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Research Paper

A Six Years Report of Linezolid Consumption Pattern in Patients Admitted to Three Teaching Hospitals, Mashhad, Iran

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Abstract

Drug resistance is one of the greatest threats to the global health. Infection with antibiotic-resistant bacteria can lead to severe disease, increased mortality, and a higher risk of complications and hospitalization. Antibiotic resistance also increases the health care system's total cost. The objective of this study is to evaluate the linezolid consumption pattern, as it is one of valuable antibiotics with limited approved indications, in three teaching hospitals over a period of 6 years. This article is a descriptive retrospective study in which all inquiries about drugs and used dosage in cases admitted to following hospitals, from 1st January 2011 to 31st December 2017, were retrieved from Hospital Information System database for analysis. A total of 97 cases (mean age 51.19 years) were studied. The prescribed dose of linezolid was between 130-1200 mg/d. The mean duration of treatment was 9.4 days. The dose and duration of treatment was appropriate in all cases. Various forms of side effects related to linezolid were observed in patients including: optic neuropathy (1%) and gastrointestinal complications (1%). No cases of serotonin syndrome were observed. Just 6.2% of patients received linezolid for inappropriate indication. This report shows that fortunately, in most of cases linezolid was prescribed properly regarding indication, dose and duration. However, further educational program and regulatory monitoring can improve the situation.

Keywords: Linezolid; consumption pattern; drug use evaluation; antibiotic.

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1. Introduction

According to the World Health Organization (WHO), antibiotics are drugs that are used to prevent and treat bacterial infections, and the term antibiotic resistance is used when bacteria change in response to the use of these drugs[1]. In other words, resistance is the continuous growth of microorganisms in the presence of cytotoxic concentrations of antibiotics. In clinical practice, antibiotic resistance leads to treatment failure [2]. Even the most resistant bacteria can be inhibited and killed by high concentrations of antibiotics. However, in some cases, patients cannot tolerate this high concentration of antibiotics [3]. Although drug resistance has been a persistent problem since the introduction of antibiotics, the increase in the number, variety, and resistant spectrum of organisms has become a major clinical problem [4]. About 50 years after the first clinical use of penicillin, some infectious organisms, such as multidrug-resistant *Acinetobacter baumannii* and *Klebsiella pneumoniae*, are practically incurable with existing antibiotics [5, 6]. Besides, in the past, most pathogens resistant to several antibiotics were found only in health care settings, where the use of antibiotics is very common. But now methicillin resistant staphylococcus aureus (MRSA) is routinely seen in the community and drug resistance has become more prevalent, which is worrying indeed [7]. On the other hand, the number of antibiotics that have entered the market over the last 30 years has decreased dramatically as pharmaceutical companies and biotechnology research institutes abandon new antibiotics and focus more on other drugs [8, 9].

Linezolid is a synthetic antibacterial drug that inhibits protein synthesis in bacteria through a special mechanism. Unlike other inhibitors of protein synthesis, oxazolidinones exert their effect at the beginning of gene translation by preventing the formation of a functional initiation complex[10]. It works against gram-positive organisms including staphylococci, streptococci, enterococci, gram-positive anaerobic cocci and gram-positive rod bacteria such as Corynebacterium, Nocardia and Listeria monocytogenes as a bacteriostatic agent (except for streptococci).Linezolid inhibits the onset of protein synthesis by preventing the formation of ribosome complexes. The specific binding site for this drug is 23SrRNA on a 50S ribosomal subunit that has no cross-resistance with other drug groups. Resistance to this drug is due to mutations at the linezolid binding site in 23rRNA[11].

Linezolid is used in vancomycin-resistant enterococcal fasciitis infections, nosocomial pneumonia, community-acquired pneumonia, and complex and uncomplicated skin and soft tissue infections caused by gram-positive susceptible bacteria. off label uses of linezolid include treatment of multidrug-resistant tuberculosis and Nocardia infections[11].

