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Article

Inappropriate Doses of Intravenous Polymyxin B after Renal Adjustment Lead to Treatment Failure

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Sub-therapeutic doses, shorter duration of therapy, female gender, bacteremia, and renal impairment were among independent predictors of polymyxin B treatment failure. In this study, we found an association between inappropriate doses of polymyxin B (<15000 or >25000 unit/kg/day) and renal impairment. Inappropriate doses of polymyxin B were significantly associated with CrCl 20-50 mL/min ($p = 0.021$, OR_{adj} 6.660, 95% CI 1.326, 33.453) and CrCl <20 mL/min ($p = 0.001$, OR_{adj} 22.200, 95% CI 3.481, 141.592). By conducting sub-group analysis only using subjects with appropriate dosage, renal impairment was not associated with polymyxin B treatment failure, thus indicating that treatment failure was due to an inappropriate dose of polymyxin B, rather than renal impairment. In conclusion, renal impairment was not directly associated with treatment failure but was due to an inappropriate dosage of polymyxin B after renal adjustment.

Keywords: Polymyxin B. Sub-therapeutic dose. Renal impairment. Treatment failure.

INTRODUCTION

The usage of intravenous polymyxins has resurged recently in clinical practice due to the emergence and dissemination of carbapenem-resistant Gram-negative 'superbugs' globally (Deris 2015). However, the clinical data on its safety and efficacy, especially on polymyxin B, are still scarce due to limited availability of polymyxin B sulfate in most countries (Nation *et al*., 2014).

Similar to colistin, nephrotoxicity is the major adverse effect of polymyxin B (Nation *et al*., 2014). The incidence of acute kidney injury during polymyxin B therapy was documented to be as high as 60% (Kubin *et al*., 2012). Polymyxins are cytotoxic to renal tubular cells, where the accumulation of polymyxins in the renal tubular cells can lead to nephrotoxicity *in vivo* (Azad *et al*., 2013, Sandri *et al*., 2013a, Zavascki, Nation, 2017). Polymyxin B dose reduction in patients with renal function impairment is recommended based on older empirical studies (Samarth Drug Information, GlobalRPh). However, recent studies using modern pharmacokinetics methodologies have suggested that polymyxin B, unlike colistin, is not eliminated by the kidney and thus does not require dosage adjustment for renal dysfunction (Zavascki *et al*., 2008, Kwa *et al*., 2011, Sandri *et al*., 2013a). In fact, it has been reported that reduction of polymyxin B dosage based on creatinine clearance of the patient could lead to a lower concentration of polymyxin B in serum, resulting in treatment failure (Sandri *et al*., 2013a).

In our previous study on predictors of polymyxin B treatment failure in critical care settings, it was found that factors such as sub-therapeutic doses of polymyxin B, shorter duration of therapy, not combining with cefoperazone/sulbactam, female gender, treatment for bacteremia, and more severe renal impairment led to higher rate of treatment failure (Ismail *et al*., 2018). The aim of the present study is to identify the reasons behind

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inappropriate dosage of intravenous polymyxin B in this cohort that led to treatment failure. This is the first clinical report that suggested a link between treatment failure and inappropriate doses after renal adjustment.

MATERIAL AND METHODS

A total of 84 patients in the intensive care unit (ICU) were involved in this retrospective cohort study. The inclusion criteria were patients aged more than 16 years who received polymyxin B therapy in ICU for more than 48 hours (h) between 1st January 2010 and 31st December 2014. The cases were identified and randomly selected from the Microbiology Laboratory database (WHO-net 5.2 database system) and Pharmacy Unit based on the non-standard items order list form. The study was approved by the Human Research Ethics Committee (Ref. no: USM/JEPem/14070255).

The appropriate doses of polymyxin B were considered as when the medication was delivered intravenously at 15000-25000 unit/kg/day (~1.5-2.5 mg/kg/day) (Samarth Drug Information). Creatinine clearance (CrCL) was estimated by Cockcroft-Gault Equation. Other operational definitions were similar to our previous study (Ismail *et al.* 2018).

The association between inappropriate polymyxin B doses with the possible reasons was analyzed using IBM SPSS Statistic, version 22 (IBM Corporation Armonk, United States). Numerical variables were presented as mean (SD) or median (interquartile range), whereas categorical variables were presented as 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 factors associated with treatment failure of polymyxin B therapy. A *p* value of less than 0.05 was denoted to be statistically significant. The possible associated factors of inappropriate doses such as age, weight, gender, type of infections, the severity of renal insufficiency, and deterioration of renal functions were included for analysis. The renal insufficiency was analyzed based on the levels of CrCL, i.e. > 50 mL/min, 20–50 mL/min, 5-20 mL/min and <5 mL/minute. These levels were categorized as such based on the manufacturer's advice on the doses of polymyxin B that should be adjusted according to these ranges of CrCL (GlobalRPh). In addition, a sub-group analysis of subjects on appropriate doses was performed to determine if the above-mentioned factors are still significant predictors of polymyxin B treatment failure.

