Colistin: The Revival of Polymyxins for the Management of Multidrug-Resistant Gram-Negative Bacterial Infections

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The emergence of multidrug-resistant gram-negative bacteria and the lack of new antibiotics to combat them have led to the revival of polymyxins, an old class of cationic, cyclic polypeptide antibiotics. Polymyxin B and polymyxin E (colistin) are the 2 polymyxins used in clinical practice. Most of the reintroduction of polymyxins during the last few years is related to colistin. The polymyxins are active against selected gram-negative bacteria, including *Acinetobacter* species, *Pseudomonas aeruginosa*, *Klebsiella* species, and *Enterobacter* species. These drugs have been used extensively worldwide for decades for local use. However, parenteral use of these drugs was abandoned ~20 years ago in most countries, except for treatment of patients with cystic fibrosis, because of reports of common and serious nephrotoxicity and neurotoxicity. Recent studies of patients who received intravenous polymyxins for the treatment of serious *P. aeruginosa* and *Acinetobacter baumannii* infections of various types, including pneumonia, bacteremia, and urinary tract infections, have led to the conclusion that these antibiotics have acceptable effectiveness and considerably less toxicity than was reported in old studies.

Polymyxins, a group of polypeptide antibiotics that consists of 5 chemically different compounds (polymyxins A–E), were discovered in 1947 [1]. Only polymyxin B and polymyxin E (colistin) have been used in clinical practice. Polymyxins have been used extensively worldwide in topical otic and ophthalmic solutions for decades [2, 3].

Colistin was discovered in 1949 and was nonribosomally synthesized by *Bacillus polymyxa* subspecies *colistinus* Koyama [4, 5]. Colistin was initially used therapeutically in Japan and in Europe during the 1950s and in the United States in the form of colistimethate sodium in 1959 [6]. However, the intravenous formulations of colistin and polymyxin B were gradually abandoned in most parts of the world in the early 1980s because of the reported high incidence of nephrotoxicity [7–9]. Subsequently, the intravenous use of colistin was mainly restricted during the past 2 decades for the treatment of lung infections due to multidrug-resistant (MDR), gram-negative bacteria in patients with cystic fibrosis [10–12]. However, the emergence of bacteria resistant to most classes of commercially available an-

tibiotics and the shortage of new antimicrobial agents with activity against gram-negative microorganisms have led to the reconsideration of polymyxins as a valuable therapeutic option. Summary data of colistin are presented in table 1.

CHEMISTRY/STRUCTURE

Colistin consists of a cationic cyclic decapeptide linked to a fatty acid chain through an α-amide linkage (figure 1*A*) [13]. Its molecular weight is 1750 Da. The amino acid components in the molecule of colistin are D-leucine, L-threonine, and L-α-γ-diaminobutyric acid. The latter is linked to the fatty acid residue, which has been identified as 6-methyl-octan-oic acid (colistin A) or 6-methyl-eptanoic acid (colistin B) [1]. Different pharmaceutical preparations of colistin may contain different amounts of these 2 components (colistin A or B) [14, 15].

Two forms of colistin are commercially available, colistin sulfate and colistimethate sodium (also called colistin methanesulfate, pentasodium colistimethanesulfate, and colistin sulfonyl methate). Colistimethate sodium is less potent and less toxic than colistin sulfate. It is produced by the reaction of colistin with formaldehyde and sodium bisulfite [16, 17]. The chemical structure of colistimethate sodium is shown in figure 1*B*. Colistin sulfate is administered orally (tablets or syrup) for bowel decontamination and topically as a powder for the treatment of bacterial skin infections. Colistimethate sodium is

Table 1. Synopsis of data on colistin (polymyxin E).

Factor	Synopsis
Brand name	Various brand names by different manufacturers and distributors throughout the world (Coly-mycin M Parenteral [Monarch] in the United States, Colomycin [Forest Laboratories] and Promixin [Profile Pharma Limited] in the United Kingdom)
Manufacturer/distributor	Several manufacturers and distributors throughout the world, including Parke-Davis, Parkedale Pharmaceuticals, Pharma-Tek, Profile Pharma Limited, and Forest Laboratories
Structure	Cationic cyclic decapeptide linked to a fatty acid chain through an α-amide linkage
Mechanism of action	Binds with the anionic lipopolysaccharide molecules by displacing calcium and magnesium from the outer cell membrane of gram-negative bacteria, leading to permeability changes in the cell envelope, leakage of cell contents, and cell death
Pharmacokinetics	Colistin sulfate is given orally; colistimethate sodium is the form of colistin given parenterally (iv, im, and by inhalation); colistimethate sodium is hydrolyzed to sulfomethylated derivatives and colistin; colistin sulfate and colistimethate sodium are not absorbed by the gastrointestinal tract; the primary route of excretion is renal
Pharmacodynamics	Exhibits bactericidal activity in a concentration-dependent mode
In vitro spectrum	It is active against gram-negative aerobic bacilli, including *Acinetobacter* species, *Pseudomonas aeruginosa*, *Klebsiella* species, *Enterobacter* species, *Escherichia coli*, *Salmonella* species, *Shigella* species, *Citrobacter* species, *Yersinia pseudotuberculosis*, *Morganella morganii*, and *Haemophilus influenzae*; it has considerable activity against *Stenotrophomonas* species; and it is not active against some gram-negative aerobic bacilli (including *Pseudomonas mallei*, *Burkholderia cepacia*, *Proteus* species, *Providencia* species, *Serratia* species, *Edwardsiella* species, and *Brucella* species), gram-negative and gram-positive aerobic cocci, gram-positive aerobic bacilli, anaerobes, fungi, and parasites
Indications	For colistimethate sodium (iv), treatment of infections caused by gram-negative bacteria resistant to other available antimicrobial agents, confirmed by appropriate susceptibility testing; for colistin sulfate (oral), bowel decontamination
Recommended iv dosage	United States: 2.5–5 mg/kg (31,250–62,500 IU/kg) per day divided into 2–4 equal doses (1 mg of colistin equals 12,500 IU); United Kingdom: 4–6 mg/kg (50,000–75,000 IU/kg) per day in 3 divided doses for adults and children with body weights of ≤60 kg, and 80–160 mg (1–2 million IU) q8h for body weights of >60 kg
Dosage adjustment for renal dysfunction	For serum creatinine level of 1.3–1.5 mg/dL, 1.6–2.5 mg/dL, or ≥2.6 mg/dL, the recommended dosage of colistin administered iv is 160 mg (2 million IU) q12h, q24h, or q36h, respectively; during hemodialysis treatment, the recommended dose is 80 mg (1 million IU) after each hemodialysis treatment
Adverse effects	Mainly nephrotoxicity (acute tubular necrosis) and neurotoxicity (dizziness, weakness, facial paresthesia, vertigo, visual disturbances, confusion, ataxia, and neuromuscular blockade, which can lead to respiratory failure or apnea)

