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A STUDY ON DRUG UTILIZATION EVALUATION OF PIPERACILLIN/ TAZOBACTAM IN A TERTIARY TEACHING HOSPITAL– AN EMPHASIZED PERSPECTIVE OF CLINICAL PHARMACIST

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ABSTRACT

Introduction: Piperacillin/Tazobactam, a broad-spectrum antibiotic combining ureidopenicillin and β-lactamase inhibitor, is used as an empirical therapy for several infections that may increase the threat of antimicrobial resistance. Drug utilization evaluation (DUE) helps in detecting inappropriate drug use and promoting rational treatment. DUE increases the role of clinical pharmacists in better analyzing drug-related issues and providing appropriate pharmacist interventions. **Aim and objective:** To evaluate the utilization of Piperacillin/Tazobactam in a major tertiary teaching hospital. **Methodology:** A prospective study was conducted with a total of 500 patients, which was divided into two phases: pre-intervention and post-intervention of each 250 subjects. In phase I, the first 250 cases were collected and evaluated. In phase II, the educational intervention was made, and the next 250 cases were collected and assessed. The collected data from both phases were compared by using a self-developed scoring system, JANS B-10. **Result:** Phase I result shows 200 cases (80%) partially appropriate, 49 cases (19.6%) appropriate, and case1 (0.4%) inappropriate. In phase II, 181 cases (72.4%) partially appropriate, 68 cases (27.2%) appropriate, and 1 case

(0.4%) inappropriate were found. The overall assessment of appropriateness, using the JANS B-10 scoring system, demonstrated an improvement from 19.6% in Phase I to 27.2% in Phase II after educational intervention. **Conclusion:** The study found that drug utilization evaluation improved the appropriate use of piperacillin/tazobactam, reducing inappropriate antibiotic consumption and enhancing effective use by patients from phase I to phase II.

Keywords: Antibiotic stewardship team; appropriate; drug utilization evaluation; inappropriate; pharmacist intervention; piperacillin tazobactam

1. INTRODUCTION

Drug utilization evaluation (DUE) is an efficient and systematic method for detecting inappropriate or unnecessary drug use that monitors, evaluates, and promotes rational drug therapy. Several factors, such as irrational drug usage, polypharmacy, improper drug selection, incorrect dose, and drug interaction, have raised morbidity, mortality, and healthcare expenditures, as well as led to the use of drugs without a record of demonstrated benefit **[1]**. DUE studies are integral in helping to understand, interpret, and improve the prescribing, administration, and use of medicines. DUE programs help to provide physicians with feedback on their performance and prescribing behavior as compared to standard protocols. Antibiotics are crucial for decreasing morbidity and mortality by reducing the bacterial disease burden and extending life expectancy. The rational use of antibiotics should not be random. It requires reflection and thought and should be based on guidelines. Pivotal points in making decisions for the selection of antibiotics include accurate diagnosis, patient's condition, location of the infection, severity of the microbial cause, sensitivities to antibiotics, pharmacokinetics and pharmacodynamics of antimicrobials, side effects, and cost **[2]**. All the drugs used in hospitals cannot be evaluated. Hence the DUE helps to identify drugs whose evaluation and improvement in use will result in more clinical impact. Generally, drugs with high volume of use, high cost, or high frequency of adverse effects are subjected to DUE studies. Fourth-generation cephalosporins, piperacillin/ tazobactam, and carbapenems are the broadest-spectrum and most expensive antimicrobials and are a cornerstone empirical therapy for hospital-acquired severe infections. Therefore, the increasing threat of antimicrobial resistance due to the inappropriate use of these broad-spectrum antibiotics warrants the development of antimicrobial resistance reduction strategies **[3, 4]**. Piperacillin is a semisynthetic ureidopenicillin with antibacterial activity

against Gram-positive and Gram-negative aerobic and anaerobic bacteria. Tazobactam, a triazolymethyl penicillanic acid sulfone derivative, is a β-lactamase inhibitor that protects piperacillin from destruction by β-lactamase enzymes. Piperacillin-tazobactam in combination retains its in vitro activity against broad-spectrum β-lactamase-producing and some extended-spectrum β-lactamase-producing Enterobacteriaceae, but not against isolates of Gram-negative bacilli harboring AmpC β-lactamases. Piperacillin/tazobactam is effective for the treatment of patients with intra-abdominal infections, skin and soft tissue infections, lower respiratory tract infections, complicated urinary tract infections, gynecological infections, and more recently, febrile neutropenia. Piperacillin/tazobactam has an excellent safety and tolerability profile and continues to be a reliable option for the empiric treatment of moderate-to-severe infections in hospitalized patients **[5]**. The study included a prospective analysis followed by clinical interventions by pharmacists to improve the utilization of piperacillin/tazobactam. This was followed by an antibiotic stewardship team to measure improvement and further identify continuous measures to optimize antibiotic use. Hence, a study was conducted to analyze DUE, followed by clinical pharmacist intervention to measure improvement and further identify continuous measures to optimize antibiotic use.