Orally administered linezolid rapidly achieves levels in the serum that exceed the concentration required to kill Gram-positive bacteria, with a maximum mean concentration of 6.8 ± 1.2 mg/L at 2–4 h post-dose. An effective concentration is maintained for at least 12 h. The concentration of the drug in the cerebrospinal fluid after administration of this dose reaches approximately 60 to 70% of its serum levels. The recommended dose in most applications is 600 mg twice daily orally[11, 12].

The toxicity of this drug is reversible hematologic side effects and is mostly mild. The most common form is thrombocytopenia (seen in about 3% of cases), especially when the drug is used for more than two weeks. Anemia and neutropenia are more likely, especially in patients who already have a bone marrow-suppressing disease. Long-term use of linezolid has been reported in cases of optic and peripheral neuropathy and lactic acidosis [11].

Worldwide, more than half of all drugs are improperly prescribed, distributed, or sold, and 50% of patients do not take their drugs properly [13]. Irrational and unprincipled prescribing of drugs is a global problem which can lead to ineffective treatment, exacerbation or prolongation of the disease, distress and injury to the patient, and higher costs [14]. The importance of evaluating drug prescription patterns using WHO drug indicators to make drug prescribing more rational in developing countries is becoming increasingly important[15, 16].

Drug Use Evaluation (DUE) is a systematic evaluation system based on standard criteria to ensure appropriate administration and rational use of drugs. DUE can evaluate accuracy of drug indication, dose, duration, route of administration and also drug interactions and adverse reactions[17]. Medication Use Evaluation [18] is a process similar to DUE, but places more emphasis on improving the patient and his or her individual quality of life, and in fact evaluates the clinical outcome[19]. It can be considered as an evidence-based analysis. This process is performed in collaboration with all members of the medical staff such as physicians, pharmacists, nurses and other medical professionals[18].

Rational use of antibiotics, especially those known as golden resources, has always been at the forefront of antibiotic stewardship programs all around the world. Given the fact that only a handful of new antibiotics have been marketed in the last two decades, the depth of the tragedy of growing infections for which effective antibiotics are not available becomes even more apparent. Linezolid

belongs to a new class of antibiotics called oxazolidinones and has a broad spectrum of antimicrobial activity against gram-positive pathogens, especially those resistant to methicillin and vancomycin. Recently, linezolid resistance has been observed, especially between enterococci and coagulase-negative staphylococci. Therefore, drug evaluation studies should be performed in relation to the use of this drug to determine the pattern of prescription and use of linezolid in hospitals. Gathering information about the instructions of Linezolid (indication, dose, duration, specialization of the prescribing physician, and route of administration) in Iran and especially in Mashhad can be the basis of short-term and long-term planning for educating the community and medical staff to prevent the improper use of this drug and ultimately prevent progressive increase in resistance to this drug in society and thus reduce costs and the resulting problems. Limited studies in Iran have evaluated the consumption pattern of linezolid, but no study has been conducted in Mashhad and they were short-term studies. The present study was conducted with the aim of investigating the pattern of linezolid consumption in three hospitals - Imam Reza, Ghaem and Montaserieh – in Mashhad over a period of six years.

2. Experimental

In this retrospective study, the pattern of linezolid use during 6 years period (2011-2017) in patients admitted to different wards of Imam Reza, Ghaem and Montaserieh hospitals, three teaching hospital, affiliated to Mashhad University of Medical Sciences, Mashhad, Iran was assessed (Ethical Code: IR.MUMS.MEDICAL.REC.1398.207). A standard protocol on linezolid indications, dosing and monitoring was designed by based on updated international consensus guidelines in literature that best matched local condition like Mandell, Douglas and Bennett's principles and practice of infectious diseases, Sanford guide for antimicrobial therapy and last version of Up to date.

