Rational use of intravenous polymyxin B and colistin: A review

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SUMMARY

Polymyxin B and colistin (polymyxin E) were introduced in clinical practice to treat Gram-negative infections in 1950s but their parenteral use waned in 1970s due to toxicity concerns. Resurgence of polymyxins use in Malaysia began approximately in 2009 due to a lack of treatment options for MDR Gram negative superbugs such as *Acinetobacter baumannii*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. However, limited experience and a lack of widespread availability of up-to-date dosing guidelines could potentially result in incorrect use of these last resort antibiotics by managing doctors. The recent report of polymyxin resistant strains is also a cause of concern. Herein, we discuss the importance of preserving the efficacy of polymyxins in hospitals, the similarities and differences between polymyxin B and colistin, issues pertaining to current use of polymxyins and strategies to improve polymyxins' prescription. Polymyxins should only be used to treat significant infections, in optimum doses and if possible, in combination with other antibiotics.

KEY WORDS:
polymyxin B; colistin; healthcare-associated infections; antimicrobial drug resistance; Acinetobacter baumannii; Klebsiella pneumoniae; Pseudomonas aeruginosa

INTRODUCTION

Polymyxin B and colistin (polymyxin E) are the only two polymyxins available for clinical use. Polymyxin B which was discovered in 1947 is an antimicrobial peptide produced by a soil bacterium *Paenibacillus polymyxa*,[1] whereas colistin is produced by a different subspecies of *Pa. colistinus*.[2] Polymyxins were first used clinically in 1950s to treat Gram-negative infections but their usage had declined in 1970s due to toxicity concerns and availability of 'safer' alternative antibiotics, aminoglycosides.[3] Interestingly, the clinical use of intravenous (IV) preparations of polymyxins have resurged at the end of last decade, as the last line treatment option for multidrug-resistant (MDR) Pseudomonas aeruginosa, *Acinetobacter baumannii* and *Klebsiella pneumoniae* infections.[3]

The reuse of IV polymyxins in Malaysia started approximately in 2009 with an increasing trend of colistin prescription observed over the years (Figure 1A). In National Antibiotic Guidelines 2014, the use of IV polymyxin is recommended as an alternative to cefoperazone/sulbactam or ampicillin/sulbactam for treatment of MDR *Acinetobacter* infections.[4] The colistin dose was suggested to be loaded at 7-9 MU stat and followed by 9 MU daily in two to three divided doses and renal adjusted dose is required. At that time, there was no recommendation for polymyxins to be used in treating *Enterobacteriaceae* or *Pseudomonas*. In fact, recommendation on the use of parenteral polymyxin B is limited and very much depended on individual institutions.

Since 2014, the use of polymyxins in the country has steadily increased in tandem with the rise of extreme drug resistance (XDR) *Acinetobacter* and carbapenem-resistant *Enterobacteriaceae* (CRE) cases and outbreaks (National Surveillance of Antibiotic Resistance, 2015). While waiting for the next guidelines review, each institution established its own guidelines on polymyxins use. With unregulated use of polymyxins, this consequently may result in, excessive use of these antibiotics in certain hospitals. Combined with poor infection control policy, the emergence and spread of the much dreaded polymyxin-resistant *Klebsiella pneumoniae* has been observed (National Surveillance of Antibiotic Resistance, 2015). In this review for Continuing Medical Education (CME), current understanding on the use of these antibiotics to prolong their efficacy in clinical practice against Gram-negative healthcare-associated infections will be elaborated.

Bad Bugs Need Drugs

Since early of the century, *Acinetobacter baumannii* and *Klebsiella pneumoniae* have become a major threat in critically ill patients and there is a rapidly growing crises in antimicrobial resistance.[5,6] These two organisms were listed as difficult to eliminate nosocomial bacteria, the "ESKAPE" pathogens.[7] *Klebsiella* spp. were the third most common nosocomial pathogen reported to the U.S. National Healthcare Safety Network.[8] Gradual increasing trend of carbapenem-resistant *K. pneumoniae* in Malaysian hospitals such as in Hospital USM has been observed from 2012 onwards (Figure 1B). This concurs with the recent report from the US that indicated carbapenem-resistance among *Klebsiella* spp. isolated from catheter-related bacteraemia, ventilator-associated pneumonia and urinary tract infection were 9.1-13.1%.[8] In Hospital USM, *Acinetobacter* spp. were among the commonest organisms isolated with a prevalence of 6.11% and an attack rate of 2.77 episodes per 1000 hospital admissions.[9] The clinical isolation rate of carbapenem-resistant *A. baumannii* in Hospital USM had reached up to 80% (Figure 1C),[10] a disturbing and worrying fact which suggests that most antibiotics are ineffective

