



Background

- Polymyxin B injection is available for inpatient use. This product is being used by the irrigation mode of administration. The proposal is to implement the intravenous route of administration with restrictions for use.
- Several changes were made to the FDA drug approval process in the 1960s which is after the time (1951) when polymyxin B was originally approved by the FDA.^{1,2} The approval process for polymyxin B was different than medications that are approved today. Thus, there is a lack of robust clinical trials on polymyxin B's efficacy, safety and pharmacokinetics.

Efficacy

Polymyxin B was FDA approved for acute infections caused by susceptible strains of *Pseudomonas aeruginosa* and for serious infections caused by the following organisms (if susceptible) when other less toxic drugs are ineffective or contraindicated: *H. influenzae* (meningeal, IT route), *Escherichia coli* (UTI), *Aerobacter (Klebsiella) aerogenes* (bacteremia), *Klebsiella pneumoniae* (bacteremia).³ It should be noted that this drug did not go through the modern drug development process and thus, pharmacokinetic evidence since its approval has indicated that it is not appropriate for UTIs. Guidelines indicate that polymyxin B is the preferred polymyxin therapy for systemic use in invasive infections other than UTIs.⁵

Safety

Polymyxin B has several black box warnings (BBW): administration by the IM and IT routes should only be done in hospitalized patients, nephrotoxicity and neurotoxicity can occur, safe use in pregnancy has not been established, concurrent therapy with other nephrotoxic or neurotoxic medications should be avoided, respiratory paralysis can occur with concurrent neuromuscular blockers.³ Paresthesia and skin hyperpigmentation are unique side effects that can occur.⁴ *Clostridium difficile* associated diarrhea (rare) and the development of drug-resistant bacteria are other potential adverse events that may result with the use of polymyxin B.³

Uniqueness

Polymyxin B may be a treatment option for infections caused by certain multi-drug resistant (MDR) and extensively drug-resistant (XDR) organisms⁵ such as Carbapenem-Resistant Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Polymyxin B has more predictable pharmacokinetics than colistin.

Cost

Polymyxin B sulfate injection cost ~\$5 for 500MU vial.⁶ A patient weighing between 70-100kg and receiving a dose of 30,000 units/kg/day would use 5-6 vials of polymyxin B sulfate which would cost about \$25-30 per day.

Recommendation

- ❖ Add the injectable formulation of polymyxin B to formulary with restrictions.
- ❖ No changes to the formulary status of colistin
 - Amongst the polymyxins, colistin will remain the preferred therapy for UTIs and inhalation therapy

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Appendix A. Summary of safety issues and implications for pharmacy operations

