Title
The safety of polymyxin antibiotics

Journal
Expert Opinion on Drug Safety, 14(11)

ISSN
1474-0338

Authors
Kelesidis, Theodoros
Falagas, Matthew E

Publication Date
2015-11-02

DOI
10.1517/14740338.2015.1088520

Peer reviewed

HHS Public Access

Author manuscript

Expert Opin Drug Saf. Author manuscript; available in PMC 2021 April 29.

Published in final edited form as:

Expert Opin Drug Saf. 2015 ; 14(11): 1687–1701. doi:10.1517/14740338.2015.1088520.

The safety of polymyxin antibiotics

Theodoros Kelesidis, MD PhD[1], **Matthew E Falagas, MD MSc DSc**[†,2,3]

[1]University of California, David Geffen School of Medicine, Division of Infectious Diseases, Department of Medicine, Los Angeles, CA 90095, USA

[2]Alfa Institute of Biomedical Sciences (AIBS), 9 Neapoleos Street, 151 23 Marousi, Athens, Greece

[3]Tufts University School of Medicine, Department of Medicine, Boston, MA, USA

Abstract

Introduction: The emergence of multidrug-resistant gram-negative bacteria has led to the increasing use of polymyxins. Nephrotoxicity and, to a lesser degree, neurotoxicity occur often during systemic polymyxin therapy. Scientific evidence regarding safety associated with polymyxins remains limited.

Areas covered: Case reports/case series, observational studies and clinical trials assessing safety and toxicity of polymyxins were critically reviewed.

Expert opinion: Polymyxins are drugs with a narrow therapeutic range. Nephrotoxicity is associated with both host factors and polymyxin exposure, and recent studies suggest that the relative risk of nephrotoxicity is similar for colistin and polymyxin B. Studies that have examined the safety of polymyxins have several limitations. Considering the available evidence, toxicities that may develop while on polymyxin therapy most often are mild to moderate in magnitude and reversible in nature. Strategies to minimize toxicity associated with polymyxins have evolved and include avoidance of toxic medications, careful dosing, use of critical care, therapeutic drug monitoring and development of polymyxin derivatives. However, given that polymyxin use has re-emerged in an era of increased antimicrobial resistance, the presence of other treatment modalities may be limited. Therefore, clinicians must consider overall risk to benefit ratio of continuing versus stopping polymyxin treatment and optimize minimization strategies to reduce polymyxin-induced toxicities.

Keywords

antimicrobial resistance; colistin; nephrotoxicity; neurotoxicity; polymyxin B; polymyxins; safety; toxicity

1. Introduction

The limited number of new antimicrobials with activity against multidrug-resistant gram-negative bacteria (MDR-GNB) has led to increasing therapeutic use of polymyxins [1,2].

[†] Author for correspondence Tel: +30 69 46 11 00 00, Fax: +30 21 06 83 96 05, m.falagas@aibs.gr.

Overall, data regarding the effectiveness and safety of polymyxins are scarce and controversial. We have previously systematically reviewed the literature regarding polymyxin-related adverse effects. Herein, we critically review the published scientific evidence regarding polymyxin toxicity in patients without cystic fibrosis, focusing on the incidence, mechanisms, risk factors for toxicity and strategies to minimize polymyxin-associated toxicity.

2. Methods

We reviewed the literature regarding polymyxin-induced toxicity (from 1950 until May 2015) using a similar methodology as our previously published systematic review on this topic [3].

3. Types of polymyxins

Polymyxins A-E are cyclic polypeptide antibiotics [4]. Only polymyxin B and E (colistin), which have similar structure [5], have been used in the clinical setting. Colistin is available as colistimethate sodium (CMS), which is less toxic but also less potent than colistin. There is variability among different studies regarding the type of polymyxin derivative and dosing (Tables 1,2,3,4,5). Less toxic polymyxin derivatives have been made but they had reduced the antibacterial effect [6]. Novel polymyxin derivatives [7] have better a safety profile than current polymyxins but their clinical use remains to be determined.

4. Pharmacokinetics

Pharmacodynamics (PD) and pharmacokinetic (PK) data on polymyxins are limited mostly in patients with cystic fibrosis [8]. Polymyxins are primarily excreted through glomerular filtration [8]. Colistin is usually given every 8 h and various dose regimens have been suggested (Supplemental Table 1) [8–18]. Colistin exhibits a concentration-dependent bactericidal activity, and its therapeutic efficacy strictly depends on the ratio of AUC to MIC [3]. Use of higher daily doses with loading doses and longer intervals between doses have been suggested to maximize efficacy [9,19,20] but these strategies need to be further validated.

5. Safety of polymyxins

Polymyxins are considered toxic antibiotics and their use has been associated with numerous adverse outcomes including mortality, nephrotoxicity, neurotoxicity, allergic and topical reactions (Table 1). Although numerous retrospective cohorts, case controls and controlled studies have shown that polymyxins are associated with numerous toxicities (Tables 2,3,4), recent meta-analyses based on a large sample size do not support a differential toxic effect of polymyxins compared to other antimicrobials. In a meta-analysis [21] of 6 controlled studies (359 patients) and 14 single-arm studies (437 patients) of ventilator-associated pneumonia (VAP) caused by MDR GNB treated with intravenous and/or aerosolized colistin, there were no differences in toxicity between colistin and other antimicrobials. In a meta-analysis that included 14 controlled studies (including two randomized controlled trials [22,23]) of 1167

patients with VAP caused by MDR GNB, colistin had similar efficacy and safety profile compared to β-lactams for the treatment of MDR GNB VAP [24].

5.1 Mortality

Studies have shown conflicting results regarding the association of polymyxins with mortality [25–29]. In two different meta-analyses of 1167 [24] and 796 [21] patients with a single infection, VAP, there were no differences in the all-cause mortality for patients treated with colistin versus other antibiotics. It is unclear if use of polymyxins may contribute to overall mortality through their nephrotoxic effect [26,28,30,31]. However, we [32] and others [26,33] have found a protective effect of dose on mortality regardless of the development of AKI. These findings corroborate recent studies that have shown that higher doses of polymyxins result in the higher AUC/MIC index that best predicts polymyxins activity [34–36]. However, in most studies important variables that might affect 30-day mortality were not evaluated. Thus, well-designed randomized controlled trials in specific patient populations are needed to address the question whether polymyxins are associated with all-cause mortality.

5.2 Nephrotoxicity

Renal toxicity is the most common adverse effect related to the use of polymyxins and varies from proteinuria to AKI that requires cessation of therapy in up to 21% of cases [37,38] and renal replacement therapy (RRT) up to 28% of cases (Table 1) [30,33,39–41]. Recent studies use a standardized-based definition of drug-related nephrotoxicity to determine severity of toxicity based on criteria that can detect AKI with high sensitivity and specificity and can be used to compare the results of different studies (Table 1) [37,42–44]. AKI is usually dose-dependent and reversible after stopping antimicrobial therapy with polymyxins [2]. Nephrotoxicity after exposure to polymyxins usually occurs within the first 5 – 7 days of therapy (49 – 78% of cases) [44]. Polymyxin B was initially considered to be more nephrotoxic when compared with CMS [3] but recent studies showed similar rates of nephrotoxicity (Table 4) [2,26,39,45–50]. Thus prospective studies are needed to determine the differential effect of polymyxins on nephrotoxicity.

5.2.1 The exact pathogenesis of nephrotoxicity associated with polymyxins is unclear—Colistin and polymyxin B have similar chemical structures and mechanisms of action. Reabsorption of polymyxin through renal cell receptors such as megalin in combination with oxidative stress [51,52] may cause toxicity to the kidneys [53]. CMS may induce membrane permeability [54] resulting in cell lysis [3,55]. Overall the mechanism of action of polymyxins is similar to the action of detergents on the cell membrane of GNB [3].

5.2.2 Risk factors related to polymyxin renal toxicity—Numerous risk factors related to the host and polymyxins are associated with polymyxin nephrotoxicity (Table 1) [2,3,26,28,31,38,39,43,44,56–58]. However, associations from small retrospective studies should be interpreted with caution since they may reflect comorbidities in patients rather than true causality. Data regarding the association between the colistin dose and nephrotoxicity are still conflicting [28,32,43,44,59]. Relationships between higher daily dose [26,31,43,44], total cumulative dose [2,30,37,41,42,56], duration of treatment

[2,3,38,56,57] and increased risk of nephrotoxicity have been described but other studies failed to confirm these observations (Table 1) [28,30,40,43,44]. The trough colistin level was independently associated with nephrotoxicity in a prospective study [60]. Clinical and experimental studies support a dose threshold for nephrotoxicity of polymyxin B [29]. Variability in the steady-state polymyxin plasma concentrations and clearance among different patients and drug–drug interactions may explain controversial findings among studies. Overall, it is recommended that the renal function is monitored closely in patients receiving prolonged treatment with polymyxins [3,61].

