

# THE USE OF POLYMYXINS TO TREAT CARBAPENEM RESISTANT INFECTIONS IN NEONATES AND CHILDREN

## Abstract

### *Introduction*

The incidence of healthcare-associated multidrug resistant bacterial infections, particularly due to carbapenem resistant organisms, has been on the rise globally. Among these are the carbapenem resistant *Acinetobacter baumannii* and *Enterobacteriaceae*, which have been responsible for numerous outbreaks in neonatal units. The polymyxins (colistin and polymyxin B) are considered to be the last resort antibiotics for treating such infections. However, pharmacokinetic and pharmacodynamic data on the use of polymyxins in neonates and children are very limited, and there are safety concerns.

### *Areas covered*

In this review the authors summarize the global burden of multidrug resistance, particularly carbapenem resistance, in the neonatal and pediatric population, and the potential wider use of polymyxins in treating these infections.

### *Expert opinion*

Both colistin and polymyxin B have been shown to have similar efficacy in treating multidrug resistant infections but have safety concerns. However, polymyxin B appears to be a better therapeutic option, with more rapid and higher steady state concentrations achieved compared to colistin and less reported nephrotoxicity. There are virtually no data in neonates and children currently; there is therefore an urgent need for pharmacokinetic and safety trials in this population to determine the optimal drug and dosing regimens and provide recommendations for their use in treating carbapenem resistant infections.

## Key points

- Hospital-acquired multidrug resistant Gram-negative bacterial infections are a major cause of morbidity and mortality in neonates globally
- The incidence of these infections is rising world-wide
- A major concern is the increase in carbapenem resistant infections
- Polymyxins are considered as the last resort antibiotics for treating carbapenem resistant infections and their use has subsequently increased
- However, pharmacokinetic and pharmacodynamic data on the use of polymyxins in neonates is very limited, and there are safety concerns.

**Key words:** neonate, multidrug resistance, carbapenem resistance, colistin, polymyxin B

## 1. Introduction

Globally, approximately 5.8 million children under five years of age die every year <sup>1</sup>. A significant proportion (45%) of these deaths occur during the neonatal period (first 28 days of life). The major causes of neonatal deaths worldwide include prematurity (35%), intra-partum asphyxia (24%) and sepsis (15%). Low- and middle income countries (LMIC) carry the burden of more than 90% of these deaths <sup>2</sup>.

Bacterial infection is one of the leading causes of deaths during the neonatal period. These infections are either acquired from the mother around the time of delivery or from the environment, either at home or in a healthcare facility. Healthcare-associated infections (HAI) are associated with major morbidity and mortality. The reported incidence ranges from 6% to 38% of admitted neonates, with the burden of disease being higher in LMIC <sup>3-5</sup>. Organisms most commonly responsible for HAIs include Gram-negative pathogens such *Klebsiella species*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*; and Gram-positive pathogens such as coagulase negative *Staphylococci* (CoNS) and *Staphylococcus aureus*. Recently many of these organisms have developed resistance to multiple groups of antimicrobial agents and are therefore called multidrug resistant (MDR) organisms. This review summarizes the burden of multidrug resistance, particularly carbapenem resistance, in the neonatal population, and the use of polymyxins in treating these infections.

## 2. Epidemiology of MDR organisms

The most commonly used definition for multidrug resistance is non-susceptibility, intermediate sensitivity or resistance to at least one agent in 3 or more antimicrobial classes. The term extreme drug resistance (XDR) has been used to define MDR organisms that are resistant to at least one agent in all antimicrobial classes except 2 or fewer <sup>6</sup>. Resistance to carbapenem antibiotics poses a particular global health challenge, especially in LMIC, where therapeutic options are limited and mortality rates are reported to be as high as 50% <sup>7,8</sup>. A number of studies have reported a high prevalence of carbapenem resistant organisms (CRO) in neonatal units; however, most are from high-income countries <sup>9-12</sup> with very few from LMIC <sup>7, 13-15</sup>. The common CRO are the carbapenem resistant *Enterobacteriaceae* (CRE), in particular *Klebsiella species*, and the non-lactose fermenters, namely the *Acinetobacter* and *Pseudomonas species*.

*Acinetobacter baumannii* is a non-lactose fermenting Gram-negative bacterium that has emerged as a leading pathogen in many neonatal units and is responsible for numerous hospital outbreaks <sup>7, 13, 16</sup>. The main concern with *Acinetobacter baumannii* is its ability to accumulate multiple and varied mechanisms of antimicrobial resistance rapidly, leading to multidrug resistance. *Acinetobacter baumannii* has developed resistance to various classes of antimicrobials including penicillins, aminoglycosides and cephalosporins but of major concern is the more recent emergence of carbapenem resistant *Acinetobacter baumannii* (CRAB) <sup>17, 18</sup>.

Multidrug resistant infections with *Enterobacteriaceae*, such as *Klebsiella pneumoniae*, are also increasing in neonatal intensive care units and are associated with numerous hospital outbreaks <sup>13, 19, 20</sup>. The most common mechanism of resistance in *Enterobacteriaceae* is extended spectrum beta lactamase (ESBL) production. The

implication is the World Health Organization (WHO) recommended first-line antibiotics for neonatal sepsis of penicillin/ampicillin will be ineffective. The increasing prevalence of ESBL-producing pathogenic organisms has led to increasing use of carbapenems worldwide for treating these infections, and consequently the emergence and spread of carbapenem resistance<sup>9, 10</sup>. Although the literature is limited in the neonatal population, there are now a few case reports highlighting the problem of carbapenem resistant *Enterobacteriaceae*<sup>21, 22</sup>.

