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Antimicrobial drug utilization pattern in a tertiary level intensive care unit in Northern India: Antimicrobial Stewardship Programme need of the hour

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ABSTRACT

Background: Antimicrobial drugs are the most frequently prescribed drugs in hospital settings with intensive care unit (ICU) patients showing the highest consumption of these drugs. Antimicrobial overuse and misuse is attributed to antimicrobial resistance (AMR). AMR in coming years will emerge as a global pandemic, maiming the modern health-care system. High consumption of antimicrobial drugs is one of leading factors contributing to AMR. **Aims and Objectives:** This study aimed at evaluating the prescription pattern of antimicrobial drugs in ICU and estimates the burden of inappropriate antimicrobial drug utilization in ICU settings of a tertiary level teaching hospital. **Materials and Methods:** The current study was conducted on 100 patients over a period of 6 months, admitted in surgical ICU (SICU), and neuro SICU (NICU) of a tertiary level hospital in Jammu and Kashmir, India. Study patients were identified through daily review of pharmacy records and antimicrobial drugs prescribed for the initial 5 days of ICU admission were documented in a well-designed questionnaire consisting all the necessary information regarding antibiotic therapy. **Results:** Out of the 100 enrolled study subjects, 98% received an empiric therapy. Majority of the patients were given a combination antimicrobial therapy during the initial 5 days of ICU admission. The most common antibiotic prescribed as monotherapy was ceftriaxone during the initial 2 days of ICU stay followed by piperacillin-tazobactam and meropenem in the next 3 days. Amikacin was the most frequently prescribed antibiotic in combination therapy during first 2 days followed by vancomycin in the consecutive days. A total of 27 antimicrobial drugs belonging to 15 classes were prescribed to the study participants during the initial 5 days of ICU admission. **Conclusion:** The study reports a very high consumption of antimicrobial drugs in ICUs with maximum of antimicrobial therapies prescribed empirically. A robust action plan, consisting of proper protocol for prescribing empiric antimicrobials, regular monitoring of antibiotic consumption in ICUs with a system of prospective audit, and feedback and timely interventions are a keystone of good antibiotic stewardship and should be the focus in ICU and NICU.

Key words: Antimicrobial drugs; Antimicrobial resistance; Antimicrobial stewardship programme

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INTRODUCTION

Discovery of antibiotics in 20th century was one of the greatest contributions of science to mankind. Antibiotics have not only made it possible to treat infectious diseases but the success of various sophisticated interventions in modern medicine such as organ transplant, joint replacements, and treatments of cancer is largely

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attributed to antibiotics.[1] However, the overuse and misuse of antimicrobials have resulted in a menace called antimicrobial resistance (AMR). AMR has emerged as one of the most serious public health threats that result in declaring it as a silent pandemic by the World Health Organization (WHO). Since the development of newer antibiotics is declining while at the same, the rate of AMR is rising at an alarming rate. We are currently at the verge of losing all the milestones that have been achieved in modern medicine so far.[2]

AMR as defined by the WHO occurs when bacteria, viruses, fungi, and parasites change over time and no longer respond to medicines making infections harder to treat and increasing the risk of disease spread, severe illness, and even death. As a result of drug resistance, antibiotics and other antimicrobial drugs become ineffective and infections become increasingly difficult or impossible to treat. In one study, it was estimated that 4.95 million deaths were associated with AMR in 2019, including 1.27 million deaths attributable to bacterial AMR. AMR is a leading cause of death around the world, with the highest burden in low-resource settings.[3] Drug-resistant superbugs could claim 10 million lives a year and cost the global economy a cumulative loss of US$100 trillion by 2050.[4]

The intensive care unit (ICU) is the epicenter of infections in a hospital; this is mainly due to its extremely vulnerable population of critically ill patients, and the high use of invasive procedures (mechanical ventilation, intubation, and catheterization). Consequently, a higher risk of mortality and morbidity is seen in ICU patients.[5] According to a global point prevalence study, 70% of ICU patients on any given day are administered at least one antibiotic.[6] Antibiotics in ICU are mostly overused which promotes the AMR.[7,8]

In the present study, we attempted to evaluate the pattern of antimicrobial drug utilization and estimate the burden of its consumption in ICUs of a tertiary care hospital.