available in parenteral formulations and can be administered intravenously, intramuscularly, or by nebulization. The term "colistin" for parenteral administration throughout this review refers to the formulation of colistimethate sodium.
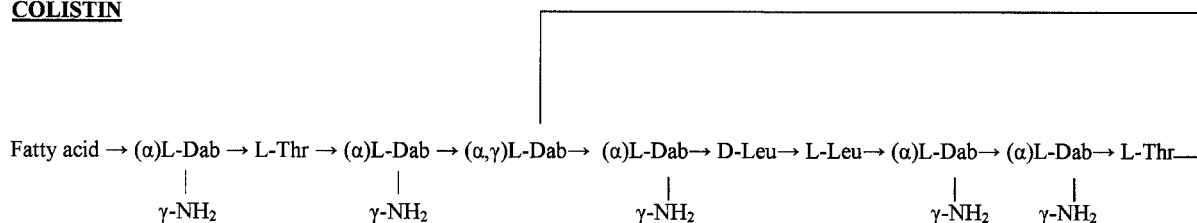
MECHANISM OF ACTION AND RESISTANCE

The target of antimicrobial activity of colistin is the bacterial cell membrane. The initial association of colistin with the bacterial membrane occurs through electrostatic interactions between the cationic polypeptide (colistin) and anionic lipopolysaccharide (LPS) molecules in the outer membrane of the gram-negative bacteria, leading to derangement of the cell membrane. Colistin displaces magnesium (Mg^{+2}) and calcium (Ca^{+2}), which normally stabilize the LPS molecules, from the negatively charged LPS, leading to a local disturbance of the outer membrane. The result of this process causes an increase in the permeability of the cell envelope, leakage of cell contents, and, subsequently, cell death [18–20]. With electron microscopic examination, numerous projections appear on the cell wall of gram-negative bacteria exposed to colistin. Figure 2 shows the bacterial cytoplasmic membrane to be partially damaged and part of the cytoplasmic material released in fibrous forms through cracks [21].

In addition to the direct antibacterial activity, colistin has also potent anti-endotoxin activity. The endotoxin of gram-negative bacteria is the lipid A portion of LPS molecules, and colistin binds and neutralizes LPS. The significance of this mechanism for in vivo antimicrobial action, namely prevention of the endotoxin's ability to induce shock through the release of cytokines, is not clear, because plasma endotoxin is immediately bound by LPS-binding protein, and the complex is quickly bound to cell-surface CD14 [22].

Gram-negative bacteria can develop resistance to colistin through mutation or adaptation mechanisms. Mutation is inherited, low-level, and independent of the continuous presence of the antibiotic, whereas adaptation is the opposite. Almost complete cross-resistance exists between colistin and polymyxin B [23–25]. Studies of polymyxin-resistant *Pseudomonas aeruginosa* strains have suggested that alterations of the outer membrane of the bacterial cell (reduction in LPS, reduced levels

COLISTIN

Fatty acid → (α)L-Dab → L-Thr → (α)L-Dab → (α,γ)L-Dab→ (α)L-Dab→ D-Leu→ L-Leu→ (α)L-Dab→ (α)L-Dab→ L-Thr
           | | | | |

γ-NH₂ is written as γ-NH$_2$ at each branch:

γ-NH$_2$ γ-NH$_2$ γ-NH$_2$ γ-NH$_2$ γ-NH$_2$

COLISTIMETHATE SODIUM

Fatty acid → (α)L-Dab → L-Thr → (α)L-Dab → (α,γ)L-Dab→ (α)L-Dab→ D-Leu→ L-Leu→ (α)L-Dab→ (α)L-Dab→ L-Thr

Each branch:

γ-NH$_2$
|
CH$_2$
|
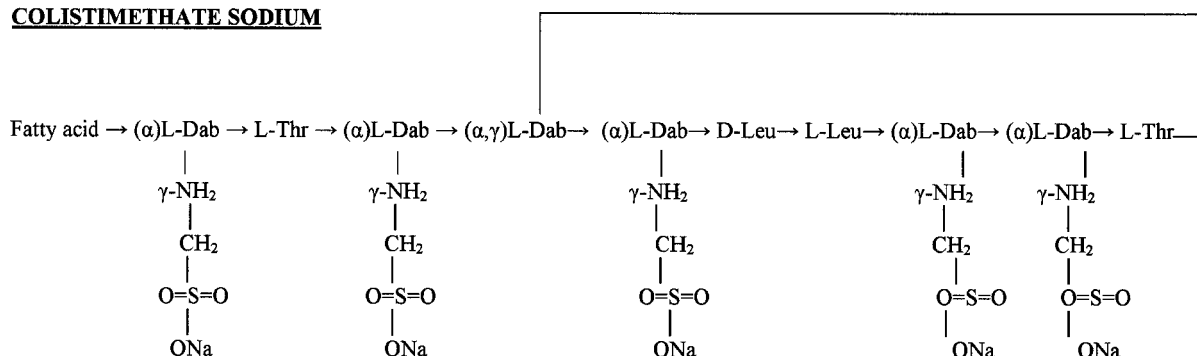O=S=O
|
ONa

(five such branches)

Figure 1. Chemical structure of colistin and colistimethate sodium. The fatty acid molecule is 6-methyloctanoic acid for colistin A and 6-methylheptanoic acid for colistin B. α And γ indicate the respective -NH$_2$ involved in the peptide linkage. Dab, diaminobutyric acid; Leu, leucine; Thr, threonine.

of specific outer membrane proteins, reduction in cell envelope Mg^{+2} and Ca^{+2} contents, and lipid alterations) are related to the development of resistance [23, 26, 27]. In addition, a recent study in *Yersinia* species demonstrated that an efflux pump/ potassium system may be associated with resistance to polymyxin B [28]. Although enzymatic resistance of bacteria to colistin has not been reported, it is interesting that *Bacillus polymyxa* subspecies *colistinus* produces colistinase that inactivates colistin [29].

