Higher Incidence of Acute Kidney Injury With Intravenous Colistimethate Sodium Compared With Polymyxin B in Critically Ill Patients at a Tertiary Care Medical Center

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Nephrotoxicity was assessed in 173 critically ill patients receiving intravenous colistin or polymyxin B; it occurred in 60.4% and 41.8%, respectively. Further investigation is necessary to elucidate the reason for the difference in nephrotoxicity observed between the groups and to assess the impact of severity of illness and dosing/administration.

Keywords. PB; colistin; colistimethate sodium; nephrotoxicity; AKI.

Polymyxin B (PB) and colistin (colistimethate sodium) were originally used in the 1960s but were abandoned because of toxicities and the introduction of safer and effective alternatives [1–5]. Over the past decade, there has been a reemergence of their use for infections caused by multidrug-resistant (MDR) pathogens [3, 6, 7]. The nephrotoxicity rates reported in the literature with colistin and PB vary significantly [1, 4]. Recent studies using the RIFLE criteria (risk, injury, failure, loss, and end-stage kidney disease) report nephrotoxic rates of 31%–45% with colistin [8–13] and 14%–60% with PB [14–18]. These studies suggest a difference in the rates of nephrotoxicity between these agents, but there is a paucity of data that directly compare their toxicodynamics. The purpose of this study was to evaluate the incidence of nephrotoxicity with intravenous colistin compared with PB at a large academic medical center.

METHODS

This was a retrospective cohort study of patients aged ≥18 years who received intravenous PB from January 2008 through June 2009 and colistin from January 2009 through June 2010 for ≥72 hours at the University of Maryland Medical Center. The institutional review board at the University of Maryland Baltimore approved the study protocol. In patients with normal renal function, PB was dosed at 15 000–25 000 units/kg/day as a continuous infusion over 24 hours. Colistin was dosed at 5 mg/kg/day of ideal body weight (IBW) or actual body weight or as a fixed dose of 150 mg every 12 hours. Patients were excluded if they received any form of dialysis before treatment initiation. Relevant clinical data were extracted for each patient for the treatment period studied. The RIFLE criteria were used to define nephrotoxicity and evaluate the severity of Acute Renal Failure (ARF) as previously described [8, 13].

Statistical Analysis

Differences in the mean were tested using *t* tests, and differences in the proportions were tested using χ^2 test (or Fisher exact test, where appropriate). The Kaplan–Meier product limit method was used to estimate the cumulative incidence of nephrotoxicity. The main outcome was incidence of nephrotoxicity according to the RIFLE criteria. In the analysis of time to nephrotoxicity, individuals who did not have the outcome by the end of the follow-up contributed to censored observations. Difference in cumulative incidence was tested by log-rank test. A Cox proportional hazards model was constructed to estimate the relative hazards of nephrotoxicity at the univariable and multivariable levels. The assumption of proportionality was assessed by Kaplan–Meier profile for each predictor. Covariables that were known risk factors or associated with the outcome at $P < .10$ were combined in the multivariable regression analysis. Graphical display of Kaplan–Meier estimates were created using Stata version 11.

RESULTS

Baseline Characteristics and Demographics

Of 432 patients who were identified as receiving either colistin or PB, a total of 173 met the inclusion criteria, contributing a total of 2403 person-months of follow-up. A total of 106

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patients received colistin, and 67 received PB. The baseline characteristics were evenly distributed except for a higher percentage of patients with *Acinetobacter baumannii* infections in the PB group and a higher percentage of patients who received vasopressors in the colistin group ($P = .07$) (Supplementary Table 1). Both agents were predominantly used to treat MDR *Pseudomonas aeruginosa* and *Acinetobacter baumannii* infections cultured from multiple sites. The majority of the patients were intensive care unit patients (89%) with mean Acute Physiology and Chronic Health Evaluation II (APACHE II) score of 22.6 (SD, 6.4) and 22.7 (SD, 5.3) for colistin and PB, respectively ($P = .92$). The mean treatment duration in days was 11.7 (SD, 11.4) and 12.5 (SD, 11.9) for colistin and PB, respectively ($P = .66$).

Incidence of Nephrotoxicity Results

Nephrotoxicity developed in 60.4% (95% confidence interval [CI], 50.8%–69.2%) and 41.8% (95% CI, 30.7%–53.7%) of patients receiving colistin and PB, respectively ($P = .02$). The incidence rate for the colistin group compared with the PB group was 5.1 vs 2.3 per 100 person-months. Among patients who developed nephrotoxicity, the difference in time to peak serum creatinine (colistin, 2.0 mg/dL; PB, 1.6 mg/dL; $P = .03$) was not statistically significant (mean, 6.5 days vs 7.3 days; $P = .54$). With respect to severity, most patients experiencing ARF fell into the reversible kidney injury category (risk, injury, and failure) in both the colistin and the PB groups (Figure 1). Seven patients (6.6%) on colistin experienced loss of renal function (as defined by RIFLE), and only 1 patient (0.9%) in the colistin group progressed to End Stage Renal Disease (ESRD) vs none in the PB group. Older age (hazard ratio [HR], 3.29 for age 31–60 years; HR, 3.13 for age >60 years old) and baseline serum creatinine (<1.5) were independently associated with an increased risk of nephrotoxicity. In a multivariable model (Table 1) consisting of age, APACHE II score, vasopressors, hypertension, baseline renal function, and concomitant nephrotoxins, colistin use remained significantly associated with increased nephrotoxicity (HR, 2.27; $P = .002$).