2. MATERIALS AND METHODS

A prospective study was conducted for six months (November 2023- April 2024) in Ganga Medical Centre and Hospitals Pvt. Ltd., Coimbatore. The study protocol received ethics approval from the institutional ethics committee, reference number ECR/319/Inst/TN/2013/RR-19. A total of 500 patients who were prescribed piperacillin/tazobactam, patients within all age groups, both sexes and all inpatients who gave written informed consent to participate in the trial were selected. Patients who had not been prescribed piperacillin/tazobactam and pregnant and breastfeeding subjects were not allowed to participate in the study. The total 500 subjects were divided into two phases, pre-intervention and post-intervention, for each 250 subjects. A well-designed data collection form was used to collect the participant's demographic details, antibiotic usage patterns, indwelling catheter details, laboratory parameters, antibiogram and culture reports, wound and surgery details, and indications of antibiotic usage. In phase I, the collected cases were evaluated, reports were sent, feedback was obtained from the

antimicrobial stewardship program (ASP) team, and the final reports were sent to senior consultants. In phase II, the educational intervention was made by giving awareness on the need for culture reports, documenting the reason for the selection and change of antibiotics, dosing, and dose modifications through lecturers, workshop oral presentations, and giving educational materials like pamphlets, leaflets, etc. to the health care professionals. After the intervention, the next 250 cases were collected and evaluated by incorporating the feedback received. The collected data from both phases were compared using a self-developed scoring system, JANS B-10. It consists of indication, dose, frequency, duration, route of administration, dilution, defined daily dose (DDD), dose adjustment, drug interaction, and adverse drug reactions (ADR). The results were submitted to the ASP team, and the recommendations received have been forwarded to the antibiotic policy revising committee. The results were expressed in terms of percentage.

3. RESULTS

In this prospective study, the majority of patients belong to the age group of 51-60, that is 50 patients (20%) in Phase I and 59 patients (23.6%) in Phase II. In phase I, 153 patients (61.2%) were male and 97 patients (38.8%) were female and in phase II, 206 patients (82.4%) were male and 44 patients (17.6%) were female. In both the phases males were found to be higher **(Table 1)**.

Among the patients in Phase I, cases with a culture report were 82 (32.8%) and in Phase II were 92(36.8%) whereas cases without a culture report in Phase I were 168(67.2%) and in Phase II were 158 (63.2%) **(Table 2)**.

Among the cases with culture reports, cases with microbial growth in Phase I were 39(47.56%) and in Phase II were 46(50 %); cases without microbial growth in Phase I were 43(52.44%), and in Phase II were 46(50%) **(Table 3)**.

The assessment of culture sensitivity pattern shows that in phase I, cases sensitive to piperacillin/tazobactam were 21(53.85%), and in phase II were 30(65.22%); cases resistant to piperacillin/tazobactam in phase I were 8(20.51%) and in phase II were 7(15.22%); cases without piperacillin/ tazobactam in culture sensitivity reports in phase I were 6(15.38%) and in phase II were 3(6.52%); cases without culture sensitivity pattern in phase I was 4(10.26%) and phase II were 6(13.04%) **(Table 4)**.

The majority of the cases with microbial growth were *Klebsiella species* 24(61.54%), *E. coli* 4(10.26%), *Staphylococcus aureus* 3 (7.69%), and *Pseudomonas species* 3(7.69%)

in phase I. In phase II, *Klebsiella species* 25(54.33%), *Pseudomonas* 6(13.05%) and *Escherichia coli* 5(10.87%) were found **(Table 5)**.

While assessing the indication for piperacillin/tazobactam, the main indication in phase I was temperature spike 44(17.6%), purulent drain discharge 32(12.8%), specific 21(8.4%) and Ganga class III & IV diabetic foot ulcer, admitted with infection, concentrated urine on long term catheterized patients with 20(8%) each and in phase II were temperature spike 51(20.4%), specific 31(12.4%), admitted with infection 30(12%) and purulent drain discharge 26(10.4%) **(Table 6)**.

