

Resurgence of Colistin: A Review of Resistance, Toxicity, Pharmacodynamics, and Dosing

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Colistin is a polymyxin antibiotic that was discovered in the late 1940s for the treatment of gram-negative infections. After several years of clinical use, its popularity diminished because of reports of significant nephrotoxicity and neurotoxicity. Recently, the antibiotic has resurfaced as a last-line treatment option for multidrug-resistant organisms such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae*. The need for antibiotics with coverage of these gram-negative pathogens is critical because of their high morbidity and mortality, making colistin a very important treatment option. Unfortunately, however, resistance to colistin has been documented among all three of these organisms in case reports. Although the exact mechanism causing colistin resistance has not been defined, it is hypothesized that the PmrA-PmrB and PhoP-PhoQ genetic regulatory systems may play a role. Colistin dosages must be optimized, as colistin is a last-line treatment option; in addition, suboptimal doses have been linked to the development of resistance. The lack of pharmacokinetic and pharmacodynamic studies and no universal harmonization of dose units, however, have made it difficult to derive optimal dosing regimens and specific dosing guidelines for colistin. In critically ill patients who may have multiorgan failure, renal insufficiency may alter colistin pharmacokinetics. Therefore, dosage alterations in this patient population are imperative to achieve maximal efficacy and minimal toxicity. With regard to colistin toxicity, most studies show that nephrotoxicity is reversible and less frequent than once thought, and neurotoxicity is rare. Further research is needed to fully understand the impact that the two regulatory systems have on resistance, as well as the dosages of colistin needed to inhibit and overcome these developing patterns.

Key Words: colistin, polymyxin E, resistance, dosing, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*.
(*Pharmacotherapy* 2010;30(12):1279–1291)

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Antimicrobial resistance has become a worldwide health care crisis with many pathogens showing limited or no susceptibility to currently available antimicrobial treatments. Gram-negative infections are of even more concern because of the lack of effective treatments and the limited number of antibiotics in development to treat these potentially lethal pathogens.¹⁻⁵ No new antibiotics with activity against multidrug-resistant (MDR) gram-negative bacteria are expected to be released within the next 5 years. This emphasizes the need for last-line options, such as colistin, in cases where pathogens are resistant to all other antibiotics.

Colistin, a polymyxin antibiotic (polymyxin E), was first discovered in the 1940s but was not used clinically until the late 1950s. Historically, colistin was used to combat infections caused by problematic gram-negative bacteria. Reports of nephrotoxicity and neurotoxicity, however, deterred physicians from using the antibiotic, especially with the emergence of other antibiotics (e.g., aminoglycosides) that were less toxic. Between the 1970s and 1990s, colistin was not used often, and the number of studies analyzing its use and pharmacology was minimal.⁵

Recently, the lack of treatment options for MDR bacteria such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*, has led to the reemergence of colistin as an antimicrobial therapy. Because such a large gap exists between the years that colistin was used clinically, available pharmacokinetic and pharmacodynamic data are very limited. Thus, information regarding colistin toxicities and optimum dosing is not well defined, and no universal dosing for the antibiotic exists. In addition, reports have begun to surface of colistin resistance among the organisms that the drug is

currently being used to treat.^{1,2} This increased rate of resistance has emphasized the need to provide adequate, effective dosing with minimal toxicity. To review the pharmacology, resistance, toxicities, pharmacodynamics, and dosing considerations associated with colistin, we performed a search of the MEDLINE database for journal articles published from 1945–May 2010.

Dosage Forms, Elimination, Mechanism of Action, and Spectrum of Activity

Colistin is available in two forms, colistin sulfate and colistimethate sodium, administered topically and parenterally, respectively. Both forms can be inhaled. It is extremely important to note that the two forms are not interchangeable. Colistin sulfate is cationic and stable, whereas colistimethate sodium is anionic and not stable in vitro or in vivo.^{6,7} Colistimethate sodium is the form that is safer to administer parenterally because of its lower rate of toxicity.⁸ As a prodrug, colistimethate sodium is readily hydrolyzed to form partially sulfomethylated derivatives, as well as colistin sulfate, the active form of the drug.⁸ This hydrolysis of colistimethate sodium to colistin is a very important step in providing the drug's antimicrobial activity. Until colistin is formed, colistimethate sodium by itself has been shown to display little to no antibacterial activity and is considered an inactive prodrug of colistin.⁸

Colistimethate sodium is eliminated mainly by the renal route, with a fraction of the dose being converted to active colistin in vivo. Colistin undergoes extensive renal tubular reabsorption and therefore is mainly cleared by nonrenal mechanisms.^{9,10} The mechanism behind colistin's bactericidal ability is thought to be indistinguishable from that of polymyxin B, the standard of the polymyxins.¹¹ Colistin is polycationic and has both hydrophilic and lipophilic moieties. These interact electrostatically with the outer membrane of gram-negative bacteria and competitively displace divalent cations from the membrane lipids, specifically calcium and magnesium.¹² This disrupts the outer membrane and releases lipopolysaccharides.¹³ Change in the permeability of the bacterial membrane leads to leakage of the cell content and subsequently cell lysis and death.²⁻⁴ Colistin also has the ability to bind and neutralize the lipopolysaccharide molecule of bacteria, giving it antiendotoxin activity.² Colistin has a narrow antibacterial spectrum of activity, with susceptibility mostly against

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Supported in part by a grant (R01AI079330) from the National Institute of Allergy and Infectious Diseases, National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases or the National Institutes of Health.

