Toxicity in Patients

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Abstract

Polymyxin toxicity remains a significant concern that limits the clinical utility of this class of antibacterials for patient care. The most notable adverse event is the dose- and treatment-limiting nephrotoxicity that occurs in roughly 30–60% of patients receiving a systemic polymyxin. This chapter focuses on this adverse event with a detailed assessment of the incidence of, and risk factors for, polymyxin-associated nephrotoxicity. In particular, the text focuses on the impact of dose, serum concentrations, and polymyxin selection on nephrotoxicity. Additionally, less common, but clinically important adverse events are discussed.

Keywords

Colistin · Colistimethate · Polymyxin B · Nephrotoxicity · Non-renal toxicities · Gram-negative bacteria

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17.1 Introduction

Toxicity is an important consideration in evaluating the clinical utility of the polymyxins, and more remains to be learned on how to optimally use these agents. Originally introduced for use in the 1950s, polymyxin data that were published throughout the 1960s and into the early 1970s showed high rates of adverse events, notably nephrotoxicity and neurotoxicity. Although definitions were rarely given, nephrotoxicity rates of 10–50% were described and these findings were compounded by neurotoxicity rates, largely manifested as parasthesias, that, in some cases, exceeded 25% [1]. These seemingly unacceptable rates of toxicity, when combined with the new availability of less toxic antibiotics such as the aminoglycosides, and eventually the second and third generation cephalosporins, led to the polymyxins being rarely used clinically from the 1970s until the early 1990s.

In the early 1990s, starting in the cystic fibrosis population, the polymyxins (primarily colistin, formulated as its inactive prodrug colistimethate or CMS), started to have a resurgence of use because of the rise of resistant Gram-negative organisms. With the turn of the century, the spread of carbapenem-resistant *Acinetobacter baumannii* (CRAB) and multidrug resistant *Pseudomonas aeruginosa* throughout intensive care units (ICUs) in both Europe and the United States, necessitated polymyxin

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use in non-cystic fibrosis patients. This spread ultimately went worldwide, and was joined by outbreaks of carbapenem-resistant enterobacteriaceae (CRE). Therefore, the last 15 years, as previously described in this book, has led to a renaissance of the polymyxins. As these data from the "modern era" have more clear definitions of toxicity, dosing regimens utilized, and descriptions of adverse events, they will be the focus of this chapter. For the purposes of this chapter the "modern era" will consist of polymyxin literature from approximately the year 2000 except where specifically noted.

Undoubtedly, the main toxicity of concern with the polymyxins is nephrotoxicity, and it will be the major emphasis of the chapter. This dose-limiting toxicity is well studied and clinically relevant. The development of acute kidney injury, particularly in critically ill patients, can lead to increased mortality. Other toxicities that will be discussed are neurotoxicity, hypersensitivity, and potential respiratory toxicities seen with inhaled CMS.

17.2 Nephrotoxicity

Since their re-emergence, the true incidence of nephrotoxicity with the polymyxins remains highly controversial. The modern era consists of over 60 publications assessing nephrotoxicity rates with the polymyxins (over 80% of these papers relate to colistin). Initial reports in the modern era began with multiple analyses looking at the safety (and efficacy) of colistin in cystic fibrosis patients, with the reports published between 1990 and 2000. These four publications in cystic fibrosis patients suggested low incidences of acute kidney injury (0–25%) [2–5]. Furthermore, when patients did develop toxicity it was mild (although no clear definitions were given) and reversible upon discontinuation. These findings were strengthened by initial data from Europe, largely from Greece, showing colistin nephrotoxicity rates less than 20%, with many publications showing toxicity to be in the 5–19% range [6–15]. These data led many to perceive the agent to be less toxic than previously believed. However, soon thereafter, multiple studies, largely from the United States, were published showing higher incidences of colistin-associated nephrotoxicity with rates often in the 30–60% range [16–20]. Although data are more limited, similarly wide ranges of 4–60% [21–35] have been reported as the incidence of polymyxin B associated nephrotoxicity. When combining all these studies, nephrotoxicity is seen in 795/3036 (26%) of patients receiving colistin, and 364/1075 (34%) of patients receiving polymyxin B. Undoubtedly, a complication in interpreting the nephrotoxicity literature is that in the modern era polymyxin use is largely in critically ill patients often suffering from life-threatening infections. These patients have multiple risk factors (e.g. severe sepsis/septic shock, concomitant nephrotoxins) for acute kidney injury and the contribution of the polymyxin to that injury is difficult to ascertain. The primary drivers of discordant results in these data are dose of colistin/polymyxin B given, and definition of nephrotoxicity. The following sections will look at: clinical features of polymyxin nephrotoxicity; the importance of definition and dose on incidence of nephrotoxicity; the comparative nephrotoxicity of the polymyxins relative to other agents as well as each other; the impact of colistin serum levels on nephrotoxicity; the impact of a loading dose on toxicity; and, finally other risk factors identified for toxicity.

17.2.1 Clinical Features of Nephrotoxicity

Although detailed descriptions of the clinical features of acute kidney injury are lacking in the currently available literature, there are some analyses that give us insight into the onset and reversibility in patients who develop nephrotoxicity while on polymyxin therapy. In the 12 studies reporting on onset of colistin-associated nephrotoxicity, 54–100% of cases occur in the first week, with median times until onset ranging from 4 to 12 days [17–20, 24, 26, 28, 36–40]. Although not as well described, the median onset of nephrotoxicity in the nine polymyxin B studies ranged from

6 to 11 days [24, 26, 28–33]. Rates of reversibility vary widely in the literature and are complicated by whether or not authors consider deaths in their reversibility analysis. In general, if a patient survives the acute event, reversibility rates range from 20% to 100% in 18 colistin studies [12, 16–18, 26, 36, 39, 41–50], and 69–100% in five polymyxin B studies [26, 30, 31, 34, 35] that report on this feature. Further data are needed addressing the long term outcomes of patients who develop acute kidney injury.