Characteristic	Summary
Medication Information	
Drug generic name (brand name)	Polymyxin B
Drug manufacturer	multiple
Schedule of medication	n/a
Anticipated use per month, anticipated patient population	unknown
Route of administration	intravenous
Preparation	Dilute 500,000 units with 500mL of D5W (final conc 1000 units/mL)
Stability	Solutions should be refrigerated and unused solution discarded within 72 hours
Recommended storage conditions for medication, and how to manage excursions outside these conditions	See above; Prior to reconstitution, store at room temp & protect from light
Does the manufacturer require patients to meet specific criteria for treatment with this medication? If so, where may healthcare providers find these criteria?	No
Operations Information	
Is filtration required during preparation or administration of the IV medication?	No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A <input type="checkbox"/> <i>Package insert does not state that filtration is required.</i>
Can medication doses be sent to patient care units via pneumatic tube system?	No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A <input type="checkbox"/>
Does the manufacturer have a restricted or special distribution program? If so, how may healthcare providers contact the program?	No <input checked="" type="checkbox"/> Yes <input type="checkbox"/>
Safety/Policy Information	
Will this impact a dynamic alternative alert?	No <input type="checkbox"/> Yes <input type="checkbox"/> - Possibly
Is the medication (brand name, generic name, product packaging) similar to any other medications on the Institute for Safe Medication Practices (ISMP) Sound-Alike-Look-Alike (SALA) list or confused names list? If not, is the medication expected to be added to the list?	No <input checked="" type="checkbox"/> Yes <input type="checkbox"/>
Does the product package insert currently have any black box warning? For what?	No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> IM/IT route – only administered in hospitalized patients, nephrotoxicity, neurotoxicity, use in pregnancy, concurrent therapy, neuromuscular blockade
Is this medication a hazardous agent?	No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> Not noted as such in PI or Lexicomp
Is the IV medication a vesicant or irritant?	No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> Phlebitis can occur. It does state that the IM route of administration is an option but that it is also known to be painful (severe pain in children).
Is this a high-alert medication that requires an indication? <u>See MM02.</u>	No <input checked="" type="checkbox"/> Yes <input type="checkbox"/>
Are there contraindications or significant warnings against medication use?	No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> See BBW
Is special monitoring recommended when starting therapy with this medication (eg. Telemetry, BP, etc)?	No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> See BBW. Renal function and concomitant therapy must be assessed prior to initiation of polymyxin B.
Is there a Risk Evaluation and Management Strategy (REMS) program for the medication? If so, where may healthcare providers find these criteria?	No <input checked="" type="checkbox"/> Yes <input type="checkbox"/>
Does the medication require precautions for disposal? What kind? <u>See EC20 Disposal of Pharmaceutical Products; EC11 Chemo Drugs-Safety Precautions for Administration</u>	No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> Not chemo.
Will the medication be restricted: <u>MS68 Levels of Care</u> To a specific level of care (LOC)? To a specific location? To specific services/ providers? To providers credentialed in deep sedation or general anesthesia? To patients who are on the medication prior to admit?	No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> Unknown <input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> Unknown <input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> Unknown <input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> Unknown <input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> Unknown <input type="checkbox"/>

References

1. Polymyxin B. Clinical Pharmacology. Elsevier/Gold Standard. Last updated: 12/8/2009. Accessed 2/12/2019.
2. Food and Drug Administration, Milestones in the US Food and Drug Law History. Available at: <https://www.fda.gov/AboutFDA/History/FOrgsHistory/EvolvingPowers/ucm2007256.htm> Last updated: 2/1/2018. Accessed 2/11/2019.
3. Polymyxin B [package insert]. Fresenius Kabi USA: Lake Zurich, IL. Revised 9/2018.

4. Mattos KPH, Gouvêa IR, Quintanilha JCF, et al. Polymyxin B clinical outcomes: A prospective study of patients undergoing intravenous treatment. *J Clin Pharm Ther.* 2019 Jan 21. doi: 10.1111/jcpt.12801.
5. Tsuji BT, Pogue JM, Zavascki AP, et al. International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), 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). *Pharmacotherapy.* 2019 Jan;39(1):10-39. doi: 10.1002/phar.2209.
6. Cardinal Health Orders Express. Accessed 2/12/2019.

Introduction

Available medications within the polymyxin class of anti-infectives include Polymyxin B and colistin (Polymyxin E). Polymyxin B was first approved by the FDA in 1951 with Colistin following in 1968.^{1,2} Although they are in the same class and their chemical structures differ by 1 amino acid, there are distinct and important differences between them (Table1).³

