REVIEW ARTICLE

Rational Use of Polymyxins Against Multi-Drug Resistant Gram-Negative Bacteria

Paul Sherwin O. Tarnate, MD, DPPS[1]
Cecilia C. Maramba-Lazarte, MD, MScID, MScCT[1,2]

[1] Division of Infectious and Tropical Diseases in Pediatrics
Department of Pediatrics, UP-Philippine General Hospital

[2] Department of Pharmacology and Toxicology
University of the Philippines Manila

Correspondence:
Dr. Paul Sherwin O. Tarnate
Email: psotarnate@gmail.com

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ABSTRACT

The current strategy in treating multi-drug resistant gram-negative bacterial (MDR-GNB) infections is salvage therapy by using polymyxins. However, the beginning emergence of polymyxin resistance should enforce strict antimicrobial stewardship programs to preserve polymyxin efficacy. Knowledge of structural characteristics, pharmacodynamic, and pharmacokinetic profiles of polymyxins, as well as consideration of efficacy, safety, suitability, and cost, will help in the choice of the appropriate polymyxin for therapy. Polymyxin B is the recommended polymyxin for systemic use, while colistin is recommended for lower urinary tract infections, intraventricular, and intrathecal use. Either polymyxin can be used for hospital-acquired and ventilator-associated pneumonia. Combination therapy over monotherapy remains to be advantageous due to synergism and decreased resistance development. The choice of the second drug to be used should be based on full susceptibility, or if unavailable, a drug with the least minimum inhibitory concentration relative to the breakpoint set by the Clinical and Laboratory Standards Institute. Using the mnemonic **ESCAPE** can also guide physicians in their polymyxin prescription process: (1) Checking if the pathogen is **E**xtensively resistant or multi-drug resistant; (2) checking the patient's clinical status if compatible with **S**ignificant infection; (3) using **C**ombination therapy; (4) ensuring **A**dequate dosing; (5) **P**roper preparation and administration of drug; and (6) keeping an **E**ye for response and adverse effects.

KEYWORDS: *Polymyxin B, Colistin, MDR-GNB, Polymyxins*

INTRODUCTION

Emergence of antimicrobial resistance

The emergence of multi-drug resistant gram-negative bacteria (MDR-GNB) has been raising clinical concerns due to swift and unprecedented transmission and spread, especially in health care settings.[1] In the Philippines, according to the Antimicrobial Resistance Surveillance Program (ARSP) in 2018, MDR rates continued to rise across clinically relevant gram-negative bacteria (GNB). MDR rates for *Escherichia coli* and *Klebsiella pneumoniae* blood isolates were at 46% and 59%, respectively. *E. coli* has notable carbapenem resistance rates at 5%, but *K. pneumoniae and Pseudomonas aeruginosa* have even higher rates at 16-19%. However, *Acinetobacter baumannii* exhibited an alarming carbapenem resistance at 56%. [2]

Current antimicrobial use

In relation to the current global situation, data from hospitals show that more than 90% in some cohorts are being treated with antibiotics to cure or protect against secondary infection during hospitalization.[3] Unfortunately, the patients at greatest risk for superbugs are the ones who are already more vulnerable to illnesses. Inappropriate use of antimicrobials (e.g., disregard for the spectrum of activity, inappropriate dosing, timing, and duration) led to the emergence of MDRs.

Use of salvage therapy

A further complication is that there has been a slow-down in the development of newer antimicrobials in the development pipeline, forcing clinicians to use "salvage" therapy from old but less studied drugs such as polymyxins.[4,5] However, there is still limited clinical experience with the use of these drugs in terms of appropriate dosing to limit adverse effects without sacrificing efficacy. This could potentially lead to misuse and resistance development of these last resort antimicrobials.[6]

Usage timeline of polymyxins

Polymyxins were initially discovered in 1947, derived from products of strains of *Bacillus polymyxa* (Polymyxin B) and *Bacillus colistinus* (Colistin). They were used parenterally but eventually lost their favor when anti-*Pseudomonas* aminoglycosides came into the picture. They subsequently fell into disuse by the 1980s due to safety concerns, including nephrotoxicity. The resurgence in the use of polymyxins in clinical practice was due to the recent development of multi-drug resistance. In the Philippines, polymyxin use was considered as the last therapeutic option for multi-MDR-GNB in the mid-2010s (see Fig. 1).

