, received intravenous CMS for >72 h and not on renal replacement therapy prior to the initiation of CMS). No patient was categorized at the L or E level of RIFLE at the time of the peak serum creatinine and no patient required renal replacement therapy, despite the fact that several had evidence of acute tubular necrosis on urine microscopy. Patients who received CMS for >14 days had a 3.7-fold increased risk of nephrotoxicity. This risk did not appear to be related to daily dose of CMS, but rather the total cumulative dose. This indicates the need to carefully monitor kidney function in patients requiring prolonged therapy with CMS [63] and to avoid prolonged treatment courses whenever possible. Importantly, at 1 month after cessation of CMS serum creatinine concentrations had returned to baseline, with a mean ($\pm$ SD) difference of 0.04 ± 0.3 mg/dL ($P = 0.34$).

It is important to place in perspective the potential for nephrotoxicity caused by CMS/colistin. First, the overwhelming evidence from studies reviewed previously [6–8] and from the recent Walter Reed study [63] is that renal injury caused by CMS/colistin is relatively mild and almost always reversible over weeks to months after ceasing therapy. Secondly, CMS/colistin is not the only antibiotic that is potentially nephrotoxic. Interestingly, in relatively recent studies conducted in people with cystic fibrosis, the potential for nephrotoxicity from CMS/colistin compared favorably with the aminoglycosides [65, 66]. Finally, as with many other areas of patient management, risk:benefit must be considered. The use of CMS/colistin to treat a life-threatening infection caused by a Gram-negative pathogen that is resistant to virtually every other currently available antibiotic must be weighed against the potential for drug-induced mild, reversible kidney injury.

Mechanisms of antibacterial activity and resistance

The bactericidal effect of colistin is extremely rapid but there is limited knowledge of the mechanism of antibacterial activity. Since there is only one amino acid difference between colistin and polymyxin B, it is believed that they have the same mechanism of action [8]. Polymyxin B interacts with the LPS of the outer membrane of Gram-negative bacteria and competitively displaces divalent cations (Ca^{2+} and Mg^{2+}) from the negatively-charged phosphate groups of the lipid A of LPS [6–8, 67, 68]. Both the positive charged amine groups and the hydrophobic fatty acyl chain of polymyxin B play important roles in the interaction with bacterial LPS [5, 8, 67, 68]. Hancock presented a self-promoted uptake model to explain the antibacterial mechanism of cationic peptides [68].

Currently resistance to colistin is relatively rare, probably due to its low usage over the last 50 years [69]. However, polymyxin-resistant bacteria have been identified [10–13] and several molecular mechanisms of resistance have been characterised in Gram-negative pathogens. The most common mechanisms of resistance to colistin are modifications to LPS, the initial site of action of colistin. In *Escherichia coli* [70, 71], *Salmonella enterica* serovar Typhimurium [72], *K. pneumoniae* [73] and *P. aeruginosa* [74], net LPS negative charge is reduced due to the modification of the lipid A with 4-amino-4-deoxy-L-arabinose (L-Ara4N) and/or phosphoethanolamine (PEtn). A recent study indicated that resistance to colistin in *A. baumannii* is associated with mutations in the PmrAB two-component system [75]; however, modification of lipid A was not examined in that study. In *Burkholderia cenocepacia*, the LPS O-antigen or inner core sugars act to shield the lipid A negative charge and two UDP-glucose dehydrogenases contribute to the viability and polymyxin B

resistance [76]. The presence of capsule is critical for polymyxin resistance in *K. pneumoniae* [77, 78] and *Neisseria meningitidis* [79]. In addition, tolerance to colistin in *P. aeruginosa* biofilms is linked to metabolically active cells, and controlled by the *pmr* and *mexAB-oprM* genes [80].

While the mechanisms of resistance to colistin are still to be fully elucidated, there are signs of increasing rates of resistance in clinical isolates [10–13]. A recent investigation of risk factors for isolation of colistin-resistant bacteria identified, from a multivariate statistical model used to explore possible co-variables, that CMS/colistin use was the only independent risk factor [81]. This highlights the importance of using CMS/colistin judiciously and optimizing its dosage regimens based on yet to be completed population pharmacokinetic, pharmacodynamic and toxicodynamic studies.

Combination therapy with colistin

Considering the increasing resistance to colistin, systematic examination of the potential for synergy between colistin and other antibiotics is warranted. A limited number of clinical studies have prospectively evaluated the efficacy of combinations of CMS/colistin with other antibiotics. The majority have been conducted *in vitro*, in animal infection models or involve retrospective clinical studies. This review focuses on the studies on the combinations with CMS/colistin since 2008. For previous studies, please refer to recent reviews [8, 82].