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Table 1. Diverse Cases of Colistin-Resistant Isolates

Organism, Location	Findings
<i>Acinetobacter baumannii</i>	
Australia ¹⁵	93.8% of 16 clinical isolates were heteroresistant to colistin.
Spain ¹⁷	19.1% of 115 clinical isolates were resistant to colistin.
Korea ¹⁸	27.9% of 214 isolates were resistant to colistin, with most of these resistant strains susceptible to conventional antibiotics.
Western Pacific ¹⁹	3.3% of 30 isolates were resistant to colistin, 23% of the 30 isolates were colistin heteroresistant.
United States ²⁰	Ventilator-associated pneumonia in a 55-year-old woman was initially susceptible to colistin (MIC 0.5 mg/L); after i.v. therapy, high-level colistin resistance developed (MIC > 1024 mg/L)
Australia ²¹	17 colistin-resistant isolates were compared with 17 susceptible strains. The resistant strains had increased susceptibility to conventional antibiotics, with substantial decreases in the MICs (up to 16 times lower). Colistin-resistant strains also had a decreased ability to form biofilms.
United States ²²	19 patient isolates were examined: 7 from patients who had previously been exposed to colistin therapy, 12 from patients who had not. All isolates demonstrated heteroresistance. The proportion of colistin-resistant subpopulations in patients previously exposed was higher (0.000211% vs 0.000053% in control patients).
Argentina ²³	46.4% of 28 isolates from 28 different patients in an ICU showed colistin heteroresistance. A 22-year-old man initially susceptible to colistin developed resistance (MIC 32 mg/L) after receiving intrathecal colistin for 48 hrs.
<i>Pseudomonas aeruginosa</i>	
Australia ²⁴	47.8% of 23 clinical isolates from patients with cystic fibrosis were resistant to colistin.
Germany ²⁵	34.9% of nonmucoid and 51.9% of mucoid strains were susceptible to colistin among 385 isolates obtained from patients with cystic fibrosis.
United Kingdom ²⁶	Colistin-resistant isolates were obtained from 6 children with cystic fibrosis over a 5-yr period; the children had previously received aerosolized colistin for a mean duration of 3.1 yrs.
<i>Klebsiella pneumoniae</i>	
Greece ²⁷	18 colistin-resistant isolates were identified in a tertiary hospital over a 16-mo period.
Australia ²⁸	27.27% of 22 isolates were colistin resistant; colistin heteroresistance was seen in 93.8% of the 16 colistin-susceptible isolates.
South Korea ²⁹	6.8% of 221 isolates were colistin resistant.

MIC = minimum inhibitory concentration; ICU = intensive care unit.

common gram-negative isolates. Most significantly, it displays in vitro activity against MDR gram-negative pathogens such as *A. baumannii*, *P. aeruginosa*, and *K. pneumoniae*. Colistin also has activity against other isolates, such as Enterobacteriaceae, *Stenotrophomonas maltophilia*, *Escherichia coli*, *Salmonella* species, *Shigella* species, *Haemophilus influenzae*, *Bordetella pertussis*, and *Legionella pneumophila*.²

Reports of Colistin Resistance

As mentioned earlier, in the case of MDR gram-negative organisms such as *A. baumannii*, *P. aeruginosa*, and *K. pneumoniae*, the need for alternative treatments has led to the reemergence of colistin. Although colistin has been shown to be effective for the treatment of a wide variety of infections,^{3, 14} its use for treating infections caused by these three gram-negative organisms has been impeded by occurrences of colistin resistance. Development of resistance to colistin is a serious concern. As colistin is the last line of defense against these virulent pathogens, resistance to this antibiotic may have devastating

effects if no other treatment options are available to combat the infection. Cases of colistin resistance, as well as the mechanisms behind its development, are discussed in the following sections.

Acinetobacter baumannii

The increasing prevalence of *A. baumannii* infections coupled with its escalating resistance to available treatments and the lack of drug development to cover this pathogen has made it one of the most difficult gram-negative infections to treat and control.^{1, 15} The Clinical and Laboratory Standards Institute susceptibility breakpoint for *A. baumannii* is 2 mg/L or lower, and the resistance breakpoint is 8 mg/L or higher.¹⁶ Although colistin is often considered a reliable agent to treat *A. baumannii*, reports of resistant strains to this antibiotic are on the rise.^{17–20} Recent studies have shown varying rates of resistance as well as the occurrence of heteroresistant strains (Table 1).^{15, 17–29}

In one study, 265 strains of *Acinetobacter* were collected from two Korean hospitals.¹⁸ Of those 265 isolates, 214 (81%) were determined to be *A.*

baumannii. With use of the broth microdilution method, 27.9% of these isolates were found to be resistant to colistin (minimum inhibitory concentration [MIC] > 16 mg/L) with a minimum concentration required to inhibit 90% of bacteria (MIC₉₀) of 32 mg/L. The *A. baumannii* strains were further classified into three subgroups based on phylogenetic clustering. In subgroups II and III, most isolates were colistin resistant (64.8% and 88.9%, respectively) but typically remained susceptible to other conventional antibiotics (carbapenems, β -lactams, and ciprofloxacin). In contrast, the *A. baumannii* isolates in subgroup I had a much lower rate of resistance to colistin (7%), with an increased resistance profile to other antimicrobials.