PHARMACOKINETIC/PHARMACODYNAMIC PROPERTIES OF COLISTIN

Data about the pharmacokinetic and pharmacodynamic properties of colistin were reported in old studies that mainly used microbiological methods for the measurements of the concentrations of the drug and its derivatives [30–32]. These methods lack the ability to differentiate colistimethate sodium from colistin [33]. In addition, a considerable proportion of pharmacokinetic and pharmacodynamic studies of patients with cystic fibrosis were done [6, 34, 35]. Also, preparations of colistin by various manufacturers or even in different lots of the same manufacturer may contain different proportions of colistin A and B [34, 36].

Colistin sulfate and colistimethate sodium are not absorbed by the gastrointestinal tract with oral administration. In aqueous solutions, colistimethate sodium is hydrolyzed and forms a complex mixture of partially sulfomethylated derivatives and colistin [37]. Under different conditions of temperature and time, different proportions of colistimethate sodium are hydrolyzed to colistin. In a recent in vitro study, 31.2% of colistimethate sodium in human plasma was hydrolyzed to colistin in 4 h at 37°C [38]. Solutions of colistin salts are relatively stable at a pH of 2–6, but they become unstable at a pH of >6. The primary route of excretion is through glomerular filtration [35, 39]. Approximately 60% of colistimethate sodium is excreted as unchanged drug in the urine during the first 24 h after dosing. No biliary excretion has been reported in humans. In a study of 12 patients with cystic fibrosis who received intravenous colistimethate sodium at 160 mg (2 million IU) every 8 h (for patients with body weights of >50 kg) or 80 mg (1 million IU) every 8 h (for patients with body weights of <50 kg), the mean ($\pm$SD) half-life of colistimethate sodium was 124 $\pm$ 52 min, and the mean half-life of colistin sulfate was 251 $\pm$ 79 min. Mean ($\pm$SD) total body clearance and mean ($\pm$SD) volume of distribution of colistimethate sodium were 2.0 $\pm$ 0.5 mL/min/kg and 340 $\pm$ 95 mL/kg, respectively [35].

Old experimental studies have shown that colistin is tightly bound to membrane lipids of cells of many body tissues, including liver, lung, kidney, brain, heart, and muscles [40]. Release of tissue-bound drug is very slow and is not completed even at 5 days after the last administered dose. Sulfomethylation of colistin appears to decrease not only antibacterial activity
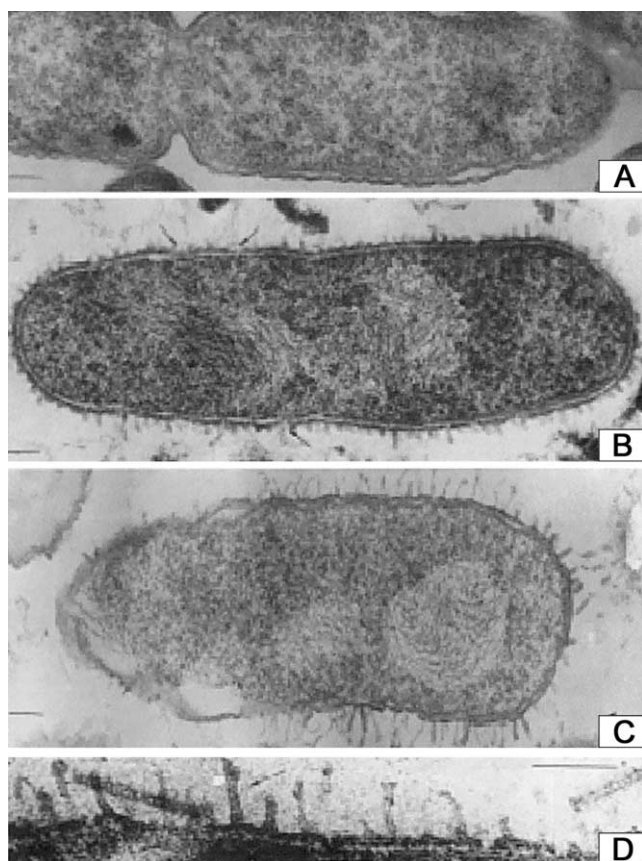
Figure 2. Sections of a *Pseudomonas aeruginosa* strain showing the alterations in the cell following the administration of polymyxin B (25 μg/mL for 30 min) and colistin methanesulfate (250 μg/mL for 30 min). (Provided with permission from the American Society for Microbiology). *A,* untreated cell; *B,* cell treated with polymyxin B; *C,* cell treated with colistin methanesulfate; *D,* cell treated with polymyxin B (from panel *B*) at higher magnification. Bar = 0.1 μm.

but also membrane binding [41]. Approximately 55% of colistin was found to be bound with plasma proteins of rats, dogs, and calves in experimental studies following intravenous administration of colistin [42–44]. Both colistin sulfate and colistimethate sodium exhibit their bactericidal activity in a concentration-dependent manner [34]. Old reports have suggested that colistin is poorly distributed to the pleural cavity, lung parenchyma, bones, and CSF. However, in a recently published case of meningitis due to MDR *Acinetobacter baumannii,* the intravenous administration of 1 million IU of colistin every 6 h resulted in sufficient CSF penetration to cure the infection (the concentration of colistin in the CSF was 25% of the serum concentration) [45].

SPECTRUM OF ACTIVITY

Colistin has excellent bactericidal activity against most gram-negative aerobic bacilli, including *Acinetobacter* species, *P. aeruginosa, Klebsiella* species, *Enterobacter* species, *Escherichia coli,*

Salmonella species, *Shigella* species, *Citrobacter* species, *Yersinia pseudotuberculosis, Morganella morganii,* and *Haemophilus influenzae.* Colistin has also been shown to possess a considerable in vitro activity against *Stenotrophomonas maltophilia* strains (83%–88% of the tested isolates were susceptible to colistin in 2 recent studies) [46–48]. Colistin has also been reported to be potentially active against several mycobacterial species, including *Mycobacterium xenopi, Mycobacterium intracellulare, Mycobacterium tuberculosis, Mycobacterium fortuitum, Mycobacterium phlei,* and *Mycobacterium smegmatis* [49–51].

However, *Pseudomonas mallei, Burkholderia cepacia, Proteus* species, *Providencia* species, *Serratia* species, *Edwardsiella* species, and *Brucella* species are all resistant to colistin. In addition, colistin is not active against gram-negative and gram-positive aerobic cocci, gram-positive aerobic bacilli, all anaerobes, fungi, and parasites [1, 36].