The majority of the *in vitro* studies on combinations with colistin examined, using checkerboard methods or static time-kill, rifampicin, imipenem, meropenem, ciprofloxacin, gentamicin, ceftazidime, doxycycline, minocycline, azithromycin, piperacillin and co-trimoxazole against *P. aeruginosa*, *A. baumannii* and *K. pneumoniae* [82]. Although rifampicin is the most commonly studied antibiotic in combination with colistin, carbapenems have been extensively examined in the past two years. Souli et al. reported that the combination of colistin and imipenem was synergistic (50% of isolates) or indifferent (50%) against colistin-susceptible blaVIM-1-type metallo- β -lactamase-producing (MBL) *K. pneumoniae* strains, while it was antagonistic (55.6%) and rarely synergistic (11%) against colistin-resistant strains [83]. Interestingly, after 24-h exposure to the tested combination, resistance to colistin (MICs 64 to 256 mg/L) was observed in 7 of 12 isolates that were initially susceptible to colistin. In contrast, among 4 isolates initially susceptible to imipenem that showed regrowth at 24 h in the presence of the combination, none developed resistance to imipenem [83]. In another study, sub-inhibitory concentrations of meropenem (0.06 to 8 mg/L) and colistin (0.12 to 1 mg/L) showed synergy against 13 out of 51 *P. aeruginosa* isolates at 24 h, while the combinations of meropenem (0.03 to 64 mg/L) and colistin (0.06 to 8 mg/L) showed synergy against 49 *A. baumannii* isolates [84]. Using static time-kill, synergy was shown with meropenem (1 $\times$ MIC) and polymyxin B (0.25, 0.5, and 1 $\times$ MIC) against 8 genetically unique meropenem-resistant (MICs $\geq$ 24 mg/L) *A. baumannii* isolates [85]. Although synergy was observed with the combination of colistin and tigecycline against MDR *A. baumannii* isolates using checkerboard methods, time-kill studies did not confirm the synergy [86, 87]. Caution is required when interpreting fractional inhibitory concentrations of antibiotic combinations, including those with colistin. Recently, the phenomenon of colistin-heteroresistance has been reported in *A. baumannii* clinical isolates [88–91]. Colistin-heteroresistance is the existence of colistin-resistant subpopulations within an isolate that is susceptible based upon MIC. The proportion of colistin-heteroresistant isolates was significantly higher among those collected from patients treated with colistin [91]. When colistin-heteroresistant isolates were exposed to colistin alone *in vitro*, resistance rapidly emerged [92]. These findings highlight the potential for emergence of resistance with use of CMS/colistin monotherapy against *A. baumannii*. A

recent report demonstrated substantially increased susceptibility of the colistin-resistant subpopulation to antibiotics which are inactive (e.g. those normally considered active only against Gram-positive bacteria) or have borderline activity against the parent colistin-heteroresistant clinical isolates [89] and has been confirmed [93]. This unexpected finding raises the prospect of investigating rational combinations to increase colistin efficacy against *A. baumannii* while minimizing potential for emergence of resistance. Such an approach may be different from conventional synergy concepts; rather it may rely on colistin targeting its susceptible subpopulation while the second antibiotic (e.g. rifampicin) targets the colistin-resistant subpopulation [89].

Two recent clinical studies indicated that the combination of intravenous CMS and rifampicin is effective and safe in severe infections caused by MDR *A. baumannii* [62, 94]. In a prospective uncontrolled case series, Bassetti et al. observed clinical and microbiological responses in 22 of 29 critically-ill patients (19 nosocomial pneumonia and 10 bacteremia due to MDR *A. baumannii*) treated with intravenous CMS (2 million IU (160 mg CMS) three times a day) plus intravenous rifampicin (10 mg/kg every 12 h) [62]. No renal failure was observed in patients with normal baseline renal function while 3 patients who had previous renal failure, developed nephrotoxicity when treated with CMS. No neurotoxicity was observed. In retrospective study, Song et al. evaluated the effectiveness and safety of the combination of CMS and rifampicin in 10 patients with VAP due to MDR *A. baumannii* strains (only susceptible to colistin based upon MICs) [94]. After treatment with intravenous CMS (150 mg 'colistin base activity' every 12 h, i.e. 400 mg CMS/12 h) plus rifampicin (600 mg daily), 7 (70%) of 10 patients benefited from the combination therapy, six of whom were cured microbiologically and one complicated by superimposed infection after clinical improvement. Although hypomagnesaemia or mild hepatitis was observed in two patients, modification of the therapeutic regimen was not required and renal dysfunction did not develop during treatment. This study indicated that 7 – 11 days of combination therapy with CMS and rifampicin was safe without serious adverse events in patients without underlying renal disease [94].

It should be noted that, due to practical and ethical considerations, a major limitation of most clinical studies on antibiotic combinations is the lack of control groups without the combination treatment. In addition, no pharmacokinetic information is available to confirm concentrations of formed colistin and the second antibiotic at infection sites. Considering the potential for rapid development of resistance to colistin or polymyxin B [91, 92, 95], further pre-clinical and clinical investigations on rational combinations with CMS/colistin are urgently required in order to increase the usefulness of this last-line antibiotic against Gram-negative 'superbugs'.

Conclusion

It is remarkable that colistin, a 50 year-old antibiotic, is increasingly being used in the 21st century for the treatment of life-threatening infections. The diversity in labeling and dosage recommendations of the pharmaceutical formulations requires urgent attention for international harmonization. Studies reported in the last 1 – 2 years have progressed our understanding of the pharmacokinetics and pharmacodynamics of this 'last-line' antibiotic. There is still much to be achieved, however, to allow its use to be optimized. One of the most important aspects currently being addressed is elucidation of the population pharmacokinetic, pharmacodynamic and toxicodynamic relationships that will form the basis for dosage regimen recommendations for various categories of patients. In addition, a systematic investigation of colistin combination therapies warrants greater attention as an additional means to increase efficacy while minimizing the potential for emergence of colistin resistance.

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* Special interest

** Outstanding interest

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