One of the main reasons behind the preferential use of colistin over polymyxin B was the anecdotal belief that colistin was the safer option with respect to nephrotoxicity. However, modern-day data suggests that polymyxin B might be the safer option with respect to kidneys, debunking this historical notion.[7]

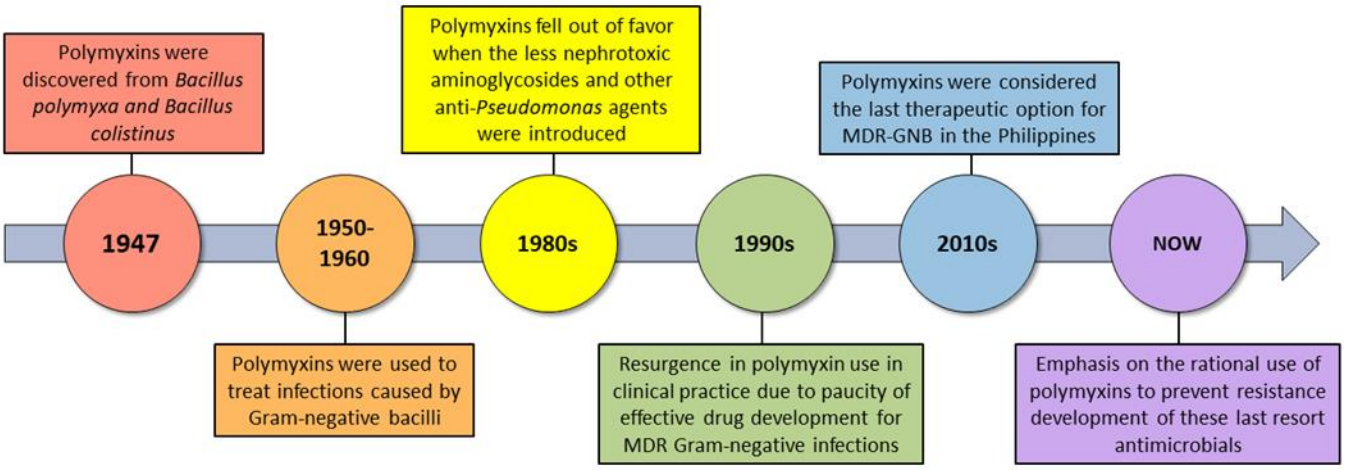

Figure 1. Development and usage timeline of polymyxins

Polymyxin resistance begins

There have been increasing reports of polymyxin resistance among carbapenem-resistant GNBs.[8–11] In the Philippines in 2018, there was actual documentation of the emergence of colistin-resistance gene *mcr-1* in *E. coli* clinical isolates. Both isolates came from patients admitted in a tertiary hospital in Quezon City, Philippines, with no prior colistin treatment nor travel history within 6 months prior to admission. The first isolate came from a diabetic foot wound of a 75-year-old female, while the second isolate came from a blood sample of a 61-year-old male with urinary tract infection. This may be indicative of local transmission of *mcr-1* from community settings within the Philippines. This implicates plasmid-mediated polymyxin resistance via the *mcr-1* gene.[12]

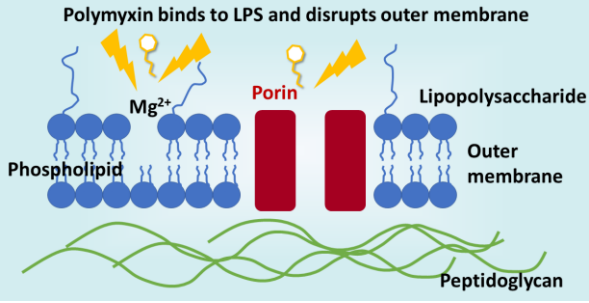

Figure 2. Interaction between polymyxin and gram-negative bacterial cell wall

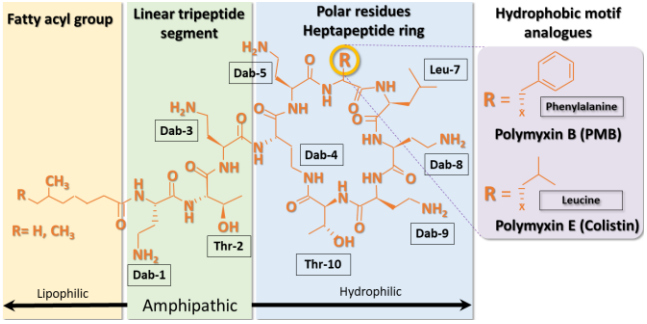

Figure 3. Chemical structure of Polymyxins.
Dab = diaminobutyric acid; *Thr* = threonine; *Leu* = leucine

