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Review Article

A Review of Polymyxin-B Dosage for Patients with Renal Impairment

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Abstract

Since polymyxin B has a restricted therapeutic range and increased danger of both neurological damage and kidney damage, it is no longer the first choice for treating emerging gram-negative bacteria with multiple antibiotic resistance. The optimal dose schedule for patients with renal impairment regarding polymyxin B, it is provided as a chemically active formulation and primarily removed via methods other than kidney, is still up for debate. Similar to colistin, polymyxin-B effectively combats gram-negative aerobic bacterium that is resistant to several drugs such as Pseudomonas aeruginosa, Acinetobacter baumannii, Escherichia coli that produces carbapenemase, and Klebsiella pneumoniae. As a result, polymyxins cause cell apoptosis by inducing pan-caspase activation through many routes in a manner that is dependent on time and concentration. One of the most frequent and undesirable side effects of polymyxins is the development of AKI. A great deal of pharmacokinetic studies that have been published to far concur that creatinine clearance affects polymyxin B clearance; nevertheless, there is ongoing debate on the extent of this influence

Keywords: Polymyxin-B, kidney damage, gram-negative bacterial infection, creatinine clearance.

Introduction:

Since polymyxin B has a restricted therapeutic range and increased danger of both neurological damage and kidney damage, it is no longer the first choice for treating emerging gram-negative bacteria with multiple antibiotic resistance. Nonetheless, for treating these infections, polymyxin B has been employed as the final choice, making it one of the oldest approved antibiotics still in use. However, clinicians have come to dislike polymyxin B due to its toxicity profile [1, 2, 3].

While polymyxin B and colistin have distinct metabolic routes, they share comparable chemical structures and antibacterial action in vitro. Polymyxin-B has lower pharmacokinetic (PK) variability than colistin because it is delivered in its pharmacologically active form [1]. 60%–70% of colistin is eliminated by the kidneys as a prodrug, and the urinary tract transforms it into its active form. Consequently, it was decided to modify the colistin dosage in accordance with renal function. The optimal dose schedule for patients with renal impairment regarding polymyxin B, which is provided as a chemically active formulation and primarily removed via methods other than kidney, is still up for debate [4, 5]. It has also been suggested by a number of studies that polymyxin B is not as nephrotoxic as colistin. Global consensus recommendations for polymyxin dosage were created in 2019 to help physicians. Because of its better PK qualities and reduced likelihood of kidney damage, as advised, polymyxin B was suggested as the recommended treatment over polymyxin-E. As a result, in many hospitals, polymyxin B is now the most commonly used polymyxin [6, 7, 8, 9, 10].

Few clinical researches have been done in the last 30 years on the range of antibiotics, drug kinetics, pharmaceutical dynamics, toxicity, and polymyxin therapeutic uses, particularly polymyxin B. Partially due to a rise in Enterobacteriaceae impervious to carbapenems (CRE), polymyxin B usage has grown [11, 12, 13]. A. baumannii had a rate of persistence against imipenem of up to 73.2%, according to 2018 data made accessible by the Chinese antibacterial monitoring system. In contrast, P. aeruginosa and Klebsiella pneumoniae had resistance rates of 30.7 and 37.6%, respectively. Among the primary medications utilized in combo treatment for pan-drug resistance, A. baumannii, P. aeruginosa, and K. pneumoniae is polymyxin B, which

has been regarded as the final therapy for gram-negative infections [2, 14, 15, 16].

Polymyxin-B:

There are 10,000 units in 1 miligram of polymyxin-B. Bacilli that's resistant to numerous medicines and are gram negative, such as Pseudomonas aeruginosa and Acinetobacter spp., are responsible for systemic infections, which include sepsis, meningitis, pneumonia that is acquired in a hospital, and intraabdominal infections. IV: 20000-25000 units/kg loading dose, then 12 hours of 12,500-15,000 units/kg maintenance medications [6, 17, 18]. The table provides the polymyxin-B monitoring parameters, mechanism of action, and reference range [6, 19].

Table 1: Polymyxin-B parameters

Polymyxin-B parameters	Comments
•Monitoring parameters	Neurologic symptoms and superinfection indicators; renal function (treatment cessation may be necessary if urine output decreases and BUN rises).
•Referencing Range	The desired serum concentration for susceptible organisms is 2 mg/L, regardless of the stated minimum inhibitory concentration. For adults, serum values greater than 5 mcg/mL are harmful.
•Mechanism of Action	Binds to phospholipids, changes the bacterial cytoplasmic membrane permeability, and causes damage that allows intracellular components to seep out.

