ORIGINAL ARTICLE

Study of Antimicrobial Utilization and Cost of Therapy in Medicine Intensive Care Unit of a Tertiary Care Hospital in Eastern India

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Abstract

Introduction: High utilization of antimicrobial agent (AMA) and inappropriate usage in an intensive care unit (ICU) intensifies resistant organism, morbidity, mortality, and treatment cost. Prescription audit and active feedback are a proven method to check the irrational prescription. To analyze and compare the utilization of drugs, the World Health Organization (WHO) proposed daily defined dose (DDD)/100 patient days and days of therapy (DOT)/100 patient days to measure utilization of AMAs. Data of AMAs utilization are required for planning an antibiotic policy and for follow-up of intervention strategies.

Materials and methods: A prospective observational study was conducted for 1 year from July 2018 to June 2019 and the data obtained from ICU of a tertiary care hospital. The demographic data, the disease data, and the utilization of different classes of AMAs [WHO–Anatomical Therapeutic Chemical (ATC) classification] as well as their cost were recorded. Total number of patient days, DDD, DDD/100 patient days, and DOT/100 patient days were calculated as proposed by the WHO. Statistical analysis was performed using statistical software SPSS version 25.0. The descriptive analysis was performed using summary statistics median [interquartile range (IQR)].

Results: A total 939 patients were included, out of them 332 (35.4%) were female. The median age of the total patients was 58 (45–70). The median length of stay in ICU was 3 days. Mortality rate during our study period was 38.6%. The highly utilized AMAs in our study was ceftriaxone (36.95 DDD/100 patient days) followed by piperacillin/tazobactam (31.57), meropenem (26.4), doxycycline (21.53), and polymyxin B (21.38). The association between APACHE II and SOFA score with use of restricted antibiotics found to be statistical significant (*p* value 0.018 and 0.000, respectively). The cost of antibiotics per patient and patient days were $449.97 and $93.77, respectively, while median value of total cost was $2,343.26.

Conclusion: Ceftriaxone was the highest utilized AMA. The risk of receiving restricted antibiotics intensified with increasing prevalence of multidrug resistance bacteria and associated comorbidities. High treatment cost is responsible for higher utilization of restricted antibiotics in ICU.

Keywords: Antibiotics, Cost analysis, Drug utilization study, Multidrug resistant.

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Introduction

Antimicrobial resistance is currently a global threat and growing apace influencing all individuals of all ages, all countries irrespective of race, ethnicity, and religion. The World Health Organization (WHO) delivered a report which stated most of the resistance happened because of improper and widespread use of antibiotics.[1] Till date about 5,000 antimicrobial agents (AMAs) have been discovered, out of which 100 drugs are used clinically. The resistance to AMAs is increasing over tim.[2] It was evidenced that currently available AMAs will be resistance in the future days. In perspective on proceeding with resistant pathogens, significant efforts will be expected to contain resistant development in order to keep up viability of available AMAs.[2] The Indian Council of Medical Research (ICMR) developed antibiotic stewardship program which is having primary goal is, "to optimize safe and appropriate use of antibiotics to improve clinical outcomes and minimize adverse effects of antibiotics".[3]

In hospital settings, most of the critically ill patients usually admitted to the intensive care unit (ICU). The patients admitted to the ICU are more prone to be developed newer infections and AMAs are most often used.[4] This attributed to higher uses of antibiotics in ICU other than general wards.[5] The most effective antibiotic treatment in ICU can be drawn up by knowing most common bacterial isolates with their susceptibility. It is also important to sustain the effectiveness of the AMAs.[6] Every institution should have an antimicrobial strategy or guideline which can be unit specific or institution based that guided the physicians to prescribe effective antibiotics rationally and it ought to be updated annually. To frame this guideline or for convenient updating of guidelines and to check adherence to it, audit of the prescription and drug utilization is utmost needed.[6] World Health Organization provided a guideline in 1977 for drug utilization research which is defined as, "the marketing, distribution, prescription, and use of drugs in society, with special emphasis on the resulting medical, social, and economic consequences".[7]

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In perspective of this, it was proposed to study the drug utilization patterns of AMAs and reason ability of their uses in Department of Critical Care Medicine of our institution that would help us to (a) determine most commonly utilized AMAs in our department and (b) compute average expenses of AMAs prescribed.

Materials and Methods

We have conducted a prospective study in Department of Critical Care Medicine of a tertiary care hospital in Bhubaneswar, Odisha, and the data were collected from July 2018 to June 2019 after ethical committee consideration. Data were collected from patients or relatives using paper-based questionnaire methods. The questionnaires were formed as per the WHO guidelines.

