A REVIEW ON POLYMYXINS IN ICU

M. SOLDUZIAN

PHARM D BCPS

ASSISTANT PROFESSOR OF PHARMACOTHERAPY

TABRIZ UNIVERSITY OF MEDICAL SCIENCES

INTRODUCTION

- The polymyxins comprise a separate class of antibiotics and include a number of different compounds. However, only polymyxin B and polymyxin E (also known as colistin) are in clinical use. They were isolated from Paenibacillus polymyxa and became available for clinical use in the 1950s.
- Colistin was historically given as an intramuscular injection for the treatment of gram-negative bacterial infections, but fell out of favor after aminoglycosides became available because of its significant side effects, particularly nephrotoxicity.

INTRODUCTION (CONT.)

- More recently, intravenous polymyxin B and colistin have been used more frequently in the treatment of otherwise panresistant nosocomial infections, especially those due to Pseudomonas and Acinetobacter spp. They are also used in aerosolized form for patients with cystic fibrosis.
- In Iranian market only colistin is available.

COLISTIN

- Vials of 1000000, 2000000, and 4500000 IU
- May be administered IV or IM
- Compatible with D5W, normal saline , half saline, quarter saline, and Ringer's solution
- Infuse over 30 minutes to 1 hour
- Intrathecal/intraventricular (off-label route): Administer only preservative-free solutions via intrathecal/intraventricular routes.
- Inhalation (off-label route): Administer solution via nebulizer (vibrating plate nebulizer may be preferred

MECHANISM OF ACTION

- Polymyxins are bactericidal drugs that bind to lipopolysaccharides (LPS) and phospholipids in the outer cell membrane of gram-negative bacteria. They competitively displace divalent cations from the phosphate groups of membrane lipids, which leads to disruption of the outer cell membrane, leakage of intracellular contents, and bacterial death.
- In addition to their bactericidal effect, the polymyxins can bind and neutralize LPS and may reduce the pathophysiologic effects of endotoxin in the circulation

SPECTRUM OF ACTIVITY

- Polymyxins have a narrow antibacterial spectrum limited to a subset of gram-negative bacilli. They are primarily used for infections due to multidrug-resistant organisms, such as carbapenem-resistant Enterobacteriaceae (Escherichia coli, Klebsiella pneumoniae, some Enterobacter spp), Pseudomonas aeruginosa, and Acinetobacter baumannii. Other susceptible organisms include Haemophilus influenzae, Bordetella pertussis, Legionella pneumophila, Salmonella spp, Shigella spp, and the majority of Stenotrophomonas maltophilia strains (74 percent of 23 tested isolates in one report).
- On the other hand, Burkholderia cepacia, Serratia marcescens, Moraxella catarrhalis, Proteus spp, Providencia spp, and Morganella morganii are all resistant to polymyxins. Other inherently resistant organisms include all gram-positive bacteria and gram-negative cocci.

RESISTANCE

- Resistance to the polymyxins is rare, although there have been increasing reports of polymyxin resistance among carbapenem-resistant gram-negative bacill.
- the identification of plasmid-mediated resistance to the polymyxins via the mcr-1 gene raises concern for continued widespread dissemination of resistance
- A common mechanism appears to be modification of the lipid A component of lipopolysaccharide (LPS). Other mechanisms may include cessation of LPS production or activation of efflux pumps

RESISTANCE

- The CLSI-recommended breakpoints for colistin and polymyxin B for Enterobacterales, P. aeruginosa, and Acinetobacter species are:
  - MIC ≤2 mcg/mL: Intermediate
  - MIC ≥4 mcg/mL: Resistant

PHARMACOKINETICS

- Colistimethate sodium (CMS) is a prodrug that is hydrolyzed after intravenous or inhaled administration to produce several derivatives, including the active drug colistin.
- CMS has a half-life of 124 minutes, whereas colistin (base) has a half-life of 251 minutes. Colistin has a calculated volume of distribution of 0.34 L/kg. CMS is excreted in the urine, and colistin is non-renally excreted. No biliary excretion has been reported in humans.
- The distribution of colistin to the pleural cavity, lung parenchyma, bones, and cerebrospinal fluid (CSF) is relatively poor. Colistin CSF penetration is low (CSF-to-serum ratio of 5 percent), and bactericidal concentrations are not achieved

DOSING AND ADMINISTRATION

- Initiating IV therapy with a CMS loading dose of 300 mg CBA (~9 million IU) infused over 0.5–1 hours and to administer the first maintenance dose 12–24 hours later is recommended.
- This incidence range of nephrotoxicity is comparable to historical rates when loading doses were not used.
- The timing of the commencement of the maintenance dose should be based on the interval of the maintenance dose (e.g., if the patient is placed on colistin every 12 hours, the maintenance dose should start 12 hours later).
- For a patient with normal renal function, administer a daily dose of 300–360 mg CBA (~9–10.9 million IU), divided into two and infused over 0.5–1 hour at 12-hour intervals is recommended.