Pharmacokinetics of Polymyxin-B:

The table provides information on polymyxin-b s pharmacokinetics, covering absorption, distribution [19, 20], protein binding [9, 17], half-life of elimination [7, 21], time to peak [19], and excretion [22].

Pharmacokinetics of polymyxin-B	Comments
• Absorption	Not taken up by the gastrointestinal system.
• Distribution	Patients that are extremely sick have inadequate tissue diffusion. Peripheral Vd: 0.33 L/kg Central Vd: approximately 0.09 L/kg Fails to get across the blood-brain barrier and enter the CSF or the eye.
•Protein binding	Approximately 60% Critically ill patients: 79% to 92%
•Elimination half life	10.1 to 13.6 hours
•Peak time, intramuscular serum	IM: within 2 hours
• Excretion	Within the first 12 hours of treatment, less than 1% of the drug remains unchanged in the urine; as the course of treatment progresses, the percentage of unchanged drug in the urine can reach up to 60%.

Spectrum of Activity:

Range of actions with regard to the majority of gram-negative aerobic bacilli, colistin exhibits high bactericidal action. These include Acinetobacter species (MIC90≤2 mg/L), P. aeruginosa (MIC90≤4 mg/L) [23], K. pneumoniae (MIC90≤1 mg/L), E. coli (MIC90≤2 mg/L), and Enterobacter spp. (MIC50<1 mg/L). Furthermore, it might have antimicrobial activity against Salmonella spp. (MIC90≤1 mg/L), Shigella spp. (MIC90≤0.5 mg/L), Citrobacter spp. (MIC90≤1 mg/L), Haemophilus influenza, Yersinia pseudotuberculosis, and many mycobacterial species. Colistin is resistant to Providentia spp., Serratia spp., and Brucella spp. [22, 24].

Similar to colistin, polymyxin-B effectively combats gram-negative aerobic bacteria that are resistant to several drugs, such as Pseudomonas aeruginosa, Acinetobacter baumannii, Escherichia coli that produces carbapenemase, and Klebsiella pneumoniae. Notably, certain bacteria exhibit inherent resistance to polymyxins, including Serratia sp., Proteus sp., Providencia sp., Morganella sp., and Burkholderia cepacian [25].

Various Polymyxin Variations:

The polymyxins B and E share a great deal of similarities in their chemical compositions, mode of action, resistance profiles, and range of activities. But in terms of pharmacokinetics and pharmacodynamics, they differ

greatly. The parenterally administered version of each polymyxin is a noteworthy distinction. The active version of polymyxin B is administered, whereas the inert prodrug colistin methane sulphonate (CMS) is given for colistin.

Polymyxin E can be inhaled, injected intramuscularly, intrathecally, or intravenously. Intramuscular, intrathecal, intravenous, and ophthalmic administration are the ways that polymyxin B is given [26].

Unlike colistin (polymyxin E), which is eliminated in urine as a colistimethate sodium (CMS) prodrug, polymyxin-B is an active medication that is only slightly excreted in urine [25].

Mechanism of Nephrotoxicity:

Over the past ten years, a great deal of research has been done on the processes of nephrotoxicity created by polymyxins, which has aided in the investigation of various approaches to lessen the harm that these medications bring to the kidneys. The process of enthusiastic proximal tubule reabsorption that colistin and polymyxin B (polymyxin B) both go through in the kidneys is a first step in the chain of events that results in nephrotoxicity [27]. The endocytic receptor megalin and other transporters work together to mediate a significant intracellular buildup of the drug during this process [28].

Studies using animal specimens and cell culture experiments have allowed for a deeper examination of this phenomenon because it has been shown that polymyxins have a high intracellular concentration in renal cells from humans (HK-2) as well as rats (NRK-52E) [29, 30]. Reduced renal function and histological damage are the outcomes of drug-induced cell death caused by polymyxin buildup. Research conducted on animals has demonstrated that exposure to polymyxins can result in dose- and time-dependent tubular necrosis, enlarged tubules in the kidneys, and cast development [31].

Death receptor activation, mitochondrial damage, modifications to the function of the endoplasmic reticulum, and the process of autophagy are the main mechanisms leading to kidney cell apoptosis [29, 31, 32].

During the process of cell destruction, the routes for receptors for death are among the most vulnerable [31]. Exposure of rats to polymyxins results in an increase in membrane-anchored FasL, which connects with a death receptor Fas, activating caspase-8 and then caspase-3, the last enzyme responsible for DNA fragmentation and cellular apoptosis [29]. Mitochondrial fragmentation is facilitated via the emission of reactive oxygen molecules through the activation of the death receptor pathway, which also increases oxidative stress.

