Rational use of antibiotics

Dijkmans, A.C.

CHAPTER 6

COLISTIN: REVIVAL OF AN OLD POLYMYXIN ANTIBIOTIC

Ther Drug Monit 2015; 37(4): 419-27

Dijkmans AC,[1,2] Wilms EB,[3] Kamerling IMC,[1,2] Birkhoff W,[1] Ortiz Zacarías NV,[1] van Nieuwkoop C,[4] Verbrugh HA,[5] Touw DJ[6]

1 Centre for Human Drug Research, Leiden, The Netherlands
2 Leiden University Medical Center, Leiden, The Netherlands
3 The Hague Hospital Pharmacy, The Hague, The Netherlands
4 Haga Teaching Hospital, The Hague, The Netherlands
5 Erasmus Medical Center, Rotterdam, The Netherlands
6 University Medical Center Groningen, Groningen, the Netherlands

ABSTRACT

Colistin (polymyxin E) is a positively charged decapeptide antibiotic that disrupts the integrity of the outer membrane of the cell wall of gram-negative bacteria by binding to the lipid A moiety of lipopolysaccharides, resulting in cell death. The endotoxic activity of lipopolysaccharides is simultaneously inhibited. Colistin is increasingly being prescribed as rescue treatment for infections with multidrug-resistant bacilli. Nephrotoxicity and, to a lesser degree, neurotoxicity occur often during systemic colistin therapy, and have severely limited its application in the past. However, these side effects are largely reversible and can be managed through close monitoring. The prodrug colistimethate sodium (CMS) is less toxic and is, therefore, the preferred formulation for parenteral administration. Importantly, resistance to colistin seems to emerge often unless it is combined with another antibiotic, but further studies into this phenomenon are necessary. Pharmacokinetic and pharmacodynamic properties have received little attention, partly because of the physicochemical peculiarities of polymyxin antibiotics, especially their propensity to stick to other molecules and surfaces. The ratio between the area under the curve of free colistin and the pathogen's Minimal Inhibitory Concentration (MIC) best predicts microbiological and clinical responses, but more studies are needed in this area. Likewise, further standardization is needed in production and labeling of colistin formulations, and in the way the susceptibility of bacteria to colistin is determined.

INTRODUCTION

After the discovery of antibiotics[1] and their introduction into clinical practice, it was generally believed that infectious diseases would become history. However, this idea was proven to be wrong, and resistance to antibiotics has become an enormous global burden. Especially, gram-negative bacteria, including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae*, are becoming more and more resistant to an increasing number of antibiotics. As a consequence, mortality due to untreatable bacterial infections is increasing.

Physicians have to be aware of the risks of prescribing colistin because inappropriate use of antibiotics is the most important reason for emergence of resistance.[2] Lack of proper infection control has allowed resistant clones to spread further, sometimes even worldwide. In addition, there is an almost empty pipeline of new antibiotics. Pharmaceutical industry has shown little interest in marketing new antibiotics because of high development costs, relatively small return on investments, and the limited size of this niche in the pharmaceutical market.[3] New antibiotics tend to be categorized as 'reserve antibiotic,' resulting in further delay in reaping financial benefit for the pharmaceutical industry.

As there are presently no new antibiotics available for some multiresistant bacteria, an old molecule, colistin, is increasingly being applied over the last years. Colistin (polymyxin E) is an antimicrobial agent that has hardly been used since the reporting of its side effects decades ago. Consequently, there is a lack of relevant knowledge for its clinical use nowadays. Colistin consists of a mixture of colistin A and B. Two chemical formulations are used therapeutically: colistin sulfate and colistimethate sodium (CMS). The latter is a prodrug and is, both in vivo and *in vitro*, converted into a complex mixture of partially sulfamethylated derivatives and partly into active antibiotic colistin. CMS is less toxic than colistin sulfate when used intravenously or by inhalation.[4,5] Unfortunately, there is no unanimously accepted model for the pharmacokinetic and pharmacodynamic properties of colistin. In addition, the exact mechanisms of colistin resistance have not been fully elucidated yet.

Colistin's first life

Colistin was isolated in 1949[6] from the *Bacillus polymyxa* 'Colistinus' and became available for clinical use in 1959.[7] Colistin is a cyclic deca-peptide antibiotic containing 10 linked amino acids (*figure 1*).

Soon after its discovery, it turned out that colistin was identical to polymyxin E.[8] In the 60s, much was learned about the different types of polymyxins (A-E), including colistin, the latter being a mixture of polypeptides. Although most of the mechanism-of-action studies have focused on polymyxin B, the mechanism of action of other polymyxins, including colistin, is thought to be the same.[8] The purpose of this article is to review this antibiotic, in light of its increasing use in the era of emerging drug resistance.

METHODS

Systematic search strategy

The MEDLINE/PUBMED and OVID/EMBASE databases were searched systematically in April 2014 to identify relevant articles on colistin. The search terms concentrated on synonyms of colistin in article titles, to be as specific as possible. The following MEDLINE/PUBMED and OVID/EMBASE searches strategies were performed.

MEDLINE/PUBMED

('Colistin'[Major] OR colistin*[ti] OR 'Polymyxin E'[ti] OR 'Polymyxin E1'[ti] OR 'Polymyxin E2'[ti] OR 'Polymyxins'[ti] OR 'colistinmethanesulfonic acid' [Supplementary Concept] OR Colistimetha*[ti] OR colisticin*[ti] OR Colimycin[ti] OR 'Coly-Mycin'[ti] OR 'Coly Mycin'[ti] OR Totazina[ti] OR Colifin[ti] OR Colobreathe[ti] OR Tadim[ti] OR Colomycin[ti]) AND (eng[la] OR dut[la]).

OVID/EMBASE

(colistin*.ti. or Polymyxin E.ti. or Polymyxin E1.ti. or Polymyxin E2.ti. or Polymyxins. ti. or Colistimetha*.ti.or colisticin*.ti. or Colimycin.ti. or Coly-Mycin.ti. or Coly Mycin. ti. or Totazina.ti. or Colifin.ti. or Colobreathe.ti. or Tadim.ti. or Colomycin. ti.) AND (dutch or english).lg.

The search strategies were designed with specialist librarians and were restricted to English and Dutch. There were no publication or date restrictions.