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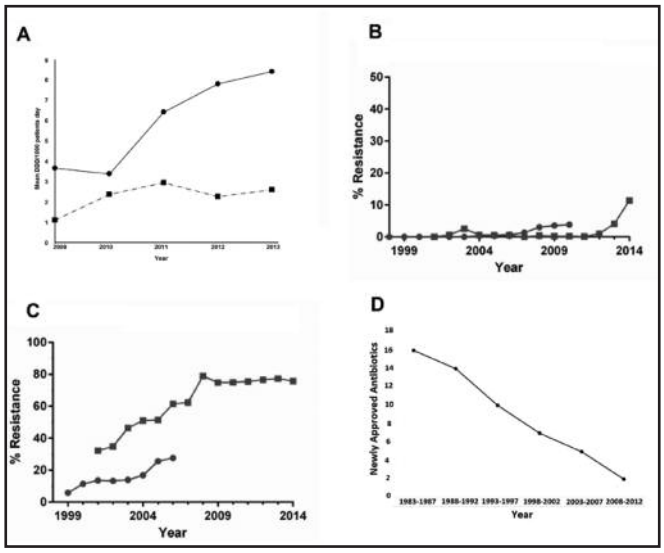

Fig. 1: (A) The prescription of IV polymyxin B (▪) and colistin (●) in Malaysia. (B) The trend of imipenem-resistance among Klebsiella pneumoniae isolates from clinical specimens in the US (●) and Hospital USM (▪). (C) The trend of imipenem-resistance among Acinetobacter baumannii isolates from clinical specimens in the US (●) and Hospital USM (▪). (D) New antibiotics approved by the U.S. Food and Drug Administrations, 1983–2012. Adapted/reproduced from Malaysian National Antibiotic Guidelines 2014, Deris 2015 and Infectious Diseases Society of America 2011.

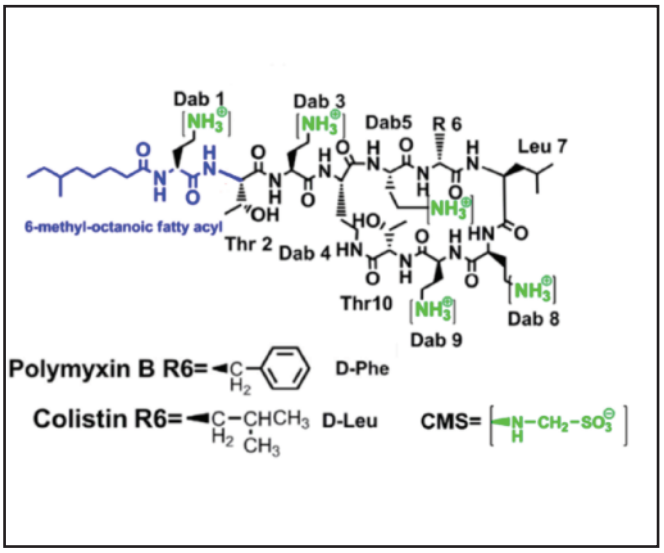

Fig. 2: Chemical structure of polymyxin B and colistin. The different between polymyxin B and colistin is at R6 which is D-phenylalanine in polymyxin B and D-leucine in colistin. In colistin methanesulphonate, there is addition of a sulphomethyl group to the primary amines of colistin leading to a change in the electrostatic charges. Thr: threonine; Leu: leucine; Phe: phenylalanine; Dab: a,g-diaminobutyric acid. CMS: colistin methanesulphonate. Reproduced from Deris et al. 2014.

Table I: New European Medicines Agency (EMA) approved for European colistin methanesulphonate product in 2015. Adapted from European Medicines Agency, 2015.

Patient's condition	Creatinine Clearance (mL/min)	Daily Dose Approved	Approximate colistin base activity (CBA) equivalent
Not on Renal Replacement Therapy	≥50	9 MIU	300 mg
	30 to <50	5.5-7.5 MIU	183-250 mg
	10 to <30	4.5-5.5 MIU	150-183 mg
	<10	3.5 MIU	117 mg
Haemodialysis (HD) (Twice daily dosing is recommended)	No-HD days	2.25 MIU (2.2-2.3 MIU)	75 mg
	HD days	3 MIU/day on HD days, to be given after the HD session.	100 mg
CVVHF/ CVVHDF (Three times daily dosing is recommended)		As in patients with normal renal function. (9 MIU/day)	
Children	≤40kg	75.000-150.000 IU/kg/day divided into 3 doses.	
	>40 kg	Use of the dosing recommendation for adults	

against this microorganism in local hospitals. With the plasmid-mediated carbapenemase genes in the circulation, therapeutic options are indeed limited as the microorganisms are often resistant to almost all available antibiotics except polymyxins.