RESULTS

We found a significant association between inappropriate polymyxin B doses and renal insufficiency at a CrCl of 20–50 mL/min (p=0.021, OR_{adj} 6.660, 95% CI 1.326, 33.453) and CrCl of <20 mL/min (p=0.001, OR_{adj} 22.200, 95% CI 3.481, 141.592) (Table I). Figure 1 shows the relationship between polymyxin B doses, CrCl, and clinical outcome of polymyxin B therapy. Seventeen cases were treated with polymyxin B <15000 units/kg/day and one case were treated with polymyxin B 30000 units/kg/day. Out of these 18 cases treated with an inappropriate dose of polymyxin B, only 4 cases recorded treatment success whereas the remaining 14 cases suffered from treatment failure. There was a significant difference between this sub-group and the 46 cases of treatment success and 20 cases of treatment failure in appropriate dose sub-group (p=0.0004).

Table II shows the simple logistic regression model to determine the predictors of treatment failure in appropriate doses sub-group (n = 66). The significant associated factors of treatment failure were female gender (p=0.025), bacteremia (p=0.039), short duration of therapy (p=0.003), not combining with cefoperazone/sulbactam (p=0.027), and combination with other antibiotics (p=0.004). The severity of renal function and baseline creatinine clearance were not significantly associated with treatment failure with p=0.118 and 0.137 respectively.

TABLE I – Potential associated factors for inappropriate polymyxin B dose (<15000 or >25000 units/kg/day) (n=84)

	Appropriate dose (n=66)	**Inappropriate Dose (n=18)**	**Single logistic regression**		**Multiple logistic regression†**	
Variables	**No (%) or Mean (SD)**	**No (%) or Mean (SD)**	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**
Age (Year)*	50.0 (18.9)	60.6 (14.1)	1.04 (1.00, 1.08)	0.041		
Body weight						
≥ 80kg	9 (13.4)	2 (11.8)	0.859	0.856		
< 80kg	58 (86.6)	15 (88.2)	(0.168, 4.403)			
Gender						
Male	46 (68.7)	13 (76.5)	1.48	0.531		
Female	21 (31.3)	4 (23.5)	(0.43, 5.09)			
Creatinine Clearance (mL/min)*	58.4 (33.8)	29.8 (21.1)	0.953 (0.925, 0.983)	0.002		
Renal impairment severity						
- CrCl ≥50 mL/min	37 (55.2)	2 (11.8)	1.00	0.005	1.00	0.005
- CrCl 20-50 mL/min	25 (37.3)	9 (52.9)	6.660 (1.326, 33.453)	0.021	6.660 (1.326, 33.453)	0.021
- CrCl <20 mL/min	5 (7.5)	6 (35.3)	22.200 (3.481, 141.592)	0.001	22.200 (3.481, 141.592)	0.001
Type of infection						
- Bacteremia	31(46.3)	8 (47,1)	1.032	0.953		
- Pneumonia	36 (53.7)	9 (52.9)	(0.355, 2.999)			
Organism						
- Acinetobacter	59 (88.1)	15 (88.2)	1.017	0.984		
- Mixed Acinetobacter or other organism	8 (11.9)	2 (11.8)	(0.195, 5.295)			

† Age and renal impairment severity were entered to multiple logistic regression models
* Mean (SD)