A comprehensive database of the retrieved articles was built and electronically checked for removing any duplicates. The abstracts of all publications identified were then independently reviewed by the authors. All articles that focused on multidrug resistance gram negatives (such as *A. baumannii*, *P. aeruginosa*, Enterobacteriacea), pharmacokinetics, pharmacodynamics, critically ill patients, treatment outcome, or mode of action were included for full-text review.

To search for potential additional relevant references, the reference lists of included articles were screened as well as relevant guidelines and references from the product information. A final check to update the systematic search was repeated just before the article submission (November 2014) to include any new contribution on this issue.

RESULTS

The combined search in the databases PUBMED/ MEDLINE and OVID/EMBASE retrieved 2569 records, 880 of which were excluded being duplicates (*figure 2*). Of the remaining 1689 records screened by title and abstract, 1617 were excluded as they were judged not pertinent to the topic, whereas 55 references were examined in full text. Thirty-three references were found through handsearching (also including guidelines and product information).

Mechanisms of action

Polymyxins preferentially bind to the lipopolysaccharide (LPS) component of the outer membrane of gram-negative bacteria and damage it as a consequence.[9] Gram-positive bacteria do not contain LPS in their cell wall and, as a consequence, are not susceptible to polymyxins.

With the binding of polymyxins to the lipid A, a key component of the LPS, the 3-dimensional structure of the LPS is altered. This leads to an increased permeability of the cell envelope, which results in leakage of the cell contents and finally in cell death.[10-12] This process is called osmotic destruction. It has been described that polymyxins – in addition to osmotic destruction – are able to kill bacteria by penetrating into the cytoplasm where they interact with nuclear material and ribosomes.[13]

Because the activity of polymyxins involves a displacement of the divalent cations calcium and magnesium that normally stabilize the LPS, the bactericidal activity of polymyxins can be antagonized by physiological concentrations of calcium and magnesium at the level of the cell wall.[14,15] Furthermore, it is known that the endotoxic activity of LPS is significantly reduced because of the binding of polymyxin to the lipid A component of LPS. In this way, polymyxins inhibit LPS-induced activation of leukocytes, and as a consequence, the production of tumor necrosis factor–a and other interleukins.[16] Although antiendotoxin effects of colistin have been proven and validated in animal models,[17] this feature of colistin has not yet been evaluated in clinical practice.

Susceptibility testing

The routine disc diffusion test is not a reliable method to determine colistin susceptibility, because of the fact that the test fails to detect low-level resistance.[18,19] The European Committee on Antimicrobial Susceptibility Testing and the Clinical and Laboratory Standards Institute recommend in their current guidelines colistin susceptibility testing by measuring the MIC. Therefore, broth microdilution is the standard method in most parts of the world. Colistin has, at neutral pH, a polycationic nature, causing it to adhere to many materials, which results in unreliable results.[20] For that reason, polysorbate 80, a dispersing agent, has been added to the media, but this did not result in a gold standard.[21,22] In our opinion, the appropriateness of polysorbate 80 supplementation of the media during MIC testing remains to be proven. In conclusion, further work needs to be performed to gather information to change the current ISO 20776-1 standard.[23]

Colistin resistance

As with all other antibiotics, resistance against colistin has emerged.[24-26] Recently, the European Medicines Agency warned in their report[27] about the increasing resistance to

colistin, especially in southern European countries where colistin has been frequently used in agriculture. The mechanism of resistance against colistin is likely to be the target modification, that is, changes in the lipid A component of the LPS structure.[28] Among enteric pathogens and *P. aeruginosa*, the addition of aminoarabinose and/or phosphoethanolamine residues to the lipid A moiety of LPS removes its negative charge, and, thus, abolishes the affinity of the positively charged colistin for the bacterial cell wall, resulting in resistance. In *A. baumannii*, a complete loss of the LPS structure has been observed as the basis for colistin resistance.[29] Mutations in several genes (parRS, pmrAB, phoPQ, and cprRS) involved in the regulation and synthesis of LPS have been identified in clinical and laboratory-induced colistin-resistant strains.[2,30-32] Importantly, aminoglycosides are also cationic antimicrobials that may simultaneously become less effective by the LPS modifications described above.

Toxicity

In 1970, Koch-Weser et al[25] reported significant side effects of colistin. Nephrotoxicity – consisting of proteinuria, hematuria, and appearance of cylinders in the urine, as well as an increase in the blood levels of urea and creatinine – occurred in 20% of the patients treated with CMS. Apart from nephrotoxicity, neurotoxicity in the form of paresthesias, muscle weakness, peripheral neuropathy, and neuromuscular blockade resulting in respiratory paralysis was described.[25]

These effects and the emergence of new antibacterial agents with fewer side effects led to the disappearance of colistin from clinical practice in the 1970s. A more recent analysis of risks showed colistin dose, the presence of hypoalbuminemia, and the concomitant use of nonsteroidal anti-inflammatory drugs to be independent risk factors for nephrotoxicity.[33] A high body mass index has also been associated with colistin nephrotoxicity, possible because of overdosing based on actual body weight.[34] Importantly, the trough colistin level has been shown to be an independent risk factor for nephrotoxicity.[35]

Recent studies show that, although nephrotoxicity often develops, the level of toxicity might be acceptable. In healthy Japanese volunteers, transient signs of nephrotoxicity or neurotoxicity were observed only after repeated dosing of 75,000 IU/kg body weight CMS.[36]

In a series of intensive care patients treated with a 9-MIU loading dose and 4.5 MIU twice daily as maintenance dose, signs of acute kidney injury were observed in 18% of patients, but they were limited in severity and did not lead to interruption of CMS administration. Also, kidney function recovered after cessation of CMS.[37] In 2 other studies, signs of nephrotoxicity were observed in 14.3% and 18.6% of the patients treated with 3 MIU 3 times daily.[38,39] In a study in which intensive care patients received an average of 4.5 MIU of CMS daily during an average period of 21 days, nephrotoxicity was noted in 8% of patients.[40] Depending on the dose, formulation of CMS, duration, patient category and definitions of nephrotoxicity and (reversible) nephrotoxicity were reported in 10%–50% of patients exposed to this agent.[41,42]

Age, disease status, duration, dose, and concomitant administration of other potentially nephrotoxic drugs (ie, vancomycin and nonsteroidal anti-inflammatory drugs) were risk factors for the development of nephrotoxicity. In a nonrandomized study, 21 intensive care patients with ventilatorassociated pneumonia treated with CMS were compared with 14 similar patients treated with imipenem. Imipenem had twice the risk of developing nephrotoxicity (42% for imipenem versus 19% for colistin, no statistically significant difference).[43]