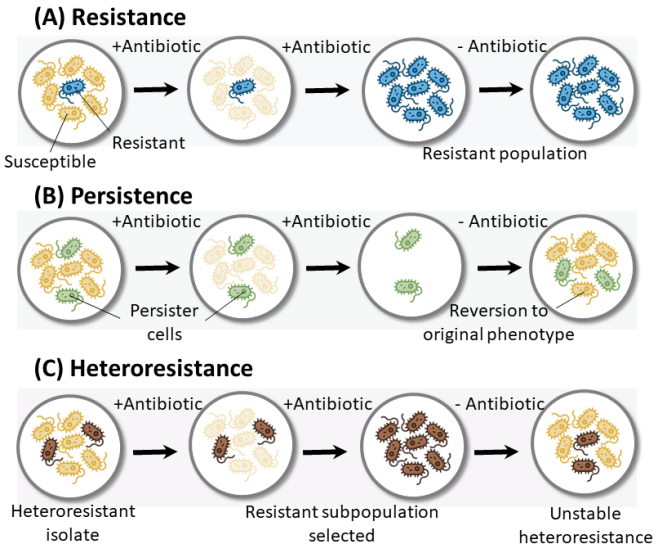

Figure 4. Bacterial heterogeneity and variance in behavior

Rational use of polymyxins

This leads us to signal the need to establish strict antimicrobial stewardship programs and strategies for the rational use of polymyxins to preserve their efficacy.[5,12] This article will (1) illustrate the structural characteristics, basic pharmacokinetics, and pharmacodynamics of polymyxins; (2) emphasize the importance of using combination therapies instead of monotherapy in using polymyxins; (3) present benefits and disadvantages in using polymyxin B or colistin depending on specific situations; and (4) formulate a simple guide in the use of polymyxin class of antibiotics in a healthcare setting using the ESCAPE mnemonic.

POLYMYXIN CLASS (B and E)

Chemistry and mechanism of action

Polymyxins are bactericidal antibiotics that are cationic, while GNB cell walls have anionic lipopolysaccharides (LPS). The interaction (see Fig. 2) between polymyxins and the gram-negative bacterial cell wall results in the displacement of calcium and magnesium from the phosphate group, leading to destabilization of the monolayer, reduction of the circulating endotoxin, and ultimately cell death.[13,14]

Polymyxin B and polymyxin E/colistin (see Fig. 3) share a common sequence, and the only difference is *R* at position 6, for which phenylalanine is the amino acid for polymyxin B and leucine for colistin.[5] Thus, these two polymyxins are basically similar: having the same structure with just one amino acid difference, but with the same mechanism of action. Like other peptide antibiotics, the presence of hydrophilic and lipophilic

groups makes them amphipathic, a property essential for its mechanism of action, as previously discussed.

Bacterial heterogeneity and resistance mechanisms

Figure 4A illustrates the concept of bacterial resistance. Applying antibiotic pressure would kill the bacteria, but a certain resistant subpopulation would remain despite the presence of the antibiotic. Resistant cells thereby give rise to a new population that is genetically distinct from the original one.[15]

Ongoing researches have been exploring polymyxin resistance mechanisms, and these include: (1) modification of bacterial LPD lipid A component; (2) halting of LPS production—once LPS is lost, there is nothing for polymyxins to target; (3) efflux pump production; and (4) plasmid-mediated resistance in which the resistance gene can be transferred to other bacteria.[16]

In contrast to resistant cells, there are bacterial subpopulations that exhibit a different kind of behavior, such as persistence (Figure 4B). Antibiotic pressure kills the bacteria but persister cells, which are phenotypic variants that can survive antibiotic treatment, remain. The difference is that they cannot grow in the presence of the antibiotic. When treatment ceases, persisters can switch back to the antibiotic-sensitive phenotype and give rise to a new population that is genetically identical to the original one.[15]

