Risk factors for acute kidney injury in patients treated with polymyxin B at a Tertiary Care Medical Center

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ABSTRACT

Introduction: Polimyxins were originally abandoned due to high rates of nephrotoxicity. However they have been recently reintroduced due to activity against carbapenem-resistant Gram-negative organisms. Recent literature suggests a lower rate of nephrotoxicity than historically reported. **Objective:** To determine the rate of polymixins-associated nephrotoxicity as defined by the RIFLE criteria. **Methods:** A retrospective cohort of all adult patients who received polymixin B at a terciary hospital from December 2010 to March 2011was performed. **Results:** 61 patients (43%) fulfilled the RIFLE criteria for renal injury and 28 patients (13.7%) needed dialysis. Independent predictors for nephrotoxicity were hypotension (OR, 2.79; CI 1.14-5.8; p = 0.006) and concomitant use of vancomycin (OR, 2.86; CI, 1.27-6.4; p = 0.011). **Conclusions:** In this retrospective cohort, nephrotoxicity (as defined by RIFLE criteria) occurred among 43% of treated patients. The concomitant use of vancomycin and hypotension were independent risk factors of nephropathy. Further studies are needed, particularly with polymyxin B, to clarify if the characteristics of this drug and colistin are overlapping.

Keywords: polymyxin B; dialysis; acute kidney injury; risk factors.

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INTRODUCTION

Polymyxins were developed approximately 60 years ago, but their use was discontinued in the 1980s (the exception being patients with cystic fibrosis) due to concerns with nephropathy and the introduction of safer therapies. However, this group of drugs was reintroduced in clinical practices all over the world, primarily as a consequence of the onset of multi-resistant gram-negative bacteria, among which are *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.[1-4]

There is a marked disparity between the polymyxin-associated rates of nephrotoxicity reported in older and more recent studies. Older studies reported rates close to 100%,[5] while more recent studies described nephrotoxicity rates close to zero.[6] And this disparity remains unchanged in current studies.[7-9] The most important factor behind these differences might be the variations concerning the definition of nephrotoxicity adopted by the authors of the papers (a systematic review found 15 different definitions for the term).[10] However, other aspects such as drug doses, concurrent use with other nephrotoxic medications, and the characteristics of the studied populations may have had some bearing on the disparities between studies.

Once polymyxin is deemed as a drug of last resort to treat infection caused by multi-resistant gram-negative bacilli, prescribing it might be inevitable. Therefore, studies in this area have become particularly important.

This study aimed to assess the incidence of nephropathy in patients seen at a tertiary hospital associated with the use of polymyxin B. The definition of acute kidney injury (AKI) of the RIFLE criteria was adopted. Additionally, the study looked into the risk factors associated with nephrotoxicity caused by polymyxin B, given that most of the knowledge in this area revolves around colistin (polymyxin E) or the combined use of polymyxin B and E, with few studies analyzing the impacts of prescribing polymyxin B alone.

Methods

This retrospective cohort study enrolled adult patients administered polymyxin B from December 2010 to March 2011 at the Hospital Nossa Senhora da Conceição. A list produced by the hospital's pharmacist contained the names of the patients given polymyxin B within the time period of the study. The following exclusion criteria were applied: patients started on dialysis before being prescribed polymyxin B; individuals under the age of 18 years; and patients treated with polymyxin B for less than 48 hours. The Ethics Committee of the institution approved the study on November 2011 and gave it permit no. 11-242.

The following data were collected from each of the included patients: demographics; previous comorbidities such as diabetes, hypertension, chronic kidney disease etc.; use of nephrotoxic agents; hypotensive events (requiring the prescription of vasopressor drugs); albumin; Charlson comorbidity index; serum creatinine levels before and immediately after the end of polymyxin B therapy. Data concerning the use of polymyxin, the total dose administered and the length of treatment were also noted. The patients included in the study were not offered measures designed to avoid the loss of renal function during the study.

The primary endpoint was onset of acute kidney injury as per the RIFLE criteria for AKI and kidney failure, in which acute kidney injury is defined as a two-fold increase in serum creatinine levels from baseline and kidney failure as a three-fold increase in serum creatinine levels from baseline. Prescription of dialysis and death were secondary endpoints.

The data sets were compiled using Microsoft Excel®, (version 7 for Windows). Data entry was performed by two individuals and compared for possible typing errors. Continuous variables were described in the form of mean values and standard deviations; categorical variables were described in the form of frequencies and percent values. Student's *t*-test was used to compare continuous variables, while the chi-square and Fisher's exact test were used in the analysis of categorical variables. Backward elimination and stepwise logistic regression were used to assess the relationships between variables and onset of nephropathy. Statistical analysis was performed using software package SPSS® (*Statistical Package for the Social Sciences* v. 17.0 for Windows). Statistical significance was attributed to events with a p value under 5% ($p < 0.05$).