Patients who received linezolid for at least three doses were evaluated by an infectious disease specialist and clinical pharmacist according to the abovementioned protocol (table1). By referring to the hospital information system (HIS), the list of patients who received Linezolid during the study period was extracted and then the relevant information in was completed by referring to the medical records unit in a prepared form. This information include the patient's demographic data (case number, sex, age, weight), reason for hospitalization, diagnosis and clinical signs and symptoms, laboratory and Para clinical findings including culture results and antibiogram and complete blood count, concomitant diseases and medications, hospitalization ward, and also information related to Linezolid use (indication, total prescribed dose and duration, and route of administration and any probable drug interaction and adverse reaction). Moreover, specialization of the prescribing physician and getting advice from an infectious disease specialist if prescribing physician had other specialty was also recorded.

Table 1. Indication, dose and duration of the approved period under the supervision of an infectious disease specialist and clinical pharmacist (20]

infection	dosage, route and frequency of administration		duration of treatment
	Age<12yo	Age>12yo	
nasocomial pneumonia	10mg / kg IV Every 8 hours	600mg / kg IV Every 12 hours	10 to 14 days
Community-acquired pneumonia including recurrent bacteremia			
complicated skin infection			
Vancomycin-resistant Enterococcus faecium infections including recurrent bacteremia	10mg / kg IV Every 8 hours	600mg / kg IV Every 12 hours	10 to 28 days

Data recruited from the prepared forms were gathered and analyzed with SPSS version 26. We have shown the results as mean ± standard deviation for continuous quantitative variables and number (percentages) for nominal qualitative variables. The characteristics of the subjects were presented by descriptive statistical methods including central indices, dispersion and frequency distribution in the form of appropriate tables and figures. The frequency of the correct consumption pattern (based on the correct indication, the duration of the correct use, the correct prescribed dose) was reported in general and separately for the three hospitals.

3. Results

In the present study, 97 cases were studied, of which 83 were hospitalized in Imam Reza Hospital,

10 in Montaserieh Hospital and 4 in Ghaem Hospital. The mean age of the subjects was 51.19±24.37 years.
The most common underlying diseases were hypertension (28.9%), cardiovascular disease (20.6%) and diabetes mellitus (16.5%), respectively (table 2). Among patients, 19 patients underwent dialysis and 7 had elevated serum creatinine levels.

Table 2. Frequency of concomitant disease in patients

Concomitant disease	Number	%
Hypertension	28	28.9%
Cardiovascular disease	20	20.6%
Diabetes mellitus	16	16.5%
Liver disease	5	5.2%
Hematologic cancer	5	5.2%
Immune deficiency	1	1.5%
History of bone marrow transplant	1	1.0%

Overall, 6.2% of the cases reported in this study received linezolid for inappropriate indication. In general, the patients in this study received the minimum dose of 130 mg per day and the maximum dose of 1200 mg per day from linezolid, which in all cases was the appropriate dose. The mean duration of treatment with this drug was 9.4 days (±5.38). As the duration of treatment is 10 to 14 days based on prepared protocol, the duration of treatment with linezolid among patients in this study can be considered appropriate.

The route of administration was intravenous (95 cases) and oral (2 cases).
Regarding the indication of linezolid and the source of infection in patients, 87 cases were examined, ignoring 10 patients with incomplete information. The most common source of infection were bacteremia (43.3%), skin and soft tissue infection (12.4%) and urogenital infection (11.3%), respectively (Table 3).

Table 3. Frequency of different types of infection sources in patients

infection source	number	%
bacteremia	42	43.3%
skin and soft tissue	12	12.4%
urinary-genitalia	11	11.3%
respiratory	8	8.2%
vascular catheterization	5	5.2%
intraabdominal	5	5.2%
bone and joint	2	2.1%
endocarditis	1	1.0%
nervous system	1	1.0%

On the other hand, the most common microorganisms involved in these infections were VRE or poly microbial (Table 4).

