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Evaluation of Piperacillin/Tazobactam Use and Resistance Pattern in a Teaching Hospital, Northwest Iran

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ABSTRACT

Background: Inappropriate use of broad-spectrum antibiotics has contributed to the emergence of resistant microorganisms, increased treatment costs, morbidity and mortality, drug toxicity, and prolonged hospitalization period. Determining the epidemiology of antibiotic resistance in various hospital wards allows for more precise drug selection in the hospital setting. This study evaluated the use and resistance pattern of a broad-spectrum antibiotic, Piperacillin/tazobactam, in Imam Khomeini, a referral teaching hospital in Urmia, Iran.

Methods: All hospitalized patients who were treated with Piperacillin\Tazobactam from January to August 2018 were included. Demographic (age, sex, weight, comorbidities) and clinical data (Indication, dosing, duration of the treatment, susceptibility test, creatinine clearance, need for dose adjustment, clinical outcome, and mortality) of the patients were collected, and the compliance of piperacillin\tazobactam administration and its resistance pattern was assessed according to Lexi-comp- 2019 recommendations.

Results: Among 177 patients, 88.7% received piperacillin\tazobactam without any appropriate susceptibility tests. The piperacillin disk was used in only 33.3% of the culture-positive cases in our research, with 70% resistance. Acinetobacter was the most common bacteria found in our culture-positive samples. The average duration of piperacillin\tazobactam treatment was 8.52 ± 5.84 days. Indications in 8.5%, doses in 18.5%, prescription period in 19.7%, and dose intervals in 31.4% of the cases were inappropriate. Piperacillin\tazobactam was mainly administered for pneumonia (34.5%)

Conclusion: This study showed an injudicious use of Piperacillin/tazobactam in our hospital, evidenced by the significant number of inappropriate doses, intervals, and treatment duration. Decision-making based on susceptibility tests using appropriate and accurate methods, close monitoring of the patients' clinical status, including creatinine clearance, and antimicrobial stewardship programs may optimize the rational administration of broad-spectrum antimicrobials and avoid the emergence of bacterial resistance.

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Introduction

One of the most serious issues facing healthcare systems today is the inappropriate use of medications .Drug use evaluation (DUE), medication use evaluation (MUE), and drug utilization review (DUR) are common terminologies in the literature that are defined as an authorized, structured, and ongoing review of prescribing, dispensing, and administration pattern of the drug. It guarantees the rational and appropriate use of medications to achieve the best outcomes (1).

Antibiotics are the most frequently ordered drugs in hospitals, and about one-third of hospitalized patients receive antimicrobial therapy (2). Inappropriate use of antimicrobials increases the resistance rate, leading to delayed effective therapy, increased hospitalization length, and increased

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clinical and financial burden of infectious diseases (3). Evaluating the appropriate utilization of antibiotics is an important first step toward improving the rational use of antibiotics and decreasing their resistance (4). A clinical evidence-based therapy, therapeutic benefits, safety, cost-effectiveness, and optimal drug dose with suitable duration are the five criteria determining the appropriate drug use (5). Piperacillin/tazobactam is a β-lactam/β-lactamase inhibitor combination with a broad-spectrum activity against most Gram-positive, Gram-negative aerobic, and anaerobic bacteria making this antibiotic one of the most critical antibiotics for the management of serious infections such as lower respiratory tract infections, intra-abdominal infections, skin and soft tissue infections, and febrile neutropenia (6,7). The usual dosing of the Piperacillin/tazobactam indication can be found in Table 1. It is primarily excreted unchanged in the urine, and the dose should be adjusted in patients with decreased creatinine clearance (Table 2) (8).

Considering the importance of Piperacillin/tazobactam as a broad-spectrum antibiotic in treating serious infectious diseases and the consequences of irrational use, the present DUE study aimed to evaluate the utilization and resistance pattern of Piperacillin/tazobactam in Imam Khomeini teaching hospital. The results of this study may help healthcare providers and health program managers to identify the common drug use flaws and establish logical antibiotic implementation strategies that guard against the emergence of resistance.

Table 1. The most important indications for the use of Piperacillin/tazobactam and its recommended dose as an intravenous infusion over 30 minutes.