Similar results were seen in a second study, which compared 17 colistin-resistant isolates of *A. baumannii* to 17 susceptible strains.²¹ Like the previous study, this study also used the broth microdilution method for MICs. Generally, the strains resistant to colistin had increased susceptibility to conventional antibiotics, with substantial decreases in the MICs (up to 16 times lower). The colistin-resistant strains were also found to have a decreased ability to form biofilms, which is associated with diminished antibiotic susceptibility in *A. baumannii*.²¹

In several studies, colistin also exhibited heteroresistance.^{15, 19, 22, 23} Heteroresistance occurs when subpopulations within the strain exhibit reduced susceptibility although the overall MIC is not altered. This makes detection of resistant subpopulations impossible with MIC alone. In one study of 16 *A. baumannii* isolates, all 16 strains were initially susceptible to colistin with an MIC of 2 mg/L or lower.¹⁵ However, when concentrations of colistin up to 32 times MIC were used, significant regrowth of *A. baumannii* was noted at 24 hours. By the conclusion of the study, 15 of 16 isolates exhibited heteroresistance. Other studies had similar outcomes, with some heteroresistant strains showing regrowth within 6 hours, regardless of the dosing schedule initiated.^{30–32}

A recent study of clinical isolates from the Western Pacific region showed 1 (3.3%) of 30 isolates to be resistant to colistin and 7 isolates (23%) to be colistin heteroresistant.¹⁹ Although lower than that of previously reported cases of colistin resistance or heteroresistance, these findings still emphasize not only the need for adequate dosing, but also the potential use of combination therapy to eradicate these resistant subpopulations.

Pseudomonas aeruginosa

The high mortality rate associated with *P. aeruginosa* is in part related to its multiple mechanisms of resistance, with some clinical isolates showing panresistance to all United States Food and Drug Administration–approved antibiotics.¹ It has a Clinical and Laboratory Standards Institute susceptibility breakpoint of 2 mg/L or lower, and a resistance breakpoint of 4 mg/L or higher. Infections and resistance due to *P. aeruginosa* is of even more concern in patients with cystic fibrosis, as it is the most common colonizing pathogen in the lungs and has higher rates of resistance in this population.²⁵ Although colistin is usually regarded as salvage therapy and is sometimes the only therapeutic option to treat *P. aeruginosa*, cases of isolates resistant to colistin have emerged (Table 1).

In 385 strains of *P. aeruginosa* isolates from 57 adults with cystic fibrosis, only 34.9% of nonmucoid and 51.9% of mucoid strains were susceptible to colistin (MIC < 0.5 mg/L).²⁵ Furthermore, the MIC distribution pattern in this study showed two populations of MICs, which may be indicative of emerging resistance.

A second study of 23 clinical isolates from patients with cystic fibrosis found 11 of these strains to be resistant to colistin, with MICs exceeding 128 mg/L.²⁴ Also, cases of colistin-resistant *P. aeruginosa* were seen in six children with cystic fibrosis after they received aerosolized colistin for a mean duration of 3.1 years.²⁶ This rise in colistin resistance by *P. aeruginosa* is beginning to surface in the cystic fibrosis population, possibly secondary to the widespread use of inhaled colistin in these patients. Because *P. aeruginosa* plays a large role in the lung destruction and eventual respiratory failure seen with cystic fibrosis, continued development of resistance would be detrimental.

Klebsiella pneumoniae

The need for alternative antimicrobials to treat *K. pneumoniae* has risen with the increased prevalence of *K. pneumoniae* carbapenemases-, extended-spectrum β -lactamase (ESBL)-, and metallo- β -lactamase (MBL)-producing strains of this bacteria. Although reports of colistin resistance with this pathogen are sparse, they are significant, as current and future treatment options for ESBL- and MBL-producing *K. pneumoniae* are limited.

In one study, 18 colistin-resistant (MIC > 8 mg/L) *K. pneumoniae* isolates were obtained from

Table 2. Potential Mechanisms of Resistance

Regulatory System	Gene	Contributing Factors	Mechanism or Site of Action	Effect
PmrA-PmrB ³⁴⁻⁴³	<i>PmrE</i>	PhoP-PhoQ activation	Reduces negative charge of the bacteria's lipid A and lipopolysaccharides	Reduced binding affinity
	<i>PmrHFIJKLM</i>	Mildly acidic pH High iron concentrations Low magnesium concentrations		
PhoP-PhoQ ^{33, 35-37, 44-48}	<i>OprH</i>	Exogenous polyamines Low magnesium concentrations	OprH proteins occupy membrane magnesium sites and reduce the binding site for colistin	Reduced binding affinity
Alterations in cell morphology ⁴⁹	Unknown	Unknown	Spherical (vs rod shaped), reduced number and length of pili, increased topographic variability, finer surface texture	Increased rate of resistance

13 patients over a 16-month period in an intensive care unit in Greece.²⁷ All of these patients had a long duration of both colistin treatment (median 27 days) and hospitalization (median 69 days), which likely contributed to the development of resistance. Most recently, 6.8% (15 of 221 isolates)²⁹ and 27.3% (6 of 22 isolates)²⁸ of collected *K. pneumoniae* isolates were found to be colistin resistant in South Korea and Australia, respectively.