When exposed to polymyxins, the usual filamentous shape of the mitochondria is drastically altered to a fragmented variant. More mitochondrial damage is caused by the altered mitochondrial shape, which also increases superoxide generation and causes the loss of the membrane potential of the mitochondria. Proapoptotic proteins like caspase-9 are activated by this intrinsic mitochondrial pathway, which also causes the death of cells and stimulation of caspase-3 [29]. Furthermore, proapoptotic genes, including development halt and damage to DNA 153 (GADD153), that trigger caspase-12 and then downstream caspases, are activated by the endoplasmic reticulum in response to prolonged stress, resulting in cellular death [31].

And last, exposure to excessive polymyxin concentrations can inhibit the regular autophagy process, which eliminates damaged proteins and organelles. This leads to a breakdown in the regulation of cell damage and a disruption in the equilibrium between autophagy and apoptosis [31]. As a result, polymyxins cause cell apoptosis by inducing pan-caspase activation through many routes in a manner that is dependent on time and concentration. The cycle that results in kidney cell death is sustained by the oxidative stress that this process generates, which further activates these pathways [29].

Risk Factors for Nephrotoxicity:

One of the most frequent and undesirable side effects of polymyxins is the development of AKI. AKI during therapy is linked to a worse prognosis, which includes increased mortality rates [18, 33, 34]. Moreover, a greater frequency of individuals with acute kidney injury undergoing polymyxin therapy are now believed to have persistent kidney failure [35, 36, 37]. Therefore, reducing the frequency of AKI in patients undergoing polymyxin therapy may have therapeutic benefits that are both short-and long-term.

Regretfully, there aren't many reported polymyxin-associated AKI risk factors that can be changed. Furthermore, patients who need polymyxin therapy are often extremely sick and suffer from a number of persistent medical conditions that, combined, may exacerbate drug-induced kidney damage [38, 39-47], AKI has been linked to a number of chronic comorbid illnesses, the most prominent of which is diabetes. [38, 48-52].

Several investigations have linked older age as one of the non-modifiable risk variables [18, 39, 48, 49, 53-55]. A small number of possibly adjustable risk variables have been found. It has been noted that one modifiable risk factor is the concurrent use of nephrotoxic medicines. Certain studies [40, 44, 48, 56] have reported the concurrent utilization of a number of generalized kidney- damaging drugs.

On the other hand, among non-antimicrobial medications, loop diuretics [38, 57], calcineurin inhibitors [41], non-steroidal anti-inflammatory medicines (NSAIDs) [58], and contrast agents administered intravenously [59] proved to constitute warning signs.

A few research have reported vancomycin [59, 60-62], whereas single studies have reported rifampin [56] and aminoglycosides [55]. Furthermore, in qualitative research, minocycline and colistin together were shown to reduce the risk of acute kidney injury; however, this may be because minocycline reduces the level of oxidative stress [63].

Albuminuria, cellular casts, and azotemia are possible signs of polymyxin B-induced nephrotoxicity; track baseline BUN, serum creatinine, and urine analysis as needed. Stop the medication if your urine output decreases and your BUN rises. According to data,

polymyxin B selectively absorbs into renal cells, which is primarily responsible for any potential nephrotoxicity [64].

Discussion:

A lower dose is advised for people with renal impairment, although the FDA in the United States (2012) did not provide any pertinent research evidence. For individuals with normal renal function, the US FDA current authorized label suggests a dosage regimen of 15,000 to 25,000 units/kg per day (1.5-2.5 mg/kg/d) [65]. But according to Tsuji et al's 2019 the dose of polymyxins should not be changed according to the international consensus criteria for their best use [6].

The idea that individuals with reduced kidney function should have their dosage of polymyxin B modified is also backed by certain studies. Yu and colleagues, 2020 showed that lung infection in individuals with impaired renal function could be effectively controlled with a relatively small amount of polymyxin B (100 mg daily for individuals weighing 50 to 75 kg) [66]. It is improbable that the body will eliminate a sizable amount of polymyxin -B with kidney replacement therapy, as demonstrated by Rigatto et al. [67], who also found that most of the removal of polymyxin B occurs through non-renal pathways. Therefore, in compliance with the Global consensus recommendations regarding the ideal use of the polymyxins, patients with impaired kidney function should not have regular doses of polymyxin B altered.