### 3. Mechanisms of resistance

There are many different intrinsic and acquired mechanisms of antimicrobial resistance which include antibiotic efflux pumps, capable of actively pumping antibiotics out of the cell; chromosomal mutations, leading to loss of specific outer membrane proteins and thus reduced affinity and influx of antibiotics to the target cell; and enzymatic degradation of antibiotics through ESBL production<sup>23, 24</sup>. The most important mechanism underlying carbapenem resistance is the production of a specific group of beta lactamases, known as the carbapenemases, which have the ability to hydrolyze the carbapenems. The three main groups of carbapenemases of clinical and epidemiological significance, reported in studies from neonatal units include KPC, NDM and OXA-48<sup>25</sup>. These beta lactamases are grouped into four classes based on their amino acid sequence (class A, B, C and D). KPC is a class-A beta lactamase, while NDM belongs to class B and OXA-48 to class D. KPC has been shown to have a very broad spectrum of action against most antibiotics, including the carbapenems. Its hydrolytic activity is inhibited minimally by clavulanic acid and boronic acid compounds. NDM has a similar spectrum of action to KPC but spares aztreonam. OXA-48 has activity against penicillins and carbapenems but is unique in that it spares the cephalosporins and aztreonam<sup>26</sup>.

### 4. MDR treatment

Therapeutic options, in MDR infections, including those secondary to CRO, are currently very limited, although multiple new agents are being tested and developed. New drugs, such as cefiderocol, now in advanced stages of development have been shown to be very effective against MDR infections as well as infections with CRO<sup>27, 28</sup>. However, these newly developed drugs are very expensive and not available in LMIC. The majority of CRO are still susceptible to the polymyxins, which are available in LMIC. However, these agents have not been well studied, especially in neonates, and have some safety concerns. Some KPC and OXA producing strains are susceptible to aminoglycosides such as gentamicin and amikacin<sup>26</sup>. However, monotherapy with these agents is not recommended. The most recent edition of the WHO model list of essential medicines for children has grouped antibiotics into three groups - access, watch and reserve, indicating which antibiotics to use for different types of infections. Group 3, the reserve group, comprises antibiotics that should be used as last-resort for life-threatening infections caused by MDR bacteria (Table 1)<sup>29</sup>. Some recent observational studies have suggested that combination therapy may be superior to monotherapy in the treatment of CRO<sup>30</sup>. However, randomized controlled trials comparing polymyxin monotherapy to combination therapy (all in adults), including a recent trial by Paul et al, have shown no clear clinical benefit of combination therapy<sup>31</sup>. Therefore, the best available option for the treatment of CRO is still unknown. However, the use of

polymyxins has increased worldwide, as they are currently considered the optimal backbone treatment for serious carbapenem resistant infections.

Table 1: WHO “Reserve” group of antibiotics

Aztreonam
4th generation cephalosporins eg. Cefepime
5th generation cephalosporins eg. Ceftaroline
Daptomycin
Fosfomycin (IV)
Oxazolidinones eg. Linezolid
Polymyxins eg. Polymyxin B, Colistin
Tigecycline

## 5. Pharmacokinetics of polymyxins

Polymyxins are a class of antibiotics consisting of 5 different compounds, namely polymyxin A, B, C, D and E. Of these, only polymyxin B and E are used in clinical practice. Colistin (polymyxin E) is an old antibiotic that was initially discovered in the late 1940s and introduced in 1959. It was subsequently withdrawn from the market in the 1970s due to safety concerns, particularly nephrotoxicity. However, the recent development of multidrug resistance has led to a resurgence in the use of colistin. Colistin is a cyclic polypeptide which binds with high affinity to lipopolysaccharides on bacterial cell membranes, leading to increased cell permeability, leakage of intracellular contents and resultant cell death. The main use of colistin is for the treatment of carbapenem resistant strains of *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and other *Enterobacteriaceae*. Emerging resistance to colistin has been reported, and is of great concern<sup>32</sup>. Most pharmacokinetic (PK) data on colistin has been derived from adult studies<sup>33,34</sup>. Colistin is administered intravenously in the form of its inactive prodrug, colistimethate sodium (CMS). A proportion (approximately 20%) of CMS is hydrolyzed in vivo to its active form colistin, and the rest excreted by the kidneys. Therefore, following parenteral administration of CMS, colistin formation is slow and it may take a long time to achieve adequate steady state concentrations, depending on whether a loading dose is used. In healthy adults CMS has a half-life of 1-2 hours, and colistin has a half-life of 14-19 hours. In critically ill adult patients colistin reaches peak plasma concentrations 7 hours after CMS administration. Clearance of colistin is mainly via the renal system, and excretion is reduced in patients with renal impairment in which case more CMS may be converted to colistin, necessitating dosing adjustments based on renal clearance. There is no general consensus on the dosing of colistin. In critically ill patients with life threatening infections, it is recommended to start CMS treatment with a loading dose in order to achieve therapeutic concentrations more quickly. In one adult study, a loading dose of 9MU followed by 4.5MU every 12 hours as maintenance resulted in an 82% clinical cure rate<sup>35</sup>. A dose of 75000 – 120000 IU/kg/day has been used in the neonatal population, without a loading dose<sup>26</sup>. However, these dosing recommendations are very old and have little evidence base.