Aims and objectives

The aim of study was to assess the magnitude and burden of inappropriate drug use in ICU (Surgical and Neurosurgical ICU) in a tertiary care hospital.

MATERIALS AND METHODS

Study design and setting

The study was conducted at Sher-i-Kashmir Institute of Medical Sciences, Soura, a multi-specialty tertiary care teaching hospital with 1100 beds in the union territory of Jammu and Kashmir, India. The study was conducted in surgical ICU (SICU) and neuro SICU (NICU) from May 2022 to October 2022. We included all ICU patients who gave informed consent to participate in the study. If patient could not give informed consent, we sought substituted consent from the patient's next of kin.

The study procedure and protocol were approved by the Institutional Ethics Committee (# RP 061/2022).

Data collection

Demographic and clinical data of patients which met the inclusion criteria were collected by a structured questionnaire. Apart from information concerning the admission to ICU, age, gender, and main cause of admission; medical history was collected. In the designed questionnaire, all antimicrobials (antibiotics, antivirals, antifungals, and antiparasitics) prescribed for initial 5 days of ICU admission were recorded from the patients' notes.

For each patient with an antimicrobial prescribed and charted, the following information was obtained and entered on the data collection form: Demographic profile, diagnosis, indications, dose of antimicrobial drugs, route of administration, frequency, and adverse reactions, if any. Besides, the patient's microbiological, hematological, and biochemical profile were also recorded.

Statistical analysis

The data were analyzed using SPSS version 24.0 and Microsoft Excel 2016. All categorical variables were shown in the form of frequency, percentage, and suitable diagrams.

RESULTS

During the study, a total of 100 patients were included from both SICU and NICU between May 2022 and October 2022. Admitted patients were 60% males and 40% females. The maximum patients (51%) were in the age group of 35–64 years. The mean age of subjects under study was 42.1 years. Majority (43%) of study population had no comorbidity, however among the patients with comorbidities, most of them (14%) presented with hypertension. Patients admitted in both ICUs were largely post-op management cases (36%) followed by road traffic accident cases (20%), hemorrhage (7%), and Guillain-Barre syndrome (5%). The overall mortality rate found was 43%.

In the current study, the data related to antibiotic consumption were analyzed for each patient for the initial 5 days of ICU admission. It was observed that all the patients were prescribed either a single or a combination of antimicrobial drugs on day 1. Table 1 depicts the type of antimicrobial drug therapy (mono- or combination therapy) in terms of percentage for the first 5 day stay of

study subjects in ICU. The most common antimicrobial prescribed was ceftriaxone in monotherapy during the first 2 days followed by piperacillin-tazobactam and meropenem during the next 3 days (Table 2). In combination therapy amikacin with ceftriaxone-tazobactam, ceftriaxone-sulbactam, and cefoperazone-sulbactam was most frequently prescribed during first 2 days, followed by vancomycin in combination with piperacillin-tazobactam and levofloxacin in the next 3 days. Table 2 illustrates the common antibiotics prescribed in monotherapy during the stay of patients for first 5 days in the ICU. Table 3 describes the common antibiotics which were frequently prescribed along with other antibiotics in a combination therapy, for the initial 5 days of ICU stay. In Table 4, the most common combination of antibiotics prescribed in ICU setup during the study period is shown. Figure 1 represents the most common classes of antimicrobial drugs given as monotherapy while Figure 2 represents the changing pattern of combination of common antimicrobial drug classes followed prospectively from initiation of therapy till the next 5 days. The results show that 3rd generation cephalosporins were prescribed to most of the patients as monotherapy, and the utilization of carbapenems increased while that of third generation cephalosporins decreased on consecutive days. Similarly, in combination therapy as shown in Figure 2; utilization of third generation cephalosporins decreases while that of carbapenems and glycopeptides increases as the days pass. Figure 3 shows the combination of antimicrobial classes which were prescribed from day 1 to day 5. The most common combination prescribed for the first 3 days is third generation cephalosporins with aminoglycosides. On