Among the study population, the empirical usage is higher with 216(86.4%) cases in phase I and 208(83.2%) cases in phase II **(Table 7)**.

While assessing the appropriateness based on the self-developed scoring system (JANS-B10), the indication was found to be the major inappropriate parameter with 102(40.8%) correct cases and 148(59.2%) incorrect cases in phase I whereas 133(53.2%) correct cases and 117(46.8%) incorrect cases in phase II **(Table 8)**.

While comparing the appropriateness of cases, 200 (80%) cases were partially appropriate (PA), 49 (19.6%) cases were appropriate (A), and 1 (0.4%) case was inappropriate (IA) in phase I whereas 181(72.4%) cases were partially appropriate, 68(27.2%) cases were appropriate and 1(0.4%) case was inappropriate in phase II **(Table 9)**.

Table 1: Distribution based on demographics among the study population. (*n* =500)

DEMOGRAPHICS		PHASE I (*n* = 250)		PHASE II (*n* = 250)	
		NO OF CASES	PERCENTAGE	NO OF CASES	PERCENTAGE
AGE	0-18	20	8%	18	7.2%
	19-30	43	17.2%	34	13.6%
	31-40	24	9.6%	28	11.2%
	41-50	32	12.8%	39	15.6%
	51-60	50	20%	59	23.6%
	61-70	44	17.6%	40	16%
	71-80	25	10%	29	11.6%
	81-90	10	4%	3	1.2%
	91-100	2	0.8%	0	0%
GENDER	MALE	153	61.2%	206	82.4%
	FEMALE	97	38.8%	44	17.6%

Table 2: Culture report-wise distribution of the study population (*n* =500)

CULTURE REPORT	PHASE I (*n* = 250)		PHASE II (*n* = 250)	
	NO OF CASES	PERCENTAGE	NO OF CASES	PERCENTAGE
Cases with culture report	82	32.8%	92	36.8%
Cases without culture report	168	67.2%	158	63.2%

Table 3: Distribution based on cases with culture reports among the study population (*n*=174)

MICROBIAL GROWTH	PHASE I (*n* = 82)		PHASE II (*n* = 92)	
	NO OF CASES	PERCENTAGE	NO OF CASES	PERCENTAGE
Cases with microbial growth	39	47.56%	46	50%
Cases without microbial growth	43	52.44%	46	50%

Table 4: Distribution based on culture sensitivity patterns among the study population. (*n*=85)

CULTURE SENSITIVITY PATTERN	PHASE I (*n* = 39)		PHASE II (*n* = 46)	
	NO OF CASES	PERCENTAGE	NO OF CASES	PERCENTAGE
No. of cases sensitive to piperacillin/tazobactam	21	53.85%	30	65.22%
No. of cases resistant to piperacillin/tazobactam	8	20.51%	7	15.22%
No. of cases without piperacillin/tazobactam in culture sensitivity reports	6	15.38%	3	6.52%
No. of cases without culture sensitivity pattern (Gram stain)	4	10.26%	6	13.04%

Table 5: Distribution based on microorganisms among the study population. (*n*=85)

MICROORGANISMS	PHASE I (*n* = 39)		PHASE II (*n* = 46)	
	NO OF CASES	PERCENTAGE	NO OF CASES	PERCENTAGE
Staphylococcus aureus	3	7.69%	2	4.35%
Klebsiella species	24	61.54%	25	54.33%
Acinetobacter	2	5.14%	3	6.53%
Pseudomonas aeruginosa	3	7.69%	6	13.05%
Fungal elements	1	2.56%	2	4.35%
Escherichia coli	4	10.26%	5	10.87%
Enterococcus faecium	1	2.56%	0	0%
Candida species	1	2.56%	2	4.35%
Methicillin- resistant *Staphylococcus aureus*	0	0%	1	2.17%

Table 6: Distribution based on the reason for antibiotic therapy among the study population. (*n*=500)

