


Use of polymyxins for carbapenem-resistant infections in children and adolescents

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Background: Polymyxins are still used in children in some regions due to limited availability of newer antibiotics.

Objectives: To describe our experience in a cohort of children who received polymyxins for suspected or confirmed carbapenem-resistant bacterial infections (CRI), and explore potential factors associated with therapeutic success.

Methods: Retrospective, observational study in children and adolescents <18 years who received IV polymyxin B or colistin therapy for suspected or culture-documented CRI and were admitted to a high complexity clinic in Cali, Colombia between 1 September 2016 and 22 June 2020. Patients' demographic, clinical and microbiological characteristics were collected and analysed; associations with therapeutic success were explored using univariate and multivariate models.

Results: There were 40 episodes of polymyxin use (polymyxin B, $n=34$; colistin, $n=6$) in 34 patients with a median age of 10 years (IQR 7–15); 65% were male. There were 17 adverse events: 3 (17.6%) neurotoxic and 14 (82.4%) nephrotoxic. Therapeutic success was achieved in 28 episodes (70%), of which 32% (9/28) had adverse events. Therapeutic success decreased by 35% with each additional year of age (OR 0.65; 95% CI 0.49–0.80) and by 7% for every hour that elapsed between the onset of fever and the start of appropriate antibiotic therapy (OR 0.93; 95% CI 0.8–0.97) and increased with concomitant non-carbapenem treatment (OR 6.87; 95% CI 1.04–71.01) and the use of adequate empirical therapy (OR 121.36; 95% CI 2.90–1147.95).

Conclusions: Several factors were associated with the therapeutic success of polymyxins, however, more than half of episodes had therapeutic failure or adverse events. Antibiotics with greater efficacy and safety are needed in regions with high rates of CRI.

Introduction

Gram-negative infections resistant to carbapenems pose a public health and clinical challenge, especially in critically ill or immunosuppressed patients.¹ Although novel antibiotics such as ceftazidime/avibactam, a combination of a third-generation cephalosporin and a new synthetic β -lactamase inhibitor, may be used as a therapeutic option,^{1,2} widespread access to these novel antibiotics, especially in low- or middle-income countries, remains restricted due to limited availability and high costs.

Thus, clinical use of polymyxins (colistin [polymyxin E] and polymyxin B) play an important role as salvage therapy for otherwise untreatable Gram-negative infections resistant to carbapenems.³ However, therapeutic outcomes associated with polymyxin use in children are not fully understood, with studies limited to small retrospective case series following colistin treatment,^{4,5} without insights into factors associated with therapeutic success or failure. The lack of data in children on polymyxin's effectiveness, appropriate dosing regimens, and associated toxicities poses a challenge to paediatric infectious

disease specialists. We describe our experience in a cohort of children receiving polymyxins for suspected or confirmed carbapenem-resistant bacterial infections (CRI), and explore potential factors associated with therapeutic success.

Materials and methods

A retrospective, observational study was conducted in a cohort of children and adolescents aged up to 18 years admitted to any hospital ward at Clínica Imbanaco in Cali, Colombia, and who received therapy with IV polymyxins (polymyxin B or colistin) due to suspected or culture-documented CRI between 1 September 2016 and 22 June 2020. Clínica Imbanaco is a referral hospital where children with the most complex acute or chronic conditions receive care. During the study period, all inpatient blood and urine cultures with Gram-negative isolates were identified by VITEK® MS (bioMérieux, Marcy-l'Étoile, France). Susceptibility testing was performed according to the manufacturer's recommendations using AST271 for urine samples and AST272 for blood culture samples in the VITEK® 2XL system (bioMérieux).

Suspected CRI was reported for patients who had a previous infection with a carbapenem-resistant bacterium, were colonized with it and developed a hospital-acquired infection following more than 7 days of carbapenem exposure in the previous 6 weeks. Patients with suspected CRI had a systemic inflammatory response syndrome, negative cultures and other microbiological studies during the current episode, and a clinical focus of infection documented on physical examination (pneumonia, colitis, etc.) or without source (i.e. culture-negative sepsis).

