A retrospective study of patients receiving polymyxin B intravenous treatment in PUMCH: real clinical practice

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Research

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Abstract

Background Polymyxin B once had to exit the market due to its toxicity. As antibacterial is widely used, the problem of drug-resistance, especially the gram-negative bacteria, has become a major threat to global health. Polymyxin B has reappeared as a last resort for the treatment of multidrug-resistant (MDR) and extensively drug-resistant (XDR) Gram-negative bacteria. With its return, the use of polymyxin B greatly increased over time in China. The aim of our study was to overview the actual clinical application of polymyxin B in patients with MDR and XDR Gram-negative bacteria in Peking Union Medical College Hospital (PUMCH), Moreover its usage characteristics were summarized in detail.

Methods: All the patients hospitalized in Perking Union Medical College of Hospital (PUMCH) from August 2018 (available in PUMCH) to December 2019 who received polymyxin B were enrolled in the study. Patients' basic information, previous medical history, antimicrobial susceptibility, the use of antimicrobials throughout the hospital stay, adverse reactions, and clinical outcomes were extracted and recorded for descriptive analysis.

Results: A total of 84 hospitalized patients received polymyxin B intravenous injection. Most of the patients had underlying conditions such as hypertension, diabetes or in the states of immunosuppression, who had already received other antibiotic therapy, particularly carbapenems, β-lactam/β-lactamase inhibitor and tigecycline, prior to receiving polymyxin B. About 73.81% of the patients had mixed infections, with pneumonia being the most common. The leading pathogens were Acinetobacter baumannii (73.81%) followed by Pseudomonas aeruginosa (28.57%) and Klebsiella pneumonia (20.23). The microbiological clearance of the targeted bacteria after therapy was 17.88%. Clinical amelioration at the last day of polymyxin B therapy was observed in 52.38% of cases, while mortality was observed in 32.14%. Nephrotoxicity and neurotoxicity were observed in 5 and 1 cases respectively.

Conclusion: Polymyxin B was used to fight against MDR and XDR Gram-negative bacterial infections under the conditions of previous treatment failure, changes of antimicrobial susceptibility, and drug intolerance in PUMCH. However, owing to lack of experience and widely recognized application criteria, the use of polymyxin B demanded more research to help achieve uniform standards and rules to guide the clinical application of polymyxin B, thus leading to better clinical outcomes.

Introduction

Patients that are infected by multidrug-resistant (MDR) or extensively drug resistant (XDR) Gram-negative pathogens are characterized of high morbidity rate and mortality rate [1]. However, most of the MDR or XDR Gram-negative bacteria remain susceptible to the traditional antibiotics polymyxin. Colistin (also named polymyxin E) and polymyxin B are the only two types of polymyxin that has been approved for clinical use in the 1950s, however their usage has declined due to their nephron- and neuro-toxicity concerns as well as the emergence of other alternatives [2–9]. With the sharply increase of MDR and XDR

Gram-negative infections and the challenges they bring, the use of polymyxin was reintroduced as a last resort.

Nevertheless, in view of the potential challenges brought by the emergence of polymyxin-resistant bacteria, polymyxin are classified as antibiotics in the “reserve group antibiotics” by World Health Organization (WHO). This group includes antibiotics and antibiotic classes that should be reserved for treatment of confirmed or suspected infections due to multi-drug-resistant organisms [10]. Also in China, polymyxin B, the only polymyxin available in clinic, is applied as the last defense against Gram-negative bacterial infection [11, 12]. For example, when the treatment with other alternative antibiotics are failed or inadequate, a temporary purchasing application will be submitted and passed after approval. Such strategies do contribute to avoid any of the empirical treatment, overtreatment, or improper treatment, and thus help to prevent polymyxin resistance. One the other hand, considering less experience of usage and the toxicity problems, a close monitoring of polymyxin B is also required. How to get the optimal use, such as timing, dose and frequency, determines the clinical outcomes.

In this study, we aimed to evaluate the application characteristics of polymyxin B in clinical practice retrospectively. By giving a study of its real principles and methods in use, the efficacy and safety of polymyxin B therapy in treatment of MDR or XDR Gram-negative infections was assessed. Moreover the rationality and future improvement measures were also discussed.

Methods

All patients prescribed with polymyxin B Sulphas for Injection (Shanghai Pharma No.1 Biochemical $ pharmaceutical CO., LTD.) from August 2018 to December 2019 in PUMCH were extracted.

This research was approved by the Ethical Committee of PUMCH for the review of patients’ medical profile. Then the medical records were fully reviewed and documented. Patients received polymyxin B for less than 72 hours were excluded.