Table 4. The frequency of different types of microorganisms involved in causing infection in patients studied

microorganism	number of cases	total%	source of infection	number
VRE	40	41.2%	Skin and soft tissue	10
			Urinary-genitalia	6
			Bacteremia	24
MRSA	2	2.1%	Endocarditis	1
			Urinary-genitalia	1

pseudomonas	4	4.1%	Skin and soft tissue	2
			Bone and joint	1
			Vascular catheterization	1
poly microbial	37	38.1%	Bacteremia	18
			Respiratory	8
			Vascular catheterization	4
			Urinary-genitalia	5
			Intraabdominal	1
			Shunt infection	1

In this study, 26 patients received linezolid monotherapy. Sixty-one percent of the patients received various other antibiotics, including glycopeptides and carbapenem. It is worth mentioning that in this study, non-linezolid antibiotics including glycopeptide and carbapenem were initially started for patients before linezolid, but after obtaining the microbiological culture results and report of resistance to glycopeptide, it was discontinued. However, 61 patients receiving carbapenem were treated with both linezolid and carbapenem concomitantly.

Linezolid mostly was prescribed in internal ICU (44.32%), surgical ICU (21.64%), internal ward (19.58%), infectious ward (10.3%), and cardiology ward (4.1%). Linezolid prescriptions in these patients were issued by various medical professionals, with infectious and internal medicine specialists being the most common prescribing specialties (85.8% and 7.2%, respectively). After that, ICU specialists (5.1%) and surgeons (2.06%) were the ones prescribing linezolid the most, respectively. It is worth mentioning that among 85.8% of infectious disease specialists, the visit of these patients was mostly done in the form of medical consultation.

Regarding the hematological side effects of linezolid, it is worth noting that after receiving linezolid, the number of white blood cells did not change significantly according to the results of tests (p value = 0.62). The percentage of neutrophil cells in patients did not change significantly (p value = 0.51). Patients' hemoglobin did not change significantly during hospitalization (p value = 0.71). Drug side effects of linezolid in various forms of optic neuropathy (1%) and gastrointestinal side effects (1%) were observed in patients. Emphasis on this issue is not insignificant that in this study no case of serotonin syndrome was seen. In this study, patients received a minimum dose of 130 mg / day and a maximum dose of 1200 mg / day of linezolid, which according to the guidelines mentioned at the beginning of the dissertation is the correct dose of this drug. The mean duration of treatment with this drug was 9.4 days (38 5.38). In general, the duration of treatment with linezolid among patients in this study can be considered appropriate.