It can be concluded that kidney dysfunction regularly occurs among patients using CMS and that kidney function should be closely monitored. However, kidney dysfunction is usually not severe, and it is reversible upon discontinuation of CMS. Compared with the early experience with CMS, we now have better facilities for monitoring renal function, better management of renal dysfunction, and awareness of the additional risk when combining CMS with other potentially nephrotoxic drugs. Also, the formulations and the level of hydrolyzed free colistin present in intravenous (IV) solutions prepared at that time could have played a role in the development of renal toxicity.[44]

Practical information on colistin

PHARMACOKINETICS

CMS, as a prodrug, is hydrolyzed into active colistin.[2,45,46] CMS can be hydrolyzed *in vitro* during storage or sample handling, leading to overestimation of colistin when measured in biological samples.[2,45,46] Before 1997, the CMS concentration was either determined by microbiological assays or not measured at all.[46] Since the introduction of novel methods including HPLC and liquid chromatography-tandem mass spectrometry,[47,48] the plasma concentration of CMS and colistin can be quantified separately, allowing the development of better pharmacokinetic models.[49]

After parenteral administration of CMS, only a small fraction is hydrolyzed to colistin, whereas most of the dose is cleared by renal mechanisms. The distribution in the body is best described by a 2-compartment model for CMS and a 1-compartment model for colistin.[50,51] In healthy volunteers, after a single IV dose, CMS has an average half-life of 0.7– 2.0 hours, whereas colistin has an average half-life of 3.0–4.0 hours. However, with repeated dosing, the half-lives of CMS and colistin change to 0.5 and 5.0 hours, respectively.[36,52,53]

In contrast, critically ill patients with normal renal function show an increased half-life, up to 4.6 hours for CMS and from 9.1 up to 18 hours for colistin.[50,51,54] In case of a poor renal function, CMS clearance is reduced, and hence more CMS is available for conversion into the active colistin, increasing the risk of overdose and toxicity. Therefore, renal function and increase in volume of distribution should always be taken in account when dosing critically ill patients (eg, intensive care patients).[49,50] In healthy volunteers, the volume of distribution of colistin is around 0.171–1.443 l/kg with a single IV dose,[36,52] which can be increased in critically ill patients.

After IV administration of CMS to healthy subjects, the maximum concentration of colistin is reached after 2 hours[36]; whereas in critically ill patients, the time to reach the maximum concentration can increase up to 7 hours. Recent pharmacokinetic studies in intensive care patients (patients with burns) have revealed that plasma concentration of colistin increases slowly, requiring between 2 and 3 days to reach the steady-state concentration of colistin.[51] Therefore, a loading dose of CMS has been proposed in patients in whom an increased volume of distribution can be expected and implemented in several studies to achieve the desired target concentration sooner and use less frequent administrations.[37,50,51,54]

Regarding protein binding, colistin has been found to bind both to albumin and alpha1-acid glycoproteins. The fraction unbound (f_u) ranges from 26%–41% in the concentration range of 0.01–2.5 mg/l.[54] Binding, however, varies widely in critically ill patients with reported levels between 6% and 72%.[55] The free concentration or unbound concentration (fu) is important because it is responsible for the antibacterial activity,[27] and this should be taken into account when measuring levels of colistin. The activity of colistin can be best predicted when the free concentration of colistin is related to the MIC, especially the area under the curve (AUC), which has a better predictive value than the C_{max} or T. MIC.[4,56,57] The parameter that correlates best with the effectiveness is the AUC of the free concentration divided by the MIC (fAUC/MIC).

TISSUE PENETRATION

Colistin hardly crosses the blood–brain barrier.[58] Conflicting results on the penetration through the lung tissue are available.[59,60] However, in clinical practice, pneumonia is successfully treated with colistin, with IV administration and by inhalation administration.[2]

Little is known about intraocular penetration of colistin. However, in an animal study, it was demonstrated that colistin penetrates the aqueous humor of the eyes, when administered topically, intramuscularly, or by subconjunctival injection.[61]

After oral administration colistin is poorly absorbed, while after administration by inhalation, the rate of absorption will depend on the condition of the lung and the type of nebulizer used. Pharmacokinetics of CMS after inhalation has been studied in both cystic fibrosis (CF) and in mechanically ventilated patients.[62-64] In general, colistin concentrations found in sputum or epithelial lining fluid were well above the MIC of 1 mg/l for up to 12 hours, with concentrations ranging from 1 to 21 mg/l found after nebulization of 1–4 MIU of CMS. Because very high CMS concentrations were also measured in sputum – around 50–500 mg/l after 1 hour of nebulization – it has beenhypothesized that inhaled CMS provides a reservoir that allows prolonged delivery of colistin from the lung.[62-64]

THERAPEUTIC DRUG MONITORING OF COLISTIN

The use of therapeutic drug monitoring (TDM) to optimize colistin dosing and minimize toxicity has not been well established yet. On the basis of pharmacokinetic studies, substantial dose adaptations have been made in specific patient populations such as patients with burns and patients in the intensive care unit and those on continuous venovenous hemofiltration.[65-67] Trials to assess the value of TDM are ongoing. The value of TDM to prevent overdosing seems most appropriate in patients with decreased renal function and in patients who are obese to avoid toxicity. Trough levels above 3 mg/l at steady state at day 7 of treatment have been associated with an increased risk of nephrotoxicity.[35]

However, TDM can aid to avoid underdosing in patients with good renal function and in infections with microorganisms in which it is questionable whether the standard dosing level of 3 times 2 MIU is sufficient. In performing TDM, the free (unbound) concentration of colistin is preferably be measured since the fraction unbound is ranging from 26%–41% in the concentration range of 0.01– 2.5 mg/l.[54] Because AUC/MIC gave the best relationship with bacterial killing, this parameter is preferably used in TDM.[64] Alternatively, a trough concentration could be used to estimate the AUC value when a pharmacokinetic model is available. In patients with reduced renal function and/or an increased volume of distribution, the concentration of colistin seems rather constant at steady state and one could argue to use C_{min} to relate to the MIC.[54,66,68]

For example, for *P. aeruginosa*, a concentration of 4 times the MIC proved to result in successful bacterial killing at a MIC value of, 1 mcg/ml.[69] An AUC/MIC of 24 mg×hours/ml · 4/1 mcg/ml=96 hours could be used as a target for total colistin. Taken f_u into account (26%– 41%), an AUC between 25–40 hours could be aimed at for unbound colistin. This value is in line with animal experiments as reported by Bergen et al.[27] They reported target fAUC/MIC values of 15–45 depending on the log-killing and localization of the infection. If this level of exposure of colistin is not feasible, combination therapy has to be instigated. For other microorganisms, similar estimations of target AUC can be made.