Eligibility Criteria

All patients who admitted to our department during study period and given consent were included to study population. Patient or relatives who did not consent were excluded from trial.

Study Context

The data regarding demographic profiles like name, IP registration number, age, and gender of individual participants those who are willing to participate were collected from the hospital databases, additionally date of admission (DOA), date of discharge (DOD), distribution of pattern of Illness based on diagnosis, culture and organisms traced, associated comorbidities [hypertension, diabetes, chronic kidney disease (CKD)], prescription of AMAs used in individual patient, reason of changing AMAs, and starting date and stopping date of individual AMAs used were also recorded from the individual patient health records. The cost of individual used AMAs in the study area were recorded from the pharmacy.

The total AMAs used in this period were classified and coded as per the WHO–Anatomical Therapeutic Chemical (ATC) classification to avoid the bias. For analysis of antimicrobial utilization, days of therapy (DOT) used as per the guideline provided by the Centers for Disease Control (CDC).[8] Likewise, WHO recommended daily defined dose (DDD) and DDD/100 patient days were also used for the analysis of AMAs utilization.[7] The calculation formula for DOT, DDD, and DDD/100 patient days were mentioned below:

- DOT = it will be calculated as difference in date of stoppage and starting of AMAs.
- DDD will be calculated as:[6]Net quantity of AMA charged/DDD of AMA as per WHO.
- DDD/100 patient days will be calculated as:[6]

Defined daily dose of AMAs used/Number of patient days × 100.

Apart from that, we have also classified AMAs as restricted and non-restricted antibiotics as per guideline provided by WHO.[6]

Cost Calculation

We have collected cost of individual AMAs used during the study period from the pharmacy. The number of treatment days for each antimicrobial was calculated by subtracting the start date from ending date of the prescription. The total number of treatment days per patient for all antimicrobials was multiplied by the average daily cost as recorded from the pharmacy. For patients, those received more than one antimicrobial simultaneously, the days of therapy for each drug were added together and multiplied with average cost for each drug. Then, all data were aggregated as per the WHO–ATC classification. For universalization, we have converted the currency from INR to USD. We have used cost per patient and cost per patient days for cost analysis purpose. We have not recorded any hospitalization cost, procedure cost, investigation cost, and other costs into consideration, because our study objective was only based on cost of AMAs used.

Statistical Analysis

After data collection, all data were entered in Microsoft excel and analyzed using statistical software IBM SPSS version 25.0. All continuous variables were analyzed using descriptive statistics as median ± interquartile range (IQR). Likewise, categorical variables were presented as frequency percentage. To find out the association of APACHE II score and SOFA with use of restricted antibiotics, we have used t test as hypothesis testing. We have set the p value < 0.05 for statistical significance.

Results

A total of 1,024 patients were admitted in the ICU during the study period, out of them 38 patients were did not consent, 47 were died or left before data were collected, and 939 were included in this study. Of the total, 332 (35.4%) were female and rest were male. The median age of the total patients during the study period was 58 (45–70). The median value of Charlson's index, APACHE II score, and SOFA was 2 (1–4), 18 (12–22), and 6 (4–8), respectively (Table 1). Patients were in the ICU ranging from 2 to 6 days with a median value 3 days (Table 2). Out of all patients admitted to the ICU, most of

Table 1: Demographic characteristics

Characteristics	*Median (IQR)*
Age	58 (45–70)
Gender (female), *n* (%)	332 (35.4)
Charlson's index	2 (1–4)
APACHE score	18 (12–22)
SOFA	6 (4–8)
Comorbidities	
Diabetes, *n* (%)	279 (31.6)
Hypertension, *n* (%)	307 (32.7)
CKD, *n* (%)	217 (23.1)
Cardiac, *n* (%)	102 (10.9)
Hepatic, n (%)	10 (1.1)
COPD, n (%)	112 (11.9)
Diagnosis	
Pneumonia, *n* (%)	509 (54.4)
Tropicals, *n* (%)	226 (24.2)
UTI, *n* (%)	31 (3.3)
Intra-abdominal, *n* (%)	8 (0.9)
Neurological, *n* (%)	59 (6.3)
Others, *n* (%)	62 (6.6)

IQR, interquartile range; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; UTI, urinary tract infection

Table 2: Outcome variables

Characteristics	
Death, *n* (%)	362 (38.6)
Length of stay (LOS)	3 (2–6)

them were admitted with comorbidities of hypertension, diabetes, and CKD with percentages of 307 (32.7%), 279 (31.6%), and 217 (23.1%), respectively. Among all, 509 (54.4%) were diagnosed with pneumonia followed by tropicals (24.2%), neurological disorders (6.3%), and urinary tract infection (UTI) (3.3%). Mortality rate during our study period was 38.6% (Table 1). The frequency of AMAs utilization was given in Table 3. It was also found that with increasing APACHE II and SOFA scores, the uses of restricted antibiotics also increased with *p* value 0.018 and 0.000, respectively, and which is statistically significant (Table 4). Five highly utilized AMAs were ceftriaxone, piperacillin/tazobactam, meropenem, doxycycline, and polymyxin B whose utilization were 36.95, 31.57, 26.4, 21.53, and 21.38 DDD/100 patient days, respectively (Table 5).

