Drug utilization study of Piperacillin-Tazobactam and Meropenem among indoor patients in a Tertiary Care Hospital - A Prospective Observational Study.

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Abstract

Background: Inappropriate and widespread use of antimicrobials leads to development of antimicrobial resistance, development of toxicities & increased cost of treatment. Piperacillin-Tazobactam and Meropenem are included under "Alert Antimicrobials"- which are to be used only when evident microbiological indication is present or if other cheaper and safer alternatives are unavailable.

As very few studies are available on Rational use of Individual Anti-Microbial agents, this study aims to find the appropriateness of use these higher antimicrobials.

Objective:

To evaluate

1) Department wise use of Piperacillin-Tazobactam and Meropenem as Empirical and Definite therapy

2) To evaluate appropriateness of Piperacillin-Tazobactam and Meropenem as per indication and Antibiotic sensitivity test.

Methods: A prospective observational study was done in wards and I.C.U. of four departments - Medicine, Surgery, Orthopedics, Obstetrics & Gynecology from January 2019 -December 2020. Data was obtained from patient record files and was analyzed for age, gender, disease characteristics and medication prescribed.

Results: A total of 185 patients were analyzed. Appropriateness of initiation of Piperacillin-Tazobactam and Meropenem as Empirical therapy was 67.40% and 20% and as Definite therapy was 76.92 % and 95.23% respectively. Antibiotic sensitivity testing was requested in 68.64% (127) cases of which department wise distri bution was surgery - 72.27%, medicine-67.74%, ortho pedics -58.3%, and obgy-50%. Of the total 12 anti-micro

bials used Piperacillin-Tazobactam and Mero penem accounted for 71.56% of total cost.

Conclusion: Piperacillin-Tazobactam & Meropenem should be used more judiciously by adopting mandatory antibiotic sensitivity testing. Empirical therapy should be avoided to prevent development of anti-microbial resi stance and to reduce expenditure. This study high lights the importance of Antibiotic policy and its timely review with joint coordination across faculties.

Keywords: Anti-Microbial Resistance, Piperacillin-Tazo bactam and Meropenem, Rationality.

Introduction

In 2011 World Health Organization has come up with a slogan "no action today no cure tomorrow". For the past one-decade world health organi zation has been working actively for creating awareness about antimicrobial stewardship [1]. With every passing year there is a multifold increase in the con Sumption of antimicrobials especially in countries where they are easily accessible.

Worldwide antimicrobials consumption has increased by 36% from 2000 to 2010 in 71 countries [2]. Many eco logical studies have found that there is a positive cor relation between irrational antimicrobials use and deve lopment of antimicrobial resistance[3].

Southeast Asian Countries have reported highest use of anti-microbials without prescription and have 2nd minimum follow up regarding rational use of anti-microbials [4].

With increasing evidence of multidrug resistance and limited availability of antimicrobials there is an urgent need for watchful surveillance, implementation of severe infection control practices and then most importantly rational use of available antimicrobials. Overall burden of antimicrobial resistance is hard to be assessed in the general population, but is more related to infants and elderly, as these age groups get infected easily and are susceptible to non-effective antimicrobial therapy.

Early detection of resistance, continuous surveillance of anti-microbials being used are important steps in main taining safe and effective antimicrobial treatment. Drug utilization study is a useful tool in analyzing whether drug therapy is rational or not by comparing observed patterns of drug use with recommended guidelines for that particular disease[5].

In 2016 in India National Centre for Disease Control published "National Treatment Guidelines for Anti micro bial use in Infectious Diseases".[6] In 2017 ICMR published "Treatment Guidelines for Infectious Diseases in Common Syndromes" based on knowledge and expertise of Infectious Disease Physicians and Clinical Microbiologist both in Public and Private sector [7].