5.2.3 The incidence of reported renal toxicity related to polymyxins varies—

We have previously reviewed the scientific literature and found significant variability in dosing practices of polymyxins and in clinical definitions of nephrotoxicity related to polymyxins. Based on evidence from large studies the overall incidence of nephrotoxicity ranged from 0 to 52.5% (Table 2) [1–3,26,28,30,31,37–44,47,56,57,60,62–82]. Many studies (Table 2) did not confirm the original association of increased nephrotoxicity with colistin [1,2]. However, despite the use of recent standardized criteria, reported rates of nephrotoxicity related to polymyxins continue to be variable and rates ranged from 20 to 76% for colistin (Table 3) [27,28,30,31,37,40–43,47,48,60–64,83–86] and 14 – 60% for polymyxin B (Table 4) [14,26,29,31,33,39,45,47–50,87–90]. In two meta-analyses of 1167 [24] and 796 [21] patients with VAP, colistin had similar nephrotoxicity compared to other antimicrobials.

5.2.4 It is difficult to accurately determine the incidence of nephrotoxicity related to polymyxins—

Except for the variable definitions of AKI used in the various studies, there were also differences with regard to total daily dose, cumulative dose, duration of treatment, use of loading dose versus no loading, frequency of dosing, formulation of polymyxin used (Tables 2,3,4). Thus, universal consistent dosing terminology needs to be used among different studies [3]. The patient populations varied among studies with regard to baseline illness severity and renal function. Most studies (except for two small randomized controlled clinical trials [22,23]) included in this review were retrospective and observational in design and had several methodological limitations such as selection bias, confounding, modest sample size and absence of appropriate controls between comparison groups. These limitations have further complicated interpretation of reported rata regarding polymyxin-related nephrotoxicity.

5.3 Neurotoxicity

Neurotoxicity is the second most common adverse effect reported with use of polymyxins (Table 1) [2,3]. Paresthesias, dizziness, nausea and vomiting are the most common reactions and are often benign [2]. Similar to nephrotoxicity, both host-related (such as neuromuscular disease and renal dysfunction) and drug exposure-related risk factors (such as increased drug exposure) are associated with neurotoxicity (Table 1) [1,3]. Neurotoxicity often develops within 5 days of treatment with polymyxins [2] whereas immediate reactions during infusion of polymyxins such as apnea have been reported.

5.3.1 Neurotoxicity is considered to be caused by the direct interaction of polymyxins with neurons—

Polymyxins interact with neurons and cause dose-dependent neurotoxicity although other studies did not find a dose-dependent relationship between polymyxins and neurotoxicity [56]. Polymyxins may inhibit the action of acetylcholine in the neuromuscular junction, extend depolarization, deplete calcium and induce release of histamine [3,91] but the overall mechanism of polymyxin induced neurotoxicity is unclear.

5.3.2 Polymyxins-related neurotoxicity is less common compared to nephrotoxicity—

Multiple recent studies with polymyxins did not report any cases of neurotoxicity [45,56], which has an overall incidence of < 7% (Table 1,2,3). However, older studies with colistin and in patients with cystic fibrosis [3] have reported higher rates of neurotoxicity. The overall incidence of paraesthesias, the most frequently observed neurotoxic effect, ranged between 7.3 and 27% [3] and may even be higher in patients with cystic fibrosis [56]. Rare serious neurologic adverse events, such as apnea, are reported in the older literature [1,2] and very scarcely in the recent literature [92]. A total of 32 cases of colistin/polymyxin-induced respiratory failure have been reported in the literature and only three of them were reported after 1970s [92]. In two meta-analyses of 1167 [24] and 796 [21] patients with VAP, there was no neurotoxicity with colistin. Improved formulations, monitoring and dosing might explain the discrepancies between recent and older studies. However, the objective interpretation of neurological symptoms may be difficult and clinicians may not identify and report neurotoxicity associated with polymyxins.

5.4 Other adverse reactions

The literature regarding other toxic side effects of polymyxins such as allergic reactions is scarce (Table 1) [93,94] since most studies focus on nephrotoxicity and neurotoxicity. These side effects have not been reported in recent studies. It is unclear if the low reported incidence of other side effects due to a true low incidence, lack of importance of these side effects or reporting biases in retrospective studies.

6. Strategies for minimizing polymyxin-induced toxicity

6.1 Supportive care is the mainstay of treatment of polymyxin-induced toxicity

Adequate hydration, close monitoring of fluid intake, urine output and electrolytes, during administration of polymyxins is recommended. Avoiding use of concomitant nephrotoxins or neurotoxins when possible is recommended although the data regarding their relationship with polymyxin-induced toxicities are conflicting (Table 1). Mannitol, exchange transfusions and RRT may reduce serum drug levels [3]. Rapid removal of colistin by hemofiltration and, more specifically, by hemoadsorption has been reported in critically ill patients with polymyxin-related nephrotoxicity and/or neurotoxicity [3]. However, RRT only removes a small amount of drug from systemic circulation [3] and is used mainly for treatment of AKI.

Mechanical ventilation is important for supportive care in the setting of neurotoxicity [3], whereas treatment with cholinesterase inhibitors or calcium infusions has unclear benefit. The use of antihistamines and heparin in polymyxin-induced respiratory failure has been

suggested based on animal studies but has not been studied in human subjects [92]. Other side effects such as bronchoconstriction usually require the administration of bronchodilators [3].

6.2 Dose adjustments or drug discontinuation may reverse polymyxin-induced toxicity

Discontinuation of polymyxin with use of alternative available antimicrobials may be advisable when feasible. Early and appropriate adjustment of the polymyxin dose based on the estimated renal function is very important [3] especially in view of the data that support dose-dependent polymyxin toxicity (Table 1). Ideal body weight (IBW) [9] and ABW should be used for dosing of colistin and polymyxin B, respectively [34]. Dosage based on ABW, rather than IBW, may increase colistin-induced AKI [43,44]. A high-dose, extended-interval dosing strategy with CMS has been suggested to minimize nephrotoxicity [9]. Mild neurological manifestations usually disappear after discontinuation of the drug [3]. In one report prolongation of the infusion time reduced the incidence of adverse events such as itching [95]. Clinicians should balance the reversible nature of polymyxin toxicities [3,33] with risks of withholding antimicrobial therapy.

6.3 Minimization strategies have an emerging role in minimizing toxicity related to polymyxins

Physicians should optimize minimization strategies [51,52,96–98], such as antioxidants [51,52], use of megalin-receptor inhibitors that may prevent polymyxin-induced nephrotoxicity [53], risk scoring systems, selection of less toxic polymyxins [7,34,47,48,99] and therapeutic drug monitoring (Table 5) [98].

7. Conclusions

Polymyxins are increasingly being used as treatment for infections with MDR-GNB. Nephrotoxicity and, to a lesser degree, neurotoxicity occur often during systemic polymyxin therapy. Considering the available evidence, AKI that may develop while on polymyxin therapy most often is mild to moderate in magnitude and reversible in nature. However, given that polymyxin use has re-emerged in an era of increased antimicrobial resistance, the presence of other treatment modalities may be limited. Therefore, clinicians must consider overall risk to benefit ratio of continuing versus stopping polymyxin treatment and optimize minimization strategies to reduce polymyxin-induced toxicities.

8. Expert opinion

Polymyxins are drugs with a narrow therapeutic range. Optimized dosing should be balanced with the possibility of toxicity. Studies that have examined the safety of polymyxins have several limitations including variability in the definition of polymyxin-induced toxicities, small sample size, retrospective study design, confounding by indication, absence of appropriate reference group for comparison to polymyxins, variability in dosing of polymyxins and in baseline characteristics between groups.

Despite current dosing used strategies, high rates of polymyxin-induced nephrotoxicity are still seen. However, the increasing antimicrobial resistance which often leaves polymyxins

as the only therapeutic option, the magnitude of encountered kidney toxicity, which is often reversible, the inconsistent relationship between other concomitant nephrotoxins and polymyxin-induced kidney toxicity, the absence of reported polymyxin-induced neurotoxicity in recent studies, support the use of polymyxins in certain clinical scenarios.