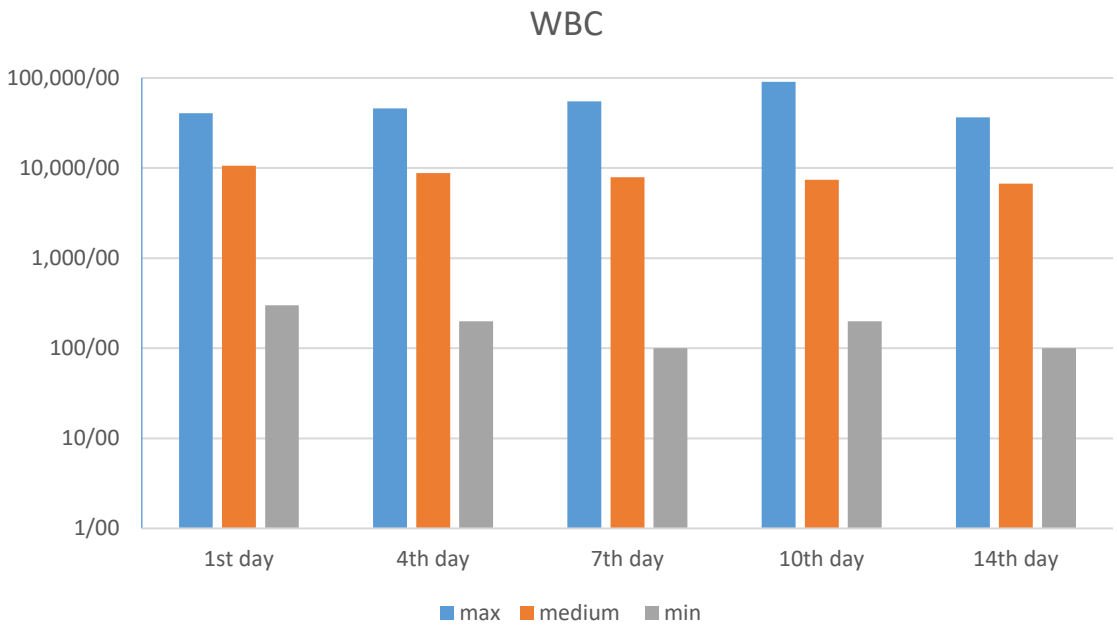

Figure 1. Comparison of white blood cell frequency in patients in the first days up to 14th day of hospitalization

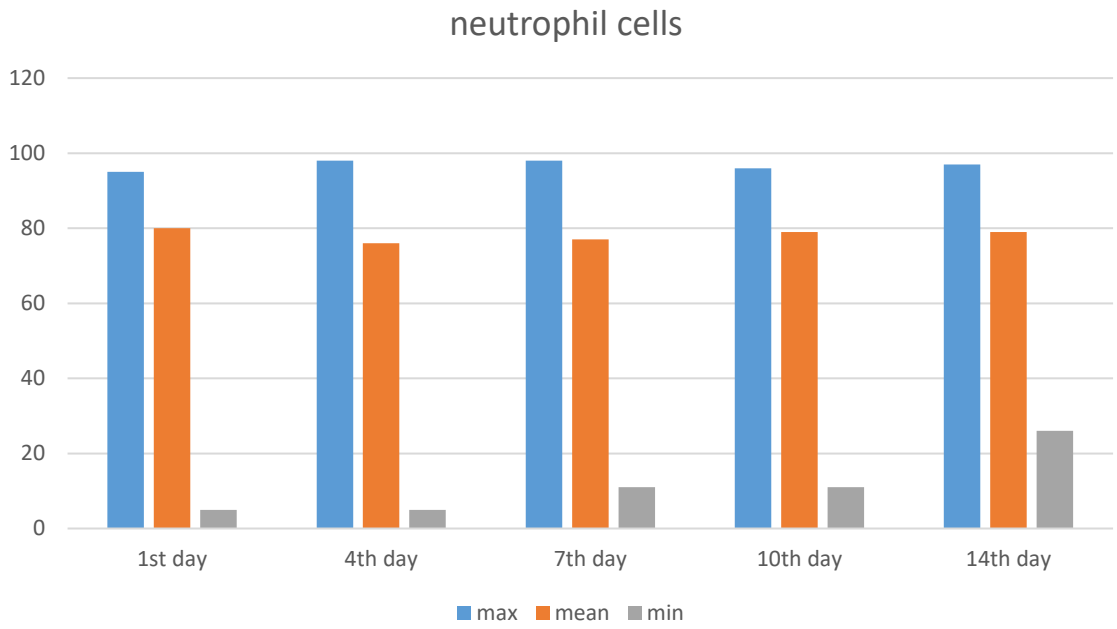

Figure 2. Comparison of neutrophil cell frequency in patients in the first days up to 14th day of hospitalization