DOSING AND ADMINISTRATION (CONT.)

Table 2. Look-up Table of Daily Doses of CMS[a]

Creatinine clearance, mL/minute[b]	Daily dose of CMS for plasma colistin $C_{ss,avg}$ of 2 mg/L[c]	
	mg CBA/day	Million IU/day
0	130	3.95
5 to < 10	145	4.40
10 to < 20	160	4.85
20 to < 30	175	5.30
30 to < 40	195	5.90
40 to < 50	220	6.65
50 to < 60	245	7.40
60 to < 70	275	8.35
70 to < 80	300	9.00
80 to < 90	340	10.3
≥ 90	360	10.9

CBA = colistin base activity; CMS = colistin methanesulfonate; $C_{ss,avg}$ = average steady-state plasma concentration;
[a]To achieve a desired target plasma colistin $C_{ss,avg}$ of 2 mg/L for patients with narrow windows of creatinine clearance. Reproduced from reference 6 with minor modifications.
[b]Adjusted body weight should be used to estimate creatinine clearance.
[c]Daily dose administered in two divided doses 12 hours apart.

DOSING AND ADMINISTRATION (CONT.)

- Only 30–40% of patients are expected to achieve a plasma colistin Css,avg of 2 mg/L or more, although almost 80% of such patients may achieve a Css,avg of 1 mg/L or greater.
- PK data do not support the need for weight-based dosing.
- The daily dose is divided into two doses, administered12 hours apart, and each dose is infused over 0.5–1 hour. If the daily dose is not reduced in patients with decreased renal function, there is an increased probability that the plasma colistin Css,avg will be higher than 2 mg/L. This would be expected to increase antibacterial activity but is also expected to increase the likelihood of AKI.

DOSING AND ADMINISTRATION (CONT.)

- In a patient on intermittent hemodialysis (IHD), the following dosing schedule be utilized: On a non-dialysis day, administer a CMS dose of 130 mg CBA/day (~3.95 million IU/day). On a dialysis day, administer a supplemental dose of CMS 40 mg CBA (~1.2 million IU) or 50 mg CBA (~1.6 million IU) for a 3- or 4-hour IHD session, respectively.

STRATEGIES THAT CAN BE USED TO DECREASE THE INCIDENCE OF ACUTE KIDNEY INJURY IN PATIENTS RECEIVING COLISTIN

- Incidence of nephrotoxicity varies widely in the literature from 0% to more than 60%
- Risk factors include advanced age, weight irrespective of dose, hypoalbuminemia. These risk factors are not modifiable.
- Wherever possible, that concomitant nephrotoxic agents should be avoided, NSAIDS, AG, CNIs, Vasopressors, ACEIs, Contrast media, Vancomycin, Loop diuretics, Rifampin.
- Until further data become available, the routine use of antioxidants for the primary purpose of reducing polymyxin-associated nephrotoxicity is not recommended

STRATEGIES THAT CAN BE USED TO DECREASE THE INCIDENCE OF ACUTE KIDNEY INJURY IN PATIENTS RECEIVING COLISTIN

- Clinical data exploring the impact of ascorbic acid on limiting nephrotoxicity are scarce and have displayed conflicting results.
- One group assessed nephrotoxicity rates with a novel dosing regimen based on recent PK advances. Interestingly, although not the primary intent of the analysis, both bivariate (30% vs 67%; $p<0.05$) and multivariate analyses (adjusted odds ratio [aOR] 0.27, 95% CI 0.13–0.57) suggested that concomitant administration of ascorbic acid was protective against nephrotoxicity.
- Conversely, a small RCT in 28 patients failed to show any benefit of 4 g/day of ascorbic acid on the rates of colistin-associated nephrotoxicity.

DOSING IN AKI

- It is recommended that doses should not be decreased, outside of the renal dosing recommendations for colistin, particularly in patients who develop AKI when colistin or polymyxin B is being administered for a life-threatening infection, a deep-seated infection, or when the infecting pathogen has an MIC higher than 1 mg/L
- It is recommended that cessation of therapy may be considered in patients who develop AKI if infection diagnosis is uncertain or when an alternative less nephrotoxic drug is available.