Mechanisms of Resistance

Resistance to colistin can develop through adaptive or mutational mechanisms, with almost complete cross-resistance existing between colistin and other polymyxins.⁴ A variety of gene mutations cause resistance to colistin by altering the outer membrane of gram-negative bacteria, which is colistin's site of action. Although data on the precise mechanism of resistance are scant and appear to be dependent on specific bacteria, the PmrA-PmrB and PhoP-PhoQ regulatory systems play important roles in its development (Table 2).³³⁻⁴⁹ Two-component regulatory systems, such as PmrA-PmrB and PhoP-PhoQ, allow bacteria to respond to environmental changes by modifying the expression of genes. When these regulatory systems interact with one another, they have been shown to have even more profound effects.³³

One mechanism of resistance involves changes in the structure of the bacteria's negatively charged surface lipopolysaccharides and lipid A. These modifications occur as a result of the activation of the PmrA-PmrB system, which is regulated by the PhoP-PhoQ system, but can also act independently in mildly acidic conditions or with high concentrations of iron.^{34, 35} The PmrA-

PmrB system regulates two loci, PmrE and PmrHFIJKLM, which are responsible for the changes in lipid A and are essential for polymyxin resistance.^{34, 36-40} When activated, the PmrA-PmrB system adds ethanolamine to the phosphate groups of the lipopolysaccharides and lipid A and also inserts aminoarabinose at the 4' phosphate of lipid A.^{34, 35, 41, 42} These changes lower the overall charge of the lipopolysaccharide, thereby reducing the binding affinity of the cationic polymyxins.⁴³

Environmental pH and magnesium concentrations are two environmental factors that appear to greatly affect the expression of the bacteria's genes and the subsequent development of resistance. In one study of *Salmonella enterica* grown in 10 mM magnesium chloride at a pH of 5.8, the organisms were approximately 100,000 times more resistant to polymyxin B than strains grown at a pH of 7.7.⁴¹ This increase is attributed to increased activation of the PmrA-PmrB system at slightly acidic pH values and micromolar magnesium concentrations. It may be possible to monitor or correct pH and magnesium levels in order to help prevent resistance due to these environmental factors, but more information is needed before this can be determined. Because studies examining environmental pH and magnesium compared with the rate of resistance are limited, it remains unclear what steps clinicians should take. It is clear, however, that the effects of pH and magnesium require an active PmrA-PmrB system. The PmrA null mutants have failed to exhibit polymyxin resistance.⁴⁴

Low magnesium concentrations also lead to the development of resistance by activating PhoP and PmrA, which not only modifies the bacteria's lipopolysaccharides but also increases the

expression of a gene that has been shown to be a major factor in the development of resistance—the *OprH* gene.^{33, 35, 37, 44} The *OprH*, *PhoP*, and *PhoQ* genes form an operon that is controlled by both *PhoP* and magnesium concentrations and contributes to polymyxin resistance.^{35, 45} The *OprH* gene, which lies immediately downstream from the *PhoP*-*PhoQ* regulatory system, encodes an outer membrane protein, *OprH*, that has enhanced expression in low magnesium level conditions.³⁶ These *OprH* proteins occupy membrane magnesium sites and reduce the binding sites for colistin, therefore contributing to resistance.^{35, 45–47}

The presence of exogenous polyamines (spermidine, spermine, putrescine, and cadaverine) has also been shown to induce the expression of the *OprH*-*PhoP*-*PhoQ* operon, resulting in increased MICs of not only polymyxins, but also aminoglycosides, quinolones, and fluorescent dyes against *P. aeruginosa*, regardless of the presence of cations.⁴⁸ Although *OprH* is presumed to play a role in resistance, it has been proven that its presence is not necessary for resistance to occur, since *OprH*-deficient strains of *P. aeruginosa* remain polymyxin resistant.³³ Similarly, studies have shown that although *PhoP* is essential for the transcription of the *OprH*-*PhoP*-*PhoQ* operon, *PhoP*-null strains of *P. aeruginosa* retain polymyxin resistance.⁴⁵ This is significant as it exemplifies the independent role that the *PmrA*-*PmrB* system plays in polymyxin resistance, as well as the potential for other unidentified mechanisms of resistance.

Recently, the morphology and topography of colistin-resistant bacteria have been found to differ from that of colistin-susceptible cells, which could give us further insight into the genetic mechanisms leading to colistin resistance.⁴⁹ An atomic force microscopy study was performed of both colistin-resistant and colistin-susceptible strains at different growth phases.⁴⁹ Compared with spherically shaped colistin-resistant bacteria at early and mid-logarithmic phases, susceptible cells were found to be rod shaped with pili present at all phases. The number and length of pili for colistin-resistant cells were greatly reduced, which the authors note could be the reason colistin-resistant cells are unable to form a biofilm. In addition, colistin-resistant cells had a greater topographic variability and finer surface texture. In the stationary phase, elongated worm-like cells were more prevalent in the susceptible

group versus the resistant group, which showed more heterogeneity among the cells in this phase. Of interest, levels of bacterial outer membrane damage after treatment with colistin were similar for both susceptible and resistant cells, showing the ability of colistin-resistant cells to maintain interaction with the outer membrane.^{21, 49} Based on these findings, it is evident that specific studies examining the genetic mechanisms behind these morphologic and topographic differences need to be performed, so that we may better understand the resistance associated with colistin.