Pharmacokinetic data on colistin in neonates are very limited. While colistin sulfate is stable, colistimethate sodium is readily hydrolysed to a variety of methanesulfonated derivatives. Neonates have a different physiology to that of adults which affects drug disposition, metabolism and elimination<sup>36-38</sup>. The kidney, the major organ responsible for drug elimination, is immature even in term neonates, with decreased glomerular filtration and tubular secretion. Maturation is both gestational age and postnatal age dependent and nephrogenesis is ongoing. In addition, many neonatal conditions such as asphyxia and sepsis can affect renal function. To date there have only been two detailed colistin PK studies, with the more recent study conducted by Nakwan et al assessing the PK of colistin in 7 neonates after a single dose of CMS of approximately 150000 IU/kg, equivalent to 5mg/kg of colistin base activity, substantially higher than doses used in previous studies<sup>39</sup>. In this study the mean maximum plasma concentration (C<sub>max</sub>) was 3.0 +/- 0.7ug/ml, attained (T<sub>max</sub>) at 1.3 +/- 0.9 hours after the end of CMS infusion. After 6 hours, the concentration of colistin was below the minimum inhibitory concentration (MIC) breakpoint of 2ug/ml in all neonates. Based on data from previous studies it is recommended that a plasma concentration of over 2ug/ml is achieved to treat infections with an MIC breakpoint of <1ug/ml. The sub-optimal plasma colistin concentrations achieved in this study are therefore concerning. However, in this study CMS was well tolerated and no adverse effects were reported. There is little published on the PK of colistin in extravascular sites, such as the central nervous system<sup>40, 41</sup>. Therefore, knowledge of its efficacy in the treatment of meningitis, a common complication in neonates, is limited.

Polymyxin B (PMB) has also been increasingly used worldwide for treating infections with CRO. Polymyxin B shares very similar antimicrobial properties and chemical structure to colistin. They differ only by one amino acid in their peptide ring, where the D-leucine of colistin is replaced by phenylalanine of PMB. Data on the PK of PMB in neonates are limited, and most data have been derived from adult studies. The major difference between colistin and PMB is the form in which they are administered intravenously. Unlike colistin, PMB is administered directly in its active form and is eliminated by non-renal pathways. Manchandani et al examined PMB PK in 35 adults and investigated factors influencing PK variability. The mean elimination half-life of PMB was 10.1 hours, and the maximum concentration achieved was 3.4ug/ml at 24 hours. They showed that covariates such as creatinine clearance and body weight of patients might not be accurate predictors of PMB PK<sup>42</sup>. Another PK study on PMB, by Sandri et al, involved 24 critically ill adults<sup>43, 44</sup>. Intravenous doses used in this study ranged from 0.45mg/kg/day – 3.38mg/kg/day. In this study the average steady-state plasma concentration was 2.79 ± 0.90 mg/L (range, 0.68–4.88 mg/L). Higher and quicker steady state concentrations were achieved compared to CMS (from previous PK data), and fewer dosing adjustments were required. There are currently no recommended neonatal doses of PMB.

## 6. Pharmacodynamics of polymyxins

Pharmacodynamic (PD) studies report a similar profile for both drugs. In vitro studies have shown that both colistin and polymyxin B have rapid concentration-dependent killing against *Acinetobacter baumannii*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* with a minimal post-antibiotic effect<sup>45-47</sup>. However, regrowth after cessation of treatment can occur rapidly with both agents. In vitro studies using

*Pseudomonas aeruginosa* and *Acinetobacter baumannii* demonstrated that the PK/PD index that correlates most strongly with the efficacy of colistin is the ratio of the area under the free concentration–time curve to the MIC ( $fAUC/MIC$ ). In addition, Dudhani *et al.* studied *in vivo* the activity of colistin against three strains of *Pseudomonas aeruginosa* in neutropenic mouse thigh and lung infection models and reported that, consistent with the *in vitro* studies, the PK/PD index that correlated most strongly with colistin efficacy was  $fAUC/MIC$  in both the thigh infection model ( $R^2 = 87\%$ ) and the lung infection model ( $R^2 = 89\%$ )<sup>48</sup>. Little information is available on PMB from *in vivo* studies<sup>49</sup>, however given the similarity in structure, it is very likely that  $fAUC/MIC$  is the most predictive PK/PD index also for intravenous PMB. Unlike CMS, PMB is available as an active drug and is not influenced by renal function. For these reasons, a higher  $fAUC/MIC$  value than CMS is expected after the administration of polymyxin B<sup>44</sup>.

## 7. Polymyxin MIC determination

In 2016 The European Committee on Antimicrobial Susceptibility Testing (EUCAST) released a warning about several methodological issues in MIC determination for polymyxins<sup>50</sup>. A joint EUCAST and Clinical and Laboratory Standards Institute (CLSI) subcommittee recently recommended broth microdilution (BMD) as the only valid method to detect colistin susceptibility while other methods, including agar dilution and disk diffusion cannot be recommended until historical data have been reviewed or new study data have been generated.

With regard to MIC breakpoints, both colistin and PMB have demonstrated excellent *in vitro* activity against a large collection of clinical isolates of *Acinetobacter spp.* (MIC  $\leq 2 \mu\text{g/ml}$ ), *K. pneumoniae* (MIC  $\leq 2 \mu\text{g/ml}$ ), *E. coli* (MIC  $\leq 1 \mu\text{g/ml}$ ) and *P. aeruginosa* (MIC  $\leq 2 \mu\text{g/ml}$ )<sup>51</sup>.

## 8. Polymyxin clinical efficacy

Only three studies have been conducted to evaluate the efficacy of colistin in neonates (preterm and full-term) with sepsis caused by MDR organisms<sup>52-54</sup>. Of these, one is a case–control study that included 106 neonates (47 treated with colistin and 59 as unmatched controls) with proven or suspected nosocomial infections between January 2012 and October 2015 at two centres in Turkey<sup>54</sup>. No difference in treatment outcomes was reported. The efficacy of colistin treatment in neonates was also studied retrospectively by Alan *et al* and Serafettin Tekgunduz *et al* with 21 and 12 newborns respectively<sup>52, 53</sup>. All these studies showed that intravenous colistin administration appears to be efficacious for MDR infections in this population.