Table 1: Antimicrobial drug therapy type

Type of therapy	Day 1 n (%)	Day 2 n (%)	Day 3 n (%)	Day 4 n (%)	Day 5 n (%)
Monotherapy	33 (33.0)	31 (32.6)	24 (27.2)	20 (25.0)	16 (22.0)
Combination therapy	67 (67.0)	64 (67.3)	64 (72.7)	60 (75.0)	57 (78.0)

Table 2: Common antibiotics prescribed in monotherapy

Antimicrobials	Day 1 n (%) 33 (33.0)	Day 2 n (%) 31 (32.6)	Day 3 n (%) 24 (27.2)	Day 4 n (%) 20 (25.0)	Day 5 n (%) 16 (22.0)
Ceftriaxone	14 (42.4)	13 (42.0)	7 (29.1)	3 (15.0)	2 (12.5)
Ceftriaxone-tazobactam	7 (21.2)	7 (22.6)	5 (20.8)	4 (20.0)	3 (18.7)
Piperacillin-tazobactam	7 (21.2)	7 (22.6)	7 (29.1)	6 (30.0)	4 (25.0)
Meropenem	1 (3.0)	1 (3.2)	3 (12.5)	5 (25.0)	6 (37.5)

n represents the total number of patients receiving monotherapy during initial 5 days of ICU stay

Table 3: Common antibiotics prescribed in combination therapy

Antimicrobials	Day 1 n (%) 67 (67.0)	Day 2 n (%) 64 (67.3)	Day 3 n (%) 64 (72.7)	Day 4 n (%) 60 (75.0)	Day 5 n (%) 57 (78.0)
Amikacin	23 (34.3)	24 (37.5)	17 (26.5)	13 (21.7)	10 (17.5)
Ceftriaxone-tazobactam	13 (19.4)	11 (17.1)	8 (12.5)	8 (13.3)	6 (10.5)
Levofloxacin	19 (28.3)	20 (31.2)	23 (36.0)	23 (38.3)	25 (43.9)
Meropenem	11 (16.4)	12 (18.8)	14 (21.9)	19 (31.6)	23 (40.3)
Piperacillin-tazobactam	20 (30.0)	21 (32.8)	22 (34.4)	23 (38.3)	23 (40.3)
Vancomycin	20 (30.0)	21 (32.8)	26 (40.6)	27 (45.0)	31 (54.3)

n represents the total number of patients receiving combination therapy during initial 5 days of ICU stay

Table 4: The most common antimicrobial combination therapy

Antimicrobial combination	Day 1 n (%) 67 (67.0)	Day 2 n (%) 64 (67.3)	Day 3 n (%) 64 (72.7)	Day 4 n (%) 60 (75.0)	Day 5 n (%) 57 (78.0)
Ceftriaxone-tazobactam+amikacin	9 (13.4)	5 (7.8)	4 (6.25)	3 (5.0)	3 (5.2)
Ceftriaxone-sulbactam+amikacin	4 (6.0)	4 (6.25)	4 (6.25)	2 (3.3)	1 (1.7)
Cefoperazone-sulbactam+amikacin	7 (10.4)	6 (9.3)	6 (9.3)	5 (8.3)	3 (5.2)
Meropenem+vancomycin	3 (4.5)	4 (6.25)	5 (7.8)	8 (13.3)	8 (14.0)
Piperacillin-tazobactam+levofloxacin	4 (6.0)	4 (6.25)	4 (6.25)	4 (6.6)	3 (5.2)
Piperacillin-tazobactam+levofloxacin+vancomycin	4 (6.0)	5 (7.8)	6 (9.3)	6 (10.0)	8 (14.0)

n represents the total number of patients receiving combination therapy during initial 5 days of ICU stay

