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Original Article

Predictors of polymyxin B treatment failure in Gram-negative healthcare-associated infections among critically ill patients

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Treatment failure;
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Cefoperazone/sulbactam

Abstract *Background:* With increasing prevalence and spread of multidrug resistant Gram-negative infections, parenteral polymyxins resurged in clinical practice. The primary aim of the study was to determine the predictors of treatment failure and in-hospital mortality among critically ill patients treated with polymyxin B.
Methods: Demographic data, underlying diseases, procedures and details on polymyxin B therapy were retrospectively analyzed in a cohort of 84 patients who received intravenous polymyxin B in an intensive care unit from 2010 to 2014.
Results: Polymyxin B was used to treat bacteremia (46.4% of cases) and pneumonia (53.6%). Majority of the pathogens isolated were *Acinetobacter* spp. (96.4%). The mortality rate was 48.8%, of which 82.9% was attributed to polymyxin B treatment failure. The independent predictors of treatment failure were low doses of polymyxin B ($p = 0.002$), shorter duration of therapy ($p = 0.009$), not combining with cefoperazone/sulbactam ($p = 0.030$), female gender ($p = 0.004$), administered for treatment of bacteremia ($p = 0.023$) and renal impairment ($p = 0.021$). Low polymyxin B doses ($p = 0.007$), not combining with cefoperazone/sulbactam ($p = 0.024$), female gender ($p = 0.048$) and renal impairment ($p = 0.022$) were also significant predictors for in-hospital mortality.

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Conclusions: To the best of our knowledge, this is the first report on the association of inadequate dose of polymyxin B (<15,000 units/kg/day) with poor outcome in critically ill patients. Besides that, further clinical studies are warranted to evaluate the use of cefoperazone/sulbactam as second antibiotic in the combination therapy.

Introduction

The emergence and worldwide dissemination of drug-resistance in Gram-negative pathogens has progressed into a serious health concern.[1] At the same time the development of chemical entities as antibiotics against multidrug-resistant (MDR) Gram-negative infections are limited.[2–4] Several analogues against Gram-negative pathogens have been launched since 2000,[3] but not typically designed against carbapenem-resistant pathogens. As a result, clinicians have been forced to use 'old' polymyxins, which retain excellent activities against many MDR Gram-negative pathogens.[5]

Polymyxins are lipopeptide antibiotics used to treat infections caused by multidrug-resistant (MDR) Gram-negative pathogens such as *Acinetobacter baumannii*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.[4,6,7] Discovered in the 1950s, the polymyxins have never been subjected to contemporary regulation requirements before clinical use.[4,6,8] The use of intravenous (IV) polymyxins waned in the 1970s due to significant toxicity report and availability of 'safer' aminoglycosides.[6,7] However, the global spread of nosocomial infections caused by Gram-negative bacteria that were resistant to almost all other antibiotics has necessitated their resurgence into clinical practice.[4,7]

Two types of polymyxins are commercially available as parenteral preparation: polymyxin B and polymyxin E (colistin).[4,6,8] The intravenous (IV) preparation of colistin is more widely used than polymyxin B due to limitations in availability of polymyxin B sulfate in many countries.[4,8] Recent pharmacokinetics (PK) data suggested that IV colistin formulation is inferior to parenteral polymyxin B because colistin is formulated as an inactive prodrug, colistin methanesulfonate (CMS). It is estimated only <20% of CMS is converted into active colistin form *in vivo*.[6,8] Polymyxin B on the other hand is formulated as sulfate salt i.e. its active antibacterial form.[8] The PK profile of polymyxin B is uncomplicated. After filtration by renal glomerulus, polymyxin B is subjected to extensive tubular reabsorption. Finally, polymyxin B is eliminated mainly by nonrenal system.[8]

Although IV polymyxin B has better PK records, the clinical data is scarce due to its limited availability in many countries.[8] We are among the few tertiary health centers in Malaysia that have access to both polymyxin B and CMS since 2009. The aim of the present study was to identify the predictors of treatment failure and in-hospital mortality in critically ill patients who were treated with IV polymyxin B. Among others, inadequate dose of polymyxin B was found to be an independent predictor of treatment failure/poor outcome. This study is also the first to document the use of cefoperazone/sulbactam as second antibiotic significantly associated with polymyxin B treatment success and patient survival.