35 adult participants in a population pharmacokinetic investigation carried out by Manchandani et al. (2018) [21] examined the pharmacokinetic variation of polymyxin B. Wang et al. [68] afterwards carried out a study in which they enrolled 3 individuals with typical kidney function and 33 people with inadequate kidney function in 2021. They discovered that while the degree of the connection was considered clinically inconsequential, the clearance of polymyxin B was found to be strongly linked with creatinine clearance.

In a retrospective analysis in terms of the relationship between the clinical outcomes and polymyxin B dosage, Nelson et al. also discovered that when using a lower dose of polymyxin B, individuals with impaired kidney function may experience diminished effectiveness and a higher 30-day death rate [69]. Yu and colleagues (2021) created a population pharmacokinetic study (popPK) utilizing the Monte Carlo method for polymyxin B and a retrospective analysis of thirty-two adults with varying kidney function. Since the recommended dose of polymyxin B needs to be modified in accordance with the finding that creatinine clearance is a significant covariate in polymyxin B clearance [70].

In 2020, Maniara and colleagues separated individuals with impaired kidney function into two groups: one group had renally made alterations (depending on renal function, the dose of polymyxin B was modified), and the other group was not. They discovered that the renally modified group had a greater rate of renal toxicity and mortality than in the non-renally adjusted group [71].

Merely 0.04–0.86% of the dosage was found in urine in its unaltered state in research by Zavascki et al. (2008) [9] that involved eight individuals with critical conditions and got 1.0 ± 0.3 mg/kg polymyxin B over 12-48 hours. This suggests that non-renal mechanisms are primarily responsible for the elimination of polymyxin B. A case study by Kwa et al. (2011) involved a 50 kg patient whose initial value of serum creatinine was 3.5 mg/dl (calculated clearance of creatinine, 18 ml/min). Every 24 hours, the patient underwent sporadic IV infusion of 50 mg of loading and 75 mg of maintenance dosage of polymyxin B. Polymyxin Bs computed half-life of 11.5 hours is consistent with previous research in individuals with typical kidney function [72].

Using urine and blood samples, Sandri, and colleagues (2013) [20] performed Monte Carlo simulations and a population pharmacokinetic analysis on 24 critically ill individuals in 2013. The research carried out in 2016 by Thamlikitkul and colleagues [10] involved 19 adult individuals who were given IV polymyxin B (2.2 ± 0.2 mg/kg/day or 1.9 ± 0.3 mg/kg/d). The findings showed that individuals with normal and diminished renal function had identical exposures to polymyxin B; polymyxin B, s average urine recovery was 4.04%, and there was no correlation found between it and clearance of creatinine. Even yet, patients with normal kidney function and those in the kidney dysfunction group did not differ in dose level in a way that was of statistical significance.

In order to minimize toxicity and optimize dosing, Li, and colleagues (2021) created a popPK model for polymyxin B in Chinese patients undergoing kidney transplants. The results indicated that kidney capacity is a major factor in the removal of polymyxin B and that the best combination of a 75 mg loading dose and 50 mg as a maintenance dosage was the best combination for patients with renal impairments [73]. Despite the fact that Wu et.al. (2021) [74] Monte Carlo model information from the investigation by Wang and colleagues, their analysis yielded different results.

Wu gave Chinese patients advice and thought that the polymyxin B dosage needs to be modified. As they recommended that patients with renal impairment receive a 60 mg of maintenance medication each 12 hours, individuals with normal kidney function should take 1.25 milligrams per kilogram, and patients with renal impairment should take a 2.5 mg/kg loading dose.

Conclusions:

A great deal of pharmacokinetic studies that have been published so far concur that creatinine clearance affects polymyxin B clearance; nevertheless, there is ongoing debate on the extent of this influence. Clinical observational investigations, on the other hand, verified that patient groups exhibited comparable safety and efficacy indicators with or without a dose modification. We believe a dose change is worthwhile to recommend since, provided adequate effectiveness is maintained, the altered group is more cost-effective. The degree of renal impairment will, however, determine how the dosage should be changed. Important areas for future research are whether and how to modify the dosage. Numerous studies have been conducted regarding polymyxin B dose

in individuals with impaired renal function; however, due to design limitations and inconsistent findings, a consensus cannot yet be reached. Investigations using a more practical range of doses are therefore desperately needed.

Contribution of Authors:

All authors contributed to the writing as well as critically reviewed and approved the final manuscript.

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Conflicts of Interest:

The authors declares that there are no conflicts of interest.

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