ORIGINAL RESEARCH

Prospective Study of Antimicrobial Utilization, Rationality and Cost of Therapy in Patients Admitted to The Intensive Care Unit of a Tertiary Care Hospital

[1]Dr. Anu Sharma, [2]Dr. Inderpal Kaur, [3]Dr. Ajay Kestwal

[1]Associate Professor, Department of Anesthesia, GMC Amritsar, Punjab, India
[2]Associate Professor, Department of Pharmacology, GMC Amritsar, Punjab, India
[3]Senior Resident, Department Pharmacology, GMC Amritsar, Punjab, India

Corresponding Author
Dr. Inderpal Kaur
Associate Professor, Department of Pharmacology, GMC Amritsar, Punjab, India
Email: inderpalpharma@gmail.com

ABSTRACT
Introduction: Antimicrobial utilization studies involve the study of prescription and utilization of drugs in society with analysis of the medical, social, and economic consequences. **Aims:** To determine the current practice of antimicrobial usage, rationality, and economic burden of cost of antimicrobials in ICU of Government Medical College, Amritsar. **Settings and Design:** The present prospective, observational study was carried out in the ICU of a tertiary care Hospital attached to the Government Medical College, Amritsar from March 2021 to March 2022. **Material and Methods:** All the new consecutive patients irrespective of the clinical condition and sex, shifted to ICU are included. **Statistical analysis used:** SPSS software.
Results: Most frequently prescribed antimicrobial groups were beta lactam antibiotics (58.24%) followed by nitroimidazole (19.08%) Only 3.11% prescriptions followed laboratory evidence and rest of the patients were administered empirical therapy. Metronidazole formed the bulk of prescription and was the most economical for the patients (Rs. 11.25 per patient per day) Piperacillin- tazobactam combination was maximally prescribed. **Conclusions:** It is concluded that most of the prescriptions followed ICMR guidelines. Culture sensitivity is rarely done and most patient continue on empirical therapy. Formulating institutional antimicrobial prescription guidelines is the need of the hour.
Keywords: Antimicrobials utilization, Empirical therapy, ICU, DDD

INTRODUCTION

Antimicrobial resistance is growing exponentially and poses a threat to the introduction of effective, newer antimicrobials. The use of antibiotics induces a selective evolutionary pressure that increases resistance. Antimicrobial resistance is attributable to the irrational use of antimicrobial agents, and therefore optimal utilization is a necessity of the hour. India's per capita consumption of antimicrobials has increased by 66% in the last decade, making it the largest consumer of these agents.[1]Global per capita consumption of antibiotics with high resistance potential such as cephalosporins, fluoroquinolones and carbapenems has increased by 91% in a 15 year period.[2]

The most efficient means of preventing the spread and evolution of antibiotic resistance include infection prevention, optimum use, and antimicrobial stewardship.[1]Infectious disease specialists and microbiologists from throughout the nation provide input into the creation of ICMR guidelines. Data on the susceptibility of various tertiary care hospitals' antimicrobials is chosen. According to generally acknowledged standards, the recommended treatment plans are supported by evidence.Serious infections require cover with high-end antimicrobial combinations which are expensive thus increasing the cost of treatment.[3]The research reiterates the need for an antimicrobial stewardship policy in the ICU setting. There is need for inter-departmental collaboration with microbiology department for

periodic summary of antimicrobial susceptibilities of local bacterial isolates in form of antibiogram.

MATERIAL AND METHODS
The study was prospective, conducted in Department of Pharmacology in collaboration with Department of Anesthesia in a tertiary care hospital after obtaining the approval of Institutional Ethics Committee (Ethical committee approval letter no: 2225-26/D-26/2020 Batch) to assess the pattern of utilization and the adherence to the ICMR 2019 antimicrobial prescription guidelines. All the adult patients irrespective of gender and their clinical status shifted to ICU were includedin the study. Pregnant women, immune-compromised, Pediatric patientsand those already on carbapenems and third generation cephalosporin for more than 1 week at the time of admission to ICU were excluded from the study.