Current use

Aerosolized CMS is used in patients with CF to eradicate an initial pulmonary infection, to reduce the pulmonary colonization, and to prevent exacerbations of lung infections with *P. aeruginosa*. In severe pulmonary infections, inhalation is often combined with IV therapy. Colistin sulfate is also used as part of selective intestinal decontamination regimens.[70] Now that colistin is increasingly used as a rescue therapeutic antibiotic several experts advocate that an alternative agent should probably be included in the selective intestinal decontamination regimens. Otitis externa due to gram-negative bacteria, especially *P. aeruginosa*, represents another indication for the topical use of colistin sulfate often in combination with hydrocortisone.

Dosing and administration of CMS

INHALATION

Intrapulmonary delivery of colistin can be achieved either by means of nebulization of a solution of CMS or by dry powder inhalation. For the treatment of chronic pulmonary colonization with *P. aeruginosa*, adult CF patients usually inhale 1–2 MIU of CMS twice daily using a nebulizer. In children aged above 2 years, 1 MIU is inhaled twice daily. When exacerbations of infection with *P. aeruginosa* occur, 1–2 MIU of CMS is used 3 times per day by inhalation for a period of 3 months (*table 1*).

Dry powder inhalation is performed with a dose of 1.66 MIU of CMS twice daily in adults and children aged above 6 years. Safety for younger children has not been established.

IV ADMINISTRATION

For individuals. 60 kg body weight, 1–2 MIU CMS is given every 8 hours. In adults and children, 60 kg body weight, 16,000–25,000 IU/kg body weight is administered every 8 hours. For the US product Coly-Mycin M, a maximal daily dose of 5 mg/kg colistin base activity is advised (equivalent to 62,500 IU/kg and 13.3 mg/kg CMS). In patients with reduced renal clearance, the dose has to be adapted according to a schedule presented in *table 2*.

In intensive care patients with serious infection, higher doses have been recommended to compensate for the increased volume of distribution; a loading dose of 9 MIU and a maintenance dose of 4.5 MIU twice daily have been proposed.[54,68] This regimen has to be adapted to renal function. When the estimated creatinine clearance is between 20–50 ml/ min, 4.5 MIU can be dosed once daily and when clearance is, 20 ml/min, 4.5 MIU can be dosed once every 48 hours.[54,68] CMS can be administered intravenously by a bolus infusion of the required dose diluted in 50–100 ml saline in 30 minutes. Administration of 2 MIU of CMS dissolved in 10 ml water for injection is also feasible and can be used when administered through an implanted infusion device.

It is important to realize that, for safety reasons, only freshly prepared CMS solution should be used, both for nebulization and for IV infusion. After dissolving CMS, hydrolyzation of this product starts and free colistin, associated with a higher level of toxicity, will be formed. In the past, repeated inhalation of a CMS solution that had been prepared days in advance has led to fatal pulmonary damage.[74] The SmPC of Coly-Mycin M parenteral indicates that infusion solutions must be used within 24 hours and the reconstituted solution can be used 7 days if stored at 2–88˚C (SmPC Coly-Mycin M). Based on the report of McCoy (2007) and a Food and Drug Administration alert on pulmonary toxicity of Colistimethate premixed solutions, most guidelines prescribe that even in home treatment, CMS has to be dissolved just before infusion or inhalation.[62]

In patients dialyzed by continuous venovenous hemofiltration, substantial clearance of both colistin and CMS occurs and adaptation of the dose seems not necessary,[50,75,76] but further research enrolling larger numbers of patients is needed. In patients on peritoneal dialysis, CMS and colistin are poorly cleared and, therefore, the dose should be adapted as for patients with a creatinine clearance ≤ 20 ml/min.[77]

Return of colistin in clinical practice

Since the use of colistin is increasing, questions about its safety have reemerged. It seems that the side effects observed in the past are possibly less severe than was thought. In addition, more side effects may be accepted for patients with serious infections due to multiresistant organisms without other antibiotic treatment options. In *table 3*, a summary of CMS characteristics and doses are given. In the following paragraphs, we summarize information that should be taken into account when reintroducing systemic CMS in clinical practice.

Synergy with other antibiotics

Since colistin has been used as rescue treatment for multiresistant gram-negative infections, its use is associated with poor outcome.[8,78] Therefore, given the setting of multiresistant bacterial infections, colistin will often be combined with other antibiotics. However, little is known about the clinical efficacy of combined antibiotic therapy with colistin. *In vitro* data suggest that there is synergistic activity of colistin, particularly when combined with carbapenems[79] or rifampin.[80] These data are promising and are arguments for conducting randomized clinical trials on this topic. So far, in vivo studies have not been able to show a clinical benefit of colistin combination therapy, but it has to be emphasized that such studies are very difficult to conduct.[81,82]

Antimicrobial strategies against colistin resistance

One of the hypotheses is that colistin resistance develops because of underdosing.[83] At higher concentrations of colistin, there is significantly less chance of selecting colistin-resistant mutants compared with exposure to lower concentrations of colistin.[84] Thus, the dosing schedule is an important determinant of the development of colistin resistance.[29]

Monotherapy with colistin invariably leads to selection of colistin-resistant variants. The chance of emergence of resistant subpopulations is reduced when colistin is administered in combination with other antimicrobial agents,[29] including carbapenems, tigecycline, rifampin, amikacin, fosfomycin, azithromycin, vancomycin, and teicoplanin.[29] Interestingly, agents that by themselves are only effective against grampositive bacteria can, in the presence of colistin, become active against gram-negative bacteria because colistin increases their permeation of the cell wall.

Summary and suggestions for a safe and prudent use of colistin

Colistin is currently considered as rescue treatment for critically ill patients with infections caused by multidrug-resistant bacteria. Nephrotoxicity can be expected in a sizable proportion of patients receiving this agent, but this side effect seems to be less severe than initially thought[38,85] and is generally reversible.[36] However, patients on colistin should be closely monitored.