IN VITRO SUSCEPTIBILITY TESTING

Guidelines from the NCCLS about the in vitro determination of MICs of colistin for different microorganisms, by means of broth dilution and agar dilution techniques, were established in 1970. However, because of the rare use of intravenous colistin in most countries, including the United States, the NCCLS guidelines were not modified after 1981 and were withdrawn in 2000. The increased use of polymyxins during the last few years will probably lead to the reevaluation of the susceptibility break points.

A common method for susceptibility testing of colistin has been the disk diffusion method that uses a 10-μg colistin sulfate disk (Oxoid). Isolates are considered susceptible if the zone of inhibition is ⩾11 mm. It is important to emphasize again that in clinical practice it is colistimethate sodium, not colistin sulfate, that is widely used for intravenous administration. Two recent studies reported general agreement in the results obtained from agar dilution and broth microdilution methods regarding testing of colistin sulfate [46, 48]. However, it was suggested that results of the disk diffusion test should be confirmed with a dilution method, because the disk diffusion method used in their study revealed falsely susceptible microorganisms [46]. The general MIC break point to identify bacteria susceptible to colistimethate sodium is ⩽4 mg/L. Bacteria for which the colistimethate sodium MIC is >8 mg/L should be considered resistant [52]. The content of magnesium and calcium in media should probably be taken into account when performing in vitro susceptibility testing.

CLINICAL USE AND INDICATIONS

Intravenous colistin should be considered for the treatment of infections caused by gram-negative bacteria resistant to other available antimicrobial agents, confirmed by appropriate in vitro susceptibility testing. In addition, colistin appears to be a

viable option for treating patients with infections due to gram-negative bacteria that are susceptible in vitro to other antimicrobial agents, when the treatment with these agents has been clinically ineffective.

Apart from the intravenous route, colistin has been administered by 2 other parenteral routes (aerosolized and intraventricular) [53, 54]. There is extensive experience with the use of aerosolized colistin in treating patients with cystic fibrosis. Concerns about rapid development of *P. aeruginosa* strains resistant to colistin or the emergence of lung infections due to microorganisms with inherited resistance to colistin have not been confirmed after >10 years of published experience among patients with cystic fibrosis. The rate of development of resistance to colistin was slower than that to tobramycin [55]. There are also scarce reports indicating that aerosolized colistin may be beneficial as adjunctive treatment of patients without cystic fibrosis who have nosocomial pneumonia [54, 56].

DOSAGE AND ROUTE OF ADMINISTRATION

The dosage of intravenous colistin recommended by the manufacturers in the United States is 2.5–5 mg/kg (31,250–62,500 IU/kg) per day, divided into 2–4 equal doses (1 mg of colistin equals 12,500 IU). This dosage refers to adult patients with normal renal function [57]. The dosage recommended by the manufacturers in the United Kingdom is 4–6 mg/kg (50,000–75,000 IU/kg) per day, in 3 divided doses for adults and children with body weights of ≤60 kg and 80–160 mg (1–2 million IU) every 8 h for those with body weights of >60 kg [52]. However, we and others have treated patients with higher daily doses of colistin administered intravenously, up to 720 mg (9 million IU) per day (in 3 divided doses) [58, 59]. Although no systematic analyses have been reported regarding the effect of different dosage on effectiveness and toxicity outcomes, the proportion of patients who developed nephrotoxicity during colistin treatment was lower than reported in the past [8]. Modifications of the total daily dose are required in the presence of renal impairment (table 1), as guided by the manufacturers [57]. There are no available data about the need, if any, for dosage modification in patients with liver failure. In obese patients, dosage should be based on ideal body weight.

Besides the intermittent intravenous mode of administration, colistin can also be administered by continuous 24-h infusion [60]. In addition, colistin can be used intramuscularly at the same doses recommended for intravenous administration. However, intramuscular administration is not commonly used in clinical practice because of the severe pain caused at the injection site. During 1970, colistimethate sodium available for intramuscular use was provided in vials containing colistin base and a local anesthetic, dibucaine hydrochloride [8]. In addition, polymyxin B with a caine-type local anesthetic is a combination permitted by the US Food and Drug Administration (FDA) that can be administered intramuscularly, in ear drops, and in ointments.

When colistin is given by inhalation, the dosage recommended by the manufacturers in the United Kingdom is 40 mg (500, 000 IU) every 12 h for patients with body weights of ≤40 kg and 80 mg (1 million IU) every 12 h for patients with body weights of >40 kg. For recurrent pulmonary infections, the dosage of aerosolized colistin can be increased to 160 mg (2 million IU) every 8 h [61]. For spontaneously breathing patients, colistin can be administered as follows: 80 mg (1 million IU) of colistin is added to 4 mL of normal saline and swirled slowly to mix, and the solution is nebulized with 8 L/min oxygen flow and inhaled via a face mask. For patients undergoing mechanical ventilation, aerosolized colistin can be delivered by means of most ventilators [54]. In addition, usually for patients with cystic fibrosis, inhaled colistin can be administered through jet or ultrasonic nebulizers [62, 63].

There are few recent reports in the literature about the direct administration of colistin in CSF for the management of infections of the CNS due to MDR gram-negative bacteria (although not approved by the FDA). The dosage of colistin used in 2 cases for intrathecal administration ranged from 3.2 mg (40,000 IU) to 10 mg (125,000 IU) given once per day and in 2 cases for intraventricular administration ranged from 10 mg (125,000 IU) to 20 mg (250,000 IU) per day (divided into 2 doses). In these cases, no additional intravenous colistin was administered [64–66]. The dosage of colistin administered intraventricularly to a patient of ours was 1.6 mg (20,000 IU) once per day during the first episode and 3.2 mg (40,000 IU) once per day during the second episode of meningitis due to *A. baumannii*. He also received 80 mg (1 million IU) of colistin administered intravenously every 8 h [53].