Regarding the efficacy of PMB only sporadic reports have been published in paediatric patients, and none in neonates<sup>55, 56</sup>. Siddiqui *et al* conducted a retrospective cohort study on 14 critically ill children, ranging from 1 month to 15 years of age, treated with intravenous PMB for MDR Gram-negative infections. They reported a clinical efficacy of 57%<sup>56</sup>. Another retrospective review by Saleem *et al* studied 8 children with *Acinetobacter* meningitis of which 7 children received intravenous PMB and 5 also received intrathecal PMB. All patients achieved CSF culture negativity by the end of treatment<sup>55</sup>.

No studies have compared the efficacy of colistin and PMB in children or neonates. Data is available from four adult studies, many of these primarily aimed at measuring rates of nephrotoxicity. Oliveira et al compared 41 patients receiving CMS with 41 who received polymyxin B for the treatment of serious infections caused by carbapenem-resistant *Acinetobacter* spp. No differences in efficacy and toxicity were found; specifically no significance difference in clinical improvement (39% colistin versus 39% polymyxin B;  $p$  0.48), death (46% versus 54%, respectively;  $p$  0.51) and 30-day mortality (56% versus 61%, respectively;  $p$  0.66) <sup>57</sup>. In a retrospective study including 132 patients, Tuon et al compared the polymyxins' nephrotoxicity and assessed mortality as a secondary outcome. Hospital mortality was similar in patients treated with PMB and colistin (46% (44/96) and 50% (18/36), respectively;  $P$  = 0.48) <sup>58</sup>. Also, in 2014, Phe et al published a multicentre study assessing the nephrotoxicity of polymyxins in more than 200 adults. In this study, PMB use was associated with a higher mortality rate. However in a matched analysis based on the risk factors identified, excluding patients with cystic fibrosis or patients who received a lower dose of PMB, there was no difference in mortality and nephrotoxicity was lower in the PMB group <sup>59</sup>. In 2016, Rigatto et al published a study comparing the incidence of renal failure in patients treated with colistimethate sodium or PMB for more than 48 hours, with mortality as a secondary outcome. Colistin was reported to be independently associated with a higher risk of renal failure in various subgroup analyses. Despite the development of renal failure during therapy, colistin was not associated with 30-day mortality in multivariate analysis <sup>60</sup>. A recent systematic review comparing colistin versus PMB, including these four studies, reported mortality ranging from 8% to 56% in colistin-treated patients compared to 31% to 61% in polymyxin B-treated patients. There were no significant differences in unadjusted mortality between patients treated with colistin and those treated with PMB (RR = 0.71, 95% CI 0.45–1.13) <sup>61</sup>. It is important to note that all these studies did not assess mortality as their primary outcome, and therefore may not have considered important clinical characteristics associated with treatment efficacy. Indeed, antimicrobial combinations, site of infection, type of bacteria, differences in the MIC, severity of illness and surgical control of the infection may strongly influence outcomes <sup>61, 62</sup>. Furthermore, as reported by Vardakas et al, in three studies some patients received polymyxin treatment without microbiological confirmation of infection, which may have affected the analysis of mortality <sup>58-61</sup>. Randomized controlled trials are needed to rigorously define the most effective polymyxin regimen in paediatrics, especially in neonates <sup>63</sup>.

## 9. Polymyxin safety

Adverse effects due to polymyxin treatment has been reported since the early 1960s, mostly from adult studies, with rates as high as 50% <sup>64</sup>. Reported adverse effects included nephrotoxicity and less commonly, neurotoxicity. Data on polymyxin safety in the neonatal/paediatric population is limited and mostly restricted to retrospective reviews on colistin/CMS therapy. A systematic review conducted by Falagas et al, comparing old and new evidence on polymyxin toxicity in adult and pediatric patients, found that toxicity has reduced compared to previous reports, with recent reported rates of nephrotoxicity ranging from 0% to 24%. This decline was attributed to improved fluid and electrolyte management in intensive care units, as well as better monitoring of renal function and reduced concomitant use of other nephrotoxic agents. Clinical manifestations of renal toxicity included a decrease in glomerular filtration rates and an

increase in serum creatinine levels. The suggested mechanism of nephrotoxicity is increased membrane permeability, resulting in tubulopathy, and influx of salts and water, leading to cell edema and lysis<sup>64</sup>. The definitions used for nephrotoxicity vary between studies and are not standardized, and include an increase in serum creatinine > 50% above baseline, a decrease in urine output below 50% of baseline or <1ml/kg/hr, or an increase in serum creatinine of >0.5mg/dL<sup>65-67</sup>. A case series by Alan et al reported a 19% renal toxicity rate in neonates receiving treatment with colistin<sup>52</sup>. Another retrospective study conducted by Bal et al in 104 children reported nephrotoxicity in 10.5% of patients receiving colistin<sup>65</sup>. These children, however, were also receiving other concomitant nephrotoxic drugs and none of the patients who were on colistin alone developed nephrotoxicity. Another study by Jajoo et al reported nephrotoxicity in 2 of the 18 neonates treated with colistin<sup>67</sup>. In other retrospective studies in neonates, including preterm neonates, colistin was well tolerated, with no reported cases of renal impairment<sup>39, 68</sup>. Electrolyte imbalances, particularly hypomagnesemia, hyponatremia and hypokalemia, have been reported in patients receiving colistin therapy. A recent retrospective study by Serafettin Tekgunduz et al in 12 neonates treated with intravenous colistin, reported significant hyponatremia and hypokalemia in 2 patients. In this study magnesium replacement was required at least once for all patients<sup>53</sup>. Another case-control study by Ipek et al comparing 47 neonates who were treated with colistin with 59 neonates treated with other antimicrobial agents other than colistin concluded that colistin use was significantly associated with hypokalemia and hypomagnesemia<sup>54</sup>. The mechanism of electrolyte deficiency may be explained by the tubulopathy described above. In a clinical trial conducted by Ngamprasertchai et al, 73 adult patients received intravenous PMB for the treatment of XDR Gram-negative infections<sup>69</sup>. In this study nephrotoxicity occurred in 25% of cases. In the study by Siddiqui et al on 14 critically ill children, ranging from 1 month to 15 years of age, treated with intravenous PMB for MDR Gram-negative infections, nephrotoxicity, defined by an increase of 100% serum creatinine level from the baseline after the use of PMB, was observed in 21% of patients<sup>56</sup>. There are limited data on the use and toxicity of PMB in neonates.