Indication	Dose	Duration
Bloodstream infection (gram-negative bacteremia) community-acquired infection, immunocompetent host	3.375 gr/6hrs	7-14 days depending on the source, pathogen, extent of infection, and clinical response*
Bloodstream infection (gram-negative bacteremia) Healthcare-associated infection, including catheter-related, immunocompetent host, or for coverage of P. aeruginosa	4.5 gr/6hrs	7-14 days depending on the source, pathogen, extent of infection, and clinical response*
Cystic fibrosis	4.5 gr/6hrs	10 days to 3 weeks or longer based on clinical response
Diabetic foot infection, moderate to severe	3.375 gr/6hrs or 4.5 gr/8hrs. for treatment of P. aeruginosa infection: 4.5 gr/6hrs	2-4 weeks in the absence of osteomyelitis.
Intra-abdominal infection (cholecystitis)	3.375 gr/6hrs or 4.5 gr/6hrs	1 day after gallbladder removal or until clinical resolution in patients managed nonoperatively
Other Intra-abdominal infections (e.g., cholangitis, perforated appendix, diverticulitis, intra-abdominal abscess)	3.375 g or 4.5 g/6hrs.	4-7 days following adequate source control. A longer duration may be necessary for infections managed without surgical or percutaneous intervention.
Malignant (necrotizing) external otitis	4.5 gr/6hrs	6-8 weeks
Neutropenic fever	4.5 g/6-8hrs	until afebrile for ≥48 hrs. and resolution of neutropenia (ANC≥500 cells/ mm3 and increasing)
Community-acquired pneumonia with the resistant gram-negative pathogen(1), including P. aeruginosa	4.5 gr/6hrs	Minimum 5 days, a longer course may be required for P. aeruginosa infection.
Hospital-acquired or ventilator-associated pneumonia	4.5 gr/6hrs	Duration of therapy varies based on disease severity and response to therapy; Minimum 7 days, a longer course may be required for severe or complicated infection or P. aeruginosa infection.
Skin and soft tissue infection (moderate to severe infection)	3.375 gr/6hrs or 4.5 gr/8hrs. for treatment of P. aeruginosa infection: 4.5 gr/6hrs	10-14 days based on clinical response for necrotizing infection, continue until further debridement is not necessary
Urinary tract infection complicated	3.375 g/6hrs or, if Pseudomonas is a concern, 4.5 g/6hrs.	Duration of therapy depends on the antimicrobial chosen to complete the regimen and ranges from 5-14 days.
*. A 7-day duration is recommended for patients with uncomplicated Enterobacteriaceae infection who respond appropriately; if neutropenic, extend treatment until afebrile for 2 days and neutrophil recovery (ANC≥500 cells/ mm3 and increasing). For P. aeruginosa bacteremia in neutropenic patients, some experts treat for a minimum of 14 days and until recovery of neutrophils.		

Table 2. Dose adjustment of Piperacillin/tazobactam in patients with renal failure.

Creatinine clearance (ml/min)	In the recommended dose of 3.375g/6hr	In the recommended dose of 4.5g/6hr
>40	No change	No change
20-40	2.25 g/6hr	4.5 g/8hr or 3.375 g/6hr
<20	2.25 g/8hr	4.5 g/12hr or 2.25 g/6hr

Methods

This prospective, descriptive cross-sectional study was performed in Imam Khomeini referral teaching hospital in Urmia, Iran. All patients who received Piperacillin/tazobactam from January to August 2018 were included, and patients with illegible or incomplete files were excluded. The patients' demographic (age, sex, weight, comorbidities) and clinical data (Indication, dosing, duration of the treatment, susceptibility test, creatinine clearance, requiring dose adjustment, clinical outcome, and mortality) were collected. The adherence to Piperacillin/tazobactam use in terms of indication, dosing, frequency, and treatment duration was assessed in accordance with the Lexi-comp-2019 database. The Ethical Committee of Urmia University of Medical Sciences approved the research protocol (1396-09-36-2899). The data were analyzed using SPSS version 24. Quantitative and qualitative data were reported as mean ± SD and number (%), respectively.

Results

Over the study period, the data of 177 patients were recorded. The demographic and clinical data of the patients are presented in Table 3. The mean age of the patients was 55.49 ± 17.76 years, with a majority of males, 111 (62.7%). Just over half of the Piperacillin/tazobactam prescriptions were administered in the Intensive Care Unit (ICU) ward (51.4%), followed by hematology (11.3%), surgery (6.8%), and nephrology (5.6%) wards, respectively.

Table 3. Demographic and clinical data of the study population.