REASON	PHASE I (*n*=250)		PHASE II (*n*=250)	
	NO. OF CASES	PERCENTAGE	NO. OF CASES	PERCENTAGE
BASED ON DISEASE				
Poly trauma	8	3.2%	7	2.8%
Ganga class III & IV diabetic foot ulcer	20	8%	22	8.8%
Admitted with infection	20	8%	30	12%
Soakage	16	6.4%	12	4.8%
Temperature spike	44	17.6%	51	20.4%
Immunocompromised	3	1.2%	2	0.8%
Prophylactic	12	4.8%	9	3.6%
Specific	21	8.4%	31	12.4%
BASED ON LABORATORY PARAMETERS				
Elevated WBC	4	1.6%	2	0.8%
Elevated CRP	2	0.8%	1	0.4%
Pus in sedimented urine and wound	10	4%	7	2.8%
Elevated Procal	2	0.8%	3	1.2%
BASED ON DEVICE ASSOCIATED				
Concentrated urine on long term catheterised patient (? CAUTI)	20	8%	14	5.6%

Purulent drain discharge (? DAI)	32	12.8%	26	10.4%
ICD leak concentrated (? DAI)	1	0.4%	1	0.4%
BASED ON WOUND NATURE				
Necrotic tissue	15	6%	17	6.8%
Pus discharge	9	3.6%	8	3.2%
Contaminated wound	3	1.2%	2	0.8%
No reason	8	3.2%	5	2%

Table 7: Distribution based on the utilization pattern among the study population. (*n*=500)

PATTERN	PHASE I (*n*=250)		PHASE II (*n*=250)	
	NO. OF CASES	PERCENTAGE	NO. OF CASES	PERCENTAGE
Prophylactic	13	5.2%	11	4.4%
Empirical	216	86.4%	208	83.2%
Specific	21	8.4%	31	12.4%

Table 8: Distribution based on the self-developed scoring system (JANS-B10) among the study population (*n*=500)

S. No.	PARAMETERS	PHASE I (*n*=250)				PHASE II (*n*=250)			
		CORRECT		INCORRECT		CORRECT		INCORRECT	
		NO. OF CASES	%	NO. OF CASES	%	NO. OF CASES	%	NO. OF CASES	%
1	Indication	102	40.8	148	59.2	133	53.2	117	46.8
2	Dose	245	98	5	2	247	98.8	3	1.2
3	Route of Administration	250	100	0	0	250	100	0	0
4	Frequency	249	99.6	1	0.4	250	100	0	0
5	Duration	245	98	5	2	247	98.8	3	1.2
6	DDD	245	98	5	2	246	98.4	4	1.6
7	Drug Interaction	146	58.4	104	41.6	136	54.4	114	45.6
8	Dose Adjustment	246	98.4	4	1.6	248	99.2	2	0.8
9	Dilution	250	100	0	0	250	100	0	0
10	ADR	250	100	0	0	249	99.6	1	0.4

Table 9: Distribution is based on the appropriateness among the study population. (*n*=500).

S. No.	APPROPRIATENESS	SCORE	PHASE I (n= 250)		PHASE II (n= 250)	
			NO OF CASES	%	NO OF CASES	%
1	A	10	49	19.6%	68	27.2%
2	PA	7-9	200	80%	181	72.4%
3	IA	6 and <6	1	0.4%	1	0.4%

NOTE: (A), partially appropriate (PA), and inappropriate (IA)

4. DISCUSSION

The study involves the drug utilization evaluation of piperacillin/tazobactam in a tertiary care center which includes the involvement of the pharmacist in providing appropriate educational interventions that help to improve the appropriate use, increased culture sensitivity reports, proper documentation for the reason for antibiotic use in respective patient's case sheets and also helped in the revision of institutional antibiotic guidelines. The findings revealed that the majority of participants in this study were between the age of 51-60 that is 109 patients (43.6%) and 61-70 that is 84 patients (33.6%). This finding is similar to a previous study by Yogita Shekhawat *et al.* where the majority of study participants were in the age