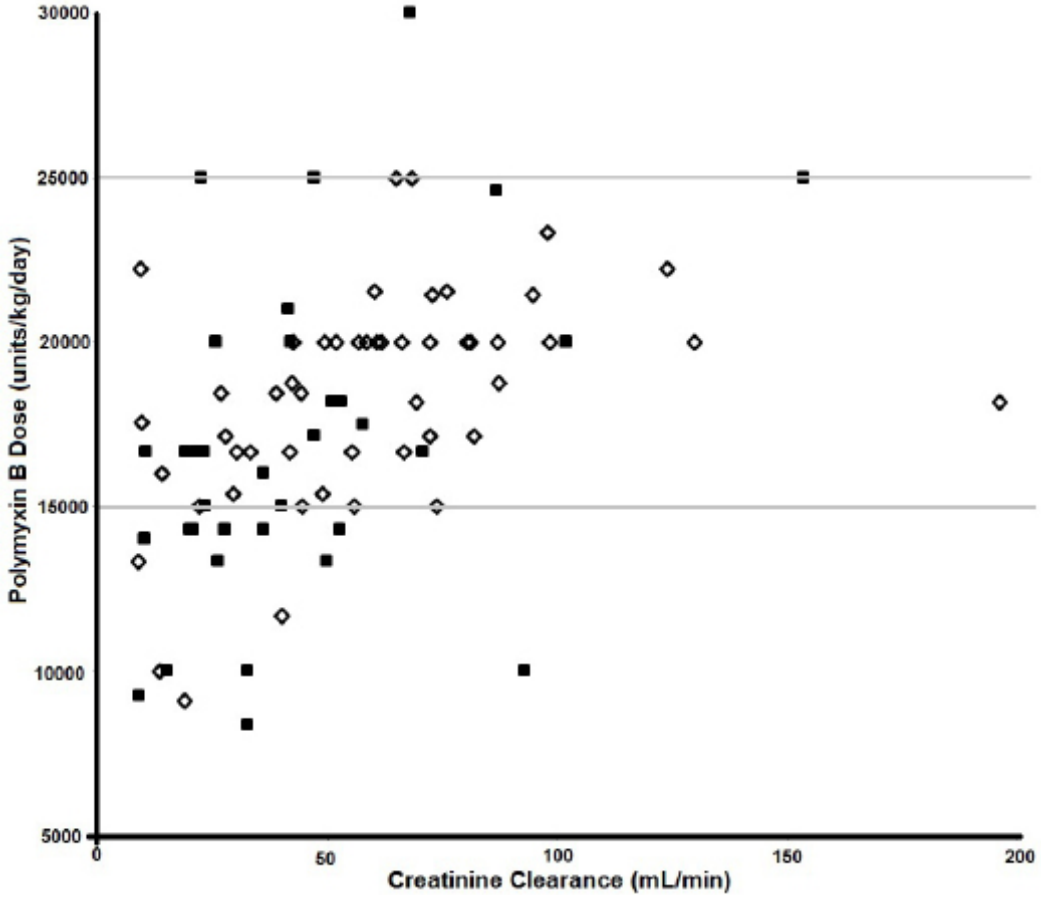

FIGURE 1 –

TABLE II – Subgroup analysis of patients treated with appropriate dose of IV polymyxin B (n=66) comparing between predictors and clinical outcomes using simple logistic regression analysis

Variables	Treatment Success (n=46)	Treatment Failure (n=20)	Single logistic regression *p* value
	No (%) or Mean (SD)	No (%) or Mean (SD)	
Demographic data			
Age (year)*	48.4 (19.6)	53.8 (17.8)	0.291
Body Weight (kg)*	64.8 (12.2)	61.3 (11.2)	0.261
Gender			
Male	36 (78.3)	10 (50.0)	0.025
Female	10 (21.7)	10 (50.0)	

(continuing)

TABLE II – Subgroup analysis of patients treated with appropriate dose of IV polymyxin B (n=66) comparing between predictors and clinical outcomes using simple logistic regression analysis

Variables	Treatment Success (n=46)	Treatment Failure (n=20)	Single logistic regression *p* value
	No (%) or Mean (SD)	No (%) or Mean (SD)	
Patient admitted from - Emergency Department - Operation theaters - Other ICU/HDU - Other wards	11 (23.9) 13 (23.8) 7 (15.2) 15 (32.6)	1 (5.0) 7 (35.0) 2 (10.0) 10 (50.0)	0.300 0.384 0.346 0.495
APACHE II Score*	27.2 (4.2)	28.5 (3.3)	0.205
Baseline creatinine clearance (mL/min)*	62.4 (33.6)	48.7 (33.8)	0.137
Days of ventilation before need polymyxin B therapy*	14.7 (11.2)	13.9 (11.4)	0.771
Type of infection - Bacteremia - Pneumonia	17 (37.0) 29 (63.0)	13 (65.0) 7 (35.0)	0.039
Organism isolated *Acinetobacter* spp. Mixed *Acinetobacter* infection or other organisms	42 (91.3) 4 (9.7)	17 (85.0) 3 (15.0)	0.450
Underlying diseases			
Hypertension	19 (41.3)	10 (50.0)	0.514
Diabetes Mellitus	16 (38.8)	9 (45.0)	0.433
Renal impairment - CrCl ≥50 mL/min - CrCl 20-50 mL/min - CrCl <20 mL/min	29 (63.0) 14 (30.4) 3 (6.5)	7 (35.0) 11 (55.0) 2 (10.0)	0.118 0.312 0.869
Ischemic heart diseases	8 (17.4)	5 (25.0)	0.477
Chronic obstructive airway diseases	4 (8.7)	1 (5.0)	0.607
Cerebral vascular diseases	5 (10.9)	0 (0.0)	0.999
Malignancy	2 (4.3)	2 (10.0)	0.389

