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Polymyxin B Nephrotoxicity and Efficacy against Nosocomial Infections Caused by Multiresistant Gram-Negative Bacteria

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Reported rates of nephrotoxicity associated with the systemic use of polymyxins have varied widely. The emergence of infections due to multiresistant gram-negative bacteria has necessitated the use of systemic polymyxin B once again for the treatment of such infections. We retrospectively investigated the rate of nephrotoxicity in patients receiving polymyxin B parenterally for the treatment of infections caused by multiresistant gram-negative bacteria from October 1999 to September 2000. Demographic and clinical information was obtained for 60 patients. Outcome measures of interest were renal toxicity and clinical and microbiologic efficacy. Renal failure developed in 14% of the patients, all of whom had normal baseline renal function. Development of renal failure was independent of the daily and cumulative doses of polymyxin B and the length of treatment but was significantly associated with older age (76 versus 59 years, $P = 0.02$). The overall mortality was 20%, but it increased to 57% in those who developed renal failure. The organism was cleared in 88% of the patients from whom repeat specimens were obtained. The use of polymyxin B to treat multiresistant gram-negative infections was highly effective and associated with a lower rate of nephrotoxicity than previously described.

The polymyxins are cationic detergents that are active against most aerobic gram-negative organisms other than *Proteus* spp., *Burkholderia cepacia*, *Neisseria* spp., and most isolates of *Serratia marcescens*, *Stenotrophomonas maltophilia*, and *Providencia* spp. The polymyxins were first discovered in 1947. Only polymyxins B and E were deemed clinically safe and used extensively for the treatment of gram-negative infections, especially *Pseudomonas aeruginosa* (8). The mechanism of action of polymyxins is thought to be based on surfactant activity, which disrupts the bacterial outer and cytoplasmic membranes (6). Resistance to these agents, although uncommon, has been shown to occur by mutation or adaptation through a change in the bacterium's outer membrane preventing the drug from reaching the inner cytoplasmic membrane (4). The polymyxins have been effective treatment for infections caused by *P. aeruginosa* (2, 11) and *Acinetobacter baumannii* (1, 11) with little development of resistance (2, 10). Nephrotoxicity, however, has limited their use.

Early reports varied widely, describing the development of renal impairment in as few as 20 to 25% and up to 100% of the patients receiving polymyxins (7, 14, 18). These drugs accumulate in tissues, especially the kidneys and brain, but the exact mechanism of molecular toxicity is unclear (9). Colistin, which was later discovered to be polymyxin E, was originally thought to be less nephrotoxic than polymyxin B. However, it was demonstrated that larger doses of this drug are required for effectiveness and thus the rate of nephrotoxicity equals that of polymyxin B (13). The high rates of nephrotoxicity associated with the use of polymyxins prompted their replacement once effective and safer antibiotics for gram-negative organisms became available.

The emergence of multiply antibiotic-resistant gram-negative bacilli, frequently susceptible only to the polymyxins, has sparked a renewed interest in these agents (5, 16, 17). Outbreaks of multiresistant *A. baumannii* have occurred in New York City (5, 17) and internationally (12). At our institution, nosocomial infections with multiresistant gram-negative bacteria have prompted the use of polymyxin B. We reviewed our recent experience with this drug, with particular attention to its nephrotoxicity.

Saint Vincent's Hospital of Manhattan is a 556-bed tertiary-care urban community hospital serving southern Manhattan. Pharmacy records were reviewed to identify all of the adult patients who received polymyxin B parenterally between October 1999 and September 2000. We retrospectively reviewed all of the available charts and abstracted the following data: demographics, underlying diseases, site(s) of infection, causative organism(s), length of stay, polymyxin B dosage, dosing frequency and duration, other medications administered, serum creatinine, development of rash and neurological changes, and clinical and microbiologic outcomes.

At our institution, when standard susceptibility testing identified multiresistant gram-negative organisms, testing for susceptibility to polymyxin B and ampicillin-sulbactam was done. Susceptibility testing for polymyxin B was performed by the Kirby-Bauer method with BBL antibiotic-impregnated discs containing 300 IU of polymyxin B (BD Biosciences, Sparks, Md.). Interpretive criteria for zones of inhibition were as follows: susceptible, ≥12 mm; intermediate, 9 to 11 mm; resistant, ≤8 mm.