Materials and methods

Settings and study design

This was a retrospective cohort study in an 800-bed academic tertiary care center, located at the North-eastern region of Peninsular Malaysia. The hospital has a 12-bedded general intensive care unit (ICU) with average monthly admission of 50 new cases. Patients aged more than 16 years who received polymyxin B therapy for Gram negative bacterial infection for more than 48 h (h) were randomly included in the study. The therapy was initiated in ICU between 1st January 2010 and 31st December 2014. Only the first treatment course was included for analysis. Using two proportions formula based on previous study,[9] 95% confidence interval, 80% power and after considering 20% drop-out rate, the required sample was 48 for each group. The study was approved by Human Research Ethics Committee, Universiti Sains Malaysia (Ref. no: USM/JEPeM/14070255). Cases were identified and selected from drug order list. Patients' demographic data, underlying diseases, clinical condition, microbiology data and outcome were recorded in a designed proforma.

Definitions

Clinical sepsis was based on international consensus definition of sepsis.[10] The therapeutic outcome of the study was based on intensivist documentation of the patients' conditions after polymyxin B therapy. Treatment success was defined as the improvement of signs and symptoms of infection whereas, treatment failure as the persistence or deterioration in patients' conditions or death.[9] For more objective outcome, the predictors of in-hospital mortality were also assessed. The adequate doses of polymyxin B were considered when it was delivered intravenously at ≥15,000 unit/kg/day (~1.5 mg/kg/day) (Polymyxin B Sulfate Injection Drug Information, Samarth Life Sciences PVT. LTD. Mumbai, India). Polymyxin B and other antibiotics therapy should be administered for more than 48 h to be considered as treatment with those particular antibiotics. Creatinine clearance (CrCl) was estimated by Cockcroft-Gault Equation. Deterioration of renal function during

polymyxin B therapy was considered when a decrease in baseline CrCl of ≥50% or doubling of baseline serum creatinine (S_{Cr}) in patients with normal renal function or an increase of baseline S_{Cr} of ≥50% or decrease of CrCl of 20% in patients with abnormal baseline renal function.[9]

Statistical analyses

Data were analyzed using IBM SPSS Statistic, version 22 (IBM Corporation Armonk, United States). Numerical variables were presented with mean (SD) or median (interquartile range) for skewed data, whereas categorical variables were presented with n (%). Variables with *p* values of less than 0.25 in simple logistic regression were subjected to a stepwise (backward selection) multiple logistic regression analysis to identify predictors of treatment failure of polymyxin B therapy and in-hospital mortality. *p* value of less than 0.05 was denoted to be statistically significant.

Results

From a total of 164 courses of polymyxin B therapy during the study period, 96 courses were randomly selected for record review. Of those selected, 12 courses were excluded from analysis, i.e. six were second course of polymyxin B therapy and another six were treated with polymyxin B for 48 h or less (five patients died within 48 h of therapy and one patient had polymyxin B initiated as empirical therapy which was de-escalated upon the availability of antimicrobial susceptibility profile).

Demographic data

Out of 84 subjects eligible for the study, 59 (70.2%) were male, mean age was 52.2 ± 18.5 (standard deviations) years, weight was 64.4 ± 12.3 kg and acute physiology and chronic health evaluation (APACHE) II score were 28.0 ± 4.4. Intravenous polymyxin B was employed to treat bacteremia in 39 cases (46.4%) and pneumonia in 45 cases (53.6%). Among the bacteremia cases, 25 cases were secondary to pneumonia, 4 cases were secondary to surgical site infections and 10 cases were primary bacteremia. Majority of the isolated pathogens leading to polymyxin B treatment were *Acinetobacter* spp. (96.4%). At the time of sepsis, all patients were mechanically ventilated, and the arterial line, urinary bladder catheter, nasogastric tube and central venous line were *in situ*.