Characteristics	Mean ± SD or N (%)
Age (year)	55.49 ± 17.76
Sex	
Male	111 (62.7)
Female	66 (37.3)
Weight	75.11 ± 23.16
Length of hospital stay (day)	17.54 ± 6.95
Creatinine clearance (ml/min)	
>40	53 (58.9)
20-40	28 (31.1)
<20	9 (10.0)
Treatment duration (day)	8.52 ± 5.84
Indication	
Pneumonia	61 (34.5)
Intra-abdominal infection	40 (22.6)
Skin infection	31 (17.5)
Surgical site infection	3 (1.7)
Urinary Tract Infection	11 (6.2)
Neutropenic fever	11 (6.2)
Others	3(1.7)
No apparent indication	15 (8.5)

According to the Lexi-comp 2019 database, 46.8% of the Piperacillin/tazobactam prescriptions were inappropriate in terms of indication, dose, treatment duration, or dosing intervals.

The exact indication was unclear in a small number of prescriptions, 15 (8.5%). Piperacillin/tazobactam was mostly ordered for pneumonia (34.5%) following intra-abdominal infection (22.6%) (Table 3).

In 30 (18.5%) prescriptions, the administered dose was not according to the guideline. Most prescriptions were 4.5 g every 8 hours (42.4%). The creatinine clearance was calculated in about half of the patients,90 (50.8%), which was below 40ml/min in 41.1% and required dose adjustment. However, it was adjusted only in 14 (37.8%) prescriptions.

Patients receiving Piperacillin/tazobactam stayed at the hospital for an average of 17.54±6.95 days. The shortest length of hospital stay was one day in 5% of the cases; The maximum length of stay was 5 months. Piperacillin/tazobactam was administered for an average of 8.52± 5.84 days, which was not according to the guideline recommendation in 32 (19.7%) patients. In 43.7% of the patients, treatment was extended beyond the indicated duration; in contrast, in 56.2% of the patients, Piperacillin/tazobactam was discontinued earlier.

About 79.6% of the patients received another antimicrobial drug, mostly Meropenem (38%), before initiating Piperacillin/tazobactam. Nearly 83% of the patients received antibiotic combinations with Piperacillin/tazobactam (average number of co-administered antibiotics was 1.59 ± 0.69): 43.5% had one, 29.9% had two, and 9.6% had three or more antibiotics with Piperacillin/tazobactam. Vancomycin was the most common co-administered antibiotic 46 (31.3%), following Teicoplanin 32 (21.8%) and ciprofloxacin 27 (18.4%).

Of 177 cases, the susceptibility test was done in 139 cases (78.5%), primarily after the initiation of empiric therapy (62.2%). Most of the samples were blood and urine (23.9%). Culture results were found to be positive just in 60 patients (43.2%), with Acinetobacter being isolated in the majority of the cases (25%). Susceptibility test with piperacillin disk using the Kirby-Bauer disk diffusion method was performed in only 33.3% Of the culture-positive cases, where a large number of them,14 (70%), were discovered to be resistant (Table 4).

Infectious disease specialists were the most frequent prescribers among other physicians in the hospital (50.3%); however, 74.1% of their prescriptions were not according to the guideline.

According to physicians' opinions recorded on patients' files, 16 out of 177 patients (9%) showed clinical response to the treatment,106 patients (59.9%) were discharged for further evaluation during clinic visits, ten patients (5.6%) were self-discharged, and 45 patients (25.4%) expired.

Table 4. The Susceptibility test results of Piperacillin/tazobactam in the study population.

Variable	N (%)
Susceptibility test	139 (78.5)
Sampling time	
Before starting Piperacillin/tazobactam	20 (14.4)
After starting Piperacillin/tazobactam	119 (85.6)
Antibiogram results	
Mixed growth	13 (9.3)
Negative	66 (47.5)
Positive	60 (43.2)
Tested without piperacillin disk	40 (66.7)
Tested with piperacillin disk	20 (33.3)
Sensitive to 100 mg piperacillin disk	6 (30.0)
Resistant to 100 mg piperacillin disk	14 (70.0)
Isolated microorganism	
Acinetobacter	15(25.0)
Pseudomonas Aeruginosa	8 (13.3)
Staphylococcus Aureus	7 (11.7)
Other	30 (50)