It is unclear whether colistin is more nephrotoxic compared to polymyxin B. Given the complexities of polymyxin PKs, and recent findings of comparatively lower nephrotoxicity rates with polymyxin B, large prospective studies using standardized diagnostic criteria for toxicity need to investigate and compare relative safety and efficacy of older and novel polymyxins in contemporary settings. These studies need to carefully control for baseline characteristics in patients that may affect rates of toxicity such as age, sex, comorbidities assessed using standardized criteria (such as the Acute Physiology and the Chronic Health Evaluation [APACHE] II score and Charlson Comorbidity Index), ICU care, use of vasopressors, degree of sepsis, fluid status, baseline renal function, concomitant exposure to other nephrotoxic (that also includes agents such as nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, vancomycin) or neurotoxic drugs and time to receipt of polymyxin. Appropriate reference or control groups (such as treatment groups with antibiotics with activity against MDR GNR such as tigecycline and ceftazidime-avibactam) matched by the above baseline characteristics for comparison of toxicities to polymyxins need to be included in future studies. Ideally, the dosing averages and plasma concentration of polymyxins for patients with or without toxicity in different categories of creatinine clearance should be determined [43]. Only after controlling for these mitigating factors that may be responsible for differences in renal dysfunction between different studies, and may complicate the interpretation of available evidence, can we have meaningful data regarding the toxicity and safety of different polymyxins.

It remains unclear whether use of higher doses of polymyxin while extending the dosing interval may increase efficacy and minimize nephrotoxicity [33,100]. In view of the increasing antimicrobial resistance and recent PK/PD data with polymyxins that suggest that an MIC breakpoint for colistin of £1 mcg/ml, might be more appropriate than 2 mcg/ml in terms of safety [9], it remains to be determined whether optimal dosing of colistin can be achieved without toxicity. Further prospective studies are warranted to more accurately describe the optimal polymyxin dosing regimen, PD, PKs, to optimize efficacy and minimize toxicity. In an era of increased antimicrobial resistance where polymyxins are often the only therapeutic option, strategies to further minimize toxicity of polymyxins are essential.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Declaration of interest

M Falagas participated in advisory boards of Achaogen, AstraZeneca, Infectopharm, Tetraphase, and Pfizer; received lecture honoraria from Cipla, Merck, Sanofi and Novartis; and received research support from Angelini, Astellas, and Rokitan. The authors have no other relevant affiliations or financial involvement with any organization

or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Wolinsky E, Hines JD. Neurotoxic and nephrotoxic effects of colistin patients with renal disease. N Engl J Med 1962;266:759–62 [PubMed: 14008070] • This is one of the first reports of toxicities associated with use of polymyxins.
2. Koch-Weser J, Sidel VW, Federman EB, et al. Adverse effects of sodium colistimethate. Manifestations and specific reaction rates during 317 courses of therapy. Ann Intern Med 1970;72:857–68 [PubMed: 5448745] •• This is the first large study that described toxicities associated with use of polymyxins.
3. Falagas ME, Kasiakou SK. Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. Crit Care 2006;10:R27 [PubMed: 16507149] •• This is a detailed systematic review of the literature regarding toxicity of polymyxins.
4. Storm DR, Rosenthal KS, Swanson PE. Polymyxin and related peptide antibiotics. Annu Rev Biochem 1977;46:723–63 [PubMed: 197881]
5. 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 [PubMed: 15825037]
6. Danner RL, Joiner KA, Rubin M, et al. Purification, toxicity, and antiendotoxin activity of polymyxin B nonapeptide. Antimicrob Agents Chemother 1989;33:1428–34 [PubMed: 2554795]
7. Vaara M Novel derivatives of polymyxins. J Antimicrob Chemother 2013;68:1213–19 [PubMed: 23412346]
8. 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 [PubMed: 16931410]
9. 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;55:3284–94 [PubMed: 21555763] • This study provides important pharmacokinetic (PK) data regarding the use of polymyxins.
10. Michalopoulos AS, Tsiodras S, Rellos K, et al. 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 [PubMed: 15679485]
11. 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 [PubMed: 12974973]
12. Claus BO, Snauwaert S, Haerynck F, et al. Colistin and neurotoxicity: recommendations for optimal use in cystic fibrosis patients. Int J Clin Pharm 2015;37(4):555–8 [PubMed: 26001357]
13. Michalopoulos A, Kasiakou SK, Rosmarakis ES, Falagas ME. Cure of multidrug-resistant Acinetobacter baumannii bacteraemia with continuous intravenous infusion of colistin. Scand J Infect Dis 2005;37:142–5 [PubMed: 15764204]
14. Teng CB, Koh PT, Lye DC, Ang BS. Continuous versus intermittent infusion of polymyxin B in the treatment of infections caused by multidrug-resistant Gram-negative bacteria. Int J Antimicrob Agents 2008;31:80–2 [PubMed: 17920246]
15. Vasen W, Desmery P, Ilutovich S, Di Martino A. Intrathecal use of colistin. J Clin Microbiol 2000;38:3523 [PubMed: 11203334]
16. Kasiakou SK, Rafailidis PI, Liaropoulos K, Falagas ME. Cure of post-traumatic recurrent multiresistant Gram-negative rod meningitis with intraventricular colistin. J Infect 2005;50:348–52 [PubMed: 15845435]

17. Li J, Milne RW, Nation RL, et al. Stability of colistin and colistin methanesulfonate in aqueous media and plasma as determined by highperformance liquid chromatography. Antimicrob Agents Chemother 2003;47:1364–70 [PubMed: 12654671]

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

19. Markou N, Markantonis SL, Dimitrakis E, et al. Colistin serum concentrations after intravenous administration in critically ill patients with serious multidrug-resistant, gram-negative bacilli infections: a prospective, open-label, uncontrolled study. Clin Ther 2008;30:143–51 [PubMed: 18343250]

20. 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 gram-negative bacteria. Antimicrob Agents Chemother 2009;53:3430–6 [PubMed: 19433570] • This study provides important PK data regarding the use of polymyxins.

21. Florescu DF, Qiu F, McCartan MA, et al. What is the efficacy and safety of colistin for the treatment of ventilator-associated pneumonia? A systematic review and meta-regression. Clin Infect Dis 2012;54:670–80 [PubMed: 22322268] •• Detailed systematic review and meta-analysis regarding the efficacy and safety of colistin for the treatment of ventilator-associated pneumonia.

22. Betrosian AP, Frantzeskaki F, Xanthaki A, Douzinas EE. Efficacy and safety of high-dose ampicillin/sulbactam vs. colistin as monotherapy for the treatment of multidrug resistant Acinetobacter baumannii ventilator-associated pneumonia. J Infect 2008;56:432–6 [PubMed: 18501431] • A small randomized controlled trial regarding the efficacy and safety of colistin compared to ampicillin/sulbactam.

23. Aydemir H, Akduman D, Piskin N, et al. Colistin vs. the combination of colistin and rifampicin for the treatment of carbapenem-resistant Acinetobacter baumannii ventilator-associated pneumonia. Epidemiol Infect 2013;141:1214–22 [PubMed: 22954403] • A small randomized controlled trial regarding the efficacy and safety of colistin compared to the combination of colistin and rifampicin.

24. Gu WJ, Wang F, Tang L, et al. Colistin for the treatment of ventilator-associated pneumonia caused by multidrug-resistant Gram-negative bacteria: a systematic review and meta-analysis. Int J Antimicrob Agents 2014;44:477–85 [PubMed: 25199968] •• Detailed systematic review and meta-analysis regarding the efficacy and safety of colistin for the treatment of ventilator-associated pneumonia.

25. Paul M, Bishara J, Levcovich A, et al. Effectiveness and safety of colistin: prospective comparative cohort study. J Antimicrob Chemother 2010;65:1019–27 [PubMed: 20299494] •• Important prospective cohort that showed association of polymyxin use with mortality.

26. Elias LS, Konzen D, Krebs JM, Zavascki AP. The impact of polymyxin B dosage on in-hospital mortality of patients treated with this antibiotic. J Antimicrob Chemother 2010;65:2231–7 [PubMed: 20685752]

27. Kwon KH, Oh JY, Yoon YS, et al. Colistin treatment in carbapenem-resistant Acinetobacter baumannii pneumonia patients: Incidence of nephrotoxicity and outcomes. Int J Antimicrob Agents 2015;45:605–9 [PubMed: 25772644]

28. 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;56:2392–6 [PubMed: 22371891]

29. Rigatto MH, Behle TF, Falci DR, et al. Risk factors for acute kidney injury (AKI) in patients treated with polymyxin B and influence of AKI on mortality: a multicentre prospective cohort study. J Antimicrob Chemother 2015;70:1552–7 [PubMed: 25604744]

30. Ko H, Jeon M, Choo E, et al. Early acute kidney injury is a risk factor that predicts mortality in patients treated with colistin. Nephron Clin Pract 2011;117:c284–8 [PubMed: 20847571]

31. Tuon FF, Rigatto MH, Lopes CK, et al. Risk factors for acute kidney injury in patients treated with polymyxin B or colistin methanesulfonate sodium. Int J Antimicrob Agents 2014;43:349–52 [PubMed: 24439066]

32. Falagas ME, Rafailidis PI, Ioannidou E, et al. Colistin therapy for microbiologically documented multidrug-resistant Gram-negative bacterial infections: a retrospective cohort study of 258

patients. Int J Antimicrob Agents 2010;35:194–9 [PubMed: 20006471] • One of the largest studies regarding the use of colistin.