The mean dose of polymyxin B received by patients included in this study was 17,700 ± 4120 units/kg/day and the mean duration of therapy was 10.3 ± 3.17 days. In 67 (79.8%) patients, the doses were equal or more than 15,000 units/kg/day. Majority of the subjects (81.0%) received polymyxin B in combination with cefoperazone/sulbactam and/or carbapenems. Only four (4.8%) patients were treated with polymyxin B monotherapy. Six (7.1%) patients experienced renal deterioration while on polymyxin B therapy. No patient had discontinuation of polymyxin B therapy despite possibility of nephrotoxicity. However in one renal deteriorated patient, polymyxin B dosage was lowered from 20,000 units/kg/day to 15,700 units/kg/day. No patient with possible nephrotoxicity received other nephrotoxic antibiotics (e.g. vancomycin or aminoglycosides) at the same time. Besides deterioration of renal function, no other documented possible adverse effect of polymyxin B was observed. In this study, 43 (51.2%) patients were discharged alive from hospital whereas the other 48.8% were documented as in-hospital mortality. Seven patients (8.3%) recovered from sepsis but died due to other causes. The remaining 34 (40.5%) patients died directly due to infections for which polymyxin B therapy was administered.

Predictors of treatment failure and in-hospital mortality

Table 1 shows the predictors of polymyxin B treatment failure in critically ill patients. There were no interactions between these predictors. The significant associated factors of treatment failure in multiple logistic regression were inadequate doses of polymyxin B ($p = 0.002$, adjusted odds ratio [OR_{adj}] 0.04, 95% confidence interval [95% CI] 0.00, 0.29), shorter duration of therapy ($p = 0.009$, OR_{adj} 0.73, 95% CI 0.57, 0.92), not combined with cefoperazone/sulbactam ($p = 0.030$ OR_{adj} 0.22, 95% CI 0.06, 0.86), female gender ($p = 0.004$, OR_{adj} 0.11, 95% CI 0.02, 0.49), treated for bacteremia ($p = 0.023$, OR_{adj} 4.66 95% CI 1.24, 17.52) and more severe renal impairment (CrCl 20—50 mL/min) ($p = 0.021$, OR_{adj} 5.84 95% CI 1.31, 26.01). There were no interactions between these associated factors. The same variables were analyzed in relation to in-hospital mortality. The significant predictors of in-hospital mortality among patients treated with polymyxin B in ICU are shown in Table 2. They were low polymyxin B doses ($p = 0.007$ OR_{adj} 0.098 95% CI 0.02, 0.52), not combining with cefoperazone/sulbactam ($p = 0.024$ ORadj 0.283 95% CI 0.094, 0.849), female gender ($p = 0.048$ OR_{adj} 0.30, 95% CI 0.09, 0.99) and renal impairment ($p = 0.022$ OR_{adj} 4.01 95% CI 1.23, 13.14).

Discussion

Treatment of healthcare associated Gram-negative infections has become a serious challenge in modern medical practice. With the emergence of MDR pathogens that showed resistance to almost all antibiotics except polymyxin B and colistin, these antibiotics resurfaced into clinical use after a period of withdrawal. Although the PK data indicated that polymyxin B has simpler clearance pathway than colistin,[8] the evidence-based data from clinical experience are scarce as a result from its limited availability to certain countries. In the present study we explored the associated factors of treatment failure after polymyxin B therapy in critically ill patients.

The clinical conditions of this cohort were homogenous as indicated by low variability in APACHE II score, and all patients were mechanically ventilated and had similar accessories *in situ*. Three variables of polymyxin B therapy were found to be independently associated with treatment failure, i.e. inadequate doses, shorter treatment course and not in combination with cefoperazone/sulbactam. Other significant predictors of treatment failure were female, renal impairment and bacteremia. Except for shorter

Table 1 Comparison between predictors and clinical outcomes of patients treated with polymyxin B using simple and multiple logistic regression analyses (n = 84).

