Polymyxin-B Combination Therapy – A Dire Need to Safeguard Our Last Hope

Sir,

We report a case of ventilator-associated pneumonia caused by extensive drug resistant (XDR) *Pseudomonas aeruginosa* managed effectively by polymyxin-B and doripenem combination.

A 34-year-old, nonsmoker male, from Pune, was transferred to our department from other hospital with a clinical diagnosis of hospital-acquired pneumonia with underlying respiratory failure. He was receiving treatment for H1N1 pneumonitis, where he clinically worsened and transferred to another hospital before shifting to our setup, where high-resolution computed tomography (HRCT) was performed which showed the bilateral dense multilobar shadow. He has received meropenem (500 mg q8 h) and amikacin (500 mg OD) for 5 days.

During admission to our department, he was in acute respiratory distress syndrome (ARDS), already tracheostomized, mechanically ventilated with fever (38.8°C) and leukocytosis (32,000/mm^3). His serum creatinine was 1.4 mg/dl started empirically on meropenem (1 g q8 h) as 30 min infusion and vancomycin (1 g q12 h). We immediately performed a fiberoptic bronchoalveolar lavage in all the involved pulmonary lobes and an MDR *P. aeruginosa* >10^5 CFU/mL was isolated in every sampled pulmonary site. This strain was susceptible only to colistin as per Vitek-2 report. E-test was asked for meropenem, doripenem, and colistin. Minimum inhibitory concentration (MIC) values were 1, 8, and 16 mg/L for colistin, doripenem, and meropenem, respectively.

We changed the antibiotic therapy in patient to intravenous polymyxin-B 7.5 lakh units 12 hourly and doripenem 1 g 8 hourly as 4 h infusion.

The patient became afebrile on day 3 and sustained defervescence was observed after 7 days. He was weaned off ventilator support on day 4, continued on polymyxin-B and doripenem for 14 days. Repeat HRCT was performed on day 13 post hospital admission which showed bilateral resolution of shadows. Serum creatinine on day 14 of polymyxin therapy was 1.2 mg/dl. After 10 days of stay in our intensive care unit, the patient was transferred to a ward where, after 5 days, he was discharged to his home. No adverse events were reported; in particular, nephrotoxicity was not observed.

We used polymyxin-B and doripenem combination therapy based on the results published by Rigatto *et al.* which showed that the combination of polymyxin-B with carbapenem lacking *in vitro* activity, was able to significantly reduce the risk of mortality in critically ill patients infected by XDR *Acinetobacter baumannii* or *P. aeruginosa*.[1] The choice of doripenem over meropenem was driven by the E-test report which showed lower MIC value for doripenem.

The pharmacokinetic edge of polymyxin-B over colistin and renal independent dosing is well understood in recent literature, which influenced our choice of combination therapy.[2]

Cheah *et al.* recently showed the importance of adaptive resistance in bacterial regrowth during polymyxin treatment and recognized the role of combination regimen as most

promising option for reducing the emergence of polymyxin resistance.[3]

Gomez *et al.* reported clinical improvement with doripenem and polymyxin-B combination therapy in complicated urinary tract infection with secondary bacteremia.[4]

Recently, Ly *et al.* evaluated the pharmacodynamics of polymyxin-B with doripenem against *P. aeruginosa* to determine the usefulness of the combinations.[5] Results showed killing activity against all strains by the combination, also complete eradication observed at concentrations of > 4 mg/L and 8 mg/L for polymyxin-B and doripenem, respectively.[5]

We believe the good clinical response observed in our case was due to *in vivo* synergy of polymyxin-B and doripenem suppressing the regrowth of heteroresistant subpopulation resulting in more potent microbiological action.

It should also be emphasized that we used polymyxin-B as per current dosing recommendations.

In conclusion, there is increasing evidence to support the use of combination therapy in carbapenem-resistant organisms, but there are many unanswered questions. Further, this combination can be evaluated by *in vitro* demonstration of enhanced killing by polymyxin-B-based combination with doripenem against XDR *P. aeruginosa*. Furthermore, setting up *in vitro* hollow-fiber and *in vivo* animal infection models with the proposed combination regimens will translate these dosing strategies to patients.

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Conflicts of interest

There are no conflicts of interest.

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