Demographic, clinical, and microbiological characteristics of patients were collected and analysed. We described episodes where colistin or polymyxin B were administered for at least 72 h. For patients with recurrent infections, more than one treatment episode was considered, provided that the patient was asymptomatic for at least 15 days and their cultures became negative between treatment episodes.

Therapeutic success was defined as clearance of bacteraemia and/or resolution of signs and symptoms of the index infection without the need for additional antibiotics to treat the isolated microorganism 30 days after therapy. Empirical antibiotic therapy was considered appropriate if the isolate displayed *in vitro* susceptibility to any systemic antibiotic administered. In suspected infections (not culture-confirmed), empirical antibiotic therapy was considered appropriate when the antibiotic administered achieved therapeutic success. Safety was assessed through the evaluation of adverse events occurring during polymyxin use. The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury (AKI) was used to classify AKI.⁶ Neurotoxicity was defined as any neurological sign or symptom during polymyxin use without an alternative explanation. Definitions of hospital-acquired infections and of specific types of infections were according to criteria from CDC.⁷

Because of the small sample size, a Bayesian logistic regression model with weakly informative prior, using a normal distribution, was adjusted to identify the factors related to therapeutic success. A Hamiltonian Monte Carlo algorithm was used to simulate samples from the posterior distributions for the model parameters. Variables were selected based on their posterior predictive checks, according to Bayesian criteria using leave-one-out cross-validation (LOO) and the widely applicable information criterion (WAIC). Results were confirmed under the frequentist approach using a logistic regression model estimated by the maximum likelihood procedure. A backward elimination algorithm was performed to identify covariates associated independently with therapeutic success.

Associations with therapeutic success were explored using univariate and multivariate models, reporting ORs with respective 95% CI for logistic and Bayesian models. An association was considered statistically significant when a *P* value <0.05 was observed under the frequentist approach

and when the unit was not found within the credible interval (OR=1) under the Bayesian approach. The Bayesian model was carried out in R using the *rstanarm* package and the logistic model in Stata 16.0 (StataCorp, College Station, TX, USA). A sensitivity analysis, including only culture-confirmed CRI, was performed.

Results

There were 40 episodes of polymyxin use (34 with polymyxin B and 6 with colistin) in 34 patients with a median age of 10 years (IQR 7–15); 65% were male. The most frequent comorbidity was ALL (35.3% [12/34]); 65% (22/34) of patients had a history of HSCT.

All infections were hospital acquired. Bloodstream infections accounted for half of all episodes (20/40) and the most frequent aetiologic microorganisms were *Klebsiella pneumoniae* (27.5% [11/40]) and *Pseudomonas aeruginosa* (27.5% [11/40]). Antimicrobial susceptibilities of the detected isolates are shown in Table S1 (available as [Supplementary data](#) at JAC-AMR Online). For 10 (25%) infection episodes, polymyxins were used due to suspected CRI (pneumonia, *n*=4; enterocolitis, *n*=3; osteomyelitis, culture-negative sepsis and central nervous system infection, *n*=1 each) (Table 1). Polymyxins were administered concomitantly with other Gram-negative acting antimicrobial agents in all cases (double therapy in 47.5% [19/40] and triple therapy in 52.5% [21/40]). Meropenem was used in 28 (70.0%) episodes, of which 18 (64.3%) had culture-documented CRI (78% [14/18] with MIC ≥16 mg/L). The median doses of polymyxin and colistin used were 25 000 IU/kg/day and 4 mg of colistin base activity/kg/day, respectively, and the median duration of therapy with both polymyxins was 8.5 days (IQR 7–12.5). Appropriate empirical antibiotic therapy was administered in 28 (70.0%) episodes. A median time of 15 h (IQR 2–66) elapsed between onset of fever and the beginning of appropriate antibiotic therapy.

There were 17 adverse events that occurred during polymyxin use: 14 (82.4%) nephrotoxic (4 that induced drug suspension or reduction of the dosage) and 3 (17.6%) neurotoxic. Ten nephrotoxic events were KDIGO stage one and 4 were KDIGO stage three. Two neurological events were paraesthesias—of the hands and feet, and perioral; and one was behavioural changes not related to the infection under treatment or any other alternative explanation. The median duration of kidney injury was 12 days (IQR 4.8–23.8). Overall, at least one concomitant nephrotoxic agent was used in 92.5% (37/40) of treatment episodes. The median total duration of fever was 4.5 days (IQR 1–10). ICU was required in 15 (37.5%) episodes with a median length of stay of 16 days (IQR 5–28). There were five deaths in total, four of them infection related.