Clinical outcomes were classified into four categories: microbiological clearance, treatment improved, treatment failure and death. A microbiological clearance was defined as the eradication of the targeted microbial. Treatment improved was defined as an amelioration of the clinical symptoms and signs caused by indicated infection. Treatment failure was defined as a continued deterioration of clinical conditions caused by indicated infection after three days of polymyxin B treatment. Death was defined as people died from any cause.

Causality assessment of adverse reactions (ADR) was done with standardized algorithm by two health professionals. Acute kidney injury (AKI) was evaluated according to the RIFLE criteria [13]. Neurological toxicity was determined by the information documented in the medical record, including the patients’ complaints and clinical examinations.

Results

A total of 84 patients were prescribed with polymyxin B for more than 72 hours in PUMCH during the study period. The baseline characteristics of these patients were showed in Table 1. The mean age of the patients was 57.20±18.49 years, among which 65.48% were males. The mean weight was 69.5 ± 17.79 kilograms. More than half of the patients had underlying health problems such as hypertension, diabetes and/or immune system diseases. All the patients had received other antibiotic treatment as shown the Table 1, with Carbapenems, Glycopeptides, and β-lactams/β-lactamase inhibitors antibiotics being the most common, during the hospitalization. Almost 95% of the patients were critically ill and received treatments in intensive care unit (ICU).

Table 1 Baseline characteristics of the patients received polymyxin B therapy in PUMCH

Characteristics	Patients
Age (years), mean ± SD	57.20±18.49
Sex, n (%)	84
Male	55(65.48%)
Female	29(34.52%)
Weigh (kg), mean ± SD	69.5 ± 17.79
Underlying conditions, n (%)	46(54.76%)
Hypertension	22(26.19%)
Diabetes	29(34.52%)
Immune system diseases	7(8.33%)
Previous exposure to antibacterial agents during hospitalization	
The third generation cephalosporins	30(35.71%)
β-lactams/β-lactamase inhibitors	53(63.10%)
Carbapenems	65(77.38%)
Tigecycline	50(59.52%)
Minocyline	11(13.10%)
Glycopeptides	59(70.24%)
Locations of hospitalization, n (%)	
Medicine ICU	19(22.62%)
Surgery ICU	41(48.81%)
Emergency ICU	16(19.05%)
Respiratory ICU	4(4.76%)
Medicine	2(2.38%)
Surgery	2(2.38%)

The clinical characteristics of these 84 patients were shown in Table 2. The length of hospital stays and the length of ICU stays were 34.85±30.79 days and 22.79±17.50 days respectively. The medication, with an average dose of 116.46±34.98 MU/day, were given at a fixed dosage but not according to the body weight. Moreover none of patients were received a loading dose. The average duration of polymyxin B treatment was 10.36±9.85 days. More than 90% of patients accepted mechanical ventilation, with tracheal intubation being the most common. The specimens submitted for bacteria culture mainly focused on sputum (79.76%), blood (70.24%), bronchoalveolar lavage fluid (BALF, 48.81%) and urine

(36.90%). Accordingly, the most common are the infections of the lung (84.52%), bloodstream (39.28%) and urinary tract (9.52%). Among the detected pathogens, Acinetobacter baumannii (73.81%) was the most common one, followed by staphylococcus bacteria (30.95%), Pseudomonas aeruginosa (28.57%), Klebsiella pneumonia (20.23%), and Stenotrophomonas maltophilia (19.05%). More than 70% of the patients had been infected by more than one type of pathogens. Tigecycline (44.05%) was the most commonly used concomitant antimicrobial agent, followed by Meropenem (35.71%), Cefoperazone-sulbactam (22.62%), Imipenem/Cilastatin (16.67%) and Minocycline (15.48%).