33. 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;54:1720–6 [PubMed: 22423120] • This study proposes a novel approach to dose colistin that may minimize toxicity.
34. Sandri AM, Landersdorfer CB, Jacob J, et al. Population pharmacokinetics of intravenous polymyxin B in critically ill patients: implications for selection of dosage regimens. Clin Infect Dis 2013;57:524–31 [PubMed: 23697744] •• A study that provides information regarding population PKs of intravenous polymyxin B in critically ill patients.
35. Dudhani RV, Turnidge JD, Coulthard K, et al. Elucidation of the pharmacokinetic/pharmacodynamic determinant of colistin activity against Pseudomonas aeruginosa in murine thigh and lung infection models. Antimicrob Agents Chemother 2010;54:1117–24 [PubMed: 20028824]
36. Tam VH, Schilling AN, Vo G, et al. Pharmacodynamics of polymyxin B against Pseudomonas aeruginosa. Antimicrob Agents Chemother 2005;49:3624–30 [PubMed: 16127031]
37. Hartzell JD, Neff R, Ake J, et al. Nephrotoxicity associated with intravenous colistin (colistimethate sodium) treatment at a tertiary care medical center. Clin Infect Dis 2009;48:1724–8 [PubMed: 19438394] • A study that describes the experience with nephrotoxicity associated with intravenous colistin treatment at a tertiary care medical center.
38. 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 [PubMed: 15642116]
39. Kubin CJ, Ellman TM, Phadke V, et al. Incidence and predictors of acute kidney injury associated with intravenous polymyxin B therapy. J Infect 2012;65:80–7 [PubMed: 22326553]
40. Kwon JA, Lee JE, Huh W, et al. Predictors of acute kidney injury associated with intravenous colistin treatment. Int J Antimicrob Agents 2010;35:473–7 [PubMed: 20089383]
41. Collins JM, Haynes K, Gallagher JC. Emergent renal dysfunction with colistin pharmacotherapy. Pharmacotherapy 2013;33:812–16 [PubMed: 23606349]
42. Doshi NM, Mount KL, Murphy CV. Nephrotoxicity associated with intravenous colistin in critically ill patients. Pharmacotherapy 2011;31:1257–64 [PubMed: 22122186]
43. 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;53:879–84 [PubMed: 21900484] • A study that describes the incidence of and risk factors for colistin-associated nephrotoxicity in a large academic health system.
44. Deryke CA, Crawford AJ, Uddin N, Wallace MR. Colistin dosing and nephrotoxicity in a large community teaching hospital. Antimicrob Agents Chemother 2010;54:4503–5 [PubMed: 20660694]
45. Oliveira MS, Prado GV, Costa SF, et al. Polymyxin B and colistimethate are comparable as to efficacy and renal toxicity. Diagn Microbiol Infect Dis 2009;65:431–4 [PubMed: 19733029]
46. Nord NM, Hoeprich PD. Polymyxin B and Colistin. A critical comparison. N Engl J Med 1964;270:1030–5 [PubMed: 14122799] • A study regarding the comparison of relative toxicities of polymyxins.
47. Akajagbor DS, Wilson SL, Shere-Wolfe KD, et al. Higher incidence of acute kidney injury with intravenous colistimethate sodium compared with polymyxin B in critically ill patients at a tertiary care medical center. Clin Infect Dis 2013;57:1300–3 [PubMed: 23840000] • A study comparing the nephrotoxicity related to colistin versus polymyxin B in critically ill patients.
48. Phe K, Lee Y, McDaneld PM, et al. In vitro assessment and multicenter cohort study of comparative nephrotoxicity rates associated with colistimethate versus polymyxin B therapy. Antimicrob Agents Chemother 2014;58:2740–6 [PubMed: 24566187] • A study regarding the comparison of relative toxicities of polymyxins.
49. Ouderkirk JP, Nord JA, Turett GS, Kislak JW. Polymyxin B nephrotoxicity and efficacy against nosocomial infections caused by multiresistant gram-negative bacteria. Antimicrob Agents Chemother 2003;47:2659–62 [PubMed: 12878536]

50. Sobieszczyk ME, Furuya EY, Hay CM, et al. Combination therapy with polymyxin B for the treatment of multidrug-resistant Gram-negative respiratory tract infections. J Antimicrob Chemother 2004;54:566–9 [PubMed: 15269195]
51. Yousef JM, Chen G, Hill PA, et al. Melatonin attenuates colistin-induced nephrotoxicity in rats. Antimicrob Agents Chemother 2011;55:4044–9 [PubMed: 21709095]
52. Yousef JM, Chen G, Hill PA, et al. Ascorbic acid protects against the nephrotoxicity and apoptosis caused by colistin and affects its pharmacokinetics. J Antimicrob Chemother 2012;67:452–9 [PubMed: 22127588]
53. Suzuki T, Yamaguchi H, Ogura J, et al. Megalin contributes to kidney accumulation and nephrotoxicity of colistin. Antimicrob Agents Chemother 2013;57:6319–24 [PubMed: 24100504]
54. Lewis JR, Lewis SA. Colistin interactions with the mammalian urothelium. Am J Physiol Cell Physiol 2004;286:C913–22 [PubMed: 14668261]
55. Berg JR, Spilker CM, Lewis SA. Modulation of polymyxin B effects on mammalian urinary bladder. Am J Physiol 1998;275:F204–15 [PubMed: 9691009]
56. Falagas ME, Fragoulis KN, Kasiakou SK, et al. Nephrotoxicity of intravenous colistin: a prospective evaluation. Int J Antimicrob Agents 2005;26:504–7 [PubMed: 16280245]
57. Mostardeiro MM, Pereira CA, Marra AR, et al. Nephrotoxicity and efficacy assessment of polymyxin use in 92 transplant patients. Antimicrob Agents Chemother 2013;57:1442–6 [PubMed: 23295926]
58. Korbila IP, Michalopoulos A, Rafailidis PI, et al. Inhaled colistin as adjunctive therapy to intravenous colistin for the treatment of microbiologically documented ventilator-associated pneumonia: a comparative cohort study. Clin Microbiol Infect 2010;16:1230–6 [PubMed: 19732088] • A study regarding toxicities of both inhaled and intravenous colistin.
59. Kim J, Lee KH, Yoo S, Pai H. Clinical characteristics and risk factors of colistin-induced nephrotoxicity. Int J Antimicrob Agents 2009;34:434–8 [PubMed: 19726164]
60. 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 [PubMed: 23957376]
61. Rocco M, Montini L, Alessandri E, et al. Risk factors for acute kidney injury in critically ill patients receiving high intravenous doses of colistin methanesulfonate and/or other nephrotoxic antibiotics: a retrospective cohort study. Crit Care 2013;17:R174 [PubMed: 23945197]
62. Lee YJ, Wi YM, Kwon YJ, et al. Association between colistin dose and development of nephrotoxicity. Crit Care Med 2015;43:1187–93 [PubMed: 25756417]
63. Omrani AS, Alfahad WA, Shoukri MM, et al. High dose intravenous colistin methanesulfonate therapy is associated with high rates of nephrotoxicity; a prospective cohort study from Saudi Arabia. Ann Clin Microbiol Antimicrob 2015;14:3 [PubMed: 25591721]
64. Ceylan B, Tanis M, Akkoyunlu ME, et al. Variables determining the development of colistin-associated renal impairment. Wien Klin Wochenschr 2015. [Epub ahead of print]
65. Kofteridis DP, Alexopoulou C, Valachis A, et al. Aerosolized plus intravenous colistin versus intravenous colistin alone for the treatment of ventilator-associated pneumonia: a matched case-control study. Clin Infect Dis 2010;51:1238–44 [PubMed: 20973727] • A study regarding toxicities of both inhaled and intravenous colistin.
66. Fekety FR Jr, Norman PS, Cluff LE. The treatment of gram-negative bacillary infections with colistin. The toxicity and efficacy of large doses in forty-eight patients. Ann Intern Med 1962;57:214–29 [PubMed: 13892094]
67. Lamb R Colistin sulphate in the treatment of specific bacterial intestinal infections. Scott Med J 1968;13:9–12 [PubMed: 4865523]
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 [PubMed: 10452626]
69. Berlana D, Llop JM, Fort E, et al. Use of colistin in the treatment of multiple-drug-resistant gram-negative infections. Am J Health Syst Pharm 2005;62:39–47 [PubMed: 15658071]

