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Research Article

Drug Utilization Evaluation of Colistin: A Retrospective Study

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ABSTRACT

Background: Colistin, is used as the last treatment line for infections concluded from multiple drug-resistant gram-negative microorganisms. Increased consumption of colistin leads to resistance to this antibiotic in many countries. This study investigated the usage pattern of colistin administration in a selected hospital in Iran.

Methods: This study was conducted in a selected hospital in Ahvaz. Inclusion criteria were all patients who received colistin during this time according to the health information system. Patients who were received less than three doses of colistin were excluded from the study. Prescription of colistin in all patients was evaluated according to the protocol extracted from the last version of Lexicomp written by Wolters Kluwer. The descriptive and analytical statistics were carried out by the R software.

Results: Among 27 patients who received colistin, pneumonia (30%) was the main diagnoses. Colistin administration was based on the microbiological culture data in 70% of cases. Considering the involved microorganism, most cases were Acinetobacter spp., followed by Klebsiella spp. Loading dose was prescribed for seven (26%) patients. In only five (19%) cases, colistin dosing, including loading dose, maintenance dose, and the interval of colistin administration, was appropriate during the study time. Increasing in serum creatinine was seen in two (7.4%) patients. In 29.4% of patients, the combination of colistin and carbapenems was observed.

Conclusion: Given the lack of appropriate dose adjustment of colistin that may lead to incidence of resistance and adverse effect, applying of the specialist clinical pharmacist will be suggested.

It is acclaimed that inappropriate and irrational use of antibiotics is one of the main problems encountering the health system with many challenges. Irrational use of antibiotics increases mortality in the community and prolongs the duration of treatment; it also increases microbial resistance to antibiotics and reduces the quality of life among the patients, as well as ultimately induces the burden of cost to the health system [1].

Drug Utilization Evaluations (DUEs) are known as a reliable and organized evaluation of healthcare provider prescription and use of the drug by patient. DUE programs help the health system to improve prescription, administration, and pattern of medicine usage.

Antibiotic resistance has been attributed to the misuse of antibiotics in the community and hospital. Generally, the crisis of antibiotic resistance is serious. Some gram-negative infections such as Pseudomonas spp and Enterobacter spp are resistant to the whole of old antibiotics. It seems necessary to develop antibiotic control programs, health promotion, and production of new antibiotics to limit antibiotic resistance and reduce the economic burden [2].

Colistin is a cyclopeptide antibiotic of the polymyxin family and is known as polymyxin E [3]. The mechanism of activity in colistin is destroying cell membrane and leads to microorganism death and it should be used as the last treatment line for infections from multiple drug-

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resistant (MDR) gram-negative microorganisms, including Pseudomonas aeruginosa, Acinetobacter baumannii, and Enterobacteriaceae [4]. The main side effects of colistin in intravenous administration are nephrotoxicity and neurotoxicity [5].

Increased consumption of colistin to treat infections has led to resistance to this antibiotic in many countries. Many mechanisms have been proposed for resistance to this antibiotic. Changes in the outer membrane are one of them [6]. Resistance to Colistin worldwide is less than 10%, which is more common in Southeast Asian countries such as Korea and Singapore. The prevalence of resistance to colistin is increasing in these countries. Failure to take the correct dose of colistin (loading dose and maintenance dose) increases the likelihood of resistance to this antibiotic [7]. Acinetobacter species resistance to colistin has been observed to a small extent in Iran [8]. For example, in Hamedan in the period 2011-20112, this type of resistance has been reported at a rate of one percent [9]. Also, the resistance of this species to colistin during 2011-2012 in Isfahan has been reported to be 11.6% [10]. This type of resistance was reported in Tehran in 2010-2009 at a rate of 12% [11].

DUEs allow the health care provider to select a more effective drug with fewer adverse effects. To the best of our knowledge, by examining the results of various interventions, we can improve the rational use of drugs and increase the effect of the intervention in society and prepare a standard protocol for patients.

This study aims to investigate the usage pattern of colistin administration based on global standards in a selected hospital in Iran.

