Survival or Safety: Balancing act with Colistin

Colistin, the most widely used polymyxin antibiotic, came to the market before the establishment of the present-day drug approval process.[1] Colistin fell out of favor due to its toxicity concerns. Today, colistin is experiencing a renaissance as a treatment against multi-resistant Gram-negative bacteria.[2] Older colistimethate sodium (CMS) dosing regimens have resulted both in subtherapeutic peak concentration and Prolonged time to reach a steady state, leading to suboptimal and delayed effective treatment.[3] Since its reintroduction, published reports regarding colistin have produced discordant results in terms of both efficacy and safety, restricting its usage in Intensive Care Units (ICUs). However, recent data from published reports do not corroborate this finding. Today, explanations for the lower overall toxicity include, fewer chemical impurities in CMS, better ICU monitoring, and avoidance of the co-administration of other nephrotoxic drugs.[4] Given the recent rates of carbapenem resistance, up to 52%, in the Indian ICU setups, colistin is likely to be used more often.

Dosing dilemma

To help resolve these dosing discrepancies, newer studies have undertaken the task of providing accurate Pharmacokinetic (PK) information to help guide CMS/colistin dosing recommendations. The published literature highlights different dosing regimens, mainly, a 9 MIU loading dose followed by 3 MIU eight hourly/4.5 MIU 12 hourly, as a maintenance dose, after 24 hours, while others used an initial loading dose based on ideal body weight followed by a maintenance dose modified according to the creatinine clearance.[5,6] Ultimately, the question remains, which of these available dosing options should be used? Unfortunately, the clinical impact of a higher or more aggressive dosing on efficacy still remains unclear and Pharmacokinetic — Pharmacodynamic (PK/PD) targets, as a function of infection type, warrant further exploration.

Access this article online	
Quick Response Code:	Website: www.jgid.org
	DOI: 10.4103/0974-777X.150881

Retrospective survey of colistin use in the Indian ICU.

Experience from two Indian ICUs about colistin use in 25 critically ill patients revealed:

1. CMS was administered as a loading dose of 9 MIU in 88% of the cases. The mean duration of CMS therapy was nine days. A combination therapy was employed in 76% of the cases with carbapenems (56%) as the most preferred choice.
2. Acute kidney injury (AKI) was observed in 37.5% of the cases. Sixty-six percent of the AKI episodes were associated with a higher (serum creatinine >1 mg/dl) baseline serum creatinine ($P = 0.028$).
3. Positive clinical response was observed in 92% of the cases.

Survival or safety: Balancing act with Colistin

In literature, the effectiveness of CMS treatment was found to range from 45 to 88%. Increasing the daily dose from 2 MIU to 9 MIU seemed to improve the clinical cure rates from 51 to 70%, respectively.[7] However, not only the daily dose, but also fractioning may affect the efficacy. A fractioned colistin regimen of 9 MIU eight hourly, is currently prescribed in ICU practice. Unfortunately, the clinical impact of a higher or more aggressive dosing for efficacy still remains unclear.[1]

The incidence of AKI varied greatly as a function of the definition used. In the present experience AKI was defined as per clinical practice guidelines by the 'Kidney Disease Improving Global Outcomes' (KDIGO).[8] The current experience emphasizes a strong relationship between CMS clearance and an underlying renal status, where 88% of the patients received a fixed loading dose of colistin as 9 MIU and 80% patients received 3 MIU eight hourly as maintenance dose. A recent study by Dewan *et al.*[9] observed AKI incidence in 16% of the cases, where a maintenance dose was adapted to creatinine clearance, by reducing the dosing frequency. Reducing the dosing frequency can help in achieving and maintaining a colistin steady-state concentration faster. However, on the contrary, an eight hourly dosing reduces the emergence of colistin resistance and renal damage, as compared to a once or twice daily regimen suggested by *in vitro* and animal models.[5,10] Other factors that can potentially affect kidney function, include, age, race, comorbidities, severity of critical illness, hemodynamic

status, and a possible receipt of other co-administered nephrotoxic agents, such as radiocontrast medium. A colistin loading dose, followed by titration of the maintenance dose, and a frequency adapted to renal dysfunction is further likely to reduce the burden of AKI.[11]

According to a recent comprehensive review, no differences were found in clinical cure with combination therapy regimens as compared to monotherapy. However, in difficult-to-treat infections caused by multi-drug resistant (MDR) gram-negative organisms, a combination therapy may curtail the emergence of CMS-heteroresistant gram-negative bacteria.[12,13]

When determining what to do, we finally need to emphasize on the important finding that even with the most aggressive of these dosing regimens, the likely colistin concentrations obtainable are relatively low and likely to result in bacteriostatic effects. Hence, we recommend a more conservative approach to dose colistin with an appropriate combination therapy, balancing the efficacy and nephrotoxicity.