Dosing and Nephrotoxicity

The average daily dose and cumulative doses were comparable in the groups that experienced toxicity and in the groups without toxicity for both drugs (Supplementary Table 2). Dose stratification showed 18 of 33 patients (54.5%), 33 of 53 (62.3%) and 13 of 20 (65%) patients receiving >3 mg/kg/day, 3–5 mg/kg/day and >5 mg/kg/day respectively of colistin per IBW developed nephrotoxicity.

DISCUSSION

The incidence of ARF was statistically significantly higher with colistin than PB (60.4% vs 41.8%). Although the rate of nephrotoxicity observed was high, most patients experienced reversible ARF, with only 1 patient progressing to ESRD in the colistin group. A higher incidence of nephrotoxicity was seen with both colistin and PB in this study compared with recent publications [9–12, 14–16]. Oliveria et al evaluated the difference in toxicities between these agents and found no difference in the rates of renal impairment (26% of patients in colistin group vs 27% in the PB group; $P = .92$) [16]. The reason for the difference in toxicity in our study is not clearly understood; however, it should be noted that a majority of the patients in our study were critically ill patients with higher APACHE II scores than those evaluated by Oliveria et al. Baseline characteristics were comparable in both groups, with the only major difference being the administration rates. Daily doses of PB at our institution were given as a 24-hour continuous infusion, and colistin doses were given intermittently over 60 minutes. Teng et al in a small retrospective study found a higher incidence of nephrotoxicity with continuous infusion PB when compared with a

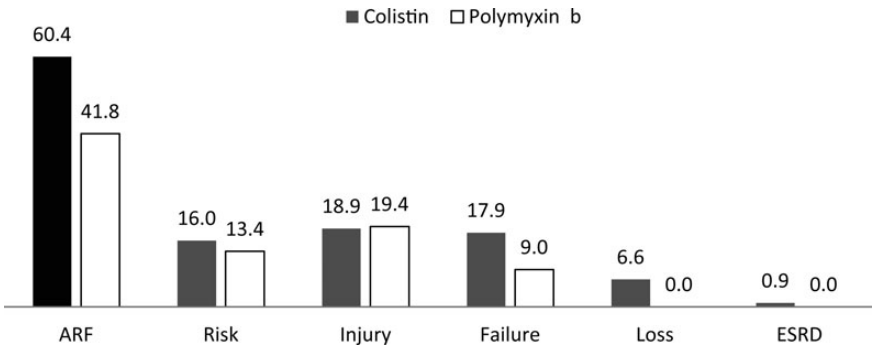

Figure 1. Severity of nephrotoxicity based on RIFLE (risk, injury, failure, loss, and end-stage kidney disease). Abbreviations: ARF, acute renal failure; ESRD, end stage renal disease.

Table 1. Univariable and Multivariable Analysis

Univariable Analysis of Risk Factors for Nephrotoxicity	Nephrotoxicity	Univariable Cox Regression Analysis	
	No. (%)	Hazard Ratio[a] (95% CI)	*P* Value
Drug			
Polymixin B	28/67 (41.8)	Referent	
Colistin	64/106 (60.4)	1.98 (1.26–3.10)	.003
Age			
<30	4/19 (21.1)	Referent	
31–60	51/86 (59.3)	3.29 (1.19–9.10)	.02
≥61	37/68 (54.4)	3.13 (1.11–8.79)	.03
Sex			
Male	52/103 (50.5)	Referent	
Female	40/70 (57.1)	1.23 (.81–1.86)	.32
Ethnicity/race			
White	52/94 (55.3)	Referent	
Other	37/76 (48.7)	0.86 (.56–1.31)	.39
APACHE II score			
<10	16/26 (61.5)	Referent	
≥11	76/147 (51.7)	0.60 (.35–1.03)	.06
ICU Stay			
No	13/19 (68.4)	Referent	
Yes	79/154 (51.3)	0.51 (.28–.92)	.03
Baseline serum creatinine, mg/dL			
<1.5	82/137 (59.9)	Referent	
≥1.5	10/36 (27.8)	0.39 (.20–.76)	.006
Treatment duration, days			
0–10	45/93 (48.4)	Referent	
11–20	33/60 (55.0)	0.67 (.42–1.05)	.08
>20	14/20 (70.0)	0.75 (.41–1.38)	.35
AKI/CRI			
No	84/149 (56.4)	Referent	
Yes	8/24 (33.3)	0.54 (.26–1.11)	.09
Hypertension			
No	49/102 (48.0)	Referent	
Yes	43/71 (60.6)	1.45 (.96–2.19)	.08
Concomitant nephrotoxins			
0	5/14 (35.7)	Referent	
1–2	36/75 (48.0)	1.41 (.55–3.60)	.51
≥3	51/84 (60.7)	1.44 (.57–3.62)	.61