A detailed history of the patient was obtained as per prescribed proforma, with information also gathered from medical records, prescriptions, and files of the patients. We also evaluated the WHO core drug prescribing indicators including:
a) Average number of antimicrobials per patient
b) Percentage of antimicrobials prescribed by generic names.
c) Percentage of antimicrobials prescribed with an injection.
d) Percentage of antimicrobials prescribed from the essential drugs list or formulary.

From the prescription data of commonly prescribed antimicrobials, the amounts ofantimicrobials consumed converted into the number of Daily Drug Dose (DDD) as per the 2010 version of ATC/DDD index. According to WHO, DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. The total use of the antimicrobials was calculated as Prescribed Daily Doses (PDD) per one hundred bed days, and this was calculated in grams by multiplying DDD with the ratio of number of DDDs to the number of treatment days.

The rationality of usage of antimicrobials was assessed using ICMR treatment guidelines 2019 and based on the clinical condition of the patients.

The cost of the antimicrobials prescribed to the patient was calculated in Indian Rupees as the average of the market costs of assorted brands of the same medicine given in a drug compendium.The data was collected,tabulated and analyzed by applying SPSS software.

RESULTS AND OBSERVATIONS
During the study period the most prevalent age-group of patients was 20-30 years age group (21.8%) followed by 51-60 years age group (21.2%). Patients over 70 years were few (2.8%). Out of total 708 patients, there was slight predominance of male patients (53.20%) over female patients (46.80%) in the ICU. Post-operative surgical cases were leading cause of admission in the ICU (54.52%) followed by RTA cases (12.15%). Few cases were admitted with Mucormycosis.Most common infection among the patients admitted in the ICU was systemic (75.14%) followed by chest infection (24.58%). Localized infection cases comprised 0.14%.(Table1)

TABLE 1: DISTRIBUTION OF CASES ACCORDING TO DIAGNOSIS

Diagnose	No.	%age
Postoperative	386	54.52
Pneumonia	58	8.19
Mucormycosis	5	0.71
Septicaemia	39	5.51
Road traffic accident	86	12.15
Uncontrolled diabetes	68	9.60
Others	66	9.32
Total	708	100.0

Most used group of antimicrobials was beta-lactamase inhibitors (58.24%) followed by nitroimidazole group (19.08%). Anti-malarial, antimycotics and tetracyclines were the least used group (0.7%). Commonest amongst the antimicrobial prescribed was metronidazole (20.88%) followed by piperacillin+ tazobactam (15.39%) and ceftriaxone (13.66%). Laboratory evidence of infection was not followed in 96.89% of prescriptions. Most common indication for prescribing the antimicrobials was therapeutic (92.77%) followed by prophylactic (7.22%). (Table 2)

TABLE 2: GROUP OF ANTIBIOTICS WITH NUMBER OF CASES

Group	No.	%age
Beta-lactams	806	58.24
Aminoglycosides	69	4.99
Fluoroquinolones	104	7.51
Tetracycline	1	0.07
Antimycotic drugs	1	0.07

Antimalarial drugs	1	0.07
Lincosamides	52	3.76
Nitroimidazoles	264	19.08
Other antibacterial	86	6.21

Antimicrobials contributing most to the cost per patient was cefepime + sulbactam (7263.46 INR), highest total cost was of linezolid (160650 INR) and total cost of antimicrobials prescribed for 1 day of treatment was four lakhs seventy-seven thousand two hundred and forty-two INR approx.The desired daily dose (DDD) prescribed daily dose (PDD) along with mean of the antimicrobials were found to have significant p-value in the range of 0.01-0.06. Table 3)