The main outcomes of interest were development of renal failure (RF), survival, and microbiologic clearance of the infecting organism(s).

RF was defined as a doubling of serum creatinine to a value

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TABLE 1. Demographic, clinical, and microbiologic characteristics of 60 patients receiving polymyxin B

Characteristic	Value[d]
Age (yr)	
Mean	61
Range	22–90
Males	39 (65)
Race or ethnicity	
White	37 (62)
Hispanic	10 (17)
Black	8 (13)
Asian	4 (7)
Other	1 (2)
Sites of infection	
Lung	39 (65)
Blood	5 (8)
Abdomen	3 (5)
Urine, bone	2 (3) each
Cerebrospinal fluid, JP[a] drain, pleural effusion	1 (2) each
Undetermined	7 (12)
Organisms	
A. baumannii	46 (77)
P. aeruginosa	2 (3)
A. baumannii + *P. aeruginosa*	2 (3)
None identified	10 (17)
Mechanical ventilation	57 (95)
Underlying diseases[b]	
Cardiac	30 (50)
Recent cardiac surgery	16 (27)
Cancer	14 (23)
Diabetes mellitus	11 (18)
AIDS	11 (18)
ESRD[c]	8 (13)
Pneumonia	8 (13)
Recent brain surgery	4 (7)
Cerebrovascular accident	3 (5)

[a] JP, Jackson Pratt.
[b] Total is greater than 100% because some patients had more than one underlying disease.
[c] ESRD, end-stage renal disease.
[d] Unless specified otherwise, the values shown are numbers (percentages) of patients.

of ≥2.0 mg/dl. Baseline serum creatinine was defined as the creatinine level on the day when the initial polymyxin B dose was administered. Creatinine levels, when available, were also recorded on the day of admission, 3 days prior to the start of polymyxin B therapy, and on days 3, 7, 10, 14, 18, 21, and 42 after initiation of polymyxin B therapy.

The association between RF and age was analyzed with the Wilcoxon rank sum test. The Fisher exact test was used to analyze the effect of the development of RF on the mortality rate.

Sixty-five patients were identified; charts were available for 60 of them. Table 1 describes the demographic, clinical, and microbiologic characteristics of these 60 patients. The cohort was composed primarily of older (mean age, 61 years), mechanically ventilated Caucasian men with multiple comorbid diseases. The lungs were the most common site of infection. *A. baumannii* was isolated from 48 patients, and *P. aeruginosa* was isolated from 4 patients.

All resistant isolates of *A. baumannii* and *P. aeruginosa* were susceptible to polymyxin B. Ninety-six percent of patients received 15,000 to 25,000 U (1.5 to 2.5 mg) of polymyxin B per kg/day; most patients (87%) received it in two divided doses. When the estimated creatinine clearance dropped below 50 ml/min, the polymyxin B dose was adjusted accordingly, i.e., 20 to 50 ml/min, 75% of the total daily dose; <20 ml/min, 33% of the total daily dose. Table 2 details the antimicrobial treatments given to the 60 patients. The mean total daily dose of polymyxin B was 1.1×10^6 U, the mean duration of polymyxin B treatment was 13.5 days, and the mean total dose was 14.1×10^6 U. The mean number of days between admission and initiation of polymyxin B therapy was 27, (range, 4 to 98). In addition to polymyxin B, all of the patients received other antimicrobials. When active in vitro, aminoglycosides and/or ampicillin-sulbactam were often used. All of the patients received other potentially nephrotoxic agents during the course of polymyxin B therapy, such as other antimicrobials (see Table 2), diuretics, antiarrythmics, nonsteroidal anti-inflammatory drugs, and colchicine. Of the seven patients who developed RF, four (57%) received amikacin, four (57%) received vancomycin, and two (29%) received both antibiotics. These proportions did not differ from the group that did not develop RF.