TOXICITY AND ADVERSE EFFECTS

The most common adverse effects of colistin therapy are nephrotoxicity and neurotoxicity. Renal toxicity mainly includes acute tubular necrosis manifested as decreased creatinine clearance and increased serum urea and creatinine levels. Neurological toxicity is associated with dizziness, weakness, facial and peripheral paresthesia, vertigo, visual disturbances, confusion, ataxia, and neuromuscular blockade, which can lead to respiratory failure or apnea. The incidence of colistin-associated neurotoxicity reported in earlier literature was ∼7%, with paresthesias constituting the main neurotoxic adverse event [8]. Recent studies of patients other than those with cystic fibrosis suggested that this incidence might be even lower [59, 67, 68]. However, the development of neurotoxic events related to colistin therapy appears to occur more frequently in patients with cystic fibrosis (29% of the patients treated with colistin experienced paresthesias, ataxia, or both) [6, 69]. Both renal and neurological toxicity are considered to be dose-dependent

and usually reversible after early discontinuation of therapy with the drug. However, there are scarce published reports of irreversible nephrotoxicity after the cessation of colistin treatment [8].

Miscellaneous other adverse reactions that have also been reported with the use of colistin include hypersensitivity reactions, skin rash, urticaria, generalized itching, fever, and mild gastrointestinal disorders. The incidence of allergic reactions due to colistin use has been reported as ~2% [8]. Furthermore, the development of pseudomembranous colitis represents an additional, although rare, potential side effect of colistin treatment. Treatment with aerosolized colistin may further be complicated by bronchoconstriction and chest tightness. However, treatment with inhaled β_2 agonists before the initiation of treatment with aerosolized colistin could prevent the development of bronchoconstriction [11]. Intraventricular administration of colistin, especially in high doses, may lead to convulsions.

Early experience with colistin revealed a high incidence of toxicity, mainly nephrotoxicity [9, 70, 71]. In a trial published in 1970 studying the safety of colistin during 317 episodes of infections, the incidence of nephrotoxicity was 20.2% [8]. Several other studies reporting high incidences of renal failure after the administration of colistin were published in ensuing years [70, 71]. The majority of these renal episodes were reversible.

However, recent data indicate that colistin-related toxicity, mainly nephrotoxicity, may be less prominent than previously thought [59, 72]. Notably, in 2 studies conducted exclusively among patients in intensive care units who received 3 million IU of colistin administered intravenously every 8 h, the incidences of nephrotoxicity were 18.6% and 14.3%, respectively [58, 59]. Only 8% of our patients from the intensive care unit setting, as well as from medical-surgical wards of the hospital, who received an average of 4.5 million IU of colistin administered intravenously for a mean duration of 21.3 days, developed nephrotoxicity [73]. Another recent study of patients with cystic fibrosis showed that renal dysfunction was potentiated by the coadministration of colistin and aminoglycosides; however, colistin on its own or in combination with other antibiotics did not appear to be highly nephrotoxic [74]. Of note, renal failure among patients treated with imipenem for ventilator-associated pneumonia due to *A. baumannii* was 2 times higher than among patients treated with colistin [67].

Possible explanations for the observed differences between the old and recent reports regarding renal toxicity might include the improvement in supportive treatment offered to critically ill patients, the close monitoring of renal function and of factors that affect it when colistin is administered, and the avoidance of coadministration of other agents with known nephrotoxicity. In addition, different formulations of colistin, containing a proportion of colistin sulfate that is more toxic than the recom-

mended form of colistin for intravenous use (colistimethate sodium), might have been used in old studies.

COADMINISTRATION WITH OTHER ANTIBIOTICS

There are few experimental and clinical studies in the literature regarding synergistic activity of colistin with other antimicrobial agents against MDR gram-negative bacteria. One clinical trial of the effectiveness of colistin in 53 patients with cystic fibrosis with exacerbations of chronic pulmonary infections due to MDR *P. aeruginosa* showed that combination of colistin with an antipseudomonal agent (azlocillin, piperacillin, aztreonam, ceftazidime, imipenem, or ciprofloxacin) was more effective than colistin monotherapy [10].

Synergistic activity of colistin with ceftazidime was also noted in an in vitro study of 2 MDR *P. aeruginosa* strains [75]. The combination of colistin, rifampin, and amikacin was synergistic in vitro and led to treatment success in an immunosuppressed patient with multiple abscesses of the lungs, perineum, and gluteus due to MDR *P. aeruginosa* [76]. Moreover, the rifampin/colistin combination had synergistic bactericidal activity against MDR *P. aeruginosa* strains in 4 patients [77]. With regard to MDR *S. maltophilia* strains, in vitro synergy of colistin with rifampin and, to a lesser extent, of colistin with trimethoprim-sulfamethoxazole was documented in a recent study [78].

OTHER POLYMYXINS

Besides polymyxin E (colistin), only polymyxin B has been used in clinical practice in several countries. The main difference between the molecules of colistin and polymyxin B is that the latter contains phenylalanine. Polymyxin B has the same mechanism of action and resistance as does colistin. Colistin sulfate has greater activity than polymyxin B against *P. aeruginosa, Salmonella* species, and *Shigella* species [79]. Polymyxin B is available in parenteral formulations and can be administered intravenously, intramuscularly, or intrathecally. In addition, polymyxin B has been extensively used topically in otic and ophthalmic solutions. It has the same clinical indications as and a pattern of adverse effects similar to those of colistin. Most of the renewed use of intravenous polymyxins during the last years in several countries has been associated with colistin. This may be explained by the fact that polymyxin B was reported to be associated with more common and severe toxicity than was colistin [6, 12, 80, 81].

FUTURE RESEARCH

Colistin was developed in an era when randomized controlled trials and pharmacokinetic and pharmacodynamic properties of antimicrobial agents were not fully established. Thus, con-

siderable additional basic and clinical research is needed on several issues, including the following:

- Additional research on the development of improved colistin formulations.
- Studies to define the optimum dosing strategies, including total daily dose, mode of administration, and dosing intervals.
- Clinical trials to evaluate colistin-related toxicity.
- Studies to elucidate the mechanisms of development of resistance to colistin.
- Randomized, controlled trials to assess the effectiveness and safety of nebulized colistin for the treatment of nosocomial pneumonia due to MDR gram-negative bacteria.
- Randomized controlled trials to evaluate the potential risks and benefits of coadministration of colistin with other antimicrobial agents.

CONCLUSIONS

In conclusion, intravenous polymyxin therapy has been reintroduced in clinical practice for treatment of infections due to MDR gram-negative bacteria. When colistin is used, we suggest the dosage of 160 mg (2 million IU) ever 8 h (or 240 mg [3 million IU] every 8 h for life-threatening infections). The duration of treatment depends on the type of infection and may be 14 days in cases of pneumonia and/or bacteremia. Clinicians should be alert for the possibility of development of colistin-related adverse reactions, mainly nephrotoxicity and neurotoxicity. Subsequently, we suggest monitoring of renal function by measuring serum creatinine levels every 2 days until more data on the value of other tests for patient monitoring become available.