On the other side, there is a steady decline in the antibiotic development pipelines as well as the approval of new antibiotics for clinical use.[11] After a long hiatus, in 2014-15 US Food and Drug Administration (FDA) approved two new second-generation cephalosporin/β-lactamase inhibitor combinations (ceftolozane/tazobactam and

ceftazidime/avibactam), that could be used to treat multidrug resistant gram negative bacteria. Of these two, only ceftazidime/avibactam is active against some carbapenem-resistant *Enterobacteriaceae* strains. However, ceftazidime/avibactam is not effective against metallo-β-lactamases such as New Delhi metallo-β-lactamases which is the most common type of carbapenemase seen in Malaysia. Hence, proper and diligent use of current antibiotics is paramount to prevent emergence and spread of resistance and eventually to preserve the efficacy of these antibiotics.

Polymyxin B and colistin

Polymyxins are cationic lipopeptide antibiotics. Polymyxin B and colistin share a common primary sequence with the only difference being at position 6 which is D-phenylalanine in polymyxin B and D-leucine in colistin (Figure 2).[12-14] The primary amines of the α,γ-diaminobutyric acid (Dab) are important residues that make the net-charge of polymyxin molecules to become positive (Figure 2).[13] These positive charges will interact with phosphate moieties of bacterial lipopolysaccharide (LPS), which are anionic in nature, to displace divalent cations (Ca^{2+} or Mg^{2+}) leading to instability of the LPS outer membrane's monolayer and subsequently killing the bacteria.[15]

IV formulation of polymyxin B is in sulphate salt, which is an antimicrobial active form. In contrast to polymyxin B, colistin parenteral preparation is in the form of colistin methanesulphonate (CMS, also known as colistimethate) which may lead to rapid renal clearance and less tissue binding that consequently reduces the toxicity.[16-17] However, the addition of a sulphomethyl group to the primary amines of colistin (Figure 2)[18] leads to reduced positive charges of CMS. Being anionic in nature, CMS is unable to interact with the negatively charged bacterial LPS. CMS is an inactive pro-drug and needs to undergo conversion to form an active entity of colistin.[12]

ISSUES WITH CURRENT USE OF POLYMXYINS

Pharmacokinetics (PK)

As stated above, the major difference of the two parenteral polymyxins available in clinical practice is that polymyxin B is administered as its active sulphate salt whereas colistin is administered in the form of inactive prodrug, CMS.[12-13] Figure 3A shows a relatively straightforward PK profiles of polymyxin B. After administration in active form, polymyxin B is subjected to renal glomerulus filtration and extensive tubular reabsorption. Finally, it is eliminated mainly by nonrenal system. However, the PK profiles of IV formulation of colistin is rather complicated (Figure 3B). After administration, CMS is predominantly excreted by kidney. Only approximately 20-25% of CMS are converted to colistin. Therefore, to attain sufficient plasma concentration of active antibacterial entity, about 5 times the amount of CMS needs to be administered to patients.[13] In addition to that, the rate and extent of *in vivo* conversion of CMS to colistin also vary due to a relatively greater inter-individual variability and a batch-to-batch variability of the CMS complex composition. The slow conversion of CMS leads to a delay in killing of bacteria by the active form of colistin. After the conversion, the fate of the formed colistin is similar to polymyxin B.[13]

Although polymyxin B and colistin are minimally excreted in urine, urinary concentrations of colistin can be relatively high due to conversion of CMS within the urinary tract, knowing CMS is extensively excreted by renal system.[13]

The mean $t_{1/2}$ and total body clearance of polymyxin B was shown to be 13.6 h and 2.4 L/h, respectively. In critically ill patients, the mean protein binding of polymyxin B has been found to be >90%.[19] With 0.5-1.5mg/kg dose polymyxin B, the maximum concentration (C_{max}) has been demonstrated to be between 2.38 to 13.9μg/mL with less than 1% is recovered in urine.[20] The body clearance of polymyxin B has very low inter-individual variability and is not influenced by creatinine clearance.[21]

On the other hand, after 150-225mg every 8h dose of CMS (~5.1-7.6 MIU/day), the C_{max} of formed colistin was only 1.15 to 5.14μg/mL.[22] The mean apparent $t_{1/2}$ and total body clearance of formed colistin were 7.4h and 13.6L/h, respectively.[22] The concentrations of formed colistin were suboptimum in lung tissue and cerebrospinal fluid (CSF).[23,24] In a large PK study, Garonzik et al. (2011) found creatinine clearance is an important covariate for the total clearance of CMS. Both CMS and formed colistin were efficiently cleared by renal replacement therapy. With the daily CMS dose of ~2.3-12.3MIU/day, the average concentration at steady state ($C_{ss,avg}$) of formed colistin in all patients ranged from 0.48 to 9.38μg/mL, and alarmingly, substantial number of subjects have <2μg/mL (Figure 4).[25] Looking to unbound colistin ranged from 26 to 41% only,[26] it is clear that the dose of colistin monotherapy up to 12.3MIU/day is still inadequate to treat Gram-negative infection with minimal inhibitory concentrations (MICs) >1μg/mL in significant proportion of patients.