Variables	No. (%) or mean (SD)		p value[†]	Adjusted[‡]	
	Treatment success (n = 50)	Treatment failure (n = 34)		Odds ratio (95% CI)	p value
Demographic data					
Age (year)*	49.4 (19.5)	56.2 (16.3)	0.102		
Body weight (kg)*	65.0 (11.9)	63.4 (13.0)	0.548		
Male	39 (78.0)	20 (58.8)	0.062	0.11 (0.02, 0.49)	0.004
Patient admitted from					
- Emergency Department	14 (28.0)	7 (20.6)	0.888		
- Operation theaters	14 (28.0)	10 (29.4)	0.566		
- Other ICU/HDU	7 (14.0)	5 (14.7)	0.633		
- Other wards	15 (30.0)	12 (35.3)	0.436		
APACHE II score*	27.6 (4.72)	28.6 (3.73)	0.298		
Baseline creatinine clearance (mL/min)*	59.1 (34.4)	43.2 (30.4)	0.039		
Days of ventilation before need polymyxin B therapy*	16.0 (14.0)	14.9 (10.9)	0.718		
Type of infection					
- Bacteremia	18 (36.0)[a]	21 (61.8)[b]	0.022	4.66 (1.24, 17.52)	0.023
- Pneumonia	32 (64.0)	13 (38.2)			
Organism isolated					
- Acinetobacter spp.	45 (90.0)	29 (85.3)			
- Mixed Acinetobacter infection or other organisms	5 (10.0)[c]	5 (14.7)[d]	0.516		
Underlying diseases					
Hypertension	20 (40.0)	17 (50.0)	0.366		
Diabetes Mellitus	17 (34.0)	15 (44.1)	0.350		
Renal impairment					
- CrCl > 50 mL/min	29 (58.0)	10 (29.4)	0.034	1.00	0.018
- CrCl 20—50 mL/min	15 (30.0)[e]	19 (55.9)[f]	0.010	5.84 (1.31, 26.01)	0.021
- CrCl < 20 mL/min	6 (12.0)[f]	5 (14.7)[e]	0.213	0.30 (0.03, 2.80)	0.288
Ischemic heart diseases	9 (18.0)	8 (23.5)	0.537		
Chronic obstructive airway diseases	5 (10.0)	4 (11.8)	0.798		
Cerebral vascular diseases	5 (10.0)	2 (5.9)	0.507		
Malignancy	2 (4.0)	2 (5.9)	0.693		
Procedures					
Planned surgery	4 (8.0)	3 (8.8)	0.893		
Unscheduled/emergency surgery	29 (58.0)	18 (52.9)	0.647		
Chest drains	7 (14.0)	5 (14.7)	0.928		
Tracheostomy	24 (48.0)	9 (26.5)	0.050		
Parenteral nutrition	18 (36.0)	11 (32.9)	0.730		
Polymyxin B therapy					
Day of polymyxin B initiation after sepsis*	3.82 (2.09)	4.29 (1.91)	0.312		
Delay therapy >72H of sepsis symptoms	23 (46.0)	12 (35.3)	0.330		
Duration of therapy (days)*	11.4 (2.87)	8.74 (2.96)	0.001	0.73 (0.57, 0.92)	0.009
Dose of polymyxin B (units/day)*	5.91 (1.35) $\times 10^5$	5.19 (1.43) $\times 10^5$	0.026		
Dose of polymyxin B adjusted to body weight (units/kg/day)*	18,300 (3300)	16,800 (5010)	0.097		
Adequate dose (≥15,000 units/kg/day)	46 (92.0)	21 (61.8)	0.002	0.04 (0.00, 0.29)	0.002

Table 1 (*continued*)

Variables	No. (%) or mean (SD)		*p* value†	Adjusted‡	
	Treatment success (n = 50)	Treatment failure (n = 34)		Odds ratio (95% CI)	*p* value
Polymyxin B regimen#					
- Combination with cefoperazone/sulbactam	37 (74.0)	17 (50.0)	0.026	0.22 (0.06, 0.86)	0.030
- Combination with carbapenems	11 (22.0)	8 (23.5)	0.869		
- Other antibiotics combination	17 (34.0)[g]	24 (70.6)[h]	0.001		
- Monotherapy	1 (2.0)	3 (8.8)	0.211		
Deterioration of renal functions while on treatment	1 (2.0)	5 (14.7)	0.057		