70. 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;49:3136–46 [PubMed: 16048915]
71. Reina R, Estenssoro E, Saenz G, et al. Safety and efficacy of colistin in Acinetobacter and Pseudomonas infections: a prospective cohort study. Intensive Care Med 2005;31:1058–65 [PubMed: 15983759]
72. Kallel H, Hergafi L, Bahloul M, et al. Safety and efficacy of colistin compared with imipenem in the treatment of ventilator-associated pneumonia: a matched case-control study. Intensive Care Med 2007;33:1162–7 [PubMed: 17530220]
73. Koomanachai P, Tiengrim S, Kiratisin P, Thamlikitkul V. Efficacy and safety of colistin (colistimethate sodium) for therapy of infections caused by multidrug-resistant Pseudomonas aeruginosa and Acinetobacter baumannii in Siriraj Hospital, Bangkok, Thailand. Int J Infect Dis 2007;11:402–6 [PubMed: 17291803]
74. Pintado V, San Miguel LG, Grill F, et al. Intravenous colistin sulphomethate sodium for therapy of infections due to multidrug-resistant gram-negative bacteria. J Infect 2008;56:185–90 [PubMed: 18280570]
75. Falagas ME, Vouloumanou EK, Rafailidis PI. Systemic colistin use in children without cystic fibrosis: a systematic review of the literature. Int J Antimicrob Agents 2009;33:503e501–13 [PubMed: 19168333] • A systematic review of the literature regarding toxicities of systemic colistin in children without cystic fibrosis.
76. Montero M, Horcajada JP, Sorli L, et al. Effectiveness and safety of colistin for the treatment of multidrug-resistant Pseudomonas aeruginosa infections. Infection 2009;37:461–5 [PubMed: 19499183]
77. Cheng CY, Sheng WH, Wang JT, et al. Safety and efficacy of intravenous colistin (colistin methanesulphonate) for severe multidrug-resistant Gram-negative bacterial infections. Int J Antimicrob Agents 2010;35:297–300 [PubMed: 20045293]
78. Rattanaumpawan P, Ungprasert P, Thamlikitkul V. Risk factors for colistin-associated nephrotoxicity. J Infect 2011;62:187–90 [PubMed: 21129401]
79. Turkoglu M, Dizbay M, Ciftci A, et al. Colistin therapy in critically ill patients with chronic renal failure and its effect on development of renal dysfunction. Int J Antimicrob Agents 2012;39:142–5 [PubMed: 22115538]
80. Yilmaz GR, Guven T, Guner R, et al. Colistin alone or combined with sulbactam or carbapenem against A. baumannii in ventilator-associated pneumonia. J Infect Dev Ctries 2015;9:476–85 [PubMed: 25989167]
81. Polat M, Kara SS, Tapisiz A, et al. Treatment of ventilator-associated pneumonia using intravenous colistin alone or in combination with inhaled colistin in critically ill children. Paediatr Drugs 2015;17(4):323–30 [PubMed: 25939411]
82. Rattanaumpawan P, Lorsutthitham J, Ungprasert P, et al. Randomized controlled trial of nebulized colistimethate sodium as adjunctive therapy of ventilator-associated pneumonia caused by Gram-negative bacteria. J Antimicrob Chemother 2010;65:2645–9 [PubMed: 20876621]
83. Vicari G, Bauer SR, Neuner EA, Lam SW. Association between colistin dose and microbiologic outcomes in patients with multidrug-resistant gram-negative bacteremia. Clin Infect Dis 2013;56:398–404 [PubMed: 23090926]
84. Balkan II, Dogan M, Durdu B, et al. Colistin nephrotoxicity increases with age. Scand J Infect Dis 2014;46:678–85 [PubMed: 25073536]
85. Temocin F, Erdinc S, Tulek N, et al. Colistin-Associated Nephrotoxicity and Risk Factors. Jpn J Infect Dis 2015;68(4):318–20 [PubMed: 25720641]
86. Cheng A, Chuang YC, Sun HY, et al. Excess mortality associated with colistintigecycline compared with colistin-carbapenem combination therapy for extensively drug-resistant acinetobacter baumannii bacteremia: a multicenter prospective observational study. Crit Care Med 2015;43:1194–204 [PubMed: 25793437]
87. Holloway KP, Rouphael NG, Wells JB, et al. Polymyxin B and doxycycline use in patients with multidrug-resistant Acinetobacter baumannii infections in the intensive care unit. Ann Pharmacother 2006;40:1939–45 [PubMed: 17018688]

88. Mendes CA, Cordeiro JA, Burdmann EA. Prevalence and risk factors for acute kidney injury associated with parenteral polymyxin B use. Ann Pharmacother 2009;43:1948–55 [PubMed: 19887593]

89. Esaian D, Dubrovskaya Y, Phillips M, Papadopoulos J. Effectiveness and tolerability of a polymyxin B dosing protocol. Ann Pharmacother 2012;46:455–6 [PubMed: 22395248]

90. Dubrovskaya Y, Prasad N, Lee Y, et al. Risk factors for nephrotoxicity onset associated with polymyxin B therapy. J Antimicrob Chemother 2015;70:1903–7 [PubMed: 25652747]

91. Duncan DA. Colistin toxicity. Neuromuscular and renal manifestations. Two cases treated by hemodialysis. Minn Med 1973;56:31–5 [PubMed: 4682585]

92. Shrestha A, Soriano SM, Song M, Chihara S. Intravenous colistin-induced acute respiratory failure: A case report and a review of literature. Int J Crit Illn Inj Sci 2014;4:266–70 [PubMed: 25337492]

93. Alothman GA, Ho B, Alsaadi MM, et al. Bronchial constriction and inhaled colistin in cystic fibrosis. Chest 2005;127:522–9 [PubMed: 15705991]

94. Hoeprich PD. The polymyxins. Med Clin North Am 1970;54:1257–65 [PubMed: 4319624] • One of the first reviews regarding toxicity of polymyxins.

95. 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 [PubMed: 14585859]

96. Sirijatuphat R, Limmahakhun S, Sirivatanauksorn V, et al. Preliminary clinical study of the effect of ascorbic Acid on colistin-associated nephrotoxicity. Antimicrob Agents Chemother 2015;59:3224–32 [PubMed: 25801556]

97. Justo JA, Bosso JA. Adverse reactions associated with systemic polymyxin therapy. Pharmacotherapy 2015;35:28–33 [PubMed: 25266910]

98. 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;42:357–60 [PubMed: 24011987]

99. Brandenburg KS, Rubinstein I, Sadikot RT, Onyuksel H. Polymyxin B self-associated with phospholipid nanomicelles. Pharm Dev Technol 2012;17:654–60 [PubMed: 21486112]

100. Falagas ME, Rafailidis PI, Kasiakou SK, et al. Effectiveness and nephrotoxicity of colistin monotherapy vs. colistin-meropenem combination therapy for multidrug-resistant Gram-negative bacterial infections. Clin Microbiol Infect 2006;12:1227–30 [PubMed: 17121631]

Article highlights.

- Polymyxins are drugs with a narrow therapeutic range.
- Optimized dosing should be balanced with the possibility of toxicity.
- Studies that have examined the safety of polymyxins have several limitations.
- Despite current dosing used strategies, high rates of polymyxin-induced nephrotoxicity are still seen.
- It is unclear whether colistin is more nephrotoxic compared to polymyxin B.
- It remains unclear whether use of higher doses of polymyxin while extending the dosing interval may increase efficacy and minimize nephrotoxicity.
- Large prospective studies using standardized diagnostic criteria for toxicity need to investigate and compare relative safety and efficacy of older and novel polymyxins in contemporary settings.
- In an era of increased antimicrobial resistance where polymyxins are often the only therapeutic option, strategies to further minimize toxicity of polymyxins such as therapeutic drug monitoring, are essential.

Table 1.

Manifestations of toxicities related to polymyxins and risk factors for development of toxicities.