Methods

This retrospective cross-sectional study was conducted between October 2019 and March 2020 in a selected hospital in Ahvaz. The study was approved by the ethics committee of Ahvaz Jundishapur University of Medical Sciences with ethical code number IR.AJUMS. REC. 1399.464. Inclusion criteria were all patients who received colistin during this time according to the health information system (HIS). Patients who were received less than three doses of colistin were excluded from the study.

Data were collected and classified according to disease diagnosis, duration of hospitalization, loading dose, maintenance doses of colistin, the interval of colistin administration, combination therapies with other antibiotics, and colistin nephrotoxicity according to RIFLE criteria, and the type of prescription used for the patient whether empiric or therapeutic according to the microbiological culture. The susceptibility of bacteria isolated from patient infection to antibiotics was determined by the disk diffusion method. Also, demographic information, including age, sex, total body weight, and the patient's ideal body weight, were documented.

The collected data were compared to the protocol of colistin use, which was extracted from the last version of the Lexicomp written by Wolters Kluwer [12]. The descriptive and analytical statistics were carried out by the R software (version 2.12.0). In the descriptive statistics, the relative frequency of the indication and administration of colistin were reported.

Results

Twenty-seven patients were included in the study. Among them, 13 cases were female, and 14 cases were male. The mean age of the patients included was 47 ± 28 years. Percent of patients receipted to the wards were as follows: surgical ICU (29.6%), medical ICU (22.2%), NICU (18.5%), Orthopedic (14.8%), CCU (7.4%), urology (3.7%), and pulmonary (3.7%). The demographic characteristics of the patients are demonstrated in (Table 1).

Table 1- Demographic characteristics of the study population

Characteristic	N = 27
Age	47 (28)
Sex	
female	13 (48%)
male	14 (52%)
Ward	
Surgical ICU	8(29.6%)
Medical ICU	6(22.2%)
NICU	5(18.5%)
Orthopedic	4(14.8%)
CCU	2(7.4%)
Respiratory	1(3.7%)
Urology	1 (3.7%)

Patients were diagnosed as follows: Pneumonia (30%), Respiratory Distress Syndrome (RDS) (15%), septic arthritis (11%), exacerbation COPD (7.4%), peritonitis (3.7%), cellulitis (3.7%), surgical site infection (3.7%), pharyngeal abscess and other diagnosis were about (40%).

In 70% of cases, colistin treatment was based on the microbiological culture data (definite therapy), and the remaining (30%) were classified as empirical treatment.

Considering the involved microorganism, most (33%) cases were Acinetobacter spp., followed by Klebsiella spp. (7.4%), In 29.8% of cases, cultures were included the combination of Acinetobacter, Klebsiella, and pseudomonas. None of the cultures in this study were resistant to colistin.

In all patients, colistin was administered as an intravenous infusion.

Loading dose was prescribed for seven (26%) of patients during the study time. The time interval between loading

and maintenance dose was 12 hours in all patients who received loading dose. In five (19%) of cases, colistin dosing, including loading dose, maintenance dose, and interval of colistin administration, was appropriate during the study, and also, it was inappropriate in 22 (81%) of cases. Among inappropriate maintenance doses, 19% and 63% were higher and lower than optimum doses, respectively.

The mean ± SD duration of colistin therapy was 7 ± 4.6 days (ranged between 1 and 17 days). The interval of the colistin administration in 44% of the patients was twice a day, and the rest of the patients received colistin three times a day. In 29.4% of the patients, a combination of colistin and carbapenems was observed. A combination of colistin with imipenem and meropenem was observed in 7.4% and 22% of the cases, respectively. The combination therapies of colistin- ciprofloxacin, piperacillin-tazobactam, ampicillin-sulbactam, and cefepime-rifampin were observed in 18, 11, 3.7, 3.7, and 3.7% of the patients, respectively.

Nephrotoxicity according to the RIFLE criteria was seen in two (7.4%) patients. The evaluation of neurotoxicity was not possible because most patients had critical status and had used sedative drugs. Allergic reactions to colistin were not observed in all patients.

Discussion

This study aims to evaluate colistin usage according to the protocol in a teaching hospital in Ahvaz [12]. This study had five important achievements; first, the relative frequency of patient diagnosis and administration of colistin in a different ward. The second incorrect dose included loading dose, time interval, and maintenance dose. The third incorrect dose included adverse effects. The fourth incorrect dose included prescribing colistin according to microbiological culture. The fifth incorrect dose included combination therapy of colistin with other antibiotics.

