Intravenous colistin (Polymyxin E) has renewed interest as a last-line treatment against antimicrobial resistant gram-negative bacterial infections, despite limited literature on paediatric prescribing practices. Point-prevalence surveys were used to obtain intravenous colistin prescribing data from 78 children and neonates, showing high variability and 60.3% received doses below the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) recommendations.

Roger Nation
roger.nation@monash.edu
Teaching pharmacokinetics and pharmacodynamics in the Bachelor of Pharmacy and postgraduate programs. Expert in polymyxins.

Matthew E Falagas
m.falagas@aibs.gr
Working for Alfa Institute of Biomedical Sciences (AIBS), Athens, Greece; Department of Internal Medicine-Infectious Diseases, IASO General Hospital, IASO Group, Athens, Greece; Tufts University School of Medicine, Boston, MA, USA. 

Narongsak Nakwan
nnakwan@hotmail.com
Working for the Department of Pediatrics, Hat Yai Medical Education Center, Hat Yai Hospital, Songkhla, Thailand; 

Funding Information:
Evidence of Dose Variability and Dosing Below the FDA and EMA Recommendations for Intravenous Colistin (Polymyxin E) Use in Children and Neonates

Maxx King Yau Chin, BSc*, Yingfen Hsia, PhD††, Herman Goossens, PhD‡, Ann Versporten, MPH‡, Julia Bielicki, MD§, Mike Sharland, MD*, Daniele Donà, MD¶

From the *Paediatric Infectious Disease Research Group, Institute for Infection and Immunity, St George’s University of London, London, United Kingdom
†School of Pharmacy, Queen’s University Belfast, Belfast, Northern Ireland
‡Laboratory of Medical Microbiology, Vaccine and Infectious Diseases Institute, University of Antwerp, Antwerp, Belgium
§Paediatric Pharmacology and Paediatric Infectious Diseases, University Children’s Hospital Basel, Basel, Switzerland
¶Division of Paediatric Infectious Diseases, Department for Woman and Child Health, University of Padua, Padua

Correspondence: Daniele Donà, MD, Paediatric Infectious Disease Research Group, Institute for Infection and Immunity, St George’s University of London, London, United Kingdom E-mail: ddon@sgul.ac.uk.

Conflicts of Interest and Sources of Funding:
The authors have no conflicts of interest to declare.
GARPEC was funded by the PENTA Foundation. bioMérieux provided unrestricted funding support for the Global-PPS.

Key Words: Dosing, Colistin, Polymyxin E, Children, Neonates

Abbreviated Title: Dosing of Intravenous Colistin - Children and Neonates

Running Head: Dosing of Colistin in Children and Neonates
Abstract:

Intravenous colistin (Polymyxin E) has renewed interest as a last-line treatment against antimicrobial resistant gram-negative bacterial infections, despite limited literature on paediatric prescribing practices. Point-prevalence surveys were used to obtain intravenous colistin prescribing data from 78 children and neonates, showing high variability and 60.3% received doses below the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) recommendations.
**Introduction:**

Rising rates of antimicrobial resistance (AMR) has prompted renewed interest in optimizing the use of colistin, a cyclic polypeptide antibiotic belonging to the polymyxins, as last-line treatment for multi-drug resistant Gram-negative bacteria (MDR-GNB), such as *Pseudomonas aeruginosa*, *Acinetobacter baumanii* and *Klebsiella pneumoniae*\(^1,2\).

In 2019, an international consensus for the optimal dosing of polymyxins in adult patients was published \(^3\), with dosing suggestions based on a detailed population pharmacokinetic (PK) analysis in 214 critically ill adult patients \(^4\). This provided an algorithm and a clinician-friendly ‘look-up’ table to determine the required daily dose for efficacy in treatment. Creatinine clearance was accounted for, and a loading dose of 300mg Colistin Base Activity (CBA) (~9 million International Units (IU) Colistimethate Sodium (CMS)) was recommended. However, this provided no guidance for dosing in children and neonates.