References

1. Storm DR, Rosenthal KS, Swanson PE. Polymyxin and related peptide antibiotics. Annu Rev Biochem **1977**; 46:723–63.
2. Nakajima S. Clinical use of colimycin F otic solution [in Japanese]. Jibiinkoka **1965**; 37:693–7.
3. Ohzawa R. The use of colimycin ear drops [in Japanese]. Jibiinkoka **1965**; 37:585–90.
4. Komura S, Kurahashi K. Partial purification and properties of L-2,4-diaminobutyric acid activating enzyme from a polymyxin E producing organism. J Biochem (Tokyo) **1979**; 86:1013–21.
5. Koyama Y, Kurosasa A, Tsuchiya A, Takakuta K. A new antibiotic "colistin" produced by spore-forming soil bacteria. J Antibiot (Tokyo) **1950**; 3:457–8.
6. Reed MD, Stern RC, O'Riordan MA, Blumer JL. The pharmacokinetics of colistin in patients with cystic fibrosis. J Clin Pharmacol **2001**; 41:645–54.
7. Brown JM, Dorman DC, Roy LP. Acute renal failure due to overdosage of colistin. Med J Aust **1970**; 2:923–4.
8. Koch-Weser J, Sidel VW, Federman EB, Kanarek P, Finer DC, Eaton AE. Adverse effects of sodium colistimethate: manifestations and specific reaction rates during 317 courses of therapy. Ann Intern Med **1970**; 72:857–68.
9. Ryan KJ, Schainuck LI, Hickman RO, Striker GE. Colistimethate toxicity: report of a fatal case in a previously healthy child. JAMA **1969**; 207:2099–101.
10. Conway SP, Pond MN, Watson A, Etherington C, Robey HL, Goldman MH. Intravenous colistin sulphomethate in acute respiratory exacerbations in adult patients with cystic fibrosis. Thorax **1997**; 52:987–93.
11. Cunningham S, Prasad A, Collyer L, Carr S, Lynn IB, Wallis C. Bronchoconstriction following nebulised colistin in cystic fibrosis. Arch Dis Child **2001**; 84:432–3.
12. Ledson MJ, Gallagher MJ, Cowperthwaite C, Convery RP, Walshaw MJ. Four years' experience of intravenous colomycin in an adult cystic fibrosis unit. Eur Respir J **1998**; 12:592–4.
13. Katz E, Demain AL. The peptide antibiotics of *Bacillus:* chemistry, biogenesis, and possible functions. Bacteriol Rev **1977**; 41:449–74.
14. Decolin D, Leroy P, Nicolas A, Archimbault P. Hyphenated liquid chromatographic method for the determination of colistin residues in bovine tissues. J Chromatogr Sci **1997**; 35:557–64.
15. Orwa JA, Govaerts C, Busson R, Roets E, Van Schepdael A, Hoogmartens J. Isolation and structural characterization of colistin components. J Antibiot (Tokyo) **2001**; 54:595–9.
16. Barnett M, Bushby SR, Wilkinson S. Sodium sulphomethyl derivatives of polymyxins. Br J Pharmacol **1964**; 23:552–74.
17. Beveridge EG, Martin AJ. Sodium sulphomethyl derivatives of polymyxins. Br J Pharmacol **1967**; 29:125–35.
18. Davis SD, Iannetta A, Wedgwood RJ. Activity of colistin against *Pseudomonas aeruginosa:* inhibition by calcium. J Infect Dis **1971**; 124:610–2.
19. Newton BA. The properties and mode of action of the polymyxins. Bacteriol Rev **1956**; 20:14–27.
20. Schindler M, Osborn MJ. Interaction of divalent cations and polymyxin B with lipopolysaccharide. Biochemistry **1979**; 18:4425–30.
21. Koike M, Iida K, Matsuo T. Electron microscopic studies on mode of action of polymyxin. J Bacteriol **1969**; 97:448–52.
22. Gough M, Hancock RE, Kelly NM. Antiendotoxin activity of cationic peptide antimicrobial agents. Infect Immun **1996**; 64:4922–7.
23. Moore RA, Chan L, Hancock RE. Evidence for two distinct mechanisms of resistance to polymyxin B in *Pseudomonas aeruginosa.* Antimicrob Agents Chemother **1984**; 26:539–45.
24. Groisman EA, Kayser J, Soncini FC. Regulation of polymyxin resistance and adaptation to low-Mg^{2+} environments. J Bacteriol **1997**; 179:7040–5.
25. Moore RA, Hancock RE. Involvement of outer membrane of *Pseudomonas cepacia* in aminoglycoside and polymyxin resistance. Antimicrob Agents Chemother **1986**; 30:923–6.
26. Denton M, Kerr K, Mooney L, et al. Transmission of colistin-resistant *Pseudomonas aeruginosa* between patients attending a pediatric cystic fibrosis center. Pediatr Pulmonol **2002**; 34:257–61.
27. Gunn JS, Lim KB, Krueger J, et al. PmrA-PmrB–regulated genes necessary for 4-aminoarabinose lipid A modification and polymyxin resistance. Mol Microbiol **1998**; 27:1171–82.
28. Bengoechea JA, Skurnik M. Temperature-regulated efflux pump/potassium antiporter system mediates resistance to cationic antimicrobial peptides in *Yersinia.* Mol Microbiol **2000**; 37:67–80.
29. Ito-Kagawa M, Koyama Y. Selective cleavage of a peptide antibiotic, colistin by colistinase. J Antibiot (Tokyo) **1980**; 33:1551–5.
30. Renard L, Sanders P, Laurentie M. Pharmacokinetics of colistin sulfate administered by intravenous and intramuscular routes in the calf [in French]. Ann Rech Vet **1991**; 22:387–94.
31. Yamada S, Mayahara T, Mitsuhashi N, Wakabayashi K, Hiratsuka K. Fundamental studies on colistin sodium methanesulfonate (colimycin). I. On the blood level, distribution, and excretion of CL-M [in Japanese]. Jpn J Antibiot **1974**; 27:8–14.
32. al Khayyat AA, Aronson AL. Pharmacologic and toxicologic studies

with the polymyxins. II. Comparative pharmacologic studies of the sulfate and methanesulfonate salts of polymyxin B and colistin in dogs. Chemotherapy **1973**; 19:82–97.