Piperacillin-Tazobactam is a fixed drug combination belonging to group of penicillin and is typically used as broad-spectrum antimicrobial. It has activity against gram negative microbes, gram positive cocci and listeria. Meropenem is a carbapenem which has activity against gram negative organism more than gram positive microbes. Both piperacillin-tazobactam and meropenem are considered as reserve antimicrobials and should be used in serious life-threatening conditions. There have been reports of resistance to Carbapenems and to last resort Colistin in I.C.U. setting from India8. There is scarcity of data about antibiograms in India considering vast area and population.

Keeping these factors in mind this study was planned to evaluate the rational use of piperacillin-tazobactam and meropenem. It aimed to evaluate weightage given by healthcare professionals for rational prescription of antimicrobials.

Hence this study was conducted with an aim to find out appropriate use of piperacillin-tazobactam and mero penem based on indication, dose, duration, antibiotic sensitivity results as per National Treatment Guidelines for antimicrobials usage.

The appropriateness of piperacillin-tazobactam and mero penem as empirical and definitive therapy as per indication, the department wise use of antibiotic sensiti vity testing while prescribing antimicrobials in study, and Daily Defined Dose of antimicrobials as per W.H.O ATC-DDD criteria was calculated.

Materials and methods

A prospective observational study was done after receiving approval from Institutional Ethics Committee. Sample size was calculated based on the prevalence of appropriate use of antimicrobials as per study done by Rivah Et al. The sample size came out to be 185.

Inclusion criteria

All admitted patients above 18yrs, undergoing treatment with piperacillin-tazobactam and mero penem in all wards and I.C.U were included in the study.

Exclusion criteria

Patients below 18yrs of age, pregnant and lactating women, patients referred from other hospitals and already consuming antimicrobials under study, patients who absconded or did not complete treatment as per physicians advise, psychiatric patients, cancer patients and patients without proper diagnosis were excluded from this study.

Data collection

Data of 185 indoor patients who were prescribed pipera cillin-tazobactam and meropenem was collected from Wards and I.C.U. of Medicine, Surgery, Pediatrics, Ortho pedics, Obstetrics and Gynecology. Data like clinical dia gnosis, anti-microbials prescribed, dose, duration, frequency, day of obtaining AST sample was collected and analyzed. Each case was individually matched with National Treatment Guidelines for Anti-microbial use. Timing of antibiotic sensitivity test and its use while advising antimicrobials was analyzed.

Calculation of DDD usage of the study drugs was done by the formula.

$$\text{No. of DDD} = \frac{\text{Number of Items issued} \times \text{Amount of Drug per Item}}{\text{W.H.O reecommended D.D.D of the drug}}$$

Statistical Analysis

Data was compiled using Microsoft excel and then analyzed using SPSS 20. Version.

Observations and Results

Data of 185 patients who received piperacillin-tazo bactam and meropenem was analyzed. Gender and age distribution was as follows

Table 1: Gender distribution

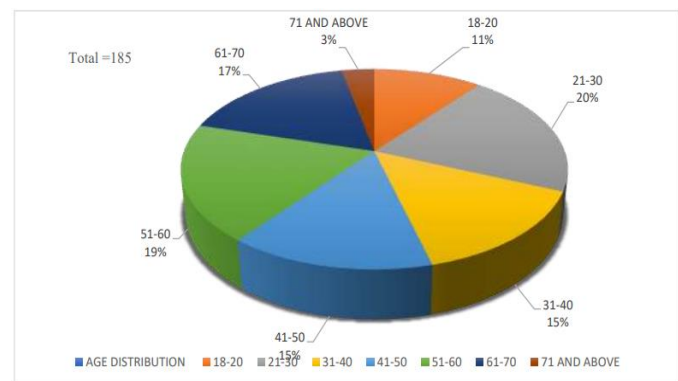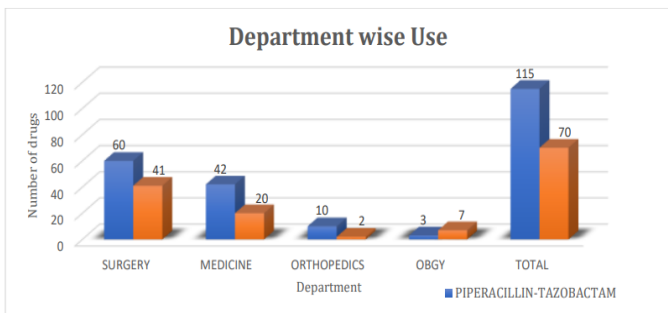| Gender	n (%)
Male	100 (54.05%)
Female	85 (45.95%)