Discussion

In the present study, we evaluated the Piperacillin/tazobactam use and resistance pattern in Imam Khomeini Hospital in Urmia, Iran, over the course of 9 months. In 38 (21.5%) of our patients, the susceptibility tests were not done at all, and in 119 patients (67.2%), the culture test was drawn just after initiation of the antibiotic, which totally makes 88.7% of the patients receive the antibiotic without any appropriate susceptibility tests. In the Kori et al. study, the culture tests were ignored in 46.7% of the patients, which was higher than in the present study (1). The piperacillin disk was used just in 33.3% of our study's culture-positive cases with 70% resistance to Piperacillin, and the remaining culture-positive cases were not tested for piperacillin susceptibility. The high resistance level may be due to applying only Piperacillin disks for susceptibility tests without tazobactam content. These observations necessitate applying appropriate actions to modify the susceptibility test procedure to prevent inaccurate clinical judgment and decrease physicians' doubt about the results.

Acinetobacter was the most prevalent detected microorganism in our culture-positive cases, while Korai et al. reported E.coli as the most recovered microorganism (10.5%); in our study, the E.coli was included in 8.3% of cases(1). Treatment continuation with piperacillin-tazobactam despite the negative antibiogram test results may be related to clinical recovery in ill patients or the poor reliability of the physicians to laboratory results, which may demonstrate the need for education and improvement of the applied techniques. In another study with 610 orders of Piperacillin/tazobactam for 596 patients, despite having culture-negative results in 265 (43%) of them, the antibiotic was continued for unknown reasons in most of the cases (60%) (9).

According to our results, a high percentage of the cases had some types of error in Piperacillin/tazobactam administration in terms of indication (8.5%), dose (18.5%), treatment duration (19.7%), and dosing interval (31.4%).

The most common indications for Piperacillin/tazobactam were pneumonia (34.5%) and intra-abdominal infections (22.6%). This was in line with the Beahm et al., study in 2016, which reported pneumonia (42%) and intra-abdominal infections (25%) as the most common indications(10). Korai et al. in 2019 reported that the highest indication was presumptive treatment (21.7%) and trauma (17.8%)(11), while Yousef Khan et al. in 2008 described sepsis (34%) and hospital-acquired pneumonia (10%) as the highest used indications (9). Conversely, Saleh et al., in 2019, in Tabriz Sina Hospital, reported skin and soft tissue infections (74.3%), pneumonia (15.7%), and intra-abdominal infections (5.7%) as the most common indications (12). In the majority of the investigations, Piperacillin/tazobactam was administered for pneumonia and intra-abdominal infection. In Saleh et al. study, the primary indications vary according to the hospitals' main specialty domain (burn-center hospital) (12).

While Korai et al. found a lesser percentage of 2.44, we observed that 8.5% of prescriptions did not include Piperacillin/tazobactam in an appropriate indication (11).

The Piperacillin/tazobactam dose was incorrect in 18.5% of the patients in the present study, while it was recorded

at 12.7% and 10% in other studies (11). The significant incidence of dosing errors in our study might be attributable to the restricted availability of Piperacillin/tazobactam dosages in the hospital and the failure to consider creatinine clearance. As an example, when the 3.375-gram vials were unavailable, in some cases, the dosing of 3.375 grams every 8 hours was changed to the underestimated incorrect dose of 2.25 grams every 6 hours.

In other studies, the improper duration of Piperacillin/tazobactam administration was found to be greater in the previous studies (42%, 21.9%, and 32.8%, respectively(11)(13)(12), compared to our study (19.7%).

Interestingly the proportion of inappropriately administered dose intervals in the current study (31.4%) was about three times higher than in the Korai et al. study (12.7%)(11). The dosage form limitations in our hospital may be accounted for some parts of this fault.

Studies conducted by Korai and Parviz et al., found that the most prevalent error in Piperacillin/tazobactam was the length of treatment time. However, in our research, the most often error seen in Piperacillin/tazobactam prescriptions was the interval between doses (1,12).

Piperacillin/tazobactam was mainly used in ICU (51.4%), as in Yousef Khan et al.'s research (32%) (9).

Our patients were totally hospitalized for an average of 17.54 ± 6.95 days with a mean duration of 8.52± 5.84 days dedicated to receiving Piperacillin/tazobactam treatment. In the Raveh et al., study, the length of hospitalization and duration of Piperacillin/tazobactam treatment was shorter (7.1± 3.9 days and 6.8 ± 3.7 days, respectively), which might take the attention to focus on its contributing factors, including lack of antimicrobial stewardship programs in our hospital(14).