17.2.2 Impact of Definition

One of the primary features of polymyxin literature in the "old era" that made toxicity difficult to interpret was the lack of definitions for toxicity endpoints. While nephrotoxicity definitions in the modern era are well described in most analyses, the actual definition varies greatly, which significantly impacts both the incidence of and risk factors for nephrotoxicity. In the ~50 colistin-associated nephrotoxicity papers in the modern era, four definitions predominate. Two of these four definitions are commonly utilized in the 11 unique polymyxin B toxicity analyses.

The most common definition seen in 14 (29%) of the colistin analyses are the RIFLE criteria [16–20, 26, 28, 40–43, 50–52]. The RIFLE criteria present a grading system for toxicity, and represent a relatively sensitive measure for detecting modest decreases in renal function. The minimum criteria for acute kidney injury with the RIFLE criteria are a serum creatinine rise to 1.5× the baseline creatinine or a decrease in creatinine clearance of 25% in order to meet the "Risk" stage. In the 14 colistin studies using this definition, nephrotoxicity was seen in 465/1232 (38%), which is a similar rate to the (12/40) 30% rate seen with three studies using similar criteria for defining toxicity of an increase of serum creatinine of 0.5 mg/dL from baseline [36, 53, 54].

Interestingly, when those same criteria (increase in serum creatinine of 0.5 mg/dL) are applied with additional conditions (e.g., serum creatinine has to be above the upper limit of normal), the rates significantly decrease. In the nine analyses (18% of total toxicity papers) using this definition, nephrotoxicity rates are much lower, and seen in 60/541 (11%) of patients [10–14, 55–58].

The fourth commonly utilized toxicity definition seen in 8 (16%) of the colistin nephrotoxicity papers requires a much more significant rise in serum creatinine for toxicity to be met if a patient has normal baseline renal function (usually defined as a serum creatinine of ≤1.2 mg/dL), than if a patient has some degree of baseline renal insufficiency [15, 38, 44, 59–63]. The most common version of this definition requires the serum creatinine to rise to ≥2.0 mg/dL in normal renal function, while in patients with abnormal renal function an increase in serum creatinine of 1.5 times the baseline value is needed. Therefore, both a patient with a baseline creatinine of 0.6 mg/dL and one with a baseline of 1.3 mg/dL would need a rise to ≥2.0 mg/dL to reach the toxicity endpoint, despite the fact that would be a greater than tripling of creatinine in one instance. Using this definition, nephrotoxicity rates were lower and seen in 76/507 (15%) of patients. Importantly, as the toxicity endpoint is easier to meet in those with baseline renal insufficiency with this definition, it often leads to conclusions that chronic kidney disease (baseline creatinine greater than the upper limit of normal) is a risk factor for colistin-associated nephrotoxicity. Using this definition Montero showed nephrotoxicity in 5/107 (5%) of patients with normal renal function compared to 5/14 (36%) of patients with baseline renal insufficiency [61]. Similar results by Bassetti [62] and Betrosian [63] show the importance of this definition on both lowering the overall incidence of nephrotoxicity (poor detection of mild-moderate toxicity in patients with low baseline creatinine), and identification of baseline renal insufficiency as a risk factor.

While the number of nephrotoxicity analyses with polymyxin B (n = 15) limit the ability to robustly perform a similar analysis, the data, as scant as they are, support similar conclusions. When limiting only to definitions used in three or more different studies, analyses that used the more sensitive RIFLE criteria showed toxicity in 122/310 (39%) of patients [26–28, 35], whereas

analyses using a much less sensitive measure of requiring a doubling of serum creatinine +/− additional conditions (e.g. to a creatinine ≥2.0 mg/dL) showed a lower cumulative toxicity incidence of 16/96 (17%) [23, 30, 34].

17.2.3 Impact of Dose

While dosing in patients with normal renal function is relatively consistent in the polymyxin B literature (1.5–2.5 mg/kg/day), this is not the case with colistin. Because of substantially different daily dose recommendations in the package inserts of the different colistimethate products used around the world, until recently daily doses utilized in Europe have commonly been ~50 to 75% of the daily dose used in the United States, Korea, Thailand, Brazil and Australia. The last few years has seen doses in Europe more similar to those used in other countries. Additionally, as the dose outside of Europe is a weight-based recommendation without clear instruction of what dosing weight to use (ideal body weight, total body weight, or adjusted body weight), the actual doses that patients receive can vary significantly and are often poorly described. This is of particular importance as multiple studies have shown a dose-dependent toxicity with both polymyxin B and colistin.