The relative frequency of patient diagnosis and administration of colistin in different wards

The results of this study demonstrated that 29.6% of the patients were receipted to the surgical ICU, versus other wards that had higher reception. In similar studies, conducted in Shiraz, Tehran, and Mashhad, most of the study population were receipted to internal ICU (43%), ICU (83%), and burns ward (more than 50 %), respectively.

Among 27 patients who received colistin, pneumonia (30%) was the main diagnose. In three studies conducted in Iran, pneumonia was the main indication of colistin. [13-15].

Incorrect dose included loading dose, the interval of colistin administration, and maintenance dose

Loading dose was prescribed for seven (26%) of the patients during the study time. During the study time, colistin dose was appropriate in five (19%) of cases, and in 22 (81%) of cases, it was inappropriate. Among inappropriate doses, 19% and 63% were higher and lower than optimum doses, respectively. The administration time interval was twice a day in 44% of patients, and the rest patients received colistin three times a day. All the doses were compared according to the protocol extracted from the last version of Lexicomp written by Wolters Kluwer [12]. Prescription of colistin was lower than the optimum dose in 22% and 13% of cases in other studies [14-15].

In a review study, Visser Kif et al. demonstrated that the risk of the development of resistance and hetero-resistance increases with under-dosing of colistin, which is important as the last line drug against MDR gram-negative microorganisms [16]. It seems that the increased rate of under-dosing of colistin may lead to resistance and hetero-resistance in this hospital in the long term.

Secondly, a loading dose is used in serious infections for rapid therapeutic response. The result of this study in the prescription of a loading dose of colistin was similar to some studies conducted in Iran [13-14]. Given the main indication of colistin was pneumonia and also to achieve a rapid therapeutic response, the necessity of loading dose of colistin should be considered in more patients.

In this study, the interval of colistin administration was twice a day in 44% of the cases. The interval dose of colistin administration in other studies was twice a day in 71% and 74%. [14-15]. The mean ± SD duration of colistin therapy was 7 ± 4.6 days (ranged between 1 and 17 days).

In the international guidelines for the management of sepsis and septic shock, the mean duration of treatment in sepsis is between 7-10 days [17]. In low-risk patients with respiratory infections, procalcitonin levels of <0.25 µg/L can guide the decision to withhold antibiotics. Although, in critically ill patients with sepsis, procalcitonin levels of <0.5 µg/L can guide the discontinuation of antibiotics [18]. It seems that the duration of treatment, the incidence of resistance, and cost of treatment can be decreased by measurement of procalcitonin level. It was not measured in this study. Therefore, the necessity of applying procalcitonin level should be defined for physicians in this hospital.

Adverse effects

Nephrotoxicity according to RIFLE criteria was seen in two (7.4%) patients. RIFLE criteria are recommended for evaluating the nephrotoxicity of colistin in recent studies

[19]. Recent studies have reported the rate of nephrotoxicity of colistin between 10%-30% [20]. Nephrotoxicity of colistin is mostly mild, reversible, and dependent on dose [5, 19]. In the study conducted in Iran, increasing in serum creatinine during the study was observed in 53.49% and 51% of cases, respectively [13-14]. This discrepancy may be due to less duration of treatment and awareness of physicians to risk factors of colistin nephrotoxicity. Risk factors for colistin-associated nephrotoxicity are categorized as dose and duration of colistin treatment, administration of colistin with other nephrotoxic agents, presence of sepsis and septic shock, and severity of patient illness, factors related to the patient, such as age, sex, hypoalbuminemia, and hyperbilirubinemia [19].

In this study, two patients had colistin-induced renal toxicity. A 51-year-old man with the diagnosis of a pharyngeal abscess was prescribed colistin, according to microbiological culture data, with once a history of dialysis. He received colistin in combination with piperacillin-tazobactam while receiving the correct dose based on the guideline, and demonstrated increases in serum creatinine. The reason for nephrotoxicity in this case considering the correct dose may be the past medical history of the patient that had afflicted to Chronic Kidney Disease (CKD), Stage 3.