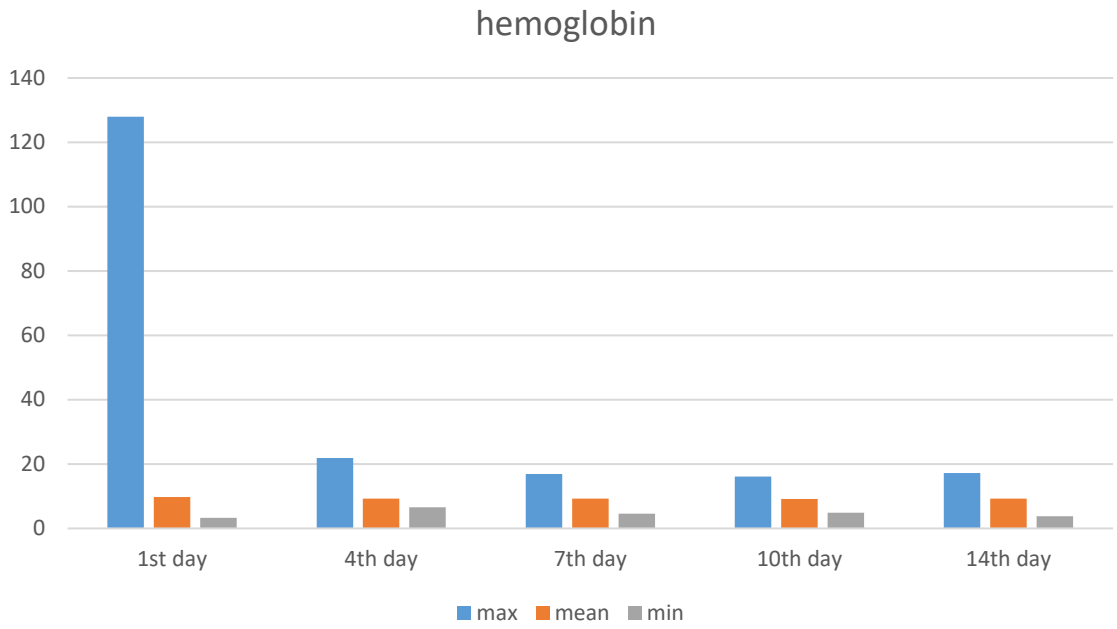

Figure 3. Comparison of hemoglobin in patients in the first days up to 14th day of hospitalization

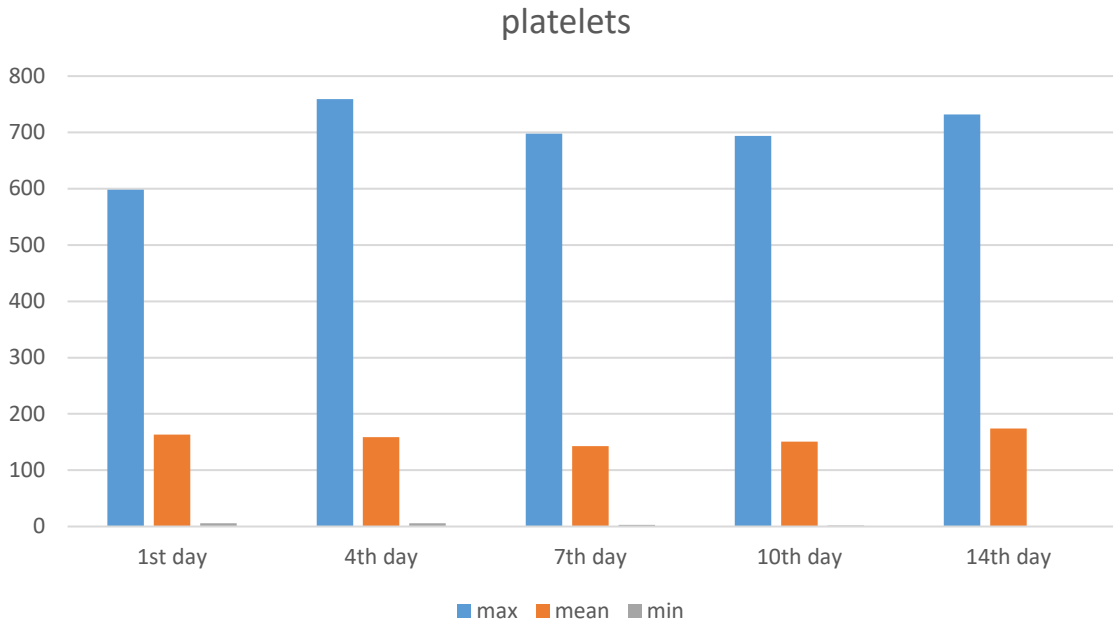

Figure 4. Comparison of platelets frequency in patients in the first days up to 14th day of hospitalization

