SHORT COMMUNICATION

# DRUG USE RECOMMENDATIONS FOR COLISTIN INJECTION IN THE ADULT POPULATION

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**Background:** Colistin, also known as Polymyxin E, was the first polymyxin antibiotic. This bactericidal antibiotic plays a vital role as salvage therapy for untreatable gram-negative. Colistin dosing regimens differ worldwide. The published guidelines have different recommendations on the dosing regimens. Further confusion exists due to two different dosing units. Currently, Pakistan has no national guidelines for colistin use. The guideline was developed to improve the safety profile by developing standardization in colistin use and thus reduce the confusion amongst clinicians. **Method:** The guideline was developed by a panel of five actively practising infectious disease specialists (physicians and pharmacists) with clinical and research expertise in this particular field. Different literature and international guidelines along with institutional data were used to develop the guideline. **Conclusion:** The guideline provides ten recommendations on prescribing, transcribing, posology, preparation, administration and monitoring of colistin use. The guideline will give Pakistani healthcare providers a standard approach to using rationally and effectively, and to clear confusion and questions about this medicine.

**Keywords:** Colistin; Guideline; Pakistan; Resistant

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## INTRODUCTION

Colistin, also known as Polymyxin E, was the first polymyxin antibiotic. This bactericidal antibiotic plays a vital role as salvage therapy for untreatable gram-negative infection in particularly multidrug-resistant (MDR) and extensive drug-resistant (XDR) *Pseudomonas aeruginosa, Acinetobacter baumannii*, and *Enterobacteriaceae.* Recent studies in Pakistan have shown an increased risk of emergence of resistance against colistin.[1,2] Though, new medications have been approved for grgram-negativeDR and XDR, however, their utility is still unknown. Furthermore, due to their high cost, its accessibility is low. Hence, it is of high essence to establish the rational use of the drug on a national level to reduce the risk of the emergence of its resistance.

Colistin dosing regimens differ worldwide.[3] Further confusion exists due to two different dosing units. Few guidelines have been published on this subject. In 2016, the South Africa Society of Clinical Pharmacy (SASOCP) developed a guideline for colistin use for adults and paediatrics.[4] In 2018, The Association of Scottish Antimicrobial Pharmacists (ASAP) presented a guideline to standardise colistin use.[5] In 2019, an international guideline was released and endorsed by highly reputed international societies.[6] These guidelines have different recommendations on the dosing regimens as shown in Table-1

**Table-1: Dosing recommendations from different guidelines**

| Glomurular Filter Rate | 2019 US Guideline | 2018 ASAP Guideline | 2016 SASOCP Guideline |
|---|---|---|---|
| >90 | 10.9 MU | 9 MU | 9 MU |
| 80-90 | 10.3 MU | | |
| 70-80 | 9.0 MU | | |
| 60-70 | 8.3 MU | | |
| 50-60 | 7.4 MU | | 4 MU |
| 40-50 | 6.6 MU | 6 MU | |
| 30-40 | 5.9 MU | | 2 MU |
| 20-30 | 5.3 MU | 5 MU | |
| .10-20 | 4.8 MU | | |
| .5-10 | 4.4 MU | 3.25 MU | 1 MU |
| 0-5 | 3.9 MU | | |

The implementation of these guidelines in clinical settings remains difficult, especially in low-resource settings.[7] A well-recognized Asian hospital developed its institutional guideline based on the 2019 guideline. Regardless the guideline was implemented that resulted in half of the patients receiving inappropriate doses, and a higher incidence of acute kidney injury (51.6%).[8] The authors of the study strongly recommended developing an institution-based guideline to aid healthcare providers in adjusting the doses and choosing the right dose and frequency. Moreover, Colistin imposes a major safety error risk. Research shows that 65.9% of medication errors are caused due to colistin, primarily because of inappropriate loading doses and wrong dose adjustments.[7] Hence it is imperative that a local guideline should be developed that could be easily implemented in all clinical settings.

Currently, Pakistan has no national guidelines for colistin use. Few Pakistani private

hospitals have developed their institutional guideline which are different from these international guidelines. Hence this guideline will give Pakistan healthcare providers a standard approach to using rationally and effectively, and to clear confusion and questions about this medicine. Implementation research relating to applying clinical guidelines in clinical setting conducted in Pakistan have shown positive results.[9]

## MATERIAL AND METHODS

The guideline was developed by a panel of five actively practising infectious disease specialists (physicians and pharmacists) with clinical and research expertise in this particular field. Different literature and international guidelines were shared amongst the panel members which are evaluated and discussed in a series of meetings. Institutional data relating to colistin use were also evaluated.

Evidence was discussed during the meeting. Based on the meeting a preliminary guideline was prepared. The finalized guideline was implemented in the institution after the approval. Data relating to colistin were collected to conduct a drug utilization review. The results of the drug utilization review will be published in future.

Based on these experiences, a draft document was prepared to address major concerns relating to colistin use and provide recommendations. This document was reviewed by different members of the Medical Microbiology & Infectious Diseases Society of Pakistan (MMIDSP) and the Pakistan Society of Hospital System Pharmacists (PSHP). (Acknowledgment Section) The comments and suggestions submitted by these members were reviewed and changes were brought where necessary.