Toxicity

Early use of colistin was linked to multiple reports of nephrotoxicity and neurotoxicity.² It was from this fear of toxicity that its use was halted shortly thereafter.^{2–4, 50–52} Reports over the past decade, however, have shown that the toxicity associated with the polymyxins is much less than originally believed.^{5, 50, 53–56} The results from earlier reports were most likely a result of a lack of pharmacokinetic, pharmacodynamic, and toxicity studies.² Also, incorrect dosing, which may have resulted directly from confusing dosage forms and units, and the presence of other nephrotoxic drugs or conditions may have contributed to these toxicities.⁵⁷ Several studies have since examined the safety of colistin, and their results give us further insight into the toxicities associated with the antibiotic (Table 3).^{51, 53–56, 58–62}

Nephrotoxicity

Several studies have proven satisfactory safety profiles with intravenous colistimethate sodium 160 mg 3 times/day in patients with normal renal function.^{58, 63, 64} The authors of two studies found that no serious adverse effects occurred with this dosage regimen in the cystic fibrosis populations that they studied, and that there were no notable changes in renal function.^{58, 63} Furthermore, colistin has recently been found to have a more favorable toxicity profile compared with the aminoglycosides, which were originally used in place of colistin because of their suspected decrease in toxic effects.^{55, 65} Another group found an observable decrease in renal function in patients receiving aminoglycosides, which was further worsened by coadministration of colistin.⁵⁵ Colistin used as monotherapy or in combination with nonnephrotoxic antibiotics, however, did not appear to cause renal damage. Two additional studies concluded that colistin

Table 3. Colistin Nephrotoxicity Studies

Study Location	Findings
Greece ⁵¹	Deterioration of renal function found in 4 (8%) of 50 patients (2 required renal replacement therapy); baseline serum creatinine levels increased by a mean \pm SD of 0.3 ± 0.8 mg/dl during treatment with colistin in the study group, but decreased by 0.2 ± 1.3 mg/dl at the end of treatment.
Argentina ⁵³	Mean \pm SD serum creatinine levels remained within normal range after treatment with colistin; these levels before and after treatment were 0.9 ± 0.2 and 1.0 ± 0.3 mg/dl, respectively, in the colistin group and 0.9 ± 0.2 and 1.0 ± 0.3 mg/dl, respectively, in the noncolistin group.
Taiwan ⁵⁴	Twelve (14%) of 84 patients experienced nephrotoxicity after colistin treatment; nephrotoxicity was reversible in 7 patients, and 2 patients required short-term hemodialysis for 2–3 wks; long-term dialysis was not needed in any of the cases.
United Kingdom ⁵⁵	When coadministered with aminoglycosides, colistin enhanced the apparent nephrotoxicity of aminoglycosides. When administered with nonnephrotoxic antibiotics alone, however, colistin was not associated with loss of renal function.
Argentina ⁵⁶	Clinically significant increases in serum creatinine level were seen in 6 (11%) of 54 patients. The increases were more common in patients with previous renal impairment vs those with normal renal function at baseline (13% vs 7%).
United Kingdom ⁵⁸	Among the 12 patients who completed colistin treatment, no significant changes in renal function were seen over 13 days of treatment. In 2 patients, blood urea nitrogen concentrations increased by > 50% from baseline; in 1 patient, serum creatinine level increased from 0.92 to 1.74 mg/dl.
Greece ⁵⁹	Median serum creatinine level increased by 0.25 mg/dl during colistin treatment, but returned close to baseline (0.01 mg/dl higher) at end of treatment. Maximum absolute increase in serum creatinine level was 1.4 mg/dl. Only 1 patient had an increase of > 50% their baseline serum creatinine level.
United States ⁶⁰	Peak serum creatinine level during CMS treatment met RIFLE criteria for nephrotoxicity in 45% of patients, and 21% of patients stopped CMS therapy due to nephrotoxicity. Patients who received CMS for > 14 days were 3.7 times more likely to experience nephrotoxicity. Serum creatinine levels returned to baseline within 1 mo after colistin discontinuation.
Greece ⁶¹	A 0.2-mg/dl increase in serum creatinine level was seen at end of treatment compared with baseline values. Three (14.3%) of 21 patients experienced nephrotoxicity. Cumulative dose of CMS was statistically significantly correlated with the difference between serum creatinine levels at the end and start of CMS therapy.
South Korea ⁶²	15 (31.9%) of 47 patients who received colistin experienced nephrotoxicity; 3 (20%) of the 15 patients required renal replacement therapy. Renal function recovered in 9 (90%) of the 10 patients reassessed for renal function after 1 mo. Hypoalbuminemia and concurrent use of nonsteroidal antiinflammatory drugs were the only independent risk factors for nephrotoxicity.

CMS = colistimethate sodium; RIFLE = risk, injury, failure, loss, and end-stage kidney disease.

was generally well tolerated in critically ill patients.^{53, 59} In one of the studies,⁵⁹ serum creatinine level slightly increased by 0.25 mg/dl from baseline during treatment, but it is important to note that the study was performed in patients with decreased renal function. Although this increase in creatinine level is of concern, no serious adverse effects occurred, and there were no data suggesting renal toxicity.

Although the nephrotoxicity associated with colistin is not as toxic as originally thought, it is still an adverse effect that must be considered when administering the antibiotic. A few recent studies have given us more insight into colistin-induced renal impairment. One group of authors examined the occurrence of acute renal failure with use of the RIFLE—risk, injury, failure, loss, and end-stage kidney disease—criteria, by completing a retrospective review of patients (aged ≥ 18 yrs) who received intravenous colistimethate sodium (≥ 72 hrs) between

January 2003 and December 2007.⁶⁰ Among the 66 patients, they found that the peak serum creatinine level during colistimethate sodium treatment met the RIFLE criteria for nephrotoxicity in 45% of patients, and that 21% of patients stopped colistimethate sodium therapy due to nephrotoxicity. The probability of renal toxicity increased in proportion to the overall total colistimethate sodium dose, and patients who received colistimethate sodium for longer than 14 days were 3.7 times more likely to experience nephrotoxicity. These findings are consistent with those of another group, who similarly found the change in serum creatinine level to be correlated with the cumulative dose of colistimethate sodium administered in their prospective cohort study.⁶¹ Also, in the first study mentioned, the authors found that serum creatinine levels returned to baseline within 1 month after cessation of colistin,⁶⁰ suggesting reversibility of nephrotoxicity after discon-

tinuation. A third group of authors performed a case-control study to evaluate the occurrence of nephrotoxicity and to analyze the characteristics and risk factors of patients who develop nephrotoxicity.⁶² Hypoalbuminemia and concomitant use of a nonsteroidal antiinflammatory drug were the only statistically significant independent risk factors.