Table 1: Comparison of Polymyxin B and colistin^{3,4}

	Polymyxin B	Colistin (Colistimethate for injection)
Mixture	Polymyxin B1 and B2	Colistin A and B
MOA	Bactericidal activity. Exact MOA unknown. May be due to the electrostatic and hydrophobic interactions that cause the bacterial outer membrane to be disrupted	
Resistance	Develops through chemical modification or loss of the lipopolysaccharide target, cross resistance exists	
Administered as	Active drug	Inactive prodrug (colistin methanesulfonate – CMS or colistimethate)
Urine concentrations	Low	High (CMS, colistin). CMS converts to colistin within the urinary tract (CMS is unstable in the aqueous environment)
Plasma concentrations	Rise rapidly (relative to colistin)	Rises slowly, even with a loading dose, since CMS needs to convert to active drug. Concentrations may be lower in patients with good renal function since the renal elimination of CMS decreases the conversion of CMS to colistin.
Therapeutic drug monitoring	Properties of the medication would suggest that TDM would be able to optimize therapy.	Difficult to determine the colistin level in the blood at that time of lab draw vs the colistin that was converted from CMS since the time of lab draw.
FDA approved indications	Infections caused by susceptible strains of <i>Pseudomonas aeruginosa</i> and for serious infections caused by the following organisms (if susceptible) when other less toxic drugs are ineffective or contraindicated: <i>H. influenza</i> (meningeal, IT route), <i>Escherichia coli</i> (UTI), <i>Aerobacter aerogenes</i> (bacteremia), <i>Klebsiella pneumoniae</i> (bacteremia)	Treatment of infections due to sensitive strains of certain gram-negative bacilli (e.g., <i>Enterobacter aerogenes</i> , <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Pseudomonas aeruginosa</i>) which are resistant to other antibacterials or in patients allergic to other antibacterials
Black Box Warning	Yes, several warnings.	No
Cost⁸	~\$5 for 500MU vial (\$25/day for 70kg)	~\$10 for 150mg vial (\$30/day for 70kg)

Pharmacokinetics

	Per Package Insert
Absorption	Not absorbed from the GI tract
Distribution	Poor tissue perfusion Does not pass the BBB into CSF
Metabolism	---
Elimination	Kidney***

***There is disparity between the package insert and the more recent literature on polymyxin B's elimination pathway. Polymyxin B is thought to be eliminated by non-renal mechanisms. It does undergoes tubular reabsorption which can contribute to the renal toxicity.³ Since it is eliminated by non-renal mechanisms, it is not the preferred polymyxin for UTIs.⁷

Pharmacology

- See table 1

Warnings, Precautions, Adverse Reactions

- Polymyxin B has several black box warnings (BBW): administration by the IM and IT routes should only be done in hospitalized patients, nephrotoxicity and neurotoxicity can occur, safe use in pregnancy has not been established, concurrent therapy with other nephrotoxic or neurotoxic medications should be avoided, respiratory paralysis can occur with concurrent neuromuscular blockers.⁵
- Paresthesia and skin hyperpigmentation are unique side effects that can occur with this medication.⁶
- *Clostridium difficile* associated diarrhea and the development of drug-resistant bacteria are other potential adverse events that may result with the use of polymyxin B.⁵

Drug Interactions

- Avoid neuromuscular blockers (curariform muscle relaxants) and neurotoxic medications (e.g., ether, tubocurarine, succinylcholine, gallamine, decamethonium, sodium citrate)⁵
- Avoid concomitant nephrotoxic medications when feasible (calcineurin inhibitors, vasopressors, loop diuretics, IV contrast, NSAID, ACEI, vancomycin, rifampin, aminoglycosides)⁷

Dosage and Administration

Dosage and administration information varies widely based on the reference used. The chart below contrasts the difference in dosing information between the package insert and the International Consensus Guidelines for Optimal Use of the Polymyxins.

