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Colistin Utilization Evaluation in a Major Teaching Hospital in Iran

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ABSTRACT

Background: Colistin is an old antibacterial agent which is used in multiple drug resistant (MDR) infections. Due to increased rate of MDR infections, the use of this agent is raised in worldwide. The aim of this study was to identify colistin utilization patterns in a teaching hospital.
Methods: This retrospective cross-sectional study was performed between Augusts 2017 and December 2017 at Firoozgar hospital affiliated to Iran University of Medical Sciences, Tehran, Iran. All colistin prescriptions for adult patients during the study period were enrolled for appropriateness evaluation according to the Lexi comp acquired by Wolters Kluwer and National Health Service (NHS) guideline.
Results: Among 70 patients who received colistin, pneumonia (70%) was the chief indication of colistin prescription. In 96% of cases, colistin was prescribed according to microbiological laboratory results. In 14% of patients, colistin administration was before providing microbiological laboratory evidence. Seventeen percent of the patients received loading dose of colistin. The interval between loading and maintenance doses were incorrect in all of these patients. 73% and 67% of the prescribed doses at the initiation and end of colistin therapy were appropriate. The time interval and duration colistin therapy were appropriate in 78% and 52% of patients, respectively. The mean of creatinine clearance reduced statistically significant, 81.95 ± 39.89 and 70.85 ± 38.80 in the first and end of days of colistin therapy, respectively (P: 0.004).
Conclusion: These findings support the requirement for physicians' educational programs and suitable strategies for appropriate prescriptions.

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Introduction

Drug Utilization Evaluations (DUEs) is as a certified, organized and continuous review of healthcare provider prescribing, pharmacist provision, and patient use of medication. DUEs provides a comprehensive review of patients' prescription and medication administration process to certify that decision making and patient outcomes are appropriate. DUE programs participate in helping health care systems to improve the prescription, administration, and use of medications (1).

Colistin found in the late 1940s and lunched in 1959 (2). However, after alarms were increased nephrotoxicity, this drug was withdrawn from the market in the 1970s (3). Unfortunately, currently by the rise in the occurrence of multiple drug-resistant (MDR) hospital developed infections, usage of colistin has been increased once again (4).

The aim of this study was to identify colistin utilization patterns in a teaching hospital and to demonstrate the importance of the need to reconsider prescribing strategies for colistin administration.

Methods

This retrospective cross-sectional study was performed between August 2017 and December 2017 at Firoozgar hospital affiliated to Iran University of Medical Sciences, Tehran, Iran. The study protocol was approved by ethics committee of Iran University of Medical Sciences. In this period of time, patients who received colistin were enrolled in this study.

In the mentioned hospital, all attending physicians ordinarily complete a designed form approved by food and drug department of Iran University of medical sciences, to request colistin from the inpatient pharmacy. This form comprises two parts; the first part contains patient demographics data (age, gender, ward and the reason for the admission) and the second part includes data on reasons for colistin prescription, total amount of colsitin requested, the interval of colistin administration and the duration of treatment.

For evaluation of the utilization pattern of colistin, the above mentioned completed forms were provided to clinical pharmacist from the data collection of the pharmacy. Laboratory data including various type of culture, Blood Urea Nitrogen (BUN) and creatinine level was extracted from Hospital Information System.

The appropriateness of colistin prescription was assessed by last version of Lexicomp acquired by Wolters Kluwer and National Health Service (NHS) guideline (5, 6).

Data was entered from the mentioned forms to SPSS® 20 Software for statistical analysis.

The numerical and nominal variables are stated as mean ± standard deviations (SD) and percentage, respectively.

Results

Data from 70 patients were composed; 30 were female and 40 male. The mean age of included patients was 62.28 ± 20.2 years. Eighty-three percent of the study patients were admitted to Intensive Care Units (including medical, neurosurgical, surgical and neurovascular).

The causes for the colistin administration were as follow: pneumonia (66%), urinary tract infection (13%), sepsis (7%), meningitis (4%), skin/soft tissue infection (4%) and spontaneous bacterial peritonitis (2%). Colistin therapy was performed according to the microbiological culture results in 95% of cases. Microbiological culture was not obtained in 5% patients. In 14% of patients, colistin administration was before providing microbiological laboratory data. Considering the involved microorganism, most (36%) cases were Acinetobacter spp. followed by Klebsiella spp. (17%), Pseudomonas spp. (14%) and Escherichia coli (4%). In 13% cases, cultures included combination of mentioned organisms. According to culture results, 56% and 7% microorganisms were sensitive and resistance (Acinetobacter spp.) to colistin, respectively. In 33% of cases, the sensitivity to colistin was unknown.

Colistin was administered as intravenous infusion in all patients. In addition, 4 patients received nebulized colistin along with IV infusion. In 100% of the cases, the methods of preparation, dilution and duration of infusion were correct.

Seventy three percent of the prescribed doses at the initiation of colistin therapy were appropriate. Among inappropriate first doses, 14% and 13% were higher and lower than optimum doses, respectively. Loading dose was prescribed for 12 (17%) the patients during the study time. The interval between loading and maintenance doses were incorrect in all of these patients. In 67% of cases, colistin maintenance dose was appropriate during the study.