Neurotoxicity

Adverse effects such as paresthesias, visual alterations, ataxia, and neuromuscular blockade are possible with polymyxins as a class. These neurologic effects, however, are usually reversible after the cessation of treatment and usually occur in patients receiving prolonged treatment. Cases of neurotoxicity due to colistin have been mild and rare, with the current rate of neurotoxicity estimated to be 0–7%.⁶⁶ Little to no data exist on colistin alone causing neurotoxicity in patients. One study showed that in 21 patients treated with colistin for ventilator-associated pneumonia, there were no reports of neuromuscular blockade after patients were evaluated with an electrophysiologic study to detect the presence of neuromuscular transmission blockade and critical illness polyneuropathy.⁶⁷ Colistin was concluded to be a safe treatment alternative. Another study that included 17 patients who received colistin for more than 4 weeks of treatment, found that one patient appeared to develop neuropathy believed to be caused by colistin.⁵⁹ The authors concluded that despite this one finding, colistin was a safe and efficacious alternative therapy.

Summary

The toxicities associated with colistin have been found to be better correlated with the total cumulative amount of colistimethate sodium administered versus single or daily doses, and may occur more frequently in patients with hypoalbuminemia and concurrent nonsteroidal antiinflammatory drug use. Taking these risk factors into consideration when dosing can help to prevent adverse events. Although recent studies have found colistin-induced serum creatinine level increases, this adverse effect has been found to be reversible. Overall, many studies have shown that colistin is generally well tolerated, with less nephrotoxicity and neurotoxicity than was once thought.

Optimization of Colistin Dosing

Lack of Universal Dose Unit

We refer the reader to excellent review articles that extensively address this contemporary issue.^{2, 5, 68} The limited data on colistin's pharmacokinetic and pharmacodynamic properties create immense confusion in assessing optimal dosing regimens that maximize antibacterial activity and minimize toxicity.^{2, 5} Before attempting to determine optimal dosages for colistin, a universal dose unit measurement is needed when referring to the amount of drug being administered. The uncertainty related to dosing colistin is because some products use milligrams, whereas others use international units (IU). It has been established that there are approximately 12,500 IU per 1 mg of colistimethate sodium.⁵ For example an average dose of colistimethate sodium is 2 million IU, which corresponds to 160 mg of drug.

To add further confusion, some products use milligrams of "colistin base activity" rather than milligrams of colistimethate sodium. It must be emphasized again that colistimethate sodium and colistin cannot be used interchangeably, especially when dosing. There are approximately 2.67 mg of colistimethate sodium per 1 milligram of colistin base.⁵ To continue the example above, 2 million IU equals 160 mg of colistimethate sodium, which is equivalent to approximately 60 mg of colistin base. As can be seen by this complexity, the use of a unified dosage form and unit would greatly benefit the discussion of colistin dosing.

Discrepancies Between Recommended Dosage Regimens

Once the proper dosage form and unit are established, the optimal dosage for patients must be decided. Because colistin is an older drug, there is little to no information on pharmacokinetics, pharmacodynamics, and toxicity to establish a safe and effective dosage regimen. Therefore, current dosage regimens are primarily derived from manufacturers' package inserts. The manufacturer of Colomycin (Xellia Pharmaceuticals, Copenhagen, Denmark) recommends that patients weighing more than 60 kg receive 1–2 million IU 3 times/day, equivalent to colistimethate sodium 80–160 mg 3 times/day, with a recommended daily upper limit of 6 million IU, or 480 mg of colistimethate sodium.⁶⁹

Table 4. Comparison of Intravenous Colistin Dosage Recommendations for the Two Products Available in the United States

Dose Unit	Colomycin ^{a,69}	Coly-Mycin M ^{b,70}
IU of colistimethate sodium	Body weight ≤ 60 kg: 50,000–75,000 IU/kg/day Body weight > 60 kg: 1–2 million IU 3 times/day	83,375–166,750 IU/kg/day
mg of colistimethate sodium	Body weight ≤ 60 kg: 4–6 mg/kg/day Body weight > 60 kg: 80–160 mg 3 times/day	6.67–13.3 mg/kg/day
mg of colistin base activity ^c	Body weight ≤ 60 kg: 1.5–2.25 mg/kg/day Body weight > 60 kg: 30–60 mg 3 times/day	2.5–5 mg/kg/day

Colomycin dosage recommendations are based on IU of colistimethate sodium, and Coly-Mycin M dosage recommendations are based on colistin base activity. For comparison purposes, the dosage recommendations of the two products were also converted from values in their respective units to values in the other units.

^aSupplied as 1 or 2 million IU of colistimethate sodium/vial; maximum recommended daily dose is 6 million IU (480 mg).

^bSupplied as 150 mg of colistin base activity/vial; maximum recommended daily dose is 300 mg of colistin base activity (800 mg of colistimethate sodium).