[a] Primary bacteremia (3 cases), secondary to pneumonia (14 cases) and secondary to surgical site infection (1case).
[b] Primary bacteremia (7 cases), secondary to pneumonia (11 cases) and secondary to surgical site infection (3 case).
[c] Mixed *Acinetobacter* sp. and *K. pneumoniae* (3 cases), mixed *Acinetobacter* sp. and *P. aeruginosa* (1 case) and mixed *Acinetobacter* sp. and other organism (1 case).
[d] *K. pneumoniae* (2 cases), *P. aeruginosa* (1 case), mixed *Acinetobacter* sp. and *K. pneumoniae* (1 case) and mixed *Acinetobacter* sp. and other organism (1 case).
[e] Three cases admitted to ICU with renal replacement therapy.
[f] Five cases admitted to ICU with renal replacement therapy.
[g] Cloxacillin (3), linezolid (2), teicoplanin (1), sulfamethoxazole/trimethoprim (2), ciprofloxacin (2), ampicillin/sulbactam (2), tigecycline (1), vancomycin (1), penicillin (1), metronidazole (1) and ceftriaxone (1).
[h] Vancomycin (4), ampicillin/sulbactam (4), teicoplanin (3), cloxacillin (2), linezolid (2), penicillin (2), ceftazidime (2), piperacillin/tazobactam (2), sulfamethoxazole/trimethoprim (1), ciprofloxacin (1), metronidazole (1), rifampicin (1), cefoperazone (1), erythromycin (1), azithromycin (1). The total cases were not necessarily similar to the table because some patients were treated with >1 antibiotics.
†Simple logistic regression analysis.
‡Multiple logistic regression analysis. Age, gender, baseline creatinine clearance, type of infection, renal impairment, tracheostomy, duration of polymyxin B therapy, dose of polymyxin B, dose of polymyxin B scaled to body weight, adequate doses, combination with sulperazones, other antibiotic combinations, monotherapy and deterioration of renal functions were entered to multiple logistic regression models. No interaction and multicollinearity found.
*Mean (SD).
#Some patients might be treated with >1 antibiotics other than polymyxin B.

treatment course and bacteremia, these factors were consistent with the predictors of in-hospital mortality.

To the best of our knowledge, this is the first report which revealed inadequate dose of polymyxin B as an independent predictor of treatment failure (and in-hospital mortality) in critically ill patients. In previous study on the use of polymyxin B in ICU, Rigatto et al. did not find any association between dose and outcome in a low variability of polymyxin B doses (~2–3 mg/kg/day) cohort.[11] To some extent, our finding was in agreement with other studies on overall hospital populations.[12,13] These studies indicated the low dose of polymyxin B (<1.3 mg/kg/day[12] and <200 mg/day[13]) was associated with patients' mortality. In the present study, our cut-off value for inadequate polymyxin B dose was 15,000 units/kg/day (~1.5 mg/kg/day) as it was the lowest dose suggested by the drug manufacturer for patients with normal renal function (Polymyxin B Sulfate Injection Drug Information). This is in line with recent PK/PD data that recommended polymyxin dose of 15,000–25,000 unit/kg/day are appropriate for infection with pathogens of ≤1 μg/mL polymyxin B MIC.[14]

In addition to focusing on the polymyxin B dose in ICU patients, another key difference of the current study from the previous ones was the use of cefoperazone/sulbactam as second antibiotic in majority of patients (64.3%). The β lactams–sulbactam combination antibiotics have been suggested for the MDR *Acinetobacter* infections (96.4% of cases in this study) because sulbactam has been demonstrated to exhibit intrinsic bactericidal properties against some Gram-negative bacteria.[15] Although polymyxin combination therapy against Gram-negative infections resulted in a favorable outcome in many clinical studies,[11,16,17] combination with cefoperazone/sulbactam has not been investigated before. As mentioned earlier, the combination of polymyxin B and cefoperazone/sulbactam in this study significantly associated with good clinical outcome. We would like to propose further evaluation on this combination against MDR *Acinetobacter* infections in animal models and randomized clinical trial.