We recommend adjusting the dose on renal function and measuring markers for (early) kidney damage[84] whenever colistin is administered. Regarding the prevention of the development of resistance, colistin should only be given in combination with other antimicrobial agents.

The registered dose of 2 MIU 3 times daily may not be optimal for intensive care patients with a severe infection with multiresistant microorganisms. For those patients, a loading dose of 9 MIU followed by 2 times daily 4.5 MIU could safely be given and a steady-state serum concentration of colistin was reached faster. However, these data were based on limited research.[37,86] To avoid underdosing, free colistin levels should be measured. A FAUC/MIC ratio of at least 25–40 seems optimal,[4] but there is still no consensus on this topic. Prolonged colistin trough levels. 3 mg/l should be avoided.

To redeploy the use of colistin safely and effectively, more clinical and basic research is required. There is need for additional clinical pharmacological studies in healthy volunteers that enable us to predict pharmacokinetic behavior in critically ill patients. With proper translation, safe IV doses for different groups of patients can be identified. Finally, research is needed into which antimicrobial agent(s) that can best be combined with colistin to reduce the risk of the emergence of colistin resistance.

REFERENCES

1 Fleming A. On the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of B. influenzae. *Br J Exp Pathol.* 1929;10:226–236.
2 Li J, Nation RL, Turnidge JD, et al. Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections. *Lancet Infect Dis.* 2006;6:589–601.
3 Morel CM, Mossialos E. Stoking the antibiotic pipeline. *BMJ*. 2010;340: c2115.
4 Bergen PJ, Landersdorfer CB, Zhang J, et al. Pharmacokinetics and pharmacodynamics of 'old' polymyxins: what is new? *Diagn Microbiol Infect Dis.* 2012;74:213–223.
5 Westerman EM, Le Brun PP, Touw DJ, et al. Effect of nebulized colistin sulphate and colistin sulphomethate on lung function in patients with cystic fibrosis: a pilot study. *J Cyst Fibros.* 2004;3:23–28.
6 Wright WW, Welch H. Chemical, biological and clinical observations on colistin. *Antibiot Annu.* 1959;7:61–74.
7 Geus JP. Behandeling van infecties door gram-negatieve bacteriën met colistine (Colimycine). Ned Tijdschr Geneeskd. 1961;105:669.
8 Yahav D, Farbman L, Leibovici L, et al. Colistin: new lessons on an old antibiotic. *Clin Microbiol Infect.* 2012;18:18–29.
9 Velkov T, Thompson PE. Structure—activity relationships of polymyxin antibiotics. *J Med Chem.* 2009;53:1898–1916.
10 Newton BA. The properties and mode of action of the polymyxins. Bacteriol Rev. 1956;20:14–27.
11 Peterson AA, Hancock RE, McGroarty EJ. Binding of polycationic antibiotics and polyamines to lipopolysaccharides of Pseudomonas aeruginosa. *J Bacteriol.* 1985;164:1256–1261.
12 Zhang L, Dhillon P, Yan H. Interactions of bacterial cationic peptide antibiotics with outer and cytoplasmic membranes of Pseudomonas aeruginosa. *Antimicrob Agents Chemother.* 2000;44:3317–3321.
13 Schindler PR, Teuber M. Action of polymyxin B on bacterial membranes: morphological changes in the cytoplasm and in the outer membrane of Salmonella typhimurium and Escherichia coli B. *Antimicrob Agents Chemother. 1*975;8:95–104.
14 Chen CCH, Feingold DS. Locus of divalent cation inhibition of the bactericidal action of polymyxin B. *Antimicrob Agents Chemother.* 1972;2:331–335.
15 Davis SD, Iannetta A, Wedgwood RJ. Activity of colistin against Pseudomonas aeruginosa: inhibition by calcium. *J Infect Dis.* 1971;124:610–612.
16 Baeuerlein A. Transepithelial activation of human leukocytes by probiotics and commensal bacteria: role of Enterobacteriaceae-type endotoxin. *Microbiol Immunol.* 2009;53:241–250.
17 Senturk S. Evaluation of the anti-endotoxic effects of polymyxin-E (colistin) in dogs with naturally occurred endotoxic shock. *J Vet Pharmacol Ther.* 2005;28:57–63.
18 Antimicrobial Susceptibility Testing: Breakpoints 20European Committee on Antimicrobial Susceptibilty Testing EUCAST; 2013.
19 CLSI. Performance standards for antimicrobial susceptibility testing: Twenty Second Informational Supplement M100–SWayne, PA, USA: Clinical and Laboratory Standards Institute; 2012.
20 Colistin is extensively Lost during Normal Experimental conditions. Available at: http://www.abstractsonline.com/plan/ViewAbstract.aspx? mID=2789&sKey=7504fdb1-3935-4908-96f9-9460e52bbec9&cKey=985ade82-9618-4ec1-b893-7fa42500121f&mKey=0c918954-d607-46a7-8073-44f4b537a439.
21 Hindler JA, Humphries RM. Colistin MIC variability by method for contemporary clinical isolates of multidrug-resistant Gram-negative bacilli. *J Clin Microbiol.* 2013;51:1678–1684.
22 Sader HS, Rhomberg PR, Flamm RK, et al. Use of a surfactant (polysorbate to improve MIC susceptibility testing results for polymyxin B and colistin. *Diagn Microbiol Infect Dis.* 2012;74:412–414.
23 Clinical Laboratory testing and *in vitro* diagnostic test systems–Susceptibility testing of infectious agents and evaluation of performance of antimicrobial susceptibility test devices–Part reference method for testing the *in vitro* activity of antimicrobial agents against rapidly growing aerobic bacteria involved in infectious diseases. Geneva: International Standards Organisation; 1-1-2013.
24 Adams MD, Nickel GC, Bajaksouzian S, et al. Resistance to colistin in Acinetobacter baumannii associated with mutations in the PmrAB two-component system. *Antimicrob Agents Chemother*. 2009;53: 3628–3634.
25 Koch-Weser J, Sidel VW, Federman EB, et al. Adverse effects of sodium colistimethate. Manifestations and specific reaction rates during courses of therapy. *Ann Intern Med*. 1970;72:857–868.
26 Moffatt JH, Harper M, Harrison P, et al. Colistin resistance in Acinetobacter baumannii is mediated by complete loss of lipopolysaccharide production. *Antimicrob Agents Chemother.* 2010;54:4971–4977.
27 Bergen PJ, Landersdorfer CB, Zhang J. Pharmacokinetics and pharmacodynamics of 'old' polymyxins: what is new? *Diagn Microbiol Infect Dis.* 2012;74:213–223.
28 Westerman EM, Le Brun PPH, Touw DJ, et al. Effect of nebulized colistin sulphate and colistin sulphomethate on lung function in patients with cystic fibrosis: a pilot study. *J Cyst Fibros.* 2004;3:23–28.
29 Cai Y, Chai D, Wang R, et al. Colistin resistance of Acinetobacter baumannii: clinical reports, mechanisms and antimicrobial strategies. *J Antimicrob Chemother.* 2012;67:1607–1615.
30 Barrow K, Kwon DH. Alterations in two-component regulatory systems of phoPQ and pmrAB are associated with polymyxin B resistance in clinical isolates of Pseudomonas aeruginosa.
31 Fernandez L, Gooderham WJ, Bains M, et al. Adaptive resistance to the "last hope" antibiotics polymyxin B and colistin in Pseudomonas aeruginosa is mediated by the novel two-component regulatory system ParRParS. *Antimicrob Agents Chemother.* 2010;54:3372–3382.