Figure 1: Age Distribution

Figure 1 depicts that distribution of patients was highest in age group of 21-30yrs and 51-60yrs.

Department wise use of piperacillin-tazobactam, and meropenem was as follows

Table 2: Department wise use of drugs used in study.

Both piperacillin-tazobactam and meropenem were maximally used in surgery and then in medicine department.

Distribution of use of piperacillin-tazobactam, and meropenem as per system of infection involved.

Table 3: System wise distribution of drugs used in study.

Site of Infection	Piperacillin-Tazobactam n=115	Meropenem n=70	Total Patients n=185
Abdomen	34 (29.57%)	21(30%)	55(29.73%)
Skin and Soft Tissue	34 (29.57%)	14 (20%)	48(25.95%)
Respiratory	19 (16.52%)	13 (18.57%)	32(17.30%)
Urinary	10 (8.7%)	6 (8.57%)	16 (8.65%)
C.N.S.	9 (7.83%)	4 (5.71%)	13 (7.03%)
Musculo-Skeletal	4 (3.48%)	2 (2.86%)	6 (3.24%)
Genital	0	6 (5.71%)	6 (3.24%)
Others	5 (4.33%)	4 (8.58%)	9 (4.86%)

System wise analysis showed piperacillin-tazobactam & meropenem were utilized highest in abdominal ailments followed by skin and soft tissue infections as shown in table 3.

The use of piperacillin-tazobactam and meropenem with respect to type of therapy was as follows.
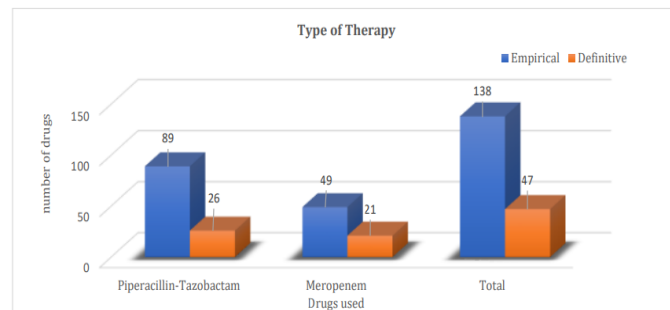
Figure 2: Type of therapy

As evident from Fig. 2 -piperacillin-tazobactam was used more than meropenem as empirical therapy.

Table 4: Appropriateness as Empirical therapy.

DEPARTMENT	PIPERACILLIN - TAZOBACTUM	PIPERACILLIN - TAZOBACTUM APPROPRIATENESS	MEROPENEM	MEROPENEM- APPROPRIATENESS
SURGERY	52	38 (73%)	25	1 (4%)
MEDICINE	29	22 (75%)	15	5 (33%)
ORTHOPEDICS	6	0	2	1 (50%)
OBGY	2	0	7	3 (43%)
TOTAL	89	60 (67.4%)	49	10 (20.1%)
Total appropriate use	70 (50.7%)			

Table 4 reveals appropriateness of empirical use of piperacillin-tazobactam was 67.42% while that of meropenem was 20.1%. Total appropriateness of both drugs combined was 50.7%.

Table 5: Appropriateness as per Definitive therapy.