According to the study by Korai et al., more than half of the patients (63.1%) received one or more other antibiotics along with Piperacillin/tazobactam; most of them were clindamycin (13.8%) and vancomycin (12.5%) (11). In our study, these numbers were higher, and well over three-quarters of the patients received antibiotic combinations with Piperacillin/tazobactam (83%). The most co-administered antibiotics were vancomycin (39.2%) and teicoplanin (21.8%). Concomitant administration of vancomycin with Piperacillin/tazobactam may increase the risk of nephrotoxicity, and kidney function monitoring is recommended (15).

The frequency of dose adjustment was higher in the Korai et al. trial (85.5%) when compared to our research's results (77.4 %)(11). A tiny fraction of our patients (6.8%) was on dialysis, and dose correction was done in 60% of them. These findings thus need to be interpreted with caution as the sample size and precise setting of previous studies were not equal to ours.

This study demonstrated that monitoring antibiotic use according to recommended guidelines focused on indications, dose, intervals, and duration of the treatment was a fundamental step for ensuring rational drug use. To maintain efficacy and financial control over rational drug administration and prevent the emergence of antimicrobial resistance, it is also necessary to educate the healthcare providers and engage clinical pharmacists to monitor the justification for every medication provided, especially antimicrobials and expensive drugs. Preventing improper administration, improving patient safety, and lowering costs may be accomplished by performing microbial culture tests prior to antimicrobial therapy and monitoring kidney function for dosage adjustment. It is recommended to Establish a central committee for DUE studies by the Ministry of Health to coordinate, summarize, and evaluate all information and allocate the national budget for the ongoing implementation of DUE studies in hospitals, feedbacking the study results to healthcare providers using appropriate software facilities, and setting up antimicrobial stewardship programs in all the hospitals. DUE studies might be an effective tool for initiating discussions among pharmacists and clinicians to achieve high standards of rational drug utilization in hospitals.

The main drawbacks of this research were the small sample size, poor methodology of susceptibility tests, and lack of clear data on the exact indication. The susceptibility tests should be checked to be according to Clinical & Laboratory Standards Institute (CLSI) guidelines with accurate disks. The findings of this study must be integrated with other clinical criteria pertaining to patients' conditions and management. Further prospective studies considering the financial burden cost and clinical pharmacist interventions are required.

In conclusion, the majority of the culture-positive samples were reported to be resistant using the Piperacillin disk diffusion test, interestingly without a tazobactam disk. Administration of Piperacillin-tazobactam in our hospital was not entirely consistent with guidelines, mainly in terms of the accurate dose interval, duration, and dose, respectively. Therefore, including the appropriate antibiotic disk, close monitoring of the administered drugs, and implementation of antimicrobial stewardship programs may optimize the rational administration of this critical and broad-spectrum antimicrobial, avoid the emergence of bacterial resistance, increase patient safety, and reduce overall costs.

Table 5. Comparison of the Piperacillin/tazobactam use pattern studies.

Author	Hatamkhani et al.	Parviz S. et al.	Korai et al.	Beahm et al.	Khan et al.	Esmaeil et al.
Year	Present study	2019	2019	2016	2008	2008
Sample size (n)	177	70	152	91	610	200
Applied guideline	Lexi-comp (2020)	UpToDate and American Hospital Formulary Services	Standard Guideline	Alberta Health Services (AHS) approved Guideline	Hospital's Guideline	Approved Criteria for the use of PIP/TAZ in the hospital
The most frequent indication (%)	Pneumonia (34.5)	Skin and soft tissue (74.3)	Presumptive (21.7)	Pneumonia (42)	Sepsis (34)	none
Total appropriate administrations (%)	37.8	48	33.51	61	57	73.5
appropriate indication (%)	91.5	none	97.6	none	none	none
appropriate dose	81.5	90	87.2	none	100	none
appropriate duration of treatment (%)	80.2	67.2	78.1	none	78	58
Requiring dose adjustment (%)	41.1	12.9	None	none	34.9	43.5
The dose adjustment was not done (%)	62.2	0.0	None	none	0.0	0.0
Dose adjustment based on creatinine clearance	none	100	85.5	none	100	100
Most common recovered pathogen (%)	Acinetobacter (25)	none	E. coli (10.5)	none	E. coli	none
Obtaining microbial culture (%)	78.5	75.7	38.2	none	100	82
Most common Co-prescribed antibiotic	Vancomycin	Vancomycin	Clindamycin	none	none	none

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