Dose controversy

Prior to 2015, there is a disagreement in the recommended dosage of the US and European products of intravenous formulation of colistin. The recommended upper limit dosage for adults using CMS from the US is approximately 800mg/day (~9 million units/day, 300 mg/day CBA), whereas the CMS from Europe has a recommendation of 480 mg/day for adults (5.4 million units/day, ~ 180mg/day colistin based activity (CBA).[27] The recommended dose for European product is very low and may potentially lead to treatment failure. In contrast, when the US recommendation is wrongly calculated as 800 mg/day CBA, a fatal drug overdose could occur (>2000 mg/day of CMS).[27] With either dose, the formed colistin takes 2–3 days before reaching its steady state.[28] At present. it is recommended that a loading dose for IV CMS is used according to body weight followed by a maintenance dose based on the patient's renal conditions.[10,25] Both U.S. Food and Drug Administration (FDA)[29] and European Medicines Agency (EMA)[30] have approved the new prescription recommendation in 2015. Unfortunately, confusion may still arise as both countries do not use similar dosing units, with international units (IU) used for European products and CBA for the US products. Since the IV colistin formulation available in Malaysia is mainly procured from Europe, Table I shows the new recommended dose according to European product guides.

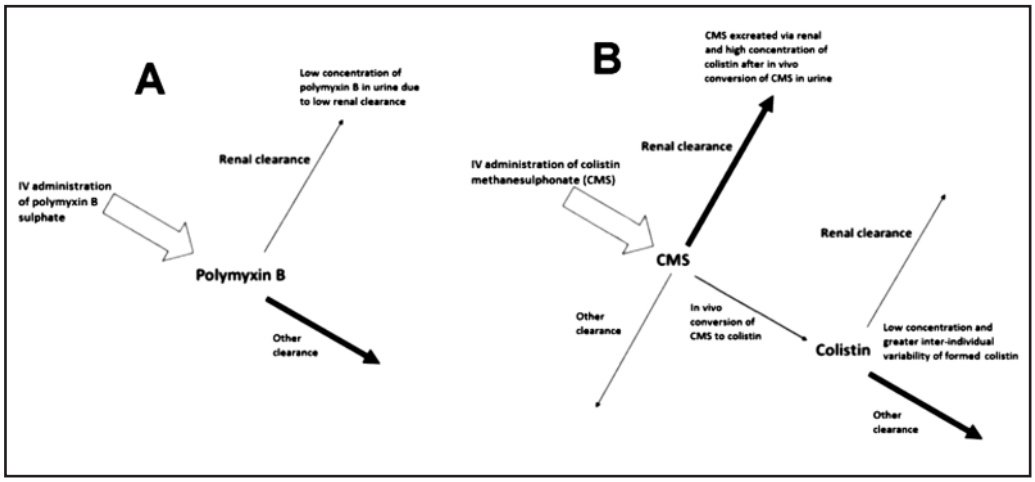

Fig. 3: Pharmacokinetic pathways following intravenous administration of polymyxin B (A) and colistin methanesulphonate (B). The thickness of the arrows indicates the relative magnitude of the respective clearance pathways when kidney function is normal. Adapted from Nation et al. 2014.