Figure 1 demonstrates patient outcomes with respect to the development of RF stratified by baseline serum creatinine levels. Of the 41 evaluable patients with baseline serum creatinine levels of <2.0 mg/dl, 7 (17%) met our criteria for RF. None of the nine evaluable patients whose baseline creatinine was ≥2.0 mg/dl developed RF.

Overall, 7 (14%) of the 50 patients evaluable for nephrotox-

TABLE 2. Antimicrobial treatment

Treatment	Value[a]
Total daily dose of polymyxin B (10^6 U)	
Mean	1.1
Range	0.12–2.25
Duration of polymyxin B treatment (days)	
Mean	13.5
Range	1–56
Total cumulative dose (10^6 U)	
Mean	14.1
Range	0.24–56
Additional antimicrobials[b]	
Vancomycin	42 (70)
Ampicillin-sulbactam	31 (52)
Imipenem	31 (52)
Aminoglycosides	28 (47)
Metronidazole	27 (45)
Cephalosporins	18 (30)
Fluoroquinolones	15 (25)
Trimethoprim-sulfamethoxazole	13 (22)
Other extended-spectrum penicillins	9 (15)
Macrolides, tetracyclines, chloramphenicol, rifampin, linezolid, aztreonam, clindamycin, amphotericin B, pentamidine, acyclovir	<5 (8) each

[a] Unless otherwise specified, the values shown are numbers (percentages) of patients.
[b] The total is >100% because most patients received more than one antimicrobial.

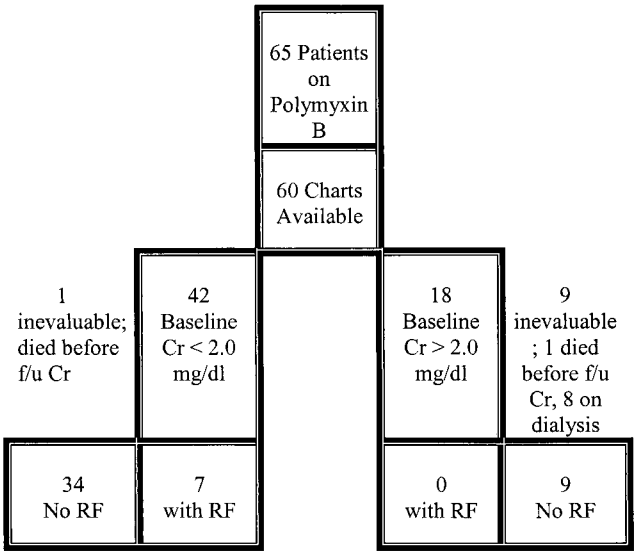

FIG. 1. Renal outcome stratified by baseline serum creatinine (Cr). f/u, follow-up.

icity developed RF, all by day 14. One patient developed RF by day 3, three patients did so by day 7, two did so by day 10, and one did so by day 14. These seven patients had a mean age of 76 years, compared to the mean age of 59 years of those who did not develop RF ($P = 0.02$). Their mean daily dosage of polymyxin B was 1.3×10^6 U (range, 1×10^6 to 1.5×10^6 U), compared to the 1.1×10^6 U (range, 0.12×10^6 to 2.25×10^6 U) of those who did not develop RF. The mean number of days of polymyxin B treatment was 10.4 (range, 3 to 28), compared to 14.0 (range, 1 to 56). The mean total cumulative dose was 13.8×10^6 U (range, 4.5×10^6 to 42×10^6 U), in comparison to 14.1×10^6 U (range, 0.24×10^6 to 56×10^6 U). The mean change in creatinine from the baseline to day 10 was +1.2 mg/dl for those patients who developed RF (all with baseline creatinine levels of <2.0 mg/dl), −0.1 mg/dl for those patients with baseline creatinine levels of <2.0 mg/dl and no RF, and −0.9 mg/dl for patients with baseline creatinine levels of ≥2.0 mg/dl and no RF.

The mortality rate of the entire group was 20% (12 of 60). The mortality rate of those who developed RF was 57% (4 of 7), compared with the 15% mortality rate (8 of 53) of the patients who did not develop RF ($P < 0.02$). Three patients who developed RF survived; two had a return of normal renal function, and one continued to require dialysis.