17.2.3.1 Different Scheduled Doses of Colistin and Rates of Nephrotoxicity

In the colistin literature five different dosing schedules predominate. They are 3–6 MU (100–200 mg CBA)/day, 9 MU (300 mg CBA/day), 3–9 MU (100–300 mg/day), 5 mg/kg/day CBA (for 70 kg patient, 350 mg CBA/day or 10.5 MU/day), and 2.5–5 mg/kg/day CBA (175–350 mg CBA/day or 5.3–10.5 MU/day). The fact that inconsistent or poorly described renal dosing strategies were employed further complicates these data, however, the impact of these different scheduled dosing strategies on nephrotoxicity rates is very apparent. In 19 studies including 1358 patients receiving 2.5–5 mg/kg of CBA a day, nephrotoxicity was seen in 500 (37%) of patients [8, 16–20, 24, 26, 28, 36, 37, 44, 47–50, 52, 55, 61]. This is in contrast to lower toxicity rates seen in studies where patients received daily doses of 3–6 MU (7%, n = 259) [7, 9, 10, 12, 13, 53, 56, 62, 64], 9 MU (16%. n = 315) [6, 15, 39, 45, 60, 63, 65], and 3–9 MU (21%, n = 415) [38, 42, 52], respectively. This stepwise increase in toxicity rates as daily doses rise from 3–6 MU/day to 9 MU/day to doses greater than 9 MU/day seen in patients being dosed on mg/kg of CBA/day shows the importance of dose used on the incidence of nephrotoxicity reported.

17.2.3.2 Individual Studies Assessing the Association Between Dose and Nephrotoxicity for Colistin

In the 14 studies assessing risk factors for colistin-associated nephrotoxicity, 6 showed an association between either daily dose (n = 5) or cumulative exposure/duration of therapy (n = 3). Hartzell and colleagues found that patients with toxicity had a cumulative colistin exposure of 6454 ± 3421 mg of CBA as compared to an exposure of 4727 ± 3263 mg in those who did not (p = 0.005) [16]. In a multivariate analysis, Rattanaumpawan showed that duration of colistin (OR. 1.1 (95% confidence interval 1.03–1.19)), a CBA dose of 3–5 mg/kg/day (OR 3.1 95% CI 1.3–7.5), and a dose of >5 mg/kg/day (OR 15.3 (3.9–60.6) were risk factors for nephrotoxicity [37]. Pogue and colleagues showed a similar stepwise increase in risk of nephrotoxicity from 3.3 (0.8–13.0) to 23.4 (5.3–103.6) when the dose went from 3 to 4.9 mg/kg/day to ≥5 mg/kg/day [18]. Similar findings were seen in three other analyses [17, 24, 52], and highlight the dose-dependent nature of colistin-associated nephrotoxicity.

17.2.3.3 The Impact of Dose on Toxicity with Polymyxin B

In the nine studies analyzing risk factors for polymyxin B associated nephrotoxicity in the "modern-era", two showed an association between dose (n = 1) and duration (n = 1) of polymyxin B and toxicity. Elias and colleagues ana-

lyzed predictors of nephrotoxicity in 235 patients eligible for the toxicity endpoint. Patients receiving ≥200 mg/day of polymyxin B had an adjusted odds ratio of 4.5 (1.6–12.9) for the development of severe renal impairment [21]. Mostardiero and colleagues analyzed polymyxin use in 92 (90 received polymyxin B, 2 received colistin) solid-organ transplant patients [29]. In multivariate analysis, duration of polymyxin therapy (OR 1.06 (1.00–1.12) was independently associated with renal dysfunction.

Two more recent analyses have also assessed the impact of polymyxin B dose and incidence of nephrotoxicity. Nelson and colleagues assessed safety and efficacy endpoints related to polymyxin B dose with 109 patients able to be assessed for the safety endpoint [66]. In this analysis receipt of daily doses ≥250 mg were associated with higher rates of acute kidney injury (8/12 (67%) receiving this dose developed AKI, versus 31/97 (32%) of those who received lower doses; p = 0.03) and in multivariate analysis daily doses ≥250 mg were an independent predictor of AKI (OR 4.32, 95% CI 1.15–16.25.) Similarly, Rigatto and colleagues assessed risk factors, including dose, for AKI in patients receiving polymyxin B therapy [67]. In bivariate analysis, AKI developed in 33/103 (32%), 109/202 (54%), and 47/105 (44%) of patients receiving <150 mg, 150–199 mg, and ≥200 mg of polymyxin B daily, respectively (p = 0.001). In accordance with these results, polymyxin B doses ≥150 mg/day were highly associated with AKI in multivariate modeling (HR 9.81, 95% CI 2.37–40.62), but no additional risk was seen with doses ≥200 mg/day.

Much like difference in toxicity definitions, dosing variability driven by differences in package insert recommendations, contribute considerably to the discordant results seen for nephrotoxicity in the polymyxin literature. This is much more apparent in the colistin literature, as the doses vary more greatly than in the polymyxin B literature. However, with recent clinical practices moving towards the upper end (or even slightly beyond the upper end) of the package insert dosing recommendation for polymyxin B, a similar association is becoming apparent.

17.2.4 Polymyxin Nephrotoxicity Rates in Comparison to Other Antimicrobials

Another difficulty in interpreting the polymyxin nephrotoxicity literature is that most analyses are descriptive in nature, thus making it difficult, if not impossible, to assess the independent impact of the polymyxin exposure on toxicity. There are 12 studies (11 colistin, 1 polymyxin B) comparing the safety of these agents with other antimicrobial classes, and the findings of these studies are summarized in Table 17.1.