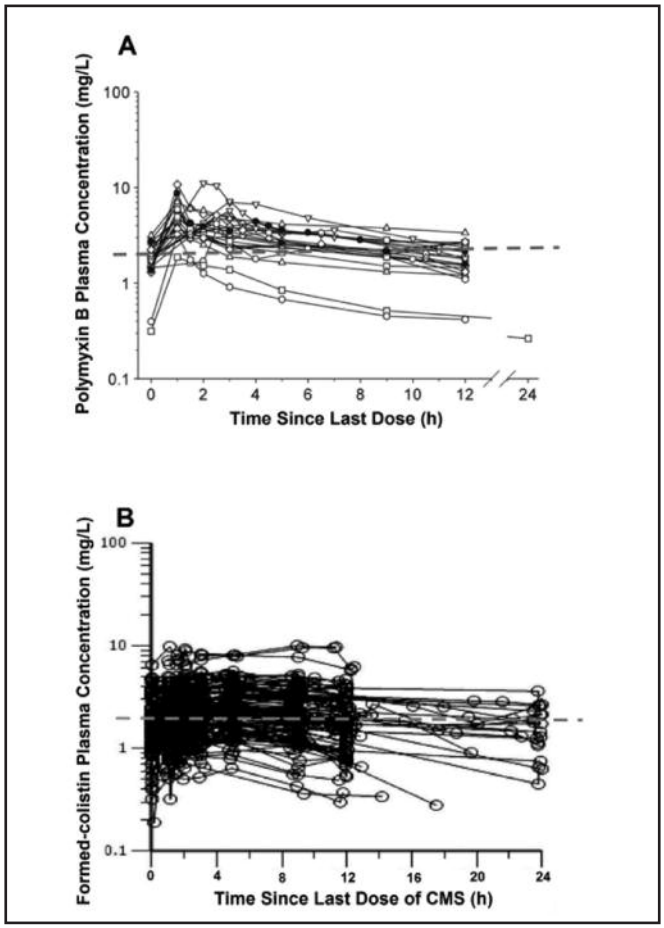

Fig. 4: Steady-state plasma concentration-time profiles of polymyxin B in 24 patient (A) and steady-state plasma concentration-time profiles of the formed-colistin after CMS dose in 105 critically ill patients (B). A dash horizontal line indicates plasma concentration of 2μg/mL which is a cut-off MIC of susceptible. With the fact that >90% of polymyxin B and ~70% of colistin are bound to plasma protein, there are significant proportion of patients with unbound polymyxin concentration <1μg/mL. Adapted from Sandri et al. 2013 and Garonzik et al. 2011.

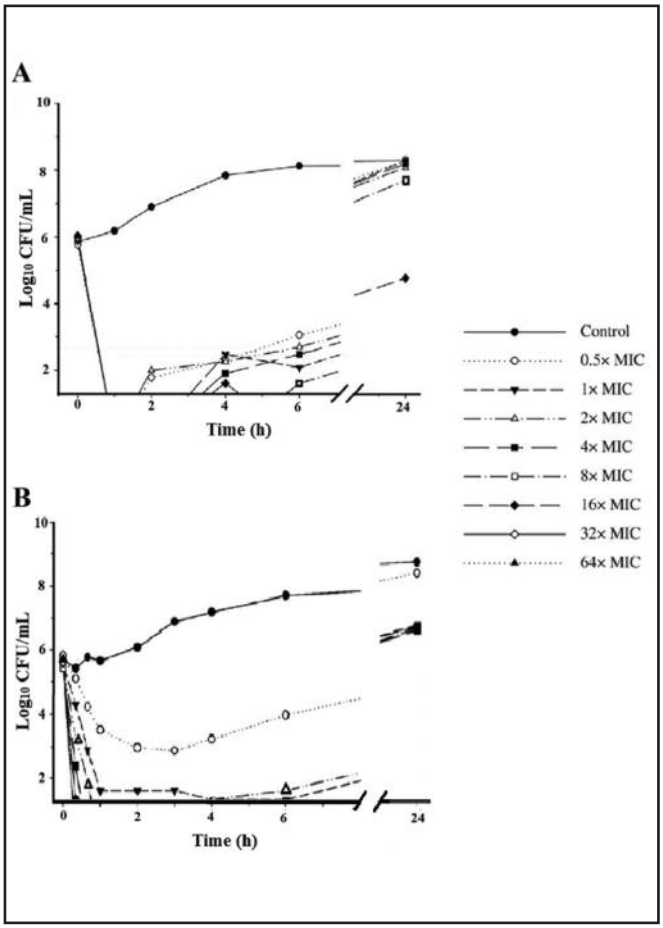

Fig. 5: Time-kill curves of colistin indicated regrowth of K. pneumoniae ATCC 13883 (A) and A. baumannii ATCC 19606 (B) after 2-4 h exposure to colistin. The limit of detection is 20 CFU/mL (approximately 1.3 on log10 scale) and the limit of quantification is 400 CFU/mL (approximately 2.6 on log10 scale). Adapted from Poudyal et al. 2008 and Li et al. 2006.

Pharmacodynamics (PD)

Considering that only one amino acid difference exists between polymyxin B and colistin, it is very likely that polymyxin B and colistin have similar PD behaviour.[13] Two important observations have been reported from polymyxins PD studies. The first observation is, after a rapid concentration-dependent killing, bacteria regrowth occurred as early as 2h in time-kill experiments at concentration up to 64×MIC (Figure 5).[31-33]

Similar observation has been reported in studies using in vitro one compartment PK/PD model,[34-36] hollow-fibre infection model (HFIM) system[37] and animal model.[38,39] These regrowth of *K. pneumoniae, A. baumannii* and *P. aeruginosa* were later on found to be due to heteroresistant subpopulations (in a virtually susceptible isolates). The population analysis profiles (PAPs) were performed by subculturing of serial dilutions of bacterial suspension on colistin/polymyxin B containing Mueller–Hinton agar, thus the number of resistant subpopulations in the suspension can be counted. The PAPs revealed the proportion of resistant bacterial cell was up to 1 in 1.29×10^5 susceptible bacterial colony-forming units (CFU).[33] These pre-existing polymyxin-resistant bacterial cells will grow when the susceptible cells die due to bactericidal effect of polymyxins.