Neurotoxicity, a less commonly seen adverse effect of the polymyxins, has been attributed to the interaction of the polymyxins with lipid-rich neurons. The reported neurological manifestations of polymyxin toxicity from previous adult studies included dizziness, weakness, paresthesia, seizures and apneas<sup>64</sup>. Neurotoxicity in neonates attributable to polymyxin therapy has not been reported.

Very few studies, mostly in adults, have directly compared the toxicity of colistin with PMB. A recent prospective study on adult ICU patients compared nephrotoxicity rates in patients receiving colistin to those receiving PMB<sup>70</sup>. In this study, nephrotoxicity was defined as a two-fold increase in baseline serum creatinine or a 50% decrease in creatinine clearance. Sixty-one patients were treated with colistin and 51 patients with PMB. Nephrotoxicity was significantly higher in patients receiving colistin versus PMB (39% vs 12%). This finding is in keeping with another multicentre prospective study in adult patients comparing nephrotoxicity rates between the 2 drugs, which also concluded that colistin was significantly associated with higher rates of nephrotoxicity compared to PMB<sup>60</sup>. A recent meta-analysis comparing colistin and PMB has reported less nephrotoxicity with PMB compared to colistin<sup>61</sup>. PMB may therefore be the better choice of drug for treating infections with MDR organisms only susceptible to the polymyxins.



## 10. Conclusion

The global incidence of MDR Gram-negative bacterial infections in the neonatal population is rising. Of concern is the increasing emergence of infections with CRO. Polymyxins are one of the few current therapeutic options for treating these infections, despite huge gaps in knowledge regarding their use in neonates. Studies from adults have suggested that both CMS/colistin and PMB have similar efficacy but have safety concerns, in particular nephrotoxicity and related electrolyte abnormalities. The major concern with colistin is that it is administered in its inactive form, CMS, which requires in-vivo enzymatic hydrolysis to its active form. This conversion is incomplete, slow and unpredictable. It therefore appears that PMB might be a better treatment option because, unlike colistin, PMB is administered directly in its active form and is eliminated by non-renal pathways and therefore achieves more rapid and higher steady state concentrations. PMB may also have less nephrotoxicity when compared to colistin. There is an urgent need for PK and safety trials of PMB in neonates and children to ensure optimal dosing for treating infections with CRO.

## 11. Expert opinion

Despite the global increase in the incidence of MDR Gram-negative bacterial infections in neonates, including infections with CRO, the optimal choice of drug for treating these infections is still unknown. These infections are associated with high mortality if not treated adequately and in a timely fashion. Of the polymyxins, polymyxin E (colistin) and B are bactericidal drugs that have been used in the clinical setting for treating these multidrug resistant Gram-negative infections, particularly infections caused by Enterobacteriaceae, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Resistance to polymyxins has been reported and is increasing worldwide, and greater knowledge of the PK and PD of polymyxins in neonates is paramount to prevent the further development of resistance to these drugs. Colistin is administered intravenously in the form of its inactive prodrug, colistimethate sodium (CMS) and is mainly excreted by the kidneys. There is no general consensus on the standard dosing of colistin and currently used doses for treating serious Gram-negative MDR infections may be sub-optimal. A loading dose at the start of treatment may be beneficial in achieving concentrations above the MIC breakpoint more quickly. In adults, a loading dose of 9MU followed by 4.5MU every 12 hours has been recommended. A dose of 75000 – 120000 IU/kg/day has been used in the neonatal population, but data suggests this is unlikely to achieve therapeutic concentrations. Excretion is reduced in patients with renal impairment, therefore dosing adjustments should be made in these patients. Polymyxin B is administered intravenously in its active form and is excreted by non-renal pathways. Data on the optimal dose of PMB is also extremely limited. CMS/colistin and polymyxin B have been shown to have similar efficacy in adult studies but have safety concerns. However, polymyxin B appears to be a better therapeutic option, with quicker and higher steady state concentrations achieved compared to colistin. The most commonly reported adverse effect of the polymyxins is nephrotoxicity. Nephrotoxicity has been reported to be significantly higher in patients receiving colistin compared to PMB. Neurotoxicity is a less commonly seen adverse effect of polymyxins. Electrolyte imbalances, particularly hypomagnesemia,

hyponatremia and hypokalemia, have also been reported in neonates receiving colistin therapy. There is a great need for future PK and PD trials in neonates and children on polymyxins, to determine the optimal choice of drug and dosing regimen and provide recommendations. The next step is to conduct both a single dose PK study of polymyxin B in neonates and children and a randomized multidose PK and safety study trial directly comparing colistin and polymyxin B in the same population. Other questions that need to be addressed include the benefits of using polymyxins in combination with other antimicrobials versus monotherapy, as results from studies have been conflicting. If combination therapy is to be used, the best antimicrobial combination to optimize synergy and reduce risk of resistance is yet to be determined. Future clinical trials are also needed to look at other therapeutic options and define the best available treatment. Currently, there are newer agents that have been recently registered or are in late stage clinical development, which will hopefully soon be available for clinical use. While awaiting the development of these antibiotics, it is important to use the polymyxins optimally, while reducing the development of toxicity and resistance and only new trials will provide the information now urgently required