In general, the comparative data suffer from similar limitations to the ones previously discussed; namely inconsistent dosing, definitions of nephrotoxicity, and small sample sizes. There are three studies that show a statistically significant difference between a polymyxin and a comparator. Paul and colleagues compared nephrotoxicity in patients on colistin to those receiving other active agents for infections due to *A. baumannii*, *P. aeruginosa,* or enterobacteriaceae [60]. Using a definition for nephrotoxicity that differed in patients with normal baseline creatinine (serum creatinine >2 mg/dL, a decrease in creatinine clearance of 50% or the need for renal replacement therapy) from those with baseline renal insufficiency (increase in serum creatinine of 50%, decrease in creatinine clearance of 50%, or the need for renal replacement therapy), the authors showed an increase of toxicity with colistin (26/168 (16%) vs. 17/244 (7%) for comparators, p = 0.006.) The second analysis by Kvitko and colleagues was a comparison of toxicity in patients receiving polymyxin B compared to those receiving other anti-pseudomonal agents for the treatment of *P. aeruginosa* bacteremia [22]. In this analysis, nephrotoxicity, defined as an increase in serum creatinine ≥50% for the baseline value, occurred in 16/45 (36%) of patients on polymyxin B compared with 10/88 (11%) of patients on other anti-pseudomonals (p = 0.002). Interestingly, the third analysis showing a significant difference between a polymyxin and comparator showed rates of nephrotoxicity, using a definition of doubling of serum creatinine or a decrease in creatinine clearance of 30%, to

Table 17.1 Polymyxin nephrotoxicity rates in comparison to other antimicrobials

Author	Polymyxin, n	Comparator, n	Scheduled Polymyxin dose	Nephrotoxicity definition	Toxicity
Rocco [27]	147 colistin or colistin + vancomycin/ aminoglycoside	132 vancomycin or aminoglycoside	3.9 mg/kg/ day CBA	RIFLE	57 (41) colistin vs. 54 (41) other; p = NS
Chan [21]	7 "polymyxin"	30 aminoglycoside	2.5–5 mg/kg/ day CBA	Increase Scr 0.5 or decrease Clcr 50%	4/7 (58) polymyxin vs. 6/30 (20) aminoglycoside; p = 0.07
Durakovic [38]	26 colistin	26 "other anti-pseudomonals"	3 MU q8h	Scr ≥ 1.7 or increase ≥50% if pre-existing renal insufficiency	3 (10) colistin vs. 0 for "other" p = 0.07
Lim [50]	20 colistin	35 inactive antimicrobials	2.5–5 mg/kg/ day CBA	Inc Scr 50% to a value ≥1.3 or RRT	10/20 (50) colistin vs. 10/35 (29) inactive; p = 0.10
Paul [55]	168 colistin	244 other agents for A. baumannii, P. aeruginosa, or enterobacteriaceae	6–9 MU/day	Baseline Scr ≤ 1.2: Scr >2 or dec Clcr 50% or RRT baseline >1.2: 50% increase in Scr, 50% decrease in Clcr or RRT	26/168 (16) colistin vs. 17/244 (7) comparators
Gounden [51]	21 colistin	23 tobramycin	2 MU q8h	Increase Scr to >50% the upper limit of normal	4/21 (19) colistin vs. 2/23(9) tobramycin; p = 0.07
Koomanachai [40]	78 colistin	15 inactive antimicrobials	5 mg/kg/day CBA	Doubling of Scr or decrease of 30% in Clcr	24/78 (31) colistin vs. 10/15 (67) inactive; p = 0.02
Betrosian [58]	15 colistin	13 ampicillin/sulbactam	3 MU q8	Baseline Scr ≤ 1.2: Scr >2 or decrease Clcr 50% or RRT baseline >1.2: 50% increase in Scr, 50% decrease in Clcr or RRT	5/15 (33) colistin vs. 2/13 (15) ampicillin/sulbactam; p = 0.4
Kallel [7]	60 colistin	60 imipenem	2 MU q8	Scr > 1.7, BUN >28	0% in each group
Montero [56]	21 colistin	14 imipenem	2.5–5 mg/kg/ day CBA	Baseline Scr ≤ 1.2: Scr >2 or decrease Clcr 50% or RRT baseline >1.2: 50% increase in Scr, 50% decrease in Clcr or RRT	5/21 (24) colistin, 6/14 (42) imipenem; p = NS
Reina [8]	55 colistin	130 others for A. baumannii or P. aeruginosa	5 mg/kg/day	Scr ≥ 2, 50% decrease in Clcr or RRT	0% in each group
Kvitko [62]	45 polymyxin B	88 other anti-pseudomonals	Not listed	Increase Scr ≥ 50%	16/45 (36) polymyxin B vs. 10/88 (11) others; p = 0.002

Scr serum creatinine, *Clcr* creatinine clearance, *BUN* blood urea nitrogen, *RRT* renal replacement therapy

be higher with inactive therapy (i.e. agents lacking in vitro activity against the causative pathogen) than colistin (24/78 (31) colistin vs. 10/15 (67) inactive; p = 0.02.) [47] It should be noted however, that mortality was 80% in the inactive therapy group, and thus worsening sepsis due to inactive agents likely influenced the development of acute kidney injury. While the other analyses do not show statistically significant increases in toxicity with polymyxins, they are often numerically higher, and the failure to see statistical significance is often due to small sample sizes. Based on these data, it is reasonable to conclude that in general the polymyxins are more nephrotoxic than other antimicrobials.

17.2.5 Comparative Toxicity of Colistin and Polymyxin B

As previously discussed, one of the primary drivers between preferential use of colistin over polymyxin B in both the "old" and "modern" era of the polymyxins was the belief that colistin was less nephrotoxic than polymyxin B. This theory was largely debunked when data showed that larger doses of colistin (in the form of CMS) were needed for efficacy, and when the two were "on equal terms" that toxicity would be equal. To date there are six analyses and one meta analysis available in the literature attempting to assess the comparative nephrotoxicity of the polymyxins.