Another kind of behavior that proves to be one of the bigger problems in MDROs is heteroresistance (Figure 4C). Similarly, antibiotics kill bacteria, but heteroresistant cells survive and grow even in the presence of the antibiotic. Once antibiotic pressure drops, the cells revert to the antibiotic-sensitive state. Heteroresistant cells are persister cells that grow under antibiotic therapy.[15]

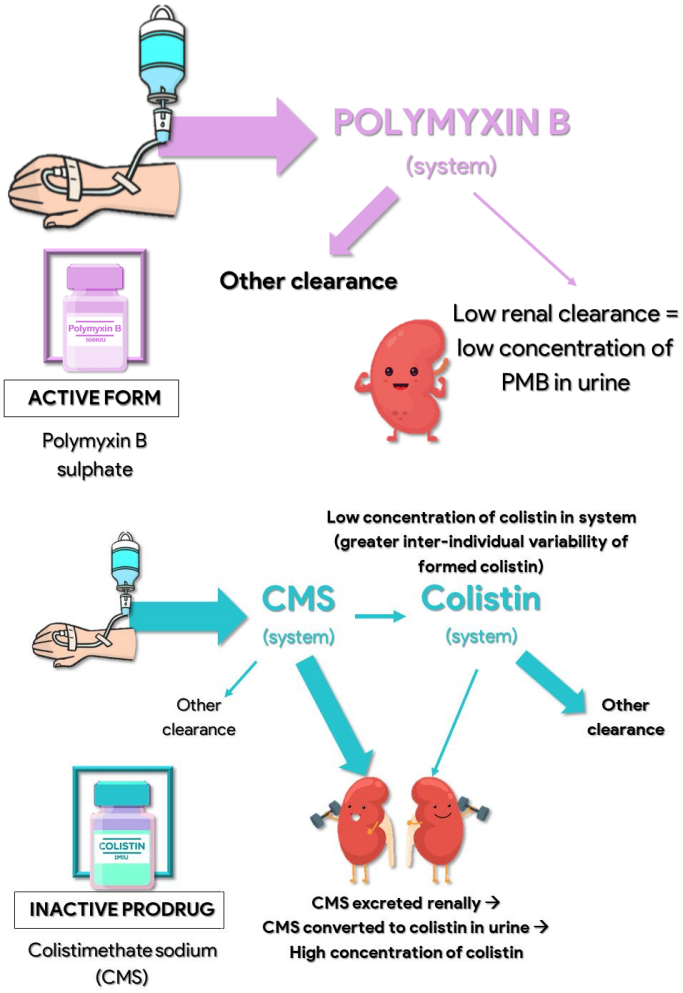

Figure 5. Pharmacokinetic pathways after intravenous polymyxin administration. *Note: Arrow thickness and font boldness indicate relative extent of clearance provided that renal function is normal*

Problem of Heteroresistance

Reaching optimum concentrations of an antibiotic can kill bacteria, but unfortunately, the presence of heteroresistant subpopulations can lead to bacterial regrowth. One of the proposed solutions to this problem is source control. It has been shown that polymyxins bactericidal activity is inhibited when exposed to a high initial inoculum. This may pose problems in treating infective endocarditis or deep-seated abscesses without prior adequate source reduction. With adequate source control, most of the initial inoculum will be removed, thus enabling antibiotics to eradicate the remaining bacterial population.[5]

Minimum inhibitory concentrations (MIC)

The Clinical and Laboratory Standards Institute (CLSI) has established recommended breakpoints for *P. aeruginosa* and *Acinetobacter* species for both colistin and polymyxin B. On the other hand, no breakpoints were made yet for *Enterobacteriaceae*, but epidemiologic cut-offs were defined (MIC ≤2µg/mL).[16,17] MIC breakpoints have already been determined for *Acinetobacter* (MIC ≤2µg/mL) and *Pseudomonas* (MIC ≤2µg/mL).[17] There are no major differences in breakpoints between colistin and polymyxin B because they are essentially similar.

Dosing and conversions

Conversion might be a little tedious when it comes to colistin because some practitioners variably use Colistin Base Activity (CBA) units, International Units (IU), or milligrams (mg). Approximately 1 CBA is equivalent to 30,000 IU per mg. On the other hand, polymyxin B conversion is easier, since 1 mg is equal to 10,000 IU. Either polymyxin requires loading doses to achieve desired antibiotic concentrations, followed by recommended maintenance doses:

1. Colistin loading dose is 150,000 IU/kg, followed by maintenance dose of 150,000 IU/kg/day divided q8 hours (for neonates) or 75,000 IU/kg/day divided q8 hours (for children); and
2. Polymyxin B loading dose is 2.5 mg/kg, followed by maintenance doses of 2.5-3 mg/kg/day divided q12 hours.