POLYMYXIN COMBINATIONS

- In two different types of scenarios:
  - The first is when the polymyxin is combined with an agent to which the infecting pathogen is susceptible
  - The second is when the polymyxin is combined with an agent to which the pathogen lacks in vitro susceptibility

CARBAPENEM RESISTANT ENTEROBACTERIACEAE

- It is recommended that for invasive infections due to CRE, polymyxin B or colistin be used in combination with one or more additional agents to which the pathogen displays a susceptible MIC
- If a second active agent to which the infecting CRE displays a susceptible MIC is unavailable, it is recommended that polymyxin B or colistin be used in combination with a second and/or third non-susceptible agent
- Resistance to polymyxins develops fast used alone.
- Colistin + meropenem combination therapy for the management of carbapenem-resistant gram-negative bacilli. In this study, only nine patients (2%) had isolates susceptible (MICs of 8 mg/L or lower) to meropenem. Both clinical failure and 28-daymortality occurred in a lower proportion of patients with CRE receiving the colistin + meropenem combination

CARBAPENEM RESISTANT ACINETOBACTER BAUMANNII

- It is recommended that for invasive infections due to CRAB, polymyxin B or colistin should be used in combination with one or more additional agents to which the pathogen displays a susceptible MIC
- If a second active agent to which the infecting CRAB displays a susceptible MIC is unavailable, it is recommended that polymyxin B or colistin should be used alone as monotherapy (Weak recommendation)

CARBAPENEM RESISTANT PSEUDOMONAS AERUGINOSA

- It is recommended that for invasive infections due to CRPA, polymyxin B or colistin should be used in combination with one or more additional agents to which the pathogen displays a susceptible MIC
- If a second active agent to which the infecting CRPA displays a susceptible MIC is unavailable, it is recommended that polymyxin B and colistin be used in combination with a second and/or third nonsusceptible agent (e.g., a carbapenem). Preference should be given to a nonsusceptible agent with the lowest MIC relative to the respective susceptibility breakpoint
- Combination therapy (mainly colistin plus a b-lactam) was associated with higher cure rates than monotherapy with colistin or a b-lactam (11/15 [73.3%] vs 6/19 [31.6%], respectively; p=0.016).

INHALED POLYMYXINS

- It is recommended that patients requiring IV polymyxin therapy for suspected or documented XDR gram-negative HAP or VAP should receive adjunctive polymyxin aerosol therapy
- It is recommended that that for polymyxin aerosol therapy, either colistin or polymyxin B is appropriate
- CMS equivalent to 75 mg colistin base activity reconstituted in 4 mL nebulized sterile normal saline that was delivered immediately via a jet or ultrasonic nebulizer for 10 minutes or until the nebulized solution container was empty.

INHALED POLYMYXINS (CONT.)

- Use of aerosolized CMS, mainly monotherapy without any IV therapy, for all XDR Pseudomonas and Acinetobacter VAPs, had equivalent results to IV therapy of less resistant strains
- Nebulized CMS may have less nephrotoxicity and provide similar clinical results, compared to IV CMS.
- In addition, the drug breakdown products can cause direct damage to lung tissue, leading to potentially serious and life-threatening side effects. This is particularly true for preparations diluted greater than 24 hours prior to use. If colistin is to be used for nebulized inhalation, it must be mixed immediately prior to administration. The optimal dose of inhaled colistin is uncertain and ranges from 75 to 150 mg colistin base activity (2.25 to 4.5 million international units CMS) twice daily

INTRATHECAL AND INTRAVENTRICULAR ADMINISTRATION OF POLYMYXINS

- Intraventricular (IVT) or intrathecal (ITH) administration of polymyxins at a dosage of 125,000 IU CMS (~4.1 mg CBA) or 5 mg (50,000 IU) polymyxin B per day with concomitant IV polymyxin is recommended for ventriculitis or meningitis caused by MDR and XDR gram-negative pathogens.
- Due to limited experience with polymyxin B, CMS is the preferred polymyxin for intraventricular or intrathecal administration.
- Seizures were reported in three cases, numbness of extremities in two cases, and cauda equina syndrome in one. 167 patients in study.

MONITORING

- Renal function should be closely monitored during administration of systemic polymyxins.
- Serum creatinine, BUN; urine output; signs of neurotoxicity; signs of bronchospasm (inhalation [off-label route]); colistin serum concentrations (to ensure adequate drug exposure particularly early in therapy)

ADVERSE REACTIONS

- **Nephrotoxicity**
  - Renal function should be closely monitored during systemic administration of polymyxins, which have been associated with hematuria, proteinuria, and oliguria and acute renal failure due to acute tubular necrosis.
- **Neurotoxicity**
  - Polymyxins have been associated with dizziness, weakness, facial and peripheral paresthesia, vertigo, visual disturbances, confusion, ataxia, and neuromuscular blockade, which can lead to respiratory failure or apnea.
  - Other neurologic manifestations include psychosis, coma, convulsions, ptosis, diplopia, areflexia, dysphagia, and dysphonia
  - Neuromuscular blockade is due to noncompetitive blockade that, unlike aminoglycoside-induced neuromuscular blockade, is not reversed by neostigmine

ADVERSE REACTIONS (CONT.)

- Other adverse effects
  - Hypersensitivity reactions (including rash, pruritus, urticaria, and fever) have been reported in 2 percent of patients.
  - Aerosolization of polymyxins into the airway can be complicated by bronchospasm; bronchodilation prior to administration may be beneficial

GOOD LUCK AND GOOD BYE