The first analysis, published in 2009 by Oliveira and colleagues, compared rates of nephrotoxicity, defined as a twofold increase in serum creatinine at any time during the treatment or an increase by 1 mg/dL if the patient had a baseline creatinine >1.4 mg/dL, between 39 patients receiving colistin and 30 receiving polymyxin B [23]. Median daily dose in the study was 6 MU (range 1–9 MU) for CMS (200 mg CBA (range 33–300 mg) and 100 mg (range 40–150 mg) for polymyxin B. The onset of renal impairment occurred in 10/39 (26%) and 8/30 (27%) (p = 0.92) of patients receiving colistin and polymyxin B, respectively, and the authors concluded there was no difference in toxicity between the two.

The second study, by Tuon and colleagues in 2013, analyzed risk factors for acute kidney injury, defined by the AKIN criteria, in patients receiving colistin and polymyxin B [24]. In bivariate analysis, the incidence of acute kidney injury was numerically higher with colistin (14/36, 39%) than polymyxin B (20/96, 21%), p = 0.06. However, when controlling for polymyxin dose and concomitant vancomycin in the multivariate model, colistin (compared to polymyxin B) use was not significantly associated with an increased risk for toxicity (adjusted odds ratio 1.74 [95% confidence interval 0.82–3.69]).

The third analysis, also published in 2013 by Akajagbor and colleagues [26], compared nephrotoxicity rates, defined by the RIFLE criteria, between 173 patients receiving one of the two polymyxins. Nephrotoxicity was seen in 64/106 (60%) of patients receiving colistin, and 28/67 (41.8%) of patients receiving polymyxin B, p = 0.03. When controlling for age, hypertension, vasopressors, and concomitant nephrotoxins, colistin use was independently associated with an increased risk for nephrotoxicity (Hazard Ratio 2.27 (1.35–3.82); p = 0.002).

While the previous two analyses suggested that colistin might in fact be associated with higher rates of nephrotoxicity they also suffered from the same major limitation. Since it was only recently appreciated that polymyxin B is not renally eliminated, and therefore should not have renal dose adjustments, patients with baseline renal insufficiency (likely those with creatinine clearances ≤80 mL/min) underwent unnecessary dose adjustments, and therefore likely had lower polymyxin B exposure. With both polymyxins showing a dose-dependent toxicity, this makes it extremely difficult to interpret these findings.

Phe and colleagues were the first to attempt to address this limitation. They compared nephrotoxicity rates, defined by the RIFLE criteria, of the polymyxins, in a multicenter cohort study limiting inclusion to those with stable, normal (baseline creatinine ≤1.5 mg/dL) renal function. In the overall cohort of 225 patients, nephrotoxicity was seen in 41/121 (34%) of patients receiving colistin, compared to 24/104 (23%) of patients receiving polymyxin B, p = 0.08) [28].

The authors then provided a matched cohort analysis controlling for the factors associated with colistin and polymyxin B nephrotoxicity. In this well-matched analysis (n = 38 in each group) median daily doses were 291 mg CBA (5.0 mg/kg/day of ideal body weight) for colistin (median dose 8.8 MU, dosed at 0.152 MU/kg/day) and 126 mg (2.1 mg/kg/day of ideal body weight) for polymyxin B. Nephrotoxicity was seen in 21 (55%) of patients receiving colistin compared to 8 (21%) on polymyxin B, p = 0.003.

Rigatto and colleagues published data from a large cohort (n = 491, including 81 receiving colistin and 410 receiving polymyxin B) of patients that also overcame the previous limitations, as the institutions involved in this analysis did not recommend renal dose adjustments for polymyxin B [68]. This more optimal dosing strategy was reflected in the median doses used with both colistin (median dose 300 mg CBA interquartile range (IQR) 253–300) and polymyxin B (150 mg IQR 140–187) in this analysis. Using these dosing strategies, which better reflect currently recommended doses of both polymyxins, the authors found that the rate of renal failure (the "F" category of the RIFLE criteria, or a rise in creatinine three times the baseline or a decrease in creatinine clearance ≥75%) to be significantly higher with colistin than polymyxin B (38.3% vs. 12.7%, $p < 0.001$), with colistin being an independent predictor of renal failure in the multivariate model (HR 3.35 95% CI 2.05–5.48).

The five aforementioned studies were included in a meta-analysis by Vardakas and Falagas [69]. The authors concluded that when combining these data colistin was associated with risk ratio of 1.55 (95% CI 1.36–1.78) for nephrotoxicity when compared to polymyxin B. While the findings of this meta-analysis are interesting and support the emerging conclusion that colistin is associated with increased toxicity when compared to polymyxin B, it is worth mentioning that the same limitations from the first three studies described above (inappropriate renal dosing of polymyxin B) do play a role in the findings of this meta analysis.

The sixth and final analysis assessing comparative nephrotoxicity rates in both a non-cystic fibrosis (n = 194; 45 polymyxin B and 149 colistin) and a cystic fibrosis (n = 220; 29 polymyxin B and 191 colistin) population found no association between polymyxin choice and AKI [70]. Acute Kidney Injury occurred in 21/49 (43%) and 73/145 (50%) of polymyxin B and colistin patients in the non-cystic fibrosis population (p = 0.46). Similarly there was no difference in AKI rates in the cystic fibrosis patient population (10/29 (35%) and 57/191 (30%); p = 0.77). It is worth mentioning that due to the temporal nature of this study (polymyxin B recently became the formulary preferred agent with the advent of recent pharmacokinetic and safety data) that while polymyxin B was dosed in what would be considered an optimal manner (loading dose used in 74% of non-cystic fibrosis patients followed by a median daily maintenance dose of 200 mg ± 83 mg), colistin loading doses were used less frequently (14% of non CF patients) and maintenance doses were lower than generally recommended (226 ± 106.1 mg/day CBA). Because of these dosing differences between the two polymyxins, these data are not as strong as the two aforementioned studies which showed an association between polymyxin selection and toxicity.