DEPARTMENT	PIPERACILLIN - TAZOBACTUM	PIPERACILLIN - TAZOBACTUM APPROPRIATENESS	MEROPENEM	MEROPENEM- APPROPRIATENESS
SURGERY	8	4(50%)	16	16(100%)
MEDICINE	13	11(84.6%)	5	4(80%)
ORTHOPEDICS	1	1(100%)	0	0
OBGY	4	4(100%)	0	0
TOTAL	26	20(76.9%)	21	20(95.2%)
Total appropriate use	40(85.1%)			

From data in table 5 we can conclude that appropriateness as definitive therapy of both drugs combined was 85.1%. While individually it was 76.9% for piperacillin-tazobactam and 95.2% for meropenem.

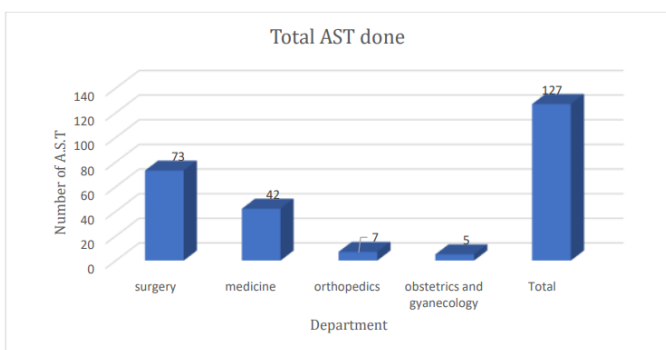Department wise appropriate use of AST was as follows

Figure 3: Department wise use of A.S.T

Use of antibiotic sensitivity test was most in surgery department followed by medicine as depicted in figure 3. Antibiotic Sensitivity was done in 127 patients out of 185 at any time during treatment.

Table 6: Appropriateness of drugs as per A.S.T.

Department wise sample sent	Total Samples Sent for AST	Appropriateness of use as per AST result	Percentage
Surgery	73	47	64.4
Medicine	42	28	66.7
Orthopedics	7	6	85.7
Obstetrics & Gynecology	5	5	100.0

Table 6 illustrates that department wise most use of A.S.T. was done by Surgery, followed by Medicine. While appropriateness was highest use was in Obstetrics and Gynecology, followed by Orthopedics, Medicine and Surgery.

Table 7: ATC/DDD chart of piperacillin-tazobactam and meropenem.

Drug	ATC code	WHO recommended DDD	Units used	Calculated number of DDD
Piperacillin-Tazobactam 4.5gm	J01CR05	14	1889	607.178
Meropenem 500mg	J01DH02	2	863	215.75
Meropenem 1 gm	J01DH02	2	568	284

Table 7 shows that Daily Defined Dose of piperacillin-tazobactam (4.5g) was 607.17 and while that of meropenem was 499.75. Both was much higher than WHO recommended dose.

Discussion

The data accessing use of piperacillin-tazobactam on the basis of medication used department wise was maximally by surgery (54.5%) department due to higher intrabdominal, skin and soft tissue infections. In other studies, however usage of study drugs was highest in medicine (50%) department [9.]

System wise usage analysis showed maximum use of drugs was for intra-abdominal infections (30%), followed by skin and soft tissue (20%) etc. In another study however the use was maximum for respiratory system (37%), followed by urinary tract (17.1%) etc. This variation may be due to different study population, and different diseases affecting them. [10]

In our study 138 (74.59%) patients were given study drugs empirically and 47 (25.41%) patients were given after sensitivity report.

These results were in accordance with other studies where empirical use was 71.4% and prophylactic use was 23.9% and 4.7% were according to culture results [11]. As our hospital is a tertiary care hospital where serious patients are admitted therefore 74% patients were given antimicrobials empirically. The appropriateness of empirical use of piperacillin-tazobactam as per diagnosis was 67.42% while other studies found that appro priate ness of piperacillin-tazobactam was variable from 57% to 73.5%.