## 12. References:

1. Collaborators GBDCM. Global, regional, national, and selected subnational levels of stillbirths, neonatal, infant, and under-5 mortality, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388(10053):1725-74.
2. United Nations. The Millenium Development Goals Report. 2015.
3. Dong Y, Speer CP. Late-onset neonatal sepsis: recent developments. *Arch Dis Child Fetal Neonatal Ed*. 2015;100(3):F257-63.
4. Dramowski A, Madide A, Bekker A. Neonatal nosocomial bloodstream infections at a referral hospital in a middle-income country: burden, pathogens, antimicrobial resistance and mortality. *Paediatr Int Child Health*. 2015;35(3):265-72.
5. Greenberg RG, Kandefer S, Do BT, et al. Late-onset Sepsis in Extremely Premature Infants: 2000-2011. *Pediatr Infect Dis J*. 2017;36(8):774-9.
6. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect*. 2012;18(3):268-81.
7. \*\*Investigators of the Delhi Neonatal Infection Study. Characterisation and antimicrobial resistance of sepsis pathogens in neonates born in tertiary care centres in Delhi, India: a cohort study. *Lancet Glob Health*. 2016;4(10):e752-60. This is a large prospective cohort study on neonates admitted to the intensive care unit. This study provides valuable information on the incidence, age of onset, microbial aetiology, susceptibility and case-fatality of neonatal sepsis in a low-middle income country.
8. Ozsurekci Y, Aykac K, Cengiz AB, et al. Bloodstream infections in children caused by carbapenem-resistant versus carbapenem-susceptible gram-negative

- microorganisms: Risk factors and outcome. *Diagn Microbiol Infect Dis*. 2017;87(4):359-64.
9. Logan LK. Carbapenem-resistant enterobacteriaceae: an emerging problem in children. *Clin Infect Dis*. 2012;55(6):852-9.
  10. Logan LK, Weinstein RA. The Epidemiology of Carbapenem-Resistant Enterobacteriaceae: The Impact and Evolution of a Global Menace. *J Infect Dis*. 2017;215(suppl\_1):S28-S36.
  11. Zingg W, Hopkins S, Gayet-Ageron A, et al. Health-care-associated infections in neonates, children, and adolescents: an analysis of paediatric data from the European Centre for Disease Prevention and Control point-prevalence survey. *Lancet Infect Dis*. 2017;17(4):381-9.
  12. Zarrilli R, Bagattini M, Esposito EP, et al. Acinetobacter Infections in Neonates. *Current infectious disease reports*. 2018;20(12):48.
  13. Dramowski A, Aucamp M, Bekker A, et al. Infectious disease exposures and outbreaks at a South African neonatal unit with review of neonatal outbreak epidemiology in Africa. *Int J Infect Dis*. 2017;57:79-85.
  14. Folgori L, Bielicki J, Heath PT, et al. Antimicrobial-resistant Gram-negative infections in neonates: burden of disease and challenges in treatment. *Curr Opin Infect Dis*. 2017;30(3):281-8.
  15. \*\*Williams CMP, Isaacs D, Berkley A.J. Antimicrobial resistance among children in sub-Saharan Africa. *Lancet Infect Dis*. 2018;18:e33-44. This is a systematic review of studies of antimicrobial resistance among children in sub-Saharan Africa since 2005, providing data from 67 451 invasive bacterial isolates, providing valuable information on microbial aetiology and antimicrobial susceptibility.
  16. Hosoglu S HM, Yasar E, Uslu S, et al. Control of an Acinetobacter baumannii outbreak in a neonatal ICU without suspension of service: a devastating outbreak in Diyarbakir, Turkey. *Infection*. 2012;40:11 - 8.
  17. Dias VC, Diniz CG, Peter AC, et al. Epidemiological characteristics and antimicrobial susceptibility among carbapenem-resistant non-fermenting bacteria in Brazil. *J Infect Dev Ctries*. 2016;10(6):544-53.
  18. Lowings M, Ehlers MM, Dreyer AW, et al. High prevalence of oxacillinases in clinical multidrug-resistant Acinetobacter baumannii isolates from the Tshwane region, South Africa - an update. *BMC Infect Dis*. 2015;15:521.
  19. Eibach D, Belmar Campos C, Krumkamp R, et al. Extended spectrum beta-lactamase producing Enterobacteriaceae causing bloodstream infections in rural Ghana, 2007-2012. *Int J Med Microbiol*. 2016;306(4):249-54.
  20. Tsai MH, Chu SM, Hsu JF, et al. Risk factors and outcomes for multidrug-resistant Gram-negative bacteremia in the NICU. *Pediatrics*. 2014;133(2):e322-9.
  21. Datta S, Roy S, Chatterjee S, et al. A five-year experience of carbapenem resistance in Enterobacteriaceae causing neonatal septicaemia: predominance of NDM-1. *PLoS One*. 2014;9(11):e112101.
  22. Zhu J, Sun L, Ding B, et al. Outbreak of NDM-1-producing Klebsiella pneumoniae ST76 and ST37 isolates in neonates. *Eur J Clin Microbiol Infect Dis*. 2016;35(4):611-8.
  23. Lee CR, Lee JH, Park M, et al. Biology of Acinetobacter baumannii: Pathogenesis, Antibiotic Resistance Mechanisms, and Prospective Treatment Options. *Front Cell Infect Microbiol*. 2017;7:55.