Although it is not a universal finding, and the data are limited by study design there is a strong suggestion in the literature that polymyxin B might be less toxic to the kidneys than colistin. Prospective studies, looking at both pharmacodynamic and toxicodynamic effects of achievable concentrations of both polymyxins are urgently needed to assure that the polymyxin with the superior benefit-to-cost ratio is being utilized.

17.2.6 Serum Levels and Nephrotoxicity

There have been four analyses with colistin reporting on serum concentrations obtained and rates of nephrotoxicity, only two of which looked directly at the association between concentrations and incidence of acute kidney injury. Markou [65] and Karnik [64] reported on pharmacokinetics of colistin after administration of

intravenous CMS in 14 and 15 critically ill patients, respectively. Patients in these analyses had maximum serum concentrations 2.93 ± 1.24 and 4.6 (2.5–23.2) mcg/mL, respectively. Although nephrotoxicity was not clearly defined or incidence stated in either of these analyses, zero patients had any "clinically significant changes in laboratory values" related to renal parameters. Conversely, in the largest currently available pharmacokinetic study in critically ill patients where the median steady state colistin level was 2.36 (0.48–9.38) mcg/mL, Garonzik and colleagues reported that 43/89 (48%) of patients who did not have pre-existing need for renal replacement therapy had a rise in serum creatinine of ≥50% [71].

Sorli and colleagues published the first analysis assessing the association between serum levels and nephrotoxicity defined by the RIFLE criteria [42]. The investigators performed colistin trough sampling after 3 days of treatment and looked at the influence of those levels on nephrotoxicity at day 7 and the end of therapy. A concentration-dependent toxicity was seen at both endpoints with a 2% toxicity rate at day 7 if the day 3 serum colistin concentration was ≤1.04 mcg/mL, compared to a 32% rate if the concentration was between 1.05 and 2.2 mcg/mL, and a 65% rate if the concentration was >2.2 mcg/mL. A similar concentration dependent effect was seen at the end of therapy, with day 3 concentrations >2.2 mcg/mL being associated with an 85% chance of toxicity at the end of therapy.

More recently, Forrest and colleagues published a toxicodynamic analysis from a pharmacokinetic study which included 153 critically ill patients who could be assessed for a nephrotoxicity endpoint [72]. In this analysis the authors demonstrated a clear association between average colistin steady state concentrations, baseline renal function, and both the incidence and severity of colistin-associated nephrotoxicity. For patients with a baseline creatinine clearance <80 mL/min, average colistin steady state concentrations of 1.88 mcg/mL or higher increased the incidence and severity of acute kidney injury, whereas in patients with creatinine clearances ≥80 mL/min concentrations ≥2.25 mcg/mL increased this risk. These toxicity thresholds identified are consistent with those demonstrated in the aforementioned study by Sorli and colleagues. Furthermore, much like in the Sorli analysis, the rates of acute kidney injury were very high when these thresholds were met with roughly 50% and 65% of patients in the different baseline renal function groups demonstrating a ≥ 50% reduction in creatinine clearance at or above these concentrations.

17.2.7 Polymyxin Loading Dose and Nephrotoxicity

Recent pharmacokinetic data have stressed the importance of a loading dose, usually in the 270–360 mg CBA range, in order to rapidly obtain target serum concentrations with colistin, and more limited data suggest that, although not as crucial, a loading dose of 2–2.5 mg/kg can help more rapidly achieve steady state concentrations with polymyxin B. The chief concern, in light of the dose-dependent toxicity described in this chapter is the impact that a one-time large dose might have on nephrotoxicity. To date, limited evidence exists exploring the safety (and efficacy) of a polymyxin loading dose. The four studies to date assessing the impact of a polymyxin loading dose are limited by differing definitions of loading dose, different polymyxins being used, small numbers, and the fact that analyzing the impact of the loading dose on AKI rates was not the primary objective of the study.

Nelson and colleagues found that rates of nephrotoxicity in patients receiving a polymyxin B loading dose (defined as initial dose ≥2.5 mg/kg) was not associated with an increased risk of AKI [66] (AKI occurred in 9/19 (47%) of patients who received a loading dose versus 30/90 (33%) of those who did not; p = 0.30). Conversely, in an analysis of 81 colistin patients Rigatto and colleagues found that renal failure occurred in 17/22 (77%) of patients who received loading doses compared to 14/59 (24%) who did not ($p < 0.001$) [68]. It is worth mentioning that the primary intent of this analysis, as described above, was to

compare AKI rates in patients receiving colistin and polymyxin B, and a post hoc analysis of these 81 colistin patients showed significant differences between patients who received loading doses and those who did not, including differences in baseline renal function and chronic comorbidities. Nonetheless, when controlling for these differences in the post hoc analysis, receipt of a colistin loading dose was associated with an increased risk of AKI (HR 5.2; 95% CI, 2.3–12.0).

Crass and colleagues assessed the incidence of AKI in the 56 patients who received a loading dose with either colistin or polymyxin B and 138 who did not, and found no association in either bivariate (HR 0.67 95% CI 0.39–1.17) or multivariate (HR 0.78 95% CI 0.42–1.46) analyses between receipt of a polymyxin loading dose and AKI [70]. Finally, while Shields and colleagues found an association with colistin loading dose and AKI on day 7 in bivariate analysis [73] (42/118 (36%) vs. 31/131 (24%); p = 0.05), this did not persist on multivariate analysis when concomitant vancomycin and higher maintenance dose strategies were controlled for (p = 0.28).