Clinical spectrum of toxicity	Host-related risk factors	Exposure-related factors
Mortality	In a prospective study [25] of patients with various infections, colistin was associated with higher mortality 39% (78/200), versus 28.8% (85/295) for comparators (p = 0.018) In a meta-analysis of clinical studies of VAP with colistin, colistin and control groups did not differ in all cause mortality, or toxicity [21]	Not determined
Nephrotoxicity:	Obesity [28,29,39]	Length of polymyxin therapy [2,3,38,56,57]
ATN, renal insufficiency, elevated blood urea nitrogen, elevated creatinine, proteinuria, hematuria [1,2]. Severity based on RIFLE criteria	Preexisting renal disease [1,47,57] Age [26,28,41,44,47,48,84] but other studies did not show age as risk factor [30,37,40,42,43]	Daily polymyxin dose [26,31,43,44] but not confirmed in other studies [30,37,41,42] Cumulative dose [37,39,56,65] but not confirmed in other studies [28,30,40,43,44]
Risk category: 15 – 44% of cases	Diabetes [28]	Concomitant nephrotoxins such as
Injury category: 5 – 47% of cases	Hypertension [47]	vancomycin, aminoglycosides, diuretics, IV
Failure category: 13 – 80% of cases	Hypoalbuminemia [40,62–64] but this also	contrast, vasopressors, calcineurin
Renal replacement therapy 0 – 28%	relates to fluid overload and cardiorenal	inhibitors, ACEI, ARBs,
Persistence in nephrotoxicity as defined by	syndrome	NSAIDs [31,39–44,47,60]
Loss and ESRD: variability in how Loss and	Hyperbilirubinemia [30,40,64] but other	Rifampin may be nephrotoxic and risk
ESRD criteria are defined but overall few	studies did not confirm this [28]	factor for colistin-associated toxicity [43]
cases		
Neurotoxicity: Peripheral paresthesias are the most common form of neurotoxicity. Dizziness, facial flushing, drowsiness, mental confusion, irritability, partial deafness, blurred vision, dysarthria (slurred speech), numbness of the extremities, vertigo, ataxia, hallucinations, seizures, ataxia, and even neuromuscular blockade and apnea	Renal impairment [1,2] Myasthenia gravis patients may be at increased risk for neuromuscular blockade and adverse reactions such as respiratory arrest [56] Hypoxia [2,3] Female sex [2,3]	Increased drug exposure, either as greater length of therapy or higher polymyxin dose [1,3] Old intramuscular polymyxin preparations [2] Concomitant medications (i.e., sedatives, anesthetics, muscle relaxants, narcotics, corticosteroids, other neurotoxic antibiotics such as aminoglycosides and cephalothin) [2,3]
Allergic reactions: Pruritus, rash, dermatitis, vomiting, drug fever, eosinophilia. An incidence of − 2% has been reported in old studies [2,56]	Allergy to bacitracin [3]	Chemical irritation and release of histamine [3]
Local side effects: Pain at the site, convulsions and meningismus after intraventricular or intrathecal administration of polymyxins, low-grade conjunctivitis after repeated ophthalmic application of polymyxin [94]	Not reported	Older preparations of polymyxins
Inhaled polymyxins: may cause airway airways causing minor irritation (cough, sore throat) or bronchoconstriction and chest tightness [24]. These adverse reactions have not been reported in recent studies [21,58,65]	Patients with asthma or atopy [93]	Chemical irritation [93]
Systemic side effects: Ototoxicity, drug fever, gastrointestinal disturbances such as pseudomembranous colitis, hepatotoxicity based on old case report but this was not shown in studies [56]	Not reported	Not reported

AIDS: Nonsteroidal anti-inflammatory agents; ATN: Acute tubular necrosis; ACEI: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; ESRD: End-stage renal disease NS; VAP: Ventilator associated pneumonia.

Table 2.

Large studies (> 40 patients) reporting data on polymyxin-induced toxicity (no standardized criteria to define nephrotoxicity) in patients without cystic fibrosis. Specific mean dose and duration of treatment (at least 48 h of use for all studies) are reported where available. In all cases colistin dosing was based on institutional standards that corresponded with package insert recommendations for both dosing and renal function adjustments; in certain cases the dosing regimen was ultimately decided by the treating clinician.

Year/ref	n	Dosage of colistin (mean ± SD or range)/duration of treatment	Definition of reported toxicities	Reported adverse effects
1962 [66]	48	Adults: 150 mg BID (> 10 d)	↑ in Cr	17/48 (35.4%) had reversible↑ of Cr; 13/48 (27.1%) patients had paresthesias; 3/48 (6.3%) had ataxia and 3/48 (6.3%) pruritus
1968 [67]	93	100,000 – 300,000 lU/kg/day (7 – 10 d)	↑ in Cr	No nephrotoxicity, rash (n = 1), vomiting (n = 1)
1970 [2]	317	Total of < 1 gr (n = 205), 1 – 2 gr (n = 69), > 2 gr (n = 43)	Nephrotoxicity: ↑ in Cr, acute tubular necrosis, hematuria	Nephrotoxicity: 64/317 (20.2%) courses; Neurotoxicity: paresthesias, respiratory insufficiency, apnea, nausea, vomiting, dizziness, weakness, neuropathy, confusion, psychosis, seizure: 23/317 (7.3%) courses; Allergic reactions: 7/317 (2.2%)
1999 [68]	60	152.8 mg (~ 2 MIU) (60 – 300 mg) (2 – 34 d)	↑ in Cr	22 pts (26.8%) had nephrotoxicity; 11/41 (26.8%) with normal and 11/19 (57.9%) with abnormal renal function
2003 [49]	60	1.1 MIU (1 – 56 d)	> 50% ↑ in Cr, > 2.0 mg/dl	7/50 pts (14%) had nephrotoxicity
2005 [69]	80	Aerosol: 12 ± 8 d. IV or IM: 11 ± 6 d. IT: 8 d	> 50% ↑ in Cr or 1 mg/dl vs baseline level	No significant nephrotoxicity
2005 [10]	43	3 MIU TID (> 48 h)	> 50% ↑ in Cr or 1 mg/dl vs baseline level	Nephrotoxicity: 5/8 pts (62.5%) with chronic renal failure developed acute or chronic renal failure during COL therapy
2005 [70]	50	4.5 MIU (21.5 d)	> 50% ↑ in Cr and > 1.3 mg/dl or RRT	4/50 pts (8%) had nephrotoxicity; 1 pt polyneuropathy
2005 [71]	55	13 ± 5 days	> 50% ↑ in Cr and > 2.0 mg/dl or RRT	No significant nephrotoxicity
2006 [100]	71	COL group: 4.6 ± 2.3 MIU (14.2 ± 7.3 d). COL + meropenem: 5.5 ± 2.2 MIU (17.8 ± 11.4 d)	> 50% ↑ in Cr	Nephrotoxicity: 0/14 (0%) in the COL group vs 4/57 (7%) in the COL-meropenem
2007 [72]	60	2 MIU TID (5 – 22 d)	> 50% ↑ in Cr	No nephrotoxicity
2007 [73]	93	2.5 mg/kg/d BID	> 50% ↑ in Cr	Nephrotoxicity: 24/93 (30.8%)
2008 [74]	60	4.4 mg/kg/d (20 d)	> 50% ↑ in Cr	Nephrotoxicity: 10.9% of pts
2009 [59]	47	2.25 g	> 50% ↑ in Cr	Nephrotoxicity: 5/47 (31.9%), 3 (20%) had RRT
2009 [75]	370	Variable; 25 studies (case series and reports)	> 50% ↑ in Cr, urine casts, haematuria, proteinuria	Nephrotoxicity: 10/355 (2.8%) of the evaluable children. Other adverse events were reported in 2.6% of children
2009 [76]	121	2.5 – 5 mg/kg/d in 3 doses (15 d)	> 50% ↑ in Cr	Nephrotoxicity: 10/121 (8.3%)
2009 [45]	41	6 MIU (1 – 9 MU) (0 – 38 d)	> 50% ↑ in Cr or 1 mg/dl vs baseline level	Nephrotoxicity: 10/39 (26%)
2010 [77]	84	5.0 mg/kg/day (> 48 h)	> 50% ↑ in Cr, # > 20% in CrCL, need for RRT	Nephrotoxicity: 12/84(14%) pts; Neurotoxicity: 4/84 (3.5%) pts (seizure or altered mental status)