24. Shin B, Park W. Antibiotic resistance of pathogenic *Acinetobacter* species and emerging combination therapy. *J Microbiol.* 2017;55(11):837-49.
25. \*\*Bush K. Past and Present Perspectives on beta-Lactamases. *Antimicrobial agents and chemotherapy.* 2018;62(10). This is a comprehensive review of beta lactamases describing their origin, resistance mechanisms in Gram-negative and Gram-positive organisms and the more recent classifications combining molecular and biochemical characteristics.
26. Iovleva A, Doi Y. Carbapenem-Resistant Enterobacteriaceae. *Clin Lab Med.* 2017;37(2):303-15.
27. Kazmierczak KM, Tsuji M, Wise MG, et al. In vitro activity of cefiderocol, a siderophore cephalosporin, against a recent collection of clinically relevant carbapenem-nonsusceptible Gram-negative bacilli, including serine carbapenemase- and metallo-beta-lactamase-producing isolates (SIDERO-WT-2014 Study). *Int J Antimicrob Agents.* 2018.
28. Dobias J, Denervaud-Tendon V, Poirel L, et al. Activity of the novel siderophore cephalosporin cefiderocol against multidrug-resistant Gram-negative pathogens. *Eur J Clin Microbiol Infect Dis.* 2017;36(12):2319-27.
29. WHO Model List of Essential Medicines for Children 2017; 6th Edition. Available from: <http://www.who.int/medicines/publications/essentialmedicines/en/>.
30. Zusman O, Altunin S, Koppel F, et al. Polymyxin monotherapy or in combination against carbapenem-resistant bacteria: systematic review and meta-analysis. *The Journal of antimicrobial chemotherapy.* 2017;72(1):29-39.
31. Paul M, Daikos GL, Durante-Mangoni E, et al. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. *Lancet Infect Dis.* 2018;18(4):391-400.
32. Giamarellou H. Epidemiology of infections caused by polymyxin-resistant pathogens. *Int J Antimicrob Agents.* 2016;48(6):614-21.
33. Couet W, Gregoire N, Marchand S, et al. Colistin pharmacokinetics: the fog is lifting. *Clin Microbiol Infect.* 2012;18(1):30-9.
34. Labuschagne Q SN, Gous A, Bronkhorst, et al. Colistin: adult and paediatric guideline for South Africa. *South Afr J Infect Dis.* 2016;31(1):3-7.
35. Dalfino L, Puntillo F, Mosca A, et al. High-dose, extended-interval colistin administration in critically ill patients: is this the right dosing strategy? A preliminary study. *Clin Infect Dis.* 2012;54(12):1720-6.
36. Friis-Hansen BJ, Holiday M, Stapleton T, et al. Total body water in children. *Pediatrics.* 1951;7(3):321-7.
37. Anderson BJ, Woollard GA, Holford NH. A model for size and age changes in the pharmacokinetics of paracetamol in neonates, infants and children. *British journal of clinical pharmacology.* 2000;50(2):125-34.
38. Kearns GL, Abdel-Rahman SM, Alander SW, et al. Developmental pharmacology, drug disposition, action, and therapy in infants and children. *The New England journal of medicine.* 2003;349(12):1157-67.
39. \*\*Nakwan N, Usaha S, Chokephaibulkit K, et al. Pharmacokinetics of Colistin Following a Single Dose of Intravenous Colistimethate Sodium in Critically Ill Neonates. *Pediatr Infect Dis J.* 2016;35(11):1211-4. This is one, and the most recent, of only 2 detailed colistin PK studies conducted in neonates. It is

a prospective study which evaluated the PK of colistin after a single dose of IV CMS in 7 neonates.

40. Imberti R, Cusato M, Accetta G, et al. Pharmacokinetics of colistin in cerebrospinal fluid after intraventricular administration of colistin methanesulfonate. *Antimicrobial agents and chemotherapy*. 2012;56(8):4416-21.
41. Ziaka M, Markantonis SL, Fousteri M, et al. Combined intravenous and intraventricular administration of colistin methanesulfonate in critically ill patients with central nervous system infection. *Antimicrobial agents and chemotherapy*. 2013;57(4):1938-40.
42. \*Manchandani P, Thamlikitkul V, Dubrovskaya Y, et al. Population Pharmacokinetics of Polymyxin B. *Clinical pharmacology and therapeutics*. 2017. This is a large PMB PK study involving 35 adults. This study also investigated factors influencing PK variability.
43. Sandri AM, Landersdorfer CB, Jacob J, et al. Population pharmacokinetics of intravenous polymyxin B in critically ill patients: implications for selection of dosage regimens. *Clin Infect Dis*. 2013;57(4):524-31.
44. Tran TB, Velkov T, Nation RL, et al. Pharmacokinetics/pharmacodynamics of colistin and polymyxin B: are we there yet? *Int J Antimicrob Agents*. 2016;48(6):592-7.
45. Cheah SE, Wang J, Nguyen VT, et al. New pharmacokinetic/pharmacodynamic studies of systemically administered colistin against *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in mouse thigh and lung infection models: smaller response in lung infection. *The Journal of antimicrobial chemotherapy*. 2015;70(12):3291-7.
46. Poudyal A, Howden BP, Bell JM, et al. In vitro pharmacodynamics of colistin against multidrug-resistant *Klebsiella pneumoniae*. *The Journal of antimicrobial chemotherapy*. 2008;62(6):1311-8.
47. Tran TB, Cheah SE, Yu HH, et al. Anthelmintic closantel enhances bacterial killing of polymyxin B against multidrug-resistant *Acinetobacter baumannii*. *The Journal of antibiotics*. 2016;69(6):415-21.
48. Dudhani RV, Turnidge JD, Coulthard K, et al. Elucidation of the pharmacokinetic/pharmacodynamic determinant of colistin activity against *Pseudomonas aeruginosa* in murine thigh and lung infection models. *Antimicrobial agents and chemotherapy*. 2010;54(3):1117-24.
49. Tam VH, Schilling AN, Vo G, et al. Pharmacodynamics of polymyxin B against *Pseudomonas aeruginosa*. *Antimicrobial agents and chemotherapy*. 2005;49(9):3624-30.
50. The European Committee on Antimicrobial Susceptibility Testing (EUCAST). Warnings concerning antimicrobial susceptibility testing products or procedures. 2016. Available from: [http://www.eucast.org/ast\\_of\\_bacteria/warnings/](http://www.eucast.org/ast_of_bacteria/warnings/).
51. Bergen PJ, Landersdorfer CB, Zhang J, et al. Pharmacokinetics and pharmacodynamics of 'old' polymyxins: what is new? *Diagn Microbiol Infect Dis*. 2012;74(3):213-23.
52. Alan S, Yildiz D, Erdeve O, et al. Efficacy and safety of intravenous colistin in preterm infants with nosocomial sepsis caused by *Acinetobacter baumannii*. *American journal of perinatology*. 2014;31(12):1079-86.