The safety of a polymyxin loading dose remains unclear. The data presented here are limited by small numbers as well as the lack of uniform definition of a loading dose (three of the four studies did not clearly define what constituted a loading dose). Further data, in larger populations with clearly defined (and pharmacokinetically optimized) loading doses are clearly warranted to further assess this strategy.

17.2.8 Other Risk Factors for Polymyxin Nephrotoxicity

While dose and subsequent concentration are important predictors of nephrotoxicity, several other risk factors have been identified in the literature. In 18 publications looking at risk factors for nephrotoxicity with either colistin or polymyxin B, 15 identified at least one additional factor in either bivariate or multivariate analyses. In addition to many variables related to polymyxin therapy (daily dose, cumulative dose, duration of therapy), concomitant nephrotoxins [17, 18, 25, 35, 37, 50, 61] (including vancomycin), chronic kidney disease [21, 25, 50, 61], age [17, 30, 37], and body mass index [19, 35] are seen repeatedly as predictors of toxicity. Other risk factors that have been identified are malignancy [48], length of stay [48], concomitant rifampin [18], hypoalbuminemia [46], and site of infection [25].

17.2.9 Conclusion

While debate continues to exist about just how nephrotoxic the polymyxins are, there is little doubt that (a) they are nephrotoxic and (b) they are more nephrotoxic than other agents used for Gram negative infections. Importantly, the relationship between dose, serum/plasma levels, and rates of toxicity suggest that there is potential for minimizing this toxicity with therapeutic drug monitoring. Unfortunately, the feasibility of doing that with colistin is difficult, due to issues with continued conversion from the prodrug (CMS) to active colistin unless samples are very carefully collected, processed, stored and analysed. This represents a potential advantage for polymyxin B, for which therapeutic drug monitoring would be more straightforward.

In addition to identifying the appropriate or optimal dose, other strategies to minimize polymyxin nephrotoxicity would include minimizing the use of concomitant nephrotoxins. Another potential strategy for limiting toxicity would be the co-administration of anti-oxidants; however, clarity on this preventative strategy is urgently needed. As oxidative stress is considered to have a key role in tubular cell apoptosis, interest surrounding the possible protective role of antioxidants has emerged. Animal data have suggested that co-administration of ascorbic acid can mitigate colistin-associated nephrotoxicity [74]; however, clinical data to date have been mixed [75, 76]. Adequately powered and well controlled studies are needed to clearly address the question.

Furthermore, it will be interesting to see if dose frequency strategies can mitigate

nephrotoxicity. A study in rats suggested dividing daily CMS doses thrice daily could decrease the incidence and severity of renal lesions when compared to twice daily administration of the same daily dose [77] These data, in addition to the in vitro data suggesting the potential for resistance suppression with more frequent dosing [78], are the basis for expert recommendations of dividing the daily dose of CMS (e.g. divided daily dose administered 8 hourly). While this is a reasonable approach, the relevance of these findings is questionable given that these analyses had significantly different Cmax and Cmin concentrations (high C_{max}, low C_{min}), particularly with less frequent dosing, and clinical pharmacokinetics from critically ill patients suggest a relatively constant, flat, concentration-time profile in human patients given the slow conversion from CMS to colistin [71]. Conversely, data with polymyxin B suggest a saturable toxicity similar to the aminoglycosides which would more lend itself towards a once-daily dosing strategy [79]. Future analyses should analyze dose frequency strategies on the incidence of toxicity in patients. Finally, further research is needed to identify if one polymyxin, when dosed optimally, truly is less nephrotoxic than the other.

17.3 Neurotoxicity

Neurotoxicity is much less commonly reported in the modern literature, and even when investigated, rates tend to be much lower than rates in the "old" polymyxin era. This seemingly safer use of the agents is undoubtedly related to the patient population now treated with polymyxins. In the old era polymyxins were used as first-line agents for treating a wide variety of infections, including infections in relatively healthy individuals. Conversely, in the modern era, use is often limited (due to concerns relating to toxicity and emergence of resistance) to critically ill patients with no other treatment options; therefore, many of the toxicities mentioned in the old literature are often not evaluable or are undetected due to heavily sedated or otherwise unresponsive patients. Therefore, all incidences of neurotoxicity in the modern literature must be analyzed with this understanding.

In total 19 studies assess possible colistin-associated neurological toxicity [6, 7, 10, 13–16, 23, 43, 45, 47–49, 54, 59, 61–64], with 8 of them reporting at least one case of an adverse event. Four studies have investigated neurological toxicity possibly related to polymyxin B with three of them reporting two instances each of an adverse event. No analysis showed greater than a 7% neurotoxicity rate, and not all neurological adverse events were considered associated with the polymyxin.

Manifestations of neurotoxicity possibly associated with colistin have varied greatly. Averbuch and colleagues reported on two patients who had convulsions, although neither was considered drug related as one patient had uncontrolled epilepsy, and the other had multifocal encephalopathy [43]. Hartzell and colleagues reported on two patients (out of a cohort of 66) who had parasthesias [16], while Sabuda [54] and colleagues described four cases of neurological adverse events in patients receiving colistin. In this analysis patient 1 had somnolence, but was on gabapentin, baclofen, tizanidine and these agents were considered more likely as a root cause. Patient 2 suffered from dizziness, but MRI showed progression of cancer. The authors only stated that patient 3 had "neurotoxicity". Patient 4 was probably the most convincing, as this patient was on 500 mg CBA/day (15 MU/day) and had encephalopathy, respiratory muscle weakness with no other obvious cause. Kasaikou reported on a patient who developed polyneuropathy on day 25 of colistin therapy [10], however the patient continued treatment for 11 more days and it gradually subsided. Durakovic described a patient who developed Jackson's partial epilepsy with a secondary generalization in which the investigators reduced the dose and the seizure activity ceased [45]. Cheng and colleagues described neurotoxicity in 4 (3.5%) of 115 patients manifesting as focal seizures in the extremity in 3 patients, and as altered mental status in the fourth [48]. Encouragingly, none of the patients had permanent sequelae. Kallel reported on one patient receiving colistin who had

muscular weakness during hospitalization that recovered at 1 month follow up [7]. Finally, Linden and colleagues described a case that manifested as diffuse weakness on day 10 of colistin therapy that resolved 1 week after cessation of colistin therapy [80].