A relatively larger volume of diluent is required for polymyxin B (around 300-500 mL of D5 fluid for every 500,000 IU) compared to colistin (10 mL NSS to reconstitute 1M IU with 50 mL NSS to infuse).

Pharmacokinetics

The two polymyxins differ pharmacokinetically. Figure 5 shows the pharmacokinetic pathway following intravenous administration of polymyxin B and colistin.

Generally, polymyxin B has a superior pharmacokinetic profile because it is already formulated in its active antimicrobial form. After IV administration, the drug gets to the system already in its active form, achieving desired concentrations in plasma rapidly and reliably performing its killing duty.[7] Eventually, it is subjected to renal filtration and tubular reabsorption, with a low concentration of polymyxin B in urine due to low renal clearance. Most of the drug undergoes non-renal elimination.[5]

On the other hand, the pharmacokinetic pathway of colistin is rather complicated because it is administered in the form of an inactive prodrug, colistimethate sodium, or colistin methanosulphate (CMS). CMS is predominantly excreted by the kidney and is converted to colistin in urine; hence, a high urinary concentration of colistin is expected. Only about 20-25% of CMS are converted to colistin, and this conversion estimation has great inter-individual variability. Thus, to obtain sufficient plasma concentration of active colistin, about five times the amount of CMS is needed to be administered. This slow conversion of CMS also leads to a delay in bacterial killing. The rest of colistin undergoes non-renal elimination after.[5,14]

POLYMYXIN USE IN CHILDREN

There is lack of data in the use of polymyxins among the pediatric age group, especially in the critically ill. However, several studies regarding the use of colistin and polymyxin B in children have been made and are cited within this article.

Pharmacokinetic and pharmacodynamic data on polymyxin use are mostly derived from adult studies, as studies involving neonates and children are very limited. The first pharmacokinetic study involving intravenous CMS use in critically ill neonates was published by Nakwan *et al.* in 2016. It was found that approximately 150,000 IU/kg of CMS was well tolerated with no adverse effects, albeit with suboptimal plasma colistin concentrations. Further studies exploring higher daily doses and different dosing regimens were recommended.[18]

In terms of efficacy of polymyxin use in neonates, a case-control study involving forty-seven (47) neonates admitted in two centers in Turkey has shown that CMS was effective for treating MDR-GNB infections in neonates but was significantly associated with low magnesium and potassium, which led to its discontinuation.[19] On the other hand, two retrospective studies done in Turkey involving neonates have shown good recovery rates and effective MDR-GNB microbiologic clearance with the use of CMS. However, CMS use was associated with reversible acute kidney injury and electrolyte imbalances.[20,21] A similar retrospective study involving neonates was also done in the Philippines (see the section on *Choosing the Right Polymyxin: Safety*). Large prospective controlled studies

are needed to confirm CMS efficacy and safety in neonates.

In contrast, there are only sporadic published reports involving polymyxin B (PMB) use. There were no studies yet involving neonates, but there are some published involving children (see also section on *Monotherapy vs. Combination Therapy: Clinical outcomes in Polymyxin B monotherapy*). A retrospective study involving polymyxin use for bacterial meningitis in children showed successful results.[22] Similarly, a retrospective study involving the use of polymyxins (including PMB) for the treatment of intracranial infections in children after the neurosurgical operation has shown effectiveness with no noted serious adverse effects.[23]

No studies yet have been published that compared the efficacy of CMS and PMB in children or neonates. Randomized controlled trials are needed to meticulously outline the most effective and safest polymyxin regimen in pediatrics.