Table 2 Clinical characteristics of the 84 patients

Characteristics	Patients
Length of hospital stays (days), mean ± SD	34.85±30.79
Length of ICU (days), mean ± SD	22.79±17.50
Time of respirator (hours), mean ± SD	353.05±346.11
Polymyxin B dosage (MU/day), mean ± SD	116.46±34.98
Treatment duration (days), mean ± SD	10.36±9.85
Mechanical ventilations, n (%)	81(96.43%)
Tracheal intubation	60(71.43%)
Tracheotomy	21(25.00%)
Without mechanical ventilations	3(3.57%)
Samples, n (%)	
Blood	59(70.24%)
Sputum	67(79.76%)
Bronchoalveolar lavage fluid	41(48.81%)
Urine	31(36.90%)
Swab	18(21.43%)
Wound secretion/tissues	9(10.71%)
Incision secretion	8(9.52%)
Cerebral spinal fluid	4 (4.76%)
Others	15 (86.90%)
Type of infection, n (%)	
Pneumonia	71(84.52%)
Bacteremia	33(39.28%)
Urinary tract infection	8(9.52%)
Skin and soft tissue infection	7(8.33%)
Causative bacteria	
Acinetobacter baumannii	62(73.81%)
Klebsiella pneumonia KPC	9(10.71%)
Klebsiella pneumonia ESBL+	8(9.52%)
Pseudomonas aeruginosa	24(28.57%)
Stenotrophomonas maltophilia	16(19.05%)
Staphylococcus bacteria	26(30.95%)
Others	15(17.86%)
Single bacteria infection	22(26.19%)
Mixed bacteria infection	
Type of the pathogen=2	22(26.19%)
Type of the pathogen≥3	40(47.62%)
Concomitant antimicrobial agents, n (%)	
Tigecycline	37(44.05%)
Minocycline	13(15.48%)
Sulbactam	5(5.95%)
Meropenem	30(35.71%)
Cefoperazone-sulbactam	19(22.62%)
Ceftazidime	5(5.95%)
Imipenem and Cilastatin	14(16.67%)
Fluconazole	6(7.14%)

Teicoplanin	7(8.33%)
Daptomycin	4(4.76%)
Amikacin	12(14.28%)
Antifungal agents	18(21.43%)

The outcomes of the patients received intravenous polymyxin B were shown in Table 3. A microbiological clearance was seen in 17.88% of the patients at the end of treatment. An improvement of clinical symptoms and signs of infection occurred in 34.52% of the patients. The in-hospital mortality resulted from any cause was 32.14%. Polymyxin B related nephrotoxicity occurred in 5 (5.59%) patients. Only one (1.19%) patient complained of peripheral sensory neuropathy.

Table 3 Clinical outcomes following polymyxin B intravenous therapy

Clinical Outcomes, n (%)	Patients
Microbiological clearance	15(17.88%)
Treatment improved	29(34.52%)
Treatment failure	13(15.48%)
In-hospital mortality	27(32.14%)
Adverse reactions	6(7.14%)
Nephrotoxicity	5(5.95%)
Neurotoxicity	1(1.19%)

Discussion

Polymyxin has been used into clinical in the 1950s, but has been taken off the market attribute to its toxicity concerns. With the increasing severity of MDR and XDR strains of Pseudomonas aeruginosa, Acinetobacter baumannii, and Enterobacteriaceae [14], polymyxin as a salvage treatment has resurged. Although polymyxin was decades-old antibiotic, there still seem to have some confusions related to their proper use. A consensus therapeutic guidelines for their optimal use and dosing in adult patients were released [15].

Compared to the clear results of colistin [16–19], both the preclinical and clinical data were scarce for polymyxin B [19, 20–22]. However, given their similar molecular structures and in vitro activity [23, 24], to date a similar pharmacokinetics and pharmacodynamics (PK/PD) therapeutic target for colistin (AUCss,24 hr target of 50–100 mg. hour/L) was recommended for polymyxin B. But it was worth noting that a growing body of evidence indicated there were many differences between the two types of polymyxin, including formulations [25], toxicodynamic [26], and pharmacokinetic characteristics [27, 28]. Thus, any additional data, even observational study in the natural state, assessing polymyxin B application characteristic are urgently and meaningful.

Polymyxin B started being utilized with strict limitations since August, 2020 in our hospital. To limit the usage, we adopted a temporary procurement policy. The application for the use of the drug should be

submitted by the doctor and then checked by the pharmacist. From our results we could see polymyxin B was mainly used in critically ill patients. All of them had already exposed to other antibiotics, especially β-lactams/β-lactamase inhibitors, Carbapenems, Tigecycline, and Glycopeptides antibiotics. The reasons to resort to polymyxin B mainly lied in previous treatment failure, changes of antimicrobial susceptibility, and drug intolerance (eg. Tigecycline related decrease of erythrocyte, leucocyte and platelet systems). The patients received the treatment of polymyxin B mainly suffered from lung infection and/or bloodstream infection. About 68.86% (57/84) of patients were given with a fixed doses of polymyxin B (50 MU, bid) without a loading dose. First it's worth pointing out that it was recommended all patients should have administered with a loading dose [29], priority should be given to critically ill patients with severe pneumonia or sepsis. It was also recommended that both loading dose (20,000–25,000 IU/kg equivalent to 2.0–2.5 mg/kg over 1 hour) and maintenance dose (12,500–15,000 IU/kg TBW equivalent to 1.25–1.5 mg/kg every 12 hours) should be determined based on total body weight (TBW). A dose of 500,000 IU might led to the problem of inadequate exposure. Moreover, data from the rat model of pulmonary infection with intravenous administration of polymyxin B suggested that [22] even higher drug exposures might still fall short of the concentration required to killing bacteria in lower respiratory infections. Although some studies reported the use of high doses (> 30,000 IU/kg equivalent to 3 mg/kg) [30, 31], more research should be done to further investigate the safety and efficacy of high dose regimens in different clinical scenarios.