Results

Two hundred and five individuals met the enrollment criteria. Sixty-two patients were excluded (38 for being on dialysis before being started on polymyxin; 23 for taking polymyxin for less than 48 hours; and one for being under the age of 18 years). The characteristics, comorbidities, and antimicrobial therapy specifics for the patients who developed or were free of nephropathy are presented in Table 1.

According to the RIFLE criteria, 72 (50.3%) patients did not experience significant changes in their glomerular filtration rates; nine (6.3%%) met the criteria for being at risk; 38 (26.6%) met the criteria for injury; and 23 (16.1%) for *failure*. Sixty-one patients (43%) met the endpoint criteria set for the study (injury and failure) and 28 (13.7%) were prescribed renal replacement therapy.

Table 1 Comparison of patients with and without renal injury

	Com (81)	Sem (61)	*p*
Males	42 (53.2%)	37 (46.8%)	0.27
Age	60.12 (DP: 16.04)	61.7 (DP:17.45)	0.38
Comorbidities			
Hypertension	27 (33.8%)	29 (48.3%)	0.081*
Smoking	22 (27.5%)	22 (36.18%)	0.277
Diabetes	19 (23.8%)	16 (26.7%)	0.693*
Heart failure	12 (15%)	3 (5%)	0.058*
Ischemic heart disease	10 (12.5%)	6 (10%)	0.645*
COPD	15 (18.8%)	12 (20%)	0.853*
Liver disease	3 (3.8%)	1 (1.7%)	0.464*
Stroke	14 (17.5%)	10 (16.4%)	0.862*
Dementia	4 (5%)	5 (8.3%)	0.426*
Tumor	18 (22.5%)	16 (26.7%)	0.569*
HIV/AIDS	5 (6.3%)	3 (5.0%)	0.753*
Peripheral arterial disease	2 (2.5%)	2 (3.3%)	0.770*
Chronic kidney disease	4 (5%)	2 (3.3%)	0.630*
Polymyxin B			
Time on drug (days)	7.27	7.93	0.57**
Cumulative dose (IU/kg)	187.666	202.744	0.31**
Other antibiotics			
Vancomycin	47 (58%)	48 (80%)	0.006*
Cefepime	33 (41.3%)	27 (44.3%)	0.720*
Site of infection			
Respiratory tract	58 (72.5%)	43 (70.5%)	0.793*
Urinary tract	5 (6.3%)	9 (14.8%)	0.094*
Abdominal	6 (7.4%)	5 (8.2%)	0.862*
Baseline creatinine > 1.5	16 (19.8%)	4 (6.6%)	0.043*
Hypotension	30 (37%)	33 (54.1%)	0.043*
ICU	57 (71.3%)	46 (75.4%)	0.581
Time of hospitalization	58.7 (SD:67)	44.26 (SD:29)	0.95**
Albumin (g/dL)	2.93	2.95	0.21***
Charlson index (mean)	4.62	4.50	0.668***

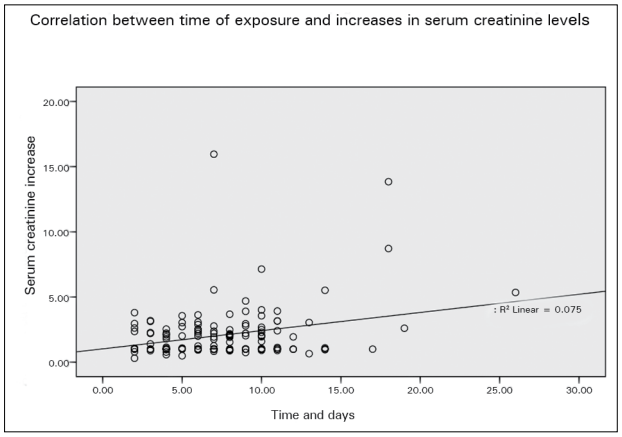
X^2 with Yates*, Mann-Whitney U**, Test *t* students for independent samples***.

The mean dose of polymyxin was 12,771 IU/kg (standard deviation 6596 IU/kg). The mean cumulative dose of polymyxin was higher (202,764 UI, standard deviation 152,469 UI) in the patients diagnosed with nephrotoxicity *versus* the individuals not affected by it (175,446 UI, standard deviation 154,491 UI). However, the difference was not statistically significant ($p = 0.30$). A correlation was found between drug dose and serum creatinine levels (r = 0.27, alpha < 0.001), and between time of drug use and serum creatinine levels (r = 0.27, alpha 0.001), as shown in Graphs 1 and 2.