MONOTHERAPY VS COMBINATION THERAPY

Polymyxin B *in vitro* performance

A study by Tam et al. in 2011 measured the potency of polymyxin B components against three standard wild-type bacterial strains and three clinical MDR strains (*P. aeruginosa, A. baumannii,* and *K. pneumoniae*) using the broth dilution method, and they found out that there were no substantial differences in potency against wild-type and MDR strains. Another *in vitro* study measured the activity of polymyxin B against 217 strains of carbapenem-resistant *A. baumannii* from different patients, and they identified 98.2% of the strains being susceptible to polymyxin B.[24] A similar *in vitro* study done in Mexico measured susceptibility of highly lethal and biofilm-producing clones of MDR *A. baumannii* to polymyxin B, and results were promising at 100% susceptibility rate.[25]

Clinical outcomes of polymyxin B monotherapy

Although *in vitro* studies show satisfactory efficacy of polymyxin B against drug-resistant isolates, some clinical studies show guarded results. A retrospective study by Nelson *et al.* in 2011 examined the clinical outcomes of 151 patients receiving polymyxin B therapy for carbapenem-resistant GNB bloodstream infections (*K. pneumoniae* 60.9%, *A. baumannii* 21.2%, and *P. aeruginosa* 11.3%). They noted a 30-day mortality at 37.8% and clinical cure by 7th day at 63.6%. Another retrospective study involving pediatric cases in a developing country (critically ill children less than 15 years old) likewise measured clinical outcomes of children receiving polymyxin B against MDR-GNB infections showed only a modest survival of 8 out of 14 children—57.1%.[26]

Risk factors for monotherapy failure

A retrospective study conducted by Dubrovskaya *et al.* in 2013 investigated the risk factors for polymyxin B treatment failure among carbapenem-resistant *K. pneumoniae* (CRKP). The group found out that the only identified independent risk factor after the multivariable analysis is baseline renal insufficiency, for which it is associated with six (6) times greater chances of clinical failure. The study also showed relatively higher treatment success—clinical cure at 73% (29/40) and microbiologic cure at 28% (17/32)—as well as low 30-day mortality at 28%. However, what this study also found is that with monotherapy, 45% (18/40) had repeat CRKP infection and 7.5% (3/40) had breakthrough infections intrinsically resistant to polymyxin B. One of the recommendations of this study was to give it as a combination with other antibiotics to prevent emergence of resistance.[27]

Advantages of combination therapy

Combination therapy basically provides advantages in the treatment of MDR infections, namely: (1) effectively increasing bactericidal activity via synergism; and (2) reducing the development of resistance compared to monotherapy.[28]

Synergism in combination therapy

A study done in Australia illustrated via scanning electron microscopy the synergistic killing of MDR *K. pneumoniae* by using polymyxin B and chloramphenicol. Chloramphenicol monotherapy was shown to be ineffective (no significant cell wall change) since it is only bacteriostatic and is involved in protein synthesis inhibition. Polymyxin B monotherapy caused projections and blebs on the bacterial surface, which is consistent with its mechanism of action. However, there was also rapid regrowth and resistance emergence with monotherapy. Combination treatment showed denser projections and blebs than polymyxin B monotherapy, and there were no polymyxin-resistant isolates noted.[29]

Other combination treatment studies differ in treatment regimen used and the organisms they chose to target, but their results show polymyxin and beta-lactam/carbapenem combination most effective in

eradicating MDR / extremely drug-resistant (XDR) organisms and has lower mortality reports.[30,31] A study conducted by Teo *et al.* in 2015 identified bactericidal polymyxin B-based combinations against XDR *A. baumannii.* The clinical samples came from Thammasat University, Thailand, and the combination treatment regimen they used include polymyxin B plus imipenem, meropenem, doripenem, rifampicin, and tigecycline. Polymyxin B monotherapy against the XDR strain is satisfactory at 87.8%. However, whenever polymyxin B is combined with carbapenems, bactericidal activity rose to 100%. This supports the premise that combination therapy is superior to monotherapy.[32]

Combination therapy synergism was also well-described in a study done in Israel in which they meta-analytically pooled the synergy rates across 39 studies. They had found that even when the strains were carbapenem-resistant, synergy rates from polymyxin B and carbapenem combination against *Acinetobacter* were still acceptable (77% versus 71% for resistant strains) and even increased against *Klebsiella* (44% versus 55%) and *Pseudomonas* strains (50% versus 59%).[32]

Less resistance development in combination therapy

The meta-analysis of Zusman *et al.* also showed that polymyxin monotherapy led to resistance development in almost 100% of the strains *in vitro* after 24 hours. Resistance was found to appear earlier for monotherapy at 24 hours than with combination therapy at 72 hours (if at all). Combination therapy also successfully suppressed polymyxin-resistant populations,[33] further supporting its advantage against monotherapy.