32 Fernandez L, Jensen H, Bains M, et al. The two-component system CprRS senses cationic peptides and triggers adaptive resistance in Pseudomonas acruginosa independently of ParRS. *Antimicrob Agents Chemother.* 2012;56:6212–6222.

33 Pogue JM, Lee J, Marchaim D, et al. Incidence of and risk factors for colistin-associated nephrotoxicity in a large academic health system. *Clin Infect Dis.* 2011;53:879–884.

34 Gauthier TP, Wolowich WR, Reddy A, et al. Incidence and predictors of nephrotoxicity associated with intravenous colistin in overweight and obese patients. *Antimicrob Agents Chemother.* 2012;56:2392–2396.

35 Sorli L, Luque S, Grau S, et al. Trough colistin plasma level is an independent risk factor for nephrotoxicity: a prospective observational cohort study. *BMC Infect Dis.* 2013;13:380.

36 Mizuyachi K, Hara K, Wakamatsu A, et al. Safety and pharmacokinetic evaluation of intravenous colistin methanesulfonate sodium in Japanese healthy male subjects. *Curr Med Res Opin.* 2011;27:2261–2270.

37 Dalfino L, Puntillo F, Mosca A, et al. High-dose, extended-interval colistin administration in critically ill patients: is this the right dosing strategy? A preliminary study. *Clin Infect Dis.* 2012;54:1720–1726.

38 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–R83.

39 Michalopoulos AS, Tsiodras S, Rellos K, et al. Colistin treatment in patients with ICU-acquired infections caused by multiresistant Gramnegative bacteria: the renaissance of an old antibiotic. *Clin Microbiol Infect.* 2005;11:115–121.

40 Kasiakou SK, Michalopoulos A, Soteriades ES, et al. Combination therapy with intravenous colistin for management of infections due to multidrug-resistant Gram-negative bacteria in patients without cystic fibrosis. *Antimicrob Agents Chemother.* 2005;49:3136–3146.

41 Giamarellou H, Poulakou G. Multidrug-resistant gram-negative infections. *Drugs.* 2009;69:1879–1901.

42 Falagas ME, Kasiakou SK. Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. *Crit Care.* 2006;10:R27.

43 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;36:1111–1118.

44 Bergen PJ, Landersdorfer CB, Lee HJ, et al. 'Old' antibiotics for emerging multidrug-resistant bacteria. *Curr Opin Infect Dis.* 2012;25:626–633.

45 Marchand S, Lamarche I, Gobin P, et al. Dose-ranging pharmacokinetics of colistin methanesulphonate (CMS) and colistin in rats following single intravenous CMS doses. *J Antimicrob Chemother.* 2010;65:1753–1758.

46 Li J, Nation RL, Milne RW, et al. Evaluation of colistin as an agent against multi-resistant Gram-negative bacteria. *Int J Antimicrob Agents.* 2005;25:11–25.

47 Li J, Milne RW, Nation RL, et al. A simple method for the assay of colistin in human plasma, using pre-column derivatization with 9-fluorenylmethyl chloroformate in solid-phase extraction cartridges and reversed-phase high-performance liquid chromatography. *J Chromatogr B Biomed Sci Appl.* 2001;761:167–175.

48 Gobin P, Lemaitre F, Marchand S, et al. Assay of colistin and colistin methanesulfonate in plasma and urine by liquid chromatography-tandem mass spectrometry. *Antimicrob Agents Chemother.* 2010;54:1941–1948.

49 Li J, Milne RW, Nation RL, et al. Use of high-performance liquid chromatography to study the pharmacokinetics of colistin sulfate in rats following intravenous administration. *Antimicrob Agents Chemother.* 2003; 47:1766–1770.

50 Garonzik SM, Li J, Thamlikitkul V, et al. Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. *Antimicrob Agents Chemother.* 2011;55:3284–3294.

51 Plachouras D, Karvanen M, Friberg LE, et al. Population pharmacokinetic analysis of colistin methanesulfonate and colistin after intravenous administration in critically ill patients with infections caused by gramnegative bacteria. *Antimicrob Agents Chemother.* 2009;53:3430–3436.

52 Couet W, Gregoire N, Gobin P, et al. Pharmacokinetics of colistin and colistimethate sodium after a single 80-mg intravenous dose of CMS in young healthy volunteers. *Clin Pharmacol Ther.* 2011;89:875–879.

53 Li J, Milne RW, Nation RL, et al. Pharmacokinetics of colistin methanesulphonate and colistin in rats following an intravenous dose of colistin methanesulphonate. *J Antimicrob Chemother.* 2004;53:837–840.

54 Mohamed AF, Karaiskos I, Plachouras D, et al. Application of a loading dose of colistin methanesulfonate in critically ill patients: population pharmacokinetics, protein binding, and prediction of bacterial kill. *Antimicrob Agents Chemother.* 2012;56:4241–4249.