Year/ref	n	Dosage of colistin (mean ± SD or range)/duration of treatment	Definition of reported toxicities	Reported adverse effects
2010 [32]	258	3 – 9 MIU (100 – 300 mg CBA) (> 72 h, mean 17.9 d)	> 50% ↑ in Cr, ↑ >1.3 mg/dl in Cr, need for RRT	Nephrotoxicity: 26/251 (10.3%)
2010 [25]	200	6 – 9 MIU in 3 doses (480 – 720 mg of COL or 180 – 270 mg of CBA)	Cr ↑> 2 mg/dL; > 50% ↓ in GFR, need for RRT	Nephrotoxicity: 26/168 (15.5%); was significantly more frequent among patients treated with COL, with an OR > 3 Neurotoxicity (seizures): 2/196 (12.5%)
2011 [78]	139	1200 mg (75 – 5000 mg) (1 – 25 d)	> 50% ↑ in Cr, need for RRT	Nephrotoxicity: 73/139 (52.5%)
2012 [79]	55	2 – 3 MU TID (5 – 7.5 mg/kg/day)	> 50% ↑ in Cr, ↑ >2 mg/dl in Cr, ↓ > 50% in CrCL, need for RRT	Nephrotoxicity: 13/55 (23.6%) in the non- CRF group, of which 7 (53.8%) were within 7 days of therapy
2012 [21]	796	In the 6 controlled studies (359 patients): aerosolized COL 355 mg/70 kg/d ± 289.91 (9.25 ± 0.35 d) IV COL: 252.49 mg/70 kg/d ± 85.90 (4 ± 2.58 d). In the single-arm 14 studies, (437 patients) aerosolized COL (80.03 mg/70 kg/d ± 32) (13.93 ± 2.28 d), IV COL: 209.58 mg/70 kg/d ± 80.08 (14.98 ± 4.56 d)	> 50% ↑ in Cr, ↑ >2 mg/dl in Cr, ↓ > 50% in CrCL, need for RRT	Nephrotoxicity was similar among COL and control groups (5 studies; 344 patients) (OR, 1.14 [95% CI, 0.59 – 2.20; p = .69]; Neurotoxicity was similar among the COL and control group (3 studies; 183 patients) (OR, 1.39 [95% CI, .17 – 11.61; p = .76]). In one study colistin (7.8%) did not differ compared to control groups (2.0%) with regards to respiratory toxicity [82] (p = 0.36)
2013 [57]	92	1.5 – 2.5 g (1 g = 10,000 IU)/kg/d	> 50% ↑ in Cr, ↑ >2 mg/dl in Cr, ↓ > 50% in CrCL, need for RRT	Nephrotoxicity: 30/92 (32.6%) pts; 15 (16.3%) pts required RRT during polymyxin treatment
2014 [24]	1167	14 studies: 2 RCTs, 4 case-control, 8 cohort	> 50% ↑ in Cr, ↑ >2 mg/dl in Cr, ↓ > 50% in CrCL, need for RRT	Nephrotoxicity: no significant differences between COL IV vs COL IV + inhaled COL (OR = 1.13, 95% CI 0.65 – 1.96, p = 0.67), COL vs b lactam group (OR = 1.26, 95% CI 0.62 – 2.58, p = 0.52), COL combined therapy vs COL monotherapy (OR = 0.55, 95% CI 0.15 – 1.99, p = 0.37)
2015 [62]	329	IBW: 4.55 mg/kg/d (AKI group) vs 4.43 mg/kg/d (not AKI); p = 0.021	> 50% ↑ in Cr	Nephrotoxicity: 143/329 (43.5%) pts. The median onset time of nephrotoxicity was 6 days. 64/143 (44.8%) patients recovered
2015 [80]	70	75 mg TID or 150 mg BID	NR	Nephrotoxicity: 9/70 (12.86%)
2015 [81]	50	2.5 – 5 mg/kg per day in 2 – 4 doses; inhaled COL: 75 mg BID for pts aged > 1 year	> 50% ↑ in Cr	Nephrotoxicity: 1/50 (2%) patient (reversible) Mild bronchoconstriction in 3 pts after inhaled COL

BID: Two times per day; COL: Colistin; CBA: Colistin base activity; CMS: Colistimethate sodium; Cr: Creatinine; CrCL: Creatinine clearance; CRF: Chronic renal failure; d: days; GFR: Glomerular filtration rate; IBW: Ideal body weight; IV: Intravenous; MIU: Million international units; OR: Odds ratio; RRT: Renal replacement therapy; Pts: Patients; Ref: Reference; RRT: Renal replacement therapy; TID: Three times per day.

Table 3.

Large studies (> 40 patients) reporting data on polymyxin-induced nephrotoxicity defined using standardized criteria in patients without cystic fibrosis. RIFLE (risk, injury, failure, loss and end-stage kidney disease) criteria were used to define nephrotoxicity in all cases except for one [31] where the acute kidney injury network (AKIN) criteria were used. No neurotoxicity was reported in any study. Specific mean dose and duration of treatment (at least 48 h of use for all studies) are reported where available. In all cases colistin dosing was based on institutional standards that corresponded with package insert recommendations for both dosing and renal function adjustments.

Year/ref	n	Dosage of colistin*/duration of treatment	Reported nephrotoxicity
2009 [37]	66	4.4 (AKI group) vs 4.2 mg/kg/d (not AKI group), respectively	30/66 (45%) of pts and 21% stopped therapy. Mean cumulative dose of CMS was associated with developing AKI 38/71 (53.5%) of pts. Mean cumulative dose of CMS was associated with developing AKI
2010 [40]	71	54.3 mg/kg (range 27.5 – 94.5 mg/kg). The median duration of CMS treatment was 13 d	
2011 [42]	49	ABW: 2.9 mg/kg/d (AKI group) vs 2.6 mg/kg/d (not AKI group); IBW: 4 vs 3.8 mg/kg/d	15/49 (31%) of pts and only 2 pts (4%) had irreversible AKI. Mean doses of CMS administered but not median cumulative dose were associated with AKI
2011 [30]	119	5 mg/kg (3 MIU/100 mg COL) (7.7 ± 6.4 d)	65/119 (54.6%) of pts
2011 [43]	126	5.48 mg/kg/d IBW (AKI group) vs 3.85 mg/kg/d IBW (not AKI group) (p = .02)	54/143 (43%) of pts. In all cases AKI was reversible
2012 [28]	42	1.81 mg/kg/d (AKI group) and 2.19 mg/kg/d (not AKI)	20 (48%) of pts. Median cumulative dose of CMS was not related to AKI
2013 [60]	102	Variable: 1.5, 2.9, 4.4, and 1.5 mg/kg/d (IBW)	26 (25.5%) of pts on day 7 and 50 (49.0%) pts at the end of treatment. In adjusted analysis, trough COL levels were associated with AKI but not the daily COL dose, the cumulative dose and the peak levels. Once steady state is achieved, peak and trough serum levels were essentially the same
2013 [83]	76	3.7 (AKI group) vs 1.6 mg/kg/day (not AKI); p < .001	27 (36%) of pts
2013 [41]	174	4.06 mg/kg/d (AKI group) vs 3.96 mg/kg/d (not AKI)	84 (48%) of pts including 12 (7%) who required RRT
2013 [47]	106	150 mg every 12 h or 5 mg/kg/day of IBW or ABW	60.4% of pts. The incidence rate was 5.1 per 100 person-months
2013 [61]	147	4 MIU loading dose of CMS followed by a daily dose (divided into 3 doses) of 130,000 IU/kg (IBW)/d (median length of CMS therapy: 11 d)	35% of pts had AKI as per in the CMS alone group vs 46% in the CMS + other nephrotoxic antibiotic group
2014 [48]	121	Total daily dose (275.2 ± 106.8 mg/day); Daily dose: 4.1 ± 1.0 mg/kg (ABW)/d) or 4.6 ± 1.8 mg/kg (IBW)/d (10.5 ± 9.7 d)	40 (48.2%) of pts. Duration of therapy (OR, 1.08; 95% CI, 1.02 – 1.15; p = 0.02), and daily dose by IBW (OR, 1.40; 95% CI, 1.05 – 1.88; p = 0.02) were risk factors for AKI. In the matched cohorts, AKI was more common in the COL group vs the PMB group (55.3 vs 21.1%; p = 0.003)
2014 [31]	36 (COL); 96 (PMB)	The mean daily dose of CMS was 9 MIU	Overall, 34/132 (25.8%) of pts had AKI. 14/36 (38.9%) of pts in the COL group had AKI. The median time from the beginning of therapy to the development of AKI was 7.5 d (range 2 – 21 d; no difference between COL and PMB groups)
2014 [84]	198	2.5 – 5.0 mg/kg/day for pts with normal renal function	77/198 (46.1%) of pts had AKI. Old age was risk factor for AKI
2015 [62]	329	4.55 (AKI group) vs 4.43 mg/kg/d (not AKI group), respectively; p = 0.021	143 (43.5%) of pts. The median onset time of AKI was 6 d. The dose of COL was predictor of AKI only in pts with an eGFP < 60 ml/min/1.73 m^2
2015 [63]	67	9 MIU loading dose then 3 MIU 8 hourly. Average dose of CMS was 0.11 (± 0.04) MIU/kg/d. Average total dose of CMS and duration of	51/67 (76.1%) of pts had AKI

Year/ref	n	Dosage of colistin*/duration of treatment	Reported nephrotoxicity
		therapy before AKI were 66.71 (± 43.45) MIU and 8.70 (± 6.70) d, respectively	
2015 [85]	129	300 mg/day CBA (2 × 150 mg/day)	62/129 (48.1%) of pts developed AKI
2015 [27]	120	2.5 – 5 mg/kg/day divided into two to four equal doses	61/120 (51%) of pts developed AKI. Higher daily dose of CMS per IBW was risk factors for CMS-associated AKI, which did not relate to mortality.
2015 [86]	55	2.5 – 5 mg/kg/d of CBA divided over 8 or 12 h	11/55 (20.0%) of pts developed AKI
2015 [64]	112	5 mg/kg/d (IBW)	66/112 (58.9%) of pts developed AKI within 7 d of COL therapy in 52 (78.8%) cases and within 8 – 23 d in 14 (21.2%) cases

ABW: Actual body weight; AKI: Acute kidney injury; CI: Confidence interval; COL: Colistin; CMS: Colistimethate sodium; CBA: Colistin base activity; d: days; eGFR: Estimated glomerular filtration rate; IBW: Ideal body weight; IV: Intravenous; MIU: Million international units; OR: Odds ratio; PMB: Polymyxin B; Pts: Patients; Ref: Reference; RRT: Renal replacement therapy; vs: Versus.