Multivariable Analysis for Independent Risk Factors for Associated Nephrotoxicity	Hazard Ratio (95% CI)	*P* Value
Colistin[b]	2.27 (1.35–3.82)	.002
Age 31–60 y[c]	4.03 (1.22–13.3)	.022
Age > 61 y[c]	3.24 (.95–11.0)	.06
Hypertension	1.57 (.94–2.61)	.08
Vasopressors	1.16 (.66–2.03)	.60
1 or 2 concomitant nephrotoxins[d]	3.25 (.75–14.1)	.11
≥3 concomitant nephrotoxins[d]	2.50 (.56–11.1)	.23
APACHE II score (≥11)[e]	0.34 (.07–1.75)	.20
Baseline serum creatinine, mg/dL (≥1.5)[f]	0.20 (.08–.48)	.0003

Table 1 continued.

Abbreviations: AKI, acute kidney injury; APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; CRI, APACHE chronic renal inefficiency; ICU, intensive care unit.

[a] Based on univariable Cox Proportional hazard regression.

[b] In comparison with polymyxin B.

[c] In comparison with age ≤30 years.

[d] In comparison with 0 concomitant nephrotoxins.

[e] In comparison with APACHE II score ≤10.

[f] In comparison with baseline serum creatinine ≤1.5.

60–90 minute infusion. There is no published evidence that supports a lower incidence of nephrotoxicity with a continuous infusion of polymyxins, making it less likely that differences in administration rate could explain the difference observed in our study [19]. Similar to other studies, older age was an independent risk factor found to be associated with a statistically significant increase in toxicity [9, 14]. Other risk factors such as concomitant administration of other nephrotoxic agents, documented preexisting renal insufficiency, and higher APACHE II scores that have been associated with an increased risk of nephrotoxicity were not found to increase the risk in this study, although APACHE II scores were high in all groups in this study. Intensive care unit stay, higher APACHE II scores, and baseline renal insufficiency appear to be protective against the development of nephrotoxicity. This is a counterintuitive finding, and our hypothesis is that intensive care unit patients with higher APACHE II scores likely had or developed worsening renal function, which caused them to be dosed conservatively and possibly decreased their drug exposure and risk of toxicity.

The average daily dose and cumulative doses administered were comparable in the nephrotoxic and non-nephrotoxic arms with both colistin and PB, but with dose stratification of colistin based on milligrams per kilograms per day of IBW, in doses <3 mg/kg/day, 3–5 mg/kg/day, and >5 mg/kg/day, an increase in the percentage of patients that developed nephrotoxicity with an increase in dose (54.5%, 63.23%, and 65%, respectively) was observed. Recently, similar studies found that nephrotoxic frequency increased with dose and reached 69% when doses ≥5.0 mg/kg per day were administered [11].

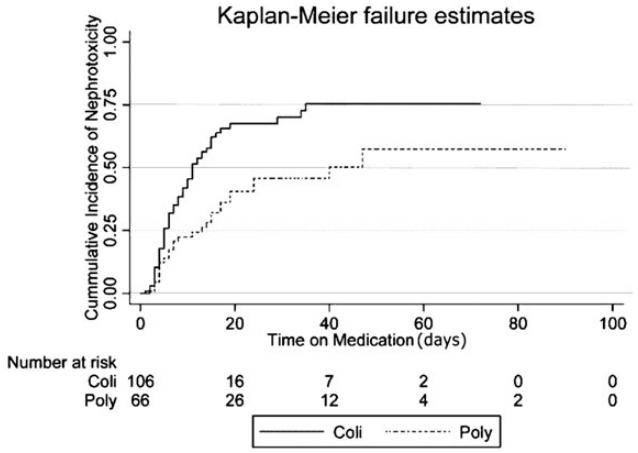

Figure 2. Time to nephrotoxicity (Kaplan–Meier curve).

Deryke et al observed that obese patients (who received excessive doses because actual body weight was used for dosing) were 13.2 times more likely than nonobese patients to develop nephrotoxicity [12]. This is an important finding because obese patients dosed based on actual body weight of colistin would receive doses >5 mg/kg/day of IBW, likely increasing their risk of nephrotoxicity.

This study has the inherent limitation of a retrospective study because there may be other factors not documented that could have affected nephrotoxicity. Also dose adjustments that were made or drug discontinuation because of ARF were not captured. Colistin and PB were used in two different time periods, hence variations in practice might account for some of the differences observed. Nonetheless, our study has a temporal design, which allows the estimation of incidence rates and relative risk of nephrotoxicity.

Patients receiving intravenous colistin had 2-fold increased risk of nephrotoxicity compared with patients receiving PB. This study provides additional strength to previous results by characterizing the temporal relationship between these medications and the development of nephrotoxicity. Our finding is similar to more recent publications and supports the need for close monitoring of renal function for patients receiving these agents. Further investigation is needed to determine the etiology of the differences in nephrotoxicity observed, including the impact of severity of illness, IBW dosing, and infusion type as well as differences in efficacy.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (hhttp://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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