CHOOSING THE RIGHT POLYMYXIN

International Consensus Guidelines

Recent international consensus guidelines on the use of polymyxins were released last 2019, as endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ECSMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP). This guide in choosing the right polymyxin will heavily reference this consensus guideline[7] and will consider four (4) main factors: efficacy, safety, suitability, and cost, as summarized in Table 1.

Efficacy

Systemic use

In terms of efficacy, one should take into account the differences in pharmacokinetics between the two polymyxins. The preferred agent for invasive infections is polymyxin B due to its pharmacokinetic advantage in that it is already in its active form, which can reliably reach desired concentrations to perform its bactericidal function. Risk of acute kidney injury is also associated less with polymyxin B use.[5,7]

Lower urinary tract infections

Colistin has superior activity in the urinary system. It is the preferred agent for the treatment of lower urinary tract infections given that the prodrug CMS renal clearance is eventually converted to active colistin in the urinary tract.[5,7,14]

Hospital-acquired pneumonia

It is recommended by the guideline to use either polymyxin as an adjunctive treatment for XDR gram-negative hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP). No comparison yet between CMS and polymyxin B has been made in this regard. Since only about 9% of colistin reaches the lungs, the problem lies with the actual aerosol delivery of CMS.[7] Recommendations for the dosing varies among randomized controlled trials. In terms of outcomes, a meta-analysis done in Sweden has shown improved clinical response and lower mortality with the use of adjunctive aerosol CMS therapy. However, there was documentation of nephrotoxicity with its use, and analysis was shown to have outcome inconsistencies.[34] A retrospective cohort study done in Turkey involving children aged 1 month to 18 years with conducted culture-proven VAP due to colistin-only susceptible (COS) GNB showed that adjunctive aerosol CMS therapy in addition to IV colistin led to shorter median time to bacterial eradication but no significant difference in VAP outcomes.[35] Although ECSMID has released a position paper to avoid routine adjunctive inhaled antibiotics, the joint guidelines state that benefits may outweigh the risks in this case.

Intraventricular/Intrathecal

Colistin remains to be the preferred agent for intraventricular (IVT) or intrathecal (ITH) use. Only 5% of IV colistin typically penetrates the cerebrospinal fluid.[7]

Drug combinations guide

Typically, for carbapenem-resistant *Enterobacteriaceae* and carbapenem-resistant

Pseudomonas aeruginosa, choose an appropriate polymyxin and combine it with a second drug with evidence of susceptibility. If the second drug is unavailable, use a non-susceptible drug with the lowest MIC relative to its breakpoint. The same rule applies to CRAB, but contentiously, the guidelines advise monotherapy if the second drug is unavailable. However, this is a weak recommendation with moderate quality of evidence due to study confounders and low sample size and has only won panel voting at 8-7. Monotherapy has limitations in terms of bacterial synergism and resistance development.[7]

Safety

The consensus guidelines recommend the preferential use of polymyxin B—especially for countries where both colistin and polymyxin B are available—due to its lesser rate of polymyxin-associated acute kidney injury. In addition, polymyxin B does not require renal adjustments. CMS requires renal adjustments depending on creatinine clearance.[7] A meta-analysis involving MDR-GNBs has shown that there was no significant difference in mortality between the use of colistin and polymyxin B, but colistin administration was found to be an independent risk factor for the development of nephrotoxicity, even if the relative colistin dose was lower than polymyxin B dose used.[36]

A recent retrospective study done in the Philippines involving neonates with MDR-GNB infections determined adverse effects (including acute kidney injury) of intravenous colistin. Nephrotoxicity was seen in only 4% of patients (n=175), although the clinical outcome of mortality was at 50.7%. Further studies involving neonates and children are recommended to elucidate further rate of nephrotoxicity of polymyxin use in this population.[37]

Suitability

Take note that concomitant use of other nephrotoxic agents should be avoided in patients receiving polymyxins. Checking for comorbidities and medication history (e.g., calcineurin inhibitors, loop diuretics, NSAIDs, ACEIs, vancomycin, rifampicin, aminoglycosides) will be helpful in the decision making of choosing antimicrobials. However, in cases where polymyxin + aminoglycosides are the needed combination for a specific MDR infection, this might be unavoidable and should still be considered for use.[7]

Table 1. Factor analyses in choosing the right Polymyxin.