TABLE 3: MAJOR ANTIMICROBIALS PRESCRIBED IN ICU ALONG WITH DDD & PDD

Antimicrobials	No.of cases	DDD		PDD		p-value
		Mean	SD	Mean	SD	
Amikacin	76	1.048	0.053	1.089	0.085	0.005
Amoxiclav	76	3.158	0.271	3.286	0.351	0.012
Azithromycin	26	1.123	0.014	0.805	0.057	0.001
Ceftriaxone	189	2.914	0.314	2.246	0.107	0.001
Cefuroxime	34	1.162	0.128	0.856	0.068	0.001
Ciprofloxacin	29	1.644	0.510	1.606	0.311	0.603
Clindamycin	44	1.827	0.181	1.032	0.450	0.036
Imipenem	21	2.001	0.321	1.288	0.411	0.001
Levofloxacin	49	0.776	0.224	0.969	0.105	0.001
Linezolid	82	1.185	0.133	1.124	0.228	0.039
Meropenem	61	3.100	0.328	2.353	0.516	0.001
Metronidazole	289	1.586	0.511	1.577	0.327	0.801
Ofloxacin	20	0.610	0.011	0.553	0.032	0.001
Vancomycin	11	2.000	0.102	1.855	0.081	0.012
Cefepime + Sulbactam	13	3.004	0.773	2.123	0.561	0.002
Ceftriaxone + Sulbactam	50	3.920	0.444	2.800	0.821	0.001
Piperacillin + Tazobactam	213	13.391	0.637	9.698	0.810	0.001
Others	44	6.796	1.222	2.365	0.254	0.001
No antibiotics	57	-	-	-	-	-

The median cost of meropenem was highest (2979), followed by median cost of imipenem (1376) and piperacillin tazobactam (669). (Table 4)

TABLE 4: MEDIAN COST OF THE MAJOR ANTIMICROBIALS PRESCRIBED IN ICU

Antimicrobials	Prescriptions	Median cost
Amikacin	76	90.00
Amoxiclav	76	140.97
Azithromycin	26	110.00
Ceftriaxone	189	61.84
Cefuroxime	34	236.00
Ciprofloxacin	29	11.67
Clindamycin	44	375.33
Imipenem	21	1376.00
Levofloxacin	49	207.63
Linezolid	82	398.89
Meropenem	61	2979.00
Metronidazole	289	12.47
Ofloxacin	20	173.48
Vancomycin	11	370.00
Cefepime + Sulbactam	13	425.00
Ceftriaxone + Sulbactam	50	169.00
Piperacillin + Tazobactam	213	669.00
Others	44	200.00
No antibiotics	57	0

Maximum duration of stay in the ICU was less than one week while the mean ICU stay was 3.8±1.53 SD. The number of prescriptions as per ICMR guidelines for antimicrobial prescribing was 97.20% as per our study

DISCUSSION

Antimicrobial resistance is growing exponentially due to overuse which is inducing a selective evolutionary pressure thus increasing resistance. The most efficient means of preventing the spread and evolution of antibiotic resistance is antimicrobial stewardship.[4]For formulating local AMM use policies and for AMM surveillance we need antimicrobial utilization data. Drug utilization studies (DUS) are common in west but rarely done in India..Only 67 of the 318 DUSs published up until 2012 in the WHO SEARO region, according to a systematic study, were from India.[5]Since it is necessary to perform more DUS in comparable contexts, to look for trends and modifications in the use of AMM so this research was carried out in a teaching hospital for tertiary care center in Punjab, India.

In this study, the mean age of enrolled patients is 31.1 years. Maximum patients were in age group 20-30 years followed by 51-60 years group. The study was conducted during COVID -19 pandemic and when elective surgeries were on the hold and the ICU intake included mainly post-operative serious patients as well as the roadside accident cases primarily comprising of younger age group.In this study, post-operative cases formed the bulk of ICU admissions (54.52%) followed by roadside accidents (12.15%). Beta-lactamase inhibitors (Piperacillin+tazobactam,n=166) were the most frequently used group (58.24%) followed by nitroimidazoles (19.08%). Metronidazole (n=288) was the most commonly prescribed. Similar results were obtained by Khirsaria et al; wherein beta-lactamase inhibitors were more frequently used followed by nitroimidazoles.[6] According to Obeid et al, lincosamides (clindamycin) was prescribed to most patients (50%) followed by beta-lactamase inhibitors (ceftriaxone-43%, carbapenem-32%, ceftazidime 27%). Glycopeptides (vancomycin) were the third most commonly prescribed group(26%).[7]Al-Zakhwani et al found that beta-lactamase inhibitors were most commonly prescribed antimicrobials in the ICU (meropenem-33%, ceftriaxone 31%) followed by glycopeptides (vancomycin-24%).[8]