Therapeutic success was achieved in 70% (28/40) of episodes; of which 32% (9/28) had adverse events. In Bayesian multivariate analysis (Table 2), for each additional year of age increase, the probability of obtaining therapeutic success decreased by 35% (OR 0.65; 95% CI 0.49–0.80). For every hour that elapsed between the onset of fever and the start of appropriate antibiotic therapy according to antibiogram, the probability of therapeutic success decreased by 7% (OR 0.93; 95% CI 0.88–0.97). The use of adequate empirical therapy increased the chance of therapeutic success (OR 121.36; 95% CI 2.90–1147.95), as did concomitant treatment with non-carbapenems (OR 6.87; 95% CI 1.04–71.01). Sensitivity analysis including only patients with

Table 1. Clinical characteristics of episodes with polymyxin treatment according to therapeutic outcome

Variables	Total (n=40)	Therapeutic failure (n=12)	Therapeutic success (n=28)
Age, years, median (IQR)	10.0 (7.0–15.0)	15.0 (10.7–16.0)	9.0 (4.7–13.0)
Sex, male, n (%)	28 (70.0)	9 (75.0)	19 (67.9)
Type of insurance, n (%)			
Contributive	25 (62.5)	6 (50.0)	19 (67.9)
Subsidized	15 (37.5)	6 (50.0)	9 (32.1)
Comorbidities, n (%)			
ALL	15 (37.5)	7 (58.3)	8 (28.6)
AML	9 (22.5)	2 (16.7)	7 (25.0)
Aplastic anaemia	7 (17.5)	3 (25.0)	4 (14.3)
Chronic diseases	3 (7.5)	0 (0.0)	3 (10.7)
Other conditions ^a	6 (15.0)	0 (0.0)	6 (21.4)
History of HSCT, n (%)	28 (70.0)	10 (83.3)	18 (64.3)
HSCT phase, n (%)			
Conditioning	13 (32.5)	2 (16.7)	11 (39.3)
Pre-engraftment	7 (17.5)	2 (16.7)	5 (17.9)
Engraftment to 100 days post-transplant	11 (27.5)	2 (16.7)	9 (32.1)
>100 post-transplant days	9 (22.5)	6 (50.0)	3 (10.7)
Infection site, n (%)			
Bloodstream infection	20 (50)	6 (50)	14 (50)
No bloodstream infection ^b	20 (50)	6 (50)	14 (50)
Microbiological isolation, n (%)			
<i>P. aeruginosa</i>	10 (25)	3 (25)	7 (25)
<i>K. pneumoniae</i>	10 (25)	1 (8.3)	9 (32.1)
<i>Escherichia coli</i>	4 (10)	1 (8.3)	3 (10.7)
Polymicrobial infection ^c	3 (7.5)	1 (8.3)	2 (7.1)
<i>Pseudomonas</i> spp.	2 (5)	1 (8.3)	1 (3.5)
<i>Klebsiella</i> spp.	1 (2.5)	0	1 (3.5)
None	10 (25)	5 (41.6)	5 (17.9)
Appropriate empirical antibiotic therapy, n (%) ^d	28 (70)	9 (75)	19 (67.9)
Time from fever to appropriate antibiotic therapy, h, median (IQR)	15 (2–66)	24 (7.5–69)	4.0 (2–72)
Concomitant Gram-negative treatment, n (%)			
Carbapenem	28 (70)	11 (91.7)	17 (60.7)
Not carbapenems	12 (30)	1 (8.3)	11 (29.3)
Fosfomycin	4	0	4
Aminoglycosides	3	0	3
Ciprofloxacin	2	1	1
Tigecycline	2	0	2
Ceftazidime/avibactam	1	0	1
Meropenem MIC, mg/L, n (%)			
8	4 (10)	1 (8.3)	3 (10.7)
≥16	26 (65)	6 (50)	20 (71.4)
Concomitant nephrotoxic agent, n (%)			
None	3 (7.5)	1 (8.3)	2 (7.1)
1	20 (50)	3 (25)	17 (60.7)
≥2	17 (42.5)	8 (66.7)	9 (32.1)
Neutrophil count, ×10 ³ cells/mm ³ , median (IQR) ^e	1.07 (0.03–3.06)	0.96 (0.01–2.63)	1.16 (0.05–4.09)
Platelet count, ×10 ³ cells/mm ³ , median (IQR) ^e	29.5 (13.25–110.75)	18.5 (8.75–96.25)	40.5 (13.25–115.75)
CRP, mg/dL, median (IQR) ^e	83.7 (40.20–163.25)	127 (72.27–221.25)	60.85 (30.62–151.45)
Baseline GFR, n (%) ^e			
Normal	36 (90)	11 (91.7)	25 (89.3)
Abnormal	4 (10)	1 (8.3)	3 (10.7)