For many years, information relating to the pharmacokinetics and pharmacodynamics of colistin and outdated and conflicting literature about dosing resulted in confusion about its efficacy and safety. The discrepancies in the dosage recommendations between these guidelines also contributed to uncertainty amongst clinicians.[7] Furthermore, unavailability of local substantial data, the clinical impact of colistin is difficult to analyze due to the heterogenous dosing regimen.[10] Keeping in view the heterogenicity in the clinical outcome of colistin, the guideline was developed with the aim of improving the safety profile by developing standardization in colistin use and thus reducing confusion amongst clinicians.

The guideline provides recommendations for patients equal to or greater than 18 years old or patients having actual weight equal to or more than 40 kilograms. The guideline does not provide any recommendations for paediatric patients, patients less than 40 kilograms or patients who have undergone organ transplant surgery. The guide provides recommendations on four aspects of colistin use, which are:

A. Prescribing and transcribing
B. Posology
C. Preparation and administration
D. Monitoring

Due to non-standardization, colistin is prescribed in different ways that include CMS, colistimethate, polymyxin E, etc. Thus, creating confusion amongst healthcare professionals.

It is recommended that medication should be prescribed by its generic name and since the international non-proprietary name is colistin it is commended that the term colistin be used during prescribing, preparation and administration

Internationally, colistin is prescribed in two different units: International Unit (IU) and milligrams (mg) of colistin-based activity. The IU units are preferred in European countries whereas mg is preferred in the USA.[11] The conversion factor is 1 million IU corresponds to ~33 mg CBA, and 1 million IU also corresponds to ~80 mg of the chemical CMS. Due to a lack of standardization, confusion exists.

The registered products are available in two strengths: 1 million IU and 3 million IU. Both units are mentioned in packing and literature.

Conversion calculation is required to ensure the correct dose. Unfortunately, its training is not uniform in all institutions. Hence it is recommended to use IU as a standard prescribing, dispensing and administration unit for colistin. In adults, colistin is generally prescribed in millions abbreviation “MIU” can be used but in capital letters.

The International Guideline of Polymyxin has provided the dosing guideline of colistin based on the available literature and experts’ opinions. The guideline suggested loading dose keeping in view the criticality of patients. The rationale may be based on the available pharmacokinetic data that have shown that 9 MIU helps to achieve the required blood concentration, i.e., achieve a target plasma colistin of 2 mg/L more effectively than 6 MIU.[12,13] The maintenance dose is recommended based on creatinine clearance in two divided doses. The guideline recommends against the use of weight-based dosing due to a lack of pharmacokinetic data.

Administration of loading dose on colistin has been found to have no significant effect on renal functions, clinical response or mortality.[14] However, the pharmacokinetic study has shown that it takes around 36 hours to achieve a steady concentration of 2 mg/L with normal renal function.[15] Another study has shown that after 4 hours of loading dose, 66% of the patients had predicted colistin concentrations of 2 mg/L, but without a loading dose the corresponding

number would have been 7%, and it would have taken 25 hours before 66% of the patients reached the same concentration target.[16]

Loading dose for colistin is suggested in two ways, (weight-based and standard). Either standard loading dose 9 MIU or use according to body weight (adjusted body weight rather than actual body weight). Keeping in view the geographical difference in weight and genetics, of the population and reducing the risk of adverse drug effects, it is recommended, to "dose banding" in loading dose. Dose-banding" is a strategy used frequently for self-administered "over-the-counter" medications to simplify patient administration and to help prevent medication errors. In dose-banding, the ranges (or bands) of body weight and corresponding rounded doses are predefined. The individual dose of a particular patient is calculated according to a single body weight value per band, usually the midpoint of the body weight band in which the actual body weight of the patient lies. The dose-banding strategy has several potential advantages over individualized milligram-per-weight or non–non-non-dose-banded dosing such as avoiding error through individualized dose calculations, enabling more cost-efficient batch preparation, reduced turnaround and patient waiting time, reduced medication wastage, and easier detection of prescription dose errors.[17]

It is recommended that colistin should be initiated with a loading dose. The dose bands were prepared by a multi-disciplinary team comprising three ID physicians and two pharmacists

| Actual Body Weight (Kg) | Loading Dose |
|---|---|
| < 40 Kg | 4 MIU |
| 41-60 Kg | 6 MIU |
| >60 kg | 9 MIU |

The usual dosing recommendation is 3 million IU three times daily; however, the 2019 guideline has recommended ~9–10.9 million IU), divided into two doses at 12-hour intervals.[6] Furthermore, the 2019 guideline[6] have recommended dosing guidelines for 3 different renal clearances from 90 ml/minute to 50 ml/minute.

In normal subjects, CMS has a half-life of 1–2 hours and colistin 14–19 hours.[18] PK studies have shown that after the administration of a loading dose of 9 MIU, followed by a 4.5 MIU twice-daily maintenance dose, patients had a median concentration of 1.6 (0.4–4.8) µg/mL.[16,19] Hence, it is recommended to use a twice-daily regimen compared to a three-times-daily regimen. The rationale is that active drugs have a longer half-life than the prodrug.