group of 61-70 **[6]**. In this study the majority of study participants were male with 153 patients (61.2%) and 206 patients (82.4%) in phase I and phase II respectively. Similar to these findings, Mohammad Ismail *et al*. found that the majority of participants were males (57%) **[7]**. The number of cases having culture reports increased from 82 cases (32.8%) in phase I to 92 (36.8%) in phase II. This observation underscores the significance of the recommendations provided to physicians regarding the selection of cultures, whether originating from infected sites or other locations, to effectively identify the presence of infections. In the majority of cases, the indications for the use of piperacillin/tazobactam were found to be temperature spikes that is 44 cases (17.6%) in phase I and 51 cases (20.4%) in phase II. These findings are similar to those of a previous study by Savera Arain *et al.* highlighted the inappropriate use of piperacillin/tazobactam due to its broad-spectrum nature. Physicians inappropriately prescribed piperacillin/tazobactam empirically for conditions such as fever of unknown origin, complicated cholecystitis, appendicitis, and suspected skin and soft tissue infections, which deviated from guideline recommendations **[8]**. These findings provide insights into the prevalence of indications for piperacillin/tazobactam usage in the study, highlighting areas for potential clinical improvements. In this study, the analysis of piperacillin/tazobactam utilization patterns shows that empirical usage was predominant with 216 cases (86.4%) in phase I and 208 cases (83.2%) in phase II. This empirical usage was primarily driven by considerations such as polytrauma, specific wound characteristics (including contamination, unhealthy, necrotic, and open wounds), concentrated urine in long-term catheterized patients, purulent drain discharge, temperature spikes, the presence of pus, signs of soakage, and variations in laboratory values. Specific usage accounted for 21 cases (8.4%) cases in phase I and 31 cases (12.4%) in phase II, primarily guided by culture sensitivity reports. These findings show the prevalence of empirical approaches in clinical practice.

In this study, the evaluation of drug use appropriateness using the JANS B-10 scoring system, indications represent a notable improvement of 12.4% in the from phase I to phase II. In the assessment of the dose of piperacillin/tazobactam prescribed, in phase I 245 cases (98%) and phase II 247 cases (98.8%) were with the correct dose. This reflects a slight increase of 0.8% in the appropriateness of dose from Phase I to Phase

II. A study conducted by Punit. J. Shah *et al*. aimed to evaluate the appropriate use of piperacillin/tazobactam in a community health system. They compared four hospitals and found that 9% of the prescribed doses were incorrect in those hospitals **[9]**. The route of administration and dilution was appropriate in both phase I and phase II, with a perfect score of 100%. The frequency of piperacillin/tazobactam usage a slight improvement of 0.4%. the duration and DDD of piperacillin/tazobactam therapy improved by 0.8% from phase I to phase II. These findings emphasize the importance of accurate dosing practices and their potential impact on treatment outcomes. In both Phase I and Phase II of the study, drug interactions were identified, but not clinically significant within the trauma care center setting. In patients with chronic kidney disease (CKD), dose adjustments were done based on factors such as age and creatinine clearance, and the results were implemented correctly in 246 cases (98.4%) during phase I and 248 cases (99.2%) in phase II. A single adverse drug reaction, that is piperacillin-induced itching, was observed in phase II of the study. These findings emphasize the importance of meticulous dosing and monitoring practices in patient care within the trauma care center setting. This study indicates an improvement in phase II, underscoring the significance of timely professional education provided to healthcare professionals through pharmacist intervention. This is consistent with the study conducted by Savera *et al.* where clinical pharmacist intervention improved the empiric use of piperacillin/tazobactam, reducing it from Cycle A (n = 34) to Cycle B (n = 21) cases **[8]**. According to the JANS B-10 scoring system, in phase I of the study, 200 cases (80%) were determined to be partially appropriate, while 49 cases (19.6%) were determined as appropriate, and 1 case (0.4%) was classified as inappropriate. In phase II, 181 cases (72.4%) were found to be partially appropriate, 68 cases (27.2%) were found as appropriate, and 1 case (0.4%) was found as inappropriate (**Table 9**). The overall assessment of appropriateness, using the JANS B-10 scoring system, demonstrated an improvement from 19.6% in Phase I to 27.2% in Phase II. These findings highlight the importance of optimizing the appropriateness of empirical antibiotic prescribing practices in healthcare settings.

5. CONCLUSION

The use of piperacillin/tazobactam in the hospital is mainly empirical and therapeutic. From the overall data, the empirical use of piperacillin/tazobactam has decreased from phase I to phase II, while the therapeutic use

has increased from phase I to phase II. The proper documentation of the empirical use of piperacillin/tazobactam in individual patient case sheets was promoted which helps in better identification of indications of piperacillin/tazobactam. There is a significant increase in the total number of cultures sent and the specific use of piperacillin/tazobactam. All these suggest that the rational and safe use of antibiotics has increased. This study recommends similar drug utilization evaluation of antibiotics, educational intervention, and revision of hospital antibiotic guidelines, which helps in controlling spiraling expenditure on antibiotics and the emergence of multidrug-resistant organisms. The brief study period may have restricted the larger difference between phase I to phase II which could be a consideration for studies with prolonged durations in the future.

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