CRP, C-reactive protein; GFR, glomerular filtration rate.

^aLymphoma, n=2; hemophagocytic lymphohistiocytosis, n=2; dendritic cell leukaemia, n=2.

^bUrinary tract infection, n=10; pneumonia, n=4; enterocolitis, n=3; osteomyelitis, culture-negative sepsis and central nervous system infections, n=1 each.

^c*P. aeruginosa* and *Salmonella* group, *Pseudomonas putida* and *E. coli*, *K. pneumoniae* and *E. coli*.

^dAppropriate empirical antibiotic therapy: administration of an antibiotic for the isolated or suspected bacteria to which it is susceptible.

^eObtained at time of diagnosis of infection.

Table 2. Logistic model of factors related to clinical success with polymyxin

Variable	Frequentist approach, OR [95% CI]		Bayesian approach, OR [95% CI]	
	univariate	multivariate	univariate	multivariate
Age, years	0.78 [0.64–0.95]*	0.65 [0.47–0.90]*	0.78 [0.65–0.90]	0.65 [0.49–0.80] ^a
Sex				
Female	Ref.	—	Ref.	—
Male	0.70 [0.15–3.25]	—	0.67 [0.16–2.33]	—
History of HSCT	0.36 [0.06–1.98]	—	0.33 [0.06–1.25]	—
Comorbidities				
No leukaemia	Ref.	—	Ref.	—
Leukaemia	0.38 [0.08–1.73]	—	0.37 [0.09–1.26]	—
Appropriate empirical antibiotic therapy	1.42 [0.31–6.55]	138.39 [1.23–15526.18]*	1.53 [0.43–6.67]	121.36 [2.90–11477.95] ^a
Time from fever to appropriate antibiotic therapy, h	0.99 [0.98–1.01]	0.92 [0.87–0.98]*	0.99 [0.98–1.01]	0.93 [0.88–0.97] ^a
Infection site				
Bloodstream infection	Ref.	—	Ref.	—
No bloodstream infection	—	—	—	—
Concomitant treatment	1.00 [0.25–3.87]	—	1.00 [0.31–3.17]	—
Carbapenems	Ref.	—	Ref.	Ref.
No carbapenems	7.12 [0.80–63.16]**	—	7.75 [1.68–92.32]	6.87 [1.04–71.01] ^a
Other nephrotoxic agents		—		—
No	Ref.	—	Ref.	—
Yes	1.18 [0.10–14.42]	—	1.03 [0.06–9.96]	—
Neutrophil count, ×10 ³ cells/mm ³	1.00 [0.99–1.00]	—	1.00 [0.99–1.00]	—
Platelet count, ×10 ³ cells/mm ³	1.00 [0.99–1.01]	—	1.00 [0.99–1.01]	—
CRP mg/dL	0.99 [0.99–1.00]	—	0.99 [0.99–1.00]	—
Basal GFR				
Normal	Ref.	—	Ref.	—
Abnormal	1.32 [0.12–14.14]	—	1.69 [0.23–26.28]	—
Microbiological isolation		—		
None	0.20 [0.03–1.15]	—	0.20 [0.04–0.78]	—
<i>Pseudomonas</i>	0.40 [0.73–2.24]	—	0.39 [0.09–1.73]	—
Other pathogens	Ref.	—	Ref.	—

CRP, C-reactive protein; GFR, glomerular filtration rate; Ref., reference value.