Most common combination prescribed is piperacillin/ tazobactam (n=166) followed by amoxicillin/clavulanic acid (n=70) and cefoperazone+sulbactam (n=19). According to Khirsaria et al, the most common combination was ceftriaxone-metronidazole (19%).[6] Similar finding of antimicrobial usage was found by Kollef et al.[9] According to Obeid DF, the most common combination of antimicrobials in the ICU was amoxicillin/clavulanic acid (9%) followed by cefazone+sulbactam (8%) and piperacillin/tazobactam (7%).[7]

In this study 3.11% of prescriptions followed laboratory evidence of infection. Rest of the patients were administered empirical therapy. Our findings support past research showing first-line empirical medication for critically ill patients is frequently insufficient and must be modified once the results of the antimicrobial susceptibility tests are known.[10]In this study, we found that generic medicines were prescribed in 72.03% of prescriptions. As per a cross-sectional study by Nebyu et al on prescribing practices using WHO prescribing indicators and factors, 83.14% generic medicines were prescribed.[11] In another drug utilisation study by Shahbazi et al, generic medicines prescribed were 13.18%.[12]Mahendra et al, in his study has shown that 54,23% prescriptions were generic and 45.77% were brand drugs.[13]

As per this study, antimicrobials contributing most to the cost per patient was cefepime + sulbactam (7263.46 INR), followed by ofloxacin (6182.97 INR) and vancomycin (2047.65 INR) . Serious infection required cover with high-end antimicrobial combinations which are expensive thus increasing the cost of treatment.

According to the cost analysis of antimicrobials in this study, the major increase in antimicrobial per day of prescription in ICU was due to newer, more expensive antimicrobials prescribed to a select few patients. The median cost of meropenem was highest (2979 INR), followed by median cost of imipenem (1376 INR) and piperacillin/ tazobactam (669 INR). (T

In our study, the defined daily dose (DDD), prescribed daily dose (PDD) along with the mean of the antimicrobials were found to have significant p-value. Highest mean DDD was of piperacillin+tazobactam-13.391 and its mean PDD was 9. 698. Lowest mean DDD was of ofloxacin-0.610 and its mean PDD was 0.553. The current findings revealed that amongst the broad-spectrum antimicrobial agentspiperacillin+tazobactam was widely used in our ICU.According to Bimba HV et al, the total DDDs/100 patient days of antimicrobials was 5616.[14]

In this study 92.77% antimicrobials were prescribed for therapeutic indications and 7.22% for prophylactic indications. The majority of the cases had already been diagnosed with a condition, so they were given the appropriate antimicrobials. Prophylactic prescription is restricted to patients with immunocompromised conditions, infective endocarditis, metabolic disorders and prosthetics implant cases which were relatively fewer in this study period in the ICU. According to Bimba HV et al, 78.7% antimicrobials were prescribed for therapeutic indications and 21.2 % for prophylactic use.[14]

In this study, 97.2% of antibiotic prescriptions met the ICMR standards. Infectious disease specialists and microbiologists from throughout the nation provide input into the creation of ICMR guidelines. Data on the susceptibility of various tertiary care hospitals' antimicrobials is chosen. According to generally acknowledged standards, the recommended treatment plans are supported by evidence.

The research reiterates the need for an antimicrobial stewardship policy in the ICU setting. There is need for inter-departmental collaboration with microbiology department for periodic summary of antimicrobial susceptibilities of local bacterial isolates in form of antibiogram.

There are limitations in this research as it was conducted during the COVID-19 pandemic and that was a major confounder affecting the subset of patients admitted in the ICU. Moreover, the study cannot be generalised to other tertiary care hospitals as Guru Nanak Dev Hospital has inflow of patients from neighbouring satellite towns which is unique to this establishment.

Future research focusing on concurrent antimicrobial resistance monitoring and identifying patient and physician traits associated with specific prescription patterns may help to improve antibiotic stewardship. More research is needed to evaluate the long-term benefits of implementing a strong antimicrobial stewardship policy. Since the study was carried out during Covid-19 pandemic, intake of patients mainly included seriously ill patients, which was the major limitation of the study.