Optic neuropathy (1%) and gastrointestinal side effects (1%) were also found in limited number of patients. An increase in creatinine in patients (7.2%) due to concomitant use of linezolid with other nephrotoxic drugs was observed as a side effects and it is worth noting that linezolid alone does not lead to this complication.

4. Discussion

The present study provides a comprehensive report on linezolid usage pattern in a Mashhad's hospitals in Iran. After evaluating the results of this study, the appropriateness of using linezolid was judged based on the location of infection, type of pathogen and susceptibility results (according to blood culture results and antibiogram) and in general 6.2% of cases received linezolid for inappropriate indication. Among them, 2.1% of the

sources of infection were related to Staphylococcus MRSA, which despite the lack of a place for the use of linezolid in their treatment, this drug was used. It is worth mentioning that these patients were on dialysis and because of difficult dose adjustment of vancomycin in population, it was replaced by linezolid. It is also important to note that 4.1% of the infectious microorganisms reported in this study were Pseudomonas, for which the use of linezolid was not reasonable.

Inappropriate antibiotic consumption could lead to the increase of overall financial burden of healthcare[21, 22]. Antimicrobial use is the major determinant in the development of resistance[23, 24]. A 2006 study by Walker et al. In nine hospitals in different Canadian states was conducted to evaluate the drug use of linezolid [25]. Due to the higher prevalence of MRSA in Quebec, Ontario, Alberta and British Columbia than in other parts of Canada; these states were selected for the study. Pharmacy databases at each of these hospitals were used to identify hospitalized patients receiving intravenous or oral linezolid treatment for an active infection.

Overall, the appropriate use of linezolid was 53% which was much higher than our study. The average length of hospital stay was 40.6 days. Linezolid was initially used to treat sexually transmitted infection [23] s and bacteremia, and MRSA being the most common pathogen, which was much less common in present study. The oral form of linezolid was the most commonly prescribed form, which was in consistent with our findings. As a result, Linezolid was used appropriately in about half of the cases surveyed. Walker et al. developed an accurate algorithm at the beginning of their study for the terms "appropriate" and "inappropriate" which is lacking in our study had a lack there of, but did not report the exact duration of linezolid treatment and only the average hospital stay was presented. So, the appropriateness of treatment duration could not be judged.

A 2016 study by Farsad et al. aimed to evaluate drug utilization based on patients' medical records with an objective to assess appropriate usage of critical antibiotics such as Carbapenems, Linezolid and Teicoplanin which have been identified as the last resort drugs. The other objective of this study was to identify prescriptions errors and to help reduce these errors. The study was performed at special wards of Shahid Rajaie Hospital, Tehran, Iran. The program was conducted from March to August 2015. Post CABG adults older than 18 years in five different units including one ICU and four CCUs were included in the study. The selection of patients were according to their treatment with Imipenem, Meropenem, Linezolide or Teicoplanin as an empiric treatment or based on culture results. Patients who were identified to have allergy to studied medications, psychiatric illness, history of seizure, pregnant and patients taking MAOI were excluded from their study. DUE forms were designed considering number of ordered and prescribed antibiotics, dosage and frequency of administration, indication for each antibiotic based on Mandell and IDSA and CDC guidelines and information about the patients such as serum creatinine, smoking, past medication history about studied antibiotics, past medical history such as heart or kidney disease. Medical records of patients investigated and necessary information were extracted. and some parameter such as ClCr calculated. Appropriate or inappropriate antibiotic prescriptions were evaluated according to factors such as dosage or duration (separately or combined), dosage adjustment in patients with renal impairment, antibiotic choice and indication. A total of 136 in-patients were evaluated during a five month study. Data regarding the usage frequency and amount of studied antibiotics according to duration of treatment among 122 patients was recorded. The results of this study indicated that among 136 in-patients who had taken at least one of these antibiotics including Imipenem, Meropenem, Linezolide or Teicoplanin, antimicrobial prescription assumed inappropriate for 63 patients (46.32%), The most common reason was incorrect dosage (16.39%) and the least one was not being drug of choice(2.4%).this inappropriateness was occurred mostly in diagnosis of respiratory infection, skin infection and sepsis. The results of this study demonstrates the need for revision in program of prescribing antibiotics in the direction of using antibiotic practice guidelines especially regarding usage of Teicoplanin and Meropenem in specific complication such as respiratory infection and skin infection[26].