Adapted from reference 5.

The manufacturer of Coly-Mycin M (Parkedale Pharmaceuticals, Inc., Rochester, MN) recommends 2.5–5 mg/kg/day colistin base activity in 2–4 divided doses, equivalent to colistimethate sodium 6.67–13.3 mg/kg/day or 83,375–166,250 IU/kg/day.⁷⁰ The recommended maximum daily dose of colistin is 10 million IU, or 800 mg of colistimethate sodium, from the manufacturer of Coly-Mycin M, which is approximately double the recommended daily dose from the manufacturer of Colomycin. Table 4 provides a comparison of the two products.

It should be of concern that the manufacturer of Coly-Mycin M recommends approximately double the dose of that recommended by the manufacturer of Colomycin. This lack of uniformity between manufacturers could lead to underdosing, inevitably leading to treatment failure and development of resistance.⁶⁸ More information is needed before we can begin to determine which regimens provide the best outcomes with acceptable safety.

Use of Pharmacodynamics to Guide Optimal Dosing

To fully optimize regimen selection of colistimethate sodium and colistin, it is important to appreciate the pharmacodynamics of colistin. Colistin is a rapidly bactericidal antimicrobial that possesses a significant postantibiotic effect against *P. aeruginosa*, *A. baumannii*, and *K. pneumoniae*.²⁴ The colistin area under the concentration-time curve (AUC):MIC ratio has been found to be the parameter best associated with efficacy.^{71, 72} Researchers used neutropenic murine thigh and lung models to determine the pharmacokinetic-pharmacodynamic index of

colistin that best correlates with efficacy against *P. aeruginosa*, and to determine the index target values needed for specific antibacterial effects.⁷¹ For both the thigh and lung models, the unbound AUC:MIC (*f*AUC:MIC) ratio was the pharmacokinetic-pharmacodynamic index that had the strongest relationship to bacterial burden, with *R*² values equaling 87% and 89% for the two models, respectively. The time where free drug concentration above the MIC (*f*T>MIC) was also closely correlated with efficacy, with *R*² values equaling 84% and 88% for the thigh and lung models, respectively. The researchers noted, however, that *f*AUC:MIC ratio is still the pharmacokinetic-pharmacodynamic index most likely to be associated with colistin's activity because the scatter for the *f*T>MIC was relatively large in the 20–30% range, and because concentration-dependent killing has been seen with colistin in vitro. In the lung infection model, *f*AUC:MIC ratio target ranges for the three different strains of bacteria were 15.6–22.7, 27.6–36.1, and 53.3–66.7 for 1-log, 2-log, and 3-log bacterial kill, respectively. For the thigh infection model, target values ranged from 12.2–16.7, 36.9–45.9, and 105–141 for 1-log, 2-log, and 3-log kills, respectively. Although pharmacodynamic similarities among the two different sites of infection were seen, the observed differences emphasize the dosing alterations that may be needed based on site and type of infection.

Particularly in severe infections such as endocarditis, infections of prostheses, and ventilator-associated pneumonia, a high density of bacteria is known to exist, which may impact colistin pharmacodynamics.⁷³ Recently, the antibacterial activity of colistin was shown to be

attenuated when facing a higher bacterial density. Investigators determined the extent and rate of killing by colistin to be greatly decreased at high compared with low inocula.⁷³ Against a genetically characterized clinical isolate of *P. aeruginosa* (PAO1), colistin killing was 23-fold slower at 10^9 and 6-fold slower at 10^8 compared with 10^6 colony-forming units, and 32-fold higher concentrations were required at 10^9 versus 10^6 colony-forming units. Although animal and in vivo studies are needed to further assess this inoculum effect, this study highlights the fact that higher colistin doses may be needed to treat sequestered, deep-seated infections with high bacterial densities.

When optimizing regimens for colistin, frequency of dosing is another important aspect to determine. One group of researchers evaluated the antibacterial activity and emergence of resistance that occurred with three different dosing intervals: 8, 12, and 24 hours.⁷² Three different dosage regimens were used: 0.23 mg every 8 hours (0.30-mg loading dose), 0.39 mg every 12 hours (0.45-mg loading dose), and 0.89 mg every 24 hours (0.90-mg loading dose). The every-8-hour regimen simulated the expected maximum concentration (C_{\max} 3 mg/L) and minimum concentration (0.75 mg/L) at steady-state concentrations when colistin is given according to the manufacturer's recommendations. The every-12-hour and every-24-hour regimens were designed to provide higher target C_{\max} values (4.5 and 9.0 mg/L, respectively). The researchers found overall bacterial killing and regrowth to be similar among the three regimens. However, emergence of resistance increased as dosing interval increased, and the 8-hour regimen was the most effective at minimizing resistance. Concentrations remained above the MIC for approximately 80%, 72%, and 53% of the 72-hour treatment period for the 8-, 12-, and 24-hour dosage regimens, respectively. As colistin resistance continues to rise, these findings are important to keep in mind. In addition, other infection-specific considerations that can alter pharmacodynamics must be taken into account when dosing colistin and colistimethate sodium.

Dosing in Critically Ill Patients

In critically ill patients with multiorgan dysfunction and severe infections due to MDR organisms, treatment options are especially limited. Colistin remains a necessary last-line option for these patients. What is most

concerning, however, is the lack of clinical guidelines and the presence of unclear dosing recommendations in this patient population.