The second important PD observation is, the attenuation of polymyxin bactericidal activity against high bacterial density inoculum.[40] At lower bacterial concentration (~10^6 CFU/mL), colistin at 1×MICs was able to reduce the bacterial viable count by 4-$\log_{10}$CFU/mL but at high inoculum (~10^9 CFU/mL) the reduction was <1-$\log_{10}$CFU/mL. The extent of killing of *P. aeruginosa* isolates by colistin were also markedly inhibited at high initial inoculum compared to low initial inoculum.[40] To some extent, the *in vitro* PK/PD model has demonstrated similar findings when comparing 10^6 and 10^8 -CFU/mL inoculum of *K. pneumoniae*.[35] This literally means that polymyxins are likely to be ineffective for the treatment of infective endocarditis or deep seated abscess without adequate source reduction.

Plasmid-mediated polymyxin resistance gene, mcr-1

Recently in November 2015, Liu et al., described the presence of a plasmid-mediated polymyxin-resistance gene, *mcr*-1, in Enterobacteriaceae from food animals and patients in China.[41] In fact, the *mcr*-1 gene emerged in Malaysia earlier in 2013 when Yu et al. (2016) retrospectively screen more than 900 isolates in their stock culture which have been archived since 2009. They found the polymyxin-resistant gene in *E. coli* isolated from poultry, pigs' food, environment and human urine.[42] An expression of *mcr*-1 resulted in the addition of a phosphoethanolamine moiety to the outer Kdo residue of LPS in *E. coli*.[41] This is the first known polymyxin-resistance mechanism that is capable of a horizontal transfer, thus increases the likelihood of global spread. After that, the *mcr*-1 gene has been reported from almost all continents except from Oceania and Antartica.[43-47] The spread of this gene need to be controlled by, among others, by rational use of polymyxins.

STRATEGIES FOR IMPROVED POLYMYXIN PRESCRIPTION

Significant infections

Among the three Gram-negative superbugs that need polymyxin therapy, the significance of *Acinetobacter* acquisition may be the most questionable one. In the era of antibiotic-resistant superbugs, whenever possible, the use of antibiotics should be limited to significant infections only. However, it is difficult to differentiate between colonisation and infection in many instances. Most of the time, the decision to treat on the basis of a positive culture result is in the hands of the physician in-charge.[48] In general, polymyxin therapy should be initiated if the culture material from sterile body site is positive and the patient has symptoms or signs of sepsis. On the other hand, non-sterile body site specimens need to be carefully interpreted to avoid inappropriate use of these chemotherapeutic agents. The CDC definition of health-care associated infections surveillance can be used as a guide to differentiate between colonization and infection. Colonization is the presence of microorganisms on skin, on mucous membranes, in open wounds, or in excretions or secretions but are not causing adverse clinical signs or symptoms.[49] Sepsis markers e.g. procalcitonin are very helpful in decision making to treat the infections.[50] In addition to that, the significant mild local infections can be treated with local antiseptic dressing. This should further reduce unnecessary administration of parenteral polymyxins.

Adequate doses

There is no doubt adequate early attainment of polymyxin concentration in the serum is critical for bactericidal activity.[51] In view of slow conversion of CMS to active form of colistin, Garonzik et al. suggested a loading dose should be given to all patients. The maintenance doses are recommended in according to renal function and renal replacement therapy.[25] The EMA recommends the loading dose of 9 MIU (~300 mg CBA) for critically ill patient.[30] In fact, latest guidelines by the Clinical and Laboratory Standards Institute (CLSI) indicate that CMS should be given with a loading dose and at maximum recommended dose for the treatment of *Enterobacteriaceae, Pseudomonas aeruginosa* and *Acinetobacter*.[52]

With the latest FDA and EMA recommended dose, Nation et al.[53] found that the colistin $C_{ss,avg}$ was relatively low in patients with creatinine clearance ≥80mL/min. They also observed a very wide inter-patient variability (up to approximately 12-fold) in the plasma colistin $C_{ss,avg}$ across all four renal function groups.[53] Their team in Monash University have developed an Apple app on recommended individual colistin dosing that are freely available at https://itunes.apple.com/au/app/colistindose/id1336806844?mt=8&ign-mpt=uo%3D4. Looking at the narrow therapeutic range of colistin, a therapeutic drug monitoring practice needs to be considered for optimum CMS dosage regimen in individual patients.