Saiprasad Patil, Kapil Zirpe[1], Dipnarayan Mukherjee[2], Anoop Hajare, Krishnaprasad Korukonda, Amit Bhargava

Medical Services, Glenmark Pharmaceuticals Ltd., B. D. Sawant Marg, Chakala, Andheri (E), Mumbai, [1]Neurointensive Care, Ruby Hall Clinic, Pune, [2]Clinical Microbiology, Woodlands Hospital, Kolkata, India

Address for correspondence:
Dr. Saiprasad Patil, E-mail: saipras300@gmail.com

REFERENCES

1. Ortwine JK, Kaye KS, Li J, Pogue JM. Colistin: Understanding and applying recent pharmacokinetic advances. Pharmacotherapy 2014 [In Press].
2. Michalopoulos AS, Tsiodras S, Rellos K, Mentzelopoulos S, Falagas ME. Colistin treatment in patients with ICU-acquired infections caused by multiresistant Gram-negative bacteria: The renaissance of an old antibiotic. Clin Microbiol Infect 2005;11:115-21.
3. Daikos GL, Skiada A, Pavleas J, Vafiadi C, Salatas K, Tofas P, *et al.* Serum bactericidal activity of three different dosing regimens of colistin with implications for optimum clinical use. J Chemother 2010;22:175-8.
4. Balkan II, Dogan M, Durdu B, Batirel A, Hakyemez IN, Cetin B, *et al.* Colistin nephrotoxicity increases with age. Scand J Infect Dis 2014;46:678-85.
5. Bergen PJ, Li J, Nation RL, Turnidge JD, Coulthard K, Milne RW. Comparison of once-, twice- and thrice-daily dosing of colistin on antibacterial effect and emergence of resistance: Studies with Pseudomonas aeruginosa in an *in vitro* pharmacodynamic model. J Antimicrob Chemother 2008;61:636-42.
6. Boisson M, Gregoire N, Couet W, Mimoz O. Colistin in critically ill patients. Minerva Anestesiol 2013;79:200-8.
7. Markou N, Markantonis SL, Dimitrakis E, Panidis D, Boutzouka E, Karatzas S, *et al.* Colistin serum concentrations after intravenous administration in critically ill patients with serious multidrug-resistant, gram-negative bacilli infections: A prospective, open-label, uncontrolled study. Clin Ther 2008;30:143-51.
8. Khwaja A. KDIGO Clinical Practice Guidelines for Acute Kidney Injury. Nephron Clin Pract 2012;120:179-84.
9. Dewan A, Shoukat M. Evaluation of risk of nephrotoxicity with high dose, extended-interval colistin administration. Indian J Crit Care Med 2014;18:427-30.
10. Wallace SJ, Li J, Nation RL, Rayner CR, Taylor D, Middleton D, *et al.* Subacute toxicity of colistin methanesulfonate in rats: Comparison of various intravenous dosage regimens. Antimicrob Agents Chemother 2008;52:1159-61.
11. Dalfino L, Puntillo F, Mosca A, Monno R, Spada ML, Coppolecchia S, *et al.* High-dose, extended-interval colistin administration in critically ill patients: Is this the right dosing strategy? A preliminary study. Clin Infect Dis 2012;54:1720-6.
12. Petrosillo N, Ioannidou E, Falagas ME. Colistin monotherapy vs. combination therapy: Evidence from microbiological, animal and clinical studies. Clin Microbiol Infect 2008;14:816-27.
13. Michalopoulos AS, Karatza DC, Gregorakos L. Pharmacokinetic evaluation of colistin sodium. Expert Opin Drug Metab Toxicol 2011;7:245-55.

How to cite this article: Patil S, Zirpe K, Mukherjee D, Hajare A, Korukonda K, Bhargava A. Survival or safety: Balancing act with Colistin. J Global Infect Dis 2015;7:3-4.

Source of Support: Glenmark Pharmaceuticals Ltd., Case record form.
Conflict of Interest: Nil.