55 Chen G, Thamlikitkul V, Jacob J, et al. Plasma protein binding of colistin in critically-ill patients receiving intravenous colistin methanesulfonate. abstract A2-11Paper presented at: 51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). *American Society for Microbiology;* September 17-20 Chicago, *IL*. Available at: http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=8df031f3-1992-47c5-9a73-0a9ea6581faa&cKey=00762a70-08d3-4227-8cf5bc3b40e083&mKey=0c918954-d607-46a7-8073-44f4b537a439.

56 Bergen PJ, Bulitta JB, Forrest A, et al. Pharmacokinetic/pharmacodynamic investigation of colistin against Pseudomonas aeruginosa using an *in vitro* model. *Antimicrob Agents Chemother.* 2010;54:3783–3789.

57 Dudhani RV, Turnidge JD, Nation RL, et al. fAUC/MIC is the most predictive pharmacokinetic/pharmacodynamic index of colistin against Acinetobacter baumannii in murine thigh and lung infection models. *J Antimicrob Chemother.* 2010;65:1984–1990.

58 Markantonis SL, Markou N, Fousteri M, et al. Penetration of colistin into cerebrospinal fluid. *Antimicrob Agents Chemother.* 2009;53:4907–4910.

59 Markou N, Fousteri M, Markantonis SL, et al. Colistin penetration in the alveolar lining fluid of critically ill patients treated with IV colistimethate sodium. *Chest.* 2011;139:232–233.

60 Imberti R, Cusato M, Villani P, et al. Steady-state pharmacokinetics and BAL concentration of colistin in critically Ill patients after IV colistin methanesulfonate administration. *Chest.* 2010;138:1333–1339.

61 Pryor JG, Apt L, Leopold IH. Intraocular penetration of colistin. *Arch Ophthalmol.* 1962;67:612–615.

62 Ratjen F, Rietschel E, Kasel D, et al. Pharmacokinetics of inhaled colistin in patients with cystic fibrosis. *J Antimicrob Chemother.* 2006;57:306–311.

63 Yapa WS, Li J, Patel K, et al. Pulmonary and systemic pharmacokinetics of inhaled and intravenous colistin methanesulfonate in cystic fibrosis patients: targeting advantage of inhalational administration. *Antimicrob Agents Chemother.* 2014;58:2570–2579.

64 Athanassa ZE, Markantonis SL, Fousteri MZ, et al. Pharmacokinetics of inhaled colistimethate sodium (CMS) in mechanically ventilated critically ill patients. *Intensive Care Med.* 2012;38:1779–1786.

65 Akers KS, Rowan MP, Niece KL, et al. Colistin pharmacokinetics in burn patients during continuous venovenous hemofiltration. 2Oct pii: AAC.03783-[Epub ahead of print].

66 Bode-Boger SM, Schopp B, Troger U, et al. Intravenous colistin in a patient with serious burns and borderline syndrome: the benefits of therapeutic drug monitoring. *Int J Antimicrob Agents.* 2013;42:357–360.

67 Koomanachai P. Pharmacokinetics of colistin methanesulfonate and formed colistin in end-stage renal disease patients receiving continuous ambulatory peritoneal dialysis. *Antimicrob Agents Chemother.* 2014.

68 Dalfino L, Puntillo F, Mosca A, et al. High-dose, extended-interval colistin administration in critically ill patients: is this the right dosing strategy? A preliminary study. *Clin Infect Dis.* 2012;54:1720–1726.

69 Daikos GL, Skiada A, Pavleas J, et al. Serum bactericidal activity of three different dosing regimens of colistin with implications for optimum clinical use. *J Chemother.* 2010;22:175–178.

70 Halaby T, Al NN, Kluytmans J, et al. Emergence of colistin resistance in Enterobacteriaceae after the introduction of selective digestive tract decontamination in an intensive care unit. *Antimicrob Agents Chemother.* 2013;57:3224–3229.

71 SmPC ColiFin PARI 1 MIU Powder for solution for inhalation. Germany: PARI Pharma GmbH; 2014.

72 SmPC colomycin injection. England: Forest Laboratories UK Ltd.;1-11-2012.

73 SmPC Coly-mycin M parenteral. NDA 50-108/S-0 Rochester, USA: Parkedale Pharmaceuticals, Inc.; 2006.

74 McCoy KS. Compounded colistimethate as possible cause of fatal acute respiratory distress syndrome. *N Engl J Med.* 2007;357:2310–2311.

75 Markou N, Fousteri M, Markantonis SL, et al. Colistin pharmacokinetics in intensive care unit patients on continuous venovenous haemodiafiltration: an observational study. *J Antimicrob Chemother.* 2012;67:2459–2462.

76 Karvanen M, Plachouras D, Friberg LE, et al. Colistin methanesulfonate and colistin pharmacokinetics in critically ill patients receiving continuous venovenous hemodiafiltration. *Antimicrob Agents Chemother.* 2013;57:668–671.

77 Koomanachai P, Landersdorfer CB, Chen G, et al. Pharmacokinetics of colistin methanesulfonate and formed colistin in end-stage renal disease patients receiving continuous ambulatory peritoneal dialysis. *Antimicrob Agents Chemother.* 2014;58:440–446.

78 Paul M, Bishara J, Levcovich A, et al. Effectiveness and safety of colistin: prospective comparative cohort study. *J Antimicrob Chemother.* 2010;65:1019–1027.

79 Zusman O, Avni T, Leibovici L, et al. Systematic review and metaanalysis of *in vitro* synergy of polymyxins and carbapenems. *Antimicrob Agents Chemother.* 2013;57:5104–5111.

80 Lee HJ, Bergen PJ, Bulitta JB, et al. Synergistic activity of colistin and rifampin combination against multidrug-resistant Acinetobacter baumannii in an *in vitro* pharmacokinetic/pharmacodynamic model. *Antimicrob Agents Chemother.* 2013;57:3738–3745.

81 Durante-Mangoni E, Signoriello G, Andini R, et al. Colistin and rifampicin compared with colistin alone for the treatment of serious infections due to extensively drug-resistant Acinetobacter baumannii: a multicenter, randomized clinical trial. *Clin Infect Dis.* 2013;57:349–358.

82 Huang DB, Pastagia M, Chiang T. Challenges to conducting a clinical trial of combination therapy of colistin and rifampicin for extensively drugresistant Acinetobacter baumannii. *Clin Infect Dis.* 2014;58:141–142.