Despite an increase of 13% in global consumption of polymyxins \(^5\), there is limited literature on colistin use in children and neonates \(^2\). Dosing can be confusing as preparations may be labelled as IU of pro-drug, CMS, or mg of active drug, CBA. The Food and Drug Administration (FDA/EMA) suggest 2.5 – 5mg/kg/day CBA, whereas the European Medicines Agency (EMA) expresses this as 75,000 – 150,000 IU/kg/day CMS. However, a 2019 PK study has highlighted that doses of 6mg/kg CBA may result in suboptimal plasma concentrations of colistin in children \(^6\).

This study aimed to explore variation in current pediatric and neonatal prescribing practices of intravenous (IV) colistin, and to compare these to current FDA/EMA dosing recommendations.

**Material and Methods:**
Data were obtained from two international data collection networks, focused on antibiotic prescription patterns and resistance in hospitals: Global Antimicrobial Resistance, Prescribing and Efficacy Among Neonates and Children (GARPEC) and Global Point Prevalence Surveys (Global-PPS). Point-prevalence surveys (PPS), between 2015 and 2017, were used to collect antibiotic prescribing data in hospitalized children and neonates. Participation was voluntary and no incentives were offered. Local ethics approval was obtained at each participating hospital, if required. All data were anonymized without patient identifiers. Further details of the methodology have been published [7]. Neonates were defined as ≤30 days of age and children were aged between >30 days and <18 years. Descriptive analyses on the combined dataset were carried out on patients who received IV colistin (Polymyxin E). Categorical variables were expressed as percentages. Colistin doses are expressed as mg CBA (0.375mg CBA ≈ 12,500 IU CMS). Prevalence of IV colistin prescribing and 95% confidence intervals (CIs) were estimated. Linear regression was calculated for the dose of IV colistin and the weight of the patient. Statistical significance was defined as p<0.05. Statistical analyses and graphs were produced using R (Version 3.4.1).

**Results:**

**Overview**

The combined dataset resulted in 21,560 prescriptions from 17,181 patients, spanning 6 World Health Organization regions. Of these, 61 children and 17 neonates were prescribed IV colistin. The overall point prevalence rate of IV colistin prescription was estimated at 0.36% (95% CI: 0.29 – 0.45).

Colistin was most frequently prescribed in South-East Asia (38.5%) and Europe (35.9%).

*Characteristics of Patients Receiving Colistin*
The mean age was 5.92 years (SD 5.55) in children and 12.63 days (SD 7.33) in neonates. 60.7% of children and 58.8% of neonates were male. The most common diagnoses were bacterial Lower Respiratory Tract Infections (LRTI) in 37.7% of children and sepsis in 76.5% of neonates. Indications were healthcare associated infections (symptoms occurring >48 hours post-admission) in 52.5% of children and 58.8% of neonates. Comorbidities were found in 72.1% of children and 64.7% of neonates. Targeting of treatment was found in 43.1% of children and 29.4% of neonates, with empirical treatment in 27.6% of children and 41.2% of neonates. The remaining treatment statuses (29.3% of children and 29.4% of neonates) were not recorded. The mean number of co-administered antibiotics was 3.12 drugs (SD 1.33). Nephrotoxic antibiotics, such as aminoglycosides, were co-administered in 21.8% of patients. No patients received concurrent inhaled or intraventricular colistin.

Variation in Colistin Dosing

In children, the total daily dose of IV colistin ranged from 0.46 to 10.67mg/kg CBA. The frequency of each individual dose varied, with 56.9% receiving the total dose divided into 3 doses per day, 32.8% receiving 2 divided doses per day, and 10.3% receiving 1 dose per day. In neonates, the total daily dose of IV colistin ranged from 0.24 to 7.92mg/kg CBA. 88% receiving colistin in 3 divided doses per day, and the remaining 12% received colistin twice per day.

Dosing of Colistin Below FDA/EMA Recommendations

Each total daily dose of IV colistin were plotted in Figure 1. Overall, 60.3% of patients received doses below the lowest FDA/EMA recommendations of 2.5mg/kg/day CBA (63.8% of children and 58.8% of neonates).
There were no statistically significant differences between the characteristics of those who were given doses below the recommendations, versus those who were not. A diagnosis of sepsis was noted more frequently in neonates and children who received doses below the FDA/EMA recommendations, at 90% and 24%, respectively.