	Polymyxin B	Colistin
Efficacy	For routine systemic use since it is already administered in its active form	Alternative for systemic use, given as a prodrug; Superior activity for lower urinary tract infections; preferred for IVT/IT use
Safety	Lesser rate of nephrotoxicity; no renal adjustments required	Associated with colistin-associated nephrotoxicity; needs renal adjustments for AKI
Suitability	Exert caution when given for patients with concomitant nephrotoxic agent use; administered as intravenous form	Exert caution when given for patients with concomitant nephrotoxic agent use; administered as intravenous form
Cost	Slightly more expensive than colistin	Slightly less expensive than polymyxin B

IVT = intraventricular; IT = intrathecal; AKI = acute kidney injury

Cost

The cost will matter in the choice of polymyxin, especially in resource-limited countries, and it will play a factor in ensuring commitment to therapy. The current average price for a CMS 2M IU vial is ₱ (Philippine Peso) 1,700.00 and for a polymyxin B 50 mg vial is ₱2,200.00. Thus, for a 5-kg child, the estimated cost for the first 72 hours is as follows: ₱1,500.00 for CMS and ₱2,200.00 for polymyxin B (this is assuming no wastage of the contents).

GUIDE TO PRESCRIBING POLYMYXINS

This guide uses the mnemonic ESCAPE (alluding to ESKAPE organisms) to summarize the steps in choosing polymyxins for the treatment of MDR/XDR infections (see Figure 6).

Step 1. *Extensively resistant or multi-drug resistant organisms*. Check if the pathogen implicated in the infection is culture-based. Keep in mind that even if the pathogen is drug-susceptible, there can be heteroresistant subpopulations present *in vivo*.

Step 2. *Significant infection.* Check the patient's clinical status and sepsis markers (if available)—do they depict colonization or infection? Although it is difficult to

differentiate colonization from infection in many instances, the decision to treat remains in the hands of the primary physician. Careful attention and interpretation must be given to culture material (sterile versus non-sterile) and utilization of sepsis markers (e.g., procalcitonin) to aid in decision making to treat infections.

Step 3. *Combination therapy* provides advantages in effectively increasing bactericidal activity via synergism and reducing resistance development versus monotherapy.

Step 4. *Adequate doses.* Check proper dosing, especially if adjustments are needed in the presence of acute kidney injury (in the case of CMS).

Step 5. *Proper preparation and administration* must be observed to maximize drug efficacy (pay attention to dilution and infusion rates).

Step 6. Keep an *Eye for response and check for adverse effects* such as renal function and neurologic status.

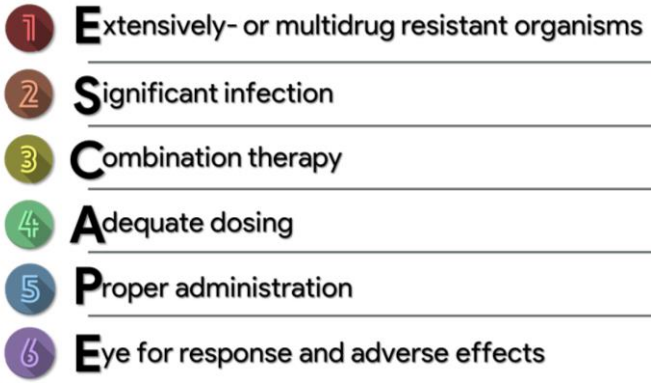

Figure 6. Prescribing Polymyxins using the ESCAPE mnemonic

CONCLUSION

In view of the emergence of multidrug-resistant and extremely drug-resistant gram-negative infections, the use of polymyxins as salvage therapy came to light. The beginning emergence of polymyxin resistance also signals the need to prescribe polymyxins for infections rationally. Knowledge of polymyxin similarities in structural characteristics and mechanism of action, as well as differences in their pharmacokinetics, will aid in choosing the right polymyxin for each situation. It should also be noted that the presence of heteroresistant bacterial subpopulations can lead to regrowth if not addressed. Combination therapy remains advantageous over monotherapy due to increased bactericidal activity through synergism and decreased resistance development. Efficacy, safety, suitability, and cost should always be considered in choosing one polymyxin over the other. Using the mnemonic ESCAPE can aid physicians in guiding their rational prescription process.

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