83 Lim LM, Ly N, Anderson D, et al. Resurgence of colistin: a review of resistance, toxicity, pharmacodynamics, and dosing. *Pharmacotherapy.* 2010;30:1279–1291.

84 Cai Y, Li R, Liang B, et al. *In vitro* antimicrobial activity and mutant prevention concentration of colistin against Acinetobacter baumannii. *Antimicrob Agents Chemother.* 2010;54:3998–3999.

85 Falagas ME, Rizos M, Bliziotis IA, et al. Toxicity after prolonged (more than four weeks) administration of intravenous colistin. *BMC Infect Dis.* 2005;5:1.

86 Chen L, Mediavilla JR, Endimiani A, et al. Multiplex real-time PCR assay for detection and classification of *Klebsiella pneumoniae* carbapenemase gene (bla KPC) variants. *J Clin Microbiol.* 2011;49:579–585.

87 Samenvatting van de produktkenmerken. Tadim Colisnemethaatnatrium poeder voor infusie 1 MIE; RVG 109891;Profile Pharma Ltd;Clinchester, West Sussex, UK: 8-11-2011.; 8-11-2011.

TABLE 1 Pharmaceutical Products Containing CMS.

Brand Name	Product	CMS, MIU	CMS, mg	Colistin base, mg	Manufacturer
ColiFin Pari	Powder for solution for inhalation	1 MIU*	80[71-73]	33.3	Pari Pharma GMBH, Germany
		2 MIU*	160	66.6	
Colistin	Powder for solution for injection or Infusion	1 MIU*	80	33.3	Forest Laboratories Ltd, UK
Colobreathe	Powder for inhalation (dry powder)	1.66 MIU*	125	55.5	Forest Laboratories Ltd, UK
Tadim	Powder for solution for injection,infusion, or inhalation	1 MIU*	80	33.3	Profile Pharma Ltd, UK
Colomycin	Powder for solution for injection, infusion, or inhalation	1 MIU*	80	33.3	Forest Laboratories Ltd, UK
		2 MIU*	160	66.6	
Coly-Mycin M parenteral	Powder for solution for injection or Infusion	5 MIU	400	150*	JHP Pharmaceuticals, USA

**Labeled amount. Apart from the listed products, in some countries other brands and generic products are available.*

TABLE 2 Suggested colistin dose and frequency adapted to renal clearance.[72,73]

Creatinine clearance (% of Normal)	Dose in MIU (SmPC Colomycin)	Dose in mg colistin base activity (SmPC Coly-Mycin M)	Frequency/ Day	Daily dose in MIU (SmPC Colomycin)	Daily dose in mg colistin base activity (SmPC Coly-Mycin M)
76%–100%	1–2	100–150	3	4–6	300–450
40%–75%	1–1.5	75–115	2	2–3	150–230
25%–40%	1	66–150	1 or 2	1–2	133–150
<25%	1–1.5	100–150	1/36 h	0.6–1	100

TABLE 3 Summary of Colistimethate Sodium dosing and product characteristics.[87]

For injection formulation	
Bottle with 1 million units	=80 mg colistimethate sodium
Bottle with 2 million units	=160 mg colistimethate sodium
For infusion	Dissolve required dose in 50 ml 0.9% NaCl and administer over 30 min
Contraindications	
Hypersensitivity for polymyxins, myasthenia gravis	
Dose (children)	
Normal	3 times daily 16,000–25,000 units/kg
Dose	
Normal	3 times daily 1–2 million units
Dose adjustment in cases of renal failure after normal loading dose Creatinine clearance (% of normal)	
<76	No adjustment
40–75	2 times daily 1–1.5 million units
25–40	1–2 times daily 1 million units
<25	1–1.5 million units every 36 h
Dose in critically ill (ICU) patients[48,49]	
Maximum dose	Loading dose 9 million units, followed by 2 times daily 4.5 million units
Dose adjustment in critically ill (ICU) patients with renal failure Creatinine clearance (ml/min)	
<50	No adjustment
20–50	Once daily 4.5 million units
<20	4.5 million units every 48 h
Dose with patient with renal replacement therapy	
CVVHD	Dose as with normal renal function[38,63,64]
Peritoneal dialysis	1–1.5 million units every 36 h[65]
Adverse reactions	
Nephrotoxicity	≈10%–50% dose dependent, reversible
Neurotoxicity	≈7% dose dependent, reversible paresthesias, dizziness, ataxia
Hypersensitivity	≈2%

CVVHD, continuous venovenous hemofiltration.

FIGURE 1 **Two-dimensional chemical structure of colistin A.**

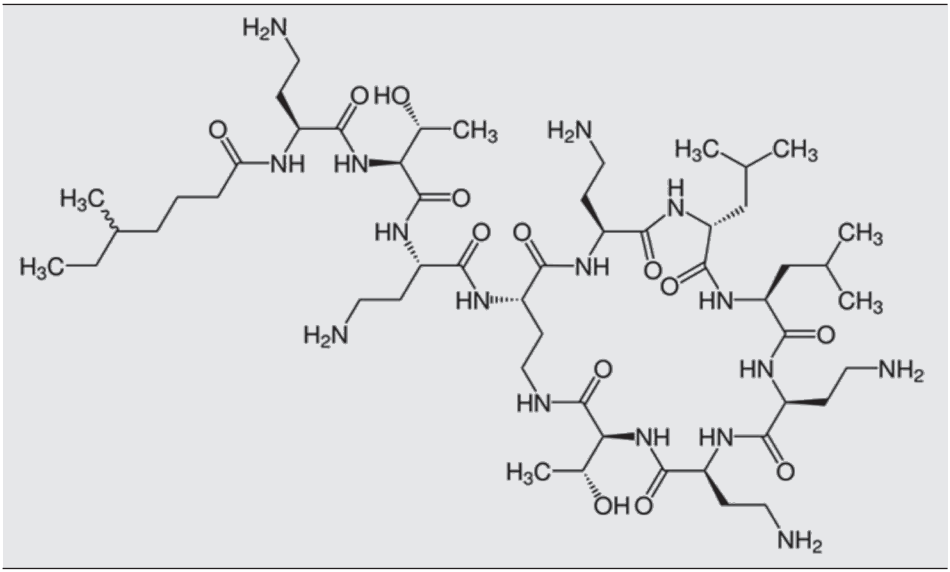

FIGURE 2 **Systematic search process and references included.**