33. Li J, Milne RW, Nation RL, Turnidge JD, Smeaton TC, Coulthard K. Use of high-performance liquid chromatography to study the pharmacokinetics of colistin sulfate in rats following intravenous administration. Antimicrob Agents Chemother **2003**; 47:1766–70.

34. Li J, Turnidge J, Milne R, Nation RL, Coulthard K. In vitro pharmacodynamic properties of colistin and colistin methanesulfonate against *Pseudomonas aeruginosa* isolates from patients with cystic fibrosis. Antimicrob Agents Chemother **2001**; 45:781–5.

35. Li J, Coulthard K, Milne R, et al. Steady-state pharmacokinetics of intravenous colistin methanesulphonate in patients with cystic fibrosis. J Antimicrob Chemother **2003**; 52:987–92.

36. Catchpole CR, Andrews JM, Brenwald N, Wise R. A reassessment of the in-vitro activity of colistin sulphomethate sodium. J Antimicrob Chemother **1997**; 39:255–60.

37. McMillan FH, Pattison IC. Sodium colistimethate. I. Dissociations of aminomethanesulfonates in aqueous solution. J Pharm Sci **1969**; 58: 730–7.

38. Li J, Milne RW, Nation RL, Turnidge JD, Coulthard K. Stability of colistin and colistin methanesulfonate in aqueous media and plasma as determined by high-performance liquid chromatography. Antimicrob Agents Chemother **2003**; 47:1364–70.

39. Li J, Milne RW, Nation RL, Turnidge JD, Smeaton TC, Coulthard K. Pharmacokinetics of colistin methanesulphonate and colistin in rats following an intravenous dose of colistin methanesulphonate. J Antimicrob Chemother **2004**; 53:837–40.

40. Kunin CM, Bugg A. Binding of polymyxin antibiotics to tissues: the major determinant of distribution and persistence in the body. J Infect Dis **1971**; 124:394–400.

41. Craig WA, Kunin CM. Significance of serum protein and tissue binding of antimicrobial agents. Annu Rev Med **1976**; 27:287–300.

42. al Khayyat AA, Aronson AL. Pharmacologic and toxicologic studies with the polymyxins. 3. Consideration regarding clinical use in dogs. Chemotherapy **1973**; 19:98–108.

43. Li J, Milne RW, Nation RL, Turnidge JD, Smeaton TC, Coulthard K. Use of high-performance liquid chromatography to study the pharmacokinetics of colistin sulfate in rats following intravenous administration. Antimicrob Agents Chemother **2003**; 47:1766–70.

44. Ziv G, Nouws JF, van Ginneken CA. The pharmacokinetics and tissue levels of polymyxin B, colistin and gentamicin in calves. J Vet Pharmacol Ther **1982**; 5:45–58.

45. Jimenez-Mejias ME, Pichardo-Guerrero C, Marquez-Rivas FJ, Martin-Lozano D, Prados T, Pachon J. Cerebrospinal fluid penetration and pharmacokinetic/pharmacodynamic parameters of intravenously administered colistin in a case of multidrug-resistant *Acinetobacter baumannii* meningitis. Eur J Clin Microbiol Infect Dis **2002**; 21:212–4.

46. Gales AC, Reis AO, Jones RN. Contemporary assessment of antimicrobial susceptibility testing methods for polymyxin B and colistin: review of available interpretative criteria and quality control guidelines. J Clin Microbiol **2001**; 39:183–90.

47. Niks M, Hanzen J, Ohlasova D, et al. Multiresistant nosocomial bacterial strains and their "in vitro" susceptibility to chloramphenicol and colistin [in Czech]. Klin Mikrobiol Infekc Lek **2004**; 10:124–9.

48. Hogardt M, Schmoldt S, Gotzfried M, Adler K, Heesemann J. Pitfalls of polymyxin antimicrobial susceptibility testing of *Pseudomonas aeruginosa* isolated from cystic fibrosis patients. J Antimicrob Chemother **2004**; 54:1057–61.

49. Rastogi N, Potar MC, David HL. Antimycobacterial spectrum of colistin (polymixin E). Ann Inst Pasteur Microbiol **1986**; 137A:45–53.

50. Rastogi N, Henrotte JG, David HL. Colistin (polymyxin E)–induced cell leakage in *Mycobacterium aurum*. Zentralbl Bakteriol Mikrobiol Hyg [A] **1987**; 263:548–51.

51. Rastogi N, Potar MC, Henrotte JG, Franck G, David HL. Further studies on colistin (polymyxin E)–induced cell leakage in mycobacteria:

52. Colomycin [package insert]. Bexley, UK: Forest Laboratories, UK Limited, **2002**.

53. Kasiakou SK, Rafailidis PI, Liaropoulos K, Falagas ME. Cure of post-traumatic recurrent multiresistant gram-negative rod meningitis with intraventricular colistin. J Infect (in press).

54. Michalopoulos A, Kasiakou SK, Mastora Z, Rellos K, Kapaskelis AM, Falagas ME. Aerosolized colistin for the treatment of nosocomial pneumonia due to multidrug-resistant gram-negative bacteria in patients without cystic fibrosis. Crit Care **2005**; 9:R53–9.

55. Littlewood JM, Koch C, Lambert PA, et al. A ten year review of colomycin. Respir Med **2000**; 94:632–40.

56. Hamer DH. Treatment of nosocomial pneumonia and tracheobronchitis caused by multidrug-resistant *Pseudomonas aeruginosa* with aerosolized colistin. Am J Respir Crit Care Med **2000**; 162:328–30.

57. Coly-mycin M parenteral [package insert]. Bristol, TN: Monarch Pharmaceuticals, **2002**.

58. Michalopoulos A, Tsiodras S, Rellos K, Mentzelopoulos S, Falagas ME. Colistin treatment in patients with ICU-acquired infections caused by multiresistant gram-negative bacteria: the renaissance of an old antibiotic. Clin Microbiol Infect **2005**; 11:115–21.

59. Markou N, Apostolakos H, Koumoudiou C, et al. Intravenous colistin in the treatment of sepsis from multiresistant gram-negative bacilli in critically ill patients. Crit Care **2003**; 7:R78–83.

60. Michalopoulos A, Kasiakou SK, Rosmarakis ES, Falagas ME. Cure of multidrug-resistant *Acinetobacter baumannii* bacteremia with continuous intravenous infusion of colistin. Scand J Infect Dis **2005** 37:142–5.