CONCLUSION

It is concluded that most of the prescriptions followed ICMR guidelines. Culture sensitivity was occasionally used and the patients were given empirical therapy. The risk of development of antimicrobial resistance can be overcomed by framing institutional specific guidelines for antimicrobial prescription. Hence antibiotic stewardship implementation is the need of the hour.this will ensure best clinical outcome for treatment and infections. This will minimize health care cost without compromising quality of care.

BIBLIOGRAPHY

1. Sweileh WM. Global research publications on irrational use of antimicrobials: call for more research to contain antimicrobial resistance. Global Health. 2021 Aug 24;17(1):94.
2. Klein EY, Tseng KK, Pant S, Laxminarayan R. Tracking global trends in the effectiveness of antibiotic therapy using the Drug Resistance Index. BMJ Glob Health. 2019 Apr 11;4(2)
3. Kayambankadzanja RK, Lihaka M, Barratt-Due A, Kachingwe M, Kumwenda W, Lester R, et al. The use of antibiotics in the intensive care unit of a tertiary hospital in Malawi. BMC Infect Dis. 2020 Oct 19;20(1):776.
4. Morrison L, Zembower TR. Antimicrobial Resistance. GastrointestEndosc Clin N Am. 2020 Oct;30(4):619–35.
5. Bachhav S, Kshirsagar N. Systematic review of drug utilization studies & the use of the drug classification system in the WHO-SEARO Region. Indian J Med Res. 2015 Sep 3;142:120–9.
6. Khirasaria R, Kanani N, Batta A. Utilization of antimicrobial agents in patients on ventilator in medical Intensive Care Unit at a tertiary care teaching hospital: A prospective study. Perspect Clin Res. 2019;10(3):130–6.
7. Obeid DF, Karara AH. Drug Utilization and Potential Drug-Drug Interactions within an Intensive Care Unit at a University Tertiary Care Hospital in Egypt. Pharm J Pharm Educ Pract [Internet]. 2022 Aug [cited 2022 Nov 3];10(4). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9416082/
8. Al-Zakwani I, Al-Thuhli M, Al-Hashim A, Al Balushi KA. Drug utilization pattern in an intensive care unit at a tertiary care teaching hospital in Oman. Asian J Pharm Clin Res. 2017 Feb;10(2):194–7.
9. Kollef MH, Bassetti M, Francois B, Burnham J, Dimopoulos G, Garnacho-Montero J, et al. The intensive care medicine research agenda on multidrug-resistant bacteria, antibiotics, and stewardship. Intensive Care Med. 2017 Sep;43(9):1187–97.
10. Malacarne P, Rossi C, Bertolini G, GiViTI Group. Antibiotic usage in intensive care units: a pharmaco-epidemiological multicentre study. J AntimicrobChemother. 2004 Jul;54(1):221–4.
11. Amaha ND, Weldemariam DG, Abdu N, Tesfamariam EH. Prescribing practices using WHO prescribing indicators and factors associated with antibiotic prescribing in six community pharmacies in Asmara, Eritrea: a cross-sectional study. Antimicrob Resist Infect Control. 2019 Oct 22;8(1):163.
12. Shahbazi Nia S, Hiremath SR, Prasad S. Assessment of Antimicrobial Use Pattern Using World Health Organization Prescribing Indicators at a Tertiary Hospital: A Prospective, Observational study. J Appl Pharm Sci. 2018 Jun 1;8:132–8.
13. Patel MK, Barvaliya MJ, Patel TK, Tripathi C. Drug utilization pattern in critical care unit in a tertiary care teaching hospital in India. Int J Crit IllnInj Sci. 2013 Oct;3(4):250–5.
14. Bimba HV, Roy V, Batta A, Daga MK. Drug utilization, rationality, and cost analysis of antimicrobial medicines in a tertiary care teaching hospital of Northern India: A prospective, observational study. Indian J Pharmacol. 2020;52(3):179–88.