53. Serafettin Tekgunduz K, Kara M, et al. Safety and Efficacy of Intravenous Colistin in Neonates With Culture Proven Sepsis. *Iranian journal of pediatrics*. 2015;25(4):e453.
54. Ipek MS, Aktar F, Okur N, et al. Colistin use in critically ill neonates: A case-control study. *Pediatr Neonatol*. 2017;58(6):490-6.
55. Saleem AF, Shah MS, Shaikh AS, et al. *Acinetobacter* species meningitis in children: a case series from Karachi, Pakistan. *J Infect Dev Ctries*. 2011;5(11):809-14.
56. Siddiqui NU, Qamar FN, Jurair H, et al. Multi-drug resistant gram negative infections and use of intravenous polymyxin B in critically ill children of developing country: retrospective cohort study. *BMC Infect Dis*. 2014;14:626.
57. Oliveira MS, Prado GV, Costa SF, et al. Polymyxin B and colistimethate are comparable as to efficacy and renal toxicity. *Diagn Microbiol Infect Dis*. 2009;65(4):431-4.
58. Tuon FF, Rigatto MH, Lopes CK, et al. Risk factors for acute kidney injury in patients treated with polymyxin B or colistin methanesulfonate sodium. *Int J Antimicrob Agents*. 2014;43(4):349-52.
59. Phe K, Lee Y, McDanel PM, et al. In vitro assessment and multicenter cohort study of comparative nephrotoxicity rates associated with colistimethate versus polymyxin B therapy. *Antimicrobial agents and chemotherapy*. 2014;58(5):2740-6.
60. Rigatto MH, Oliveira MS, Perdigao-Neto LV, et al. Multicenter Prospective Cohort Study of Renal Failure in Patients Treated with Colistin versus Polymyxin B. *Antimicrobial agents and chemotherapy*. 2016;60(4):2443-9.
61. Vardakas KZ, Falagas ME. Colistin versus polymyxin B for the treatment of patients with multidrug-resistant Gram-negative infections: a systematic review and meta-analysis. *Int J Antimicrob Agents*. 2017;49(2):233-8.
62. Pogue JM, Ortwine JK, Kaye KS. Clinical considerations for optimal use of the polymyxins: A focus on agent selection and dosing. *Clin Microbiol Infect*. 2017;23(4):229-33.
63. Folgori L, Bielicki J, Ruiz B, et al. Harmonisation in study design and outcomes in paediatric antibiotic clinical trials: a systematic review. *Lancet Infect Dis*. 2016;16(9):e178-e89.
64. \*Falagas ME, Kasiakou SK. Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. *Critical care*. 2006;10(1):R27. This is a systematic review of old and recent studies that have reported data on polymyxin induced toxicity. This review provides new evidence on the toxicity of polymyxins compared to historical reports.
65. Bal ZS CF, Yazici P, Anil AB, et al. The evaluation of safety and efficacy of colistin use in pediatric intensive care unit: Results from two reference hospitals and review of literature. *J Infect Chemother* 2018;24:370 - 5.
66. Cagan E BE, Asker HS. Use of colistin in a neonatal intensive care unit: A cohort of 65 patients. *Med Sci Monit* 2017;23:548 - 54.
67. Jajoo M, Kumar V, Jain M, et al. Intravenous colistin administration in neonates. *Pediatr Infect Dis J*. 2011;30(3):218-21.
68. Jasani B, Kannan S, Nanavati R, et al, Thatte U. An audit of colistin use in neonatal sepsis from a tertiary care centre of a resource-limited country. *Indian J Med Res*. 2016;144(3):433-9.

69. Ngamprasertchai T, Boonyasiri A, Charoenpong L, et al. Effectiveness and safety of polymyxin B for the treatment of infections caused by extensively drug-resistant Gram-negative bacteria in Thailand. *Infection and drug resistance*. 2018;11:1219-24.
70. Aggarwal R, Dewan A. Comparison of nephrotoxicity of Colistin with Polymyxin B administered in currently recommended doses: a prospective study. *Annals of clinical microbiology and antimicrobials*. 2018;17(1):15.