Previous study has indicated that baseline renal impairment was an independent risk factor of polymyxin B treatment failure.[9] In this study, we found baseline CrCl of 20–50 mL/min are one of the significant predictors for treatment failure and in-hospital mortality. We need to further evaluate this observation to find out either renal condition by itself or by renal dose adjustment associated

Table 2 The independent predictors of in-hospital mortality using multiple logistic regression analyses (n = 84).

Pridictors	No. (%) or Mean (SD)		*p* value[†]	Adjusted[‡]	
	Survived (n = 43)	Death (n = 41)		OR	*p* value
Male	33 (76.7)	26 (63.4)	0.185	0.300 (0.091, 0.991)	0.048
Renal impairment					
- CrCl > 50 mL/min	27 (62.8)	12 (29.3)	0.011	1.000	0.038
- CrCl 20—50 mL/min	12 (27.9)	22 (53.7)	0.005	4.009 (1.223, 13.136)	0.022
- CrCl <20 mL/min	4 (9.3)	7 (17.1)	0.056	0.752 (0.121, 4.666)	0.760
Adequate dose (≥15,000 units/kg/day)	40 (93.0)	27 (65.9)	0.002	0.098 (0.018, 0.523)	0.007
Combination of polymyxin B with cefoperazone/sulbactam	32 (74.4)	22 (53.7)	0.050	0.283 (0.094, 0.849)	0.024

[†]Analyzed by simple logistic regression.
[‡]Multiple logistic regression. Variables entered for multiple logistic regression analysis: age, gender, APACHE score, baseline creatinine clearance, type of infection, organism isolated, renal impairment, tracheostomy, delay therapy >72H of sepsis symptoms, duration of polymyxin B therapy, dose of polymyxin B, dose of polymyxin B adjusted to body weight, adequacy of polymyxin B dose, combination with cefoperazone/sulbactam, combination with other unconventional antibiotics, and deterioration of renal functions while on treatment. No interaction and multicollinearity found.

with polymyxin B treatment failure. The drug information sheet of polymyxin B used in our country suggests that 'the dose should be reduced from 15,000 unit/kg/day downwards for individual with kidney impairment' (Polymyxin B Sulfate Injection Drug Information). In addition, other manufacturer advised the adjustment of polymyxin B dose according to the estimated CrCl i.e., 20—50 mL/min:75%—100% of normal daily dose, 5—20 mL/min:50% of normal daily dose and <5 mL/min:15% of normal daily dose.[18] However, recent PK data indicated the lower doses of polymyxin B, included in patient with creatinine clearance dose adjustment, led to sub-therapeutic concentration of polymyxin B in plasma which later may result in treatment failure and development of resistance.[14]

Shorter duration of polymyxin B therapy and bacteremia were associated with treatment failure but not in-hospital mortality. In our hospital, the recommended duration of prescribing polymyxin B for both bacteremia and pneumonia is 10—14 days. Although bacterial clearance can be achieved with longer duration of polymyxin B therapy,[19] we need to balance with the possible increase risk of acute kidney injury.[20] A proper randomized controlled trial is required to define the optimum duration of therapy.

There are a few limitations of this study that should be admitted. The serum polymyxin B concentrations were not determined in this study. As a result, we were unable to explain the significant difference of the treatment outcome between male and female gender. This difference, which was independent from other variables, directed us to conduct PK investigation on our population to exclude gender differences in our population. This study also did not aim to investigate the microbiology outcome and instead used treatment outcome as the reference. However, the in-hospital mortality in our study appeared to correlate well with the clinical outcome.

In conclusion, this study found that inadequate doses of the therapy are an independent predictor of treatment failure and in-hospital mortality. When treating MDR Gram-negative infections, the dose of polymyxin B ≥ 15,000 unit/kg/day need to be maintained to avoid treatment failure, including patients with impaired renal functions. For the first time, we also noted that cefoperazone/sulbactam was an effective antibiotic to be used concomitantly with polymyxin B in settings with high prevalence of *A. baumannii* infections.

Conflicts of interest

All authors declare no conflicts of interest.

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