61. Promixin 1 MIU powder for nebuliser solution [package insert]. West Sussex, UK: Profile Pharma Limited, **2003**.

62. Weber A, Morlin G, Cohen M, Williams-Warren J, Ramsey B, Smith A. Effect of nebulizer type and antibiotic concentration on device performance. Pediatr Pulmonol **1997**; 23:249–60.

63. Faurisson F, Dessanges JF, Grimfeld A, et al. Nebulizer performance: AFLM study. Association Francaise de Lutte contre la Mucoviscidose. Respiration **1995**; 62(Suppl 1):13–8.

64. Benifla M, Zucker G, Cohen A, Alkan M. Successful treatment of *Acinetobacter* meningitis with intrathecal polymyxin E. J Antimicrob Chemother **2004**; 54:290–2.

65. Fernandez-Viladrich P, Corbella X, Corral L, Tubau F, Mateu A. Successful treatment of ventriculitis due to carbapenem-resistant *Acinetobacter baumannii* with intraventricular colistin sulfomethate sodium. Clin Infect Dis **1999**; 28:916–7.

66. Vasen W, Desmery P, Ilutovich S, Di Martino A. Intrathecal use of colistin. J Clin Microbiol **2000**; 38:3523.

67. Garnacho-Montero J, Ortiz-Leyba C, Jimenez-Jimenez FJ, et al. Treatment of multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia (VAP) with intravenous colistin: a comparison with imipenem-susceptible VAP. Clin Infect Dis **2003**; 36:1111–8.

68. Levin AS, Barone AA, Penco J, et al. Intravenous colistin as therapy for nosocomial infections caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Clin Infect Dis **1999**; 28: 1008–11.

69. Bosso JA, Liptak CA, Seilheimer DK, Harrison GM. Toxicity of colistin in cystic fibrosis patients. DICP **1991**; 25:1168–70.

70. Price DJ, Graham DI. Effects of large doses of colistin sulphomethate sodium on renal function. Br Med J **1970**; 4:525–7.

71. Randall RE, Bridi GS, Setter JG, Brackett NC. Recovery from colistimethate nephrotoxicity. Ann Intern Med **1970**; 73:491–2.

72. Falagas ME, Rizos M, Bliziotis IA, Rellos K, Kasiakou SK, Michalopoulos A. Toxicity after prolonged (more than four weeks) administration of intravenous colistin. BMC Infect Dis **2005**; 5:1.

73. Kasiakou SK, Michalopoulos A, Soteriades E, Samonis G, Sermaides G, Falagas ME. Intravenous colistin for treatment of infections due to multidrug-resistant gram-negative bacteria in patients without cystic fibrosis [P 1074]. In: Proceedings of the 15th European Congress of Clinical Microbiology and Infectious Diseases (Copenhagen). **2005**.

Mg^{++} efflux in *Mycobacterium avium* and its effects on drug-susceptibility. Zentralbl Bakteriol Mikrobiol Hyg [A] **1988**; 268:251–8.

74. Al Aloul M, Miller H, Alapati S, Stockton PA, Ledson MJ, Walshaw MJ. Renal impairment in cystic fibrosis patients due to repeated intravenous aminoglycoside use. Pediatr Pulmonol **2005**; 39:15–20.

75. Gunderson BW, Ibrahim KH, Hovde LB, Fromm TL, Reed MD, Rotschafer JC. Synergistic activity of colistin and ceftazidime against multiantibiotic-resistant *Pseudomonas aeruginosa* in an in vitro pharmacodynamic model. Antimicrob Agents Chemother **2003**; 47:905–9.

76. Tascini C, Ferranti S, Messina F, Menichetti F. In vitro and in vivo synergistic activity of colistin, rifampin, and amikacin against a multiresistant *Pseudomonas aeruginosa* isolate. Clin Microbiol Infect **2000**; 6:690–1.

77. Tascini C, Gemignani G, Ferranti S, et al. Microbiological activity and clinical efficacy of a colistin and rifampin combination in multidrug-resistant *Pseudomonas aeruginosa* infections. J Chemother **2004**; 16: 282–7.

78. Giamarellos-Bourboulis EJ, Karnesis L, Giamarellou H. Synergy of colistin with rifampin and trimethoprim/sulfamethoxazole on multidrug-resistant *Stenotrophomonas maltophilia*. Diagn Microbiol Infect Dis **2002**; 44:259–63.

79. Wright WW, Welch H. Chemical, biological and clinical observations on colistin. Antibiot Annu **1959**; 7:61–74.

80. Hoeprich PD. The polymyxins. Med Clin North Am **1970**; 54:1257–65.

81. Nord NM, Hoeprich PD. Polymyxin B and colistin: a critical comparison. N Engl J Med **1964**; 270:1030–5.

In an article in the 1 May 2005 issue of the journal (Falagas ME, Kasiakou SK. Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. Clin Infect Dis 2005; 40:1333–41), 2 errors appeared. In table 1, the synopsis for recommended iv dosage should read "United States: 2.5–5 mg/kg of colistin base (75,000–150,000 IU/kg) per day divided into 2–4 equal doses (1 mg of colistin base equals 30,000 IU); United Kingdom: 4–6 mg/kg (50,000–75,000 IU/kg) per day in 3 divided doses for adults and children with body weights of ≤60 kg, and 80–160 mg (1–2 million IU) q8h for body weights of >60 kg" (*not* "United States: 2.5–5 mg/kg (31,250–62,500 IU/kg) per day divided into 2–4 equal doses (1 mg of colistin base equals 12,500 IU); United King-dom: 4–6 mg/kg (50,000–75,000 IU/kg) per day in 3 divided doses for adults and children with body weights of ≤60 kg, and 80–160 mg (1–2 million IU) q8h for body weights of >60 kg"). In the first sentence of the first paragraph of the Dosage and Route of Administration section, the text should read "The dosage of intravenous colistin recommended by the manufacturers in the United States is 2.5–5 mg/kg of colistin base (75,000–150,000 IU/kg) per day divided into 2–4 equal doses (1 mg of colistin equals 30,000 IU)" (*not* "The dosage of intravenous colistin recommended by the manufacturers in the United States is 2.5–5 mg/kg (31,250–62,500 IU/kg) per day, divided into 2–4 equal doses (1 mg of colistin equals 12,500 IU)"). The authors regret these errors.