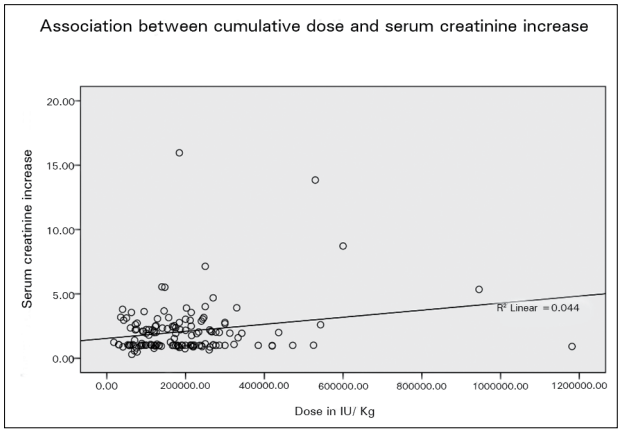
Thirty-eight percent (5/13) of the individuals suffering from nephrotoxicity and 36% (15/42) of the individuals not affected by nephrotoxicity died ($p = 0,999$). No correlations were found between loss of renal function and death.

The Charlson comorbidity index was used to assess the severity of disease and patient comorbidities. A correlation was found between the Charlson comorbidity index and death (r = 0.24, alpha = 0.004), but a correlation with development of nephropathy was not observed.

Graph 1. Correlation between time of exposure and increases in serum creatinine levels.



Graph 2. Association between cumulative dose and serum creatinine increase.



Multivariate analysis revealed that hypotension (OR 2.47; CI 1.14 - 5.35; $p = 0.021$) and concurrent use of vancomycin (OR 2.86; CI 1.20 - 6.81; $p = 0.017$) were independent risk factors for loss of renal function, as shown in Table 2.

Table 2 Backward elimination, stepwise logistic regression

Variables	α	OR	IC 95%	
Hypotension	0.006	2.792	1.333	5.848
Vancomycin	0.011	2.861	1.278	6.403

a. Variables included in step 1: hypotension, use of vancomycin, urinary tract, albumin, polymyxin B dose, DM, CHF, stroke, tumor, HIV, CKD, pulmonary tract, abdominal infection, Charlson index, male gender.

Discussion

Sixty-one patients met the RIFLE criteria for loss of renal function in our study, or the equivalent to 43% of the individuals given polymyxin - a rate greater than indicated in recently published studies.[6,10] However, this rate was similar to the findings reported by Hartzel *et al.*[11] and Levin *et al.*[12] Both studies had similar populations and used the RIFLE criteria to define nephrotoxicity. We believe the use of the RIFLE criteria in future studies with polymyxin will provide for more accurate estimates, in addition to enabling comparisons between studies.

The most important finding of our study was probably the relatively high rate of dialysis prescription: 28 patients (13.7%). Studies indicate that most patients recover their renal function after a few months.[10] Nonetheless, these rates cause concern, once dialysis is an invasive procedure with associated morbidity and mortality.[13]

Hypoalbuminemia has been suggested as a risk factor,[14] given that a high concentration of free polymyxin in patients with low albumin levels could boost renal toxicity. However, our study failed to confirm such correlation.

Similarly to previous studies, nephrotoxicity by polymyxin was correlated to the doses and duration of drug therapy.[7] However, in our study dose was not an independent risk factor for the development of nephropathy. A possible explanation is the fact that our study included only polymyxin B, and dose could be a more relevant factor for patients on colistin.

Concurrent prescription of vancomycin and hypotension were independent risk factors for nephropathy, as indicated in previous studies.[9,15]

The limitations of our study include its retrospective design and the lack of a control group. Ideally, a control group administered another antibiotic or placebo would be required allow for more definitive results. The lack of randomized clinical trials on the use of polymyxin hampers the assessment of the drug's actual risk for nephrotoxicity. However, the fact that polymyxins are administered almost exclusively to patients with infection caused by antigens sensitive only to this drug class makes it impossible for a randomized clinical trial to be performed at this time, once it would

be unethical not to prescribe polymyxins to patients whose hopes lie solely on this drug.

This was a one-of-a-kind study, once it has been the first to look into polymyxin B alone with a sizable population and outside an ICU setting. Our results bear important implications on possible interventions designed to prevent the occurrence of nephropathy associated with the prescription of polymyxins. Monitoring programs to reduce therapy duration and adjust doses must be developed. And finally, renal function must be monitored particularly among patients at risk, hypotensive individuals, and subjects prescribed vancomycin.

Only a few studies have looked into polymyxin B and colistin - and only three were included in a recent review[9,14,16] - with conflicting results in regards to the similarity of risk factors for nephropathy when both drugs were used and their rates of nephrotoxicity.

To sum up with, studies on drug nephrotoxicity are difficult to perform, once several factors connected to both patients and drugs may impact the loss of renal function. Ideally, each risk factor should be analyzed alone in an environment as homogeneous as possible (considering only outpatients, inpatients, or ICU patients, for instance). Further studies are required, particularly with polymyxin B, to clarify whether this drug and colistin have completely overlapping characteristics.

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