Our findings are similar with this range of appro priateness [12.] Empirically appropriate use of meropenem was 20.4%. While in other studies it was 64.8% and 40 %.[13,14] More inappropriate use in our study may be due to uncertainty of diagnosis at time of admission, co-morbidities of the patient, and physician's desire to get faster response.

Department wise analysis showed appropriate use of piperacillin - tazobactam as empirical therapy was maximum in medicine (75.86%) and surgery (53.84%) departments.

Appropriateness of meropenem as empirical use was highest in orthopedics (50%), followed by obs-Gynaec (42.8%), medicine (20%) and surgery (4%). Even in other studies it had been found that most inappropriate use of piperacillin- tazobactam was done by surgery department- 86% for wards and 67% for SICU 12. This observation might be because many surgical patients require broad spectrum antimicrobial coverage.

Total use of both study drugs as definitive therapy was 25.17% (47 of 185). Appropriateness for definitive use of piperacillin - tazobactam was 76.92%, and for mero penem was 95.23%. Overall total appropriateness of both drugs was 85.10%. Other studies had similar find ings where appropriateness as definitive therapy was higher 97% for higher antimicrobials.[15]

Appropriateness of use of AST depends upon steps taken after the AST reports. Appropriate use is to be considered if an antimicrobial is changed to a narrow spectrum antimicrobial after AST report or if continued with same antimicrobials when found to be sensitive. Highest number of AST was sent by surgery (72.27%), medicine (67.74%), orthopedics (58.33%), obstetrics & gynecology (50%).

In one study 52% of samples were sent for Antibiotic sensitivity testing 14 while in another it was as high as 96.6% .16 Non-compliance for sending culture report similar to our study was found in one study where maximum underusage of AST was in ob stetrics & gynae department [9.]

Highest appropriate use of AST was done by obstetrics & gynecology (100%) followed by orthopedics (86%). Regarding timing of sending AST culture one study showed 82% cases being tested before anti-microbials and another study showed 34% before anti-microbial therapy and 15.6% cases within 24 hr. of antimicrobials [17.] Reliance of treating physician on their evaluation and serious clinical conditions may be the main reason for starting anti microbials prior to AST.

In our study 99 (82%) patients were continued with same broad-spectrum anti microbials (piperacillin & tazo bactam and mero penem) while 23 (18%) patients were switched to narrow spectrum antimicrobials.

In another study antimicrobials were changed to narrow spectrum in 78% cases while in 22% cases broad spectrum antimicrobial were continued [12].

Another study indicated that antimicrobial treatment may have been appropriate empirically but there was failure to revert to narrow spectrum antimicrobials in 66% patients.[18] Therefore, it is important to re-evaluate therapy and switch to narrow spectrum antimicrobials after availa bility of AST report. These steps will help in reducing cost, reducing of superinfection, and reducing develop ment of resistance.

The appropriateness of piperacillin-tazobactam as empirical use was 26% and as definitive use was 53% while that of meropenem as empirical use was 14% and as definitive use was 47.6%. It demonstrates that appli cation of microbial culture sensitivity increases rational use of higher antimicrobials.

In a study it was found that after an educational intervention among healthcare pro fessionals the use of antibiotic sensitivity test increased to 88.29% from 65.22% and correction indication rate in use of antimicrobials improved from 94.59% to 84.38% after one month of educational intervention. [19]

From above data it is clear that educational intervention with AST appropriateness of therapy increases, leading to decrease in resistance and cost-effective treatment in disease conditions.

Conclusion

Piperacillin tazobactam and meropenem are broad spectrum antimicrobials which are under high demand in critically ill patients. Irrational use of these anti micro bials can lead to development of resistance which can be a big threat to mankind in coming decades.

Rational use of the antimicrobials under study is need of the hour. Periodic review of antimicrobial stewardship program and checking adherence to the stewardship program will help significantly to prevent antimicrobial resistance.

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