For a patient with a CrCL of 80 mL/min, the current study predicts an average steady-state colistin concentration of 4.4 mg/L, for in total of 9 MU per day.[20] Hence it is recommended 9 million IU unit daily dose in two divided doses in patients with normal renal functions.

The dosing recommendations in chronic renal failure in the guidelines are provided. The dosing recommendations are divided into eight categories which are difficult to implement in a real clinical setting. Currently, there are no pharmacokinetic studies of colistin in the Pakistani population. Hence, to simplify the dosing regimen, it is recommended that dose should be adjusted as follows:

| Colistin maintenance dosing | | | |
|---|---|---|---|
| **Renal functions** | **Creatinine clearance** | **Dose** | **Frequency** |
| Mild | 30-50 | 3 MIU | Twice daily |
| Moderate | 10-30 | 2.5 MIU | Twice daily |
| Severe | <10 | 2 MIU | Twice daily |
| Intermittent Haemodialysis dependent | | 2 MIU | Twice daily plus a supplemental dose of 2 MIU after dialysis |

The 2019 guideline[6] recommends using adjusted body weight in all patients whereas 2016 guideline[4] recommends actual body weight in non-obese patients while in obese patients, the adjusted body weight is recommended. The ASAP recommended to use of ideal body weight in obese patients.

Drug dosing is recommended by either fixed dosing, weight-based dosing, or body surface area–based dosing. Drugs whose pharmacokinetic parameters increase in proportion with increasing body size are generally used in weight-based dosing or BSA-based dosing. In contrast, dosing drugs on a fixed basis assumes that drug pharmacokinetic parameters do not increase with body size.[21] The research shows that the pharmacokinetics of colistin vary with weight. Hence it is recommended for patient weigh>20% of their ideal body weight (IBW), the adjusted body weight (AdjBW) should be used. If ABW < IBW, use ABW. The following formula is to be used:

Adjusted body weight = LBW + 0.4(TBW – LBW)

To calculate Lean Body Weight (LBW) for a MALE:
LBW (kg) = 50 + (0.906 x (height in cm – 152.4))
To calculate Lean Body Weight (LBW) for a FEMALE:
LBW (kg) = 45 + (0.906 x (height in cm – 152.4))

It is recommended to consult with a pharmacist for dose calculations.

Currently, in Pakistan, colistin is prepared and administered in various methods in different institutes. The recommendation of preparation and administration is based on drug stability and pharmacokinetic studies. In compliance with this recommendation may increase the risk of side effects.

Colistin can be diluted in sterile water for injection, normal saline, dextrose water and linger lactate. The reconstitution of colistin is stable for 7 days in room and refrigeration. However, it is strongly recommended that Colistin should be freshly prepared and used for no longer than 24 hours

Colistin can be administered as intravenous (IV) or Intramuscular (IM) however, due to severe pain caused by IM, IV is preferred.[22] Colistin is approved for IV push (administration in 3–5 mins) and slow IV infusion (administration in 15-30 mins).

Nephrotoxicity and neurotoxicity are the most substantial and frequent adverse effects of polymyxin[23] Hence it is suggested that colistin should be monitored for these adverse effects.

Colistin-induced AKI is widely reported ranging between 14.3% and 76.1%. The median time to development of AKI ranged from 5 to 12 days. In general, colistin-induced AKI is reversible however, some patients may require renal replacement therapy.[24] The factors associated with it include advanced age, chronic comorbid conditions, hypoalbuminemia, and concomitant administration of other nephrotoxic agents.[25] Currently, there are no standardized recommendations on the prevention or treatment of colistin-induced AKI. A Pakistani study has reported around 92% incidence of AKI in the colistin group.[10]

In the absence of research in this matter, it is recommended that in case of AKI caused due to colistin, discontinuation of medication is advised in patient the risk of mortality is low or an alternative antibiotic is available. However, it is recommended that serum creatinine should be monitored during the therapy. In critical care patients and AKI, the pharmacokinetics of the drug varies, hence it is recommended clinical pharmacists should be involved in dose adjustment in such patients.

The neurotoxicity adverse effects of colistin may include dizziness, muscle weakness, confusion, headache, visual disturbances, ataxia, and paraesthesia which usually occurs in the initial days of therapy. The adverse effects are said to be related to the dose or infusion rate dependent.

**Limitation:**

The guideline is intended for adults and patients with actual weight equal to or greater than 40 kilograms. Paediatric patients and adult patients with single kidneys are exempted. The major aim of this guideline is to standardize the use of colistin so that clinical outcomes to measured homogenously. This is a major limitation of the guideline. However, to determine the impact of the guideline, research is underway. Another limitation of the guideline is that it does not propose recommendations on other routes of administration for colistin use such as inhalation or intrathecal. The rationale is that the research on these routes is still in process and its clinical impact is less determined. Lastly, since no pharmacokinetic and clinical impact data is available in the Pakistani population, the guidelines do not provide clinical recommendations for its use alone or with other antibiotics. Clinicians based on their experiences and patients' conditions can vary the recommended dose.

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