(continuing)

TABLE II – Subgroup analysis of patients treated with appropriate dose of IV polymyxin B (n=66) comparing between predictors and clinical outcomes using simple logistic regression analysis

Variables	Treatment Success (n=46)	Treatment Failure (n=20)	Single logistic regression *p* value
	No (%) or Mean (SD)	No (%) or Mean (SD)	
Procedures			
Planned surgery	4 (8.7)	2 (10.0)	0.866
Unscheduled/emergency surgery	25 (54.3)	11 (55.0)	0.961
Chest drains	6 (13.0)	3 (15.0)	0.832
Tracheostomy	21 (45.7)	6 (30.0)	0.238
Parenteral nutrition	16 (34.8)	9 (45.0)	0.433
Polymyxin B therapy			
Day of polymyxin B initiation after sepsis*	3.83 (2.17)	4.80 (2.28)	0.146
Delay therapy >72H of sepsis symptoms	22 (47.8)	5 (25.0)	0.089
Duration of therapy (days)*	11.4 (2.9)	8.6 (3.0)	0.003
Polymyxin B regimen[#] - Combination with cefoperazone/sulbactam - Combination with carbapenems - Other antibiotics combination - Monotherapy	34 (73.9) 10 (21.7) 14 (30.4) 1 (2.2)	9 (45.0) 4 (20.0) 14 (70.0) 1 (5.0)	0.027 0.874 0.004 0.549
Deterioration of renal functions while on treatment	1 (2.2)	2 (10.0)	0.200

* Mean (SD)
[#] Some patients might be treated with >1 antibiotics other than polymyxin B

DISCUSSION

In the previous study, sub-therapeutic polymyxin B dose and higher severity of renal insufficiency were among the independent predictors of clinical failure during intravenous polymyxin B therapy (Ismail *et al.*, 2018). Our current study was designed to explore the reason for inappropriate polymyxin dose that led to treatment failure. The inappropriate doses of polymyxin B were significantly associated with the severity of renal impairment. In addition, after removing the subjects with inappropriate doses of polymyxin B (Table II), we found that the severity of the renal condition was not a significant predictor of the clinical outcome. By putting these findings together, it can

be concluded that the inappropriate doses of polymyxin B actually resulted from renal dosing adjustment that was required for patients with reduced CrCL, and this subsequently led to treatment failure.

Recent pharmacokinetic (PK) data indicated that polymyxin B was cleared by non-renal pathway (Zavascki *et al.*, 2008, Sandri *et al.*, 2013a, Sandri *et al.*, 2013b, Thamlikitkul *et al.*, 2017). However, the drug information pamphlet of polymyxin B suggests that 'the dose should be reduced from 15000 unit/kg/day downward for an individual with kidney impairment' (Samarth Drug Information). In fact, some manufacturers advice that the dose of polymyxin B should be adjusted according to the estimated CrCL i.e. 20–50 mL/min: 75% to 100% of normal daily dose, 5-20 mL/min: 50% of normal daily dose, and <5 mL/minute: 15% of normal daily dose (GlobalRPh). There was also published PK data to indicate that lower doses of intravenous polymyxin B, including in renal impairment patients, would result in a sub-therapeutic concentration of polymyxin B in plasma (Sandri *et al.*, 2013a). Therefore, the doses of polymyxin B should be titrated based on body weight (Sandri *et al.*, 2013a) and not be adjusted or reduced for renal impairment patients (Kwa *et al.*, 2011; Zavascki, 2011; Sandri *et al.*, 2013a; Thamlikitkul *et al.*, 2017) so as not to compromise its effectiveness. In this study, we outlined the evidence that lower dose of IV polymyxin B after renal adjustment in critically ill patients led to clinical failure of polymyxin B therapy.

In a similar study on risk factors for polymyxin B treatment failure, Dubrovskaya *et al.* found that baseline renal insufficiency was the only independent risk factor of treatment failure. However, their study was conducted in a centre which followed the protocol of dosage adjustment of polymyxin B according to creatinine clearance and they did not further determine the actual doses of polymyxin B delivered to the patients (Dubrovskaya *et al.*, 2013). Therefore, it is possible that the treatment failure in their study was due to lower polymyxin B dosing, which was indirectly shown by the baseline renal insufficiency.

In conclusion, this is the first published report based on clinical data that indicated the inappropriate dose of polymyxin B after renal dosing adjustment can lead to treatment failure. A low dose of polymyxin B in renal insufficient patients may be due to the wrong adherence to the manufacturers' advice or fluid restriction given to the patients. In line with this finding, we suggest the manufacturers of polymyxin B to amend or remove the advice on dose reduction in renal impairment patients in the drug information pamphlet to prevent unintended treatment failure.

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