Table 4.

Studies reporting data on polymyxin B-induced toxicity in patients without cystic fibrosis. In all cases PMB dosing was based on institutional standards that corresponded with package insert recommendations for both dosing and renal function adjustments.

Year/ref	n	Dosage of colistin (mean, range)*/duration (mean, range)	Definition of toxicity	Nephrotoxicity
2003 [49]	60	1.1 MIU (13.5 d, range: 1 – 56 d)	> 50% ↑ in Cr, > 2.0 mg/dl	7/50 pts (14%)
2004 [50]	29	Load 2.5 – 3 mg/kg. (19 d; range 2 – 57 d) Aerosolized PMB dose varied; the most common was 2.5 mg/kg/d divided into 4 doses	> 50% ↑ in Cr	Nephrotoxicity: 3 (10%) pts but did not stop therapy. Neurotoxicity: seizures, neuromuscular weakness, 2 (7%) pts
2006 [87]	33	IV (n = 31) dose: 1.3 MIU (range 0.19 – 3 MIU); nebulized (n = 5) dose: 2 MIU (range 1.6 – 2.2 MIU)	> 50% ↑ in Cr, ↑ > 0.5 mg/dl in Cr, ↓ > 50% in CrCL, need for RRT	Nephrotoxicity: 7/33 (21%) of pts who received PMB. Neurotoxicity: 2 (6%) pts who received PMB
2008 [14]	14	14 pts (52%) got PMB as continuous infusion (CI) over 24 h total daily dose 68.6 ± 31.4 mg (11d, range: 4 – 61). 13 pts (48%) got PMB as intermittent infusion (ITI) over 60 – 180 min every 8 – 12 h 96.5 ± 19.6 mg (8d, range: 6 – 39 d)	> 50% ↑ in Cr, ↓ > 50% in CrCL, need for RRT	5/14 (35.7%) of pts
2009 [88]	114	100 mg/day, 50 – 150 mg (0.5 – 1.5 MIU) (11.5 d, range 3 – 43 d)	> 50% ↑ in Cr, ↑ >1.8 mg/dl in Cr, need for RRT	22% of pts
2009 [45]	41	1.0 MU (range, 0.4 – 1.5). (11 d, range: 0 – 50 d)	> 50% ↑ in Cr, ↑ by > 1.0 mg/dl in Cr, need for RRT	8/30 (27%) of pts
2010 [26]	235	150 mg (IQR 100 – 200) (12 d, IQR 6 – 14)	> 50% ↑ in Cr, need for RRT	119/235 (50.6%) of pts. > 200 mg of PMB was an independent association with severe AKI (OR 4.51; 95% CI 1.58 – 12.90; p = 0.005)
2012 [89]	80	Loading dose of PMB 25,000 units/kg on day 1	RIFLE criteria	In the protocol group (n = 40), 58% of the pts had AKI vs 20% in the conventional dosing group (n = 40) (p = 0.002)
2012 [39]	73	1.8 mg/kg (ABW)(18 000 units/kg/d) (11 d). I	RIFLE criteria	60% pts had AKI. Ten (14%) patients stopped therapy and 16% had RRT
2013 [47]	67	15 000 – 25 000 units/kg/day as a continuous infusion over 24 h	RIFLE criteria	41.8% of pts. The incidence rate was 2.3 per 100 person-months
2014 [31]	132	25 000 IU/kg/d of PMB split into two doses. The median (IQR) daily dose of PMB was 2 MIU (1 – 2 MIU)	Acute Kidney Injury Network (AKIN) criteria	34/132 (25.8%) of pts had AKI. The median time from the beginning of therapy to the development of AKI was 7.5 d (IQR, 5 – 12 d; range 2 – 21 d) and there was no difference between pts treated with PMB vs CMS
2014 [48]	104	1.8 mg/kg (IBW)/d [18 000 units/kg (IBW)/d] or 1.5 mg/kg (ABW)/d [15 000 units/kg (ABW)/d]	RIFLE criteria	24 (23.1%) pts had AKI
2015 [90]	192	1.3 – 1.7 mg/kg	RIFLE criteria	88/192 (45.8%) of pts had AKI and the median onset was 9 d
2015 [29]	410	1.5 – 3.0 mg/kg/d in two divided doses	RIFLE criteria	189 (46.1%) of pts. PMB dose >/= 150 mg/day was a risk factor for AKI

ABW: Actual body weight; AKI: Acute kidney injury; CI: Confidence interval; Cr: Creatinine; CrCL: Creatinine clearance; d: days; eGFR: Estimated glomerular filtration rate; IBW: Ideal body weight; IQR: Interquartile range; IU: International units; IV: Intravenous; MIU: Million international units; OR: Odds ratio; PMB: Polymyxin B; Pts: Patients; Ref: Reference; RIFLE: Risk, injury, failure, loss and end-stage kidney disease; RRT: Renal replacement therapy; vs: Versus.

Table 5.

Minimization strategies to reduce polymyxin-induced toxicity.

Minimization strategy	Comments
Concomitant antioxidants (e.g., melatonin and ascorbic acid) [51,52]	Oxidative stress appears to play a significant role in the development of polymyxin induced-renal toxicity [51,52] In one animal study, rats treated with colistin and concomitant high-dose ascorbic acid over 7 days had significantly decreased marker for renal tubular damage, compared with those given colistin alone [52] Reduced acute tubular necrosis and renal cell apoptosis with concomitant ascorbic acid versus colistin alone was consistent with a protective antioxidant effect of ascorbic acid [52] An interim analysis of a randomized controlled study showed that coadministration of ascorbic acid did not improve colistin-associated nephrotoxicity [96]
Inhibitors of polymyxin clearance through kidneys	Renal cell receptors such as megalin may lead to selective reabsorption of polymyxin and accumulation in renal cell which may cause acute tubular necrosis and renal dysfunction [53] Both ascorbic acid and melatonin may decrease colistin clearance significantly in rats and thus may augment systemic colistin concentrations and limit the need for higher CMS doses [51,52] Inhibitors of megalin-receptor are being studied as therapy for polymyxin-induced nephrotoxicity [53]
Risk scoring systems [97]	Potential strategy to help clinicians estimate the benefit-risk ratio when considering polymyxin therapy A risk score may determine modifiable risk factors such as concomitant nephrotoxins that may be discontinued during polymyxin therapy [97]
Agent selection	Recent studies suggest lower nephrotoxicity rates [47,48] and improved pharmacokinetics of polymyxin B [34] Polymyxin B does not concentrate well in the urine and is not preferred for urinary tract infections Preliminary studies suggest that novel polymyxin derivatives and/or drug carrier systems such as nanomicelles have lower nephrotoxicity than current polymyxins [7]
Therapeutic drug monitoring [98]	Direct drug monitoring and/or early signs of toxicity significantly decrease the risk of polymyxin-induced adverse reactions Correct dosing weight is very important for therapeutic drug monitoring especially in obese patients [9,34,43,44] Clinical experience with therapeutic drug monitoring is limited by the current lack of routine assays for measurement of polymyxin concentration in clinical laboratories but relatively simple assay methods are emerging Strategies for early recognition of toxicity include close monitoring of renal function and use of novel sensitive biomarkers to identify polymyxin-induced nephrotoxicity [97] Close monitoring of the neurologic status and train-of-four monitoring, that quantifies neuromuscular blockade [97] may help identify polymyxin-associated neurotoxicity

Data taken from [51,52,96–98].