Table 3: Antibiotic utilization

Characteristics	*Median (IQR)*
Days of therapy (DOT)	75 (22–332.5)
DOT/100 patient days	1.81 (0.43–7.52)
Defined daily dose (DDD)	127.5 (28.25–808.75)
DDD/100 patient days	2.83 (0.63–17.95)
Net utilization cost (in USD)	2,343.26 (126.44–24,168.32)
Net cost per patient (in USD)	449.97
Net cost per patient days (in USD)	93.77

IQR, interquartile range, USD, US dollar (exchange rate of 1 USD = Rs 70 taken)

Discussion

In hospital settings, most of the critically ill patient are admitted to the ICU with lot of serious infections, for that AMAs are more widespread used in these settings. In clinical settings, warrants use of drugs from different classes depending upon source and severity of infections.[8] In our study, the demographic parameters of the patients revealed that the number of males admitted to the ICU was almost double to that of females and the median age of patients was around 58 years. The proportion of male and female also found to be similar to the previous study.[2,8–10] The median length of stay (LOS) was found to be 3 days in this study, which is quite similar to that of the previous studies. In other studies, conducted in North India, South India, Central India, Nepal, and USA, the average LOS in ICU was 5.75, 6.22, 7, 4, and 5.2 days, respectively.[8–11] Patients with different clinical conditions were admitted to the ICU during our study period. Among them, most of the patients were diagnosed with respiratory infections followed by tropical fever, neurological disorders, and UTI (Table 1). Almost all patients were admitted to ICU with multiple comorbidities, but among them the most common

Table 4: Risk of use of restricted antibiotics

	Restricted	*Not restricted*	
	Median (IQR)	*Median (IQR)*	*p value*
APACHE II	20 (16–25)	17 (12–21)	0.018
SOFA	7 (5–10)	5 (3–7)	0.000

IQR, interquartile range; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment

Table 5: Utilization of antimicrobial agents use in intensive care unit presented as DDD/100 patient days and DOT/100 patient days

ATC code	*Antibiotics*	*DDD/100 patient days*	*DOT/100 patient days*
J01DD04	Ceftriaxone (1 g)	36.95	36.95
J01CR02	Amoxicillin clavulanate potassium (1.2 g)	7.62	6.35
J01DD62	Cefoperazone + sulbactam (1.5 g)	3.03	2.02
J01CG01	Sulbactam (1 g)	0	0
J01FA09	Clarithromycin (500 mg)	27.9	27.9
J01FA10	Azithromycin (1 g)	0.71	0.36
J01MA12	Levofloxacin (500 mg)	1.24	0.62
J01XX08	Linezolid (600 mg)	0.24	0.24
J01CR05	Piperacillin + tazobactam (4.5 g)	31.57	32.73
J01DH51	Imipenem + cilastatin (500 mg)	7.1	7.1
J01DH02	Meropenem (1 g)	26.4	17.6
J01DH04	Doripenem (500 mg)	0.38	0.38
J01XB01	Colistin (4.5 MU)	4.79	1.6
A07AA05	Polymyxin B (5 lakh unit)	21.38	6.41
J01XA02	Teicoplanin (400 mg)	7.66	7.66
J01XA01	Vancomycin (1 g)	2.29	2.29
J01AA12	Tigecycline (50 mg)	1.33	1.33
J01CF05	Flucloxacillin (1 g)	2.89	1.44
J01AA08	Minocycline (100 mg)	0.6	0.6
J01EE01	Sulfamethoxazole + trimethoprim (80 mg)	0.13	0.07
J01DF01	Aztreonam (1 g)	0.1	0.07
P01AB01	Metrogyl (500 mg)	2.77	2.77
J01AA02	Doxycycline (100 mg)	21.53	10.76
J01FF01	Clindamycin (600 mg)	1.49	1.49
	Total AMAs used	210.1	168.74