A study was conducted in 2017 by Najafi et al. with the aim of investigating the correct use of linezolid and the role of adhering to treatment protocols in the rational administration of this drug. The results of this study showed that the use of linezolid was initially prescribed correctly in 52.9% of cases (27 cases out of 51 patients) and after preparing a scientific protocol for prescribing this drug and applying the protocol to prescriptions of physicians, the correct administration of linezolid (72 out of 48 patients) increased to 72.9%[27].

A 2013 study by Amit aimed to identify the most common antibiotics prescribed in the ICU ward of Fortis Hospital in Dehradun, India, and to calculate the average cost of antibiotics in this ward and to find the relationship between the use of antibiotics And the costs incurred with age factors and patient diagnosis were done prospectively. The total cost of antibiotics prescribed to all patients was calculated

at 1745961.21 rupees (equivalent to 99 million Iranian tomans). The total cost imposed by antibiotics was approximately 67.79% of the total drug costs in these patients. Piperacillin and tazobactam were the most expensive drugs prescribed, accounting for 20.97% of the total cost of antibiotics[28].

In a study conducted by Tavallaee et al. in 2010 at Masih Daneshvari Hospital in Tehran with the aim of evaluating drug use patterns, the factors affecting the patient's health outcome and the cost of drugs used in the ICU were also evaluated. According to the results of this study, the average hospital stay time for patients transferred from the surgical ward was significantly lower than patients transferred from the internal ward. The mortality rate was higher in inpatients. There was a significant positive correlation between the total number of drugs prescribed or antibiotics received by the patient and the mortality rate. Among the drug groups, antibiotics and sedatives were the most prescribed drugs in the ICU[29].

A 2006 study by Biswal et al. in Chandigarh, India, examined the factors influencing drug use patterns, treatment costs, as well as the relationship between drug use and survival pattern and length of hospital stay. Information was collected about the drugs used, the severity and severity of the disease and its results and consequences. According to the results of this study, more than 50% of the average drug costs were related to antibiotics. Biswal et al. concluded by noting that the use of antibiotics has a significant impact on the overall cost of the ICU [30].

In a study conducted by Alavi et al. in 2011 at Razi Educational and Medical Center in Ahvaz, 17,668 patients admitted to this center were studied. The accuracy of the use of antibiotics was assessed according to the national guidelines and guidelines in the reference books. 3119 of these patients had received antibiotic treatment, of which 20.4% were unnecessary antibiotics, which was estimated 6.2% for linezolid use in our study. The highest rate of incorrect use of antibiotics (including unnecessary use, inappropriate dose and duration) was observed in the internal medicine department and the lowest rate was observed in infectious diseases and obstetric wards[31].

5. Conclusion

Since linezolid is effective in treating many bacterial infections, as well as gram-positive organisms as well as MDR, evaluating its use is an effective approach to identifying inappropriate prescriptions and rationally improving its use. The use of linezolid in Mashhad hospitals and the overall study was the percentage of inappropriate use of this drug. In general, 6.2% of the use of linezolid in this study is estimated to be misplaced. However, even in these cases, as in others, the dose and duration of treatment were evaluated correctly.

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