Despite another patient, 61 -year-old woman with the diagnosis of cellulitis without a history of dialysis, colistin was prescribed according to microbiological culture, that received combination of meropenem and colistin had received lower than the optimum dose based on the guideline, nephrotoxicity was observed.

It may be one of the reasons for increasing serum creatinine was inappropriate management of sepsis and if the patient had received the correct dose was possible, this situation had not been observed.

The evaluation of neurotoxicity was not possible due to most patients had critical status and had used sedative drugs.

Prescribing colistin according to the microbiological culture

Colistin treatment was based on the microbiological culture data (definite therapy) in 70% of the cases, and the remaining (30%) were classified as empirical treatment. Of course, in this hospital, determining the susceptibility of bacteria isolated from patient's infection to antibiotics was by the disk diffusion method. Prediction of disk diffusion test accuracy is limited for assessment colistin susceptibility, and the MIC method is preferred [12]. Considering the involved microorganism, most cases were Acinetobacter spp. followed by Klebsiella spp. None of the cultures in this study were resistant to colistin.

In 2 studies conducted in Iran, the prescription of colistin according to microbiological culture was similar to this study [14-15]. In another study conducted in Mashhad, 20% of prescriptions were according to microbiological culture [13]. While in mentioned studies, microorganisms were similar to this study [13-15]. Prescription of colistin according to microbiological culture can be related to better training of physicians, attention to microbial resistance, and holding re-training courses in this hospital.

Combination therapy of colistin with other antibiotics

In 29.4% of patients, the combination of colistin and carbapenems was observed. A combination of colistin with imipenem and meropenem was observed in 7.4% and 22% of cases, respectively. In 18%, 11%, 3.7%, 3.7%, and 3.7% of patients, combination therapies of colistin with ciprofloxacin, piperacillin-tazobactam, ampicillin-sulbactam, and cefepime-rifampin, respectively, were observed. In similar studies , the combination of colistin with mentioned antibiotics was not observed [14-15].

The most studied combinations are colistin-rifampicin and colistin-carbapenem with synergy effect in vitro [21-22].

Combinations of colistin with tigecycline, amikacin, fosfomycin, azithromycin, ceftazidime, minocycline, and surprisingly, the glycopeptides vancomycin and teicoplanin are also reported in the studies [21, 23].

The randomized clinical trial showed that the 30-day mortality rate of patients with MDR Acinetobacter baumannii infection was not reduced by the addition of rifampin to colistin [24].

In 2018, the estimated incidence of tuberculosis in Iran was 11,000 people or 0.014 %. The mortality from the disease is estimated at 950 people or 1.2 per 100,000 population this year [25]. Considering the prevalence of tuberculosis in Iran, it is better that rifampin will not be used in combination with colistin.

In the study conducted in Lebanon (2013), the in-vitro combination of colistin with carbapenems is associated with synergistic or an additive effect. The best synergy rate was noticed for the combination of meropenem and colistin. The reason for the increased synergy with meropenem might be that most OXA and MBLS carbapenemases target with more affinity imipenem as compared to meropenem [26]. In this study, combination of colistin with meropenem and imipenem was observed in 22% and 7.4 of patients, respectively.

Another study demonstrated that a combination of colistin-sulbactam had a desirable bactericidal effect in comparison to a combination of colistin-carbapenem [27].

Another study conducted in Turkey (2013) demonstrated that mortality and morbidity of patients who received the combination of colistin with carbapenem and sulbactam decreased in the comparison to the treatment based on colistin monotherapy [28]. In this study, the mortality and morbidity rate of colistin was not determined according to the combination therapy with other antibiotics.

Recent studies ranged the seizure rate with imipenem-cilastatin from 3-33%. However, the seizure rate with meropenem is reported as less than 1% [29]. The seizure was not observed in the patients who received colistin in this study. As most of the patients in this study were critically ill, also, increased synergy with meropenem, this agent was considered a preferred carbapenem in combination with colistin as observed in the results.

Without accessing data of clinical symptoms, the accurate evaluation of response to treatment was not possible.

Conclusion

Given the lack of appropriate dose adjustment of colistin that may lead to incidence of resistance and adverse effect, so, applying of the specialist clinical pharmacist will be suggested.

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