Recent evidence has shown that the pharmacokinetics of colistimethate sodium and colistin in critically ill patients differ from those previously found among patients with cystic fibrosis.⁶⁸ In critically ill patients, who may have multiorgan failure, sepsis, or a wider range of renal impairment, the differences are important to take into account. Although the half-life of colistin is approximately 4 hours in patients with cystic fibrosis, it is longer in critically ill patients.⁶⁸ The half-life is 14.4 hours in critically ill patients, and the rate of formation of colistin from colistimethate sodium is different from previously published data.⁷⁴ In addition, larger volumes of distribution and lower concentrations of the antibiotic have been seen in critically ill patients with sepsis.⁷⁵ These differences have the ability to impact the effects of colistimethate sodium and colistin, which could require alterations in the dosage regimen. Although pharmacokinetic and pharmacodynamic data in this patient population are scarce, some studies have given us further insight into changes that may be needed when dosing critically ill patients.

One group of authors completed a population analysis to examine the pharmacokinetics of colistin after the administration of intravenous doses of colistimethate sodium in critically ill patients.⁷⁴ Patients received 3 million IU (240 mg) of colistimethate sodium intravenously every 8 hours or 160 mg every 8 hours if creatinine clearance was less than 50 ml/minute. The predicted plasma C_{\max} was 0.60 mg/L after the first dose and 2.3 mg/L at steady state. The authors found that after the first few doses of the regimen, colistin concentrations were below the Clinical and Laboratory Standards Institute MIC breakpoint of 2 mg/L for *P. aeruginosa* and Enterobacteriaceae. In addition, at steady state, plasma concentrations were below the MIC breakpoints for many of the cases. These results are of particular concern in critically ill patients, for whom a delay in appropriate treatment or suboptimal efficacy of the current regimen can lead to resistance and ultimately increased mortality. The authors speculated that a loading dose of colistimethate sodium is warranted. At 3 million IU every 8 hours, it would take 2–3 days before the steady-state concentration is achieved. Thus, the authors suggest that a colistimethate sodium loading dose of 9 or 12 million IU along with a 4.5 million IU maintenance dose every 12

hours, would lead to the same steady-state concentration at a faster rate and with less frequent administration.

Similarly, another group assessed the steady-state serum concentrations of colistin after intravenous administration of colistimethate sodium 225 mg every 8 hours in 14 patients.⁷⁵ The average C_{\max} was found to be 2.93 mg/L, which the authors noted would most likely lead to suboptimal C_{\max} :MIC ratios for strains with higher MICs (e.g., *A. baumannii* and *P. aeruginosa*). The researchers concluded that higher doses of colistimethate sodium be considered. Based on these two studies, it is evident that further investigations using higher colistimethate sodium doses must be performed in critically ill patients to determine whether there is improved efficacy without increased toxicity.

The pharmacokinetic parameters of colistimethate sodium and colistin were examined in patients with stage 5 kidney disease or severe liver disease compared with healthy subjects.⁷⁶ Clearance of colistimethate sodium was found to be lower in the group of patients with kidney disease, and C_{\max} , half-life, and AUC were higher. In addition, conversion of colistimethate sodium to colistin and overall colistin exposure were increased in these patients, and clearance of colistin was decreased. Potentially, these results would have led to the neurotoxicity that occurred in the kidney disease group, as 3 of 10 patients in this group experienced paresthesias (which resolved in 24–48 hrs), compared with no patients in the liver disease group. Previously, a regimen of 2.5 mg/kg every 48 hours in patients receiving renal replacement therapy was suggested,⁷⁷ but this regimen has been found to be inadequate in some cases.⁷⁸ This study in particular highlights the fact that dosing may need to be altered in patients with renal failure.

In critically ill patients, for whom colistin's half-life appears to be longer, the potential for a longer dosing interval may be an option. Some studies, however, have found that as the interval between colistin doses becomes more extended, the prevalence of resistance increases.⁷² This potentially serious consequence should be considered when deciding whether or not to use extended-interval dosing.

Overall, these data suggest that colistin pharmacokinetics are severely altered in critically ill patients. To maximize the AUC:MIC ratio, the predictive pharmacodynamic parameter of colistin, higher doses of colistimethate sodium

and alterations in the dosing interval may be warranted. Because of colistin's toxicities, however, these may not be achievable. In these instances, combination therapy should be considered for optimal therapy and prevention of resistance.

Conclusion

Colistin has proved to be an important alternative for MDR gram-negative infections. However, reports of colistin-resistant strains have created a potentially dangerous scenario since it is the last line of defense. Colistin resistance is largely attributed to the PmrA-PmrB and PhoP-PhoQ regulatory systems and their responses to environmental changes. The activation of the PmrA-PmrB and PhoP-PhoQ regulatory systems produces resistance by activating a variety of genes that lower the negative charge of the outer membrane and decrease the number of binding sites for the cationic polymyxins. Although studies have begun to reveal the mechanisms behind colistin resistance, further research is needed to fully understand the impact that the two regulatory systems have on resistance, as well as the dosages of colistin needed to inhibit and overcome these developing patterns.

The development of colistin resistance has also been linked to inadequate dosing. This highlights the importance of dose optimization, especially in critically ill patients with MDR bacterial infections. Although higher doses appear beneficial, the lack of pharmacodynamic and pharmacokinetic data regarding colistin makes determination of appropriate dosing difficult. Colistin remains an essential alternative for most MDR gram-negative infections; however, cases of resistant strains should be a cause of much concern. Therefore, newer agents and colistin combination therapy are avenues that should be considered to optimize therapeutic regimens in the fight against evolving and highly resistant gram-negative infections.

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