* $P < 0.05$.

** $P < 0.1$.

^aCredible interval does not contain the unit.

documented CRI confirmed the effect of age and concomitant treatment (Table S2). Six patients with recurrent infections had repeat courses of polymyxins and were no more likely to have treatment failures ($\chi^2 = 0.2$, $P = 0.64$).

Discussion

In our cohort of patients receiving polymyxin therapy, all with suspected or confirmed CRI, therapeutic success was achieved in 70% (28/40) of episodes, however 32% (9/28) of these successes were associated with adverse events. Overall, 42.5% (17/40) of episodes had adverse events during polymyxin use, while 47.5% (19/40) of episodes had therapeutic success without drug toxicity. These data highlight the need to consider novel antibiotics to treat children with CRI.

The therapeutic success described here resembles previous studies,^{4,5} although we report a higher frequency of nephrotoxicity probably related to the higher use of concomitant nephrotoxic

agents to treat malignant disorders or prevent graft versus host disease in HSCT recipients. Most patients in this cohort had received an HSCT, reflecting the extensive use of antibiotics these patients receive while treating their baseline condition, predisposing them to carbapenem-resistant infections, and highlighting the need to rationalize antibiotic use in children and adolescents with cancer.

In our study, we identified a series of factors independently associated with therapeutic success. Specifically, we identified that for each year of age increase, the odds of therapeutic success decrease by 35% for reasons that are unclear. Previously, it was reported that among children receiving polymyxin therapy, older age was associated with higher odds of developing nephrotoxicity.⁴ The use of concomitant therapy with non-carbapenem antibiotics was also associated with higher odds of therapeutic success. This observation is likely related to the high frequency of organisms with meropenem MIC ≥ 16 mg/L, supporting the current recommendations to avoid the use of meropenem for CRI with MIC > 8 mg/L.⁸

It has been reported that an inadequate empirical therapy, or a delay in the use of appropriate antibiotic therapy, is associated with higher mortality in adult patients.^{9,10} In our cohort, for each hour of delayed appropriate therapy, the odds of success decreased by 7%. Of concern, given the MDR nature of the pathogens, several infectious episodes in our study received an inappropriate empirical antibiotic. It is of paramount importance to identify risk factors for CRI in children and adolescents to increase the chances of providing early appropriate therapy.

This study has several limitations. First, this is a small cohort, which may have resulted in imprecise estimates from the model. The use of a Bayesian logistic regression model with confirmation under the frequentist approach was used to reduce this weakness. Second, it was a single-centre study preventing generalizability of results. Third, it does not include information about the specific mechanisms of carbapenem resistance, which may have impacted treatment outcomes. Fourth, for 10 episodes, polymyxins were used for suspected but not confirmed infections, which may have led to the inclusion of some patients without CRI, creating bias in the logistic models. However, suspected infections were only included when they had a high risk of CRI based on clinical and epidemiological data and such misclassification would have been non-differential for both outcome categories and therefore unlikely to have had a major effect on overall conclusions. In addition, we performed a sensitivity analysis including only culture-proven CRI, which confirmed the effect of younger age and non-carbapenem concomitant therapy as factors associated with clinical success. Finally, the sample size was small, and the data were collected retrospectively in very complex patients; however, the use of detailed definitions, the thorough review of medical charts and the use of a Bayesian logistic model in this study may have overcome these limitations.

Our study describes the characteristics of polymyxin or colistin treatment episodes in Colombia, and factors associated with their therapeutic success. However, many children and adolescents had therapeutic failure or adverse events, which is of relevance considering that newer antibiotics with better efficacy and safety are available for CRI.^{11–13} All children globally should have access to newer, safer and more effective drugs to treat CRI, including those from lower- and middle-income countries where these infections represent a growing health threat.

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Transparency declarations

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria;

educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Supplementary data

Tables S1 and S2 are available as [Supplementary data](#) at JAC-AMR Online.

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