Repeat microbiologic specimens were obtained from 41 (82%) of the 50 patients infected with multiresistant *Acinetobacter* or *Pseudomonas* bacteria; 36 (88%) of the 41 cleared the organism, and in 5 (12%), the organism persisted but sensitivity testing revealed that they remained susceptible to polymyxin B. The 36 patients who cleared the organism all received polymyxin B. Eleven patients received this as the only active antimicrobial agent, 9 patients also received an aminoglycoside and ampicillin-sulbactam, 10 received ampicillin-sulbactam, and 6 received an aminoglycoside. Four of the five patients in whom the organism persisted had a pulmonary source of infection.

Many reports in the past decade have described nosocomial infections and outbreaks due to multiresistant gram-negative organisms (1, 5, 11, 12, 17). Especially challenging in terms of treatment have been multiresistant *Pseudomonas* and *Acinetobacter* infections. With increasing antibiotic resistance of gram-negative organisms and few new available effective agents, there has been renewed interest in older antimicrobials, such as polymyxin B, an agent many of us had never administered systemically until recently. These multiresistant gram-negative nosocomial organisms have usually maintained susceptibility to polymyxin B (2, 10).

Multiresistant *A. baumannii* has become the most frequent gram-negative nosocomial pathogen at our institution. Nearly 80% of these isolates are resistant to all of the routinely tested antimicrobials, with the exception of amikacin. All of the *A. baumannii* isolates tested have been susceptible to polymyxin B, and 90% were also susceptible to ampicillin-sulbactam because of the activity of sulbactam. In this cohort of patients, when ampicillin-sulbactam and/or amikacin were active, they were often added to polymyxin B therapy.

Polymyxin B was well tolerated by most of our patients; only 14% experienced nephrotoxicity. This rate is lower than what has been reported in the literature on adults, in whom nephrotoxicity rates ranged from 17 to 100% (7, 11, 14; O. Sued, G. R. Kelley, A. Nenna, C. Dillon, L. Abusamra, G. de la Iglesia, H. Perez, and P. Cahn, 39th Annu. Meet. Infect. Dis. Soc. Am., abstr. 105, 2001). In the cystic fibrosis literature, rates of nephrotoxicity as low as 0 to 5% have been reported (3, 10, 15).

Some studies have associated nephrotoxicity of the polymyxins with baseline renal insufficiency (12, 18). In contrast, we observed nephrotoxicity only in those patients with normal baseline renal function. Similarly, Koch-Weser et al. found that renal toxicity was not associated with baseline renal function as long as appropriate doses were administered (7). Large single and/or cumulative polymyxin doses have been associated with nephrotoxicity (7, 14, 18). In our study, older age was the only predictor of the risk of RF. Daily and total cumulative doses of polymyxin B, the baseline creatinine level, gender, race or ethnicity, and underlying illnesses present were not significantly associated with the development of RF.

Since numerous other potentially nephrotoxic drugs and antimicrobials were used simultaneously in this cohort, it was impossible to implicate polymyxin as the sole or principal agent causing nephrotoxicity. Hence, the 14% nephrotoxicity rate we observed is likely an overestimate of the true rate of polymyxin-related renal impairment.

In this study of almost exclusively mechanically ventilated patients, mortality was only 20%, and 88% of those from whom repeat specimens were obtained cleared the offending organism. Levin et al., in their study, also of 60 patients, had a mortality of 37% but a comparable microbial clearance of 93% (11). Sued et al., in their study of 23 intensive care unit patients, observed a 30% mortality rate (Sued et al., 39th Annu. Meet. Infect. Dis. Soc. Am.).

In our cohort of severely ill patients infected with multiresistant *A. baumannii* and/or *P. aeruginosa*, polymyxin B therapy proved efficacious both clinically and microbiologically, with less nephrotoxicity than previously described. When confronted with infections caused by multiresistant gram-negative bac-

teria where therapeutic options may be limited, treatment with appropriate doses of polymyxin B should be strongly considered.

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