The pharmacokinetic (PK) profiles of IV polymyxin B indicates a low inter-individual variability of serum concentrations after scaling to body weight. The polymyxin B serum concentration is not influenced by renal functions.[21] Therefore, the renal dose adjustment as advised by the manufacturer is not recommended.[13] In fact, we found the polymyxin B dose of <15000units/kg/day is associated with

treatment failures in critically ill patients.[54] The current recommended doses of polymyxin B (up to 2.5mg/kg/day, 25000units/kg/day) are appropriate for a pathogen with MIC ≤1µg/mL or less severe infections with superbugs with MICs of ≤2µg/mL.[21]

Combination therapy

It has been stated above that the current recommended dose of polymyxins (particularly CMS) is associated with sub therapeutic concentrations in a large number of the patients. On top of that, a paradoxical effect has been observed whereby higher polymyxin B concentrations are associated with dramatically increased resistant subpopulations in *Acinetobacter baumannii*.[55] This highlights the need to combine other antibiotics with polymyxins to treat Gram negative superbugs. The Clinical and Laboratory Standards Institute (CLSI) has also advised the use of colistin in combination with other antibiotics in the latest Performance Standards for Antimicrobial Susceptibility Testing.[52]

A meta-analysis of in vitro polymyxin-carbapenem combination demonstrated synergy rates of 77% for *A. baumannii*, 44% for *K. pneumoniae* and 50% for *P. aeruginosa*.[56] The antagonistic interaction between polymyxin and carbapenem were identified between 2-24% of the tested strains.[56] Specifically against carbapenem-resistant (and polymyxin-susceptible) strains, the synergy rate of polymyxin-carbapenem combination were 71%, 55% and 59% for *A. baumannii*, *K. pneumoniae* and *P. aeruginosa* respectively.[56] Polymyxin-carbapenem combinations may not be a suitable combination regimen against carbapenem-resistant, polymyxin-resistant *K. pneumoniae* as the synergy rate had been observed in only 22% cases.[56] Besides carbapenem, other antibiotics that have been tested in combination with polymyxins against gram-negative superbugs include cefoperazone/sulbactam (synergy rate 4%), piperacillin/tazobactam (2%), tigecycline (12-29%), rifampicin (42%), quinolones (90% against *P. aeruginosa*), chloramphenicol (89% against *K. pneumoniae*), vancomycin (67%) and daptomycin (53%).[57]

In thigh and lung infection models, Lee et al., demonstrated that for colistin-susceptible, -heteroresistant and -resistant *K. pneumoniae* strains, the combination therapy achieved more killing at 24 h than either monotherapy.[39] A few other murine Gram-negative infection models also corroborate this observation, that polymyxin combination therapies are superior to monotherapy.[58-60] In one earlier study, Ofek et al., found that combination of polymyxin B nona-peptide (polymyxin B without the N-terminal fatty acyl chain and Dab^1) with erythromycin and novobiocin were associated with lower mortality in *K. pneumoniae* and *P. aeruginosa* peritonitis mice.[61] Polymyxin B nona-peptide lacks antibacterial activity on its own, but is able to disorganize the gram-negative outer membranes, thus enhancing hydrophobic antibiotic penetration.[61]

The major limitations for antibiotic trials are with regard to the practicality of methodologies and ethical considerations. The clinical studies on polymyxin combination therapy are mostly retrospective in nature, do not include PK information, usually involve small number of patients and have heterogeneity in case definitions and susceptibility test methods.[62] Zusman et al., recently published a meta-analysis to compare between polymyxin monotherapy and combination against carbapenem-resistant bacteria. They demonstrated that polymyxin monotherapy was associated with higher mortality rate at odd ratio (OR) 1.58 (95%CI: 1.03 to 2.42) compared with polymyxin/carbapenem combination therapy. They also found that mortality was significantly higher with polymyxin monotherapy compared with combination therapy with tigecycline, aminoglycosides or fosfomycin with OR of 1.57 (95%CI:1.06 to 2.32) for overall carbapenem-resistant bacteria and OR of 2.09 (95%CI :1.21 to 3.6) for specific *Klebsiella pneumoniae* bacteraemia. Polymyxin combination with rifampicin for treatment of *A. baumannii* infections has shown no difference in mortality compared with colistin monotherapy.[63]

CONCLUSION

Maintaining the efficacy of polymyxins in the era of resistant superbugs is critical to prolong their therapeutic utility. Currently these antibiotics are the last resort for most of the *A. baumannii*, *K. pneumoniae* and *P. aeruginosa* infections. Understanding the mechanism of bactericidal activities, mechanism of resistance, pharmacokinetics and pharmacodynamics is very important to optimum use the polymyxins. In general, polymyxin B has better pharmacokinetics profiles because of its IV formulation as an active drug. However polymyxin B concentration in urine is very minimal due to its non-renal clearance. Colistin is administered in prodrug form, CMS, which later transforms into active antibiotic *in vivo*. Loading dose of CMS is indicated because of the delay attainment of therapeutic concentration of formed colistin. Both polymyxins have similar pharmacodynamics profiles and need to be used in combination with other antibiotics to avoid treatment failure and prevent the emergence of resistant.

