27th ECCMID Vienna, Austria 22 – 25 April 2017
The congress of ESCMID

Session: EP191 Recent advances in PK/PD: efficacy and toxicity

Category: 5b. Pharmacokinetics/pharmacodynamics of antibacterial drugs & therapeutic drug monitoring

25 April 2017, 12:42 - 12:47
EP0945

Efficacy and nephrotoxicity associated with various colistin-dosing schemas for the treatment of multidrug-resistant (MDR) infections

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Background: In light of carbapenem resistance and limited antimicrobial armamentarium, colistimethate sodium has become a competing option for MDR infections. Its use has been precluded given the disparity that exists in reported rates of nephrotoxicity with intravenous administration between old and recent studies; older studies reporting rates upward of 65%, with more recent reporting 8-19%. The objectives of this study were to evaluate clinical outcomes associated with colistin therapy in patients with documented MDR infections and assess rates of nephrotoxicity according to a standardized definition.

Material/methods: A retrospective, observational, cohort study was conducted to evaluate adult patients (age≥ 18) who received at least 48 hours of colistin treatment for MDR infections between January 2009 and August 2016. MDR pathogens were defined as microorganisms resistant to at least one agent in three or more antimicrobial categories to which the organism would typically be susceptible. Patients were stratified into 2 dosing cohorts: Package insert (PI) or Garzonik equation (GE). The following outcomes were assessed: rate of AKI according to the Risk, Injury, Failure, Loss and End stage renal disease (RIFLE) criteria, microbiological cure, clinical cure, infection related mortality, 30 day mortality, and length of stay.

Results: Seventy-two patients met criteria for evaluation; 30 in the PI group and 42 in the GE group. Majority of infections were caused by *Klebsiella pneumoniae* (63%), *Pseudomonas aeruginosa* (19%) and *Acinetobacter baumannii* (9%). There was no statistically significant difference in clinical cure rates (57% vs. 92%, p=0.655) and 30-day mortality (37% vs. 40%, p=0.744) in the PI and GE groups

respectively. Applying the RIFLE criteria, there was a statistically significant difference in the number of patients with risk of nephrotoxicity in the GE group in comparison to the PI group (19 vs. 10, p=0.0007), even with similar mg/kg dose (2.8 vs. 3, p=0.418). Increased rates of nephrotoxicity were seen in the PI cohort with higher Charlson Comorbidity Index (CCI) scores. All patients (100%) who developed nephrotoxicity in the PI group had CCI scores ≥ 3 opposed to only 47% in the GE arm.

Conclusions: MDR infections pose a serious threat to hospitalized patients given its high attributable mortality. Using the Garzonik equation for colistin dosing in the treatment of MDRO infections led to similar rates of microbiological and clinical cure, however increased rates of nephrotoxicity were observed. Further studies are warranted to elucidate these results.