Considering even if the upper limit dosage was used, blood concentration of polymyxin B was still not likely to reach the effective level in special populations (eg. critically ill patients) and specific site infection (lower respiratory tract infections) [30]. The potential ADR concerns were also the main limitations for dosing [32–34]. To dissolve this problem, polymyxin B based combination regimen was recommended, which also could avoid the emergence of resistance induced by monotherapy [35–38]. Unfortunately, clinical studies aimed at assessing the effectiveness between the combination therapy and polymyxin B monotherapy was very controversial and not conclusive [39, 40]. For example, critically ill patients enrolled in the study often had complex preexisting comorbidities. These population themselves were prone to suffer from treatment failure and death, which were not associated with infection. These problem further challenged the interpretation of the all-cause mortality between the two groups. More clinical evidence no matter form randomized controlled trials (RCT) or the summary of experiences were need.

The potential risk of polymyxin B treatment was acute renal injury, which was the most common ADR (20%-60%)[41–43].In our study the nephrotoxicity was observed in only 5 cases (5.95%), which is much lower than the data reported in references. It was difficult for us to evaluate this ADR, for some of the patients had already undergone continuous renal replacement therapy. Anyway, to avoid the renal toxicity in clinical practice is very important. However, the data of exposure concentration and toxicity were still limited. The recommended maximal dose derived from a meta-analysis [44]

Therapeutic drug monitoring (TDM) could be used as an aid to clinical research as well as practical application, especially in the cases where higher doses were adopted. For the relationships between blood

concentration of colistin and its effectiveness [19] / nephrotoxicity [45–47] had been confirmed by sufficient evidence. The data also showed that the breakpoint was 2 mg/L for of colistin [25, 29, 48, 49]. However, the target concentration of polymyxin B had not been established. TDM with polymyxin B had not been carried out in our hospital, which might be the biggest disadvantages of our study. A TDM during polymyxin B treatment might help us to build a relationship between blood concentrations of polymyxin B and its clinical outcome.

Conclusion

It is crucial to maintain the service life of polymyxin B in fighting against resistant Gram-negative bacteria as long as possible. Except for clarifying the bacterium tolerance mechanism and exploitation of new antibiotics, reasonable usage and management of this ‘old drug’, as well as a strict protocol and policies for its best use in practical are also very important to prevent the emergence of resistance.

Polymyxin B should be applied with great caution in view of its toxicity concerns, concentration in the site of infection, and the combination of other antibiotics. A closely TDM, repeated physical examination and evaluation of the renal function throughout the whole process may help to optimal use of polymyxin B. However the application experience and clinical evidence about polymyxin B are still limited, more study are required to further clarify the PK/PD features, the feasibility of polytherapy, the dose adjustment, and its application in special clinical situations.

Abbreviations

ADR: adverse reactions ; BLAF: Bronchoalveolar lavage fluid; ESBL: Extended-spectrum β-lactamases; ICU: intensive care unit; MDR: Multidrug-resistant; PK/PD: pharmacokinetics and pharmacodynamics; PUMCH: Peking Union Medical College Hospital**;** WHO: World Health Organization; RCT: Randomized controlled trials; TDM: Therapeutic drug monitoring; XDR: Etensively drug-resistant

Declarations

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Availability of data and materials

All the date and material in this study were available.

Authors’ contributions

Bo Zhang and Wei Zuo contributed the idea to this study. Wei Zuo also contributed to the analysis of the data and the writing of the manuscript. Daihui Gao, Xiuli Xu and Yuhui Yang contributed to the reviwing of the medical records. Yan Zhang and Bin Wu contributed to the extract of the information of the drugs. Bo Zhang and Yang Yang contributed to the revision of the manuscript. All of the authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Peking Union Medical College Hospital (PUMCH) for the review of patients' medical profile.

Consent for publication

All the authors approve and agree the article to this publication.

Competing interests

The authors declare that they have no competing interests.

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