DDD, defined daily usage; DOT, days of therapy; ATC, anatomical therapeutic chemical; AMA, antimicrobial agents

associated comorbidity was hypertension followed by diabetes and CKD (Table 1). These findings are also similar to that of studies conducted in Bengaluru and Mangaluru.[2,8] The mortality rate in this study was found to be 38.6% (Table 2). Many of the Indian studies conducted in different geographical areas reported ICU mortality rate as around 35%. A study conducted among patients admitted to the ICU in Northern India, the mortality rate was 39.5%.[12]

In our study, we analyzed AMA utilization patterns in terms of DDD/100 patient days and DOT/100 patient days (Table 3). The median DOT/100 patient days and DDD/100 patient days in our study was 1.81 (0.43–7.52) and 2.83 (0.63–17.95), respectively (Table 3). The utilization of AMAs in total was 201.1 DDD/100 patient days (Table 5), which was quite higher than the previous studies. As this study was conducted in critical care medicine of a tertiary hospital, so most of the patients admitted with sepsis, multiorgan dysfunction, pneumonia, and lower respiratory tract infections. These clinical conditions attributed to higher utilization of antimicrobial therapies. Studies conducted among patients admitted to tertiary care hospital of Mangaluru, the total AMAs utilization was 148.97 DDD/100 patient days.[2] Another study conducted in Pokhara where utilization was 118.2/100 patient days.[10]

In this study, five highly utilized AMAs were ceftriaxone, piperacillin/tazobactam, meropenem, doxycycline, and polymyxin B whose utilization were 36.95, 31.57, 26.4, 21.53, and 21.38 DDD/100 patient days, respectively (Table 5). In support of these findings, the highly utilized AMAs among patients admitted to a tertiary care hospital was also ceftriaxone followed by piperacillin/tazobactam[2]. On reviewing different studies from India, five most highly utilized antibiotics were third generation cephalosporin followed by meropenem, metronidazole, levofloxacin, and ceftriaxone.[12]

Bacterial resistance to antibiotics has been emerged as an important factor influencing mortality and morbidity of the patients. Due to increased prevalence of multidrug resistance and as mentioned above most of the patients admitted with severe respiratory and systemic infection, the use of restricted antibiotics was also increased.[10] Apart from these, hospital-acquired pneumonia (HAP) is one of the most frequent serious complication observed among the patients admitted to ICU, this is also attributed to higher utilization of restricted antibiotics. APACHE II and SOFA are the prognostic scoring system calculated within 24 hours of admission to ICU which can be used to predict mortality.[13] In this study, it was found that on increasing SOFA and APACHE II score the use of restricted antibiotics also increased. The median APACHE II and SOFA score in restricted antibiotics were 20 (16–25) and 7 (5–10), compared to score in non-restricted antibiotics were 17 (12–21) and 5 (3–7), respectively (Table 4). In support of these findings while reviewing other Indian studies, it was found that there was significant association between APACHE II and numbers of AMAs used,[12,13] but limited study available in the database to find the association between APACHE II and SOFA with use of restricted antibiotics.

Increasing cost of antibiotics causing immense economic burden on patients who bears the expenses of treatment in India. Taking into this account, we have calculated average cost of AMAs per patient as well as per patient days. The median value of net utilization cost of antibiotics was $2,343.26 (126.44–24,168.32) and the cost of antibiotics per patients and patient days were $449.97 and $93.77, respectively (Table 3). This increasing cost of treatment was due to higher utilization of restricted antibiotics. Piperacillin/tazobactam constituted the major portion of total cost of all AMAs used $137,968 followed by polymyxin B ($103,214.29). The main reason of higher cost was the use of polymyxins in view of hospital-acquired infections. Since it is a medical ICU, we get lot of patients with infection. That could be one reason of high usage and cost. The other factor being a tertiary care and referral ICU we receive many patients after stay in other ICUs which increases the utilization of polymyxins. Utilization cost globally may be misleading because of variation in price of antibiotics. However, on reviewing studies globally, it was found that a study conducted from Turkey reported AMAs cost per patient days in ICU was $89.64[14] while other studies varied from $208 to $312.[15] On reviewing Indian studies, we found total cost of AMAs was varied from $62.34 to $28.5.[9]

The important limitation of our study was small sample size. Apart from that, all patients admitted to our ICU was not included some of them were not given consent, some were died and left before data were collected. Since it is a single-center study, the findings of our study could not be generalized to other settings. Despite the limitations, the study still included nearly a thousand patients and provides important information about antibiotics usage and cost in Eastern India.

Conclusion

The total DDD/100 patient days and DOT/100 patient days in this study were 201.1 and 168.73, respectively. The most commonly used antibiotic in ICU was ceftriaxone. Net utilization cost for AMAs used per patient was $449.97 and cost per patient days was $93.77.

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