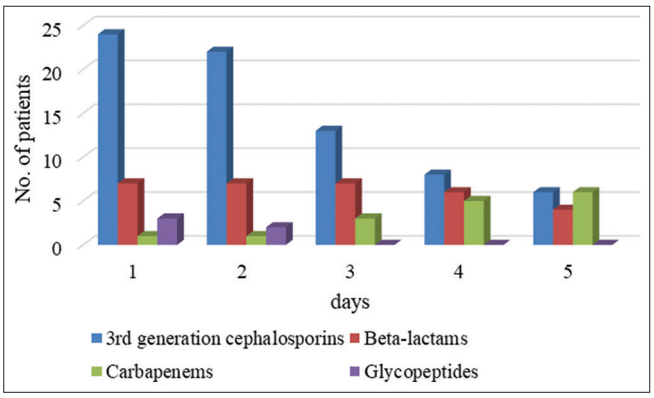

Figure 1: Common antimicrobial classes given in monotherapy

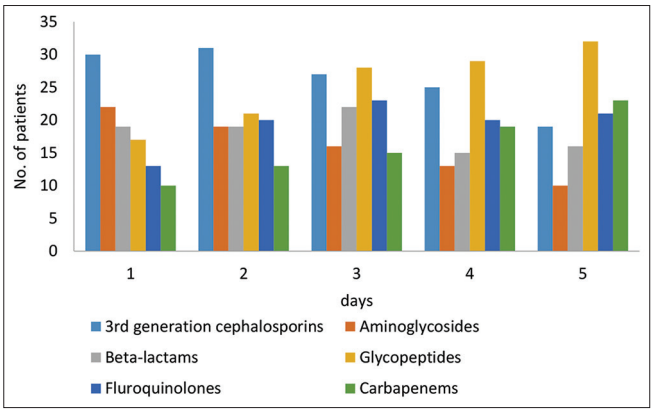

Figure 2: Changing trend of common antimicrobial classes in a combination therapy

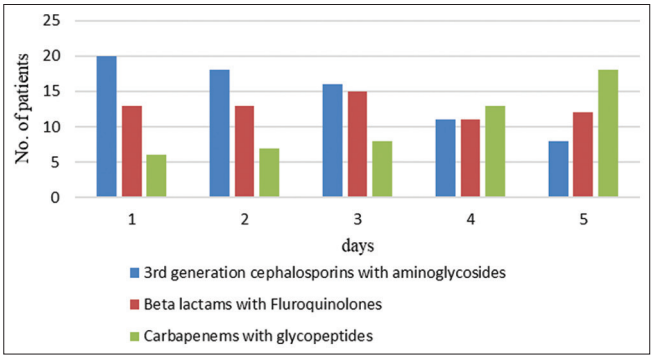

Figure 3: The most common antimicrobial class combination

4th and 5th days of ICU stay, carbapenem with glycopeptides and fluoroquinolones with beta-lactams take over.

DISCUSSION

The study aimed at evaluating the antimicrobial utilization pattern in ICUs of a tertiary care hospital. Almost all the prescribed antimicrobial therapies were empiric. A total of 27 antimicrobial drugs belonging to 15 antimicrobial classes were prescribed to the study population including access, watch as well as reserve group of antimicrobial drugs, a classification given by the WHO.[9] Most of the patients received combination therapy. The frequency of combination therapy increases despite the declining number of patients as the days pass. During the first 3 days, third generation cephalosporins were prescribed to most of the patients either in monotherapy or in combination therapy, however from day 4 the majority of patients were prescribed glycopeptides followed by carbapenems. Among the antimicrobial classes, the frequently occurring combination was that of third generation cephalosporins with aminoglycosides, carbapenems with glycopeptides and beta-lactams with fluoroquinolones. Ceftriaxone in monotherapy was prescribed to most patients, but the utilization of piperacillin-tazobactam and meropenem increased during the consecutive days. In case of combination therapy, amikacin was prescribed to majority of patients during the first 2 days of ICU admission while levofloxacin, piperacillin-tazobactam, meropenem, and vancomycin show a steep increase in utilization as the days pass. Combination of Piperacillin-tazobactam +Levofloxacin+Vancomycin was given to a majority of patients on days 4 and 5. Furthermore, the most frequent combination of antimicrobials prescribed on first 3 days of ICU admission was ceftriaxone-tazobactam with amikacin and cefoperazone-sulbactam with amikacin. However, the combination of piperacillin-tazobactam with levofloxacin and meropenem with vancomycin was prescribed to many patients on next 2 days. A similar study from Government Medical College and Hospital, Baramulla in Jammu and Kashmir also reported a very high consumption of antimicrobial drugs (n=260, 88.46%) among the patients of general medical wards. Cephalosporins (n=63, 47%) and quinolones (26.95%) show highest utilization.[10] Another study reported a very high consumption of antimicrobials (79.0%) among pediatric patients (n=205). Ceftriaxone (n=81, 50.0%) and amikacin (n=52, 32.3%) were prescribed to most of the patients.[11]