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Take-home messages on the rational use of intravenous polymyxin B and colistin in clinical practice for treatment of MDR Gram-negative superbugs

Subjects	Take-home messages
Indication	Intravenous (IV) polymyxin B and colistin should be strictly used for significant infections by polymyxin-susceptible stain of *Acinetobacter baumannii*, *Pseudomonas aeruginosa* or *Enterobacteriaceae*.
Intravenous formulation	Polymyxin B is formulated in active antimicrobial form, polymyxin B sulphate, whereas colistin is formulated in pro-drug formulation, colistin methanesulphonate (CMS).
Dose	The maximum daily dose of polymyxin B is 25000 units/kg/day (2.5 mg/kg/day). The polymyxin B dose needs to be scaled to body weight. Current pharmacokinetics evidences indicate that the polymyxin B dose is not to be adjusted according to creatinine clearance. The maximum daily dose of CMS is 9 MIU (300 mg colistin base activity) and needs renal dose adjustment for creatinine clearance < 50 mL/min. Loading dose of CMS needs to be considered because of the delay attainment of therapeutic concentration of formed colistin. The Apple app on recommended colistin dosing can be used to tailor the colistin dosage in individual patient and freely available at https://itunes.apple.com/au/app/colistindose/id1336806844?mt=8&ign-mpt=uo%3D4.
Pharmacodynamics/ pharmacodynamics (PK/PD)	Generally IV polymyxin B has superior PK profiles because it is formulated in active antimicrobial form. However the concentration in urine is lower due to non-renal clearance of active form of polymyxins. Polymyxin B has longer half-life and more protein bound compared to colistin. Polymyxin B and colistin have similar PD profiles.
Problem with current use of polymyxins	1. Sub-therapeutic concentrations in significant number of patients. 2. Heteroresistant subpopulation. Up to 1: 10^5 CFU/mL of the bacterial population is resistant to polymyxins in virtually susceptible strains. 3. Paradoxical effect of polymyxin B in which high drug exposure amplifies resistance of Gram negative bacteria. This has been observed in *Acinetobacter baumannii*.
Strategies to maintain the activity of polymyxins in the clinical settings	1. Strictly follow the antibiotic stewardship guidelines. 2. Use polymyxins in combination with other antibiotics. Most of the evidences indicate carbapenems are the best second antibiotics, including infection caused by carbapenem resistant strains. 3. Polymyxin dose should be the maximum allowable dose. 4. Strictly follow infection control measures when plasmid-transferable polymyxin-resistance gene, mcr-1 is detected.

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Questions

1. Regarding polymyxins
A. They are lipopeptide antibiotics
B. Three polymyxins are available for clinical use at the moment
C. The reduction of parenteral polymyxins use in 1970s was due to availability of alternative 'safer' antibiotic
D. They are active against *Burkholderia pseudomallei*
E. The positive charge of their amines group is critical for initial bactericidal activity

2. The strategies to improve polymyxin prescriptions include
A. adjusting polymyxin B dose according to body weight
B. adjusting polymyxin B dose according to creatinine clearance
C. administering loading dose of CMS to get early high concentration of formed-colistin
D. monitoring serum formed-colistin concentration
E. using polymyxins-carbapenem combination to treat carbapenem-resistant Gram-negative *K. pneumoniae*

3. Resistance to polymyxins among Gram-negative superbugs is predicted due to
A. emergence and spread of mcr-1 gene
B. use of polymyxin combination therapy
C. presence of heteroresistant subpopulation in virtually susceptible strains
D. inappropriately use of polymyxins to clear colonizer
E. low formed-colistin attainment with current recommended dose of CMS

4. Maintaining the efficacy of polymyxins against Gram-negative superbugs is critical due to
A. polymyxin has minimal adverse effects
B. increase cases of Gram-positive infections
C. polymyxins is the last resort antibiotics
D. lack of new antibiotics targeted carbapenem-resistant Gram-negative superbugs in the development pipeline
E. increase cases of extreme drug resistance Gram-negative infections

5. The difference of polymyxin B and colistin is/are
A. IV polymyxin B is formulated in active form whereas colistin in prodrug
B. polymyxin B is more active against *A. baumannii* than colistin
C. polymyxin B has limited concentration in urine whereas colistin has significant concentration in urine after their IV dose
D. polymyxin B has low inter-individual variability whereas colistin has greater inter-individual variability
E. polymyxin B has net positive charge whereas formed-colistin has net negative charge