Package Insert ⁵	Guideline ⁷
Intravenous (children, adults) <ul style="list-style-type: none"> ▪ 15,000 to 25,000 units/kg/day (normal renal function) ▪ 15,000 units/kg/day (renal impairment) ▪ Total daily dose not to exceed 25,000 units/kg/day 	Intravenous (adults) <ul style="list-style-type: none"> ▪ 12,500 to 15,000 units/kg (TBW) administered over 1 hour every 12 hours ▪ No dose adjustments in patients with renal impairment ▪ Total daily dose: 30,000 units/kg/day

Monitoring

- Signs and symptoms of nephrotoxicity and neurotoxicity

How Supplied

- Polymyxin B sulfate 500,000 units, powder for injection (~\$5)^{1,8}

Utilization

- Between 1/1/2017 and 12/31/2018, 59 doses of IV polymyxin B were administered within two separate hospital encounters (department: 5USE)

References

1. Polymyxin B. Clinical Pharmacology. Elsevier/Gold Standard. Last updated: 12/8/2009. Accessed 2/12/2019.
2. Colistin. Clinical Pharmacology. Elsevier/Gold Standard. Last updated: 12/12/2016. Accessed 2/14/2019.
3. Nation RL, Velkov T, Li J. Colistin and polymyxin B: peas in a pod, or chalk and cheese? Clin Infect Dis. 2014 Jul 1;59(1):88-94. doi: 10.1093/cid/ciu213.
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5. Polymyxin B [package insert]. Fresenius Kabi USA: Lake Zurich, IL. Revised 9/2018.
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7. Tsuji BT, Pogue JM, Zavascki AP, et al. International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), 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). Pharmacotherapy. 2019 Jan;39(1):10-39. doi: 10.1002/phar.2209.
8. Cardinal Health Orders Express. Accessed 2/12/2019.

Restrictions

- ❖ Polymyxin B, when administered intravenously, is restricted to Infectious Disease and Pulmonary Services. Use by other services requires formal consultation by Infectious Disease or Pulmonary. The drug will be distributed for 24 hours only unless one of those groups has been formally consulted and approved the use.

Criteria for Use

- ❖ Polymyxin B should NOT be used for urinary tract infections.
 - Colistin is preferred for UTIs since it is a prodrug and high concentrations occur in the urine. Polymyxin B is not a prodrug and there is a low concentration in the urine.
- ❖ Polymyxin B is preferred for use in severe gram negative infections, generally in combination with other antimicrobials. Polymyxin B is the preferred polymyxin antibiotic due to more predictable pharmacokinetics compared to colistin.

Dosing Guidance

1. Loading dose
 - a. A loading dose should be considered for critically ill patients (e.g., sepsis, septic shock)
 - b. 25,000 units/kg (25,000-30,000 units/kg) of total body weight administered over 1 hour
 - i. There is not a specific max or dose cap recommended, however, experience with doses over 2 million units is limited
 - ii. Infusion-related adverse events may occur with higher doses (thoracic pain, paresthesias, dizziness, dyspnea, hypoxemia)
2. Maintenance dose
 - a. For severe infections, a maintenance dose of 12,500units/kg (12,500 to 15,000 IU/kg) rounded to the nearest 50,000 units administered over 1 hour every 12 hours is recommended
3. Dose Adjustments
 - a. No dose adjustments are recommend for patients with renal impairment.
 - b. For patients on renal replacement therapy (CRRT), no dose adjustments are required. This applied to both the loading and the maintenance doses.
4. Concomitant therapy
 - a. Nephrotoxic agents should be avoided when possible (e.g., calcineurin inhibitors, loop diuretics, vasopressors, IV contrast media, NSAIDs, ACEI, and other nephrotoxic antibiotics like vancomycin)
 - b. The routine use of antioxidants for renal protection is not recommended

	Loading Dose	Maintenance Dose
Dosing regimen	20,000-25,000 IU/kg x 1	12,500 to 15,000 IU/kg Q12 hours
Duration of infusion	1 hour	1 hour
Dose adjustment for renal dysfunction	No	No
Dose adjustment for patients on CRRT	No	No

- The body weight that is to be used for the loading dose and the maintenance dose should be adjusted body weight in obese patients.

Reference:

Tsuji BT, Pogue JM, Zavascki AP, et al. International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), 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). *Pharmacotherapy*. 2019 Jan;39(1):10-39. doi: 10.1002/phar.2209.