A recent study conducted at a tertiary care hospital in Malaysia reported a clear indication of inappropriate antibiotic use with emergence of multidrug resistance organisms (MDROs).[12] The WHO in its recent report states that the main drivers of antibiotic resistance is misuse and overuse of antimicrobial drugs.[13] In a low middle income country like India where there is no potent surveillance system of consumption of antimicrobial drugs and also the easy availability of sub-standard antimicrobial drugs and the self-prescription of the same are the main contributing factors of AMR. In coming years, India may emerge as a global mecca of AMR as it currently being "The capital of AMR".[14] To tackle the inappropriate antimicrobial consumption and emergence of AMR, Antimicrobial Stewardship Programme (AMSP) should be implemented in the hospital settings. Antimicrobial stewardship as defined

by the WHO is a set of coherent actions which advocates the use of most appropriate antimicrobial drugs responsibly. Antimicrobial stewardship in other words is the tactical use of antimicrobial drug regimen including a right dose, right frequency, and right route of administration by health-care professionals. The primary aim of AMSP is improving the clinical outcomes of a patient while limiting the lethal consequences such as toxicity, selection of resistant superbugs, and emergence of AMR.[15] Extenuating the impact of AMR globally, many hospitals are implementing AMSP.[16] Building capacity for stewardship tasks, creating strict rules and regulations about antimicrobial selling and prescribing, teaching health-care professionals and providing useful interventions uniquely tailored for national settings are few of the AMSP techniques. The pre-prescription approach which requires the stewardship team's consent before prescribing the restricted antibiotics, and the post-prescription model which involves the prospective review and the feedback of antibiotics prescribed are the two core strategies of an AMSP. The antimicrobial stewardship team includes an infectious disease specialist, a clinical pharmacologist, a clinical microbiologist, an intensivist and a well-trained infection control specialist nurse.[17] In many hospitals of India AMSPs are implemented, and a government run hospital implementing AMSP reported the reduction of antimicrobial consumption from 61% to 39% just in a year.[18] In neonatal ICU of a tertiary care hospital of northern India, a high mortality rate among the newborns was seen, primarily attributed to sepsis due to MDROs. Implementing AMSP for a year in NICU decreased the antibiotic usage rate dramatically. Furthermore, the number of newborns exposed to early antibiotic therapy decreased.[19] Another tertiary care hospital in south India for tackling the AMR and reducing the utilization of last resort antimicrobial polymixins for treating MDROs, implemented AMSP saw an outstanding reduction of 45% in the prescription of polymixins.[20] In this study, we find an alarmingly high utilization of antimicrobials including the last resort carbapenems and polymyxins in our ICU setups. Implementation of an effective AMSP is the best possible approach to tackle this high consumption of antimicrobial drugs.

Limitations of the study

The study was conducted on 100 participants. It is pertinent to conduct a comprehensive study based on bigger sample size and the commonest resistant microorganisms that are prevalent in our ICU setting.

CONCLUSION

An alarmingly high usage of empiric antimicrobial consumption has been noted in our study. Several strategies such as ICU specific antibiotic policies especially AMSP and sensitization toward rational antimicrobial prescription need to be followed in letter and spirit. Moreover, point-of-care diagnostic technologies need to be adhered that will allow for rapid and reliable diagnosis of infection. These strategies can optimize antimicrobial therapy and minimize risks of emergence of multidrug - resistant bacteria due to prolonged and inadequate use of antimicrobial drugs.

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