Fifteen patients were excluded for the assessment of treatment duration; 4 patients due to interrupted treatment and 11 patients died during colistin therapy. Among 55 patients, the mean of treatment duration was 13.01 ± 6.41 days (rang, 2 to 31 days). The interval administration time and duration of colistin therapy were correct in 78% and 52% of patients, respectively.

Serum creatinine was assessed on daily basis in all of patients. According to kidney function, 34% of patients needed to dose adjustment in first dose which this adjustment was correctly done in 16% cases. The mean of clearance creatinine reduced statistically significant, 81.95 ± 39.89 and 70.85 ± 38.8 in the first and end of days of colistin therapy, respectively (P: 0.004). In 51% patients needed to dose adjustment in during study, corrected dose was only administrated in 21% cases. The evaluation of neurotoxicity was not possible due to the most our study population was critically ill patients

who had poor conditions or received sedative agents.

A level D potential drug interaction (based on Lexi-Interact definition) was observed in 60% of cases. These interactions included co-administration of colistin with vancomycin and aminoglycosides, which could lead to increase nephrotoxicity.

Discussion

In this study, we assessed colistin pattern usage in a referral hospital in Tehran. This study had two important achievements; first, the relative resistance of Acinetobacter spp. to colistin and second, incorrect interval between loading dose and maintenance dose.

The incidence of multiple drug-resistant (MDR) infections is rising (4). Prolonged hospitalization, increased morbidity and mortality and higher health care cost have been reported with MDR infections (7, 8). The treatment of gram negative infections such as Pseudomonas aeruginosa, Acinetobacter baumanii, and Enterobacteriaceae are complicated due to growing resistance mechanisms (9, 10). The use of dual carbapenem therapy and higher dosing policy has been tried; however the information on the success rate of these treatments is limited (11-13). So, the usage of older agent such as colistin has been increased (4). However, in corrected use of this agent could lead to development of resistant microorganisms.

Colistin-resistant Acinetobacter spp. has been observed in low rates in Iran (14). For example, resistance of Acinetobacter spp. to colistin was reported 1% at Hamedan in 2011-2012 (15), 11.6% at Isfahan in 2011-2012, (16) and 12% at Tehran in 2009-2010 (17). However, recent studies from different parts of Iran consisting of Tehran, Ahvaz, Shiraz and Kermanshah have indicated that the susceptibility of Acinetobacter spp. to colistin has been 100% (18-22). Our results revealed 7% of Acinetobacter spp. was resistant to colistin. However, in our study resistance to colistin was evaluated by disk diffusion test. Galani et al., reported the disk diffusion method is an unreliable technique for assessment susceptibility to polymyxins and results should be established with MIC measurement (23).

Vazin et al., reported the first colistin utilization evaluation in Iran. Pneumonia was the main reason (69% of the cases) of colistin in their center. In 87% of their cases, colistin prescription was according to microbiological data (24). They did not use the first dose in any of their patients. We have comparatively similar results to mentioned study, with the difference that some of our patients received the loading dose.

A loading dose is a first higher dose of an agent administered to achieve a rapid therapeutic response. It usually continues with a lower maintenance dose. The co-administration of loading and maintenance doses could result in complexity in prescribing, dispensing, administration and monitoring of treatment and finally could raise the likelihood of medication errors. According to the report of the National Reporting and Learning System (NRLS), 1,165 patient safety problems occurred due to loading doses between January 2005 and April 2010 (25). Based on NHS guideline, the starting time after loading dose should be 12 hours for colistin in critically ill patient with creatinine clearance higher than 50 mL/min. This time interval should increase to 24 hours in patients with creatinine clearance lower than 50 mL/min (6). In our study, 17 patients received loading dose due to critical conditions but the time interval between loading dose and maintenance dose was not correct in any of the patients.

In recent studies RIFLE criteria recommended for the evaluation of colistin nephrotoxicity (24). During the study, we observed an increase in the trend of serum creatinine levels; however the occurrence of nephrotoxicity cannot be attributed to colistine alone due to administration of other nephrotoxic agents, mainly vancomycin and aminoglycosides. In various studies, the occurrence of colistin nephrotoxicity has been reported in a range of zero to 54%. This issue can result from a variety of study conditions such as different clinical situation of patients and the presence of different risk factors for nephrotoxicity including co-administration of nephrotoxic medicines (26). However, it has been suggested that serum creatinine should be measured regularly during colistin therapy due to its adverse effect.

In conclusion, due to rising of antibiotic therapy and antibiotic resistance, various factors consisting of the selection of the correct antibiotic, dose and administration, and the time interval between doses are essential. In addition, a number of issues such as obtaining culture before antibiotic therapy, monitoring adverse drug events, laboratory evidence and duration of therapy are other important factors that should be considered. As well as, the presence of an expert clinical pharmacist along with infectious specialists is necessary in control of various aspects of antibiotic therapy.

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