Polymyxin B neurotoxicity, while much less commonly described, showed similar variations in its clinical presentation. Sobieszczyk reported on two cases of neurotoxicity, which manifested as seizures in one patient and neuromuscular weakness in the other [34]. Holloway described one patient with altered mental status, and one with distal parasthesias [31]. Finally, Weinstein and colleagues reported on two patients who experienced parasthesias (both oral, and one lower extremity as well) which resolved after discontinuation [81].

17.4 Other Toxicities

Although infrequent, incidences of other adverse events potentially related to colistin therapy have been reported in the modern literature. Pintado and colleagues described two cases of potential hypersensitivity reactions to colistin where one patient had a mild self-limiting rash, and the second had angioedema that led to discontinuation of colistin [59]. Additionally, these authors mentioned one patient who had vomiting that was temporally related to colistin administration [59]. Similarly, Durakovic reported on occurrence of an "allergic reaction" to colistin [45]. Unfortunately, no more details of this case were given. Karnik described three patients who had elevated liver enzymes, one of which was thought to be possibly related to colistin administration [64]. Additionally, the authors described one patient who had hypokalemia and hyponatremia [64].

Interestingly, an emerging body of evidence has suggested an association between polymyxin B usage and skin hyperpigmentation. Two initial reports suggested a possible association between long-term (>21 days) polymyxin B exposure and hyperpigmentation [82, 83] which was described as a darkening of the skin [82] or "gray-skin discoloration" [83]. More recently Zavascki and colleagues described a case where a patient developed a "head and neck skin darkness" that was evident by day 14 of polymyxin B which had not resolved 3 months later [84]. According to the Naranjo Adverse Drug Reaction probability scale, there was a probable association between polymyxin B and the adverse event. The same investigator published an additional case report where hyperpigmentation occurred 5 days into polymyxin B therapy and consisted of skin darkening and the emergence of round hyperchromic spots. This report included longer term follow up and the hyperpigmentation had somewhat resolved at 3 months and nearly completely resolved at the 6 month follow up visit [85]. Further investigation into this adverse event is clearly warranted.

Two analyses have looked closely at respiratory toxicities following nebulized colistin. Dominguez-Ortega described a 63-year-old man who developed severe bronchospasm after administration of nebulized colistin (in the form of CMS). Interestingly, the authors were able to successfully administer inhaled colistin to this patient in the future by inducing tolerance with a graded challenge [86]. Rattanaumpawan and colleagues reported a rate of bronchospasm 7.8% in 49 patients who received nebulized colistimethate as adjunctive therapy for ventilator-associated pneumonia, but this was not statistically higher than the 2.0% rate seen in the control arm ($p = 0.36$) [87]. Importantly, in 2007, the United States Food and Drug Administration issued a warning regarding a cystic fibrosis patient who had a potential fatal adverse reaction to nebulized colistin [88]. Within hours of receipt of nebulized colistin (in the form of CMS) the patient developed respiratory distress, which progressed to respiratory failure, and ultimately death. The analysis concluded that a component of active colistin (polymyxin E1) is toxic to lung tissue, and since the inhaled colistimethate had been premixed well before administration, significant conversion to colistin had already occurred, and this might have been the cause of the toxicity. The FDA cautioned that in the future doses of nebulized colistin should be reconstituted

immediately before administration, and clinicians be aware of this potentially fatal adverse event. Pereira and colleagues published the only analysis in the modern era looking at respiratory toxicities with inhaled polymyxin B (50 mg twice daily administration) [89]. All patients were given pretreatment with beta-agonists in order to minimize respiratory adverse events; however, the authors reported that 4 of 19 patients (21%) suffered adverse events with three described as bronchospasm and one as "cough." All four patients were able to tolerate inhalation of polymyxin B with dose reduction, although the dose reduction used was not described. The role of beta-agonists for prevention of bronchospasm warrants further evaluation.

17.5 Summary and Conclusions

By far, the most commonly manifested toxicity seen with both polymyxins is nephrotoxicity. While the reported rates might vary widely, significant attention should be given by clinicians to strategies to minimize renal toxicity. These strategies include dose optimization, minimizing risk factors (namely receipt of concomitant nephrotoxins), and in the future, selection of the optimal polymyxin. Future studies on the topic should also describe management of patients with mild-moderate nephrotoxicity to help guide clinicians (for example: in the setting of acute kidney injury, should polymyxin be continued with a dose reduction?). Clinicians should also be aware of the various manifestations of neurotoxicity described in this chapter, and alternative antibiotics (if available) should be administered if possible. Encouragingly, multiple analyses reported tolerance and resolution of mild neurotoxicity over time without discontinuation of therapy. As hypersensitivity reactions have been described, monitoring is warranted upon initiation of polymyxin therapy in patients. Finally, if patients receive inhaled colistin (in the form of CMS), clinicians should be aware of the potential for bronchospasm, and doses should be reconstituted immediately prior to administration.

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