**Renal Comorbidity and Colistin Dosing**

Renal function data were not recorded. However, 6 children were noted to have ‘renal impairment’ as a comorbidity. Doses ranged from 0.48 to 6.11mg/kg CBA. 83.3% received doses below the FDA/EMA recommendations.

**Discussion:**

To our knowledge, this is the first study exploring prescribing practices of IV colistin in children and neonates. High variation in total daily dosing was observed, with 63.8% of children and 58.8% of neonates receiving doses below the lowest FDA/EMA recommendations.

The strength of this study lies in inter-group collaboration to gather a large sample of patients across a range of countries and hospitals. PPS provides an easy to use, standardized, validated and thorough method of data collection \[^7\]. However, PPS only provides a snapshot of prescribing practices.

There is a lack of renal function data, such as glomerular filtration rate (GFR), which impacts prescribing practices. However, some doses may be appropriately low due to renal adjustments, in the 6 patients with renal comorbidities. We were unable to establish if loading doses were given, although these are not typically expected in the pediatric population.

As most patients in this study did not have renal comorbidities, the variation in doses may in part be attributed to confusion over different dosing regimens available worldwide, which can result in varying target plasma concentrations being achieved \[^1\]. Additionally, confusion over product
labelling can arise. Product vials may be labelled as IU CMS (pro-drug), mg CMS, or mg CBA (active drug). In the United States, a parenteral product of Parkedale (Coly-Mycin® M Parenteral) is labelled as containing 150mg CBA in each vial. Each vial contains ~400mg sodium CMS (5 million IU), which is based on a microbiological standardization and is equivalent to 150mg CBA. A similar European product (Colimycin Injection) contains the prodrug CMC and is labelled in IU CMS (500,000 IU, 1 million IU, or 2 million IU per vial). As ~12,500 IU CMS corresponds to 1 mg CMS, there can be 40, 80 or 160mg CMS in different vials.

Since marketing approval, colistin has not been subjected to modern drug development evaluation and information on its clinical use are scarce [1,2]. These are even more critical issues in neonates, as they have very different PK characteristics compared to adults [8]. The immaturity of neonatal renal and hepatic enzyme function adds to the complexity of PK studies. In 2013, the Prato polymyxin consensus discussed the safe and effective use of polymyxins, and highlighted the need for more PK studies, due to limited literature in guiding pediatric dosing [9]. Currently, there are only two detailed neonatal PK studies (8 neonates in 1966, and 7 neonates in 2016) [10]. The 2016 prospective study evaluated the PK of colistin after a single dose of IV CMS. It found that after a single IV dose of 150,000 IU/kg CMS (≈5mg/kg CBA), the colistin plasma concentration after 6 hours was <2ug/ml in all neonates and <1ug/ml in 5 out of 7 neonates. Data from in vitro and in vivo studies recommend achieving a plasma concentration of >2ug/ml at a steady-state to treat Pseudomonas aeruginosa infections with a MIC <1ug/L. The suboptimal colistin plasma concentration reported in neonates could, in part, reflect decreased rates of CMS conversion due to lower levels of esterases present in neonates.
A 2019 pediatric PK paper, by Ooi et al, investigated the plasma concentration of colistin in children, and assessed the appropriateness of EMA and FDA/EMA dosing recommendations \[^6\]. The study concluded that even at doses of 6.7mg/kg CBA (≈ 200,000 IU/kg/day CMS), 33% above the EMA and FDA/EMA upper limits, plasma concentration of colistin varied substantially. Only 2 out of 5 patients achieved a steady-state of >2ug/ml. Therefore, the current EMA and FDA/EMA approved doses may be suboptimal for many neonates and children.

**Conclusions**

In this study, high variation in pediatric and neonatal IV colistin dosing was found. 63.8% of children and 58.8% of neonates were dosed below the minimum FDA/EMA recommendations of 2.5mg/kg/day CBA. These findings warrant the need for further PK studies, as upper limits of dosing recommendations may be suboptimal in treating infections. International guidance on harmonization between different formulations and dosing units must also be addressed.
References:


Figure 1: Scatterplot showing total daily doses of intravenous (IV) colistin (mg/kg CBA) in A) children and B) neonates, with the lowest FDA/EMA recommended treatment line (2.5mg/kg). Data plots below the treatment line indicate doses below the lowest FDA/EMA dosing recommendations for IV Colistin.